A COMPARISON OF THE DIFFERENT ALGORITHMS FOR ESSENTIAL TREMOR AND PARKINSON'S DISEASE TREMOR DIFFERENTIATION BASED ON HAND TREMOR

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Declaration

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List of Abbreviations

ET	Essential Tremor
PD	Parkinson’s disease tremor
IMU	Inertia measurement unit
WHIGET	Washington Heights-Inwood Genetic Study of Essential Tremor
DBS	Deep brain stimulation
MDS	Movement Disorder Society
MDS-UPDRS	Movement Disorder Society-Sponsored Revision of the Unified Parkinson’s Disease Rating Scale.
MAO-B	monoamine oxidase B
DaTSCAN	Dopamine transporter scanner
^{123}I-FP-CIT	^{123}I-ioflupane
SPECT	Single photon emission computerized tomography
SWEDD	scans without evidence of dopaminergic deficit
sEMG	Surface electromyography
TSI	Tremor stability index
MHPP	Mean harmonic mean power
RE	Relative energy
EMD	Empirical mode decomposition
IMF	Intrinsic mode function
SVD	Singular value decomposition
PCA	Principal component analysis
FFT	Fast Fourier transform
USB	Universal serial bus
ROC	Receiver operating characteristics
AUC	Area under the curve

Abstrak

Essential Tremor (ET) dan penyakit *Parkinson* (PD) merupakan dua jenis masalah geletaran (*tremor*) yang paling biasa. Misdiagnosis antara kedua-dua kumpulan geletarn ini sering berlaku oleh pemeriksaan pakar, disebabkan oleh pertindihan gejala antara ET dan PD pada peringkat awal penyakit. Untuk memberi bantuan kepada pakar semasa pemeriksaan *tremor*, sistem pemantauan geletaran dan sistem *diagnosis tremor* telah dibina dengan menggunakan unit pengukuran inersia tanpa wayar, untuk mengumpul data *tremor* tangan dari pesakit dan mengklasifikasikan jenis *tremor* yand dihadapi oleh pesakit.

Empat jenis algoritma klasifikasi *tremor* telah diuji dengan 153 postural rakaman tremor dan 154 rakaman tremor lain yang diambil dari pesakit ET dan PD, iaitu *Tremor Stability Index* (TSI), *Mean Harmonic Peak Power* (MHPP), *Relative Energy* (RE) dan *Empirical Mode Decomposition – Singular Value Decomposition* (EMD-SVD). Algoritma berdasarkan intensiti gegaran, kekerapan dominan dan panjang gegaran telah digunakan untuk memilih rekod-rekod *tremor* ET dan PD untuk analisis. 43 rakaman postural (ET, n = 8 dan PD, n = 35) dan 43 rakaman rehat (ET, n = 4 dan PD, n = 39) telah dipilih. Pengagihan ciri-ciri yang diekstrak dari setiap algoritma telah diuji dengan ujian *Mann Whitney U*, dan sensitiviti, kekhususan dan ketepatan untuk setiap algoritma dalam mengklasifikasikan pesakit ET dengan betul telah dikaji dengan menggunakan lengkung operasi penerima sifat (ROC).

Keputusan menunjukkan bahawa terdapat perbezaan yang jelas antara pengagihan MHPP (p = 0.001) dan RE (p = 0.019) di antara ET dan PD. Keputusan Analisa ROC telah menunjukkan bahawa MHPP mempunyai ketepatan tertinggi dalam

mengklasifikasikan ET dan PD (85.7%), dengan sensitiviti dan kekhususannya mencapai 88.6% dan 87.5% masing-masing.

Abstract

Essential tremor (ET) and Parkinson's disease tremor (PD) are the two most common types of tremor. Misdiagnosis of among these two groups of tremors often occurs when using clinical observations, due to overlapping of symptoms between ET and PD at the early stage of disease. To assist specialist in making decisions when diagnosing the tremor, a tremor monitoring and differential diagnosis system is implemented using a wireless inertia measurement unit, to collect hand tremor data from patients and perform classifications of tremor.

Four different types of tremor classification algorithms, namely the Tremor Stability Index (TSI), Mean Harmonic Peak Power (MHPP), Relative Energy (RE) and Empirical Mode Decomposition – Singular Value Decomposition (EMD-SVD) analysis had been tested with 153 postural tremor recordings and 154 rest tremor recordings collected from ET and PD patients. A tremor detection algorithm based on tremor intensity, dominant frequency and length of tremor had been used to select recordings significance tremor of ET and PD for analysis. 43 postural recordings (ET, n= 8 and PD, n=35) and 43 rest tremor recordings (ET, n=4 and PD, n=39) had been selected. The distribution of features extracted from each algorithm was tested with Mann Whitney U test, and the sensitivity, specificity and accuracy for each algorithms in correctly classify ET patients were analysed using receiver operating curves (ROC).

The results had shown that are distinct differences between the distributions of MHPP (p=0.001) and RE (p=0.019) among ET and PD. The ROC results had showed that the MHPP had the highest accuracy in classify ET and PD (85.7%), with sensitivity and specificity of 88.6% and 87.5% respectively.

Chapter 1: Introduction

Tremor is a kind of movement disorder, which involves involuntary, rhythmic oscillation motions on parts of human body. People who suffer of tremor will face difficulties in completing daily tasks and activities including writing, eating, drinking and speaking, which significantly reduce the quality of life [1]. Aside from the physical inconvenience, tremor patients and their close persons could also suffer the mental depression and stress, and nearly half of the patients would developed social phobia [2, 3]. Tremor can be categorized into two main categories based on their prevalence timing, which are rest tremor and also action tremor. Rest tremor occurs when muscles are fully relaxed and being supported. On the other hand, action tremor occurs under several conditions when muscles are contracted, these could be when a person is maintaining parts of body in certain positions (as known as postural tremor), or he/she is doing voluntary movement (kinetic tremor), or the tremor could even only occurs when that person is doing specific task such as writing (known as task-specified tremor) [4].

Tremor can have different forms and cause by variety of factors. The most common cause of tremor is the physiologic tremor. Physiologic tremor occurs on all healthy people, and it becomes significance when our muscles are in fatigue due to heavy physical activities, or when we are in stress and anxiety [4]. Physiologic tremor is usually very insignificant and has minimal effect on our life, except for the enhanced physiological tremor that can be induced by drugs or withdrawal from certain medicines such as opioids [5]. Conversely, essential tremor (ET) and the Parkinson's disease tremor (PD) are the two most common types of tremor mostly prevalent in elders [6]. Studies show the prevalence of tremor increases with age. The median crude prevalence of ET for people above 65 years is about 4.6% and the number increase to 21.7% when a person is above 95 years [7]. The same trend happens to PD, where meta-analysis has showed that the crude prevalence of Parkinson's disease increase from 0.1% for populations with age 40 - 49 years, to about 2% for populations with 70 – 79 years, and majority (76% - 100%) of the patients will developed the tremor [8, 9].

There is a vast difference between clinical symptoms of ET and PD. Essential tremor is characterized as an action tremor, which affects symmetrically on both left and right sides of the body. In contrast, PD usually appears at rest, affects body asymmetrically, and often associated with other symptoms such as bradykinesia and also increase in muscle rigidity [4]. Yet, differential diagnosis of ET and PD could still be challenging both in early stage of the diseases and while the diseases progress [9].

1.1 Problem Statements

The common way used by specialist to perform differential diagnosis on ET and PD is by clinical observations. However, diagnosing tremor using clinical examinations is still unsatisfactory (37% of patients misdiagnose as ET out of 71 subjects, and 4 out of 16 PD patients misdiagnose in other study), due to overlapping in symptoms of ET and PD and also lack of agreement among movement disorder specialist in defining the tremors [9-11]. There is no cure for both ET and PD. However recent study had suggested that earlier treatments could help to control the progress of symptoms in Parkinson's disease, which can improve the quality of patients' lives. Misdiagnosis of ET and PD is unfavourable because it will delay the timing for patients to receive appropriate treatments [12]. Therefore a system which could assist the specialist to make decision while diagnosing the tremor would be required.

In this work, we study the different tremor classification algorithms available in classifying ET and PD based on hand tremors. Secondly, we compare the performance of each algorithms using hand tremor data available. Finally, we build a wireless tremor monitoring system and differential diagnosis system using a wireless inertia measurement unit (IMU), to study the performance of tremor classification algorithms on new samples of tremor patients.

1.2 Objectives

The objectives of this work are:

I. To determine the data separation of each features that can be extracted from hand tremors acceleration data among ET and PD groups.

II. To determine the classification performance of discriminating ET and PD tremor recordings using features extracted.

1.3 Scope of Project

The scope of this project is to learn the tremor differential diagnosis algorithms based on acceleration data of hand tremor. These algorithms will be applied on the pre-taken hand tremor data to evaluate the performance of each algorithms in differential diagnosis of ET and PD. Modifications will be done on each algorithms if needed. Finally, these algorithms will be implemented into a wireless hand tremor monitoring and differential diagnosis system, to be tested on new tremor patients samples.

Chapter 2: Literature Review

2.1 Essential Tremor

Essential tremor (ET) is one of the most common kind of tremor. ET is an action tremor which affects upper limbs, head, voice, trunk and lower limbs [13]. ET is not a disease with single entity, instead ET was used to be classified into four types [13]. The symptoms and characteristics of these tremors are summarized in Table 1 below:

Table 1: The types of essential tremor and their characteristics [13].

Types of ET	Descriptions
Type 1	• Mild hand tremulousness by enhanced mechanical-reflex oscillation • Tremor frequency decrease with inertial loading of hand • May due to enhanced physiologic tremor
Type 2	• Upper limbs tremor which is more severe tremor than Type I. • Could involves lips, chin, tongue, voice, head and sometimes leg tremor

	• Produced by a central neurogenic oscillation at a frequency that is not a function of limb inertia or reflex arc length. • Often hereditary and disabling.
Type 3	• More severe and disabling tremor compared to Type III. • Some are from the natural progression of Type 2 ET. • Many patients of this group do not have family history. • May due to other diseases but subtle symptoms overlook by specialists.
Type 4	• Non-specific action tremor of upper limbs that may due to symptoms of other diseases.

In past 20 years, ET had been redefined, and the Type 1 and Type 4 ET had been excluded from the definition of ET [13]. To separate the Type 2 and Type 3 ET from the others, several criteria on the symptoms of tremor had been set to be fulfilled, to diagnose a patient as ET patient [13]. First of all, the ET patients should have central neurogenic tremor within 4 -8 Hz, which is unaffected inertia load of the limbs [13]. To exclude the enhanced physiological tremor from ET, the amplitude of tremor, which is accessed by the tremor rating scale, is being considered when diagnose ET patients [13]. The clinical rating scales which are used to accessed severity of ET include Fahn-Tolosa-Marin scale and Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) [13, 14]. To ensure a patient to be have definite ET, the patient should have monosymptomatic bilateral postural or kinetic tremor for more than 5 years [13]. Medication treatments would be required for severe ET patients to control their symptoms. The choice of drugs includes Beta-blockers such as propranolol and Primidone [15]. Patients whose symptoms could not be controlled by medicine might require surgical treatment such as deep brain stimulation (DBS) [15].

2.2 Parkinson's Disease

Parkinson's disease is a kind of neurological disorder which involve a series of motor symptoms and non-motor symptoms [16]. The motor symptoms of Parkinson's disease is due to degenerative dopaminergic neurons in substantia nigra, which causes low concentration of dopamine in striatum of PD patients [16]. In general, there are four common types of motor symptoms which could be found on Parkinson's disease patient [16]. Table 2 shows the symptoms and their descriptions.

Table 2: Common motor symptoms found in Parkinson's disease patients and their descriptions [16, 17].

Motor symptoms	Description
Tremor	• Rest tremor at 3 – 6 Hz, disappear by doing voluntary movement or while patients asleep. • Affects hands, chins, lip, and legs but rarely affects neck or head. • 75% to 100% of Parkinson's disease patients are having tremor.

Bradykinesia	• Refers to slowness of movement • Examples are decrease in arm swing while walking, reduced in facial expression or eyes blinking. • Can be diagnosed by requesting patients to do rapid and repetitive task like fingers tapping, to observe the slowness in movement and decrease in amplitude. • Occurs in 80% to 90% of patients.
Rigidity of muscles	• Refers to the increase in resistance of flexor and extensor muscles in limbs to the passive movements. • May associate with pain. • Occurs in 80% to 90% of patients.
Postural instability	• Refers to the inability of patients to maintain the balance of their postures. • Prevail in the late stage of Parkinson's disease.

The severity of Parkinson's disease could be evaluated using clinical rating scales such as the Hoehn and Yahr scale, or the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [17]. The Parkinson's disease could not be cured. The common treatment of Parkinson's disease involved medication such as levodopa which is used to replace loss dopamine, dopamine agonist which mimics the effect of dopamine in brain, and the monoamine oxidase B (MAO-B) inhibitor which inhibits the enzyme MAO-B to breaks down brain dopamine [18]. Some severe patients where the symptoms cannot be controlled by the medicine would require surgical treatment such as deep brain stimulation (DBS) [18].

2.3 Differential Diagnosis of Tremor by Clinical Observations

The most common practice in differential diagnosis is to perform clinical observations on the symptoms of patients by specialist. The criteria for clinical classifications of tremors had been proposed by Movement Disorder Society (MDS) is known as "Consensus statement of the Movement Disorder Society on Tremor" [19]. In the first stage of the diagnosis, specialists would examine carefully if the symptoms of "shaking" on patients are real tremors, instead of other hyperkinetic disorder such as rhythmic myoclonus, asterixis or clonus which could be described as "shaking" or "tremor" [19, 20]. In the following step, specialists would try to describe the characteristics of tremors to identify the cause of tremor [19-21]. The characteristics that would be examined by specialist involved whether a tremor is action tremor or rest tremor, the tremor is unilateral or bilateral, the amplitude and frequency of oscillations of tremors [5, 20, 21]. Through the descriptions of tremors, the tremors could be classified according to their cause using guidelines provided. To confirm the results of diagnosis, specialist would studied the historical data on patients to look for how the tremor diseases progress and react to the medications [20]. The supportive symptoms such as bradykinesia, rigidity of muscle, olfactory dysfunction can be used by specialist to confirm the diagnosis results [5, 20, 21]. The clinical observations method takes time for specialist to examine all the clinical symptoms of tremor. Moreover, confusing symptoms such as isolated postural tremor in PD at the early stage of disease often leads to misdiagnosis of the causes of tremor [9, 22].

2.4 Neuroimaging Technique on Tremor Inspection

Dopamine transporter scanner (DaTSCAN) can be used to inspect the cause of tremor of the patients, if the symptoms of the tremor is unclear. The commonly used DaTSCAN is the ^{123}I-FP-CIT (^{123}I-ioflupane) single photon emission computerized tomography (SPECT) [23]. The scanning process is done by first injecting the radiotracers, ^{123}I-FP-CIT into the body of the patients 3- 6 hours before the SPECT imaging. The radiotracers will bind with the dopamine transporters, and shows the number of dopaminergic neurons in the substania nigra in brain, which can be used to detect the degeneration in striatal dopaminergic neurons in brain (the hall mark and the cause of motor symptoms in Parkinson's disease) [23]. The DaTSCAN technique has a high sensitivity (92%-97%) in the diagnosis of the Parkinson's disease of the patients, and often used to confirm the diagnostic results of the patients before the data of patients are used to test for new algorithms [24]. However, the specificity of this neuroimaging technique is not very high (74%-96%) when used to discriminate PD from ET [24]. The patients there are clinically presume as Parkinson's disease but absence of abnormality in SPECT scan results are known as "scans without evidence of dopaminergic deficit" (SWEDD) [25]. Although in many cases, the SWEDD subjects just simply do not have Parkinson's disease, there are also cases of patients who initially have normal scan results but evolve into Parkinson’s disease after some time [25, 26]. In addition, the SPECT technology is not widely available, expensive, and the diagnosis process is time consuming [22, 27].

2.5 Neurophysiological Evaluation of Tremor

Neurophysiological evaluation techniques can be used to assist in the differential diagnosis because they are widely accessible and cheap. The neurophysiological features of tremor can be quantified by using digital pads, surface electromyography (sEMG) and the accelerometers. The task-specific tremors, such as tremor while drawing Archimedes’ spiral can be quantified using a digital pad [28]. The digital pad can be used for the automatic quantification of the tremor intensity and to distinguish the tremor patients from healthy subjects [28]. Analysis characteristics of the Archimedes’ spirals such as axis of tremor in the spiral, tremor intensity, spiral diameter and density can provide a clue for specialist on the cause of tremor of each patients, however, further studies need to be conducted to validate the diagnostic validity of this method [9, 29].

The sEMG measures the current in muscles when muscles contract, and could be used to quantify tremors. While the measuring the hand tremor, the electrodes of the sEMG could be applied to the muscles of the flexor carpi ulnaris and the extensor carpi ulnaris or the first dorsal interosseus muscle and second palmar interosseus [30, 31]. A study which evaluates the sEMG signals of 100 tremor patients with different kind of tremors, and found that the tremor frequency, amplitude, tremor burst patterns of sEMG signals are not useful in differentiating middle range frequency tremors such as ET and PD. The only useful data that could be used in differentiating ET and PD is the tremor burst duration of muscles at rest [30]. Another study had suggested that the ET and PD could be differentiate by examined the latency in tremors and concentration effect of tremor when using the sEMG [31].

The oscillations of hand tremor can be captured by image based method using motion capture camera and leap motion sensor, or accelerometer devices. Motion cameras do not need interfere with the patients while capturing hand tremors, with clear advantages in setup time and the tremor recordings are completely unaffected by the weight of devices. The three dimensional positions of hand can be obtained by using two cameras with image processing algorithm, which can provide accurate displacements of the hand without being affected by the distance of the hand from the cameras [32]. The drawback of using optical devices in capturing tremor is that it constraints the position of patient to a limited space so that their hands are always able to capture by cameras [32, 33]. Moreover, the distance of hands should not be too far away from cameras to maintain the accuracy of the results [32, 33], thus bring inconvenience when measuring of task specific tremors or tremors at different posture is required.

The accelerometers have been widely used to obtain neurophysiological features due to their availability and price [22, 34, 35]. They are small and light, and can be easily mounted on any parts of body for tremor measurements. The wireless accelerometers enhances the mobility in posture of patients while recording the tremors. Tri-axial accelerometers are commonly used in studying the hand tremors, compared to uniaxial accelerometers [22, 34-36]. Pre-processing processes are needed to be done on accelerometer data, before they could be used for analysing [22, 34-36].

2.5 Tremor Data Selection

The physiologic tremor recordings need to be separated from the recordings of ET and PD, before classifications of ET and PD can be done [36]. This is due to most classifiers can only do classifications among ET group and PD group, and are not able to distinguish between tremor patients and healthy subjects [22, 34-37]. During tremor recording process, the tremor can be suppress by the voluntary movements of patients[9], hence data selection is important to ensure that only the data with clinical relevant tremors (ET and PD) is used while evaluating performance of classifiers. The selection process should be automated to achieve time saving and also prevent human bias during the study.

The automated tremor selection process can be achieved by computing the dominant frequency of the tremor recordings [38]. Since tremor data is non-linear and non-stationary, the whole tremor recordings are divided into smaller segments with divided into smaller segments of 3 to 4 seconds [36, 38]. Power spectral density (PSD) of each segments could be computed to determine the dominant frequency of each segments, and the methods could be based on parametric methods such as Burg's model, or Fast Fourier Transform (FFT) based method such as periodogram [38]. Previous studies had used a bandwidth of 2.5 – 12 Hz in data selection [13, 16], where a segment can be classified as "segment with tremor" if the dominant frequency is within the bandwidth [38].

Amplitude of tremor had been used by other study to differentiate the ET and PD tremors from physiologic tremor [36]. ET and PD have relatively higher amplitude compared to the amplitude of physiologic tremor, and a threshold value can be set to exclude the physiologic tremor data from analysis [36]. This method however will also exclude some of the patients' data with very mild tremor [13]. Acceleration data from control group (healthy subject) had been used in defining the threshold while separating the ET and PD data from physiologic tremor data [36].

2.6 Pre-processing of Accelerometer Data

Gravitational artifact is defined as the portion of an accelerometer output signal which is produced by earth's gravity [39]. One of the problem when using accelerometers in monitoring tremors is the data consist of gravitational artifact, which is very significance compared to amplitude of tremor. The effect of gravity in the accelerometer readings could be removed by applying high-pass filter on the data [22]. However this method assumes the frequency of gravitational acceleration is low. In fact, the magnitude of gravitational acceleration in changes in the readings of a uniaxial accelerometer, according to the orientation of sensor. Therefore, the high-pass filter cannot remove the gravitational artifact effectively when orientation of an accelerometer is consistently changed due to the tremor, for example the pronation-supination motion of wrist in PD. An alternative way to remove the gravity artifact in a tri-axial accelerometer readings is by finding the resultant magnitude of acceleration among the X, Y and Z axes, and subtracted by a constant of -9.81 m/s^{-2} [36]. However, this method requires the motion of hand always to be collinear to the direction of gravitational acceleration of earth to be valid. To remove the gravitational artifact from the tremor recordings effectively, the orientation of sensor has to be known throughout the recordings, to project the gravity to the sensor reference frame, and subtract from the readings of accelerometer [40]. Therefore, an inertia measurement unit (IMU) which is the integration of accelerometer, gyroscope and sometimes magnetometer, is more suitable for monitoring tremor compare to a tri-axial accelerometer. Drift might occur in the resultant acceleration data due to biases in readings of accelerometer and gyroscope [40], but it could be corrected using a high-pass filter as long as the biases are consistent.

Besides removing gravitational artifact, high-pass filter can be used to suppress the low frequency voluntary motions in the tremor recordings, which are relatively significance compared to the amplitude of tremor [36]. By knowing the fact that tremors in body have a relatively low frequency range of 3 – 12 Hz, low-pass filter can be used to filter the signals form high frequency noise [38].

2.7 Tremor Classifications

No neurophysiological techniques had been proved to have good classifications in ET and PD. A few algorithms had been developed in previous studies to extract features from hand tremors of ET and PD patients and to distinguish these two types of tremors. Examples of features being explored include change in instantaneous frequency of tremor between each cycles with the next (Tremor Stability Index, TSI), measurement of mean power of the first four harmonics in tremor (Mean Harmonic Peak Power, MHPP), ratio of total power spectral in rest tremor to the total power spectral in postural tremor of the same patients (Relative Energy, RE), ratio of tremor amplitude fluctuations in rest tremor to the postural tremor of the same subject (Temporal Fluctuations), and the singular values of intrinsic mode functions (IMF) of hand tremor (Empirical mode decomposition – singular value decomposition, EMD-SVD analysis). The extracted features could distinguish the class of tremor a patient belongs to by setting a threshold value for each features, except for the values from EMD-SVD analysis which require to associate with a support vector machine classifier. Most of the features had shown good results in classification of ET and PD in their original studies, but further studies had not been done to verify the performance of these features on larger sample size of patients. The only exception is the MHPP, which had been proven to have accuracy of about 90% or higher in three independent studies. However, the MHPP values can only be used in classifying tremors when the amplitude of each tremor recordings is similar. This is due to while obtaining the MHPP value of the patient's hand tremor, the MHPP is not normalize with the tremor amplitude of that particular patient. Instead it is normalize by the mean power hand recordings from a group of healthy subjects, thus the MHPP value for mild tremor is not compatible with severe tremor.

Chapter 3: Methodology

The methodology of this projects is divided into two parts. The first parts of the methodology discuss on the experimental procedures in verifying the performance of each tremor classification algorithms. The second part of the methodology discuss on the procedure of making a wireless hand tremor monitoring and differential diagnosis system using a wireless inertia measurement unit (IMU).

3.1 Experimental Setup for Verifying Performance of Tremor Differential Diagnosis Algorithms

Performances of four different types of tremor classification algorithms are verified in this work. They are:

I. Tremor Stability Index
II. Mean Harmonic Peak Power
III. Relative Energy
IV. Empirical mode decomposition – singular value decomposition

The temporal fluctuation algorithm has a similar concept to the relative energy, thus it has been excluded from the study.

3.1.1 Concept of Tremor Stability Index (TSI)

The tremor stability index (TSI) is defined as the interquartile range of change in tremor instantaneous frequency between each cycles of oscillation with next cycle [22]. To obtain TSI value from a hand tremor recording, first the zero-crossings of the data are found as shown in Figure 1 below. The difference in time between each odd number zero-crossings with the subsequent points is the period of each oscillations, T_n. The instantaneous frequency of each complete oscillations, f_n can be found by from T_n using the method:

$$f_n = \frac{1}{T_n} \tag{1}$$

And the difference in frequency between each cycles to the subsequence cycle Δf is computed by using equation (2) below:

$$\Delta f = f_n - f_{n+1} \tag{2}$$

Once the all the Δf have been found, the interquartile range of Δf, which is known as TSI, is computed [22].

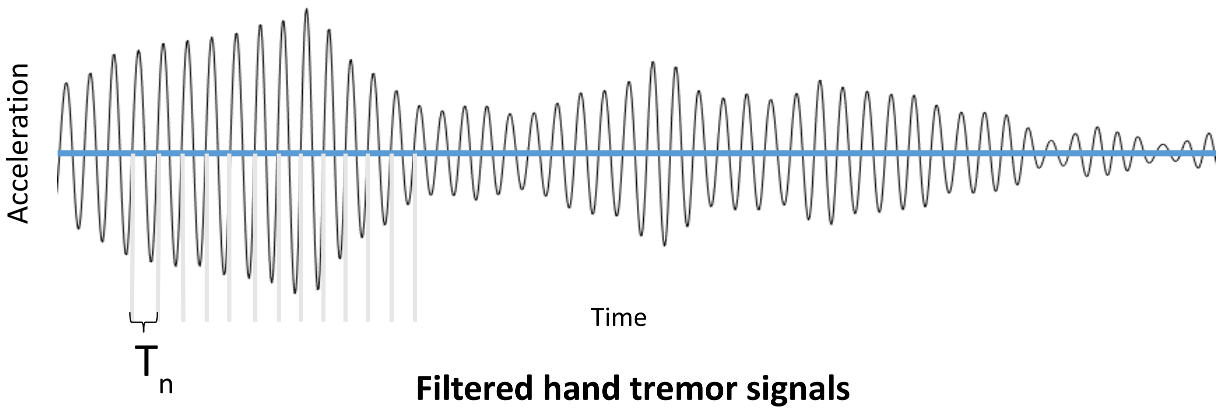

Figure 1: The pre-processed hand tremor signal. The instantaneous frequency a complete oscillation of tremor is shown as T_n in the figure.

3.1.2 Concept of Mean Harmonic Peak Power (MHPP)

Mean harmonic peak power (MHPP) is the mean power of the first four harmonics in a tremor recording [35]. To compute the MHPP of tremor, first of all, the unit of acceleration in tremor recording is converted to milligravity [35]. Next, the average power spectral density of the recording is found using Welch periodogram method with non-overlapping 1 second window. The power spectrum S(f) of the first harmonic (f_T) is found by finding the peak value in the power spectrum, and the power spectrum of the second, third and fourth harmonic is power spectrum at the integer, n multiple of peak frequency (where n = 2,3,4) as shown in Figure 2 below [35]. In the original work of MHPP, the MHPP value is normalize by a mean total power of a small group of normal subject analysed in individual laboratory [35]. This method does not allows MHPP values of two tremor recordings with significantly difference tremor intensity to be compared directly. Therefore, in this experiment, the power of the first four harmonic is normalized by dividing with the total power spectral, σ, of the same tremor recording, before it is

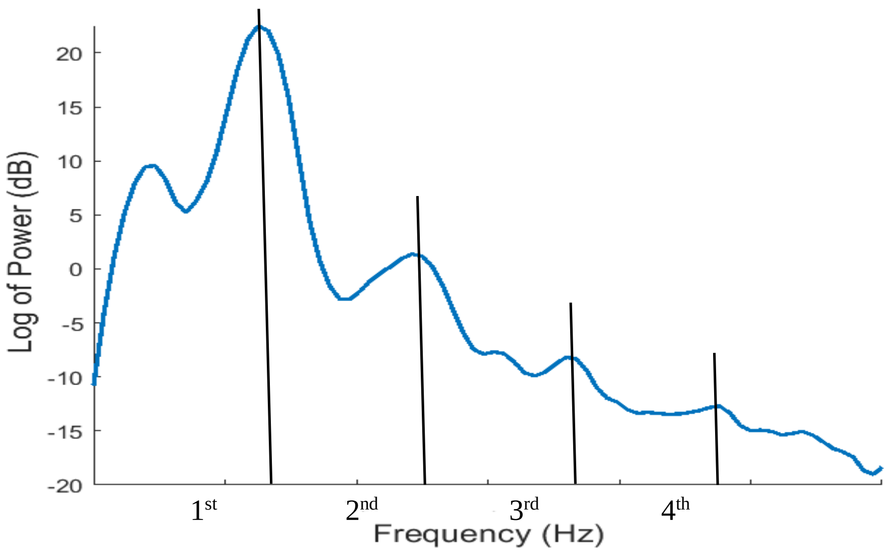

Figure 2: The log of the power spectrum of tremor. The first, second, third, and fourth harmonics frequencies are as shown in figure by black vertical lines.

logarithmically transform while computing MHPP. The method to compute MHPP is shown in equation (3) below:

$$MHPP = \frac{1}{4}\sum_{n=1}^{4}(10 * \log(\frac{S(n * f_T)}{\sigma})) \tag{3}$$

3.1.3 Concept of Relative Energy (RE)

Relative energy (RE) is the comparison of rest tremor amplitude to the postural tremor amplitude [36]. To determine the relative energy of tremors of a patient, two tremor recordings, one from postural position and another from rest position. The power spectral density of both recordings could be found by using similar method as stated while determine MHPP, and the RE could be determined using equation (4) as shown [36].

$$RE = \frac{\int_0^{20} S_A(f)df}{\int_0^{20} S_B(f)df} \tag{4}$$

Where $S_A(f)$ is the power spectral density for rest tremor and $S_B(f)$ is the power spectral density of postural tremor.

3.1.4 Concept of Empirical Mode Decomposition (EMD)

Empirical mode decomposition is the process of breaking down signals into several components known as intrinsic mode functions (IMF) [34]. The technique that is used to obtain IMFs is called sifting. The sifting process is done by first identify all the local maxima and local minima of the signal. A cubic spline line is used to connect all the local maxima to form the upper envolope, and another cubic spline join the local minima to form lower envolope. The mean of the upper and lower envolope $m_1(t)$ is found, and the first component, $h_1(t)$ which is the difference between the original signal X(t) and the m_1 is found, as shown in equation (5).

$$X(t) - m_1(t) = h_1(t)$$

$h_1(t)$ is used to replace the original signal and the sifiting process continues, until the residue $h_n(t)$ satisifies the properties of an IMF, which are:

I. The number of local extrema and local minima is equals to the number of zero-crossings or at most differ by one [34].

II. The mean of upper envelope and the lower envolope define by local maxima and minima should be equals to zero [34].

Once $h_n(t)$ fulfill the two criteria stated above, it is considered as the first IMF, $c_1(t)$. The first IMF, $c_1(t)$ is then subtracted from X(t) as shown in equation (6), and sifting process is repeated on the residue $r_1(t)$, until no more IMF can be extracted from residue $r_n(t)$.

$$X(t) - c_1(t) = r_1(t) \quad (6)$$

$$r_{n-1}(t) - c_n(t) = r_n(t) \quad (7)$$

Thus the original signal will be the sum of the IMFs and the remaining residue, as shown in equation (8).

$$X(t) = \sum_{i=1}^{n} c_i(t) + r_n(t) \quad (8)$$

3.1.5 Concept of Singular Value Decomposition (SVD)

Singular value decomposition (SVD) is a common technique used in signals processing method to in data compression. The SVD methods decompose the an m×n matrix, A into three matrices as shown in equation (9) [34],

(9)

$$A = U\Sigma V^T$$

Where U is an m×m orthogonal matrix, known as left singular vectors and V is an n×n orthogonal matrix which is called right singular vectors. Both U and V are unitary matrices, which means that the inverse of a matrix is equals to the transpose of that matrix, shown in equation (10):

$$U^{-1} = U^T \tag{10}$$

The Σ is an m×n non-negative, real numbers diagonal matrix, which consist of unique singular values of matrix A. The magnitude of singular values show the importance of a singular vector in a matrix, where the larger the singular value, the more information about the pattern of matrix contains by a singular vector [34].

3.1.6 Setup of Experiments

The performance of each algorithms is validated with hand tremor data that have been recorded. The hand tremor data available are taken with by using an IMU, SBG IG 500A. The sampling frequency of data capture by the IMU is at 100 Hz, and the acceleration components at X ,Y and Z-axes were being recorded. During data acquisition process, the IMU is mounted on the dorsal surface of hands of patients. Tremor is recorded under two hand postures, the first one required the hands of patients to fully outstretch, and in the second posture, the hands patients are completely relaxing, and being supported against gravity, as shown in Figure 3. The length of recordings are 15.34 ± 1.18 seconds (mean ± standard deviation, same for below unless stated).

3.1.7 Participants

17 ET patients, 86 PD patients (from General Hospital Penang, 1 PD patient from Hospital USM Kubang Kerian) and 66 healthy subjects are involved in this experiment. One to two postural and rest recordings (the position is as shown in Figure 3) are taken from each subjects, and a total of 282 postural recordings (ET (n=30) ,PD (n=123), and normal subjects (n=129)), and also 282 rest recordings (ET (n=30), PD (n=124), and normal subjects (n=128)) are taken in this experiment. The details of the subjects are listed in Table 3 below:

Table 3: Details of ET and PD patients involved in the experiment

Subjects	Essential Tremor	Parkinson's Disease Tremor
Age (years)	67.06±8.93	69.81±8.12
Gender	9 male, 8 female	57 male, 29 female
Hoehn and Yahr stage	Not related	2.19±1.06
Last medicine time (hours)	Not related	5.76±8.52
Deep brain stimulator	Not related	59 not involved, 27 unknown

The details of the healthy subjects had not been recorded during experiment.

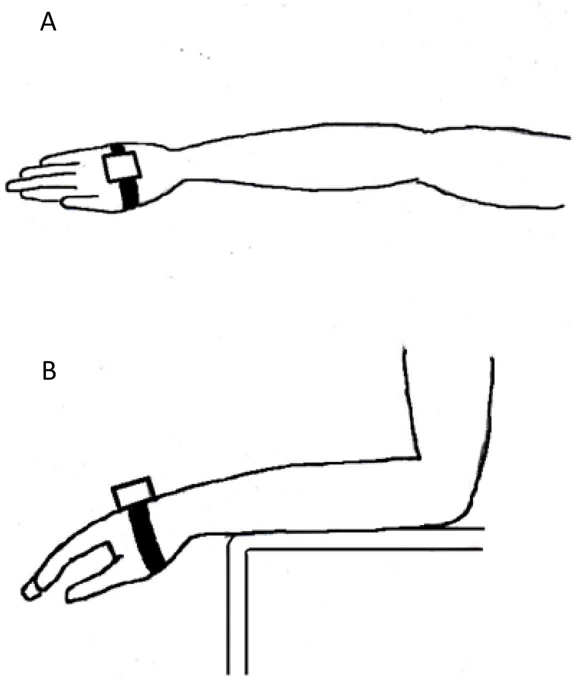

Figure 3: A) Postural arm position. The arm is fully outstretch against gravity. B) Rest posture. The arm is fully relax and supported by the handle of chair.

3.1.8 Preprocessing of Data

The hand tremor data stored in Microsoft Excel format is imported into MATLAB 2018a for preprocessing. One major difference between the data acquired by SBG IG 500A and the Xsens MTw Awinda is that the acceleration data acquire from MTw Awinda is free acceleration (acceleration data without gravitational artifact), as the data from SBG IG 500A, the acceleration data output consist of the gravity component, and this effect must be removed manually in MATLAB. The process is done by importing the orientations of sensor during measurement process into MATLAB in the form of quaternions. The gravity vector ([0 0 -9.81]) which has a magnitude of -9.81 m/s^2 in Z-axis, is rotated using the orientations of sensor, before it is being subtracted from the hand tremor data [35]. The remaining data obtained are now free acceleration data.

Subsequently, these data are filtered by high-pass butterworth filter at 0.1 Hz to remove drift in data [22].

3.1.9 Selection Criteria of Hand Tremor Data

The algorithm is implemented to filter out the data which do not consist significant hand tremor when compared to voluntary movements and physiological tremor. To perform tremor detection process on the data, a complete hand tremor recording is trimmed into multiples 1 second segments to extract the tremor data within the segments. Power spectral density (PSD) of each segments was computed using Welch periodogram method with 1 second window [38]. The data obtained from healthy subjects are then used to define the intensity level for significant tremor [36]. Two criteria are used in finding segments with significant tremor. The first criterion is the peak intentsity of oscillation for each segments should be higher than 0.005 $(m/s^2)^2$. These threshold values are set based on the tremor intensity of postural and rest hand recordings from healthy subjects. The second criterion is the dorminant frequency for each segments should be within 3 - 12 Hz [38]. Tremor recordings with more than 7 seconds of significance tremor segments are selected to test the classifying performance of each algorithms.

Out of 153 postural recordings and 154 rest recordings from tremor patients, 43 postural recordings (ET, n=8 and PD, n=35) and also 43 rest recordings (ET, n=4 and PD, n=39) are being selected to verify the tremor classification algorithms. The selected postural recordings are used to test the tremor classification algorithms based on TSI, MHPP and also the EMD-SVD values. To test the tremor classification algorithm based on RE, each postural tremor recordings is paired with a rest tremor recording from the same subject, and 62 sets of recordings are selected (ET, n=12 and PD, n=50, either