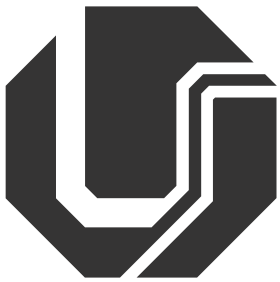
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ARIANA MOURA CABRAL

ON THE EFFECT OF VIBROTACTILE STIMULATION IN ESSENTIAL TREMOR

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ARIANA MOURA CABRAL

ON THE EFFECT OF VIBROTACTILE STIMULATION IN ESSENTIAL TREMOR

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Area: Biomedical Signal Processing

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It is difficult to imagine anything more fascinating or significant than being a part of the endeavour to advance the frontiers of knowledge on a subject that has the potential to impact the lives of others.

Thus, this study is dedicated to all those who have trembling hands, all those who have tremors.

I also would like to dedicate this study to my parents and sisters, who are my strong pillar and my springboard to explore the world around me.

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"Those who pass by us, do not go alone, and do not leave us alone
they leave a bit of themselves, and take a little of us..."

— Antoine de Saint-Exupéry

It has been a long journey to get here. Throughout all this time, I have learned many lessons and I have been (re)discovering myself at every step. The path travelled was fraught with challenges. However, none of this would have been possible without the support, guidance, assistance and encouragement of those who have stood by my side or crossed my path. Each one has contributed to my journey in a unique way and I am extremely grateful.

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ABSTRACT

Motivation: Essential Tremor (ET) is a neurological disease characterized by tremors of hands that causes motor dysfunction, interfering with activities of daily living and compromising quality of life. It is most common in individuals over the age of 65, with a prevalence of around 4.5%. However, ET can affect anyone at any age. Despite available treatments to manage tremor, ET still has no cure. This is because there is no understanding of its origin. In addition, the mechanisms behind the generation and manifestation of tremor, as well as the effect of external inputs on these mechanisms, are unclear. Studies have been conducted on the effect of external stimuli, such as inertial loads and electrical stimuli, on the motor behaviour of individuals affected by tremor. However, there is few evidence on vibrotactile stimulation. **Objective:** In this context, this study aimed to evaluate the effect of peripheral vibrotactile stimulation on the dynamics of postural tremor in individuals with ET. **Methods:** For this purpose, the involuntary movements of 18 individuals with ET were analysed during the maintenance of posture in the absence of vibrotactile stimulation and presence of four different patterns of vibratory stimulus. The simulus were applied to the fingertips, palm of the hand and forearm, using piezoelectric actuators. The involuntary movements were recorded by two inertial measurement units positioned in the hand and forearm of the limb most affected by the condition. Two types of analysis were designed, one in the time domain (focused on changes in amplitude and regularity of tremor before, during and after stimulation) and the other in the frequency domain (focused on changes in power spectral density of the tremor with and without stimulation). Thus, different signal processing methods were proposed to describe the tremor in terms of amplitude, frequency and regularity (approximate entropy). **Results:** As a result, it was observed that the response to vibrotactile stimulation was different among individuals. When comparing the involuntary activity before and after stimulation, the stimulus at 250 Hz was the only one that caused a reduction in the amplitude of tremor, mainly in the hand ($\eta^2_H > 0.1$, p-value < 0.05). However, in terms of regularity, the tremor became more unpredictable after stimulation of the limb at 250 Hz ($\eta^2_H > 0.1$, p-value < 0.05), showing a small effect size only for the Y axis ($\eta^2_H = 0.012$). For many individuals, stimulation at 250 Hz and random frequency reduced the peak power of tremor compared to the peak power when the limb was not stimulated ($\eta^2_H > 0.1$, p-value < 0.05). In terms of frequency, it was also found that vibrotactile stimulation shifted the peak frequency, regardless of the stimulus pattern ($\eta^2_H > 0.12$, p-value < 0.05). **Conclusion:** Therefore, vibrotactile stimulation is a potential way to change the dynamics of postural tremor and could be a useful clinical tool for more than only dampening tremor.

Keywords: Essential Tremor; vibrotactile stimulation; gyroscope; wavelet; approximate entropy; frequency analysis.

"Sometimes it's best not to see your whole path laid out before you. Let life surprise you..."

Clare Vanderpool

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List of Abbreviations and Acronyms

ADL Activities of Daily Living

ApEn Approximate Entropy

DBS Deep Brain Stimulation

ET Essential Tremor

ET plus Essential Tremor plus

FTM Fahn-Tolosa-Marín Tremor Rating Scale

IMU Inertial Measurement Unit

IPMDS International Parkinson and Movement Disorder Society

MAV Mean Absolute Value

PSD Power Spectral Density

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1

Vibrotactile Stimulation: an alternative treatment for Essential Tremor?

"Don't worry about the bits you can't understand. Sit back and allow the words to wash around you, like music..."

— Roald Dahl, *Matilda*

1.1 Motivation

Essential Tremor (ET) is a progressive and chronic neurological disease that affects millions of people around the world, with a prevalence of approximately 0.9 percent among the general population and 4.5 percent among the elderly population (100). During the clinical course of this disease, the involuntary motor manifestation is the one that most interferes with an individual's quality of life and well-being (82), although its clinical spectrum can also include non-motor signs (98).

Individuals with ET typically experience tremors in hands, although the vocal cords, head, neck and lower limbs may be involved (117). In the early stages of the disease, tremor appears unilaterally. Initially, this motor sign affects the hand of one side of the body, and the individual has great difficulty performing activities of daily living (ADL) or fine motor tasks, such as holding a glass, using cutlery, and signing his own name. As the disease progresses, tremors in the upper limbs become more severe bilaterally and may compromise other parts of the body (15, 82).

Unlike other movement disorders that present an overlap of motor signs, the tremor is the sole motor symptom of ET (82). Tremor commonly emerges when a limb is maintained in a fixed posture, such as arms held outstretched against gravity. Thus, the classic tremor in ET is postural tremor. Its frequency varies from 4 to 12 Hz depending on which body segment is affected (145). Generally, proximal segments are affected at lower frequencies, while distal segments are affected at higher frequencies (110).

Currently, there are a variety of treatments available to help individuals with ET improving their quality of life and reducing the impact of involuntary motor manifestations on their daily activities. However, the response to treatment is determined by the stage of the disease and the severity of the motor sign, which is unique to each individual (15).

As part of the treatment plan, initially different medications may be used. If medications and other nonsurgical approaches do not effectively manage ET, surgical procedures, such as deep brain stimulation (DBS), can be an alternative (23).

The disabling character of the tremor makes relevant the search for more personalized treatments and the comprehension of the effect of external stimuli, such as biomechanical loads and peripheral electrical and mechanical stimuli, on the motor behaviour of individuals with ET. In this sense, several studies (17, 35, 36, 73, 115, 122, 125, 135, 149) have been carried out to investigate the potential of these stimuli in the treatment of a variety of disorders, including ET.

However, little research has been conducted on the effectiveness of vibrotactile stimulation on ET. Some investigations have demonstrated that peripheral mechanical stimulation can reduce tremor. On the other hand, studies demonstrate an increase in tremor following stimulation. This indicates that there is no consensus in the scientific literature regarding the effectiveness of this type of stimuli for movement disorders, specifically ET (149). Moreover, in these investigations, the mechanisms underlying vibrotactile stimulation in tremor are unclear.

Vibrotactile stimulation may be an interesting way to alter the manifestation of tremor, as it introduces an external vibratory stimulus, and perhaps provides clues about the underlying mechanisms of tremor. This is because it is a type of surface stimulation in which mechanical stimuli are applied to the skin and can be detected by vibration sensitive receptors, such as the mechanoreceptors present in the skin.

Therefore, this research was motivated by the lack of studies evaluating the effect of vibrotactile stimulation on postural tremor. Specifically, Rocon and colleagues (95) proposed an experimental protocol that considers multiple stimulation patterns in order to assess their effect on tremor. We have contributed to a greater understanding of how vibrotactile stimulation affects tremor amplitude, regularity, and energy based on this previous research and a dataset with data from individuals with ET provided by Professor Eduardo Rocon of the Centre for Automation and Robotics (CAR), Higher Technical School of Industrial Engineering (UPM), Madrid, Spain.

1.2 Aims

The purpose of this study was to assess the effect of vibrotactile stimulation on the tremor of individuals with Essential Tremor. In particular, the main aims of this investigation included: (*i*) objectively evaluating tremor using inertial sensors; (*ii*) investigating the effect of vibrotactile stimulation in relation to the stimulation region; (*iii*) evaluating the effect of different stimulation frequencies; (*iv*) assessing the behavior of the tremor amplitude before, during, and after stimulation; and (*v*) assessing the regularity (predictability) of tremor.

1.3 Outline

This work is organized as follows: Chapter 1 presents the main motivation for the execution of this research along with its aims. Chapters 2 and 3 review basic aspects related to Essential Tremor (the type of disorder evaluated in this research) and vibrotactile stimulation (the main external stimuli used in this research), respectively. Chapter 4 presents the methods employed in data collection and analysis. The results are shown in Chapter 5, followed by the discussion (Chapter 6) and conclusions (Chapter 7). An appendix has been added to this dissertation to fully present the results of spectral analysis for all individuals. We believe this contributes for a better understanding of the behaviour of the power spectrum density at an individual level, which may contribute to the development of personalized treatments and technologies. Finally, the pieces of code in R (i.e., R scripts) used for data processing have been made available to ease the dissemination and replication of this work.

2

Many Faces of Essential Tremor

"The heart of man is very much like the sea, it has its storms, it has its tides and in its depths it has its pearls too..."

— Vicent van Gogh, *The Letters of Vicent van Gogh*

Essential Tremor is one of the most common neurological diseases affecting thousands of people worldwide (100, 133), far more frequent than some of the more well-known movement disorders such as Parkinson's disease and dystonia. This condition is most common in people over the age of 65, but it can affect anyone at any age (124). Although it has been commonly referred to as *Benign Essential Tremor* in clinical practice, it is not a benign disease. The signs and symptoms of patients with ET are complex and heterogeneous (151). In some cases, ET is not a disabling condition. In others, however, it is a severe condition that has an impact on quality of life and well-being of individuals, causing social isolation, depression, and difficulty performing daily activities.

ET is a progressive disease characterized essentially by a single motor sign, that is, tremor. In individuals with ET, the tremor is the sole motor involuntary manifestation that causes significant functional impairment in different regions of the body, particularly the upper limbs (82). In addition, its clinical spectrum includes gait abnormalities and non-motor characteristics such as hearing loss, sleep abnormalities, depression and anxiety (68, 98). Because tremor is a marked motor sign of other movement disorders as well, ET is frequently confused with other conditions, such as Parkinson's disease (21). Thus, differentiating between ET and other tremor syndromes can sometimes be difficult.

Tremor impacts the quality of life of patients with ET, either through functional impairment or embarrassment caused by the involuntary manifestations. In the early stages of the disease, it manifests unilaterally. Initially, this motor sign gradually affects the hand of one side of the body and the individual has difficulty in performing daily living activities, fine motor tasks or a coordinated and smooth execution of voluntary movements, such as holding a cutlery, tying up shoelaces or keeping the pen on the paper. As the disease progresses, tremors are more severe bilaterally and can affect various body regions. Thus, the head, neck, trunk, lower limbs and vocal cords might also be involved (82).

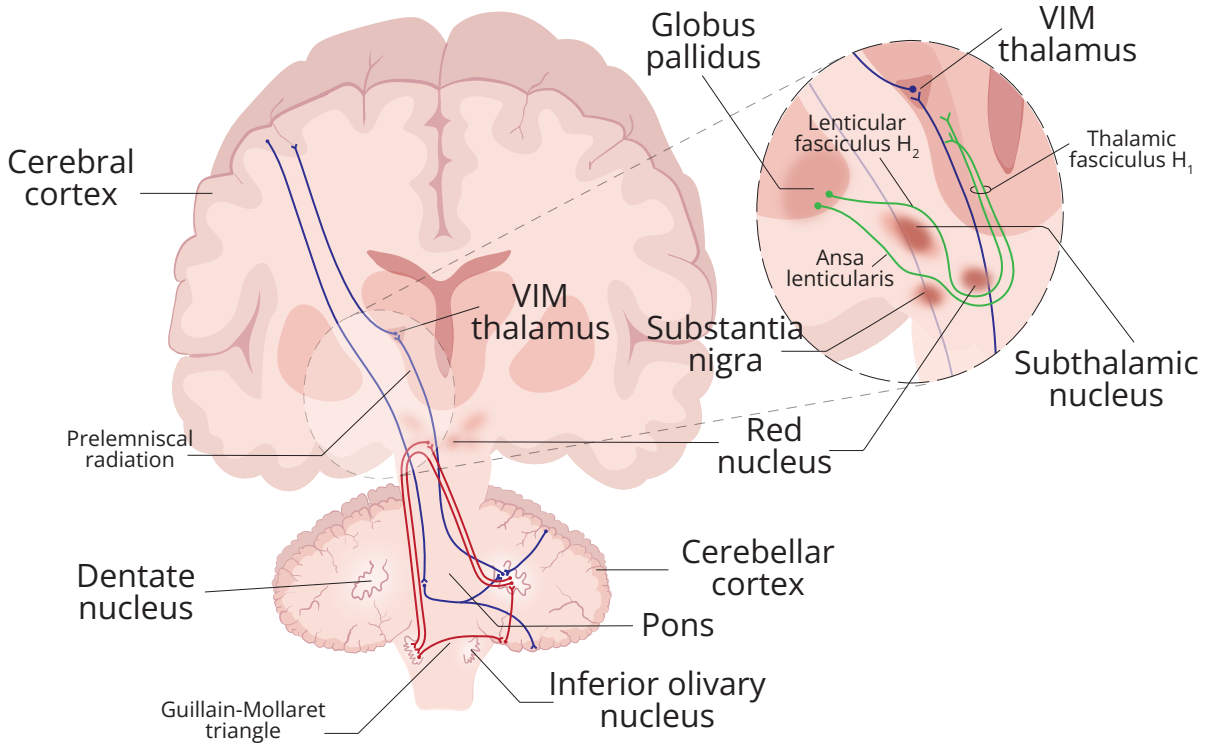


Figure 2.1 – Representation of pathways involved in the pathophysiology of ET. In red, the Guillain-Mollaret triangle loop is shown. In this pathway, the dentate nucleus connects to the contralateral red nucleus through the superior cerebellar peduncle, the red nucleus to the ipsilateral inferior olivary nucleus (ION) through the central tegmental tract, and the ION to the contralateral dentate nucleus through the inferior cerebellar peduncle. Some dentate fibers form synapses in the red nucleus, while others circumnavigate it. It is an important feedback circuit of the brainstem and deep cerebellar nuclei that regulates spinal cord motor activity. In dark blue, the cortico–ponto–cerebello–thalamo–cortical loop is shown. The cortico-ponto-cerebellar pathway connects the cerebrum to the cerebellum through the pons and contralateral middle cerebellar peduncle. The cerebello-thalamo-cortical pathway connects the cerebellum to the cerebrum through the superior cerebellar peduncle and the contralateral thalamus. The cortico–ponto–cerebello–thalamo–cortical loop plays a role in motor control.

In general, tremor tends to become more severe over time, but the disease progression is not linear. Despite the fact that the involuntary motor manifestation is initially more prominent on one side of the body, ET patients typically experience a bilateral tremor of moderate to severe amplitude during the disease's clinical course (68). As a result, the functional inability to perform fundamental movements is greater in these cases. The severity of tremor, on the other hand, is frequently more noticeable on one side, particularly the first side to manifest the disease (2).

The neurological origins for developing ET are not currently established. Its aetiology[1] is thought to be influenced by both genetic and environmental factors (157). In support of this hypothesis, many studies corroborate this assumption, reporting a positive family

[1]In medicine, *aetiology* corresponds the causes or origins of disease, the factors that cause or predispose to a particular disease or disorder.

history, that is, hereditary ET with a typically autosomal dominant pattern. In these patients with a family history of tremor, ET is known as *Family Essential Tremor* (2, 82). However, there is no agreement on the true cause of the disease. Essentially, the pathophysiological mechanisms are poorly explained, and the prevalent hypothesis is that there is an inappropriate communication between the cerebellum and some parts of the brain, such as the thalamus and cerebral cortex (133).

Some studies suggest that the neuropathology of ET involves the cerebellar–thalamic-cortical loop (11, 133, 157). This hypothesis is supported by the fact that these structures are involved in the processing of sensory information, the integration of sensory and motor information, and the coordination of movement execution (144). Basically, two circuits would be involved in the tremor generation, as shown in Figure 2.1, and abnormal oscillations would propagate through these networks, resulting in tremors. The first circuit is the cortico-ponto-cerebello-thalamic-cortical loop, while the second is the Guillain-Mollaret triangle loop (also known as the dentato-rubro-olivary pathway) (76, 113, 124, 128).

Because the mechanism of tremor generation is unknown, advances in diagnoses and treatments are compromised. Generally, diagnosis is not a simple task, mainly due to the fact that the characteristics of distinct movement disorders overlap in the early stages, which personalized treatment is important at this stage (80). ET is diagnosed based on clinical characteristics, such as a positive family history or alcohol responsiveness[2], and the exclusion of alternative diagnoses (e.g., Parkinson's disease, dystonia, and cerebellar diseases) (29). Furthermore, pharmacological treatments for tremor consist of a trial-and-error selection of anticonvulsants, such as primidone or clonazepam, and beta-blockers, such as propanolol. These treatments, however, may have a low effectiveness rate and frequently results in side effects (124, 133).

Therefore, it is important to better understand the many faces of ET in order to provide a more personalized treatment for individuals affected by this disease and enable the early diagnosis and development of technologies to improve the quality of life and well-being. In this context, it is necessary to provide further information concerning tremor, current treatment modalities, the most common instruments used in diagnosis and disease assessment, and the emerging challenges and perspectives.

2.1 My Hands Shake! After All, What Is Tremor?

The main characteristic of ET is shaking of the hands. This motor sign, however, is also common in other clinical conditions, such as Parkinson's disease, dystonia, cerebellar diseases (e.g., cerebellar stroke, neurodegenerative ataxias, paraneoplastic cerebellar

[2]Physiologically, *responsiveness* is an ability of organism to sense external and internal changes and adjust to those changes.

syndromes, cerebellitis, multiple sclerosis and multiple systemic atrophy) (68), alcohol withdrawal syndrome (1, 26, 156) or substance use disorder (8, 32), hyperthyroidism (5, 29), among others. Although tremor is often associated with pathologies, especially neurological diseases, it can also be seen in healthy individuals, but to a lesser extent (14, 111).

Who has never experienced trembling at some point in their lives? When we are very stressed, tense or anxious, it is common to experience shaky hands. Or even feeling shaky during or after a vigorous physical activity. We may also notice our trembling hands after drinking too much coffee, that is, consuming a large dose of caffeine. In these cases, the tremor is usually not a cause for concern. This is because, in healthy individuals, a more apparent tremor appears only in specific circumstances, being associated with physical overexertion, muscle fatigue or situations in which the individual is under emotional stress (14, 102, 158).

After all, what is tremor? Tremor is defined as a clinical condition characterized by involuntary oscillatory movements with a rhythmic and periodic nature, similar to sinusoidal behavior, of any part of the body around a joint axis (2, 14, 22, 35, 49, 111, 124, 151). These oscillations are caused by the alternating or synchronous action of muscle groups, which results in a back-and-forth movement of the limb around an equilibrium point, that is, a joint (8, 49). Thus, tremor can be described based on the number of times the limb oscillates back-and-forth and the amplitude of these oscillations.

Although a severe tremor is more common and disabling in individuals with movement disorders (the so-called *pathological tremor*), tremor is a manifestation of both normal and abnormal functioning of the nervous system. This means that it can also appear in healthy individuals. In this case, tremor is known as *physiological tremor* (14). In fact, everyone experiences physiological tremor (87). This is because the manifestation of this tremor type is associated with natural physiological processes (44). However, physiological tremor is usually imperceptible, that is, it is not visible to the naked eye due to its low amplitude (14).

Tremor is always present under physiological conditions. Even if it is imperceptible, most body segments are naturally in a constant state of oscillation (44). This raises an interesting question. *What are the mechanisms that cause tremors?* From a biological perspective, tremor involves a combination of peripheral and central mechanisms that tune motor control. Although knowledge of the causes of tremor is incomplete, four basic physiological mechanisms are thought to contribute to tremor expression, which include mechanical, reflex, and central mechanisms, as well as mechanisms responsible for instability of the feed-forward and feedback systems (35). Thus, the understanding of the underlying mechanisms related to the physiological tremor may help the comprehension of the associated mechanisms that may be present on the pathological tremor.

2.2 Why Do My Hands Shake Like That? Aspects That Truly Make Tremor Unique

Tremor can be described in different ways, as illustrated in Figure 2.2. From a clinical perspective, the tremor description can be based on circumstances in which it is evoked, regions of body affected, frequency, amplitude, handedness and distribution (symmetry) of motor severity. In addition, the pathological tremor can be further characterized based on the aetiology and presence or absence of other neurological signs (2, 35, 70, 102, 123, 131, 148). All these aspects describe the tremor from various perspectives and can be used to assess movement disability in individuals with tremor.

Tremor can emerge when the affected body region is in repose, such as when the hand is supported against gravity but not voluntarily activated or when hands are resting on the lap. In this case, tremor is known as *rest tremor*. In addition, the tremor can also appear during the voluntary movement, the so-called *action tremor*, whether during posture maintenance (*postural tremor*), voluntary activity (*kinetic tremor*), muscular contraction without movement (*isometric tremor*) or execution of a specific task (*task-specific tremor*) (14, 91).

Tremor can affect different body regions, including the upper limbs, head, trunk, neck, tongue, jaw, vocal cords, palate and lower limbs. Thus, when the tremor affects the hand, this is referred to as a *hand tremor*. However, if the involuntary movements occur in the head, the tremor is known as *head tremor* (123). In general, it can occur in a specific body region or in multiple body regions (148). In some pathologies, such as ET, tremor may be predominant in one region of the body and, as the disease progresses, it may affect multiple parts of the body (82).

Furthermore, only one side of the body may experience the involuntary movements, or both sides may be affected. In other words, this means that the tremor may affect the body bilaterally or unilaterally. For instance, an individual with bilateral hand tremors will exhibit symptoms simultaneously in both hands, whereas an individual with unilateral tremor will only experience symptoms in on one side of the body, such as the right or left hand.

On the other hand, the tremor severity may differ between sides of the body. Although motor signs and symptoms are present bilaterally, their severity can be symmetrical or asymmetrical (104). For instance, when both hands are equally affected by tremor, it is considered to be symmetrical. However, when a tremor is asymmetrical, one side of the body is more affected than the other. This implicates that one side of the body is dominant. As a result, all unilateral tremors are asymmetrical, but not all bilateral tremors are symmetrical.

The shaking may be imperceptible to the naked eye or extremely evident. In addition, the affected limb may oscillate more or less times in a given amount of time. In practice,

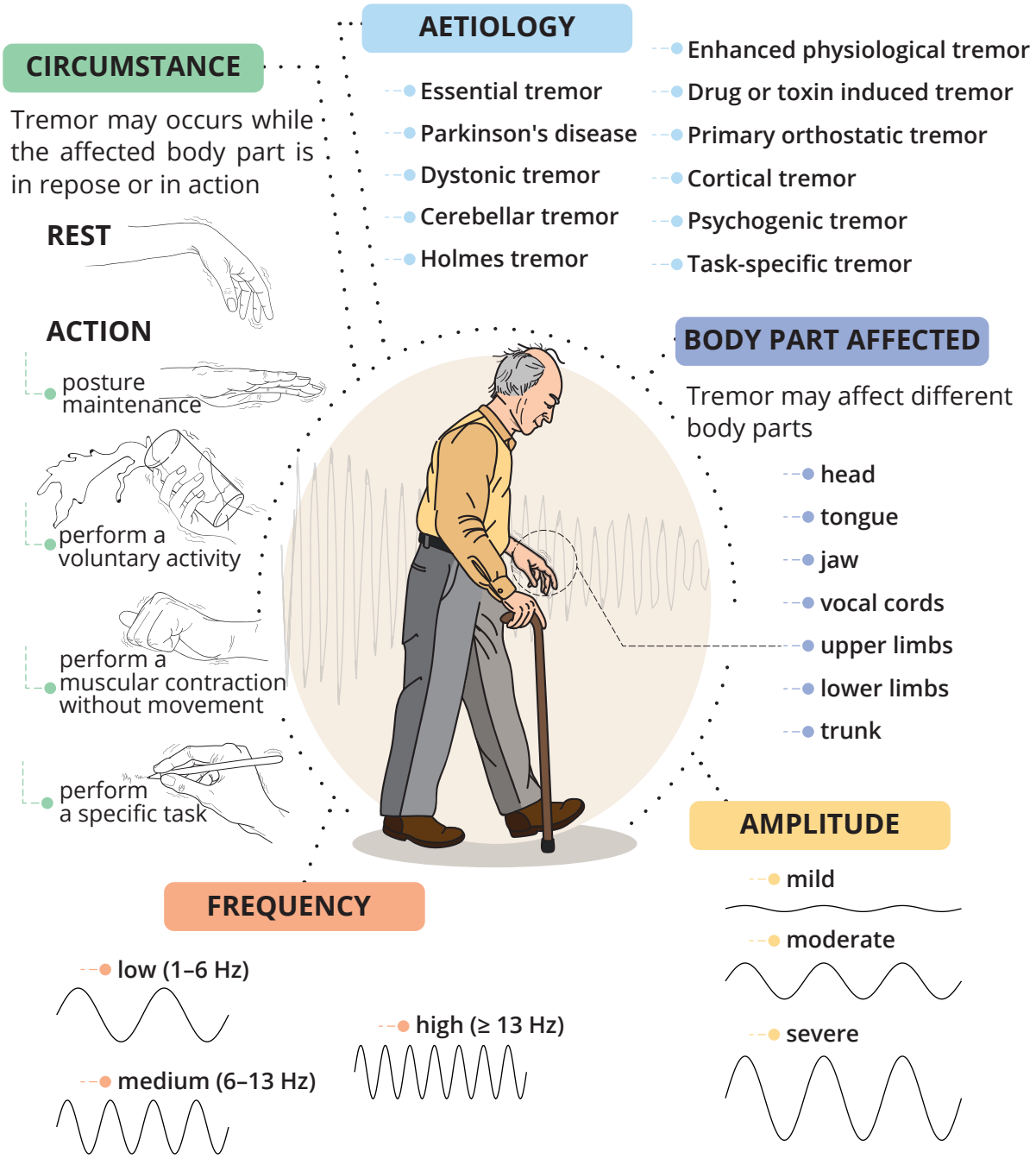


Figure 2.2 – Illustration of the various aspects that can be used to describe the tremor.

this relies on the number of times the affected limb oscillates around a given joint and the amplitude of these oscillations over time, as illustrated in Figure 2.3. Indeed, both amplitude and frequency can be of value in the understanding tremor. In this context, they can be grouped into ranges that allow the severity of the motor signs to be determined.

Based on its frequency, tremor can be categorized into different frequency bands. Thus, it can be of low ($[1, 6[$ Hz), medium ($[6, 13[$ Hz), or high (≥ 13 Hz) frequency (30, 68, 105, 131, 134). The lower the tremor frequency, the fewer the oscillations, that is, the affected limb oscillates backwards and forwards a few times per unit of time. On the other hand, high frequencies produce more oscillations, as result, the affected limb oscillates more times per unit time (Figure 2.3).

In terms of amplitude, tremor can be mild, moderate, or severe (131). This means that a small amplitude is associated with a tremor that is not visible to the naked eye, while a large amplitude is associated with a very noticeable tremor. However, there is no consensus on the values considered for each one. This is because the main clinical scales used in tremor assessment, such as Fahn-Tolosa-Marín Tremor Rating Scale (FTM) (49), Tremor Research Group Essential Tremor Rating Scale (TETRAS) (41), and Unified Parkinson's Disease Rating Scale (63), consider different scores for tremor amplitude.

In practice, the tremor amplitude is limited by the range of motion of the affected limb (Figure 2.3). However, when a body part shakes, it may not always move within the entire range of motion. The greater the range of motion, the greater the displacement of the affected limb relative to its neutral position and, consequently, the greater the amplitude of the tremor. Thus, a major challenge is to define range values for each amplitude category (mild, moderate, and severe).

2.3 My Hands Shake! Is It Essential Tremor?

Although tremor can be described under different aspects, as illustrated in Figure 2.2, its clinical classification is not an easy task. This is due to three main reasons. First, tremor can be a hallmark motor sign of several pathologies, whose characteristics are often overlapping. Second, the tremor characteristics can be interpreted differently by clinicians, due to the subjectivity of clinical scales, which are the gold standard used to assess tremor, and the level of clinicians' expertise. Third, the terminology of tremor and diagnostic criteria have been debated in recent years.

This, however, may cause misdiagnosis in patients with tremor disorders and consequently result in the employment of inappropriate treatments, generating medication-induced motor fluctuations and dyskinesias. In addition, inaccurate diagnosis in the early stages causes the disease to progress, the motor signs and symptoms become more severe and the individual loses autonomy in daily tasks. Thus, the classification of tremor and aspects considered for such have been the subject of discussion.

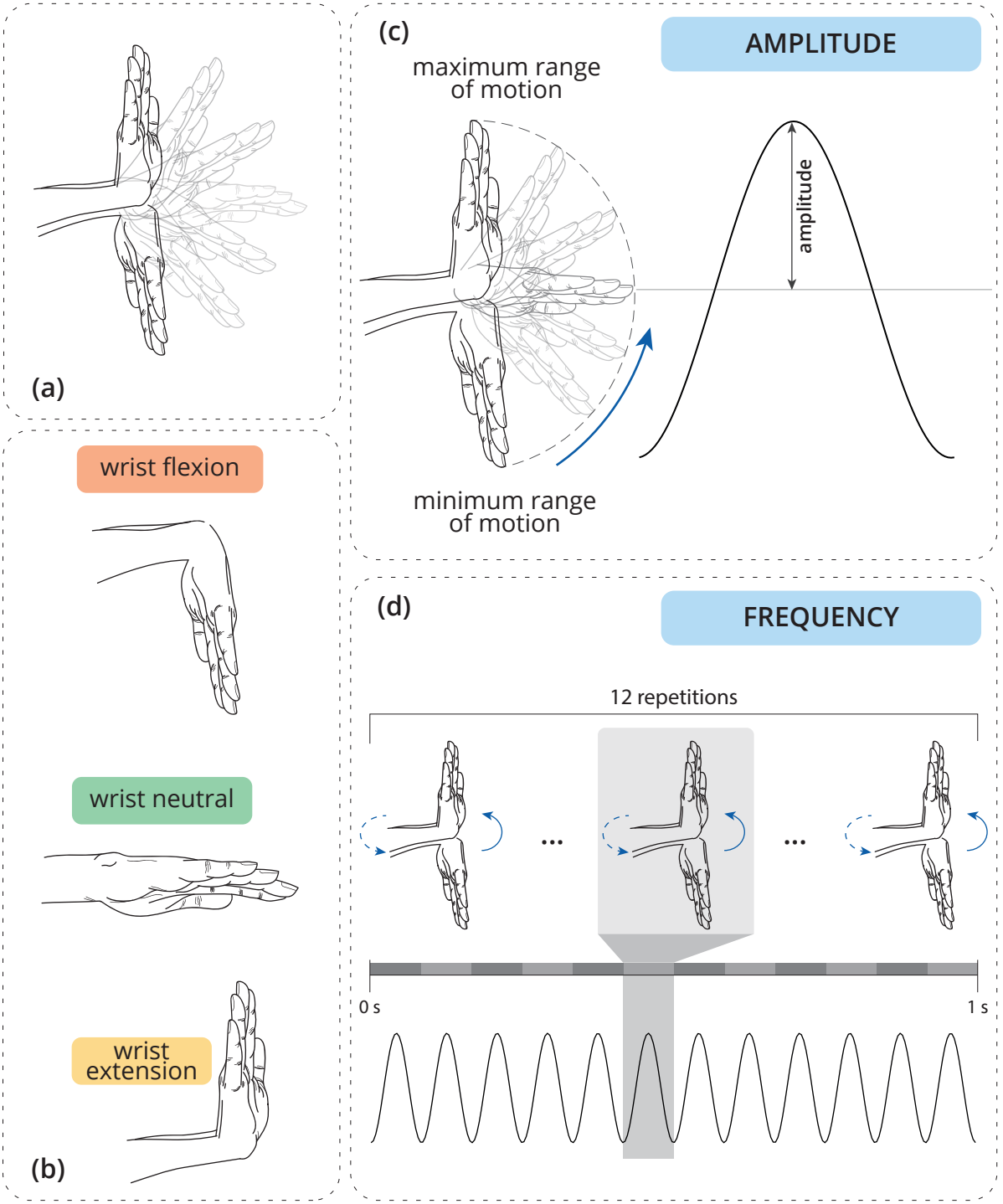


Figure 2.3 – **(a)** Illustration of a hand tremor typically seen in individuals with ET. **(b)** This tremor type resembles flexion and extension movements of the wrist. **(c)** In this case, the tremor amplitude is given by the range of motion of the affected limb around the wrist joint, which is the equilibrium point of the movement. When the wrist is fully flexed, then tremor has the minimum amplitude. As the hand moves towards its neutral position, the amplitude increases until it reaches zero. The tremor will have maximum amplitude when the wrist is fully extended. From this position, the amplitude starts to decrease as the hand moves to its neutral position, where the amplitude returns to zero. Then, the tremor amplitude decreases until the wrist reaches the maximum extension again, completing one cycle. **(d)** The tremor frequency is the number of times the affected limb oscillates backwards and forwards per unit of time. So, the tremor frequency is 12 Hz if the limb performs 12 wrist flexion and extension movements in one second.

One of the early efforts to outline the tremor classification was in 1998, with the *Consensus Statement of the Movement Disorder Society*[3] *on Tremor* (33). This consensus statement was significant at that time because it addressed different aspects of tremor and provided preliminary diagnostic criteria for tremor disorders, highlighting the necessity of debating the terminology and classification of tremor among tremor experts.

Although this statement attempted to define various types of tremors, the criteria for classification were varied, sometimes based on anatomical origin, sometimes based on the presumed underlying pathophysiology, and sometimes based on clinical phenomenology (33). Thus, several limitations were subsequently pointed out in this proposed classification scheme, particularly with regard to the definition of ET (13), whose criteria are summarised in Figure 2.4.

The limitations in conceptualizing ET were due to three key factors. First, the multiple terminologies of ET adopted over the past few years by clinicians and researchers in the field of tremor throws into question the ET nature. Second, the variety of motor and non-motor signs and symptoms reported among patients with ET throws into question the diagnostic criteria that should be used to identify this tremor type. In addition, the proposed classification was unable to differentiate between mild ET and enhanced physiological tremor. Third, the proposed classification scheme does not take into account the possibility that ET has more than one aetiology (13).

This, therefore, required a revision of the 1998 consensus statement. Thus, the new *Consensus Statement on the Classification of Tremors* was published in 2018 by the Task Force on Tremor of the International Parkinson and Movement Disorder Society (IPMDS), with the aim of updating the terminology and diagnostic criteria for tremor disorders, considering the advances in the understanding of tremor over the past 20 years (13).

More than that, this statement attempted to address the possible weaknesses of the previous concept of ET, introducing changes in its definition and recognizing a new category, called *ET plus*. The consensus diagnostic criteria for ET and ET plus are summarized in Figure 2.4. Despite the difficulty in establishing a consensus definition of ET, the proposed criteria considered ET to be an isolated tremor syndrome. On the other hand, the ET plus category was introduced to formally define what was previously known as indeterminate tremor syndrome (Figure 2.4) and perhaps divide ET into subtypes (13).

However, these definitions have divided opinions on different aspects. Some studies report benefits in the new classification scheme and look favourably on the ET plus category because the investigators support the idea that additional signs should not be overlooked in the diagnosis (34, 43, 78, 89). Other studies, however, have reported inconsistencies and controversies in the adopted definitions. In addition, although recognizing the heterogeneity of the signs and symptoms among patients diagnosed with ET, they emphasise

[3]The Movement Disorders Society is now called the International Parkinson and Movement Disorder Society.



1998

Classic Essential Tremor

Inclusion criteria

- bilateral, largely symmetric postural or kinetic tremor involving hands and forearms that is visible and persistent
- additional or isolated tremor of the head may occur but in the absence of abnormal posturing

Exclusion criteria

- other abnormal neurological signs, especially dystonia
- the presence of known causes of enhanced physiologic tremor
- historic or clinical evidence of psychogenic tremor
- convincing evidence of sudden onset or evidence of stepwise deterioration
- primary orthostatic tremor
- isolated voice, leg, tongue, or chin tremor
- isolated position- or task-specific tremors

Indeterminate tremor syndrome

- tremor with the characteristics of classic ET
- other neurological signs of uncertain significance that are not sufficient to make the diagnosis of a recognizable neurologic disorder

2018

Essential Tremor

Inclusion criteria

- bilateral upper limbs action tremor with a duration of more than 3 years
- with or without tremor in other locations (e.g., head, voice, or lower limbs)

Exclusion criteria

- other neurological signs, such as dystonia, ataxia, or parkinsonism
- isolated focal tremors (voice, head)
- orthostatic tremor with a frequency >12 Hz
- task- and position-specific tremors
- sudden onset and step-wise deterioration

Essential Tremor plus

- tremor with the characteristics of ET
- other neurological signs of uncertain significance such as impaired tandem gait, questionable dystonic posturing, memory impairment, or other mild neurologic signs of unknown significance that do not suffice to make an additional syndrome classification or diagnosis
- ET with tremor at rest should be classified as ET plus

Figure 2.4 – Diagnostic criteria for ET adopted over time, considering the Consensus Statement of the Movement Disorder Society on Tremor in 1998 (33) and the Consensus Statement on the classification of tremors of the International Parkinson and Movement Disorder Society in 2018 (13).

the implications of departing from the definitions of ET and ET plus (97, 99, 101, 155).

In practice, one of the main implications of the 2018 consensus statement is the rediagnosis of patients previously diagnosed with ET (97) and greater inconsistency in establishing more solid diagnoses, since ET plus can be employed as a temporary diagnosis. In addition, as the condition advances, the diagnosis may change from ET to ET plus due to the introduction of new neurological signs, such as impaired tandem gait, tremor at rest, questionable dystonic posturing, memory impairment or other mild neurological signs of unclear significance that are insufficient to make an additional syndrome classification or diagnosis (155).

In a retrospective review of medical records of 355 Thai patients diagnosed with ET, conducted by Lolekha and colleagues (93) from January 2019 to December 2021, the difficulty in reclassifying patients is reported. In the study, about 27% of patients did not meet the new diagnostic criteria due to tremor duration of less than 3 years. In other words, this means that these patients were left without a specific diagnosis, since they were disregarded from the reclassification conducted. As a result, they will have to undergo a new diagnostic approach and perhaps be subjected to milder forms of treatment.

The fact of considering at least 3 years as inclusion criteria for the diagnosis of ET may delay the effective diagnosis of the disease and, consequently, compromise the use of adequate treatment in the early stages, which would be very important for the early management of tremor. This demonstrates the difficulties of early diagnosis. In addition, it raises a pertinent question: *Is this time not too long for a consolidated diagnosis of individuals with ET?*

Despite the raised questions, the 2018 statement is useful because it reflects the perspectives and experience of many of the leaders in the field. For Louis and Bain, these discussions provide chances for us to reconsider our knowledge of ET and other movement disorders (99). On the other hand, these challenges emphasize the importance of an interdisciplinary clinical approach that takes into consideration the patient's history, neurological examinations, the evaluation of motor signs, and their impact on quality of life, among others (129).

2.4 Assessment of Essential Tremor

Assessment of ET is fundamental to developing an understanding of the condition, recording its natural history, monitoring motor signs, evaluating the effectiveness of treatment employed, and developing technologies to improve the quality of life of individuals with this condition. However, this assessment is not simple.

Some of the ET characteristics, such as the frequency of oscillation of the affected limb or changes in tremor amplitude over time, are difficult to assess only visually. Other characteristics, such as limitations in performing daily activities, are easier to measure

clinically because they are subjective experiences or theoretical constructs that are not directly measurable, but can be inferred through observable behaviour patterns, such as responses to rating scales (107, 137).

This way, there are evaluation methods in two distinct but complementary directions, the so-called clinical evaluation and objective evaluation. On one hand, the clinical evaluation focuses on the qualitative and subjective characteristics of the condition, such as disability, tremor severity, limitations in performing daily activities, impact of the disease on social engagement, and quality of life. On the other hand, the objective evaluation concentrate on the quantitative characteristics of the condition, such as the frequency, amplitude, waveform, regularity, and rhythmicity of tremor (45).

All of these evaluation strategies have strengths and weaknesses. This is due to several factors. Firstly, there is heterogeneity of signs and symptoms among individuals with ET. In addition, as ET progresses, symptoms appear and develop at different rates in each individual. Secondly, the characteristics of ET are influenced by various factors, such as the physical, emotional, and mental state of individual. Finally, ET can be investigated from a variety of perspectives. Thus, a comprehensive assessment is ideal for properly describing the motor and non-motor impairment of patients with ET, personalizing treatment, thoroughly monitoring disease progression, and provide a better quality of life.

2.4.1 Clinical Evaluation

Why do clinicians routinely use rating scales with their patients with ET?

Clinical rating scales are the best-known and most widely used tools for the assessment of ET during a clinical examination. This is because these scales attempt to assess several aspects of the condition for which no specified units of measurement exist, such as the clinical condition of patient, motor and mental functions, limitations related to daily activities, social engagement, and quality of life. Thus, the key idea is to make measurable what is not measurable (137).

Basically, these instruments are focused on the disease (e.g., severity of motor signs and disability) or on the patient's interests (e.g., quality of life and patients' perspectives regarding treatment benefit and harm) (107). On the one hand, this is important for a more personalised treatment because it considers both the perspectives of the clinician and patient. On the other hand, this implicates that the evaluation depends on the patients' self-reporting and level of experience of the clinician.

Thus, although they are important clinical tools to support clinicians in making decisions about patient care, clinical rating scales require human inference. This may result in intra and inter-examiner variability and compromise the accuracy, reliability and comparability of the results obtained by the clinical evaluation (106). In addition, the scales are not capable of continuously monitoring tremor and its fluctuations throughout the

day or during ADL (75). Challenges that throws into question the feasibility of ET assessment being exclusively clinical, even though scales are often considered cheap, quick to implement and easy to use in clinical practice.

What are the gold standard tools for the assessment of the severity and status of ET?

Currently, the evaluation of ET is solely clinical, that is, based on clinical rating scales. In the past years, several rating scales have been used in ET (27, 41, 81, 96, 120, 136, 138, 142, 141, 153), as summarised in Figure 2.5. Some of these scales are generic, such as the Mini-Mental State Examination (MMSE) for grading the cognitive state (53). Others, on the other hand, were developed for exclusive use in ET, such as the FTM (49, 50) or Quality of Life in Essential Tremor Questionnaire (QUEST) (153). This is because the complex nature of ET requires the use of comprehensive assessment tools that provide a broader view of signs and symptoms.

Nevertheless, only a few of the scales proposed in recent years have been recommended by IPMDS and have become gold standards in clinical practice and scientific research. To address the availability, use, acceptability, reliability, validity, and sensitivity of these most commonly used scales to assess tremor and ET status, the IPMDS conducted a review during 2012 (40). In total, seven tremor severity scales, six ADL and disability scales, and four quality of life scales were examined. However, only seven instruments were recommended.

The FTM, Bain and Findley Clinical Tremor Rating Scale, Bain and Findley Spirography Scale, Washington Heights-Inwood Genetic Study of Essential Tremor Tremor Rating Scale (WHIGET), and TETRAS were the tremor severity scales recommended by the IPMDS. Only the QUEST and the Bain and Findley Tremor ADL Scale were recommended as specific instruments for evaluating quality of life, and disability and activities of daily living, respectively (40).

A number of other scales can help to provide an assessment of ET, particularly those that assess non-motor characteristics. Although motor symptoms generally receive more attention, it is also important to monitor the non-motor characteristics of ET to provide better well-being for the patients. In this context, there are studies that employ or suggest scales such as the Beck Depression Inventory, Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, Beck Anxiety Scale, Hospital Anxiety and Depression Scale, Pittsburgh Sleep Quality Index, Fatigue Severity Scale, Wechsler Adult Intelligence Scale-III (27, 108, 138, 140), among others, as illustrated in Figure 2.5.

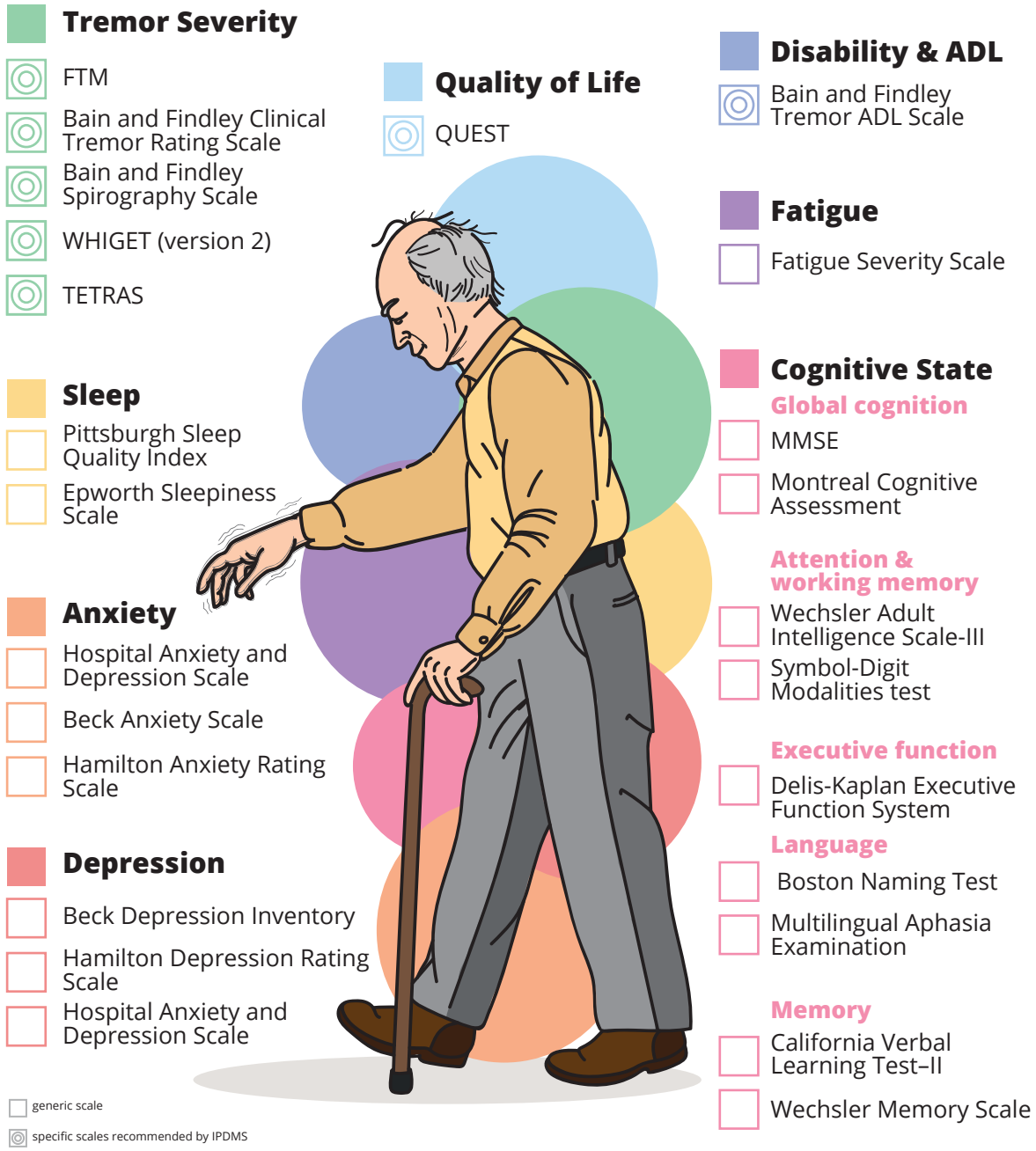


Figure 2.5 – Clinical rating scales that are frequently used to assess ET. Along with the scales advised by the IPMDS, alternatives are also provided for a more comprehensive assessment of the condition.

2.4.2 Objective Evaluation

A view of tremor from different perspectives

At present, the use of clinical rating scales is the conventional method for determining the status of ET. Although the clinical evaluation is crucial, it has inherent limitations and does not allow for a clear assessment of quantitative characteristics of the condition, such as the frequency of oscillation of the affected limb, as well as changes in the amplitude, regularity, or rhythmicity of the tremor over time, which are characteristics that are difficult to assess only visually, but which are important for characterizing ET and, more than that, understanding tremor.

In this context, an objective assessment of ET is becoming more and more necessary. Thus, several studies (6, 10, 21, 39, 44, 72, 159, 161) have been conducted in this direction, proposing the use of different sensors and instruments for acquisition of several biomedical signals with the objective to provide a complementary alternative to the rating scales. Generally, electroencephalograms, electromyograms, electrocardiograms, inertial sensors (e.g., accelerometers, gyroscopes, and magnetometers), force transducers, and goniometers are employed for the tremor recordings (67).

Each of those sensors and instruments enables the capture of a particular information, as a result, the study of the tremor from a distinct perspective (127). For instance, the analysis of inertial signals, in terms of frequency, enabled the investigation of the involuntary movement characteristic of tremor and the identification of the predominant components of tremor. On the other hand, the analysis of electromyographic signals allowed the study of the relationship between mechanisms of physiological tremor and muscular activity to be explored, whereas the analysis of electrocardiographic signals confirmed the cardioballistic contribution to physiological tremor (35, 39, 44, 46, 71).

In other words, the analysis of these signals enabled researchers over the past 67 years to investigate the frequency of tremor and consequently draw key conclusions about its generating mechanisms. This demonstrates the importance of these tools for the objective characterization of tremor, justifying the various studies in this direction, exploring the application of these sensors and instruments not only in ET, but also in other movement disorders.

After all, why use inertial sensors?

Particularly, inertial sensors are increasingly demonstrating their potential as tools to detect tremor and monitor the motor fluctuations of individuals with tremor in real time, not only in controlled environments, but also in their daily lives, that is, while they are performing ADL (12, 90). This is because the sensitivity of these sensors increased, their dimensions shrunk, their selectivity improved, and their costs dropped (109, 150).

This technology can also be embedded in devices and accessories including cell phones, watches, bands, gloves and belts because of their lightweight and compact size. Thus, this allows the movement of various body regions to be recorded, as they can be easily fixed to the body, also making on-line monitoring possible (90). In addition, compared to signals, such as the electroencephalogram and electromyogram, inertial sensors generate signals that are less vulnerable to noise, which simplifies signal processing and extraction of features that describe the involuntary movement performed by the affected limb.

Examples of inertial sensors are accelerometers, gyroscopes and magnetometers. Accelerometers measure the gravity acceleration together with the acceleration of the the object it is attached. Gyroscopes measure the angular velocity, typically in rad/s, around an axis. An advantage of gyroscopes is that their measures a not affect by external variables (e.g., gravity), easing thus the signals processing stages. Finally, magnetometers measure the Earth's magnetic field at distinct positions. This make this type of sensor very useful for the detection of the positioning of objects on three-dimensional space. It is often common to see these three inertial sensors embedded in a single board or microchip, and in these case they may be referred to inertial measurement unit (IMU). An IMU can contain from one to several of these sensors.

In this study, the use of a three-axial gyroscope has been employed. The possibility of measuring the tremor dynamics in three directions may provide a window the a better understanding of tremor dynamics and how the motion in one direction can contribute to the other (Figure 2.6), although this was no the main focuses of study in this work. Finally, it is relevant to mention that the employed technology was based on MEMS (microelectromechanical systems), which allows for the use of miniaturized, low-noise and precise sensors. All these characteristics contribute to the detection of tremor activities and motor fluctuations that may not be perceived by the naked eye.

Figure 2.7 shows examples of typical inertial signals detected by using a three-axial gyroscope positioned on dorsum of the hand (Figure 2.6). Considering that the tremor is a triaxial activity generating motion around joint axes, the use of a gyroscope may be preferable over other sensors because it can measure angular velocities around the axis of motion. From a physical perspective, it is relatively easier to interpret signals from a gyroscope and associate them of the phenomenon generating the signal.

Movement around distinct axes can highlight tremor in distinct directions and this is illustrated in the figure, for instance in Figures 2.7 (b), (c) and (d) movements of flexion and extension, adduction and abduction, and pronation and supination, respectively, are associated with tremor in these directions. Note that the sensor axis will be more sensitive to movements in its directions, highlighting the relevance of the use of three-axial sensors for understanding and selecting the most suitable axis for a specific application.

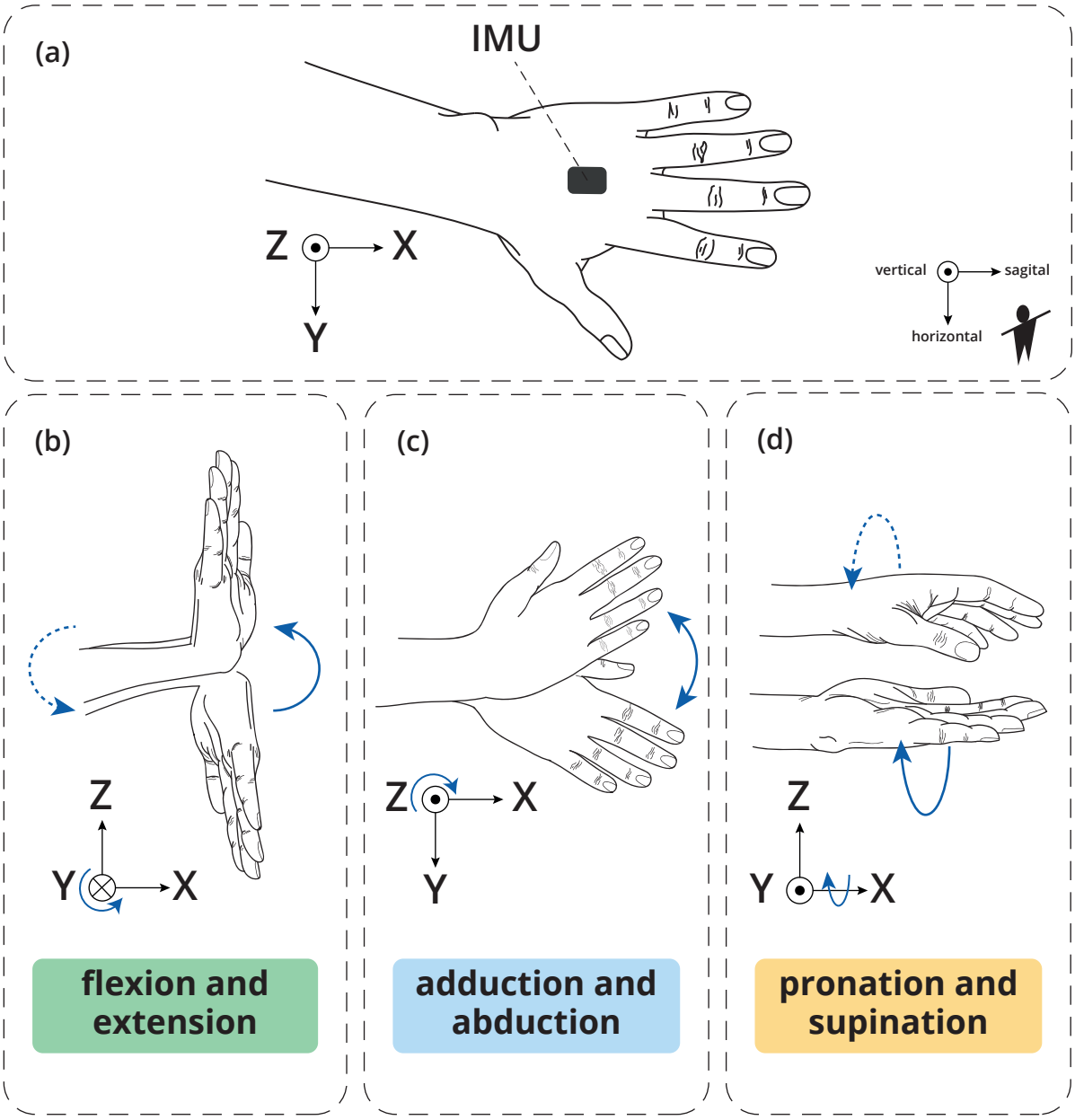


Figure 2.6 – **(a)** The orientation of the axes is very important when inertial sensors are employed to record motion. This is because all body movements occur in different planes and around different axes. In a simplified way, the limb can oscillate back and forth around one of the three axes (X, Y or Z) when the hand shakes, because wrist joint allows the three rotational movement of the hand. Then, an axis reference must be adopted to make it easier to understand the movements. For instance, the IMU can be positioned on the dorsum of the hand with the X axis parallel to the anatomical sagital axis and the Y axis parallel to the anatomical horizontal axis, considering the arm maintained parallel to the transverse plane and 90º from the coronal plane. **(b)** When the tremor resembles flexion and extension movements of the wrist, it means that involuntary movements are rotations around the Y axis. **(c)** When the tremor resembles adduction and abduction movements of the wrist, it means that involuntary movements are rotations around the Z axis. **(d)** When the tremor resembles pronation and supination movements, it means that involuntary movements are rotations around the X axis.

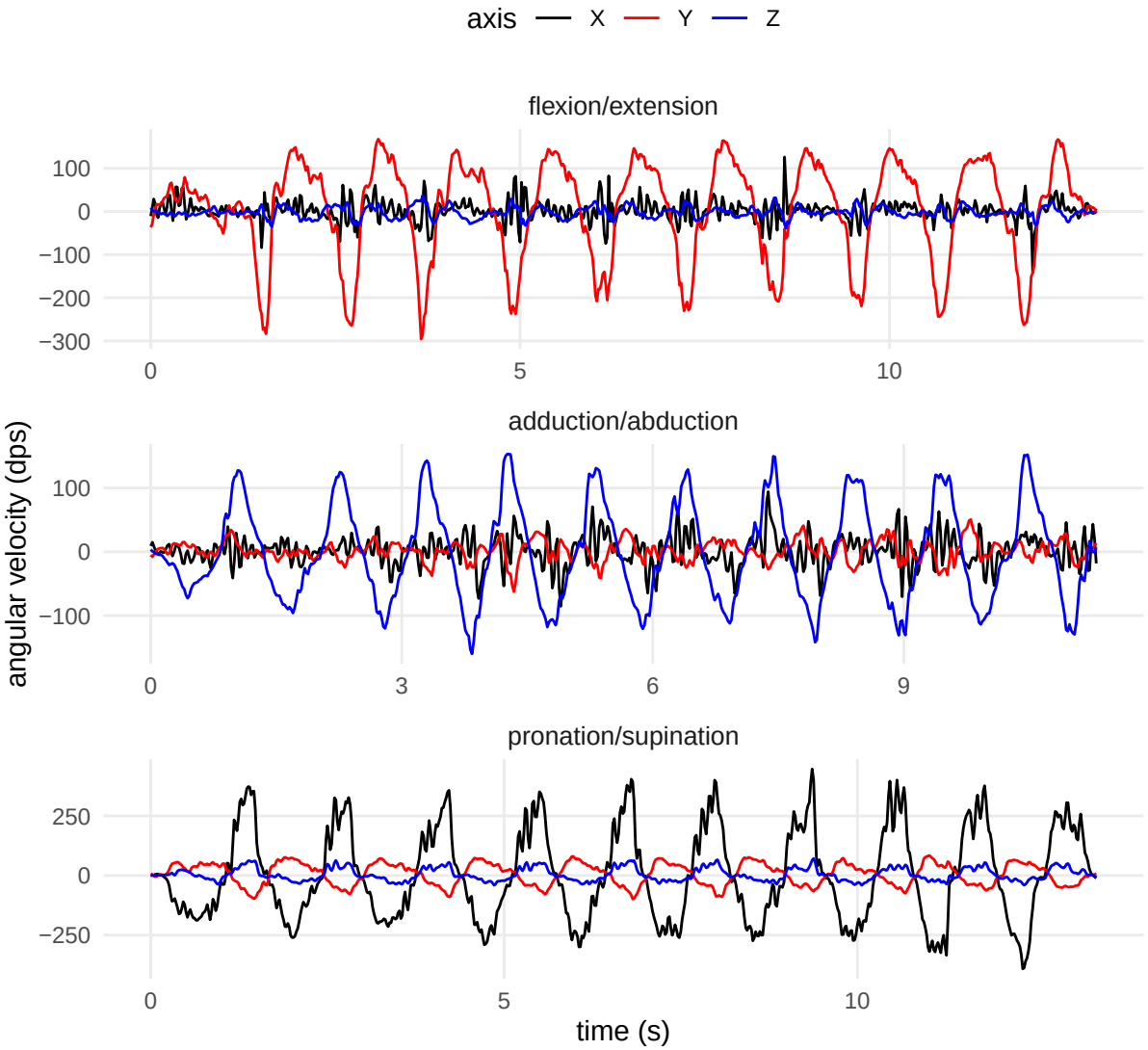


Figure 2.7 – Illustration of the gyroscope signals during 10 repetitions of wrist flexion/extension, adduction/abduction and pronation/supination, considering the positioning and orientation of the axes as shown in Figure 2.6.

2.5 Between Medicines and Surgical Procedures: The Ways to Live with Tremor

Nowadays, there is still no cure for ET. Fortunately, several treatments have been proposed to manage tremor and improve motor function (157). Generally, it is important when tremor is debilitating and impair the ability to carry out activities of daily living (151). Thus, when ET is a disabling condition that has impact on quality of life and well-being, treatment is a way of living and coping with tremor.

Basically, the management of ET is purely symptomatic (74, 79) and usually includes pharmacological and surgical treatments (2, 52, 74, 78, 79, 157), as summarised in Figure 2.8. In addition, physiotherapy and occupational therapy can be important to improve

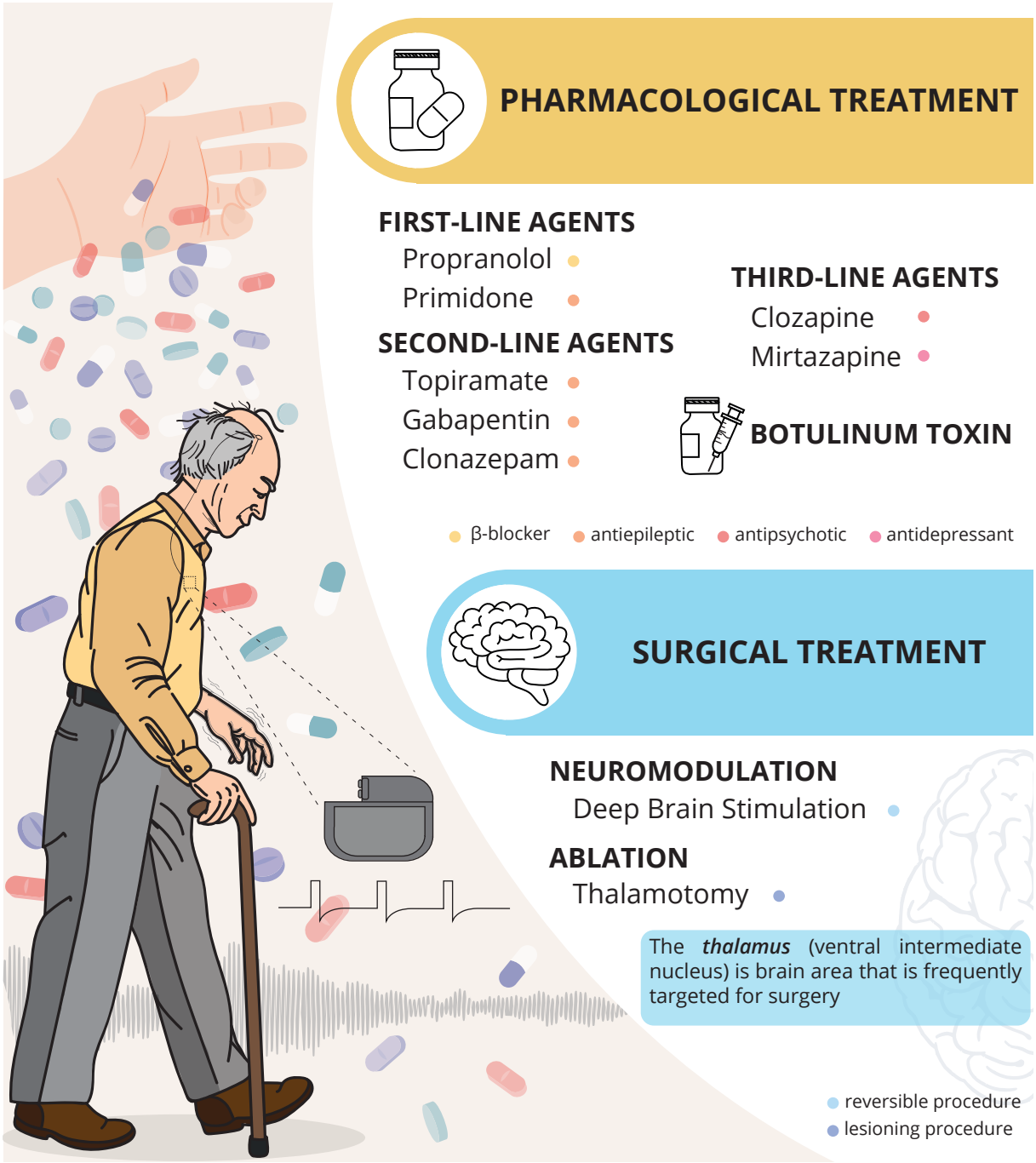


Figure 2.8 – Main established medicines and surgical procedures currently used in the management of ET.

muscular strength and coordination, reducing the impact of tremor on daily activities of individuals with ET and providing greater independence (18, 79, 154).

In the early stages, medications are commonly used to manage symptoms. These include beta-blockers, anticonvulsants and antidepressants (Figure 2.8). Among them, propranolol and primidone are the main drugs recommended for the initial treatment of the condition and are regarded as first-line agents for ET (2, 130). However, this intervention is not risk free and may be ineffective in the management of tremor in some individuals with ET. Additionally, as the condition progresses, they might lose their ther-

apeutic value, such that increasing the dose is ineffective (151).

In situations in which first-line medication is not effective, the administration of combine drugs, such as propranolol and primidone, may be also an alternative. If there is still insufficient benefit, further medications, such as topiramate, clonazepam, and clozapine, can be tried (130). In some cases, botulinum toxin type A can be injected, for example, into the flexor and extensor muscles of the wrist to reduce tremor (2, 79), although it often causes weakness in the hands (52).

Indeed, pharmacological treatments consist of trial-and-error selection of beta-blockers, anticonvulsants and antidepressants. These treatments, however, may have a low effectiveness rate and frequently results in side effects (124, 133). Thus, surgical procedure becomes the preferred treatment for patients who have severe tremor, but who derive no benefit or have side effects from pharmacological treatment (130, 151).

Thalamotomy and deep brain stimulation are the two surgical procedures employed in the management of ET. Thalamotomy is an ablative procedure in which a small tissue portion of the thalamus is damaged (130). DBS, on the other hand, is a neuromodulation procedure in which an electrode is implanted rather than a thalamic lesion. Because the electrode can be removed later if necessary, the procedure is reversible and deemed more favourable than the ablative procedure (86).

Despite these limitations of thalamotomy, this surgical procedure is still important, especially in developing countries, because neuromodulation is a more expensive procedure to implement in health systems. In addition, the ablative procedure may be more appropriate when the patient is unable to maintain the continuous care inherent to DBS, such as adjusting parameters periodically and checking the status of the battery and hardware components, which require routine clinical visits (147).

Both procedures can present risks that are inherent to any surgical procedure. In addition, there may be side effects, adverse effects or complications related to each of the procedures. In the thalamotomy, complications of speech, swallowing, or cognitive complications may occur (86). On the other hand, there are hazards associated with the surgical technique of neuromodulation and the DBS system that is implanted, such as hardware failures (20).

Despite this, the benefits of the procedures outweigh these surgical complications and justify their use. Moreover, it is undeniable that DBS can significantly improve the clinical status of individuals not only with ET, but several movement and psychiatric disorders, including Parkinson's disease, dystonia, epilepsy and Tourette syndrome. Advances in neuromodulation systems show future directions for improving DBS, considering a stimulation adaptable to the motor fluctuations of individual over time, the so-called closed-loop DBS (21).

2.6 Improving the Quality of Life in Essential Tremor Through Technology

Technological advances in medicine have contributed to more individualised health care for patients with ET and other movement disorders. This is due to advancements in neuroimaging, biomedical instrumentation, and biomedical signal processing, which have enabled the acquisition and analysis of various physiological data. For instance, imaging scans allow neurologists and other clinicians who treat neurological disorders to define surgical targets, see various brain regions, and plan the precise and accurate placement of the stimulation electrodes.

On the other hand, the emergence of neuromodulation systems, such as devices implanted in deep brain stimulation, and advances in their instrumentation have allowed the treatment of individuals not only with ET in more advanced stages. However, the implant of DBS leads is a complex procedure whose success is thoroughly dependent of its positioning. To verify the target precision and possible trajectory deviations, in addition to brain imaging, it is necessary to map neuronal activity, related to the sensorimotor regions of the target nuclei, by using microelectrode recordings (MER) (132).

The analysis of these neuronal activities in real time requires several steps of signal processing, e.g. visualisation of the Vim (ventral intermediate nucleus) unit spikes, identification of templates of neural potentials, estimate of the firing distribution of pool of neurons and the correct grouping of neuronal activity to determine, for example, the response of neurons to passive and active movements of the affected limb, as well as avoiding side effects.

In addition, biomedical signal processing has allowed the development of new ways to estimate features from tremor. This can contribute to a more precise detection of several physiological phenomena that cannot be seen by the naked eye, for instance, the detection of motor fluctuations, the visualization of information, making it easier the follow-up of treatments and of the condition of patients.

All these advances have also contributed to the development of several assistive technologies that have been proposed to improve the quality of life of individuals with tremor, reduce tremor and facilitate the ADL. Among them, wearable electrical stimulation systems for tremor attenuation, such as Cala Trio (https://calatrio.com/), assistive feeding devices, such as Gyenno Spoon (https://www.gyenno.com/spoon-en) and Liftware Steady (https://www.liftware.com/), and passive wearable orthoses, such as Tremelo (https://fivemicrons.com/products/tremelo/) (115).

3

Mechanical Vibrations: a way to change the tremor dynamics?

"Maybe you should focus on the beauty of those stars up there apart from their function. Just take them in, admire them, before you expect them to lead the way..."

— Clare Vanderpool, *Navigating Early*

Tremor is a complex phenomenon. It probably arises in circuits responsible for the control and coordination of body movements and, consequently, combines central and peripheral mechanisms. However, the interaction of these circuits for the generation of tremor, especially pathological tremor, still remains poorly understood, which motivates the investigation of tremor and raises an essential question. *Would it be possible to dampen the involuntary movements, or would there be a way to prevent the limbs from trembling?*

In this sense, studies have been outlined in recent years in order to understand those circuits and investigate possible ways to change their behaviour. For a very long time, the application of inertial loading to the affected limb has been discussed (35, 68, 73, 94, 122, 135). Several studies have found a reduction in both energy and frequency of the mechanical component of tremor when the limb was submitted to an external inertial load (35, 39, 44, 77).

This reduction in tremor and its frequency probably occurs because adding weight to the limb increases its resistance to movement, making it harder to move the limb out of its state of static or dynamic equilibrium. This implicates that the larger the inertia of the limb, the lower the number of oscillations per unit of time, that is, the lower the frequency of the tremor. This corroborates with the fact that the tremor of the distal segments, which have a lower inertia, tend to have a higher frequency (e.g., the frequency of the physiological tremor at the elbow is 3–5 Hz, at the wrist is 7–10 Hz, and at the metacarpophalangeal joint is 12–30 Hz) (68).

Although the addition of inertial load to the affected limb yields a damping of tremor, it is not very advantageous in real applications for tremor reduction. This is due to the fact that an external load does not permit the customization of a compact device that individuals affected by tremors can use in their daily lives to do tasks without wearing out

or overtaxing their limbs, especially when a high load is needed to dampen the tremor. In addition, a voluminous apparatus attached to a limb can sometimes create embarrassment or discomfort in social circumstances.

Thus, other ways of altering the tremor-generating mechanisms or dampening involuntary movements have been explored. Peripheral electrical stimulation is one of them. The idea of this type of stimulation is to send electrical signals, either through transcutaneous (non-invasive stimulation) or percutaneous (invasive stimulation) electrodes, to peripheral nerves, in order to target efferent or afferent pathways, or muscles (124), which are closely related to the manifestation of tremor in any part of the body.

These strategies have shown to be a promising way to dampen tremor (17, 36, 115, 125). However, it is unclear how electrical stimulation affects the circuits that trigger tremor. Basically, the tremor reduction is thought to be caused by the generation of muscle forces antagonistic to tremor (e.g.,when stimulation is applied to muscles) or even by decreasing the excitability of motoneurons that innervates muscles where tremor is manifested (e.g., when stimulation is applied to peripheral nerves) (124).

However, there are still substantial challenges for technologies to effectively employ peripheral electrical stimulation (17). This is because the percutaneous electrical stimulation is an invasive and obstructive process that may create adverse effects including pain, infection and discomfort. On the other hand, transcutaneous electrical stimulation is subject to low selectivity due to the use of surface electrodes. In addition, migration or rupture of the electrodes may occur in both transcutaneous and percutaneous electrical stimulation (121).

Clearly, more efforts are needed to increase the clinical evidences supporting the effectiveness of electrical stimulation in tremor suppression. Furthermore, the challenges of its practical application make it interesting to study other ways of intervention, such as peripheral vibrotactile stimulation. The use of alternative stimuli to the electrical stimulation may result in the change of tremor with less side effects to individuals.

3.1 Where It All Begins

The idea of using mechanical vibrations in tremor is not recent. During the 19th century, the work of the neurologist Jean-Martin Charcot popularised the idea of employing vibrations to treat tremor (62). Charcot proposed a vibratory chair to relieve the symptoms of Parkinson's disease which, according to the neurologist, had successful results among his patients after a few sessions (28).

However, the application of vibrations in healthcare had earlier precedents. Around the 18th century, vibrations became a topic of interest in the treatment of certain diseases (62). This was because empirical evidence indicated that patients improved during and/or after prolonged journeys by railroad or carriage. This led researchers to hypothesise that

vibrations might be very helpful in therapies, which eventually resulted in the development of several vibratory tools (28, 62).

It is believed that the French Abbé[1] St. Pierre was the first to design a vibratory chair to help individuals with melancholy and liver diseases based on this hypothesis still during the 18th century (62). Nevertheless, vibrations acquired more popularity among researchers during the 19th century and began to be used to treat disorders of the nervous system. Initially, the work of the physician Vigoroux, who used mechanical vibrations to treat individuals with hysteria and locomotor ataxia, stood out at that time (28).

However, it was Charcot who encouraged the use of vibrations for the treatment of Parkinson's disease after noticing that individuals with this condition experienced a reduction in their resting tremor when travelling in a carriage or railroad (28, 62). Furthermore, Charcot was responsible for revisiting the idea, as suggested in 1880 by the French electrician Boudet, that the local application of vibrations might be feasible to treat neuraglias and migraine (28).

All these contributions made during the 18th and 19th century led to the consolidation of the so-called whole-body vibration (i.e., a way of applying vibration to various parts of the body) which is currently employed in the sports medicine, rehabilitation and physical therapy (4, 24, 31, 114). In addition, it enabled the use of localized vibration in various healthcare applications, such as proprioceptive feedback on balance and gait of individuals with neurological diseases (7, 54), control element in closed-loop upper limb myoelectric prostheses (65), as well as tactile feedback in rehabilitation games and human-computer interfaces (3, 103, 160).

However, few studies have followed up investigating the feasibility of vibration in Parkinson's disease or other tremor disorders after the death of Charcot in 1893 (62). This may be justified by the fact that the possible physiological mechanisms behind vibrations, as well as their relationship to the circuits responsible for the generation and manifestation of tremor, were unknown at the time, although empirical evidence suggested a potential effect of vibrations.

Indeed, the understanding of vibrations and their response in human body is fundamental to studies that seek to use vibration as a mechanism of extending human sensing and also to understand how vibration evokes neural responses capable of providing the perception of the stimulus and more importantly on how responses due to vibrotactile stimulus can modulate reflex and central circuits. In this sense, its effects on humans have also been investigated for a long time.

Since the 19th century, researchers have been trying to figure out the physiological effects of vibrotactile stimulation on human body and determine ideal parameters for a vibratory sensation and perception. The sequence of four review articles by Frank Geldard (56–59), published by *The Journal of General Psychology* in 1940, provided an overview

[1] Abbé refers to a title used to designate a member of the French secular clergy.

of the early state of the art on the understanding of vibrotactile perception and response in humans.

In those papers, the author reports published studies dating back from 1876, which coincides with the time lapse when vibration began to be employed empirically on diseases of the nervous system, showing that the search for understanding the physiological mechanisms of vibration in the body was running parallel to its initial practical use. According to Geldard's review, there was initially a great gap in the comprehension of the role of biological sensors to detect and distinguish between distinct phenomena, for instance, pressure from vibration.

Although some vibration sensitive receptors were discovered as early as the 18th century (e.g., the Pacinian corpuscle was the first mechanoreceptor identified, and it is thought to have been first described in 1717 by Abraham Vater, professor of anatomy and botany) (119), the advance in understanding their physiological properties occurred years later, mainly due to the numerous contributions of cat studies such as those developed during the 20th century by Hunt, Gray, Sato, among other investigators (116).

In fact, many of the various known characteristics of vibratory receptors come from experiments on cats. For example, Sato (139) and Hunt (83) noticed that Pacinian corpuscles of cats respond to vibratory stimuli between 60 and 400 Hz, which is a frequency range similar to the human frequency range. Hunt (83) showed also that vibration can be perceived by other cutaneous receptors.

Furthermore, Echlin and Fessard (37), and Bianconi and Van der Meulen (16) showed that muscle spindles of cats can also respond to mechanical vibrations, suggesting receptors other than those present in the skin. In this same direction, human studies have shown similar results. Vibration is thought to activate the spindle endings and Golgi tendon organs in humans (19), which could cause an illusory impression of movement and, consequently, a motor response in the vibrated muscle as well as its antagonist (51, 55).

From a physiological perspective, all these findings are very important for the current understanding of how vibration acts in the human body and which structures are able to sense it. Moreover, the advances in comprehension of the physiological mechanisms behind vibration better support the investigation of its potential effects on tremor.

3.2 After All, How Do We Recognise The Vibrations Around Us?

Peripheral vibrotactile stimulation consists of applying mechanical vibrations directly to the peripheral areas of the body, usually to the skin surface of regions such as the fingertips, palm of the hand, sole of the foot and forearm, which are regions of glabrous (hairless) skin. As vibration is employed in specific region of the body, the vibratory stimulus influences motor responses locally, that is, in the stimulated limb.

Vibratory stimuli can be generated artificially by small tactile actuators (e.g., piezoelectric actuators) or vibration motors which are commonly used in various devices such as mobile phones, game controllers and haptic feedback systems. Thus, the application of peripheral vibrotactile stimulation on tremor field may be very interesting because this type of stimulation is a simple way to noninvasively introduce disturbances to the peripheral system.

When a vibrotactile stimulus is applied to the skin surface, the mechanical vibrations penetrate the skin layers and are sensed by peripheral receptors, present in the skin or in muscles and tendons adjacent to the stimulated region (146). The receptors that respond exclusively to mechanical stimuli, such as vibration, are called mechanoreceptors. Each one of them is very sensitive to stimuli at certain frequencies and is practically insensitive to other frequency bands (64, 69).

Thus, low frequency vibrations (5–15 Hz) that strike the superficial epidermis are detected by Merkel's disks. Vibrations with a frequency between 20 and 50 Hz that reach the dermal papillae of skin sensitise Meissner corpuscles, while Pacinian corpuscles, mechanoreceptors present in the deeper layers of the skin, tendons and connective tissue adjacent to the stimulation region, are more sensitive to high frequency vibrations (60–400 Hz) (61).

These receptors are associated with primary sensory neurons, whose extension enters the spinal cord through the dorsal root and culminates in a ascending tract called the fasciculus cuneatus that conveys impulses from nerve endings above the midthorax (e.g., the upper limbs). If the stimulus is sufficient to reach or exceed the threshold, an action potential is then generated that travels along the axon of the primary neurons to the spinal cord (69, 146).

From here, this tract ascends the entire length of the spinal cord, without passing to the opposite side, and synapse with secondary neurons located in the medulla oblongata, i.e. in a region called the nucleus cuneatus. Thus, the secondary sensory neurons then cross over to the opposite side (contralateral) of the medulla oblongata, forming a structure called the medial lemniscus (64, 69, 146).

In turn, the medial lemniscus ascends further into the brainstem and projects to the thalamus. From the thalamus, the sensory information is further relayed to the somatosensory cortex where the brain processes and interprets the vibratory sensations, allowing us to perceive and discriminate different vibrations, such as illustrated in Figure 3.1. Finally, appropriate motor responses are generated based on the stimulus received (64, 69, 146).

Vibration is sensed not only by the skin, but also by the muscle tendons or the muscles adjacent to the stimulated region. In these structure, vibration causes periodic changes in the length of muscle fibres. This change in muscle status, in turn, is detected by the muscle spindles, proprioceptive receptors located among the muscle fibres that are

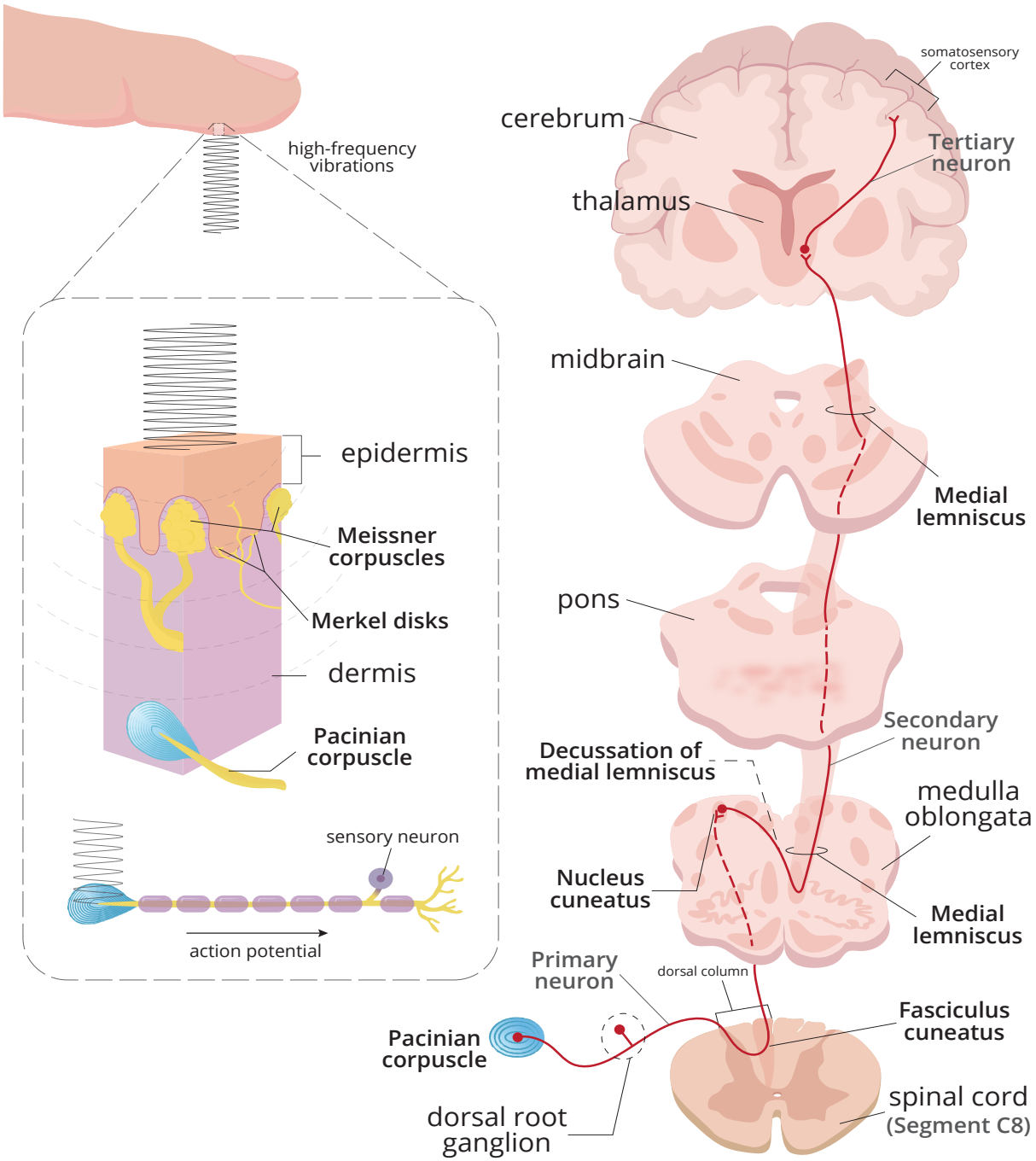


Figure 3.1 – Representation of vibratory pathway. When a high-frequency vibrotactile stimulus is applied to the skin surface of the fingertip, the mechanical vibrations penetrate the layers of the skin and are sensed by peripheral receptors known as Pacinian corpuscles. If the intensity of vibratory stimulus is sufficient to reach or exceed the threshold, an action potential is produced and is propagated towards the central nervous system. When the brain interprets the vibratory sensation that reaches the cortex, the perception of the stimulus occurs. Thus, appropriate motor responses are generated based on the stimulus received.

responsible for detecting changes in muscle length (25).

In this case, peripheral vibrotactile stimulation results an illusory sensation of stretching or displacement of the musculature and, consequently, the contraction of the antagonist muscles in an attempt to prevent the agonist muscles from being overloaded or torn, as well as may result in an involuntary sustained contraction of the stimulated muscle and reciprocal relaxation of its antagonist muscle in order to stabilize and maintain muscle tone and posture (146). Thus, this is a response called the tonic vibration reflex that usually occurs at the level of the spine, without the participation of the brain (25, 38).

In general, the effects of mechanical vibration on the human body can depend on several factors, such as the body area in contact with the vibration source, as well as the frequency, amplitude, duration and type of the stimulus (69). Therefore, these factors influenced how much a peripheral mechanical input is sensed and perceived.

3.3 The Return Of An Old Idea, But From A New Perspective

Although the mechanisms underlying tremor are unknown, it is possible that afferent pathways play a role in its manifestation. This is because these pathways are extremely important for the motor system. Basically, they are responsible for carrying peripheral sensory information to the cerebrum and cerebellum, which enable spatial awareness, motor adjustments, motricity control and balance maintenance of body segments (146).

Existence of a possible link between afferent pathways and tremor manifestation raises intriguing questions, such as: *Would it be possible to modify the dynamics of tremor through introducing external sensory input? Would it be feasible to suppress or dampen tremors simply by adding a sensory stimulus?* Finding solutions to these issues could lead to a better understanding of tremor. Moreover, it opens up possibilities for a deeper comprehension of the part played by afferent pathways in its manifestation.

In light of this context, peripheral vibrotactile stimulation may be an interesting alternative to be investigated and, perhaps, to provide basis for new treatments. This is due to the fact that the introduction of a vibratory input has the potential to alter the dynamics of these pathways and thus allow understanding the response of the motor system and the mechanisms related to the generation and manifestation of tremor when the affected limb is subjected to an external mechanical disturbance.

This therefore takes up the old idea of using vibration in tremor, but now from a new perspective. Given the current understanding behind vibrations in the body, it is reasonable to suggest that a vibratory input physiologically influences tremor manifestation in several distinct ways, either by acting as proprioceptive feedback for motor adjustment, being a sensory distraction or sensory clue, or by modulating neural oscillations.

As tremor in individuals with ET is typical manifested during posture (82), the local disturbance generated by an external vibratory stimulus may create the false impression of instability and, consequently, sensitise proprioceptive receptors in an attempt to adjust muscle activity to ensure that the limb remains in the desired position. This, therefore, may lead to less activity of the vibrated musculature or to the contraction of the antagonist musculature, resulting in better motor control and a reduction in the manifestation of tremor.

For instance, if the limb is held in a fixed posture, such as arms held outstretched against gravity, and it starts to deviate from its reference position, peripheral sensory feedback alerts the brain, which in turn activates the appropriate muscles to make the necessary adjustments or this may even cause a reflex response, at the spinal cord level. In other words, the sensory feedback allows for constant monitoring and adjustments to maintain the desired posture.

Aligned with this idea, recent studies (88, 92) have shown the feasibility of employing vibration noninvasively on muscles and tendons to suppress upper limb tremor in individuals with ET. These investigations propose that vibratory stimuli induce a muscle tonic reflex in the affected limb, resulting in an involuntary sustained contraction of the stimulated muscle and relaxation of its antagonist muscle, without brain involvement.

In addition, the peripheral vibrotactile stimulus can also sensitise mechanoreceptors, present in the skin, muscles or tendons, which are involved in the vibratory pathway that is responsible for the sensation and perception of vibrations (Figure 3.1). The processing of this afferent information, besides assisting in proprioception and, consequently, in motor adjustment, may act in a dual mode, as a sensory distraction or, conversely, as a sensory clue.

On the one hand, the sensory distraction can be very promising in reducing tremor by diverting attention away from tremor. For instance, psychogenic tremor or functional tremor instantly reduce or even disappear with distraction, such as when the attention of individual is withdrawn from the limb involved, as well as when there is distractibility with motor or mental tasks (48, 84, 152).

On the other hand, the sensory clue may cause tremor to become more pronounced. This is because attention may be drawn to the affected limb, as the vibration can be sensed in the stimulated region, producing thus an opposite effect. A curious feature of psychogenic tremor is that it can vary in response to certain stimuli, which can be associated with this dual action. In this direction, Thenganatt and Jankovic demonstrate that sometimes the intensity of tremor increases following the application of a vibratory stimulus, whereas other times it decreases (152).

Another possibility is that vibratory input may lead to modulation of neural oscillations. As it is believed that the generation of tremor is associated with the abnormal oscillatory activity of circuits involved in the processing of sensory information, the in-

tegration of sensory and motor information, as well as the coordination of movement execution (Figure 2.1), it is plausible to suggest that the introduction of a vibratory stimulus may influence these neural oscillations (95) and perhaps (de)synchronise the abnormal oscillatory patterns associated with tremor.

All those hypotheses together suggest that peripheral vibrotactile stimulation may influence the tremor dynamics. Therefore, it is conceivable that it could be an interesting tool to explore the manifestation of tremor. Clearly that the effects of vibration on the human body depend on factors, such as body area in contact with the vibration source, as well as the frequency, amplitude and duration of the stimulus (69), justifying the need for studies employing different vibrotactile stimuli on limbs affected by tremor.

4

Materials and Methods

"In maths, we always seek to understand magical things... if you have the right framework to look at something, you can get rid of a whole lot of noise that is perpendicular to that vision..."

— *Ingrid Daubechies*

4.1 Ethical Considerations

The database used in this research originated from a previously study approved by the local ethical committee at *Hospital 12 de Octubre* (Madrid, Spain) (95). The experimental protocol was carried out ethically in accordance with the Helsinki Declaration of 1975, and informed consent was obtained from all participants during the experiment. In addition, the trial was registered at the Australian New Zealand Clinical Trials Registry (ACTRN12618000819224).

4.2 Participants

This study evaluated the tremor in the most affected upper limb of individuals with ET. In general, participant eligibility included the disease diagnosis, age over 18 years, no pacemaker or deep brain stimulation implant, and no history of epilepsy, head trauma or stroke. Thus, those with other movement disorders, cognitive impairment, or upper limb injuries or limitations that made the experimental protocol unfeasible were excluded from the study.

All individuals were recruited at *Hospital 12 de Octubre* after being examined by an expert neurologist and the informed consent was obtained from them following a full explanation of the research. Individuals taking medications to manage tremor were instructed not to change their usual treatment during participation. However, the medication had to be stable for at least two weeks prior to the experimental session. The medication and daily dose for each participant are described in Table 4.1.

A total of 18 participants were considered eligible to participate in the experimental protocol. Among the individuals, there were 12 men and six women aged between 59

Table 4.1 – Demographic and clinical characteristics of the participants.

Individual	Gender	Age (years)	Duration of tremor (years)	FTM score	Medication	Dose (mg/day)
1	Male	87.87	37.35	3	Clonazepam	0.5
2	Male	78.18	26.34	3	Primidone	500
3	Male	76.01	15.33	2	-	-
4	Male	81.39	10.35	2	Primidone	500
5	Male	68.00	8.35	2	Propranolol	60
					Primidone	250
6	Male	73.42	9.47	3	Primidone	250
7	Male	77.91	10.47	3	Zonisamide	300
					Propanolol	80
8	Male	77.76	4.59	2	Primidone	375
9	Female	82.51	6.59	2	Primidone	625
10	Female	87.14	20.62	4	Propranolol	30
					Primidone	250
11	Female	66.13	10.62	1	-	-
12	Female	78.91	11.70	2	Zonisamide	100
					Gabapentine	900
13	Male	81.04	39.72	3	Zonisamide	150
14	Female	61.67	6.75	2	-	-
15	Male	79.79	1.75	1	-	-
16	Male	75.90	0.93	1	-	-
17	Male	70.49	4.94	1	-	-
18	Female	59.56	18.95	1	-	-

and 87 years (75.8 ± 7.9 years). All participants were affected by tremors for at least 11 months. Demographic and clinical characteristics of individuals are provided in Table 4.1.

4.3 Clinical Evaluation

Participants were evaluated clinically by a neurologist who was not involved in the data analysis. The severity of the postural hand tremor was determined using the Fahn-Tolosa-Marín Tremor Rating Scale (FTM), whose scores are shown in Table 4.1. This is the most commonly used tremor rating scale for assessing tremor severity in ET patients (41, 137, 140). FTM can be used to assess tremor in areas other than the upper limbs, such as the head, trunk, tongue, and lower limbs.

In particular, FTM allows the clinical evaluation of specific tasks of the hand, such as writing, feeding, holding objects and activities related to hygiene care. FTM is divided into three sections, each of which contains 21 items. The first part of the scale (part A) aims to quantify tremor in nine parts of the body during the rest, action, maintenance of posture or intentional tasks. In the second part (part B), action tremor of the upper limbs is evaluated through writing, drawing and pouring liquids. Finally, the last part

(part C) assesses functional disability related to activities of daily living (49).

This scale is based on a five-point scale, with zero indicating no functional disability and four indicating severe disability. The maximum total score is 144, with maximum subtotals of 80, 36, and 28 for items grouped by part A, B, and C, respectively. Thus, the higher the total score, the more severe the disease and the greater the involvement of different parts of the body.

4.4 Experimental Procedure for Data Collection

During the experimental procedure, participants sat comfortably in a chair with their feet flat on the floor and their backs against the backrest. They were instructed to maintain the posture of the most affected upper limb, that is, arms parallel to the transverse plane and 90^{o} from the coronal plane. Thus, the postural tremor was evaluated with the elbow joint extended and forearm pronated, as shown in Figure 4.1. To minimize the influence of the movement of other parts of the body and avoid limb fatigue, an arm rest supported the arms of subjects during the experiments.

All individuals were assessed with and without peripheral mechanical stimulation. The most affect upper limb (hand and forearm) of participants were subjected to five vibrotactile stimulation paradigms. Each stimulation paradigm lasted 240 seconds, and a 10-minute rest period was considered between them, as illustrated in Figure 4.2. Thus, each participant completed the experiment in about 60 minutes.

Initially, postural tremor was recorded in the absence of vibrotactile stimulation for four minutes in order to characterize involuntary activity without the influence of mechanical inputs. This vibrotactile stimulation paradigm (called baseline) corresponded to a control measurement for making comparisons, allowing thus to characterize the tremor of each individual during upper limb posture maintenance.

Subsequently, the participants were subjected to four vibrotactile stimulation patterns, which included both constant frequencies (50 and 250 Hz) and alternating frequencies (with increasing frequency between 50 and 450 Hz with resolution of 50 Hz and these frequencies in random order). Thus, the limbs were stimulated at 50 Hz, then 250 Hz, increasing the linear frequency of stimulation, and finally the random stimulation frequency, in the order depicted in Figure 4.2.

In addition, each of these four stimulation patterns lasted approximately four minutes, subdivided into a pre-stimulation period (1 minute), a stimulation period (2 minutes) and a post-stimulation period (1 minute), as illustrated in Figure 4.2. This subdivision was considered in order to evaluate postural tremor before, during, and after the application of the vibratory stimulation.

Data were collected using a custom wearable device. The system was proposed to stimulate mechanically the upper limb and quantitatively measure tremor. Figure 4.1

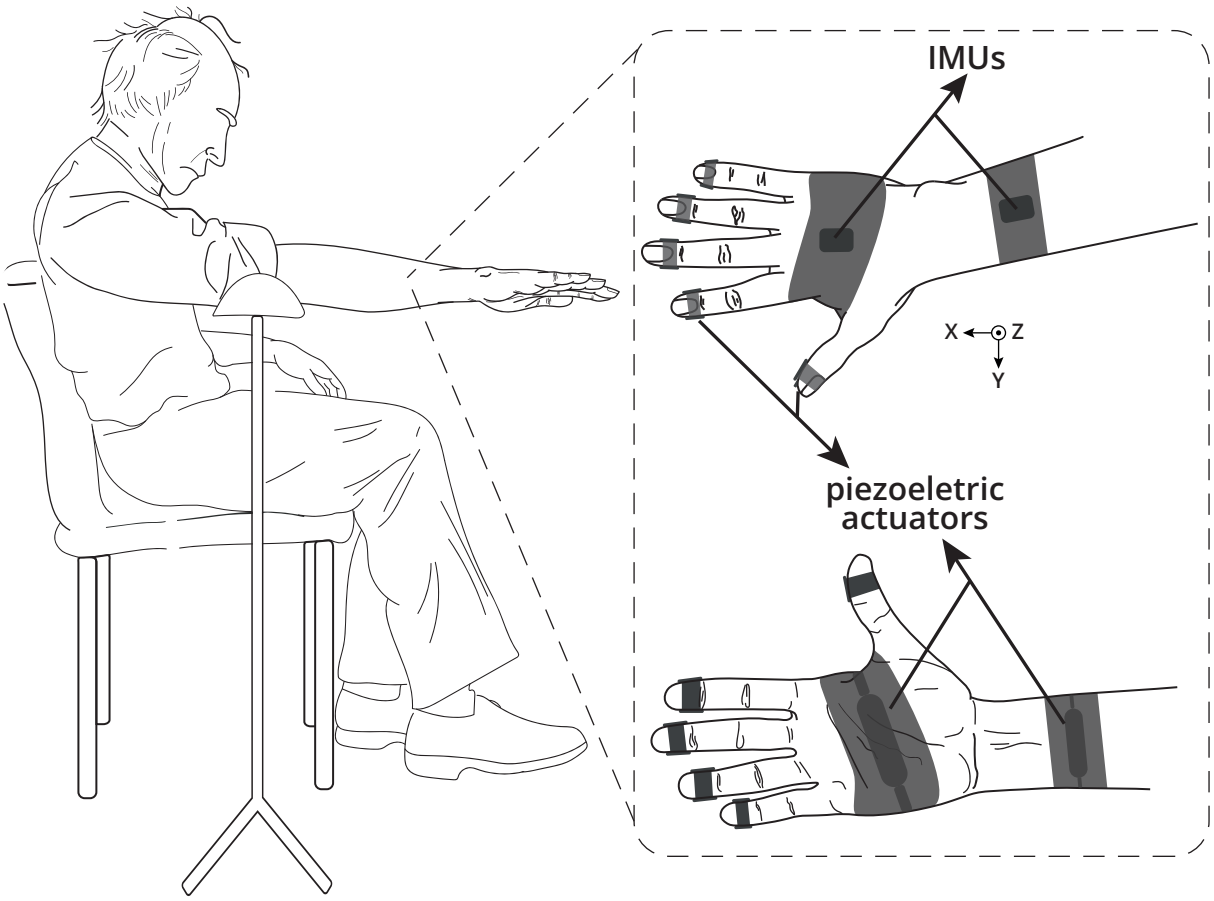


Figure 4.1 – Illustration of the experimental scenario. The participants sat in a chair with their feet flat on the floor and back against the backrest. The arms were maintained parallel to the transverse plane and 90º from the coronal plane. Inertial sensors (IMUs) were positioned at the back of the hand and forearm. Piezoelectric actuators were placed on the fingertips, hand and forearm.

shows the placement of the wearable device on the participant's limb and illustrates the main hardware elements. To detect tremor behavior, triaxial angular velocities of the forearm and hand were measured with one pair of inertial measurement units (IMUs, TechMCS, Technaid, Spain). The inertial signals were sampled at 100 Hz.

The vibrotactile stimulation was applied to fingertips, palm of the hand and forearm by using piezoelectric actuators (Mide Technology, USA - model QP-10W for the fingertips, PPA4011 for the hand and PPA-1022 for the forearm), controlled at 5 kHz through piezoelectric haptic drivers (DRV8662, Texas Instruments, USA). All participants received a constant amplitude stimulus with a voltage of 50 V for the actuator on the forearm and 75 V for the actuators on the fingers and palm of the hand.

4.5 Signal Processing

Data analysis and signal processing were performed using *R* (126), an open source programming language and environment for data visualization and statistical analysis.

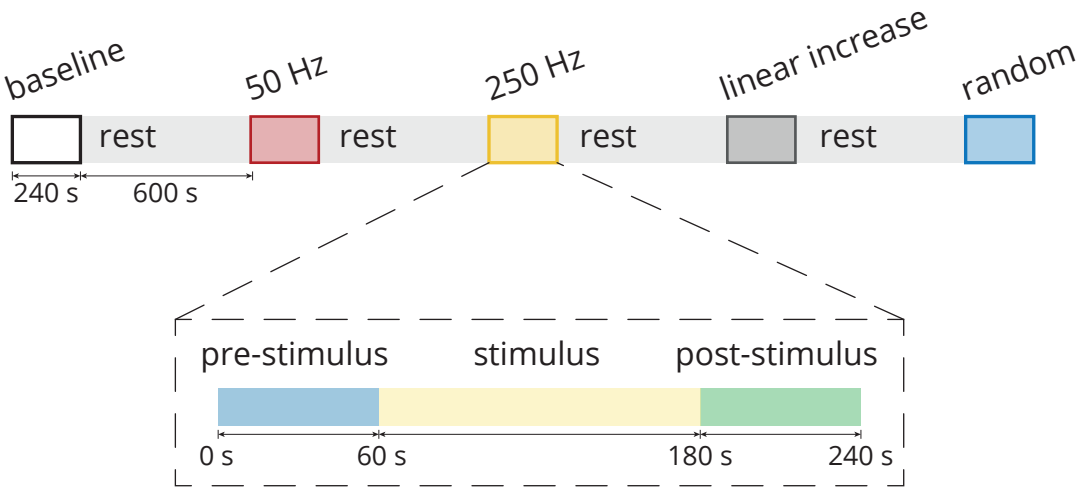


Figure 4.2 – Each individual was submitted to one of the five stimulation paradigms during posture maintenance: baseline (without vibrotactile stimulation), stimulation at 50 Hz, stimulation at 250 Hz, stimulation with increasing linear frequency and random frequency stimulation. All stimulation paradigms lasted 4 minutes, and a 10-minute rest period followed each one. Except for baseline, the stimulation paradigms contained a pre-stimulus region lasting 60 seconds, a stimulus region lasting 120 seconds, and a post-stimulus region lasting 60 seconds.

In this study, a customized *R package* was designed to support researchers in analysing tremors and performing biomedical signal processing. It enables interactive visualisation of signals in the time and frequency domains, removal of trends and artefacts, feature extraction, and statistical analysis. Figure 4.3 conceptually presents the steps used to preprocess signals for feature extraction and statistical analysis.

4.5.1 ET data set

The used database is composed of data collected from 18 volunteers with ET. For each participant, the data were stored in five text files, one file referring to the data without stimulation and four files referring to the data with stimulation for the constant frequencies (i.e., 50 Hz and 250 Hz), linear increasing (from 50 Hz to 450 Hz, with resolution of 50 Hz) and random (with the same frequencies of the stimulation pattern with increasing linear frequency, but in random order).

The data were organized in a tabular format, and each column represents one of the following variables: time (s), angular velocity (rad/s) of the hand and forearm for the X, Y and Z axes, and amplitude (in volts) and frequency (Hz) of the control signal of piezoelectric actuators positioned in the palm of the hand, fingertips and forearms. Table 4.2 specifies the variables.

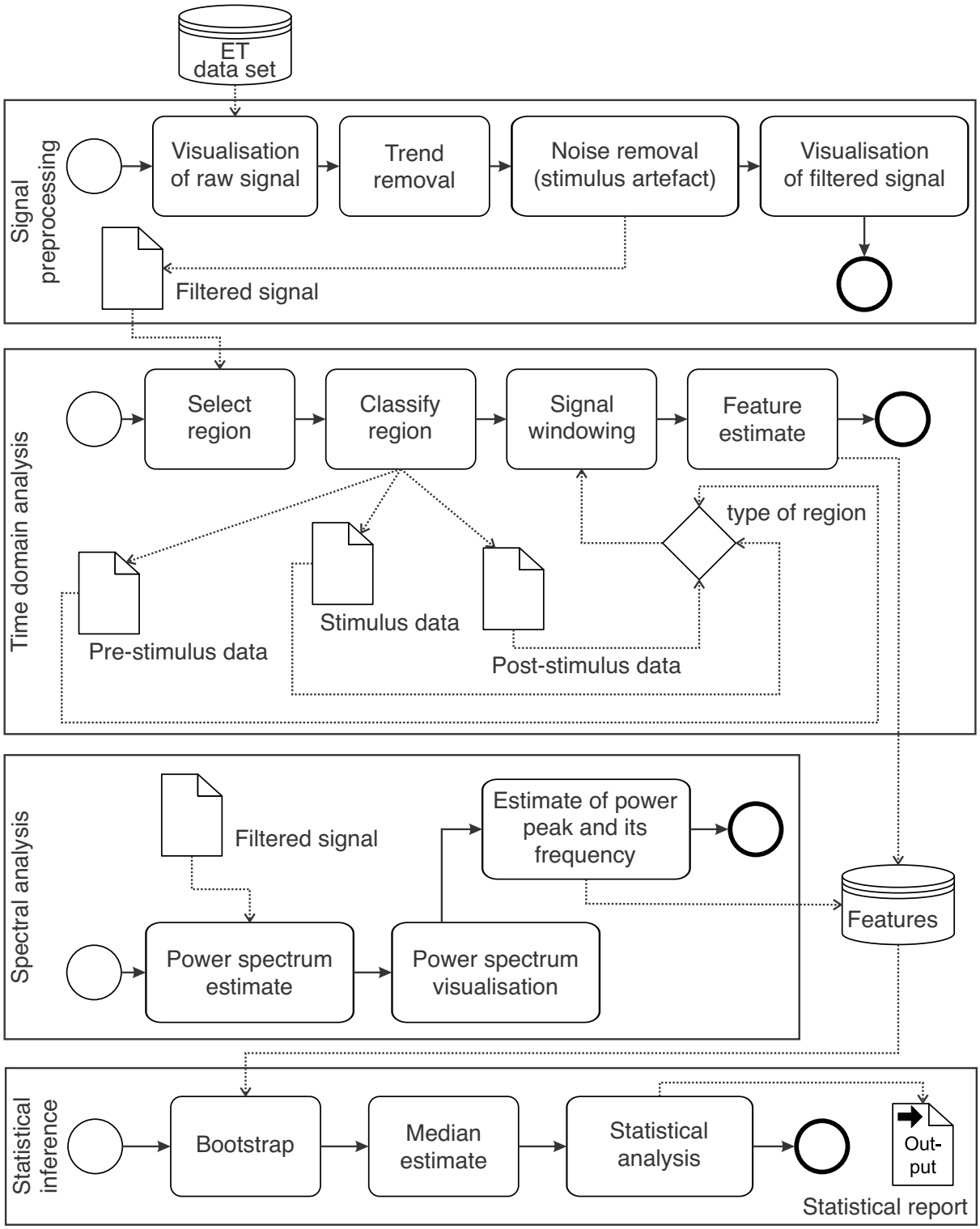


Figure 4.3 – Signal processing steps for feature extraction and statistical analysis.

Table 4.2 – Description of the variables that characterize the ET data set.

Variable	Units	Sensor	Positioning	Axis	Description
time	s	-	-	-	Period of data collection
G1X	rad/s	Gyroscope	Hand	X	Angular velocity
G1Y	rad/s	Gyroscope	Hand	Y	Angular velocity
G1Z	rad/s	Gyroscope	Hand	Z	Angular velocity
G2X	rad/s	Gyroscope	Forearm	X	Angular velocity
G2Y	rad/s	Gyroscope	Forearm	Y	Angular velocity
G2Z	rad/s	Gyroscope	Forearm	Z	Angular velocity
A1	V	Piezoelectric actuator	Fingertips and forearms	-	Control signal amplitude
f1	Hz	Piezoelectric actuator	Fingertips and forearms	-	Frequency of control signal
A2	V	Piezoelectric actuator	Palm	-	Control signal amplitude
f2	Hz	Piezoelectric actuator	Palm	-	Frequency of control signal

4.5.2 Signal Visualisation

In this study, each collected signal was carefully visualised. For each participant, 30 signals were visually inspected (5 stimulation patterns $\times$ 2 positioning regions of IMUs $\times$ 3 axes). Figure 4.4 depicts gyroscope signals captured from an individual while maintaining the posture of the most affected limb for various stimulation paradigms. Thus, for 18 participants, the data set consisted of 540 signals.

This step is frequently overlooked or not mentioned in many signal processing studies. However, it is an important step in the analysis and processing of any biomedical signal. It is significant for several reasons. Signal visualisation improves the understanding of the analysed phenomenon by displaying the behaviour and trends in the signal and guiding signal processing and statistical analyses. Furthermore, this step avoids the use of unnecessary complex tools and allows for data integrity verification.

4.5.3 Signal Preprocessing

The visualisation of the signals revealed the presence of trends as well as artefacts produced by the vibratory stimulus in the signals. Then, it was necessary to eliminate these components to obtain only the tremor-related information from the signals. For this purpose, wavelet decomposition was used to eliminate trends and stimulus-related noise from the signals. Using the Daubechies orthonormal compactly supported wavelet of length 8, the signal was decomposed into five components.

Details (d) and approximations (s) are components resulting from the signal decomposition. The approximation components detect the low-frequency oscillations of the signal,

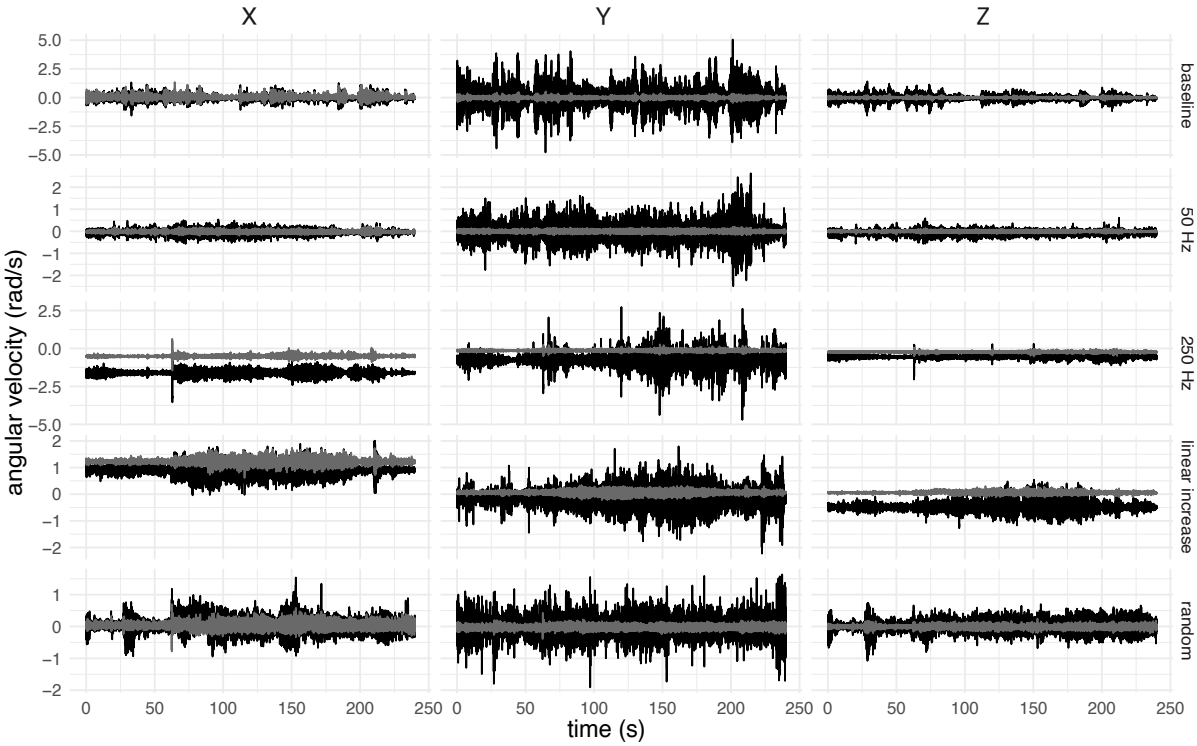


Figure 4.4 – Typical signals collected for each axis and stimulation paradigms. The signals in black are from the sensor positioned at the hand whereas the signals in gray are from the sensor positioned at the forearm.

whereas the detail components detect the high-frequency content of the signal. The strategy for signal filtering was to identify the wavelet component that best represented the noise activity and then reconstruct the signal based on the algebraic summation of its components excluding the component associated to noise, as illustrated in Figure 4.5.

This is an essential preprocessing step because it prepares the signal for further processing and analysis. Depending on the experimental conditions, acquisition hardware characteristics, biomedical signal type, data collection quality, and application purpose, it may be necessary, in addition to detrend or remove noise, to fill data gaps, resample, smooth, and find and remove outliers. In this sense, several preprocessing methods may be required.

Trend removal

Generally, inertial signals are subject to linear and non-linear trends (118). These trends are systematic changes that occur in the signal over time (112). Basically, they originate from sensor characteristics (such as the influence of the acceleration of Gravity and the Earth's magnetic field), small motions unrelated to the motion of the the investigated limb, or even the signal acquisition process itself (such as cable movement) (21).

In such cases, one of the most important preprocessing steps is to identify, model and

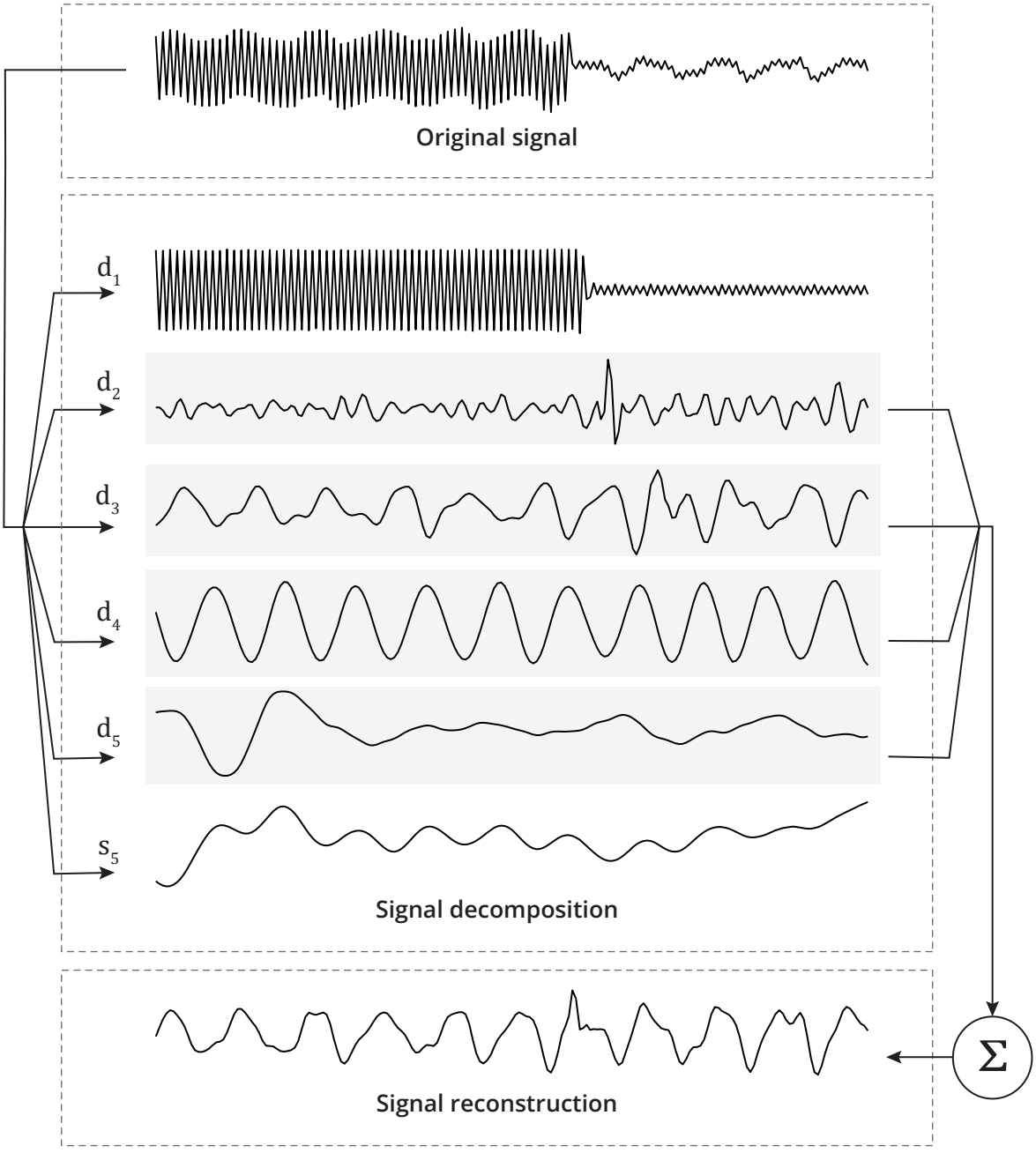


Figure 4.5 – The strategy for signal filtering, using wavelets.

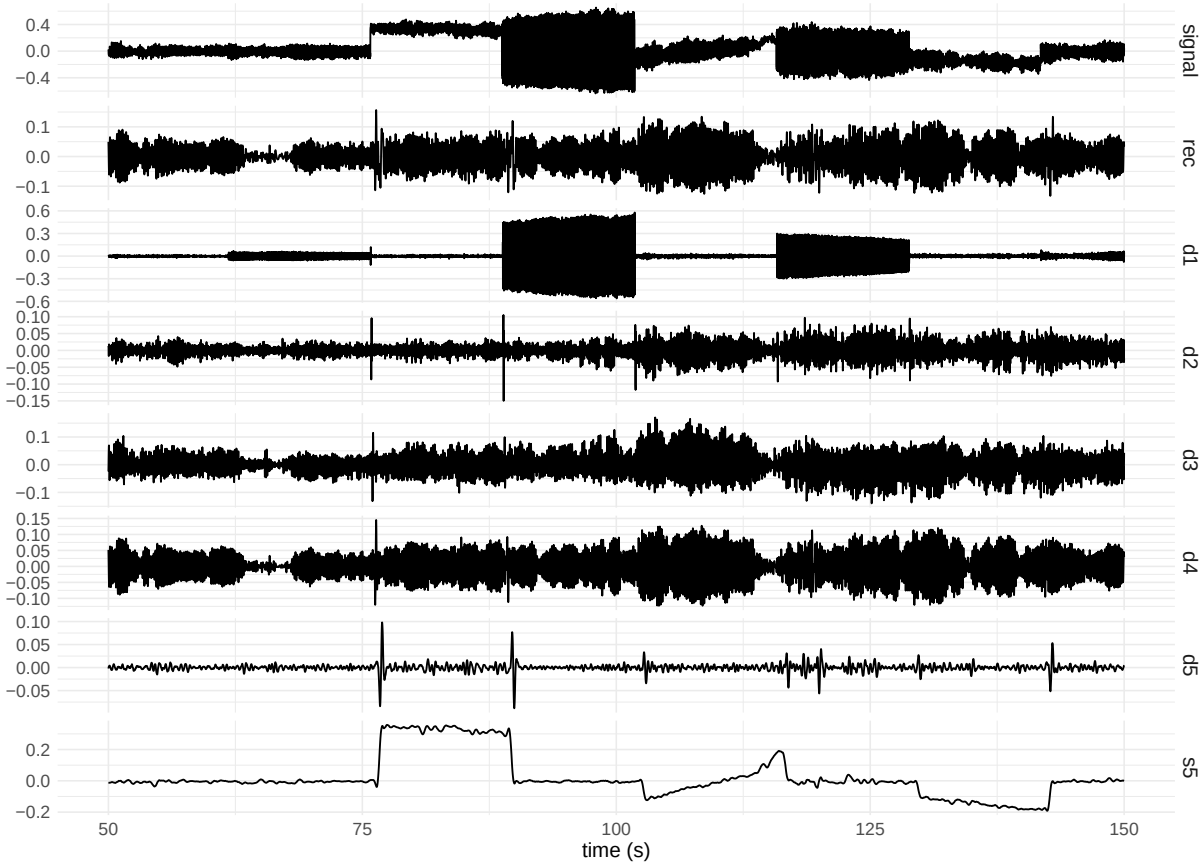


Figure 4.6 – Example of a signal acquired using a gyroscope positioned on the subject's hand. The signal was collected while the subject received a linearly increasing frequency stimulus. The detail components from $d1$ to $d5$ are shown along with the approximation component ($s5$). The filtered signal (rec) resulting from the summation of the components from $d1$ to $d5$ is shown. The trend removal of the signal is clear.

remove the trends to minimize the influence of offsets and fluctuations in the signals that do not refer to the phenomenon investigated. Because linear and nonlinear trends are associated with low-frequency oscillations, the strategy for removing this type of noise from the signals was to reconstruct the signal by removing the approximation component that best captured the signal trend.

Figure 4.6 shows an example of the outcome of the trend removal using wavelets. The original signal (top) was influenced by linear and nonlinear trends, as shown in the figure. Because the $s5$ component, which is the slowest approximation component, represents the signal trends, it was necessary to reconstruct the original signal by adding up all detail components except the $s5$ component.

Noise removal

In addition to trends, inertial signals may be susceptible to artefacts that introduce seasonal fluctuations or more complex components into the signals. This is because the inertial signals can be corrupted by external inputs, such as peripheral mechanical stimuli,

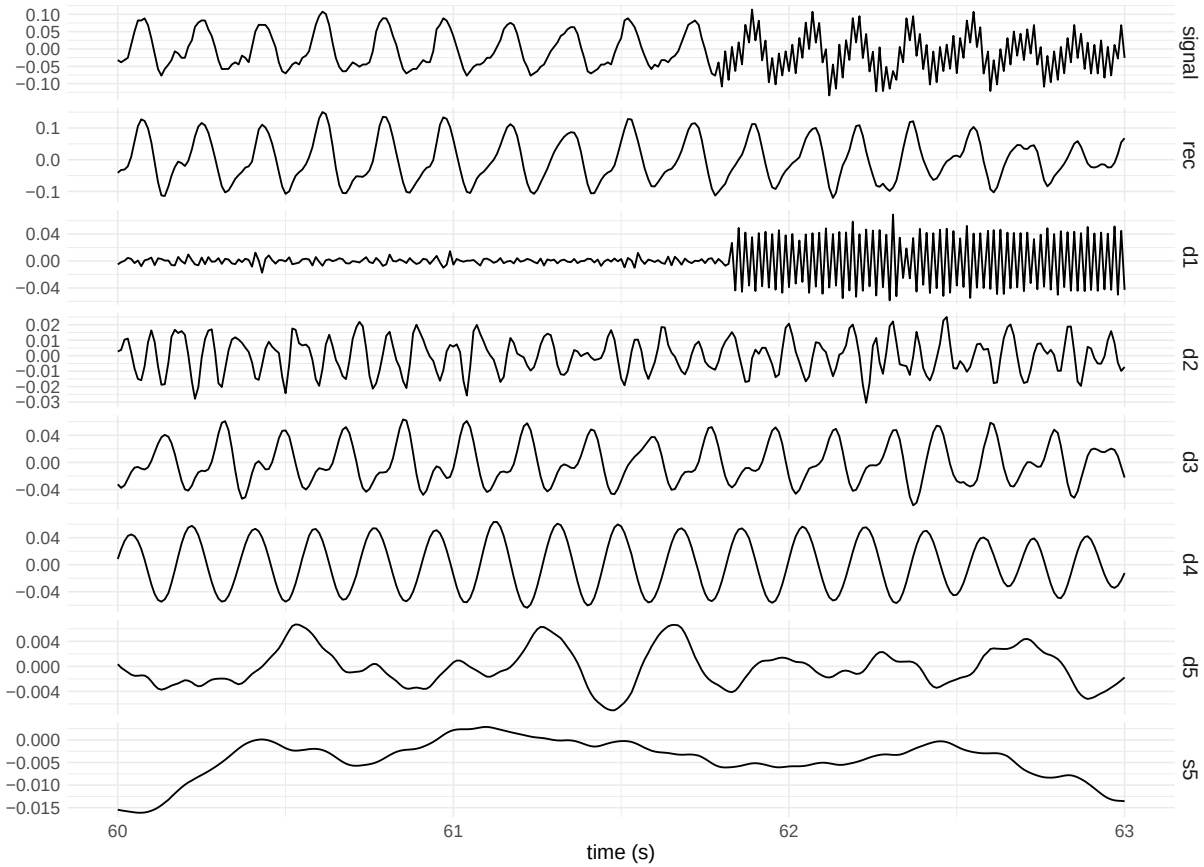


Figure 4.7 – Example of a signal acquired using a gyroscope positioned on the subject's hand. The signal was collected while the subject received a linearly increasing frequency stimulus. The influence of the stimulus on the signals can be seen from 61.78 to 63.00 seconds. The detail component $d1$ is clearly related to the noise related to the stimulus, thus the reconstructed signal (rec) was obtained by removing it along with the approximation component ($s5$).

that cause the investigated system to oscillate during signal acquisition. It was verified that the signal component $d1$ captured this type of noise. Thus, the signal was filtered by reconstructing the signal without $d1$. Figure 4.7 shows an example of the outcome of the noise removal using wavelets.

Visualisation of filtered signal

The filtered signals were visualised to ensure that their waveforms were preserved. For signal visualisation, both static and interactive plots were used. Typical results of this preprocessing step are shown in Figure 4.7, which contrasts the original signal with the filtered signal (rec).

4.5.4 Time Domain Analysis

Select, classify and windowing of signal regions

Following visualisation of filtered signals, regions of the signals were selected for processing in order to compare the dynamics of postural tremor before, during and after stimulation. In the case of the baseline paradigm, the whole signal was selected for processing. However, for the other experimental conditions, in which the tremor signals were recorded simultaneously to the stimulus, the regions of signals with and without stimuli were detected.

During signal acquisition, a controlling signal was responsible for turning on and off the piezoelectric actuator. This controlling signal has a binary-like response, with a high-level indicating stimulus presence and a low-level indicating stimulus absence. Based on this signal, the signal can be divided into three regions: pre-stimulus, stimulus, and post-stimulus. Figure 4.8 illustrates typical signals in response to different patterns of stimulus. In this figure, the behaviour of the signals during the transition between regions with and without stimuli are highlighted.

The signal windowing stage is depicted in Figure 4.9 for the case in which there is vibrotactile stimulation. To window the raw data from each region, a nonoverlapping rectangular window of 500 ms is employed. The purpose of this stage is to segment the signal such that a set of features from each region can be estimated. A similar procedure was adopted for the windowing of baseline signals.

Feature extraction

The set of estimated features of each window was summarized by the median of the feature. Two features were investigated, i.e., Approximate Entropy ($ApEn$) and Mean Absolute Value (MAV). These features are defined below.

Approximate Entropy (ApEn) It is a feature that expresses the regularity and predictability of the signal over time. Approximate entropy is defined as

$$ApEn(m, r, N) = \begin{cases} \phi^m(r) - \phi^{m+1}(r), & \forall\ m \leq 0 \\ -\phi^1(r), & m = 0 \end{cases}, \tag{4.1}$$

where

$$\phi^m(r) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} ln(C_i^m(r)), \tag{4.2}$$

N corresponds the length of signal, $m \in \mathbb{Z}^+$ corresponds the embedded dimension which represents the length of two segments in a sequence to be compared, $r \in \mathbb{R}^+$ corresponds to the filter factor which shows the tolerance for accepting similar patterns between two segments and

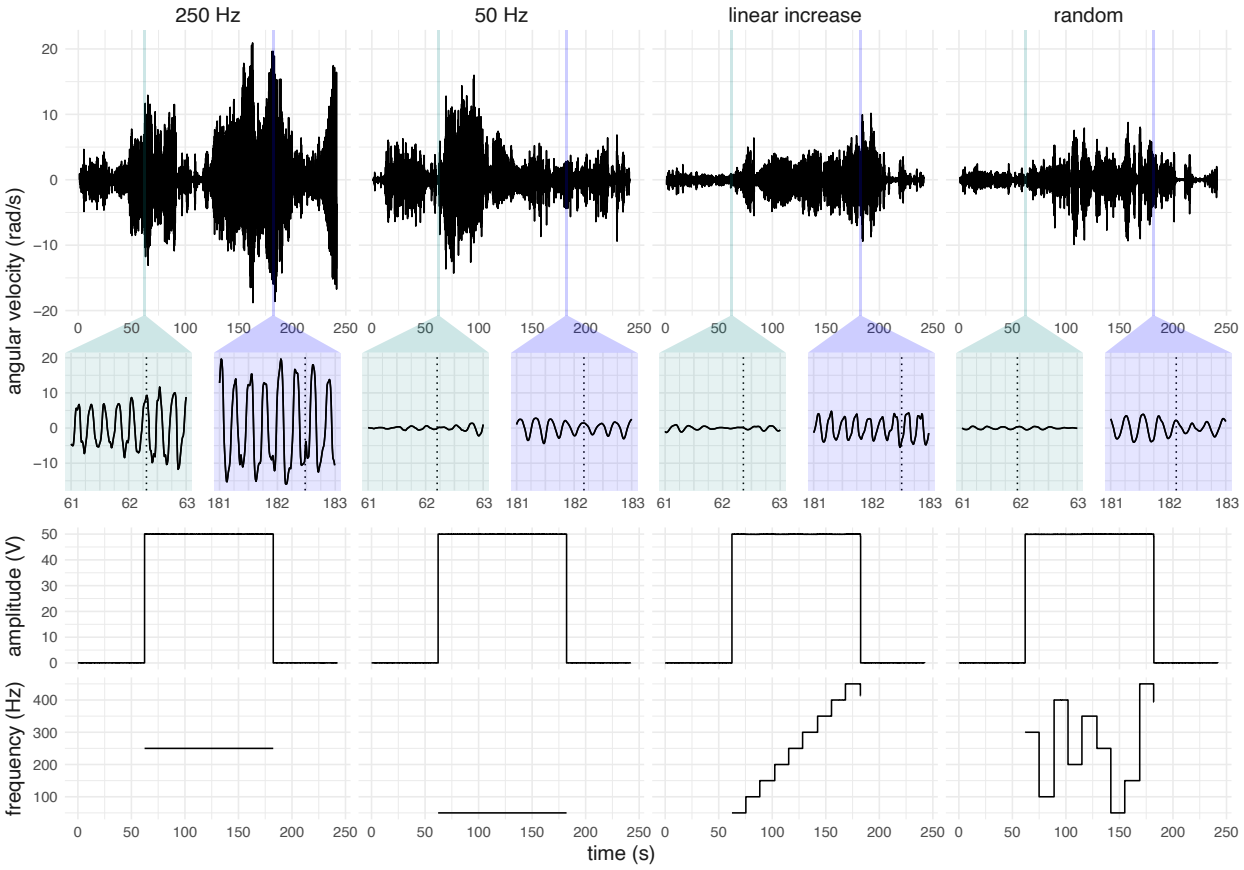


Figure 4.8 – Typical angular velocity (rad/s) in response to various stimulation patterns (50 Hz, 250 Hz, linear increase and random). In each signal, two regions were highlighted: the first is the transition between periods without and with stimulation (green area), and the second is the transition between periods with and without stimulus (blue area). Pairs of vertical dashed lines indicate the beginning (green area) and end (blue area) of the period of stimulation. The controlling signals shown in the third row of the figure give the stimulus region. At the bottom are the distinct stimulus patterns.

$$C_i^m(r) = \frac{N_i^r}{N - m + 1} \tag{4.3}$$

with N_i^r representing the number of Euclidean distances between each two segments (m – dimensional delay vectors) which is no larger than r.

This definition implies that the approximate entropy is a value between zero and two. When $ApEn$ tends to zero ($ApEn \to 0$), the signal is more regular and deterministic over time. This implies that the presence of repeating patterns in the signal makes it more predictable and thus less complex (Figure 4.10). If $ApEn$ tends to two ($ApEn \to 2$), then more unpredictable the signal is over time (Figure 4.10). That is, more complex.

Mean Absolute Value (MAV) It is a feature that captures changes in the amplitude of the signal. It is calculated by averaging the absolute values, that is,

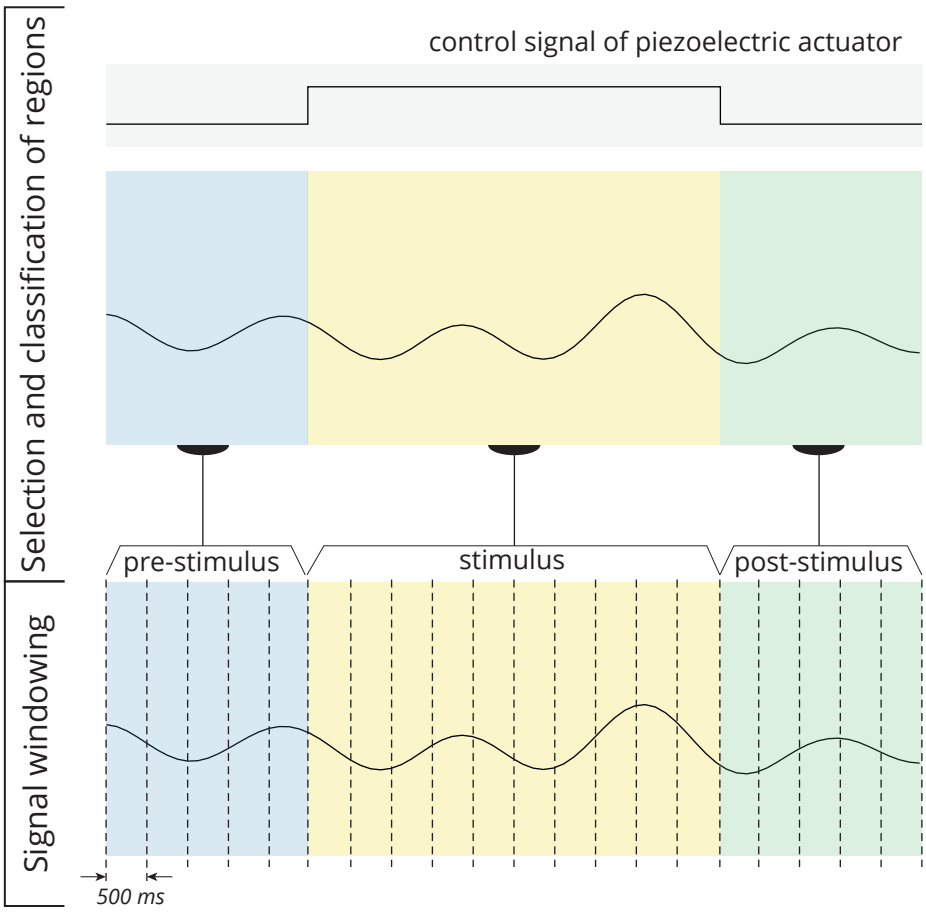


Figure 4.9 – The processes required to window the raw signals are depicted. The signals are first classified into regions based on the presence or absence of stimulus. Second, for feature extraction, the signal in each region is segmented by 500 ms windows.

$$MAV = \frac{1}{N}\sum_{i=1}^{N}|x_i|, \tag{4.4}$$

where N corresponds the number of samples of the signal and x_i corresponds to the i-th signal sample. Therefore, high MAV values imply a high order of magnitude of the signal and, consequently, of the measured quantity.

In the analysis of tremor, the assessment of amplitude and regularity may be very important to characterize the involuntary activity. This is because tremor amplitude describes the severity of involuntary movements in the affected limb, while tremor regularity allows identifying motor fluctuations and differentiating tremors or periods of involuntary activity even when they present similar amplitudes over time.

Each participant's information was represented by two 72-dimensional feature vectors (3 axes $\times$ 2 IMU positioning $\times$ 4 frequency patterns of stimuli $\times$ 3 types of regions of activity). One vector had estimates of $ApEn$ whereas the other had estimates of MAV.

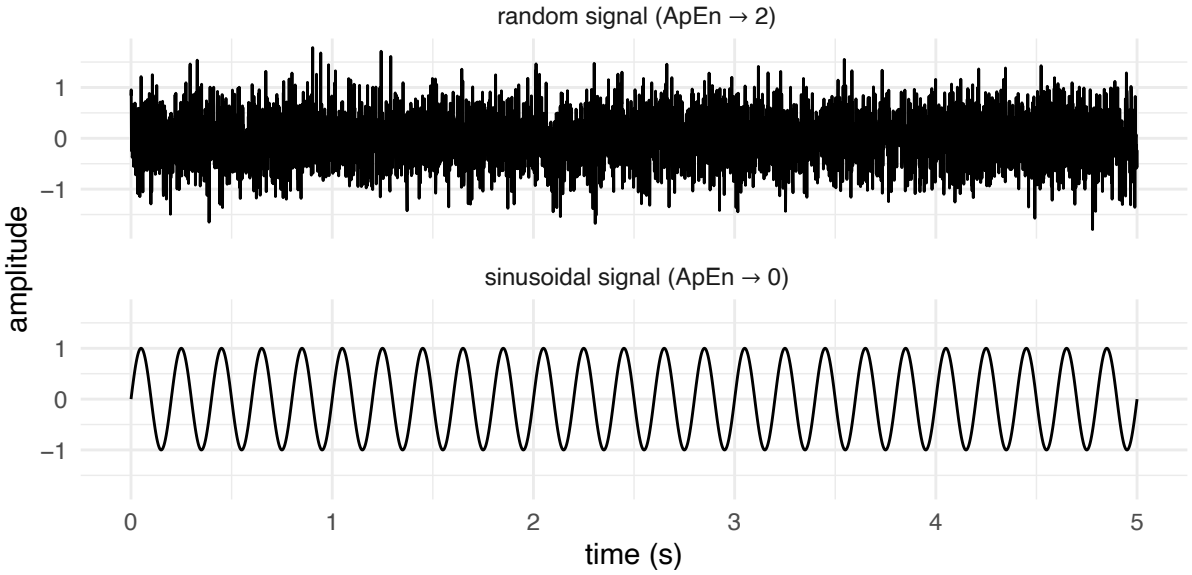


Figure 4.10 – Illustration of two synthetic signals whose approximate entropies are distinct. Random signals (*top*), whose dynamics are highly variable over time, are unpredictable signals. Therefore, they are more irregular, i.e. they have an approximate entropy tending to two ($ApEn \rightarrow 2$). In contrast, deterministic signals, such as sinusoidal signals (*bottom*), are more predictable over time. Consequently, they are more regular and, therefore, have an approximate entropy tending to zero ($ApEn \rightarrow 0$).

4.5.5 Frequency Domain Analysis

Power spectrum estimate

To analyse the frequency content of tremor and provide information about its spectral characteristics, the Power Spectral Density (PSD) was estimated for each signal. The PSD of a signal describes the power distribution as a function of frequency. Therefore, it is a method that provides insight into the predominant frequencies and their relative power levels.

In this study, the PSD was computed using the adaptive sine-multitaper approach described by Barbour and Parker, which provides an accurate and high-resolution estimate of the frequency content of signal (9). As highlighted by the authors, this method "is adaptive so that the resolution and variance are set by the spectral shape. This adaptive process eliminated the need for parameter tuning, such as the time-bandwidth product or segment length, that fixes the frequency resolution for the entire frequency interval".

Feature extraction

For the feature extraction step, the PSD was smoothed (Savitzky-Golay filter of order 7 and length 19) to ease the estimate of features. Two features were estimated from the PSD, the peak power (p_{peak}) and peak frequency (f_{peak}). Peak power corresponds to the global maximum value of the PSD, while peak frequency is the frequency associated with

this power value. In tremor analysis, these are important features. This is because they describe the component of the highest power, i.e. the main component of the signal.

4.5.6 Statistical Analysis

An overview of the statistical analysis is presented in Figure 4.11. For each feature vector

$$F_k = \{f_1^k, \cdots, f_N^k\}, \tag{4.5}$$

where $k \in \{MAV, ApEn, p_{peak}, f_{peak}\}$, $N \in \{1, \cdots, 18\}$ corresponds the number of participants and f_i^k corresponds the $k-th$ feature of the $i-th$ participant, the Bootstrap method with 95% confidence interval was used to estimate the distribution of the medians given the axis ($A = \{X, Y, Z\}$), the position of the IMU ($P = \{$*dorsum of the hand (1), forearm (2)*$\}$), the stimulation paradigms ($W = \{$*baseline, 50 Hz, 250 Hz, linear increase, random*$\}$), and, specifically for the time domain analysis, the type of activity region ($R = \{$pre-stimulus, stimulus, post-stimulus$\}$). The estimation of the medians of each F_k considered $B = 10,000$ bootstrap samples. Mathematically, this can be expressed as

$$F_k \xrightarrow{\psi} \{F_{k_b}\} \xrightarrow{\psi'} S_k \tag{4.6}$$

where

$$\psi(F_k) = \{F_{k_b}\} = F_{k_1} \cup F_{k_2} \cup \cdots \cup F_{k_B}, \tag{4.7}$$

$$F_{k_b} = \{f_i^{k,b} \mid f_i^{k,b} \in F_k\},\ \forall\ i \in \{1, \cdots, N\},\ b \in \{1, \cdots, B\} \tag{4.8}$$

and

$$\psi'(\{F_{k_b}\}) = S_k = \widetilde{F}_{k_1} \cup \widetilde{F}_{k_2} \cup \cdots \cup \widetilde{F}_{k_B},\ \forall\ b \in \{1, \cdots, B\}. \tag{4.9}$$

For the time domain, the statistical analysis considered a linear model for the evaluation of the relationship between the feature value (S_{MAV} and S_{ApEn}) and the type of region of activity, given an axis, IMU positioning and stimulation paradigm. These models are given in Equation 4.10.

$$S_k \mid A, P, W \sim R \tag{4.10}$$

For the frequency domain, the model of Equation 4.11 was considered to evaluate the relationship between the feature value ($S_{p_{peak}}$ and $S_{f_{peak}}$) and the type of stimulation paradigm, given an axis and IMU positioning.

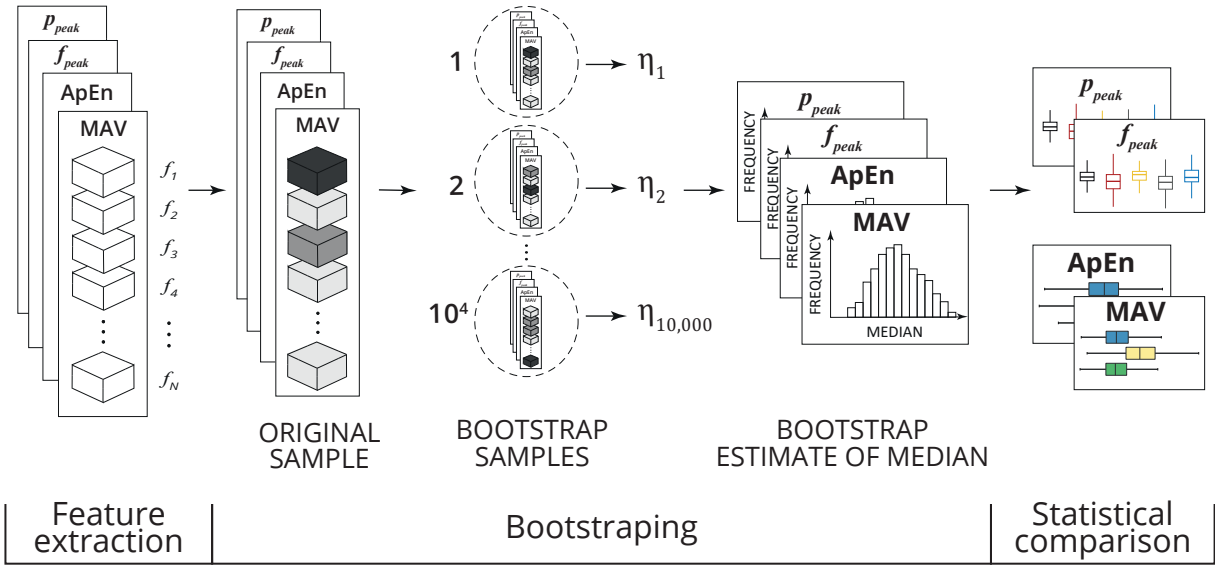


Figure 4.11 – An overview of statistical analysis. From the original samples, 10,000 bootstrap samples were estimated in total. The median of each bootstrap sample is calculated, and the distribution of the median is visualised. The boxplot for the median of each feature.

$$S_k \mid A, P \sim W \tag{4.11}$$

Initially, a parametric analysis (one-way ANOVA) was attempted and, once the assumptions of such approach were not verified, a nonparametric analysis (Kruskal-Wallis test) was carried out, considering a p-value < 0.05. Thus, the normality assumption of the one-way ANOVA was verified by the Kolmogorov-Smirnov test (p-value > 0.05) and Levene's test verified the homogeneity of variances (p-value < 0.05).

For the time domain, the statistical analyses were delineated to evaluate statistical differences among the periods of activity (period before stimulation, period during stimulation and period after stimulation) for the bootstrap variables (S_{MAV} and S_{ApEn}), given each axis, positioning of the IMU and stimulation paradigm. For the frequency domain, the statistical analyses were delineated to evaluate differences among the stimulation paradigms (baseline, 50 Hz, 250 Hz, linear increase and random) for the bootstrap variables ($S_{p_{peak}}$ and $S_{f_{peak}}$), given each axis and positioning of the IMU.

In addition, the effect size associated with the adopted statistical test was employed to verify the magnitude of the difference between groups for the analyses in the time and frequency domains. This statistical metric provides a quantitative interpretation of the difference. Basically, the larger the effect size, the greater the difference between groups.

After verifying the statistically significant difference, a post-hoc analysis was performed to determine at which levels there is a statistically significant difference between the regions of activity (time domain) and stimulation paradigms (frequency domain). Multiple pairwise comparisons were performed by means of the Tukey Honest Significant

Differences in the case of parametric approach or the pairwise Wilcoxon rank-sum test in the case of nonparametric approach, using the Bonferroni correction.

To view the behaviour of variables in the time and frequency domains, boxplots were used. Through them, it was possible to graphically summarize the distribution of each analysed group, as well as compare the typical behaviour (central trend) and the variability of the variables for each scenario.

5

Results

"And above all, watch with glittering eyes the whole world around you because the greatest secrets are always hidden in the most unlikely places..."

— Roald Dahl, *The Minpins*

This chapter presents the results of the evaluation of two features, namely MAV and ApEn, in the time domain in order to comprehend the effect of various stimulation patterns on involuntary activity (e.g., postural tremor). The analysis takes into account the placement of inertial sensors on the hand and forearm as well as the sensor axes. In addition, a complementary evaluation in the frequency domain is presented. The power spectrum density (PSD) of the signals is analysed qualitatively so that the behaviour of the PSD for particular individuals and the entire experimental group can be visualised. A quantitative evaluation is obtained through the estimation of two PSD parameters, peak power and its corresponding frequency. On the basis of these variables, it was possible to compare the effects of various stimulation patterns on the PSD.

5.1 Time Domain Analysis

Figures 5.1 and 5.2 depict the boxplots for each variable (MAV and ApEn) and one of the regions of activity (baseline, pre-stimulus, stimulus and post-stimulus) taking into account the distinct sensor axes (X, Y, and Z), stimulation patterns (50 Hz, 250 Hz, linear increase, and random) and sensor placement (hand and forearm).

In general, regardless of the positioning of the IMU and the sensor axis, the amplitude of involuntary activity without stimulation was greater than the amplitude of the pre-stimulus region for all stimulation patterns. This could be caused by the fact that the duration of these activity regions were different, involuntary activity without stimulation was recorded for 240 seconds, while the pre-stimulus region of involuntary activity with some stimulus was recorded for 60 seconds, as illustrated in Figure 4.2.

The amplitude of involuntary activity of the upper limb in the post-stimulus was greater than the amplitude in the pre-stimulus, for the stimulation patterns of 50 Hz, increasing linear frequency and random frequency. In other words, this suggests that

tremor of the hand and forearm during posture maintenance was intensified after receiving these stimulation patterns.

When stimulated at 250 Hz, the hand and forearm had different responses to stimulation. This stimulus caused a reduction in the amplitude in the hand and an increase in the forearm, with the exception of the Y axis of the sensor in the forearm, which is the axis that best describes the involuntary movements of most participants. Despite the reduction of tremor around the Y axis, this indicates that upper limb segments can respond to the same stimuli independently, and in an opposite direction. In addition, this suggests that tremor of each segment is independent from tremor of other upper limb segments.

The amplitude of involuntary activity of the upper limb in the stimulation period was greater than the amplitude in the pre-stimulus, for the stimulation patterns of 50 Hz, increasing linear frequency and random frequency. This increase during stimulation can be explained by the tremor superimposing on the mechanical input, as if their oscillations experienced a constructive interference, in which resulting oscillation corresponds to the algebraic sum of each oscillation.

Similarly, when the forearm was stimulated at 250 Hz, the amplitude of involuntary activity in the stimulation period was greater than the amplitude in the pre-stimulus, with the exception of the Y axis of the sensor in the forearm. However, an opposite behaviour was observed when the hand was stimulated at 250 Hz, which caused a reduction in the amplitude.

In terms of regularity, it was observed that there was a random behaviour of entropy, when compared the baseline with the pre-stimulus period of stimulation patterns. Although the duration of these activity regions were different (Figure 4.2), this reinforces the fact that the tremor is involuntary and its dynamics changes over time.

The entropy of involuntary activity of the hand and forearm in the pre-stimulus was lower than the entropy in the post-stimulus to 250 Hz. It suggests that this stimulus was able to alter the tremor dynamics, making it more complex, that is, unpredictable over time, although it caused a reduction in amplitude, especially in the hand.

Increasing the stimulation frequency also caused a similar effect for hand, i.e. the entropy of involuntary activity in the pre-stimulus was lower than the entropy in the post-stimulus, with the exception of the Y axis. For the other stimuli, a variable behaviour of the entropy difference between the pre- and post-stimulus was observed.

The comparison of regions of activity (baseline, pre-stimulus, stimulus and post-stimulus) was initially performed by one-way ANOVA, according to the model in Equation 4.10. However, the distribution of the residues of the model was not normal (Kolmogorov-Smirnov test) and variances across groups were not homogeneous (Levene's test), suggesting that this method was not suitable for comparing the variables.

Thus, the Kruskal-Wallis rank-sum test was employed as a non-parametric alterna-

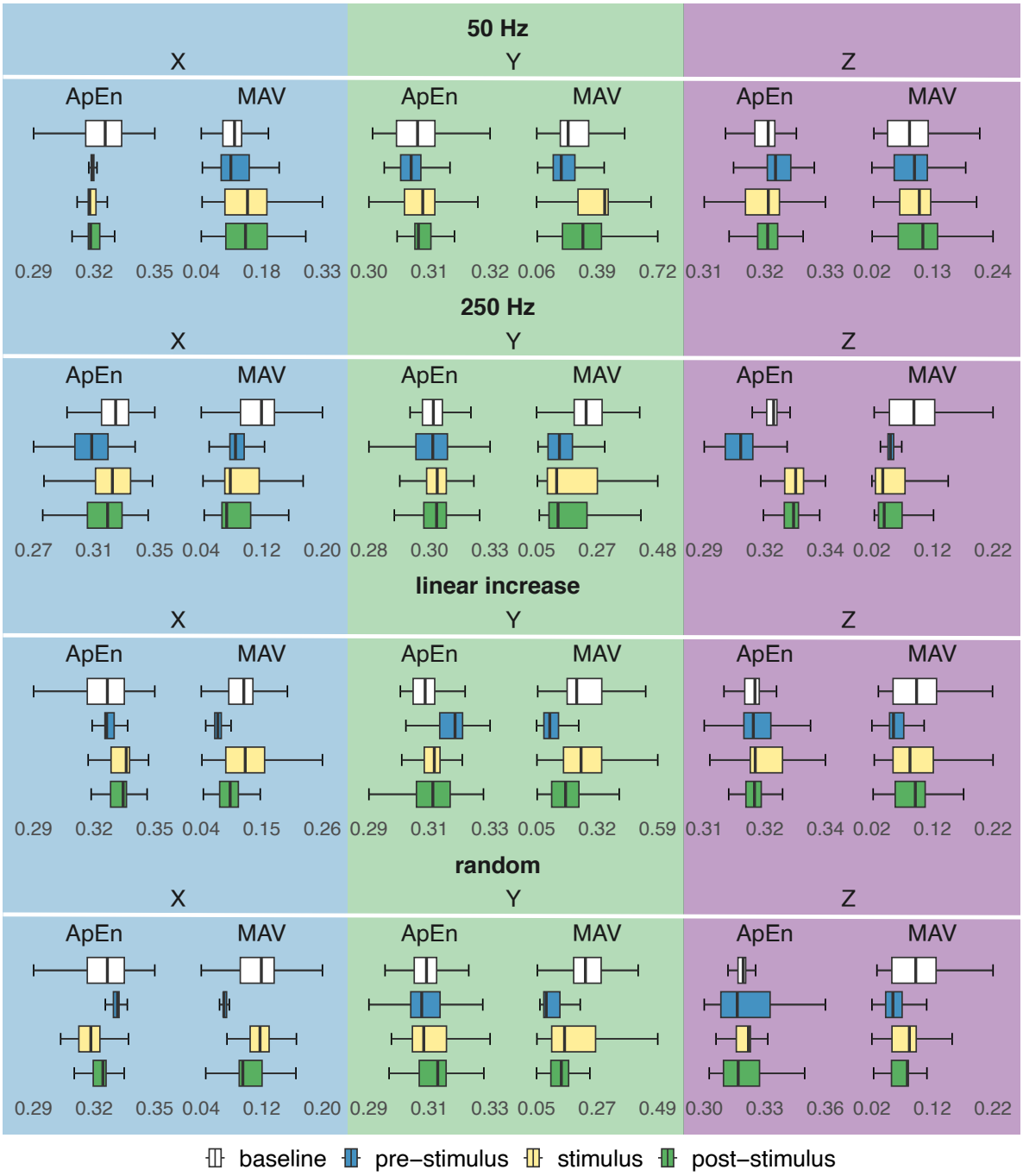


Figure 5.1 – Boxplots comparing the amplitude and regularity of the involuntary activity in the absence (baseline) and presence of the vibrotactile stimulation in the pre-stimulus, stimulus and post-stimulus regions for all stimulation patterns (the frequency of 50 Hz, 250 Hz, increasing linear and random) and each axis (X, Y and Z) from the sensor positioned at the hand. In the boxplots, the central horizontal line indicates the median, box boundaries indicate the first and third quartiles, and the whiskers indicate the minimum and maximum values. The extreme values have been removed from the analysis.

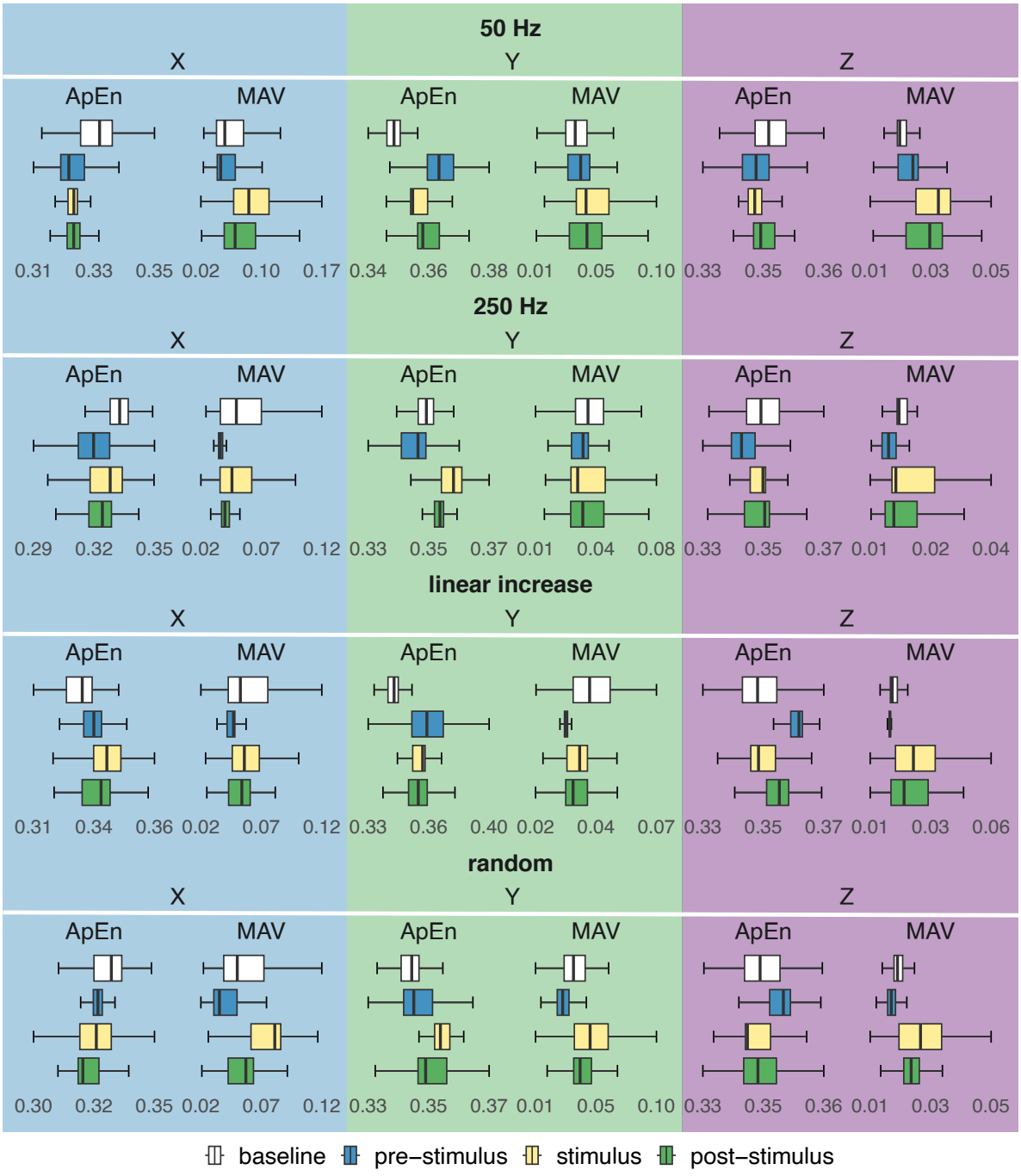


Figure 5.2 – Boxplots comparing the amplitude and regularity of the involuntary activity in the absence (baseline) and presence of the vibrotactile stimulation in the pre-stimulus, stimulus and post-stimulus regions for all stimulation patterns (the frequency of 50 Hz, 250 Hz, increasing linear and random) and each axis (X, Y and Z) from the sensor positioned at the forearm. In the boxplots, the central horizontal line indicates the median, box boundaries indicate the first and third quartiles, and the whiskers indicate the minimum and maximum values. The extreme values have been removed from the analysis.

tive to ANOVA. This test was carried out to compare the amplitude and regularity of involuntary activity in the absence of stimulation and in the pre-stimulus, stimulus and post-stimulus regions for each stimulation pattern. Significant differences ($p < 0.05$) in amplitude and regularity of involuntary hand and forearm activity were found between activity regions (baseline, pre-stimulus, stimulus and post-stimulus), as summarized in Table 5.1.

Table 5.1 – Summary of the Kruskal-Wallis test and the power associated with this statistic test for each stimulus, variable, sensor placement and axis. The magnitude of the effect size is reported as proposed by Jacob Cohen, where $\eta^2_H \in [0.01, 0.06[$ corresponds to a small effect, $\eta^2_H \in [0.06, 0.14[$ corresponds to a moderate effect, and $\eta^2_H \in [0.14, 1.0]$ corresponds to a large effect.

Stimulus	Variable	IMU	Axis	Kruskal test	η^2_H	Magnitude
50 Hz	ApEn	1	X	H(3) = 1480.471, p-value < 0.05	0.041	small
50 Hz	ApEn	1	Y	H(3) = 1819.057, p-value < 0.05	0.048	small
50 Hz	ApEn	1	Z	H(3) = 2432.388, p-value < 0.05	0.066	moderate
50 Hz	ApEn	2	X	H(3) = 9512.433, p-value < 0.05	0.258	large
50 Hz	ApEn	2	Y	H(3) = 17202.925, p-value < 0.05	0.451	large
50 Hz	ApEn	2	Z	H(3) = 3945.701, p-value < 0.05	0.102	moderate
50 Hz	MAV	1	X	H(3) = 2897.192, p-value < 0.05	0.072	moderate
50 Hz	MAV	1	Y	H(3) = 7242.740, p-value < 0.05	0.182	large
50 Hz	MAV	1	Z	H(3) = 626.964, p-value < 0.05	0.016	small
50 Hz	MAV	2	X	H(3) = 7436.396, p-value < 0.05	0.189	large
50 Hz	MAV	2	Y	H(3) = 2853.428, p-value < 0.05	0.071	moderate
50 Hz	MAV	2	Z	H(3) = 10077.743, p-value < 0.05	0.264	large
250 Hz	ApEn	1	X	H(3) = 7101.622,	0.178	large

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Table 5.1 – Continued from previous page.

Stimulus	Variable	IMU	Axis	Kruskal test	η_H^2	Magnitude
				p-value < 0.05		
250 Hz	ApEn	1	Y	H(3) = 472.060,	0.012	small
				p-value < 0.05		
250 Hz	ApEn	1	Z	H(3) = 24878.352,	0.650	large
				p-value < 0.05		
250 Hz	ApEn	2	X	H(3) = 7859.278,	0.199	large
				p-value < 0.05		
250 Hz	ApEn	2	Y	H(3) = 21052.384,	0.560	large
				p-value < 0.05		
250 Hz	ApEn	2	Z	H(3) = 4902.456,	0.128	moderate
				p-value < 0.05		
250 Hz	MAV	1	X	H(3) = 3979.793,	0.101	moderate
				p-value < 0.05		
250 Hz	MAV	1	Y	H(3) = 5341.980,	0.137	moderate
				p-value < 0.05		
250 Hz	MAV	1	Z	H(3) = 6586.893,	0.169	large
				p-value < 0.05		
250 Hz	MAV	2	X	H(3) = 5560.956,	0.155	large
				p-value < 0.05		
250 Hz	MAV	2	Y	H(3) = 1318.388,	0.033	small
				p-value < 0.05		
250 Hz	MAV	2	Z	H(3) = 4668.845,	0.125	moderate
				p-value < 0.05		
linear increase	ApEn	1	X	H(3) = 6880.632,	0.175	large
				p-value < 0.05		
linear increase	ApEn	1	Y	H(3) = 9975.713,	0.251	large
				p-value < 0.05		
linear increase	ApEn	1	Z	H(3) = 833.389,	0.022	small
				p-value < 0.05		
linear increase	ApEn	2	X	H(3) = 8658.890,	0.220	large
				p-value < 0.05		
linear increase	ApEn	2	Y	H(3) = 17110.766,	0.443	large
				p-value < 0.05		
linear increase	ApEn	2	Z	H(3) = 17347.183,	0.447	large
				p-value < 0.05		
linear increase	MAV	1	X	H(3) = 12845.085,	0.332	large

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Table 5.1 – Continued from previous page.

Stimulus	Variable	IMU	Axis	Kruskal test	η_H^2	Magnitude
				p-value < 0.05		
linear increase	MAV	1	Y	H(3) = 12179.875, p-value < 0.05	0.306	large
linear increase	MAV	1	Z	H(3) = 4226.246, p-value < 0.05	0.106	moderate
linear increase	MAV	2	X	H(3) = 4495.789, p-value < 0.05	0.116	moderate
linear increase	MAV	2	Y	H(3) = 10488.825, p-value < 0.05	0.301	large
linear increase	MAV	2	Z	H(3) = 9827.355, p-value < 0.05	0.267	large
random	ApEn	1	X	H(3) = 11495.578, p-value < 0.05	0.295	large
random	ApEn	1	Y	H(3) = 823.962, p-value < 0.05	0.021	small
random	ApEn	1	Z	H(3) = 462.826, p-value < 0.05	0.012	small
random	ApEn	2	X	H(3) = 6425.188, p-value < 0.05	0.168	large
random	ApEn	2	Y	H(3) = 13669.272, p-value < 0.05	0.366	large
random	ApEn	2	Z	H(3) = 7040.579, p-value < 0.05	0.183	large
random	MAV	1	X	H(3) = 13113.310, p-value < 0.05	0.366	large
random	MAV	1	Y	H(3) = 11720.027, p-value < 0.05	0.305	large
random	MAV	1	Z	H(3) = 5172.669, p-value < 0.05	0.133	moderate
random	MAV	2	X	H(3) = 11894.078, p-value < 0.05	0.301	large
random	MAV	2	Y	H(3) = 11286.655, p-value < 0.05	0.287	large
random	MAV	2	Z	H(3) = 13301.882, p-value < 0.05	0.358	large

The effect size (η_H^2) associated with the Kruskal-Wallis test confirmed the significance

of the statistical test results, as the effect size was greater than 0.01. Although the effect size in some comparison scenarios is small, the magnitude of the difference between groups is statistically significant ($\eta_H^2 > 0.01$), as shown in Table 5.1.

The post-hoc Wilcoxon test with Bonferroni correction was applied to evaluated multiple pairwise comparisons. Pairwise comparisons between regions of activity revealed that most of the pairwise comparisons were significantly different ($p < 0.05$) for the majority of scenarios examined, except for the pairwise comparison shown in Table 5.2.

Table 5.2 – Summary of the Wilcoxon test with Bonferroni correction for the pairwise comparisons that were not significantly different. In the table, the adjusted p-value is shown.

Stimulus	Variable	IMU	Axis	Pair	Wilcoxon test
50 Hz	ApEn	1	Z	baseline–stimulus	W = 46524224, p-value = 0.061
50 Hz	MAV	1	Z	baseline–pre-stimulus	W = 50880056, p-value = 0.181
250 Hz	ApEn	1	Y	stimulus–post-stimulus	W = 48729552, p-value = 1.00
250 Hz	MAV	2	Z	baseline–stimulus	W = 44202356, p-value = 0.158
linear increase	ApEn	1	X	baseline–pre-stimulus	W = 46982996, p-value = 0.178
linear increase	MAV	1	Y	baseline–stimulus	W = 49646356, p-value = 1.00
linear increase	ApEn	1	Z	baseline–post-stimulus	W = 43849136, p-value = 1.00
random	ApEn	1	Z	baseline–pre-stimulus	W = 47992388, p-value = 0.056

5.2 Spectral Analysis

A spectral analysis of tremor was performed to characterise postural tremor and to determine whether different stimulation frequency patterns could alter tremor characteristics such as power and frequency.

5.2.1 Qualitative Analysis of Postural Tremor

Power spectral density of a signal describes the power distribution as a function of frequency. In other words, it provides the power variance per unit bandwidth and shows the amplitudes and frequencies of each component of the signal in the frequency domain. Therefore, PSD is a highly effective method for describing the involuntary oscillatory

movement. Through visual analysis of the spectra, it was possible to determine for each participant the frequency bands with the highest power.

Figures 5.3, 5.4 and 5.5 provide an overview of the spectral analysis for three participants (Individuals 1, 7 and 17). Each figure depicts the power spectral densities of the angular velocities of the hand and forearm for the participants during posture maintenance for both the trial without vibrotactile stimulation and the trial with vibrotactile stimulation. In addition, the figures highlight the spectral behaviour of the frequency bands adjacent to the peak frequency.

In the absence of stimulation (panel *baseline* of Figure 5.3), the tremor spectra of Individual 1 exhibited a predominance of three frequency bands that resembled a pattern of side-bands, but of asymmetric amplitudes. The highest power was concentrated at 5–6 Hz for the hand (Y axis) and forearm (X axis). Although the components of the side-bands have lower power, the spectra contained peaks at 2–4 Hz for the lower side-band and at 7–9 and 10–12 Hz for the upper side-band.

Individual 1 experienced a decrease in the maximum power of involuntary activity after receiving mechanical stimulation on the upper limb for all patterns of stimulus frequency. This reduction in power suggests a decrease in the tremor amplitude of both the hand and forearm when the upper limb was stimulated while maintaining its posture. In other words, the vibrotactile stimulation was able to cause a considerable reduction in postural tremor for this participant.

For the hand, the stimulation pattern with the random frequency caused the greatest power reduction (approximately 91% reduction of the maximum power), whereas the stimulation pattern with the constant frequency of 250 Hz resulted in the lowest power reduction (approximately 52% reduction of the maximum power), as shown in panel *G1* of Figure 5.3. On the other hand, for the involuntary forearm activity, the stimulation with a constant frequency of 50 Hz resulted in the greatest power reduction (approximately 86% reduction of the maximum power), whereas the stimulation with a random frequency caused the lowest power reduction (approximately 33% reduction of the maximum power), as shown in panel *G2* of Figure 5.3.

Similarly, the power at the side-bands decreased with the vibrotactile stimulation. For the hand and forearm, there was a power reduction for the low and high frequency components. However, the involuntary activity of the upper limb segments presented a distinct response to mechanical stimulation for each band. For the lower side-band, the different stimulus patterns led to a greater reduction in the power of the low frequency components of the hand (at least 74% reduction in power). For the upper side-band, the different stimulus patterns led to a greater reduction in the power of the high frequency components of the forearm (at least 48% reduction in power).

In addition, certain stimulation patterns attenuated the frequencies in a specific range of the side-bands. The stimulation patterns of 50 Hz, increasing linear frequency and

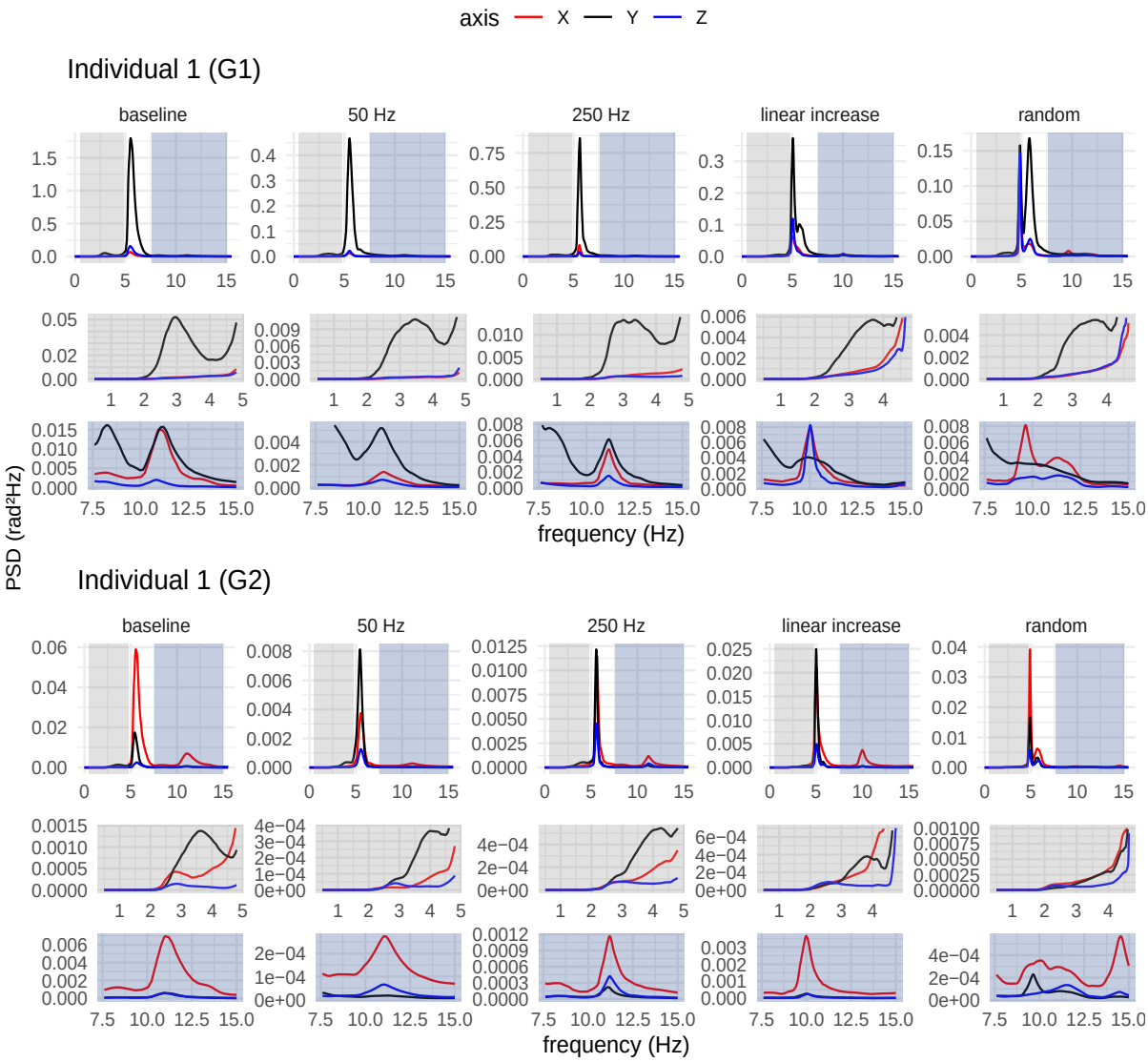


Figure 5.3 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 1** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

random frequency attenuated components at 7–9 Hz of the hand involuntary activity. On the other hand, the random frequency stimulus attenuated components at 3–5 Hz of the forearm involuntary activity. This indicates that some stimulation patterns suppressed components in certain frequency bands for Individual 1.

In contrast to Individual 1, the tremor spectra of Individual 7 exhibited a predominance of only two frequency bands during upper limb posture in the absence of stimulation (panel *baseline* of Figure 5.4). There were no oscillations of low frequency in the side-band spectra. The highest power was concentrated at 3–5 Hz for the upper limb segments (X axis). In addition, the spectra contained a peak of lower magnitude at 7–9 Hz.

Individual 7 exhibited a decrease in the maximum power of involuntary activity when

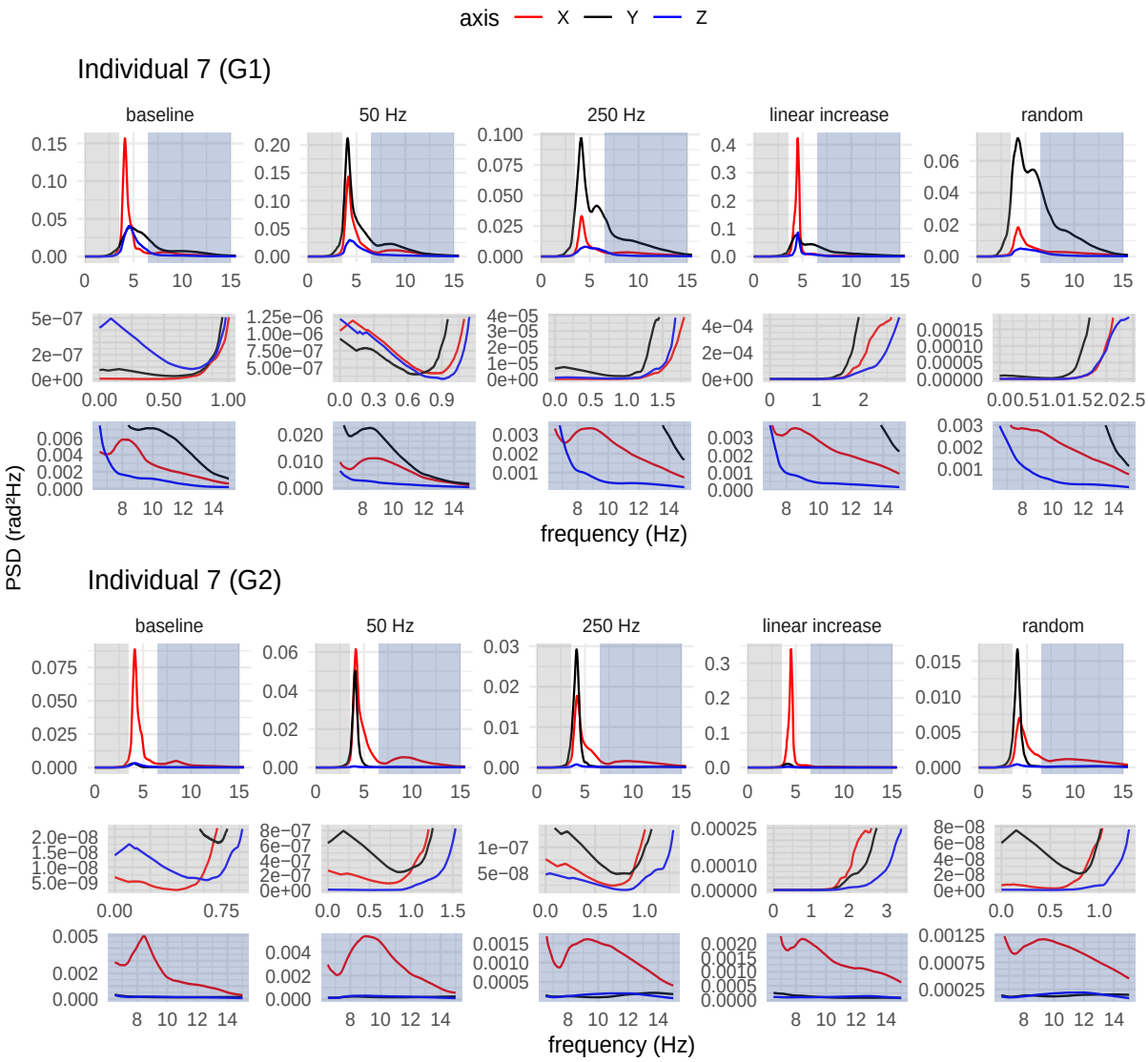


Figure 5.4 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 7** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

the upper limb received stimuli with a frequency of 250 Hz (approximately 38% and 67% reduction of the maximum power of the hand and forearm, respectively) and random frequency (approximately 53% and 81% reduction of the maximum power of the hand and forearm, respectively), as shown in panels *G1* and *G2* of Figure 5.4.

This reduction was not observed for the stimulus with increasing stimulation frequency. Indeed, the response to this stimulation pattern was opposite. When there was a linear increase in the frequency of stimulation of the upper limb segments, the maximum power more than doubled (an increase of about 169%) for the hand and tripled for the forearm (an increase of about 283%), as seen in panels *G1* and *G2* of Figure 5.4.

On the other hand, the hand and forearm of Individual 7 showed a different response

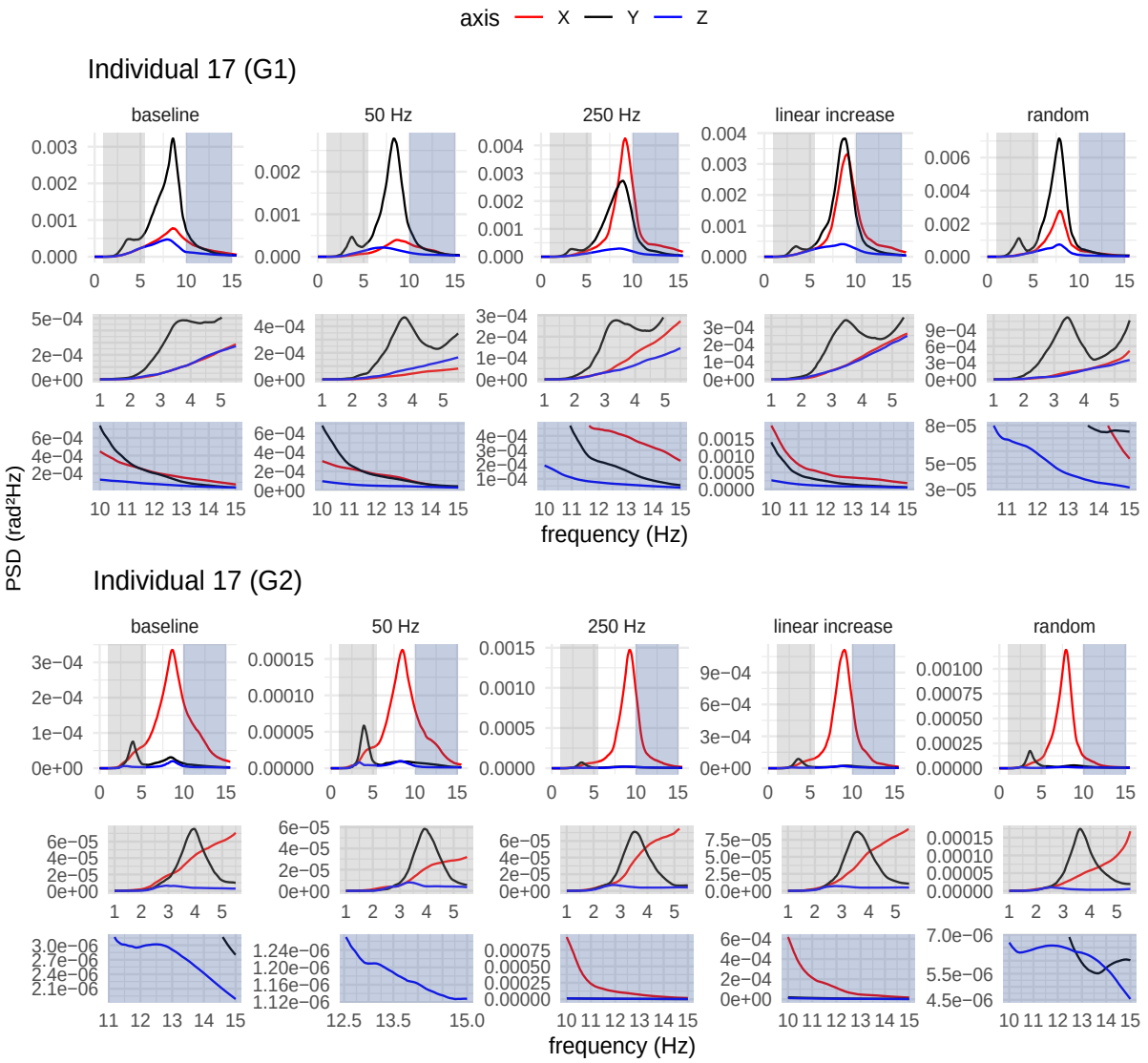


Figure 5.5 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 17** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

to the 50 Hz stimulus. For the hand, the stimulus at 50 Hz increased the maximum power (approximately 35% increase in power), as shown in panel *G1* of Figure 5.4. However, this stimulus on the forearm reduced the maximum power (approximately 31% reduction of the maximum power), as shown in panel *G2* of Figure 5.4.

Regardless of whether the maximum power increased or decreased, the effect of the different stimuli was more pronounced on the forearm than on the hand. This indicates that the upper limb segments of this participant respond differently to the same stimulus. Furthermore, it suggests that while a given stimulus can significantly reduce postural forearm tremor, it will only have a moderate effect on hand tremor.

In the hand, stimulation patterns with a constant frequency of 250 Hz, increasing

linear frequency, and random frequency shifted the upper side-band peak to a frequency range close to the peak frequency (3–7 Hz). As a result, the magnitude of the high frequency components was reduced. The magnitude of the high frequency components was 52 percent lower for the random frequency stimulus than it was without stimulation. For the 250 Hz and increasing linear frequency stimuli, the magnitude of power was 42 and 39 percent lower, respectively.

However, when the hand was stimulated at 50 Hz, there was no shift of the upper side-band peak to a frequency range close to the peak frequency. This stimulation pattern increased the power of the high frequency components, more than tripling in magnitude (approximately 217% increase in power). This suggests that this stimulation pattern can be linked to mechanisms that cause more pronounced physiological tremor (i.e., the prominent 8–12 Hz tremor) in the hand.

In the forearm, stimulation patterns with a constant frequency of 250 Hz, increasing linear frequency, and random frequency also reduced the power of the high frequency components (at least 56% reduction in power). Although the 50 Hz stimulus increased the power of the high frequency components, this stimulus on the forearm was not as pronounced as it was in the hand, resulting in only a seven percent increase in the power of the high frequency components.

Similar to individual 7, the tremor spectra of Individual 17 also exhibited two predominant frequency bands when the upper limb maintained posture in the absence of vibrotactile stimulation, but with the presence of a lower side-band in relation to the peak rather than an upper side-band (panel baseline of Figure 5.5). In the spectra, the highest power was concentrated at 6–11 Hz, which corresponds to a higher bandwidth compared to the other individuals. In addition, the spectra contained peaks of lower magnitude at 3–5 Hz.

For Individual 17, the upper limb stimulation resulted in two changes in spectral characteristics, both in terms of power and frequency. In terms of frequency, the stimuli with a constant frequency of 250 Hz and a random frequency shifted the peak frequency at least 0.5 Hz. For the hand and forearm, the stimulus at 250 Hz resulted in a peak frequency shift to higher frequencies, while the random frequency stimulation resulted in a peak frequency shift to lower frequencies, as shown in Figure 5.5.

In terms of power, Individual 17 showed a decrease in the maximum power when the upper limb was stimulated at 50 Hz. In this case, the stimulation effect was more pronounced for the forearm than on the hand. When the hand was stimulated at 50 Hz, the reduction in power of involuntary activity was approximately 14 percent. On the other hand, this stimulus in the forearm resulted in a reduction in the maximum power of approximately 52 percent.

In contrast, the stimuli with constant frequency of 250 Hz, increasing linear frequency and random frequency produced an increase in the maximum power of involuntary activity

of Individual 17. But, the magnitude of this increase distinguished between the hand and forearm for these three stimulation patterns. For both stimuli, the vibrotactile stimulation had a stronger effect on the forearm than on the hand.

When the hand was stimulated with increasing linear frequency, there was a 19 percent increase in the maximum power, while for the forearm, the amplitude increased by more than threefold (an increase of about 232% of the maximum power). Similarly, stimulation with random frequency increased the maximum power of involuntary activity in the hand and forearm by more than doubling (an increase of about 122%) and tripling (an increase of about 255%), respectively. Lastly, for the hand, the stimulus at 250 Hz caused a 32% increase in the power and, for the forearm, it increased by more than tripling (an increase of about 339%).

Among these three stimulation patterns, the random frequency and constant frequency 250 Hz stimuli resulted in the greatest increase in power. Indeed, these stimuli produced a large increase in power when compared to the power of involuntary activity when the posture of forearm was maintained in the absence of vibrotactile stimulation. This indicates that these stimulation patterns caused an increase of postural tremor for this participant.

For low frequency components, the involuntary activity of the upper limb segments exhibited a distinct response to the different stimulation patterns. The random frequency stimulus was the only pattern that caused the power to increase for the low frequency components in the hand and forearm. When the limb was stimulated with this pattern, the power of the lower side-band components more than doubled (an increase of about 131%).

Although the 250 Hz stimulus increased the peak power, it reduced the power of the low frequency components. This indicates that different tremor components respond differently to stimulation. In particular, it suggests that this stimulation pattern was able to minimize secondary components but not the main component of the tremor for Individual 17. Moreover, the effect of this stimulation pattern was more pronounced in the forearm (the power was reduced by 5% in the hand and 42% in the forearm).

The reduction in the power of the low frequency components also occurred when the hand was stimulated with increasing linear frequency (30% reduction in power) and the forearm was stimulated at 50 Hz (22% reduction in power). For the hand, the stimulus at 50 Hz had no significant effect. On the other hand, the increase in the stimulation frequency in the forearm resulted in the increase of the power (an increase of about 15%).

In general, the involuntary movement of the hand and forearm was caused by the superposition of multiple components with different frequencies and amplitudes for each individual during posture maintenance in the absence of vibrotactile stimulation. For the majority of the participants, spectral distributions were bimodal or multimodal, with distinct peaks in various frequency bands. In Appendix A, Figures A.1 to A.18 show the power spectral densities of each individual for all experimental scenarios.

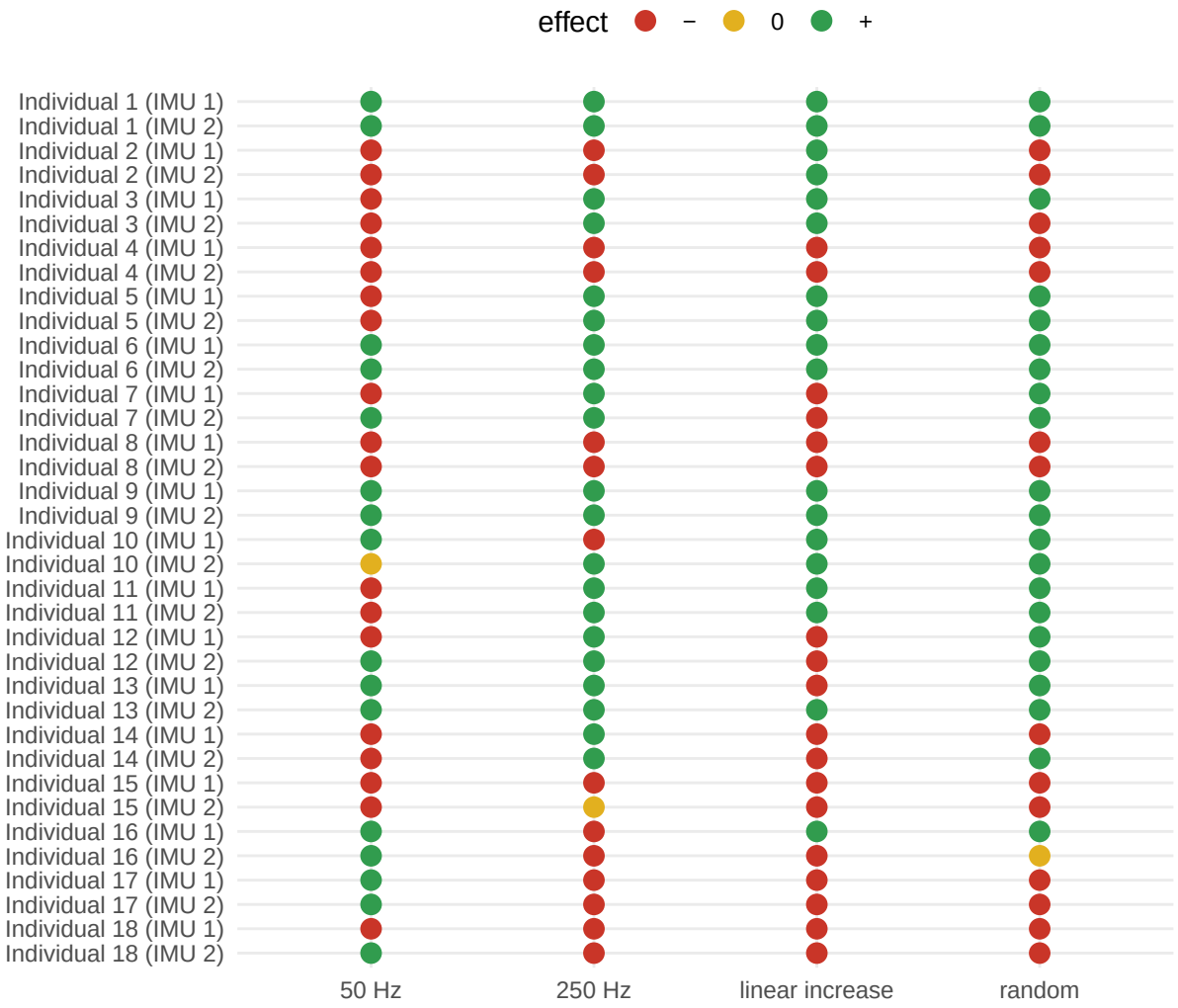


Figure 5.6 – Effect of the different stimulation patterns on the involuntary activity of individuals with ET. In this representation, each row corresponds to an individual (for both placements of the IMUs) and each column corresponds one type of the vibrotactile stimulus. The colours represent changes in the spectral magnitude of the tremor during each upper limb stimulation. Red means the stimulation pattern caused an increase in maximum power (denoted by −, i.e., a negative effect), yellow indicates that the stimulation pattern had no noticeable effect (denoted by 0, i.e., a neutral effect), and green means that the stimulation pattern caused a reduction in maximum power (denoted by +, i.e., a positive effect).

The spectra with multimodal distributions exhibited three or more predominant peaks, but of unequal magnitudes, e.g., the spectrum of Individual 1 (Figure 5.3). In these cases, the spectra contained a major peak (i.e., a global maximum) and minor peaks (i.e., local maxima) in the bands adjacent to the peak frequency. For the majority of participants, the peak frequencies of the involuntary activity of the upper limb ranged from 4 Hz to about 9 Hz. Despite the low levels of magnitude on the individual spectra, the lower side-band exhibited peaks at 1–6 Hz and the upper side-band had peaks at 7–15 Hz.

Similarly, the spectra with bimodal distributions had two predominant peaks of differ-

ent magnitudes, e.g., the spectra of Individuals 7 and 17 (Figures 5.4 and 5.5). All spectra with this distribution had a major and minor peak. Nevertheless, for some spectra, the minor peak was present on the lower frequency side of the dominant peak (1–5 Hz), as seen in the spectrum of Individual 17 (Figure 5.5). For others, the minor peak was present on the higher frequency side of the dominant peak (7–15 Hz), as seen in the spectrum of Individual 7 (Figure 5.4).

For some spectra with bimodal distribution, the frequency of the involuntary activity ranged between 3 and 5 Hz. In these cases, the spectra exhibited a minor peak in the upper side-band (7–15 Hz). For other spectra with bimodal distribution, there was a dominant peak at around 7–9 Hz, but the spectra contained a minor peak at 1–5 Hz (i.e., at lower frequencies).

Regardless of the type of spectral distribution, the involuntary activity of all participants showed a 8-12 Hz component. Tremors in this frequency band are most commonly associated with natural physiological processes, the so-called physiological tremor. Thus, this suggests the presence of physiological tremor to varying degrees during posture maintenance. Furthermore, it implies that this component may be one of the components that contribute to the severity of involuntary activity during limb posture.

The tremor can have multiple components in the same limb and the multiple peaks in the spectra suggest the coexistence of tremor components in distinct frequency bands for the individual with ET. In this sense, a vibratory input can modify one of these components to a greater or lesser extent in different ways, as seen in the spectra of Individuals 1, 7, and 17 (Figures 5.3, 5.4 and 5.5).

The effect of vibrotactile stimulation on the involuntary activity of upper limb differed between individuals, as summarized in Figure 5.6. For some participants, the power of the involuntary activity decreased with the different patterns of vibrotactile stimulation. For others, the response was the opposite, leading to an increase in power. Furthermore, only a few individuals did not show a pronounced change in the magnitude of the involuntary activity during stimulation of the upper limb (less than 5% difference).

Among the participants, two individuals (Individuals 4 and 8) experienced an increase in the maximum power of the involuntary activity for all stimulation patterns. On the other hand, there were three individuals (Individuals 1, 6 and 9) that all stimulation patterns provided a reduction in the maximum power of the involuntary hand and forearm activity, as shown in Figure 5.6.

For many individuals, the stimuli with a constant frequency of 250 Hz and random frequency played an important role as a short-term tremor suppressors. More than half of the participants presented a decrease in the maximum power when the hand and forearm were stimulated with these frequency patterns, as shown in Figure 5.7. On the other hand, the stimulus at 50 Hz was the stimulation pattern that most induced the increase in power, as shown in Figure 5.7. The increased power when the limb is stimulated at 50

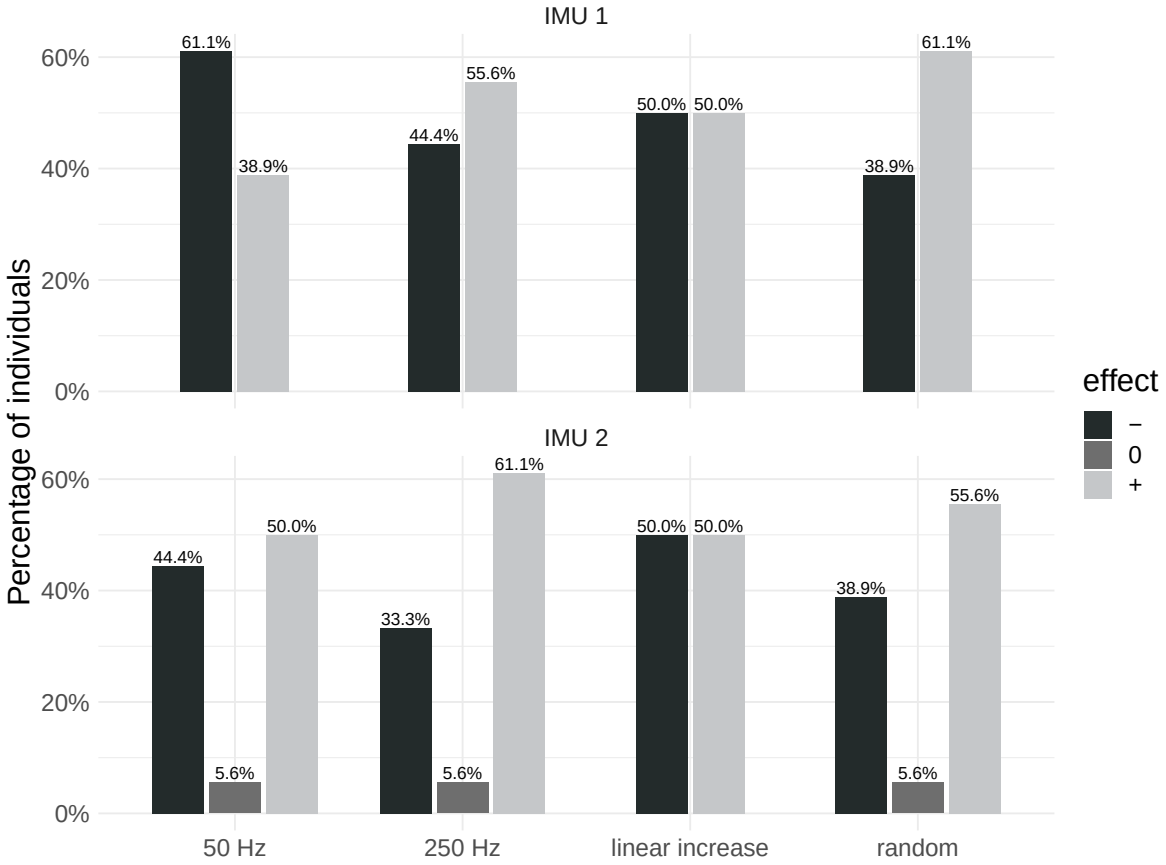


Figure 5.7 – Grouped barplots comparing the percentage of individuals whose the involuntary hand (IMU 1) and forearm (IMU 2) activity presented or did not present a response to different stimulation patterns during posture maintenance. In the barplots, each rectangular bar represents the proportion of individuals who showed an increase in the maximum power (denoted by −, i.e., a negative effect), a decrease in power (denoted by +, i.e., a positive effect), or no noticeable effect (denoted by 0, i.e., a neutral effect) when the upper limb was stimulated for each stimulation pattern (stimulation at 50 Hz, 250 Hz, increasing linear frequency, and random frequency).

Hz suggests that this stimulus may interfere with some processes that triggers postural tremor for some individuals with ET.

5.2.2 Quantitative Analysis of Postural Tremor

The boxplots of the median peak frequency and peak power are shown in Figures 5.8 and 5.9, respectively, for each axis and sensor position. These statistics were estimated using Bootstrap. Based on the boxplots, there was a shift in the powers and frequencies for different stimulation patterns when compared to the condition without vibrotactile stimulus.

When there was no stimulation, the peak power was higher on the hand than on the forearm, regardless of sensor axis. Although involuntary movement is a three-dimensional complex phenomenon, the sensor axes Y (suggesting a tremor characterised by flexion

and extension movements) and X (suggesting a tremor characterised by pronation and supination movements) on the hand (IMU 1) and forearm (IMU 2) were more sensitive to detect it. These two axes resulted in a higher power peak and greater variability.

The 250 Hz and random stimulation patterns reduced the power for most axes in the hand and forearm, except for the Y axis, which was positioned at the forearm. The 50 Hz stimulation pattern increased the power of involuntary activity on all axes except the Z axis of the IMU at hand.

The peak frequency evaluation revealed that, for the hand, there was usually a shift of the peak frequency to lower frequencies, whereas for the forearm, the effect was generally the opposite, with a shift of the peak frequency to higher frequencies. Furthermore, a common response pattern for the peak frequency behaviour was observed in the sense that there was an alternate response in the frequency as a function of the stimulus pattern. For example, a decrease from the baseline to 50 Hz, an increase from 50 Hz to 250 Hz, a decrease from 250 Hz to the linear increasing frequency stimulus, and finally an increase from linear to random stimulus.

Interestingly, the same alternating pattern was observed for the power, but in the opposite direction when compared to the frequency. For example, there was an increase from the baseline to 50 Hz, a decrease from 50 Hz to 250 Hz, an increase from 250 Hz to the linear increasing frequency stimulus, and a decrease from linear to random. In summary, when the frequency was shifted to lower frequencies, the power increased, and when the frequency was shifted to higher frequencies, the power decreased.

To verify the existence of a statistically significant difference between the peak powers (Figure 5.8) and peak frequencies (Figure 5.9) of involuntary activity with and without vibrotactile stimulation during posture maintenance, a parametric approach was initially employed through one-way ANOVA, according to the model in Equation 4.11. However, homogeneity of variances and normality of residuals were not satisfied in any of the cases, indicating that this type of method was not suitable for the comparisons.

Thus, the non-parametric Kruskal-Wallis rank-sum test was employed to verify differences between the compared groups in both cases. For the peak frequencies and peak powers, significant differences were found between the scenarios with and without stimulation for all axes and sensor positions (p-value < 0.05), as summarized in Table 5.3. It suggests that at least two of the groups had statistically significant differences in each case.

Furthermore, these differences were corroborated by the statistical power analysis, as shown in Table 5.3. The effect size (η_H^2) associated with the Kruskal-Wallis test was large for both hand and forearm peak powers, except for the powers of involuntary hand activity (IMU 1) on the Z axis, which had a moderate effect size. For the peak frequencies, the effect size was generally moderate for the hand and large for the forearm.

In practice, this means that a percentage of the variance of the dependent variable can

Table 5.3 – Summary of the Kruskal-Wallis test and the power associated with this statistic test for each axis and sensor placement. The magnitude of the effect size is reported as proposed by Jacob Cohen, where $\eta_H^2 \in [0.01, 0.06[$ corresponds to a small effect, $\eta_H^2 \in [0.06, 0.14[$ corresponds to a moderate effect, and $\eta_H^2 \in [0.14, 1.0]$ corresponds to a large effect.

Variable	IMU	Axis	Kruskal-Wallis test	p-value	η_H^2	Magnitude
peak frequency	1	X	H(4) = 5864.108	> 0.05	0.126	moderate
peak frequency	1	Y	H(4) = 7618.865	> 0.05	0.177	large
peak frequency	1	Z	H(4) = 5972.645	> 0.05	0.129	moderate
peak frequency	2	X	H(4) = 13801.219	> 0.05	0.300	large
peak frequency	2	Y	H(4) = 10307.400	> 0.05	0.213	large
peak frequency	2	Z	H(4) = 8182.998	> 0.05	0.174	large
peak power	1	X	H(4) = 10502.659	> 0.05	0.229	large
peak power	1	Y	H(4) = 13740.416	> 0.05	0.300	large
peak power	1	Z	H(4) = 5085.189	> 0.05	0.107	moderate
peak power	2	X	H(4) = 10731.292	> 0.05	0.237	large
peak power	2	Y	H(4) = 14003.810	> 0.05	0.294	large
peak power	2	Z	H(4) = 16361.918	> 0.05	0.356	large

be explained by the independent variable. For instance, for the forearm postural tremor in the X axis, about 30 percent of the variance of the peak frequency can be explained by the type of stimulation scenario (i.e., no stimulation or with stimulation, considering the frequency patterns of 50 Hz, 250 Hz, increasing linear or random).

Multiple pairwise comparison between groups, given by the Wilcoxon rank-sum test with Bonferroni correction, suggested statistically significant differences between most pairs, as presented in Figures 5.8 and 5.9. When comparing peak powers, only the stimulus with increasing linear frequency and the no stimulation scenario for the X axis of the IMU positioned on the forearm did not reveal a statistically significant difference (adjusted p-value = 1.00).

In addition, the post-hoc test indicated that there are not significant differences in peak frequencies of the involuntary hand activity around the Y and Z axes between the stimulus with constant frequency of 250 Hz and the scenario without stimulation (adjusted p-value = 1.00), and the stimulus with random frequency and the scenario without stimulation (adjusted p-value = 1.00), respectively.

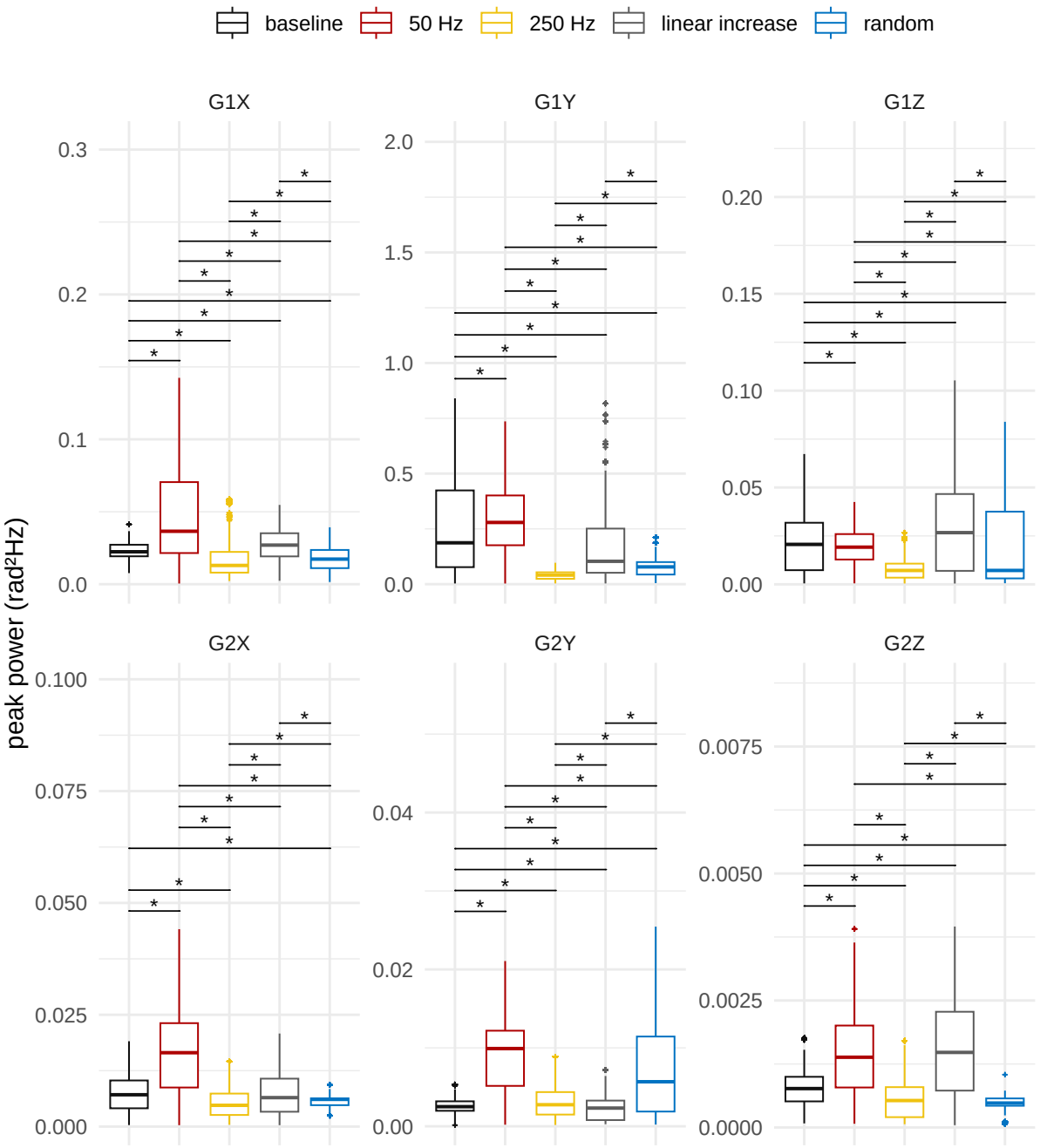


Figure 5.8 – Boxplots comparing the peak power of involuntary activity in the presence (the frequency of 50 Hz, 250 Hz, increasing linear and random) and absence (baseline) of the vibrotactile stimulation for each axis (X, Y and Z) and sensor positioning (1 corresponding to the sensor positioned on the hand and 2 corresponding to the sensor positioned on the forearm). In the boxplots, the central horizontal line indicates the median, box boundaries indicate the first and third quartiles, the whiskers indicate the minimum and maximum values, and the plus signs indicate the outliers. The extreme values have been removed from the analysis. For each axis and sensor positioning, significant pairwise comparisons between the trials with and without stimulation are denoted by an asterisk, considering the pairwise Wilcoxon rank-sum test using the Bonferroni correction to identify which groups were different.

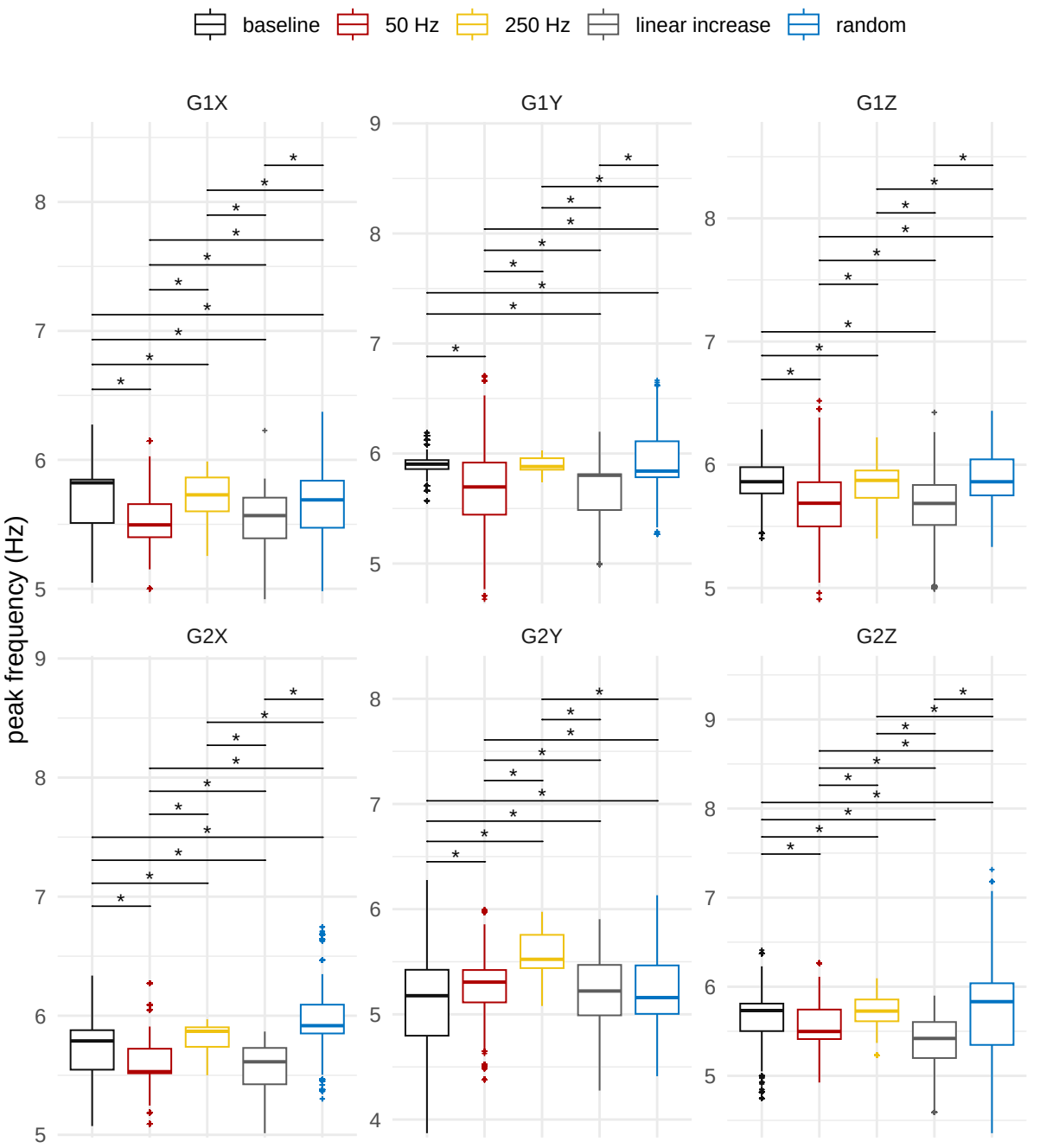


Figure 5.9 – Boxplots comparing the peak frequency of involuntary activity in the presence (the frequency of 50 Hz, 250 Hz, increasing linear and random) and absence (baseline) of the vibrotactile stimulation for each axis (X, Y and Z) and sensor positioning (1 corresponding to the sensor positioned on the hand and 2 corresponding to the sensor positioned on the forearm). In the boxplots, the central horizontal line indicates the median, box boundaries indicate the first and third quartiles, the whiskers indicate the minimum and maximum values, and the plus signs indicate the outliers. The extreme values have been removed from the analysis. For each axis and sensor positioning, significant pairwise comparisons between the trials with and without stimulation are denoted by an asterisk, considering the pairwise Wilcoxon rank-sum test using the Bonferroni correction to identify which groups were different.

6

On the Effect of the Vibrotactile Stimulation on Tremor: discussion and future directions

"Thus, the task is not so much to see what no one yet has seen, but to think what nobody yet has thought about that which everybody sees..."

— Arthur Schopenhauer

6.1 The General Effect of Vibrotactile Stimulation on the Tremor

This research investigated the effect of distinct vibrotactile stimulation patterns on the tremor of individuals with Essential Tremor. When compared to the tremor from other movement disorders, ET is a very complex condition, particularly in light of the fact that the term ET has been employed to designate a variety of tremor entities of unknown causes over the years.

Several studies have reported that it is difficult to distinguish ET from other tremor disorders (10, 42, 47, 85). This is because, depending on the progression level of ET, it can be confused with enhanced physiological tremor, Parkinson's disease and dystonia. The difficulty in diagnosing ET may be related to the lack of a complete understanding of the mechanisms underlying tremor caused by various disorders.

Furthermore, the tremor of those diseases have overlapping characteristics (21), which turns the assessment of ET a complex task since the purely clinical assessment is not able to evaluate all aspects of the condition (45) and introduces distinct levels of subjectivity in the patient's evaluation (106). In this sense, any study that seeks alternative methods to understand and characterise tremor caused by ET is critical, justifying the primary study object of this research.

The results of this study includes the understanding of the effect of distinct stimulation patterns on the tremor, the assessment of quantitative characteristics of the condition using the inertial sensors (gyroscopes), and the proposal of a sequence of signal processing steps for tremor analysis, which was implemented in *R* and made available as an *R package*, guaranteeing reproducibility of the results.

Regarding the effect of the vibrotactile stimulation on tremor, in general, it is heterogeneous, meaning that for some individuals there is an apparent reduction on tremor after stimulation and for others there may be even an increase of the tremor amplitude, independent of the type of stimulating pattern. A similar heterogeneous behaviour was observed for the tremor frequency, power and regularity.

Figures 5.1 and 5.2 depicts the overall results, considering data from all participants, reporting the behaviour of the tremor amplitude (MAV) and regularity ($ApEn$). In general, the stimulating frequency that most reduced the tremor amplitude after stimulation was 250 Hz, especially for the hand. An increase in the entropy was observed for this stimulation pattern, suggesting a change in the tremor type from a more predictable signal, resembling a sinusoidal pattern, to a nonpredictable signal.

These findings may be associated with the fact that there is maximum sensitivity in the fingertips when a vibratory stimulus at 250 Hz is applied to this region (57). In this sense, the role of Pacinian corpuscles may explain the sensitivity at this frequency. This is due to the fact that Pacinian corpuscles are mechanoreceptors sensitive to high frequency vibrations (60–400 Hz) (61). Furthermore, they are more abundant on the fingertips, which was one of the main regions stimulated in this study (Figure 4.1), compared to the glabrous skin of the forearm or palm of the hand (60).

The changes in the amplitude and regularity of the tremor may indicate a positive effect of the vibrotactile simulation on the tremor suppression. However, this effect was limited for a short period of time, for instance, approximately one minute after stimulation. This limited effect may be due to the employed experimental protocol that did not consider an increased period of analysis after stimulation, leading to pertinent questions. *How long does last the influence of vibrotactile stimulation on tremor? Is there any optimal time or time interval in which stimulation results in tremor stabilization, in terms of amplitude and regularity? Can this stimulation cause motor fluctuations after longer periods of stimulation?*

Figure 5.8 shows that in general the tremor energy reduces after simulation, particularly for the 250 Hz and random patterns. Independent of the stimulating pattern, on the hand, there was a shift in the peak frequency to lower frequencies, as seen in Figure 5.9. Conversely, on the forearm, the most predominant result was a shift in the peak frequency to higher frequencies. This may be explained by the fact that distinct body parts may respond differently to a particular stimulating pattern, as the vibration sensitive receptors are concentrated differently in the various body regions. The individualised analysis of PSD (Figures 5.3, 5.4 and 5.5) may further support the hypothesis that vibrotactile stimulation has a heterogeneous effect on the hand and forearm.

6.2 Limitations of the Experimental Protocol

Figure 4.2 depicts the experimental protocol adopted in this research. This protocol was designed with the intention to verify possible differences on the tremor pattern before, during and after stimulation, considering different stimulation patterns (95). Despite several interesting aspect of this protocol, a limiting aspect is that it limits the period of stimulation and pre and post-stimulus evaluation to fixed values, without accounting for possible variation among the participants.

For some participants the effect of the stimulus may be more acute, meaning that it can be seen just after stimulation, whereas for others this effect might appear in a longer period, meaning that based on a fixed time protocol one could not detect it (Figure 4.8). The visual analysis of the signals suggested that for some individuals there is a latency on the effect of the stimulation, further suggesting the need of customised experimental protocols that can take into account the time response of the individual.

Considering the limitations of the experimental protocol, some modifications could be implemented in future research. First, a calibration stage for the evaluation of the individual response time to the vibrotactile stimulus should be included. By using this calibration stage, it would be possible to adopt relative time periods varying from 0 to 100% allowing thus the comparison of the response of individuals independent of the pre-fixed time.

Secondly, the introduction of a random presentation of the stimulating patterns, as one type of stimulating pattern may influence the response of the other. Thirdly, the consideration of the effect of the rest time on the stimulation period. Fourth, as there is a distinct effect of the stimulating pattern of the hand and forearm, it may be necessary to include the possibility of simultaneously stimulating distinct body parts with different stimulating patterns.

Finally, a relevant aspect to observe is with regard to the tolerance of the subject to the vibrotactile stimulus, as one can have the tremor damped by a specific stimulating pattern, however the stimulus could cause pain or any other discomfort to the person. Additionally, individual responses to vibrotactile stimulation can vary, as they do for other modalities (e.g., vision, hearing, and touch) (64, 69). Therefore, the same intensity of stimulation may not be equally effective for everyone.

6.3 On the Signal Processing Stages

The signal processing stages proposed (Figure 4.3) in this research can be applied to the analysis of any type of tremor and, more importantly, it can deal with the noise produced by the stimulus, by attenuating it from the recorded signal (Figure 4.7). The analysis was designed to provide an objective evaluation of the tremor upon distinct

but complementary perspectives, i.e., the understanding of the effect of the stimulus on the tremor amplitude, which is more intuitive, as well as on the analysis of the tremor characteristics in the frequency domain and on the way the stimulation may affect the tremor regularity.

Tremor amplitude determines the symptomaticity of the condition. In clinical practice, its analysis is more common. This is because the tremor amplitude is easier to assess through observation alone, being included in several clinical scales such as the FTM (50) and TETRAS (41). However, there is a variability of the values adopted in these scales for mild, moderate and severe tremor because different scores are assigned to distinct amplitude ranges.

Moreover, the other variables (frequency, power and entropy) carry relevant information that cannot be perceived and discriminated with the naked eye (45). In this sense, the understanding of the behaviour of these inherent tremor characteristics may contribute for an improved characterisation of tremor, the effect of external inputs to its generating mechanisms, and even for its discrimination according to the disorder it is associated.

In this research, a special care was taken regarding its reproducibility, by making all the code available in the form of an R package, so-called *essential*. This allows for other research groups to perform the signal processing stages described in Figure 4.3, with the aim of extending the results of this research, as well as enabling the consolidation of methods for the objective assessment of tremor using inertial sensors.

6.4 Revisiting the Outcomes

The main purpose of this study was to assess the effect of vibrotactile stimulation on the tremor of individuals with ET. Based on the experiments and signal analysis it was possible to reach the following conclusions described below.

Assessing the behaviour of the tremor amplitude before, during, and after stimulation

In general, independent of the type of vibrotactile stimulus the amplitude of the tremor in the period without stimulation (baseline) was higher than the amplitude of the tremor in the pre-stimulation period. Although in these two cases there is no vibration action on the affected limb, this finding may be justified by the fact that the tremor underlying dynamics changes over time.

In addition, the amplitude of the tremor was generally lager for the period of stimulation when compared to the pre-stimulation period. This may be due to the fact that the stimulus may evoke changes in the mechanisms underlying the generation or manifestation of tremor, causing increased activity in the affected limb. Another hypothesis is that there may be a constructive sum of the mechanical vibration produced by the

stimulus with the natural vibration of the tremor, resulting in an increased amplitude of the tremor.

When the limb stopped receiving vibrotactile stimulation (post-stimulation period), the amplitude reduces in relation to the stimulation period. However, the amplitude is greater than the amplitude during the pre-stimulation, evidencing that for most of the patterns considered, stimulation caused a change in tremor dynamics that resulted in an increase in its amplitude.

This general behaviour is not followed by the 250 Hz stimulation pattern. For this stimulation pattern there was a reduction of the tremor when compared to the pre-stimulus period, mainly in the hand. This means that the 250 Hz pattern could be used in the development of technologies for tremor damping, for instance, a watch could be designed to monitor hand tremor and produce 250 Hz stimulation patterns to damp tremor.

Assessing the regularity (predictability) of tremor

For the 250 Hz stimulus, the regularity of the tremor in the pre-stimulation period was higher than the regularity of the tremor without stimulation. In general, there was not a consistent pattern of the regularity for the other stimulation patterns. This could be explained by the fact that the tremor dynamics changes over time. Another aspect is that the baseline period is longer than that of the pre-stimulus region.

In addition, the entropy of tremor increased in the stimulus period compared to the pre-stimulus period when the affected limb was stimulated at 250 Hz or when the hand (X and Z axes) was stimulated with increasing frequency. This suggests that there is a change in the regularity, making the tremor more unpredictable over time during the stimulation.

In general, the difference between entropies during and after stimulation and before and after stimulation was variable for most stimulation patterns, except for the stimulus with increasing linear frequency and constant frequency of 250 Hz. This variability in regularity, however, may be due to the nondeterministic nature of tremor itself due to the fact that the different stimulation patterns interfere differently in the tremor generating mechanisms, making the tremor more random or more deterministic over time in different direction and sense in space.

For the stimulation pattern with increasing linear frequency (X and Y) and constant frequency of 250 Hz (for all axes of the IMU on the forearm and for X and Z axes), there was generally a reduction of entropy after limb stimulation, compared to the stimulation period. However, these stimulation patterns presented a different response when comparing the pre-stimulus period with the post-stimulus period.

The entropy after stimulation with increasing frequency was lower than the pre-stimulus entropy only for the Y axis, suggesting that this stimulation pattern made the

tremor more regular. On the other hand, after limb stimulation at 250 Hz, there was an increase in entropy, i.e. the involuntary activity became less predictable over time.

Effects of the stimulation on the spectral parameters

In general, the stimulus at 250 Hz and the random frequency stimulus caused the reduction of the peak power when compared to the peak power estimated from the involuntary activity without stimulation. For the hand, there was a shift from the peak frequency to lower frequencies, while for the forearm, the response to stimulation was opposite. This corroborates the idea that mechanical stimulation can have different effects on different limbs when they are simultaneously stimulated by the same stimulation pattern.

In addition, it suggests that the intersegment peripheral mechanical stimulus response may be influenced by the frequency pattern or even by the stimulus generation region. For example, in this study, there were more vibrotactile stimulation pathways for the hand than for the forearm (Figure 4.1), as all fingers and palm received mechanical stimulation. On the other hand, the forearm received only one stimulation pathway located at, approximately, one-third of the wrist joint.

Individual spectral analyses suggested that postural tremor of the hand and forearm of the individuals, in the absence of vibrotactile stimulation, was caused by the superposition of multiple components of different frequencies and energies. For most participants, the spectral distributions were bimodal or multimodal, with distinct peaks in various frequency bands.

Individuals with ET usually have tremor with a frequency between 4 and 12 Hz (145). In this study, some of the participants had a peak frequency associated with higher power between approximately 3.5 and 5 Hz, while the others had a peak frequency between approximately 6 and 9 Hz. Although they present a frequency within the expected range, this difference between participants may be due to age. This is because it is believed that the frequency of the tremor reduces over the years (39, 151). On the other hand, this difference may be caused by the marked presence of physiological tremor, which is characterised by a higher frequency band in the 8–12 Hz range (35).

The lower energy peaks of both bimodal and multimodal distributions were usually in frequency bands underlying the higher power peak frequency. Spectra that had lower magnitude peaks in the upper side-band usually contained peaks at 7–15 Hz, while spectra that had lower magnitude peaks in the lower side-band usually contained peaks at 1-6 Hz.

Tremors with oscillation frequency between 1–3 Hz, known as ataxic tremors, usually manifest themselves in different regions of the body, such as the head, trunk and upper limbs. These involuntary movements have often been associated with cerebellar patholo-

gies or the response to reflexes activated by peripheral mechanisms, not being considered as a tremor per se, but as a dysmetry (66).

In this sense, the presence of low frequency components (1–3 Hz) may be related to instabilities in the reflex pathways during posture maintenance. This can be justified because skeletal muscles constantly maintain tone during the posture maintenance. This optimal motor control of posture, however, results from the combination of peripheral information with peripheral feedback from muscle spindles, joint receptors and mechanoreceptors (143).

On the other hand, tremors in the frequency range of 4–6 Hz are usually associated with pathologies, especially during the maintenance of posture or the permanence of the limb at rest against gravity (66). Therefore, the presence of components in this frequency band suggests the existence of typical oscillations present in diseases such as Parkinson's disease, which is characterized by rest tremor, and ET, which is characterized by the presence of tremors during posture maintenance.

Tremors in the higher frequency band, usually between 8 and 12 Hz, are associated with natural physiological processes, and are known as physiological tremor (35, 66). This type of tremor is not commonly seen with the naked eye, however several factors can make it noticeable, such as excessive physical exertion, muscle fatigue or emotional stress, that is, factors that activate the sympathetic nervous system (102).

Regardless of the type of spectral distribution, the involuntary activity of all participants showed a 8–12 Hz component that can be associated with physiological tremor. This suggests the presence of physiological tremor to varying degrees during posture maintenance. Furthermore, it implies that this component may be one of the components that contribute to the severity of involuntary activity during limb posture, as a constructive summation of the ET components with the physiological tremor components.

Moreover, this supports prior research findings that the mechanical and reflex components may determine tremor amplitude in ET (77). However, the predominance of high frequency components (peak frequency at 8–12 Hz) was observed in only some spectra of the participants investigated in the present study (Figures A.15, A.16 and A.17 in Appendix A), which may suggest an overlap of the frequency of physiological tremor with the frequency of pathological tremor or even the predominant presence of physiological tremor as these spectra presented minor peaks at 4–6 Hz (typical frequency values of ET).

Vibratory inputs modified these components, to a greater or lesser degree, in different ways. For instance, some stimulation patterns caused attenuation of low-frequency components, as when the hand of Individual 3 was stimulated with increasing linear frequency or when the hand of Individual 6 was stimulated at 250 Hz. In this regard, additional research on the impact of vibrotactile stimulation on particular tremor components is required, because this may contribute in differential diagnosis or perhaps the development of alternative treatments.

6.5 Future Work

The signal processing stages used in this study have a broader application. The estimation of amplitude, frequency, and regularity, as well as the joint analysis of these parameters, can be used to better characterise tremor in the context of tremor analysis. This can help distinguish between different types of tremor as well as distinguish between Essential Tremor and other tremor disorders, such as Parkinson's disease and dystonia. The correct diagnosis of the disorder is essential for a better treatment outcome as well as for a more personalised patient follow-up, avoiding the use of unnecessary medications and the consequences of their side effects.

The number of studies on the effect of other inputs, such as inertial load, on tremor is relatively large (35, 68, 73, 94, 122, 135), but the effect of vibration on tremor is still relatively new, although it has previous empirical precedents. In this context, more research is needed to determine how different vibrotactile stimulation input parameters can result in tremor attenuation. Furthermore, studies investigating the effect of stimulation on the different components of postural tremor may provide clues about the role of these oscillations and its generating mechanisms and related to its manifestation.

The understanding of the vibrotactile effect may allow one to create assistive technologies that can help improve the quality of life of individuals with ET. In addition, the understanding of the effect of vibrotactile stimulation can contribute to the improvement, for example, of closed-loop DBS (21), whether it is used as an individual calibration element of tremor severity through tremor induction (e.g. using the vibration stimulus to set a severe tremor value), or as one of the suppression elements from the tremor.

7

Final Considerations

"De tudo, ficaram três coisas:
A certeza de que estamos sempre começando,
A certeza de que é preciso continuar,
A certeza de que seremos interrompidos
antes de terminarmos..."

— Fernando Sabino, *O encontro marcado*

Essential Tremor is an unique movement disorder that is characterized by the tremor of the hands on maintaining the posture of the limb against gravity. The origin of this condition is not well established. Furthermore, there is no straightforward understanding of the effect of external inputs, such as vibration, on the generation and manifestation of tremor. These factors, however, undermine advances in diagnosis and the more individualized treatment of the condition.

Thus, the analysis of the effect of vibrotactile stimulation in ET is important so that the mechanisms involved in its generation and manifestation are better understood and, consequently, more personalised treatments can be developed. In this sense, this study evaluated, in terms of amplitude, frequency and regularity, the motor response of individuals with ET to different vibratory stimuli.

The study verified that peripheral vibrotactile stimulation is a potential way to non-invasively change the dynamics of tremor in individuals with ET. However, the findings suggest that the motor response to different stimulation patterns may be variable among individuals due to several reasons, such as the specificity and size of the receptive field of the vibration sensitive receptors, as well as the intensity and duration of the stimulus applied.

Among the different investigated stimuli, the vibratory stimuli of 250 Hz and random frequency were the ones that presented a positive effect on the motor response during the maintenance of posture, attenuating the amplitude and power of the involuntary movements of the upper limb affected by ET, when compared to the involuntary movements in the absence of stimulation. However, only the 250 Hz stimulus presented a reduction in amplitude after stimulation, compared to the pre-stimulus period.

Although the magnitude of the tremor decreased after the upper limb was stimulated at 250 Hz, the involuntary movements became more unpredictable over time, that is, there was an increase in entropy. In addition, this stimulus pattern caused the shift of the peak frequency, which may be due to changes caused by vibration in the mechanisms behind tremor manifestation.

On the other hand, individual spectral analysis showed that postural tremor is caused by overlapping components in different frequency bands. In this sense, the vibratory inputs modified these components, to a greater or lesser degree, in different ways. In some individuals, there were stimulation patterns that attenuated components of the side-bands even if their effect on the predominant component was not so expressive when the upper limb was stimulated.

These findings reinforces the idea that adding vibratory inputs to afferent pathways can modulate motor response, either by acting as a sensory cue or distraction, or by modulating abnormal oscillations related to the neural circuits responsible for the generation and manifestation of tremor. Therefore, the vibrotactile stimulation may be an interesting tool to explore the motor response of individuals with tremor to sensory inputs.

Finally, vibrations have the potential to be used clinically in the area of tremor, either to attenuate involuntary movements, or to establish in a more personalized way the degree of severity of the motor sign for better clinical follow-up. However, the clinical application of vibratory inputs lacks further studies about, for example, the duration of the motor response to vibration in individuals with ET, as well as individual level of tolerance to vibratory stimulus.

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Glossary

Aetiology

the causes or origins of disease, the factors that cause or predispose to a particular disease or disorder.

Afferent pathways

the neural pathways that transmit sensory information from the peripheral nervous system to the central nervous system. These pathways are responsible for relaying signals related to various sensory modalities, such as touch, temperature, pain, proprioception, vibratory sensitivity, and perception of different types of stimuli.

Enhanced physiological tremor

a physiological tremor of a body part that is of greater than normal amplitude that is visible to the naked eye.

Mechanoreceptor

the specialized sensory receptors that respond to mechanical stimuli. They play a crucial role in the ability to sense and perceive touch, pressure, vibration, and other mechanical sensations.

Physiological tremor

the normal oscillation of all parts of the body that is not visible to the naked eye and is the result of natural physiological processes.

Responsiveness

an ability of the organism to sense external and internal changes and adjust to those changes.

Sensory receptors

the cells specialised to respond to a particular type of external energy.

Appendix

A

Supplementary Materials

"Far and away the best prize that life offers is the chance to work hard at work worth doing..."

— Theodore Roosevelt

This appendix provides some additional information on the work carried out.

A.1 Chapter 4

A.1.1 Signal Processing

In this study, the *R package* developed for objective tremor analysis, called ***essential***, comprises functions for each of the steps outlined in Figure 4.3 that are essential for the processing and analysis of any biomedical signal. Furthermore, this package includes functions that facilitate the generation of some synthetic signals, aiming to enhance comprehension of the biomedical signal processing methods and to facilitate the interpretation of the analysed features.

The ***essential*** package is hosted on the GitHub platform (https://github.com/arianacabral/essential), and all the code and documentation can be accessed. The *R* script, which employs the ***essential*** package to generate the results presented in this study, is also available on GitHub as an *R project* named **r4et** (https://github.com/arianacabral/r4et). However, the data of the participants, which is considered sensitive data, is not shared or made available in open repositories.

A.2 Chapter 5

A.2.1 Spectral Analysis

In Chapter 5, the results of the spectral analysis for only three of the 18 participants are presented. Figures A.1 to A.18 depict the power spectral densities of the involuntary hand (IMU 1) and forearm (IMU 2) activity of all participants during posture maintenance in the presence and absence of vibrotactile stimulation.

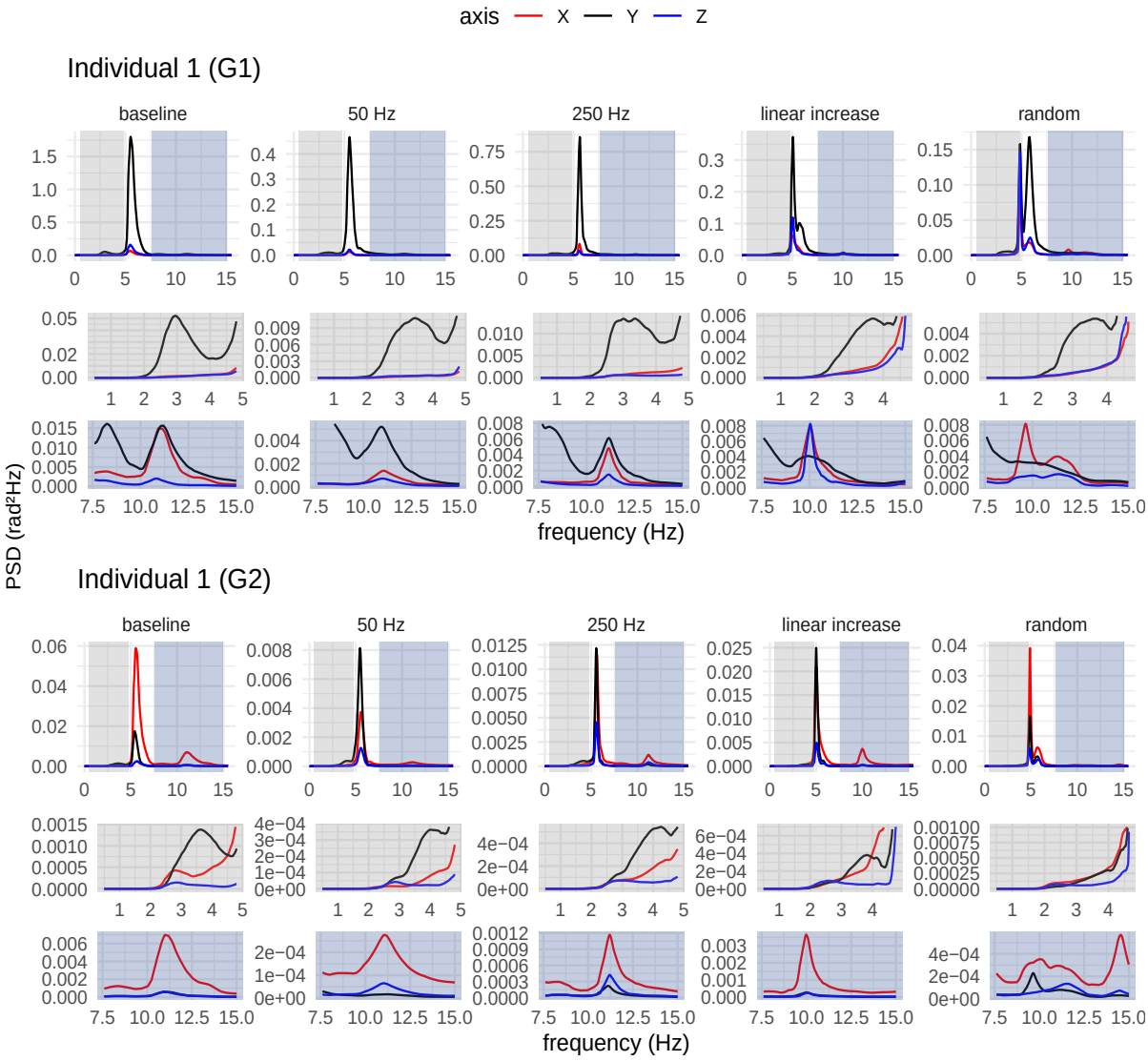


Figure A.1 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 1** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

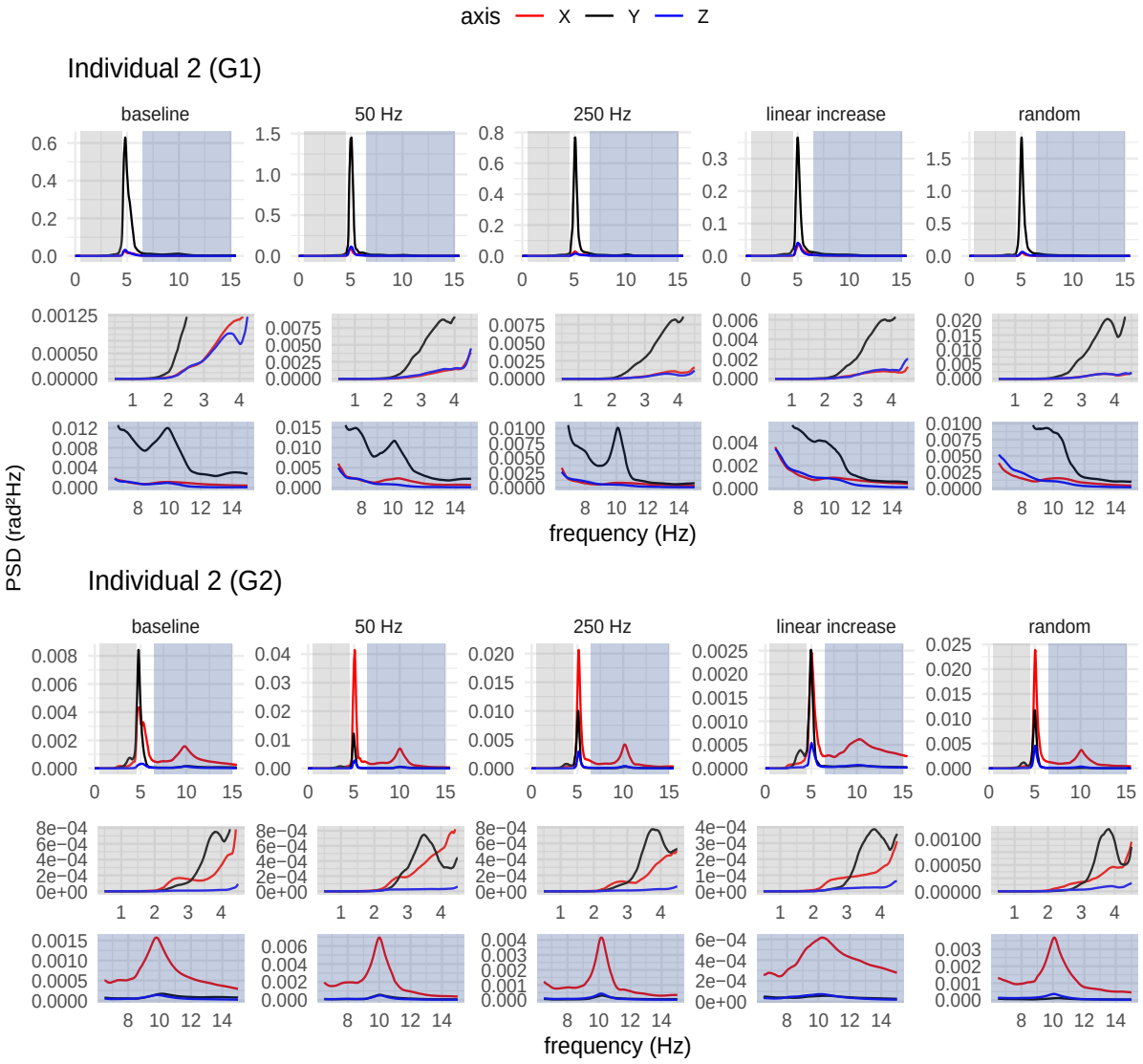


Figure A.2 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 2** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

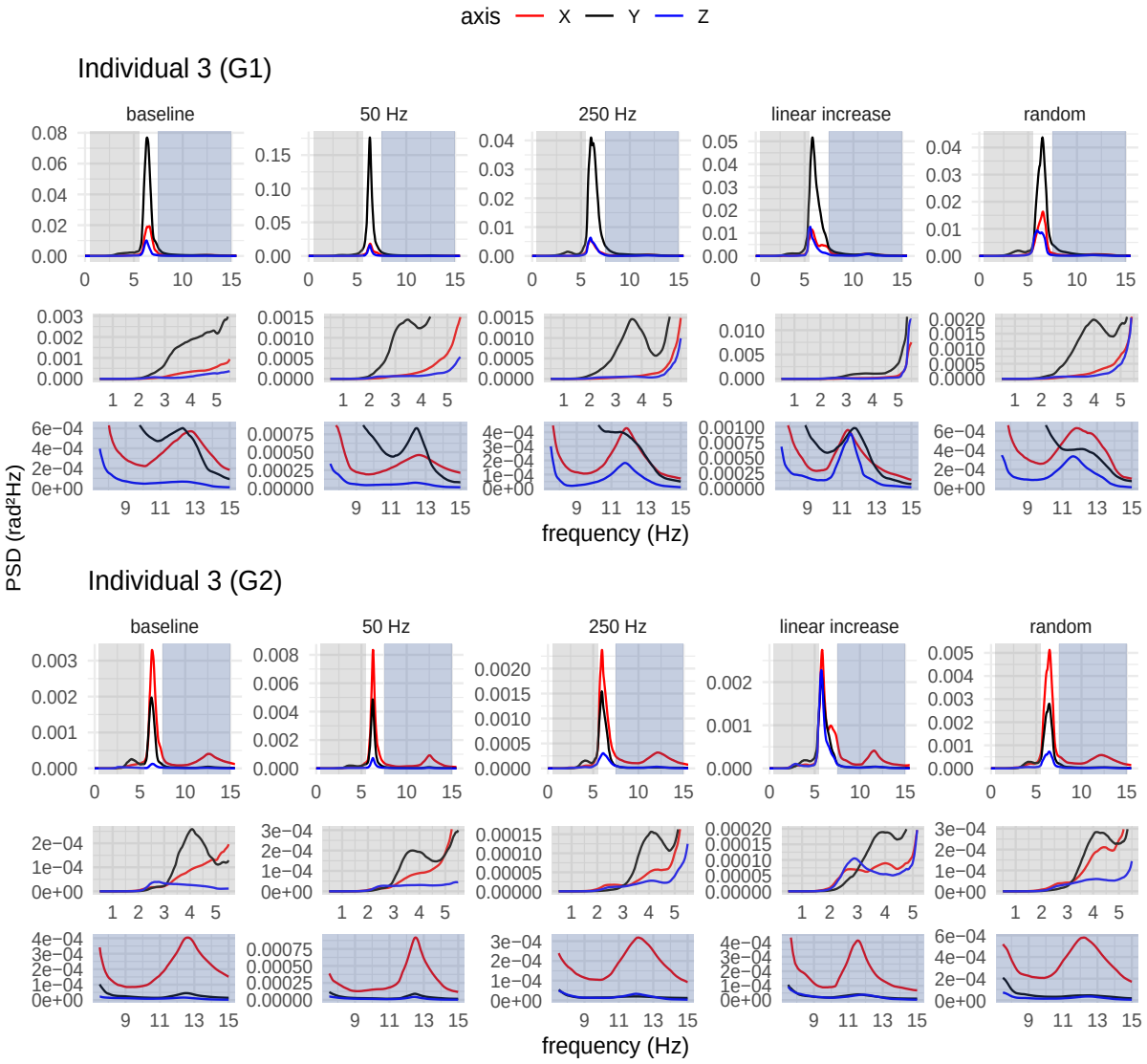


Figure A.3 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 3** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

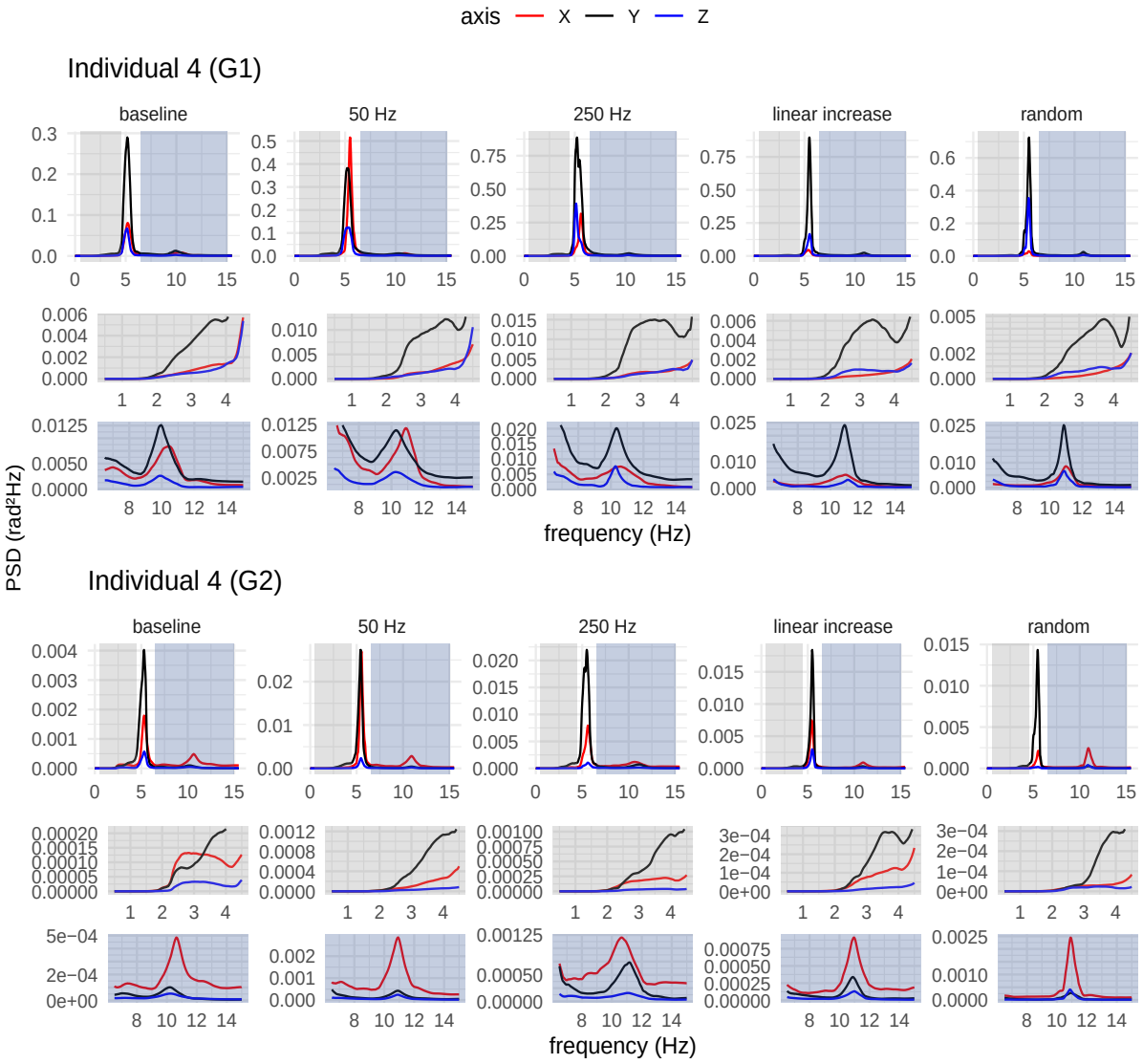


Figure A.4 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 4** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

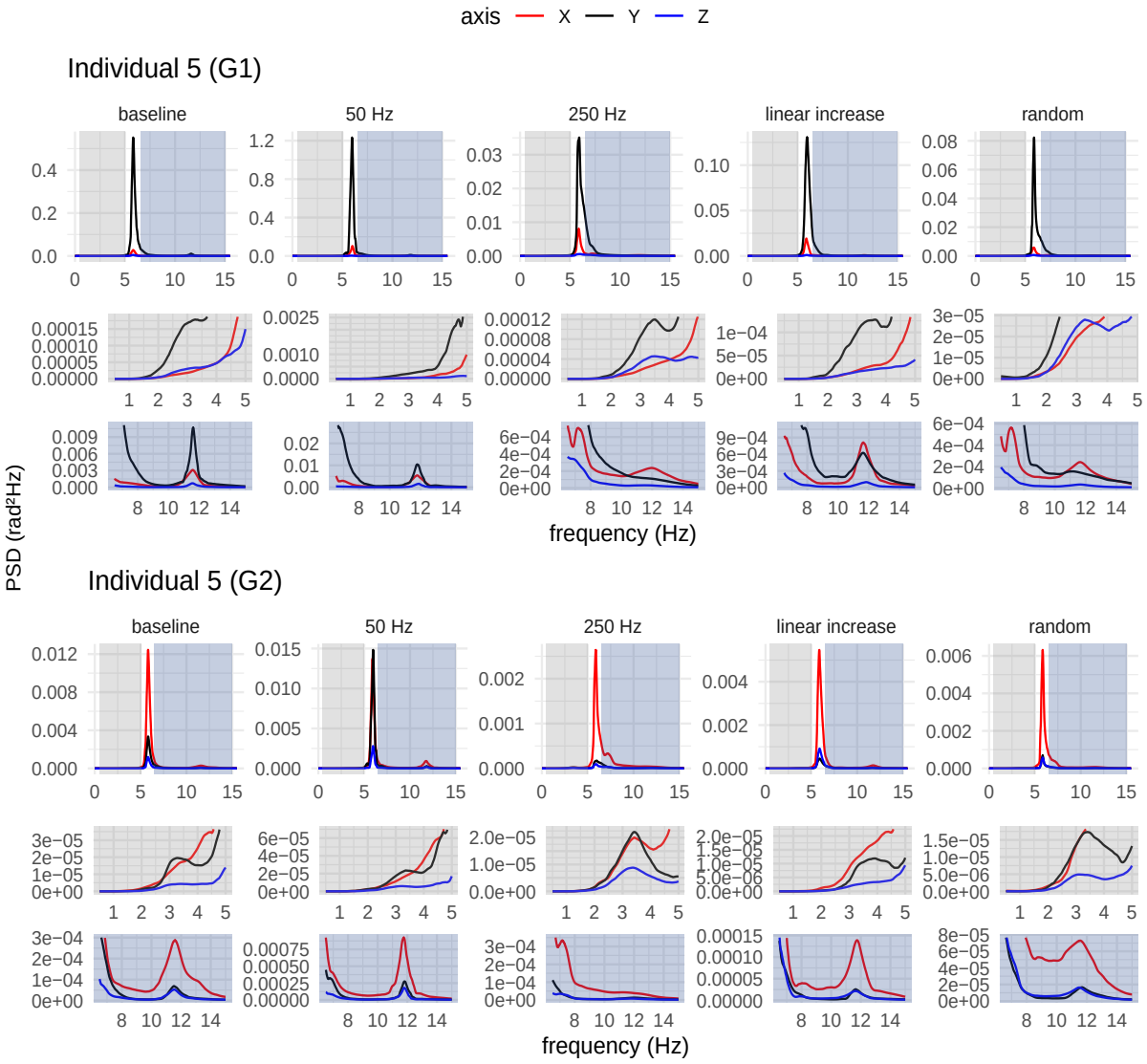


Figure A.5 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 5** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

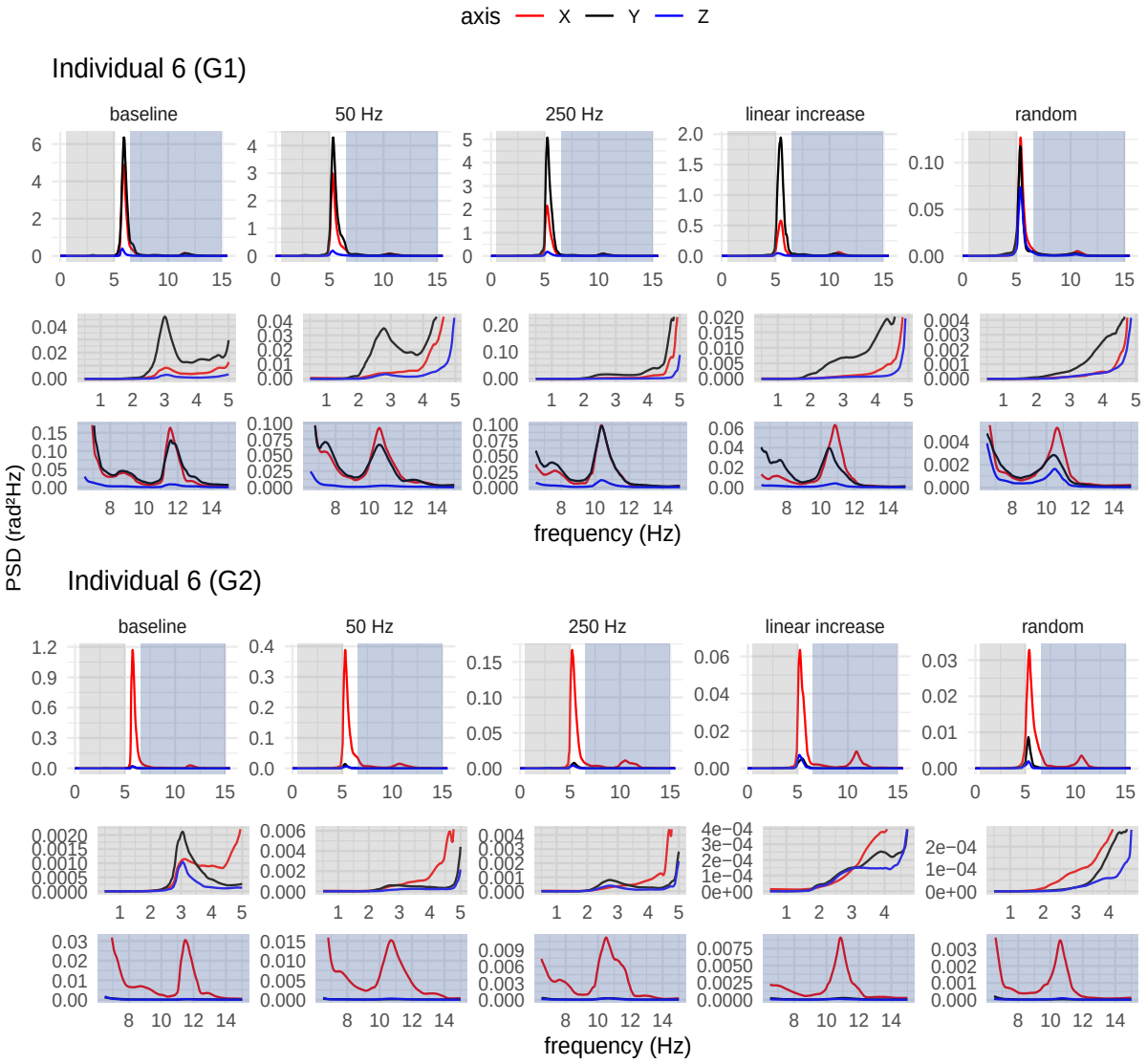


Figure A.6 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 6** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

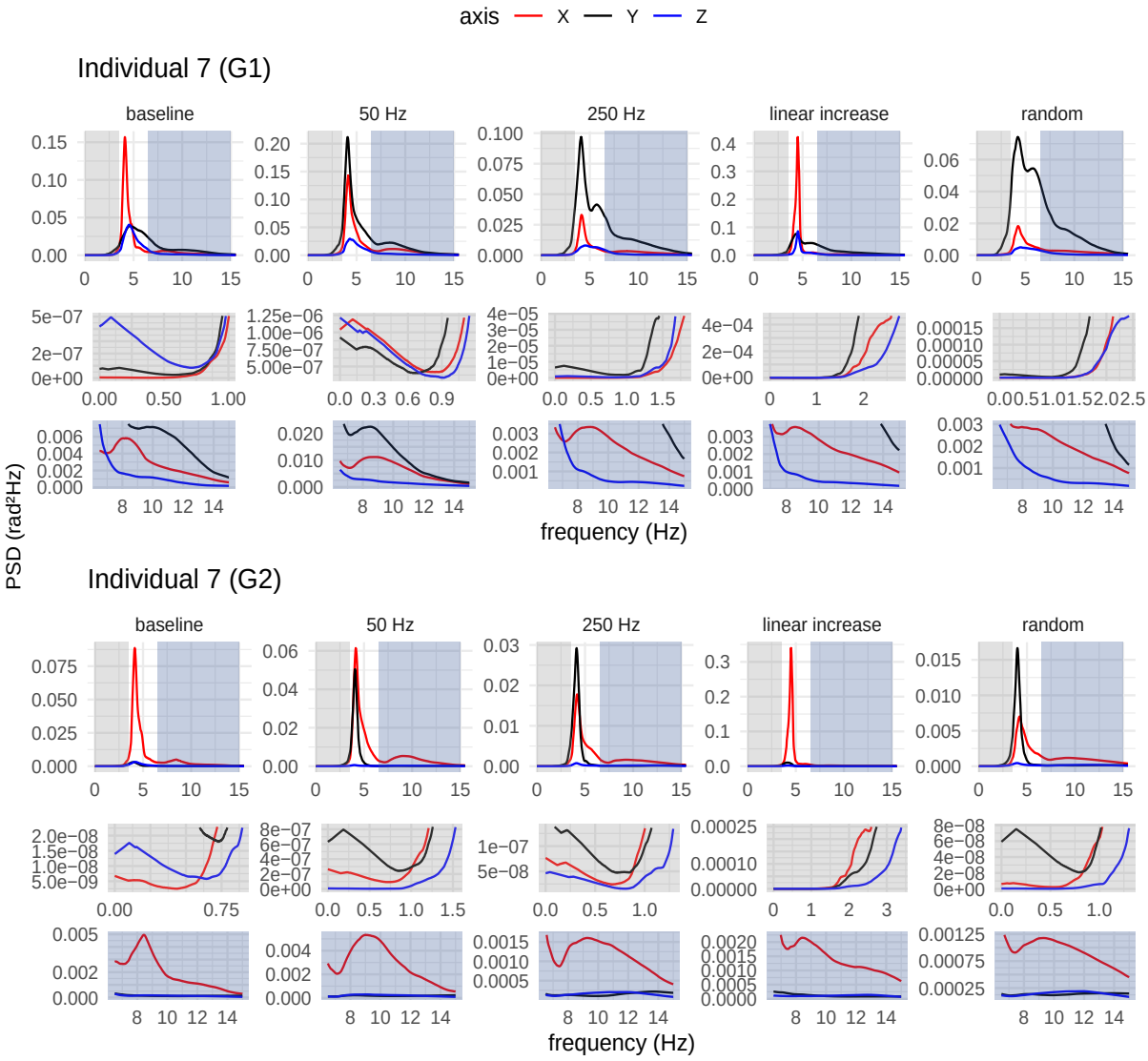


Figure A.7 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 7** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

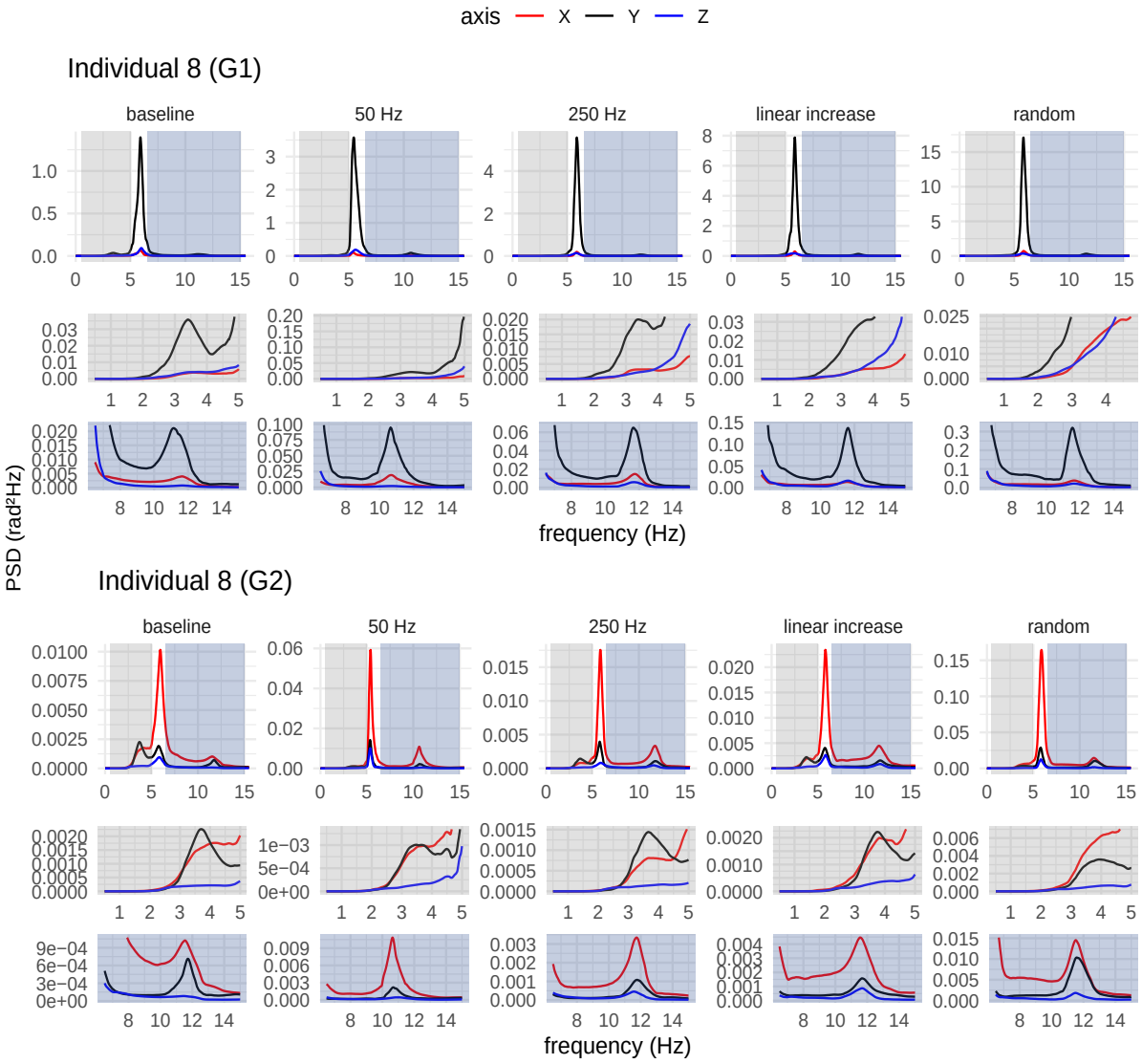


Figure A.8 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 8** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

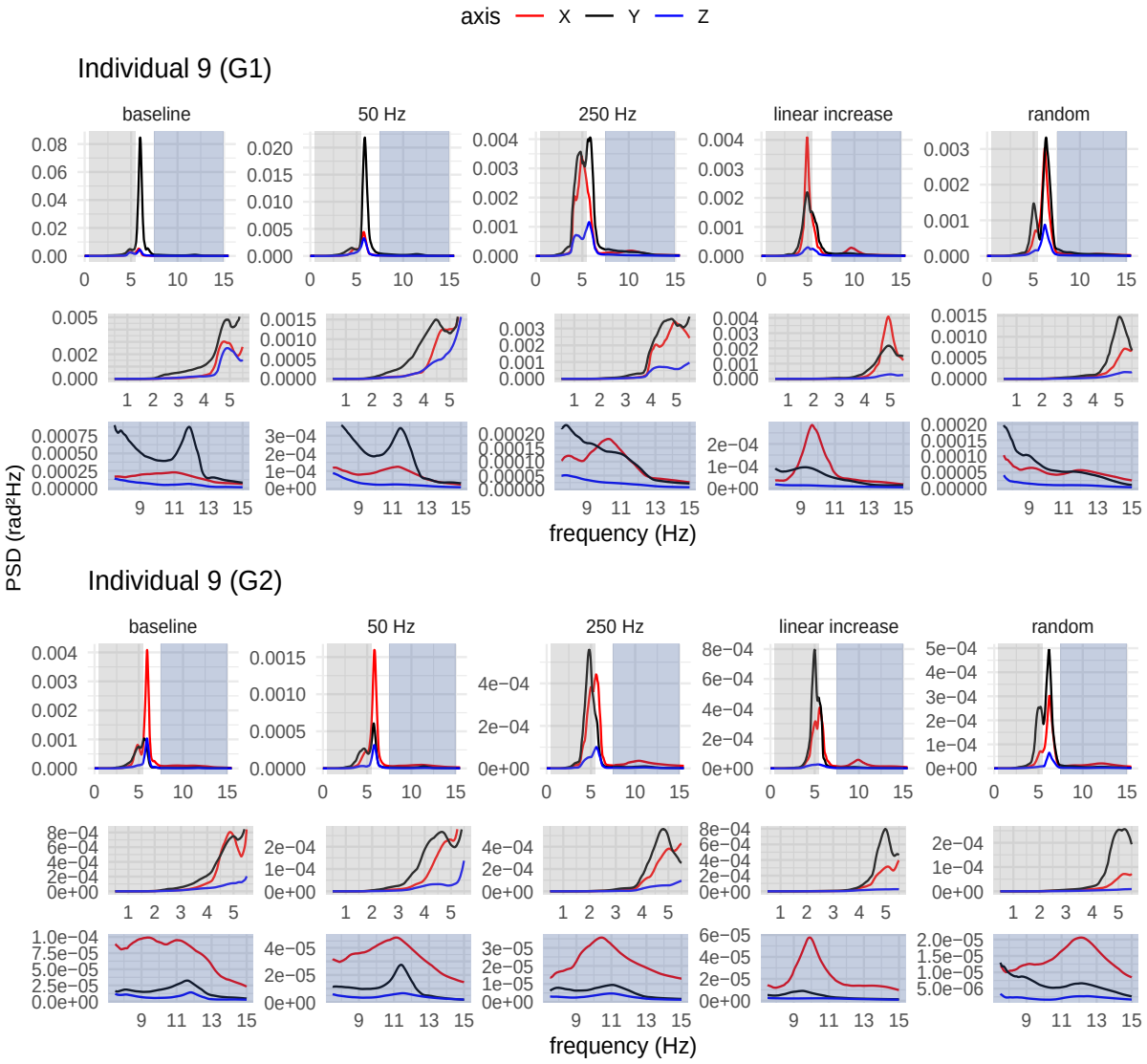


Figure A.9 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 9** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

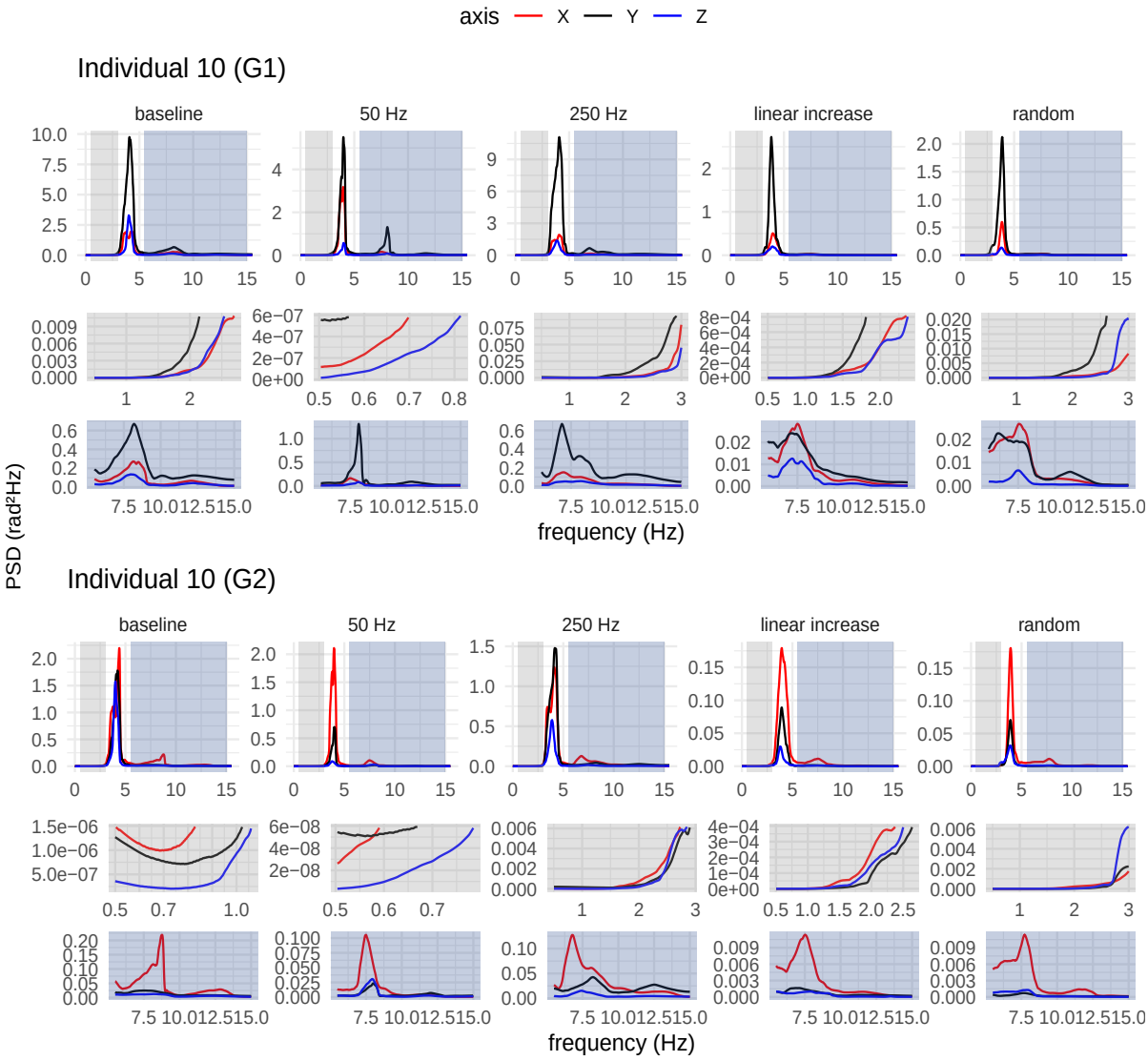


Figure A.10 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 10** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

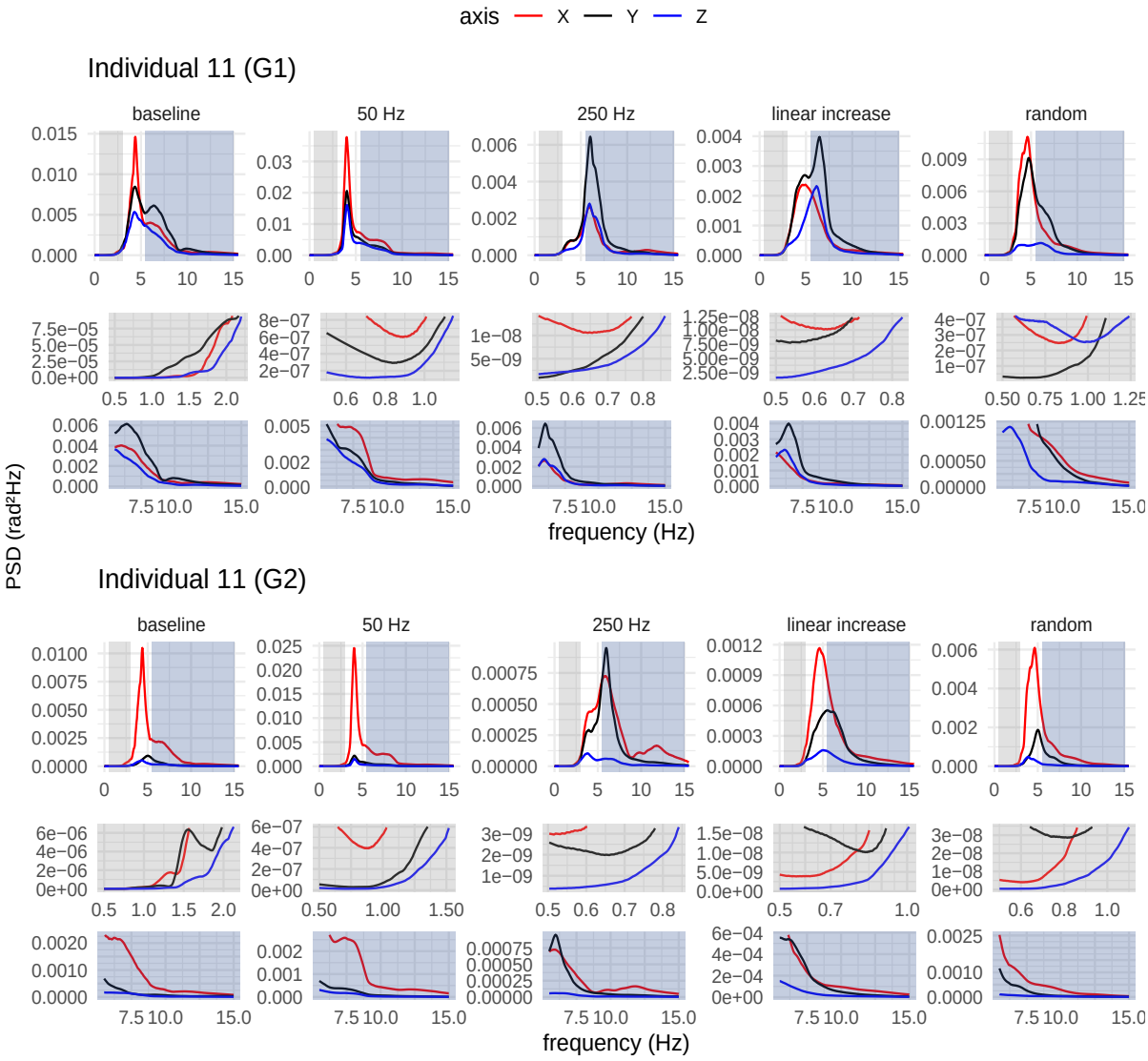


Figure A.11 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 11** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

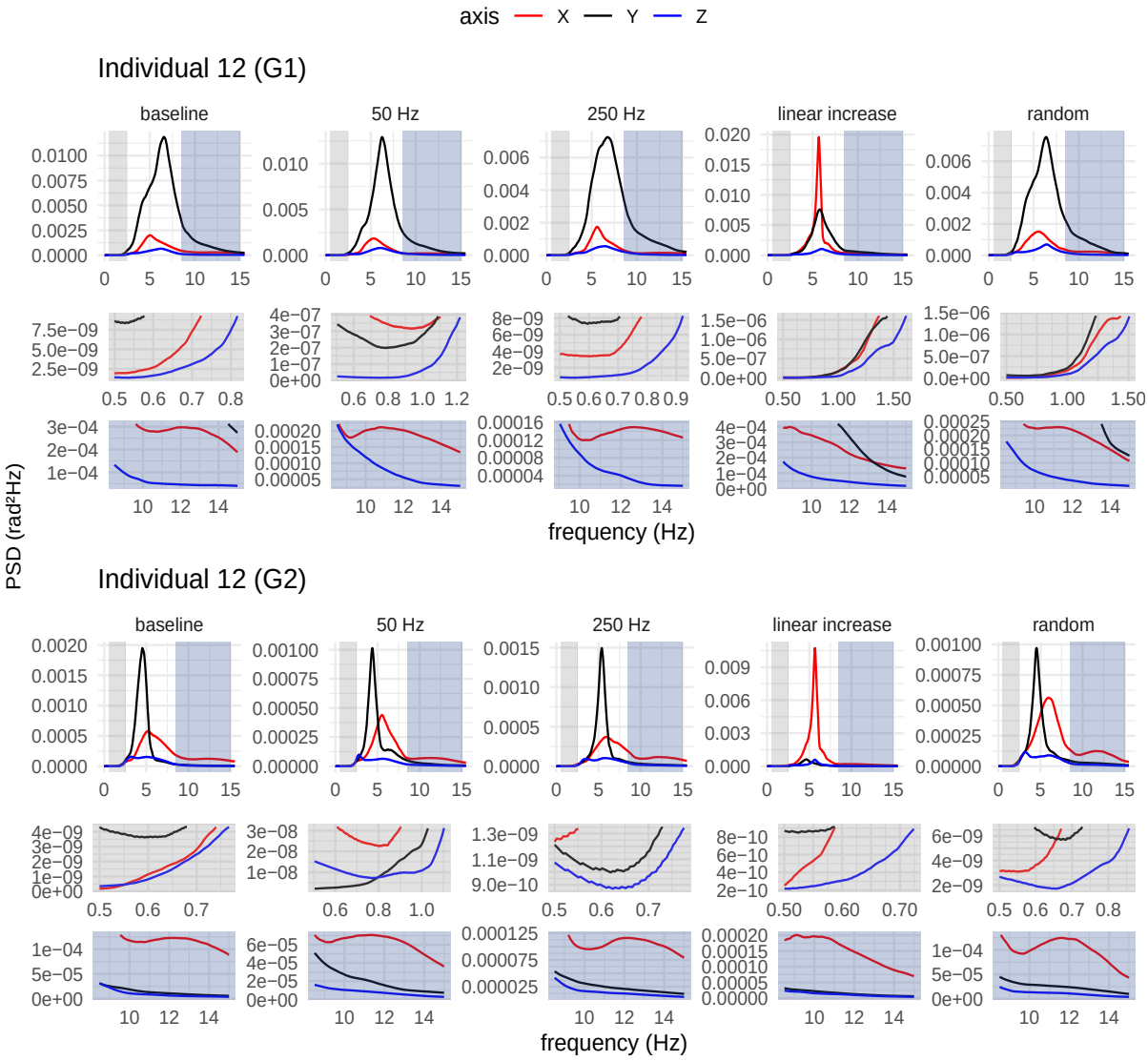


Figure A.12 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 12** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

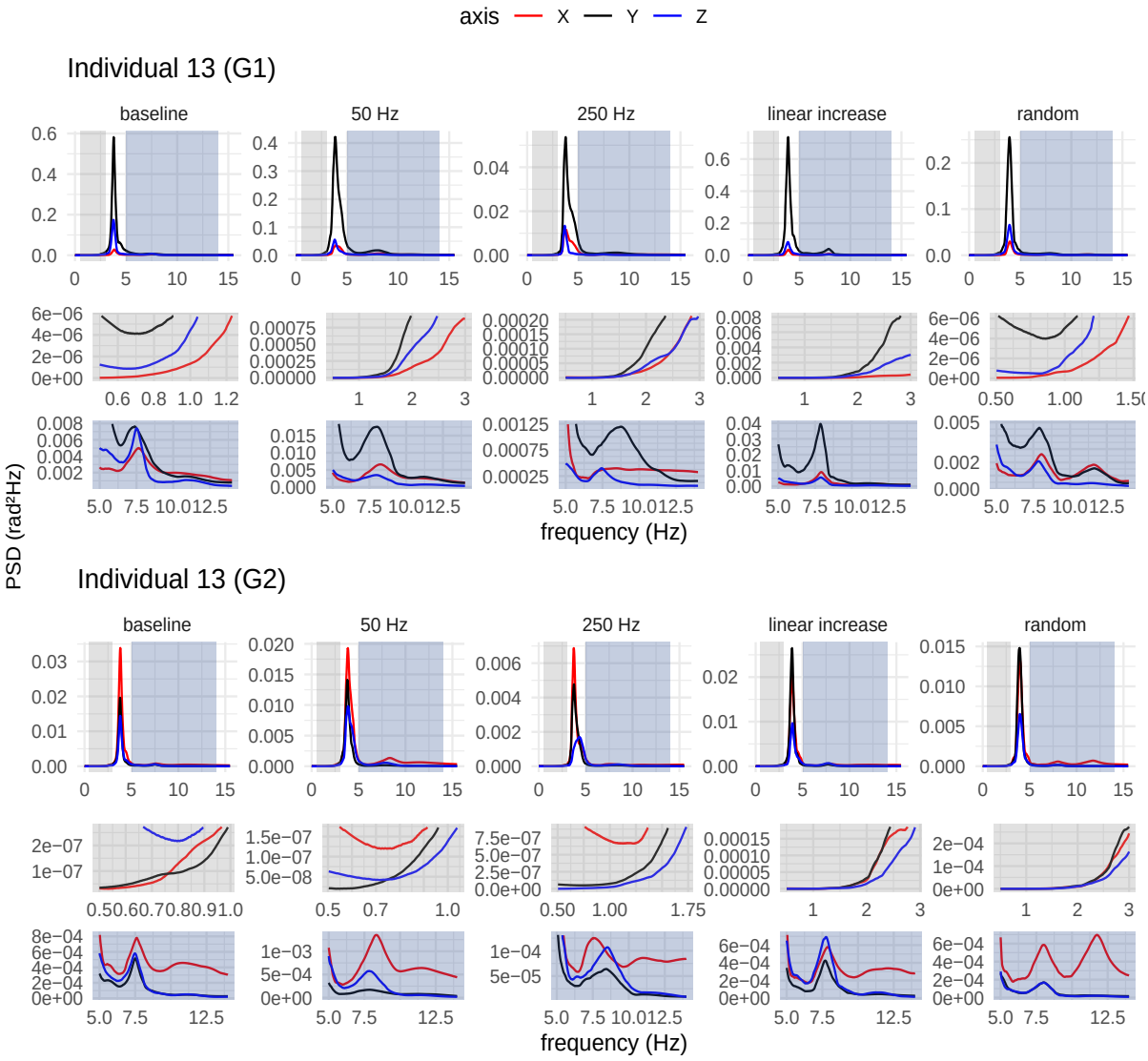


Figure A.13 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 13** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

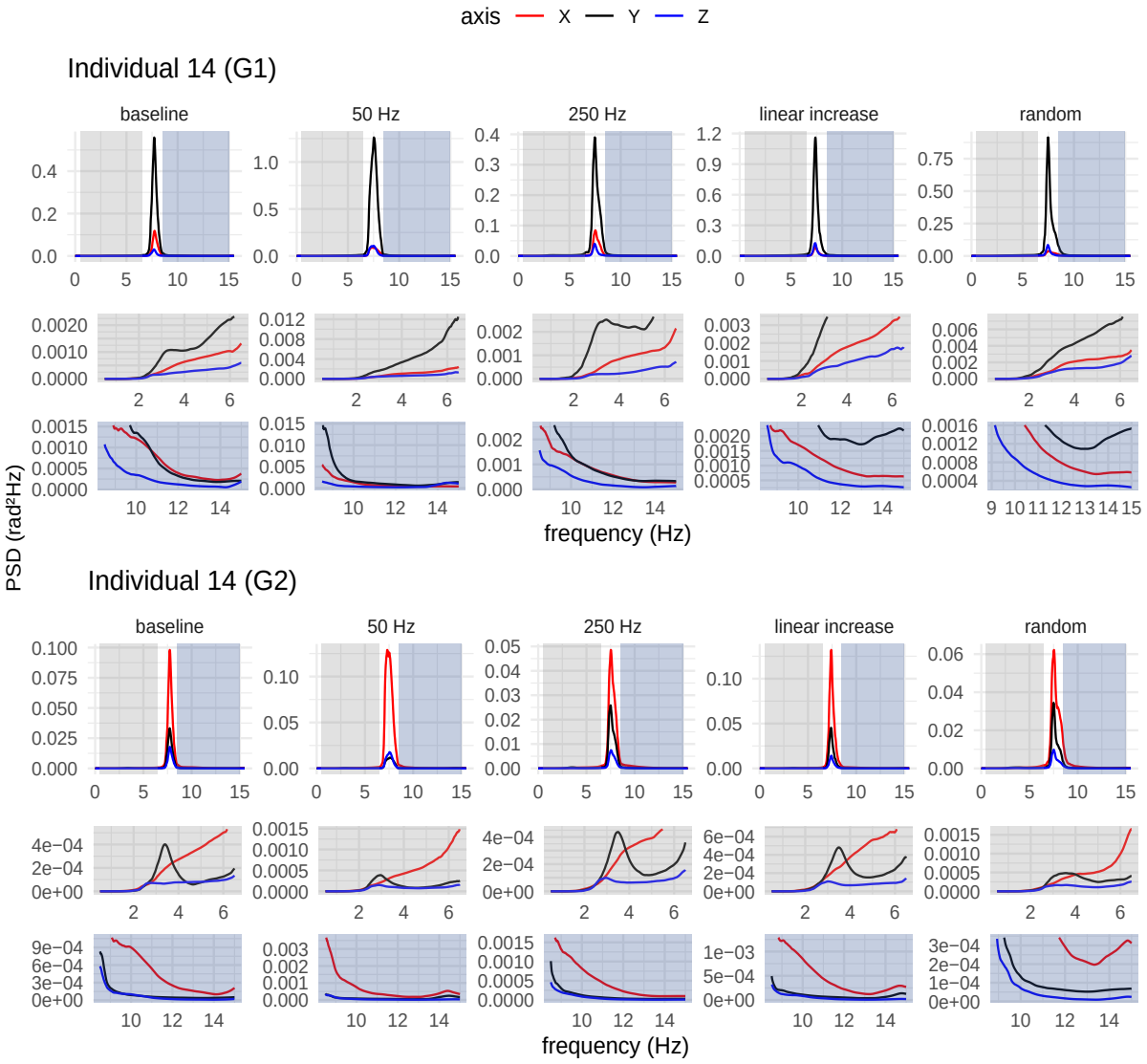


Figure A.14 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 14** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

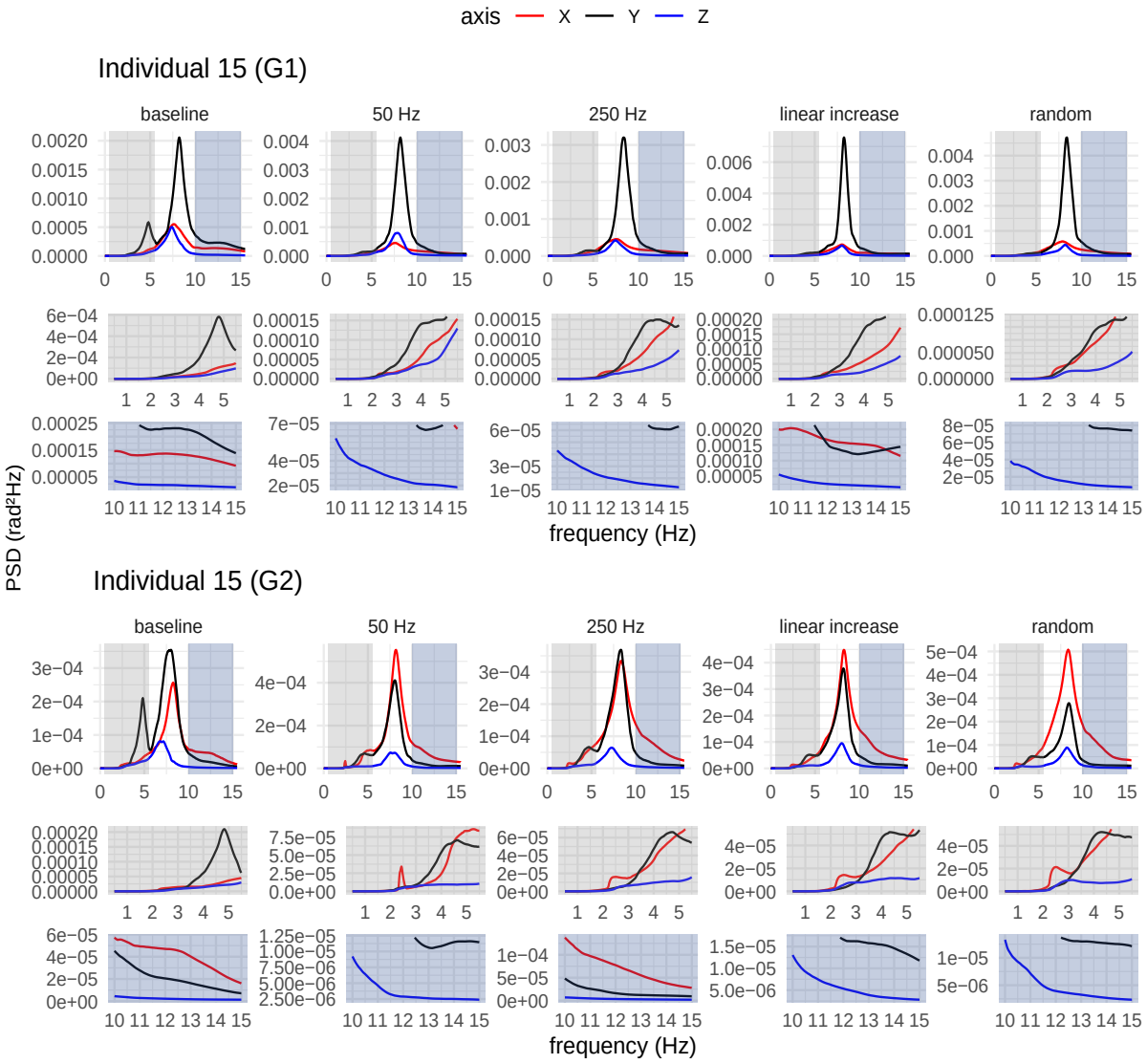


Figure A.15 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 15** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

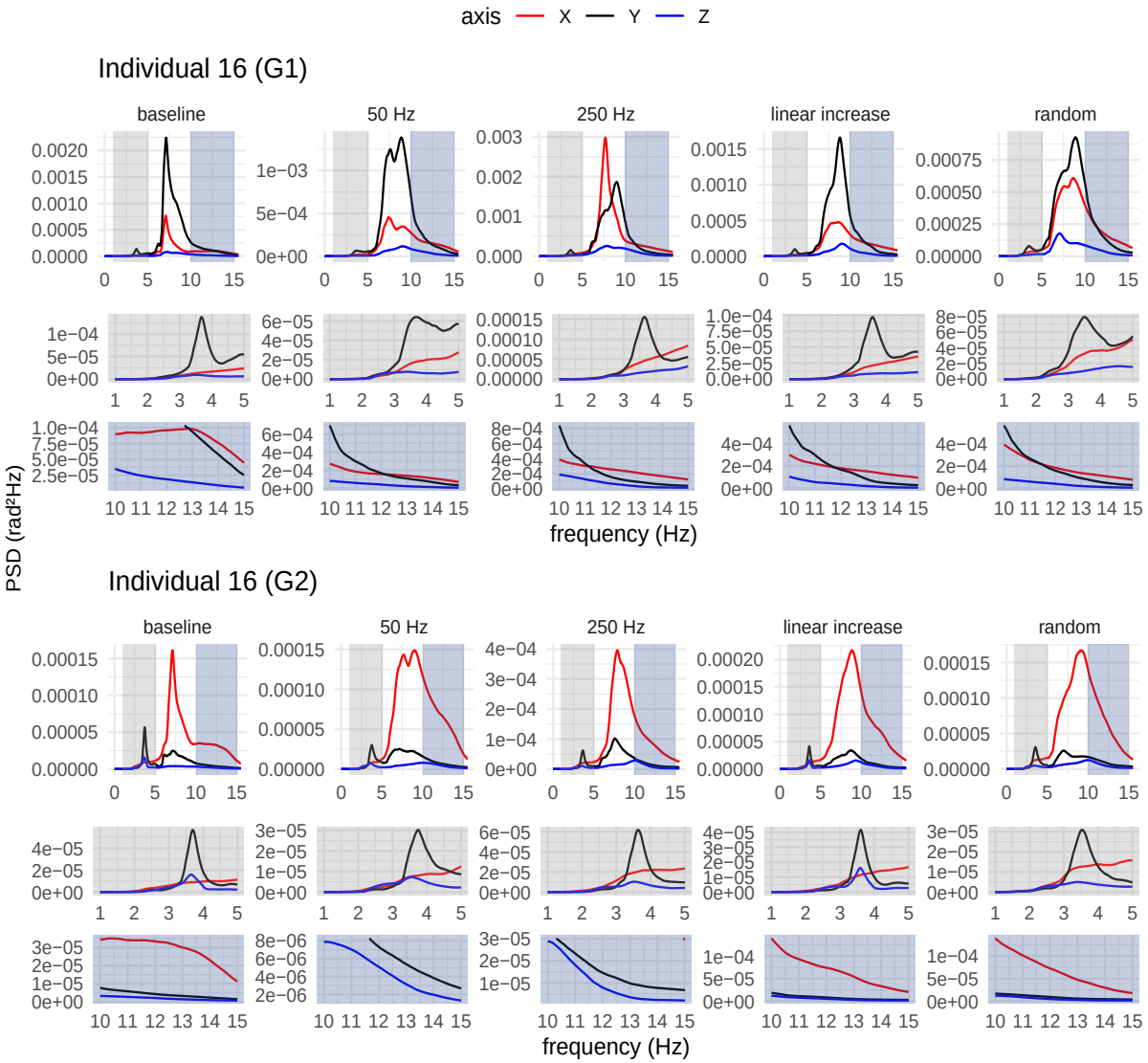


Figure A.16 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 16** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

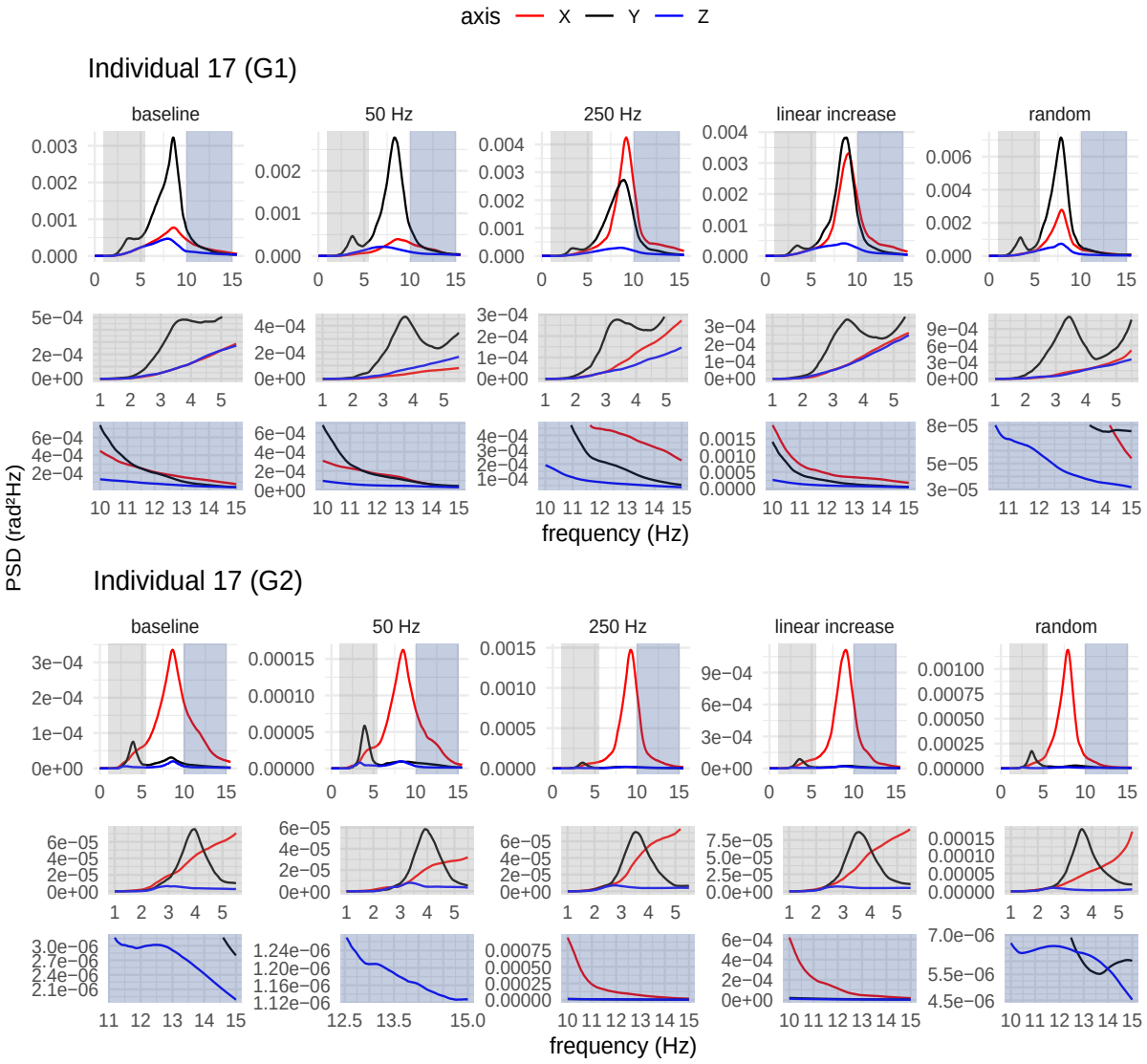


Figure A.17 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 17** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.

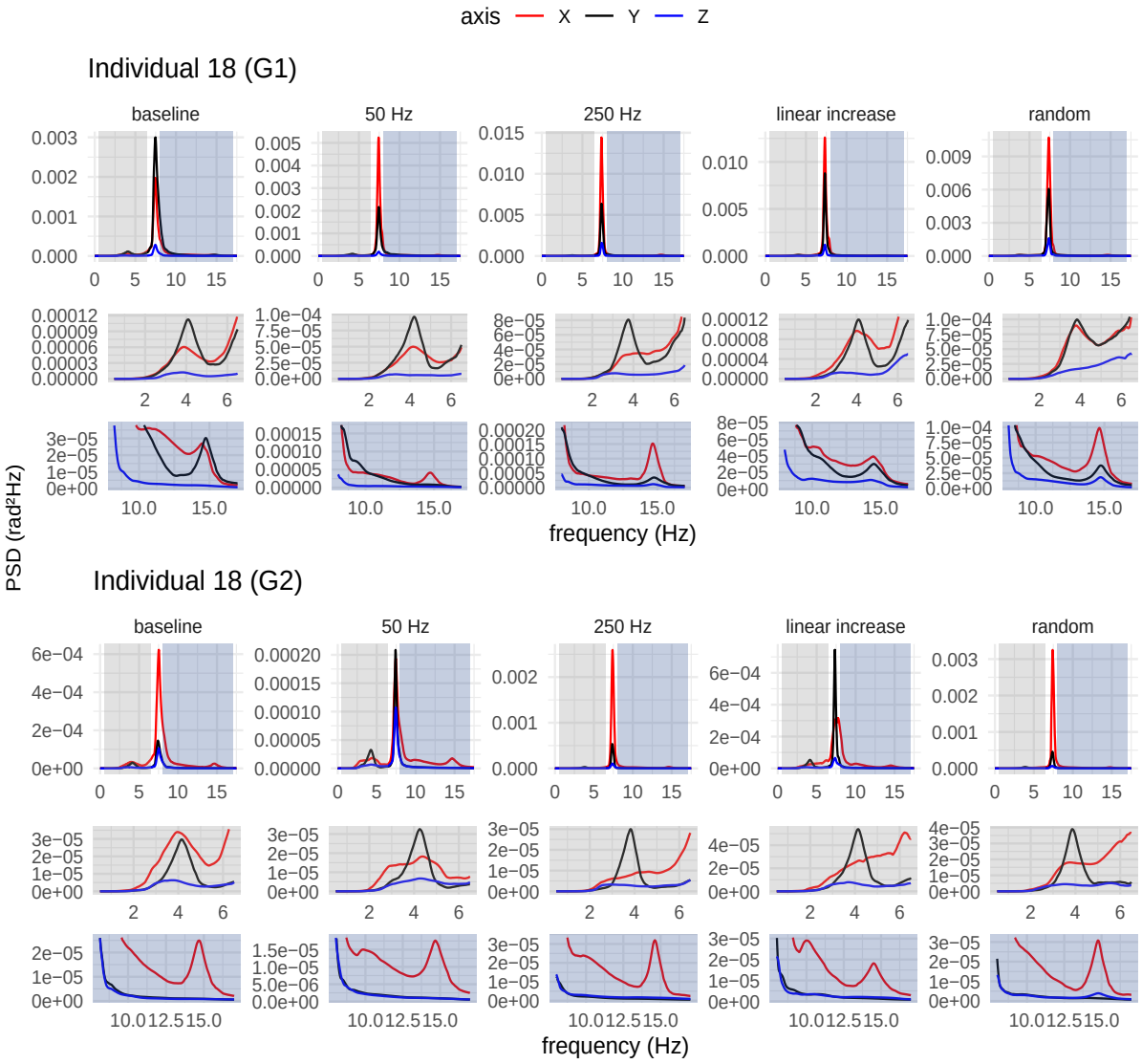


Figure A.18 – Power spectral densities of the angular velocity of the hand (G1) and forearm (G2) of **Individual 18** for each axis (X, Y and Z) during posture maintenance, without (baseline) and with (50 Hz, 250 Hz, linear and random increase) vibrotactile stimulation. The highlighted areas of the spectra (the gray and blue windows) depict the spectral behaviour for lower and higher frequency bands in relation to the peak frequency.