

Ph.D Thesis

**Easy-to-Use Biosignal Monitoring:
Wearable Device for Muscle Activity
Measurement during Sleep in Daily
Life**

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Vita brevis,
ars longa,
occasio praeceps,
experimentum periculosum,
iudicium difficile.

———Hippocrates “Aphorisms”———

Easy-to-Use Biosignal Monitoring: Wearable Device for Muscle Activity Measurement during Sleep in Daily Life

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Abstract

In recent years, medical care targets have drastically changed from acute diseases to lifestyle-related diseases such as sleep disorders, in which many lifestyle-related factors, including habitual ones, may influence each other. It is quite hard for physicians to collect all the information on lifestyle-related diseases in outpatient service within a limited time and with limited resources. Therefore, a change from reactive disease care to P4 medicine (predictive, preventive, personalized, and participatory care) has been advocated.

A healthy life depends on a well-balanced diet, moderate physical activity, and good sleep. Although sleep undoubtedly plays an important role, full understanding of how well people sleep remains an unsolved issue. Just as sleeplessness influences daily activities, it is even worse among patients with sleep disorders. Because the symptoms of sleep disorders vary, it is important to incorporate home telemedicine in the field of sleep medicine, called out-of-center sleep testing (OCST), to enable appropriate objective observation on sleep conditions outside a hospital. This requires developing easy-to-use devices that non-experts can use in their daily life environments.

By considering currently available devices for OCST together with the potential patients of each sleep disorder, this doctoral research sets periodic limb movement disorder (PLMD) as the target sleep disorder. Most patients with PLMD remain undiagnosed because of the lack of appropriate monitoring devices for its unique symptoms, namely, periodic short-lasting involuntary movements called periodic limb movements (PLMs), which mainly occur in the lower extremities. Furthermore, this lack of devices can disrupt precise treatment of patients with PLMD even after a definitive diagnosis.

This doctoral research aims to develop novel easy-to-use wearable devices for unaided surface electromyography (EMG) measurement by non-experts, specifically targeting home monitoring of PLMs by capturing their essential biosignals (i.e., surface EMG). The main contributions are the following three:

to propose a combination of target muscles for surface EMG-based PLM home monitoring; to develop an easy-to-use sock-type wearable device for unaided surface EMG measurement by non-experts; and to confirm the performance of the developed device in actual PLM home monitoring.

This dissertation first clarifies the issues and organizes the requirements in developing a surface EMG measurement device assuming unaided home use by non-experts. For the first contribution, this research investigated all the muscles related to PLMs after visually observing the induced leg movements, and determined the target muscles for surface EMG-based PLM home monitoring, then confirmed that the performance of EMG could exceed that of the current de facto standard method based on acceleration.

For the second contribution, this research developed an easy-to-use wearable device for unaided surface EMG measurement by non-experts, comprising a sock-type fabric adaptor with embedded fabric electrodes. Then, through a preliminary validation targeting voluntary movements, the device's basic performance on surface EMG measurement was confirmed to be sufficient for discriminating the presence/absence of muscle activity.

For the third contribution, through comparative evaluation against visual observation of PLMs by a physician, this research confirmed that the PLM home monitoring performance of the device was better than that of the current acceleration-based method.

These contributions can foment future researches on revealing PLMs condition outside a hospital, thus enabling better understanding of the relationship between medication and actual PLM conditions. The work here will also enable exploration of new treatment strategies based on the aforementioned findings. Finally, it will contribute to providing the big data collection essential for physicians at the bottom layer of the data, information, knowledge, and wisdom (DIKW) pyramid, which is the key enabler of P4 medicine.

Easy-to-Use Biosignal Monitoring: Wearable Device for Muscle Activity Measurement during Sleep in Daily Life

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Chapter 1 Introduction

1.1 Background and Aims

The history of human beings has evolved along with medicine. Medicine is the technology of comfort and healing for human beings: the term (from Latin: *medicina*) relates to the Latin verb *medeor*, which means “heal” [1]. The ideal aim of a physician was briefly and comprehensively summarized in tribute to Dr. Edward Livingston Trudeau (1848–1915): “*Guérir quelquefois, Soulager souvent, Consoler toujours*” [2], to cure sometimes, to relieve often, to comfort always. Medicine can thus be considered to depend on the patient’s belief in medical staff since long ago [1].

Medicine has its roots in the work of the ancient Greek physician Hippocrates (460–375 B.C.) [1]. He assumed that the human organism had a tendency toward self-healing and illustrated that “nature is a healer of disease” (Greek: *Nouson phusies ietroi*). A physician was thus expected to act as a “servant of nature” (Greek: *tes physeos hyperetes*) who applied his skill to support and consolidate the natural self-healing process of the human organism by removing disturbances [1,3]. Thomas Sydenham (1624–1689), also known as the English Hippocrates, evolved this point of view to recent clinical medicine by integrating clinical observation for diagnosis [1]. He emphasized the importance of uncovering the hidden causes of disease by studying patients, in other words, by understanding symptoms and their exacerbation or healing progress through clinical observation. Dutch physician Herman Boerhaave (1668–1738) followed Sydenham’s view and enhanced it at Leiden in the Netherlands [1]. His approach of systematic, organized medical treatment considering the whole body, comprising clinical observation with constant inspection (e.g., urinalysis, pulse taking), medical assessment, and treatment planning, sowed the seeds of clinical medicine to the present day.

Clinical medicine today aims to prevent, diagnose, and treat disease. In each of these aspects, it involves the process of collecting a lot of information to make decisions, which we can rephrase as information processing [4]. To record information from medical examinations, the problem-oriented system (POS) has

been proposed and widely used in actual clinical settings [5]. The core idea of the POS is a problem-oriented medical record (POMR) for each target patient, which is successively subdivided into a problem list, an initial plan for each disease, and progress notes [6], as shown in Figure 1. The POS is expected to improve the completeness of medical records and clarify the progress of treatment by repeating the process of creating, auditing, and modifying POMRs as in the plan-do-check-act (PDCA) cycle [5, 6].

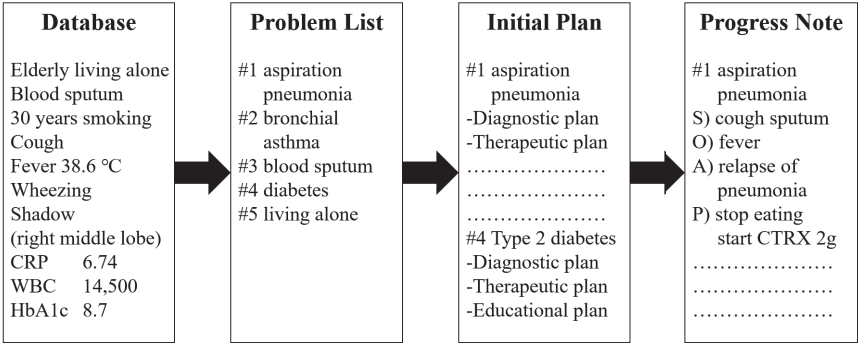


Figure 1: The four layers of a POMR. This figure is based on [6].

Progress notes in a POMR are recorded from the perspective of SOAP described below [5, 6]. This perspective indicates that physicians require sufficient subjective data as well as objective data for appropriate diagnosis and treatment planning.

- S (Subjective data): Main complaint from patient.
- O (Objective data): Clinical observations based on the physician’s five senses (e.g., visual inspection, auscultation, palpation) and inspection results.
- A (Assessment): Clinical assessment including diagnosis, clinical interpretation of data, and prognosis.
- P (Plan): Treatment plan mainly including prescriptions, or instructions on medical treatment or inspection.

In recent years, the targets of medical care have drastically changed from acute diseases (e.g., infections) to lifestyle-related diseases (e.g., sleep disorders). It is quite hard, however, for physicians to collect all the information on

lifestyle-related diseases in outpatient service within a limited time, because many lifestyle factors, including habitual ones, may influence each other. Considering that physicians must work with limited resources, several physicians have advocated a change from reactive disease care to P4 medicine (predictive, preventive, personalized, and participatory care) [7].

Toward the realization of P4 medicine, the three fundamental factors illustrated in Figure 2 are essential [7]: systems biology and systems medicine, digital revolution, and consumer-driver healthcare and social networks. This means that informatics and engineering should radically enhance the capabilities for collecting, integrating, storing, analyzing, and communicating medical information beyond limitations on time and space, as in telemedicine or e-health. In other words, as shown in Figure 3, informatics and engineering can facilitate the social demand to provide the big data collection essential, which we could rephrase “method,” for physicians at the bottom layer of the data, information, knowledge, and wisdom (DIKW) pyramid [8], to enhance the innovation cycle of systems biology and systems medicine.

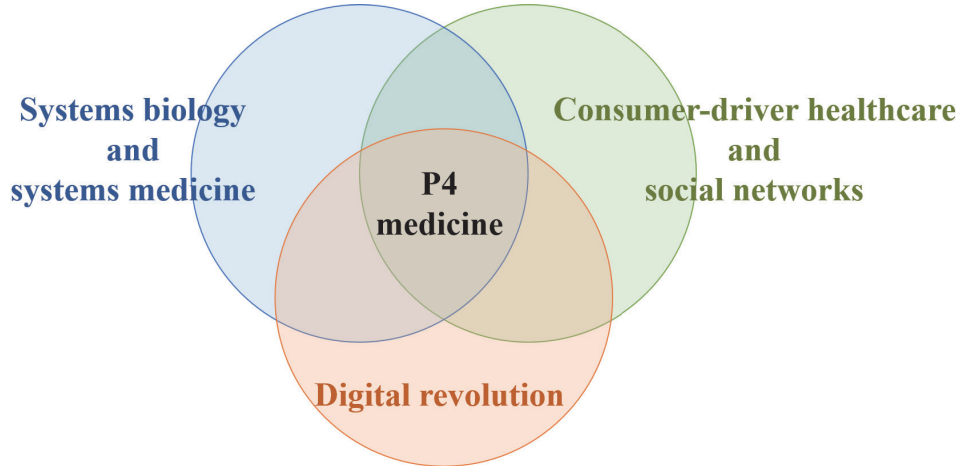


Figure 2: Three converging megatrends driving the transformation toward P4 medicine. This figure is based on [7].

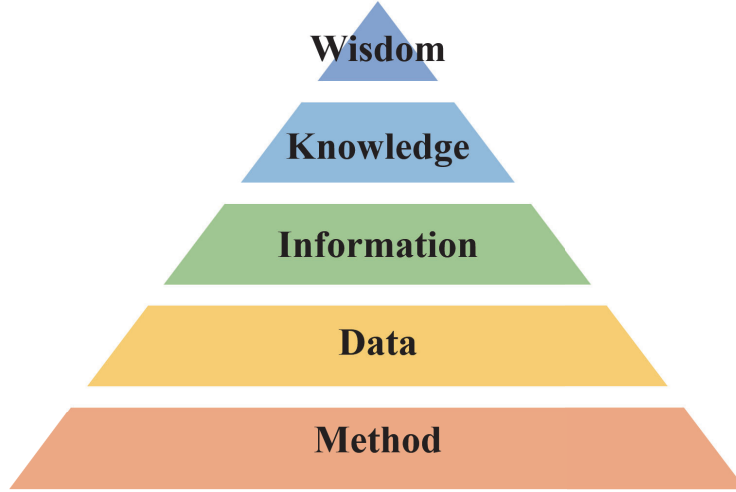


Figure 3: DIKW pyramid supported by a method enabling data collection.

1.2 Position of Research

A healthy life depends on a well-balanced diet, moderate physical activity, and good sleep. Among these, sleep undoubtedly plays an important role: we theoretically spend approximately one-third of our lives sleeping. Because we live as members of society, however, with all the attendant demands on our time, constant self-help effort to establish healthy sleep habits has become quite an important issue.

Unfortunately, understanding how well people sleep remains an unsolved issue even in Japan. Although the National Sleep Foundation (NSF) advocates a recommended sleep time range in which people need at least seven hours of sleep regardless of age [9], approximately 73.4% of Japanese sleep less than seven hours, according to the *National Health and Nutrition Survey in Japan, 2017* [10]. Just as sleeplessness is known to influence daily activities [11], it is even worse among patients with sleep disorders. This research therefore focuses on sleep disorders rather than non-pathological sleeplessness, because most sleep disorders are chronic diseases requiring both precise treatment based on the actual severity of symptoms with their night-to-night variability and constant self-help effort by patients for their own treatment.

In improving quality of life (QoL) among sleep disorder patients and reducing socioeconomic losses, it is quite important to implement P4 medicine

for sleep disorders through appropriate clinical observation of sleep-related conditions on a daily basis. Although physicians can conduct the current gold-standard multifaceted sleep evaluation method, namely, fully attended polysomnography (PSG), in a hospital laboratory, it is almost impossible to conduct PSG on a daily basis with the current limited medical resources. It is therefore important to incorporate home telemedicine in the field of sleep medicine, called out-of-center sleep testing (OCST), which can be performed outside hospitals by involving patients in the objective observation of their own sleep at home [12]. Hence, easy-to-use OCST devices should be developed for non-experts to implement appropriate objective observation of sleep outside a hospital, in a daily life environment.

By considering currently available devices for OCST together with the potential patients of each sleep disorder, this doctoral research sets periodic limb movement disorder (PLMD) as the target sleep disorder. Although potential patients with PLMD could follow the most prevalent sleep disorder obstructive sleep apnea (OSA) [13], most potential patients with PLMD remain undiagnosed. The reason is the lack of appropriate monitoring devices for its unique symptoms, namely, periodic short-lasting involuntary movements called periodic limb movements (PLMs), which mainly occur in the lower extremities. Furthermore, this lack of devices can disrupt precise treatment of patients with PLMD even after a definitive diagnosis.

Hence, this doctoral research aims to newly develop easy-to-use wearable devices for unaided surface electromyography (EMG) measurement by non-experts, specifically targeting PLMs home monitoring via its essential biosignals (i.e., surface EMG). The main contributions of this research are the following three: to propose a combination of target muscles for surface EMG-based PLMs home monitoring; to develop an easy-to-use sock-type wearable device for unaided surface EMG measurement by non-experts; to confirm the performance of the developed device in actual PLMs home monitoring.

This dissertation clarifies the issues and organizes the requirements in developing a surface EMG measurement device assuming unaided home use

by non-experts. For the first contribution, this study investigated all the muscles related to PLMs after visually observing the induced leg movements. Accordingly, this study determined the target muscles for surface EMG-based PLMs home monitoring and then confirmed that the performance could exceed that of the current de facto standard method based on acceleration.

For the second contribution, this study developed an easy-to-use wearable device for unaided surface EMG measurement by non-experts, comprising a sock-type fabric adaptor with embedded fabric electrodes. Then, through a preliminary validation targeting voluntary movements, its basic performance on surface EMG measurement was confirmed to be sufficient for discriminating the presence/absence of muscle activity.

For the third contribution, through comparative evaluation against visual observation of PLMs by a physician, this study confirmed that the PLMs home monitoring performance of the developed device was better than that of the current de facto standard method using acceleration.

These contributions can foment future researches on revealing PLMs conditions outside a hospital, which can support better understanding of the relationship between medication and actual PLMs conditions. This work will also support exploration of new treatment strategies based on the aforementioned findings, and even development of more effective application software to establish and sustain better sleep habits by considering those strategies.

1.3 Thesis Structure

The remaining chapters of this dissertation describe the aforementioned contributions together with the background, method, and evaluation in detail. The chapters are structured as follows.

Chapter 2 overviews the basic topics of this research, namely, sleep and home telemedicine in the field of sleep medicine (i.e., OCST). The overview includes fundamental knowledge of sleep itself and of sleep disorders, as well as a brief summary of OCST and recent research on next-generation OCST.

Chapter 3 illustrates the specific background of the proposed method,

together with its essential idea and the requirements. Specifically, the chapter introduces the target movements (i.e., PLMs), the essential characteristics of muscle activity and surface EMG measurement, and related research on easy-to-use wearable devices for biosignal measurement by non-experts. This chapter then introduce the core idea of the proposing method together with its requirements.

This dissertation sequentially describes the proposed method from Chapter 4 to Chapter 6. First, Chapter 4 describes selection of the target muscles for surface EMG-based PLMs home monitoring, in advance of the actual device development. This chapter includes the results of a preliminary comparative evaluation between the proposed method and the current de facto standard acceleration-based method, in which we employed commercially available devices.

Chapter 5 describes the development of the proposed easy-to-use sock-type wearable device for unaided surface EMG measurement by non-experts in detail. It also presents the results of a basic performance evaluation targeting surface EMG measurement during voluntary movements, involving both the proposed device and conventional measurement electrodes.

Chapter 6 describes overnight surface EMG measurement with the proposed device for PLMs home monitoring. It also includes the results of a preliminary performance evaluation comparing the proposed device and the de facto standard acceleration-based method using a commercially available device with medical approval.

Finally, Chapter 7 concludes the dissertation by summarizing the main findings and contributions of this doctoral research, as well as discussing the current limitations, future issues to address, and their impact on future research.

Chapter 2 Sleep and Home Telemedicine

Nutrition can be considered the most important need for living things. To obtain nutrition, the brain intensively processes information from every part of the body and acts as a commander controlling the other parts of the body. The brain, however, is a very delicate and fragile organ: it becomes weaker in continuous operation and easily falls into hypofunction due to overuse. Sleep is thus an indispensable management mechanism for the brain to maintain its roles of nurturing, regulation, and restoration for both better performance and overuse prevention [11, 14].

Although human beings require at least seven hours of sleep regardless of age [9], understanding how well people sleep remains an unsolved issue even in Japan. This issue is more critical among patients with sleep disorders that induce chronic sleeplessness. There are over 50 diagnostic terms [15], however, among sleep disorders, whose symptoms vary from each other, and their severity is not constant even in the same patient. Although each sleep disorder requires appropriate treatment based on the actual severity of the derived symptoms and its night-to-night variability, the current situation for treating sleep disorders is not sufficient to monitor patients' actual symptoms on a daily basis.

To clarify the position of this research together with its background, this chapter briefly summarizes the essential elements of sleep itself, enabling understanding of deviation from sleep normality, followed by the elements of sleep disorders and related technologies. First, 2.1 introduces the essential characteristics of sleep. Then, 2.2 introduces the inherent characteristics of sleep disorders, as well as current sleep monitoring methods in a hospital laboratory and requirements for home monitoring. Lastly, 2.3 introduces home telemedicine and sleep testing outside a hospital, called out-of-center sleep testing (OCST), and then summarizes recent research on next-generation OCST, which is essential to clarify the position of this research.

2.1 Overview of Sleep

2.1.1 Growth of Sleep and Recommended Sleep Time

Sleep itself is not constant throughout life but grows after birth; this growth of sleep is not limited to sleep time but extends over the circadian rhythm of day and night [16]. As a normal developmental stage of sleep, a newborn baby repeatedly sleeps and wakes regardless of time [16]. A baby starts sleeping through the night, however, approximately three months after birth [16]. We can also catch a glimpse of this growth in sleep via daytime sleep (i.e., naps): the rate of daytime sleep gradually decreases after birth, and it disappears at the age of 3–4 [17].

Reflecting these facts, the recommended sleep time greatly varies with age [9, 18]. Figure 4 shows the recommended sleep time range for each age group as advocated by the National Sleep Foundation (NSF) [9]. The figure confirms that we need at least seven hours of sleep regardless of age.

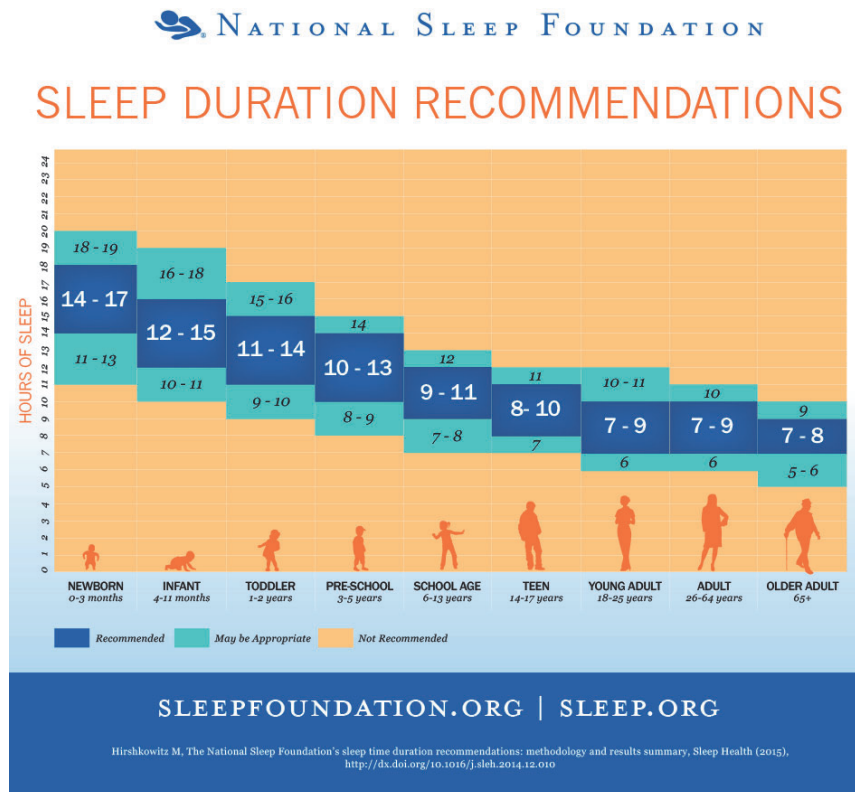


Figure 4: Recommended sleep duration for each age groups [9].

2.1.2 Architecture of Sleep and Its Status Transition

Within sleep, there are two different states on the basis of a constellation of physiological parameters: rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. REM sleep is characterized by brain activation with rapid eye movement, in which we dream a legibly realistic dream. Here, a “dream” is an image that is instantly synthesized along with random information calls from the brain’s memory, so that REM sleep is considered to be involved with regulation of the brain [19]. Conversely, in NREM sleep, the brain’s metabolic activity decreases to at most 40% as compared to the wake state [14, 19]. NREM sleep is subdivided into three stages based on electroencephalogram (EEG) levels, namely, N1, N2, and N3, and these three stages roughly parallel a depth-of-sleep continuum [11]. The deepest NREM sleep stage N3 is, so to speak, the sleep of the brain itself, and it is related to the brain’s rest, restoration, and growth [19].

Figure 5 shows an example of one night’s sleep in a healthy adult. Among healthy adults, normal sleep starts from shallow NREM sleep (i.e., N1 or N2) and then turns into deep NREM sleep (i.e., N3). Appropriately 90 minutes after sleep onset, it turns into the first REM sleep of the night [19]. This NREM-REM sleep alternation over a period of about 90-110 minutes occurs approximately four to five times through the night [11, 14, 19]. As shown in the figure, comparatively deep NREM sleep mostly occupies the beginning phase of sleep; conversely, comparatively shallow NREM sleep and REM sleep mostly occupy the last phase of sleep [14, 19].

The exact transition pattern of the sleep stages in detail is not constant but might differ from night to night even in the same individual. Adding to this, many factors including age and sex also influence the duration of overall sleep itself as well as that of each sleep stage, together with each stage’s proportion [11, 14]. Figure 6 shows the aging effect on sleep [20], indicating that aging can be related to both decreasing sleep duration and changing proportions of each sleep stage.

These kinds of changes in sleep structure are much more complicated among women: before menstruation, hormone balance changes together with the

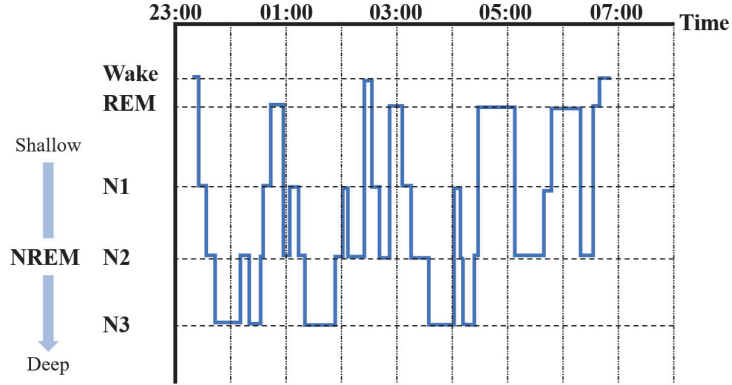


Figure 5: Example sleep stage transition during one night’s sleep. This figure is based on [11].

upcoming menstruation cause comparatively shallow sleep (i.e., increase in N2 along with decrease in both N3 and REM) and even intensifies sleepiness in the daytime [14]. These characteristics are deeply affected by lifecycle aspects like pregnancy, childbirth, and menopause [21].

Although all the aforementioned factors can cause changes in sleep, they are not problems as long as a person can wake up without difficulty. When sleeplessness occurs more than three times per week, however, an appropriate treatment plan should be considered [11] to avoid sleep deterioration, which disrupts restoration of the body and brain and can even degrade daytime activity performance.

2.2 Sleep Disorders

2.2.1 Sleep Disorders and Its Classification

Although the NSF advocates a recommended sleep time range in which we need at least seven hours of sleep regardless of age [9], approximately 73.4% of Japanese sleep less than seven hours according to the *National Health and Nutrition Survey in Japan, 2017* [10]. Furthermore, according to an epidemiological survey targeting the general Japanese adult population, 21.4% of adults complained of sleeplessness [22], 14.9% were aware of daytime sleepiness [23], and several percent (3.5% of men, 5.4% of women) had taken sleeping pills within the past month [23].

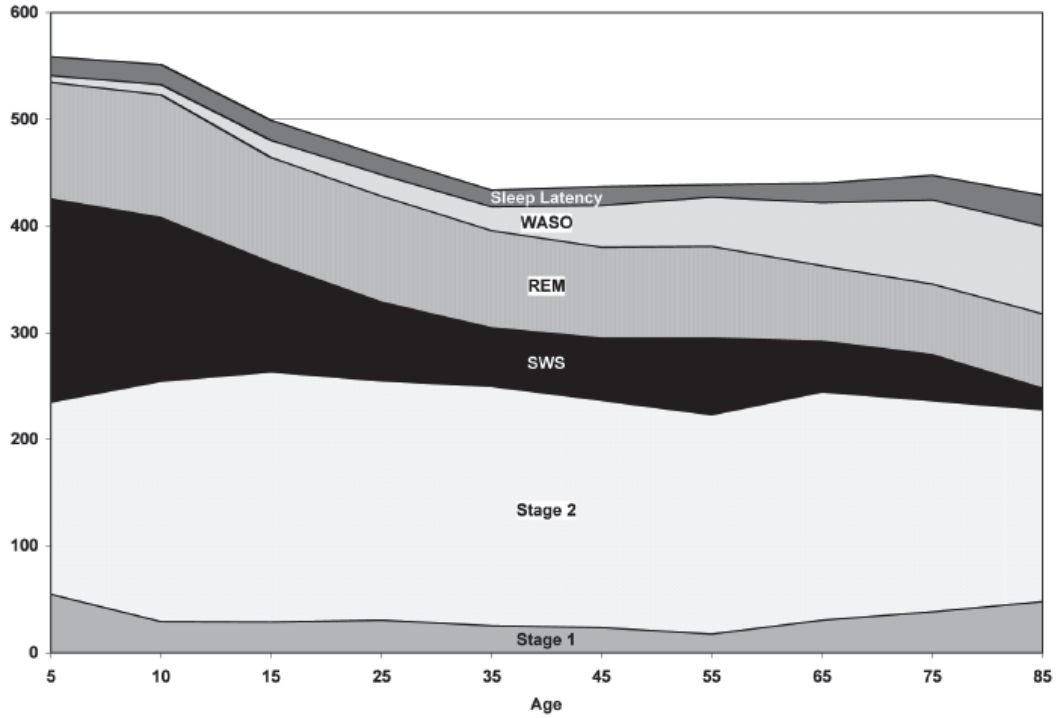


Figure 6: Age-related trends for each sleep stage and sleep latency (in minutes) [20]. The figure depicts N1 sleep (stage 1), N2 sleep (stage 2), slow-wave sleep (SWS), REM sleep, and wake after sleep onset (WASO). Note that SWS in this figure is considered the same as stage N3 described in the text.

Just sleeplessness is known to influence daily activities [11], and this is even worse among patients with sleep disorders that induce chronic sleeplessness. Sleep disorders truly disturb sleep itself, but their influence is not limited to sleep: several sleep disorders have been reported to be associated with or exacerbate other diseases [24–28]. Because these situations may also cause socioeconomic losses, represented by increased medical expenses [29, 30], appropriate treatment of sleep disorders is quite important for both improving quality of life (QoL) among sleep disorder patients and reducing socioeconomic losses. This research therefore focuses on sleep disorders rather than non-pathological sleeplessness, because most sleep disorders are chronic diseases requiring both precise treatment based on actual symptoms and constant self-help effort by patients for their treatment.

Although there are over 50 diagnostic terms in sleep disorders, they are

roughly classified into seven categories as listed in Table 1 in accordance with the representative international classification of sleep disorders, namely, the *International Classification of Sleep Disorders*, third edition (ICSD-3) [15]. Among all sleep disorders, the most common in Japan is considered to be obstructive sleep apnea (OSA) [13], which is characterized by frequent episodes of absent airflow (i.e., apnea) or decreased airflow (i.e., hypopnea) during sleep [15].

As indicated by the category names, the symptoms vary. Furthermore, their severity is not constant even in the same patient but varies from night to night. Although each sleep disorder requires appropriate treatment based on the actual severity of the derived symptoms and the night-to-night variability, it is quite difficult for potential patients or even diagnosed patients of sleep disorders to precisely perceive their actual symptoms on a daily basis.

Table 1: Sleep disorders as defined in ICSD-3 [15].

Category of sleep disorders	Number of diseases	Example disease
1. Insomnia	3	Chronic insomnia disorder
2. Sleep related breathing disorders	17	Obstructive sleep apnea
3. Central disorders of hypersomnolence	8	Narcolepsy type 1
4. Circadian rhythm sleep-wake disorders	7	Delayed sleep-wake phase disorder
5. Parasomnias	14	REM sleep behavior disorder
6. Sleep related movement disorders	10	Periodic limb movement disorder
7. Other sleep disorders		

2.2.2 Target Sleep Disorder: Periodic Limb Movement Disorder (PLMD)

Periodic limb movement disorder (PLMD) is characterized by frequent episodes of sleep deprivation due to periodic involuntary movements occurring mainly in the lower extremities, which are referred to as periodic limb movements (PLMs) [31, 32]. These PLMs may finally cause perceivable poor sleep experience represented as difficulty in falling asleep, nocturnal awakening, waking up too early in the morning, or even excessive daytime sleepiness due to sleep deprivation. The PLMs occurrence in one night changes along with

the transition among sleep stages, so that we cannot constantly observe PLMs throughout the night [15,33]; they can appear immediately with the onset of N1 sleep, be frequent during N2 sleep, and decrease in frequency in N3 sleep, and they are usually absent during REM sleep. PLMs typically occur in discrete episodes that last from a few minutes to an hour [15].

Although the exact morbidity of “primary” PLMD remains unclear [15], several findings on PLMs morbidity have been revealed to some extent. In adults, there is a significant increase in sleep disturbance symptoms with more than 15 PLMs per hour, so this is the current diagnosis threshold for PLMD [15]. The diagnosis threshold is 5 per hour in children on the basis of substantial normative data [15]. PLMs occurrence itself in children and adults younger than the age of 40 years is very uncommon but markedly increases with advancing age: over 45% of the elderly experience more than 5 PLMs per hour [15]. The population prevalence of PLMs occurrence over 15 per hour has been estimated at 7.6% of 18- to 65-year olds, with 4.5% of the total population also reporting sleep disturbance or excessive sleepiness [15]. Several reports targeting Japanese adults also support this estimation [13,34,35]. In addition, PLMs are not unique to PLMD but have also been reported to occur in approximately 80–90% of patients with restless leg syndrome/Willis-Ekbom Disease (RLS/WED) [36], whose clinically significant prevalence has been reported as 2–3% in Europe and North America [15]. Considering these findings, PLMD might be the second most prevalent sleep disorder following OSA; and at least PLMs themselves potentially affect a large number of people, many of whom possibly remain undiagnosed.

Although both PLMD and RLS/WED are suspected to be associated with A11 dopamine system dysfunction [37], the fundamental causes remain unclear and no radical treatments have been established. Physicians have reported, however, that patients with PLMD or RLS/WED accompanied by PLMD could even suffer from other fatal diseases, such as cerebral infarction and myocardial infarction [26,27], because each PLM event temporarily suppresses blood pressure. For these reasons, patients diagnosed with PLMD must undergo symptomatic treatment, including medication to suppress the number of PLMs

during sleep [36, 38]. Here, note again that the severity of PLMs shows night-to-night variability [39], and this night-to-night variability can remain even with medication. It is therefore important to monitor actual PLMs conditions on a daily basis to ensure appropriate symptomatic treatment by medication.

Aside from the above, the symptoms of RLS/WED, including PLMs, are also known to occur in some patients without primary PLMD or RLS/WED, such as pregnant healthy adults and patients with other diseases, such as iron deficiency or renal insufficiency treated with hemodialysis [40] (so-called secondary RLS/WED [41]). Although secondary RLS/WED can be resolved by appropriately treating the main causes, both the sleep quality and daytime sleepiness may worsen until then. Delayed treatment of the main causes may increase the risk of cardiovascular disease, as it does in patients with primary PLMD or RLS/WED.

Given all the above considerations together with the fact that much research targets the most prevalent sleep disorder (i.e., OSA) at the present moment, this research sets PLMD as the target.

2.2.3 Diagnostic Procedure and Treatment after Diagnosis

The diagnostic procedure for sleep disorders is divided into three steps: outpatient care, definitive diagnosis, and treatment. Figure 7 illustrates an example diagnostic procedure in Japan. To clarify the issues to address, this section summarizes the essential factors and generally used tests in each step.

Outpatient Care before Definitive Diagnosis

Toward appropriate diagnosis of sleep disorders, physicians first focus on the subjective complaints about sleep, such as nighttime sleeplessness, excessive daytime sleepiness, abnormal periods of time for sleeping, or abnormal phenomena during sleep [11]. Physicians try to comprehensively gather the information on sleep from the perspective of both the general conditions (e.g., the sleeping environment, other diseases and related health conditions, medication status) and sleep-disorder related conditions (e.g., apnea or involuntary leg movements). Then, they try to clarify the main causes of the subjective complaints.

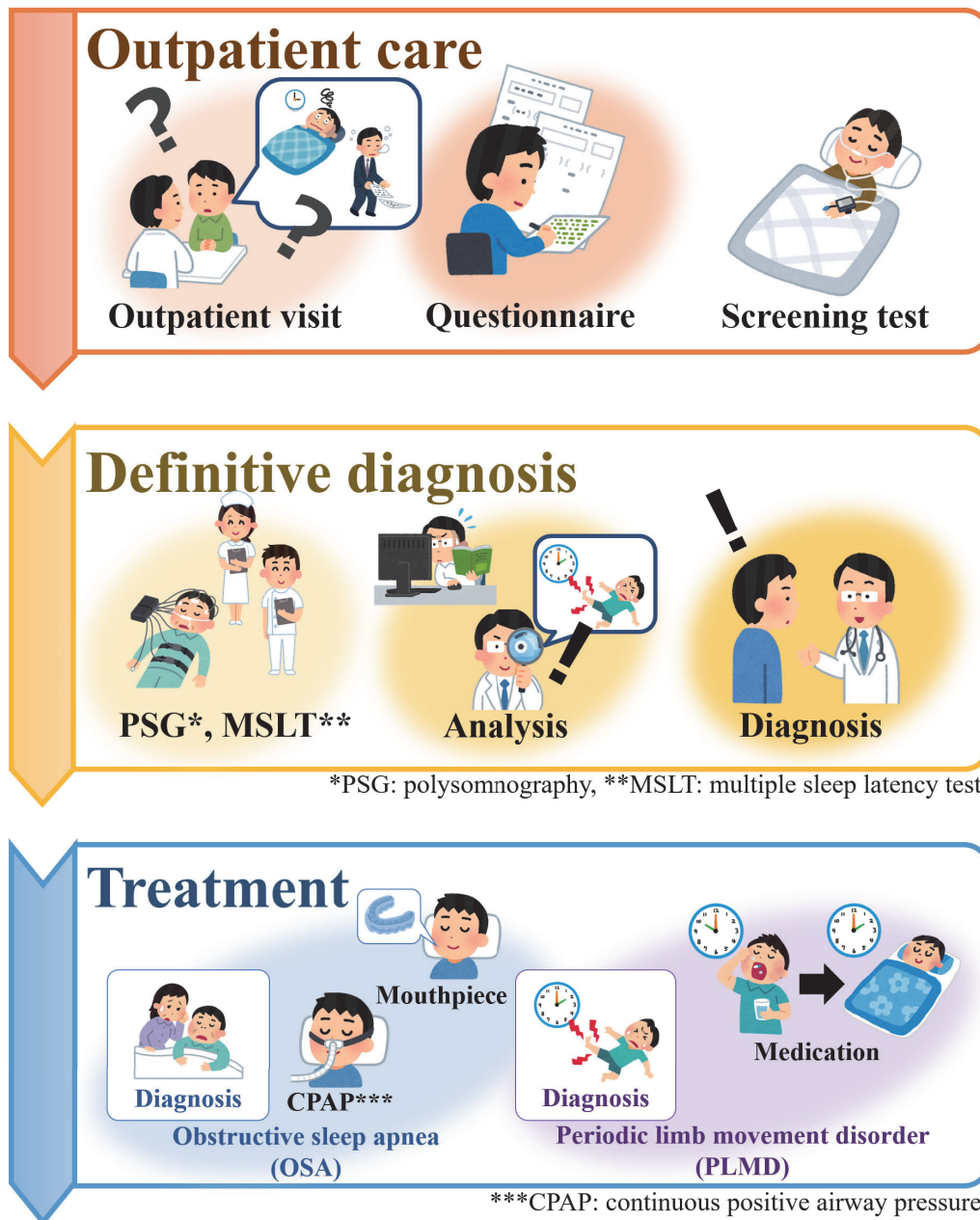


Figure 7: Diagnostic procedure for sleep disorders in Japan.

Under the clinical setting in practice, physicians first focus on the subjective complaints by using several questionnaires that reveal perceivable general conditions of sleep (e.g., the Pittsburgh sleep quality index (PSQI) [42]), excessive daytime sleepiness (e.g., the Epworth sleepiness scale (ESS) [43,44]), or abnormal phenomena during sleep (e.g., perceivable abnormal sense occurring in the lower extremities as measured by the International Restless Legs Syndrome Study Group rating scale [45,46]).

In addition to these questionnaires, physicians often use a sleep diary like that shown in Figure 8 to capture habitual bedtimes together with time in bed. Although sleep habits themselves are undoubtedly influenced by a person's social activities such as a job, physicians try to focus on the deviation from sleep normality. For instance, regarding just "sleeplessness," physicians try to find out which type of sleeplessness patients experience (e.g., difficulty in falling asleep, difficulty in staying asleep, unrefreshed sleep, or waking up too early in the morning). It is therefore important to understand the normal wake-sleep cycle of each patient by using a sleep diary to give an overview of sleep habits at a glance.

Aside from these paper questionnaires, physicians also conduct several screening tests, such as measuring the blood oxygen level with a pulse oximeter [15] (i.e., peripheral capillary oxygen saturation (SpO_2)), to gather objective evidence supporting the subjective complaints.

Definitive Diagnosis

To clarify all the activities of the brain and body during sleep together with their relationship, physicians conduct polysomnography (PSG), which evaluates sleep from various perspectives based on various biosignals: the EEG, electrooculogram (EOG), electrocardiogram (ECG), electromyography (EMG), and respiration [47]. The following subsection 2.2.4 introduces the configuration of PSG in detail.

When a potential patient mainly complains of excessive daytime sleepiness, physicians additionally conduct a multiple sleep latency test (MSLT) right after overnight PSG to quantitatively evaluate the patient's daytime sleepiness together with the sleep stages [15,48].

2019 年 11 月 1 日 ~ 2019 年 11 月 30 日

<次回、必ず受付へお渡しください>

- 1 起きていた時間 ⇒ 塗らない
- 2 実際に寝ていた時間 ⇒ 上枠を斜線
- 3 布団に入っていた時間 ⇒ 下枠を塗りつぶす



	1 起きていた時間												2 実際に寝ていた時間												3 布団に入っていた時間												
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/ 4 (月 曜日)																									0440-0954	4
/ 5 (火 曜日)																									0343-0601	5
/ 6 (水 曜日)																									0037-0613	6
/ 7 (木 曜日)																									0337-0623	7
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Figure 8: Example of an actual sleep diary (in Japanese).

Outpatient Treatment after Definitive Diagnosis

After a definitive diagnosis, physicians move on to symptomatic treatment based on the actual symptoms in the patient, because most sleep disorders are chronic diseases with no radical treatment.

As the diagnostic classification suggests, this symptomatic treatment varies among sleep disorders. For example, treatment may consist of airway maintenance by a mouthpiece or continuous positive airway pressure (CPAP) [49] for OSA, involuntary leg movement suppression by medication for PLMD [36, 38], or excessive daytime sleepiness suppression by medication for narcolepsy [50]. In this way, the treatment plan after a definitive diagnosis differs for each sleep disorder even with a simple medication, and even the appropriate amount of medicine for each patient can differ, as well. Ideally, physicians should therefore consider an appropriate treatment plan for each patient according to the symptoms and their severity, including the night-to-night variability.

2.2.4 Sleep Monitoring in Hospital Laboratory

As mentioned in 2.1.2, the change in sleep stages influences both the brain and the body. The influence is not limited to brain waves but affects eye movements and body muscle activity as well. Physicians therefore evaluate sleep stages at least based on EEG, EOG, and chin EMG, all of which are measured in PSG [47].

For the definitive diagnosis of each sleep disorder, physicians additionally measure other biosignals as shown in Figure 9: leg EMG, respiration (i.e., airflow and respiratory effort signals), SpO₂, body position, and ECG. Then, they analyze all these biosignals in accordance with the guidelines of the American Academy of Sleep Medicine (AASM), the *AASM Manual for the Scoring of Sleep and Associated Events* (hereafter, the AASM scoring manual) [47], to reveal the relationship among them. For this reason, the latter type of PSG is considered the gold standard method for multifaceted sleep evaluation.

Because PSG for definitive diagnosis simultaneously measures various biosignals throughout the night, it requires full attendance of a medical expert to ensure precise measurement by on-demand equipment rectification,

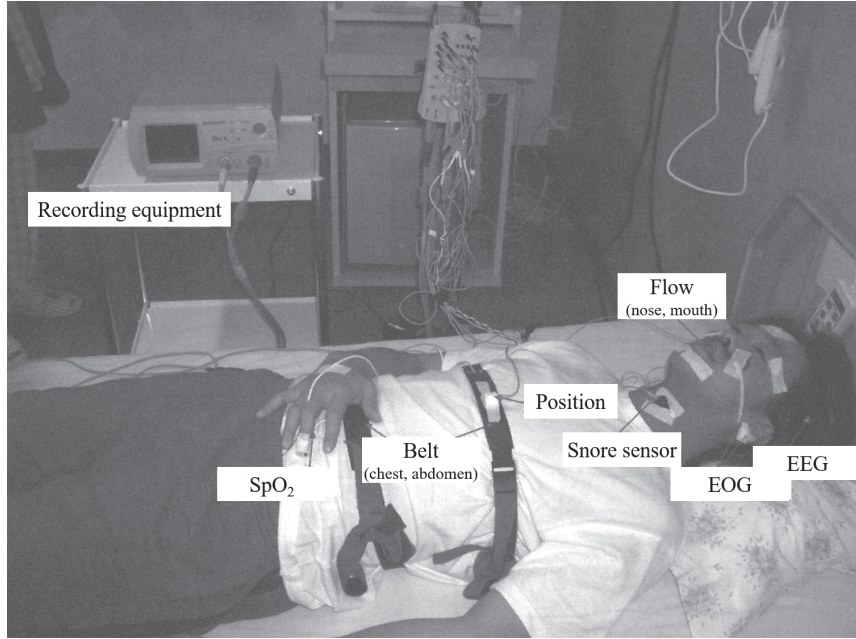


Figure 9: Example of a PSG setup from [51]. The annotations were translated by the present author. When physicians take PLMD into account, surface EMG of the bilateral tibialis anterior for PLMs evaluation would be added to the setup depicted here.

including replacement of measurement electrodes that fall from the designated place. Aside from this, it requires several cumbersome activities such as visual confirmation of all measured biosignals or even manual correction of automatically analyzed sleep stages by sight observation. This cross-sectional evaluation based on various biosignals involves the labor of physicians and well-trained medical technicians, and PSG is therefore expensive to perform, costing approximately \$700 [12]. This situation also limits the number of patients who can undergo PSG in one facility at a time.

2.2.5 Wants for Home Monitoring

In the current diagnostic procedure, physicians confront two remaining issues as shown in Figure 10: treatment dropout of potential patients before a definitive diagnosis, and treatment adherence of diagnosed patients after a definitive diagnosis.

The former issue of treatment dropout by potential patients could be related

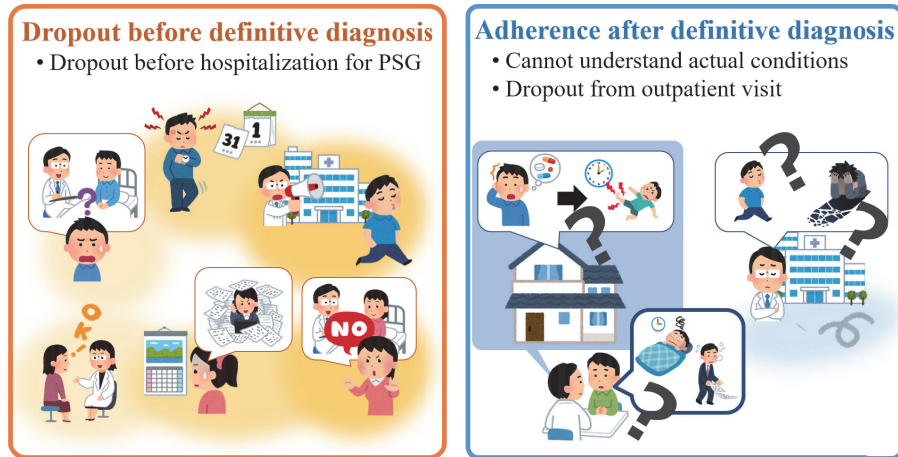


Figure 10: Remaining issues in the current diagnostic procedure.

to the current diagnostic procedure with limited medical resources. Overnight sleep condition evaluation using PSG may impose time constraints on patients themselves, because it theoretically requires at least one night of hospitalization. Because most hospitals limit the number of patients who can undergo PSG at a time, the waiting time for PSG sometimes becomes long, and this may even make it difficult to schedule the hospitalization of each patient. This situation sometimes causes treatment dropout of potential patients before a definitive diagnosis, especially when there is too little information to persuade patients to undergo PSG. For example, lack of information on current sleep conditions, including the occurrence of sleep-disorder specific symptoms and their severity, can sometimes cause dropout of potential patients.

The latter issue of treatment adherence by diagnosed patients could also be related to the lack of usual sleep monitoring at a patient's home. Because most sleep disorders are chronic diseases, patients diagnosed with sleep disorders might do an outpatient visit every few months to get therapeutic medicine or for therapeutic equipment rectification after a definitive diagnosis, especially in Japan because of its national health insurance. Within the very limited time of outpatient service (e.g., 10–15 minutes at most), physicians must perceive a patient's actual sleep conditions during the last few months, including sleep

disorder-specific symptoms and their severity, as precisely as possible, and then determine a treatment plan, including medication or therapeutic equipment rectification, for the next few months. Although patients can perceive their own general sleep conditions (e.g., sleep, sleeplessness, or excessive daytime sleepiness), it is quite difficult or practically impossible for them to accurately perceive sleep disorder-specific symptoms and their severity, because these symptoms mainly occur during sleep. Furthermore, the symptoms of several sleep disorders such as PLMs are known to show night-to-night variability [39]. Of course, patients diagnosed with a sleep disorder may have undergone PSG once before, but the results can suffer from the “first-night effect,” which causes noticeably worse sleep during the first night in a new place such as a hospital laboratory [16]. The results of PSG for definitive diagnosis therefore go no further than a snapshot of one night; we cannot regard them as the representative results of a patient. Physicians are thus ultimately compelled to determine treatment plans for upcoming months from limited information.

Toward realization of both early detection and appropriate treatment of sleep disorders according to the patient’s actual conditions during sleep, it is quite important to clarify the actual conditions, including the severity of sleep disorder-specific symptoms, on a daily basis. With the current limited medical resources, however, it is realistically impossible to conduct fully attended PSG in a laboratory on a daily basis, nor is there a rapid increase in certain hospitals where physicians can conduct PSG with well-trained experts. Consequently, there is a limit on diagnosis based on limited information.

Considering this situations, we need to consider how to observe patients’ sleep conditions outside a hospital on a daily basis by involving them especially for the purpose of a screening test or follow-up observation. We therefore require new types of devices for portable monitoring, which can be easily handled by unaided non-experts, to measuring sleep-related information as precisely as possible even in a daily life environment, including a patient’s home.

2.3 Home Telemedicine and Sleep Testing outside Hospitals

2.3.1 Home Telemedicine

Along with the remarkable progress in information and communication technology (ICT) in recent years, medical practice using ICT, including home telemedicine and e-health, has been progressing. Considering the current situation surrounding clinical medicine, it is important to disseminate appropriate medical care that can ensure safety, necessity, and effectiveness.

Reflecting this social condition, the currently available home telemedicine covered by Japan's national health insurance is quite limited and roughly divided into online medical consultation and home monitoring [52, 53]. Regarding home monitoring, only the following three treatments are currently covered by the national health insurance [53]: implantable cardiac pacemaker, CPAP, and home oxygen therapy (HOT). Note again that CPAP is therapeutic equipment for OSA.

Aside from these, although it is not currently covered by the national health insurance, home blood pressure monitoring in hypertension treatment has been gathering momentum, as confirmed by its guidelines [54]. We can therefore expect that home monitoring will further expand in the future.

2.3.2 Out-of-Center Sleep Testing (OCST) and Its Classification

Out-of-center sleep testing (OCST), also known as a home sleep test (HST) or portable monitor, is a well-validated alternative to PSG when physicians investigate sleep conditions outside a hospital [12]. We can therefore rephrase OCST as home monitoring in the field of sleep medicine. Because OCST uses a smaller number of more compact, less cumbersome sensors that do not require a medical technologist throughout the biosignal monitoring, non-expert patients can perform OCST by themselves at home, as the name suggests. This is especially beneficial for patients such as children or older people who might feel anxious staying overnight in a sleep laboratory to undergo PSG.

The AASM classifies OCST into four types, as listed in Table 2, according to the attendance of medical experts and the number of channels for sleep-related signal monitoring [55]. Type I indicates fully attended PSG in a hospital

laboratory for definitive diagnosis of sleep disorders, whereas types II, III, and IV indicate OCSST without the attendance of experts. According to this classification, OCSST uses fewer sensors as the type number increases; for instance, the commonly used type IV OCSST only measures a few biosignal channels such as SpO_2 or respiration. However, this AASM classification of OCSST is not sufficient; we cannot compare several different OCSST devices by using only this classification, because the measurement targets in each type of OCSST may vary. Furthermore, the AASM classification assumes the OCSST used for a (potential) OSA patient, reflecting the latest ICSD-3 [15], and comparing OCSST devices targeting other diseases such as PLMD would be more difficult.

Table 2: AASM classification for OCSST*.

Type	Portability	Attendance	Channels, n	Signals	≥ 2 Airflow/Effort Channels	Identifies Sleep/Awake Status	Measures AHI ^a
I	Facility-based	Yes	14-16	EEG, EOG, chin EMG, ECG/HR ^b , airflow, effort, SaO_2	Yes	Yes	Yes
II	Portable	No	≥ 7	EEG, EOG, chin EMG, ECG/HR ^b , airflow, effort, SaO_2	Yes	Yes	Yes
III	Portable	No	≥ 4	Airflow and/or effort, ECG/HR ^b , SaO_2	Yes	No	No, but estimates AHI
IV	Portable	No	1-3	All monitors that do not fit into type III classification	No	No	No, but estimates AHI

* Mainly quoted from [55], but several items were expressly added here.

^a AHI = apnea hypopnea index

^b HR = heart rate

^c SaO_2 = arterial oxygen saturation ¹⁾

To enable comparative evaluation of OCSST with the same specifications, another OCSST classification called SCOPER [56] focuses on both the measurement targets and the sensor types used for their measurement. It first classifies OCSST from the perspective of measurement targets, namely, sleep (S), cardiovascular (C), oximetry (O), position (P), effort of respiration (E), and respiration (R); then, it subclassifies OCSST into categories based on the sensor

¹⁾ Theoretically, SaO_2 indicates the oxygen saturation calculated by blood collection, whereas SpO_2 is calculated by a pulse oximeter. SpO_2 can be regarded as SaO_2 under clinical practice.

type (e.g., $S_3C_4O_2P_2E_3R_2$). Table 3 summarizes the SCOPER classification with its subclasses. In this classification, one commonly used AASM type IV OCST device measuring SpO_2 would be classified as $S_xC_xO_1P_xE_xR_x$, with most of the x lower than 4 or 0 (i.e., n/a).

Table 3: SCOPER classification for OCST [56].

	Sleep	Cardiovascular	Oximetry	Position	Effort	Respiratory
1	S ₁ —Sleep by 3 EEG ^a channels with EOG and chin EMG	C ₁ —more than 1 ECG lead can derive events	O ₁ —Oximetry (finger or ear) with recommended sampling ^b	P ₁ —Video or visual position measurement	E ₁ —2 RIP ^c belts	R ₁ —Nasal pressure and thermal device
2	S ₂ —Sleep by less than 3 EEG ^a channels with or without EOG or chin EMG	C ₂ —Peripheral arterial tonometry	O _{1x} —Oximetry (finger or ear) without recommended sampling (per Scoring Manual) or not described	P ₂ —Non-visual position measurement	E ₂ —1 RIP ^c belt	R ₂ —Nasal pressure
3	S ₃ —Sleep surrogate: e.g. actigraphy	C ₃ —Standard ECG measure (1 lead)	O ₂ —Oximetry with alternative site (e.g., forehead)		E ₃ —Derived effort (e.g., forehead versus pressure, FVP)	R ₃ —Thermal device
4	S ₄ —Other sleep measure	C ₄ —Derived pulse (typically from oximetry)	O ₃ —Other oximetry		E ₄ —Other effort measure (including piezo belts)	R ₄ —End-tidal CO ₂ (ETCO ₂)
5		C ₅ —Other cardiac measure				R ₅ —Other respiratory measure

^a 3 EEG channels: frontal, central, and occipital.

^b Proper oximetry sampling is defined as averaging over 3 s and a minimum sampling rate of 10 Hz (25 Hz desirable).

^c RIP: respiratory inductance plethysmography.

2.3.3 Current OCST in Practice and Remaining Issues

The currently available OCST is beneficial with regard to easy enough unaided home use, which can mitigate the waiting time for PSG [57]. At present, type IV OCST measuring oxygen saturation (i.e., SpO_2) can be used for definitive diagnosis of patients suspected of having OSA [15]. That is, if potential OSA patients satisfy the criteria, they can be diagnosed as having OSA without undergoing PSG. This revision in ICSD-3 [15] addresses the issue of treatment dropout by potential OSA patients, with less cost and less effort by medical experts.

Although other OCST approaches are not currently used for definitive diagnosis of any sleep disorders, acceleration-based devices have been collecting evidence for OCST to target follow-up observation among diagnosed patients. Here, a small watch-like acceleration-based device is used for collecting objective sleep-related information such as the sleep onset latency, total sleep time, and sleep efficiency [58]. Aside from this purpose, acceleration-based devices that can be worn around the ankle [59–63] are also practically used for PLMs monitoring at home as a follow-up observation for PLMD. Figure 11 shows examples of the above OCST devices.



Figure 11: Examples of OCST devices in practice

However, two issues remain in current OCST. The first issue is the overall accuracy in cross-sectional evaluation targeting sleep. Because OCST only records a few sleep-related biosignals as compared to PSG, it is sometimes impossible to conduct cross-sectional sleep evaluation because of the lack of sensors. For example, current OCST with commercially available devices cannot evaluate sleep stage transitions, which in principle requires monitoring EEG, EOG, and chin EMG. This issue becomes significant when physicians evaluate

patients with sleep disorders other than OSA. Reflecting the fact that the AASM only allows using OCST for definitive diagnosis of OSA at present, several OCST devices target only OSA-related biosignals. Furthermore, although several OCST devices target PLMs monitoring at home, they only measure alternative signals (i.e., acceleration), not the essential biosignals (i.e., surface EMG), and this may cause the second issue as follows.

The second issue is the accuracy of each device itself. Several OCST devices are only capable of measuring alternative signals, which only allow estimation; this tends to be noticeable as well when targeting sleep disorders other than OSA, such as PLMD. For instance, PSG with surface EMG of the bilateral tibialis anterior for definitive diagnosis of PLMD is, of course, the most reliable evaluation of PLMs, but currently there are no OCST devices for PLMs monitoring based on surface EMG of the bilateral tibialis anterior. Physicians therefore currently use acceleration-based devices that can be worn around the ankle as an alternative method for PLMs monitoring at a patient's home. Although several acceleration-based devices have received medical approval, it is difficult in principle to appropriately distinguish PLMs from voluntary movements. Acceleration around the lower extremities easily changes along with body movements, whereas it does not necessarily change along with PLMs; hence, these devices over-detect or overlook PLMs [61]. This situation would be unpreferable especially when physicians intend to conduct the follow-up observation. Recall that this approach is no more than indirect evaluation of sleep conditions. For each alternative sleep-related signal, we should therefore independently develop an appropriate evaluation method that is compatible with the AASM scoring manual used in PSG. Accordingly, these methods may become useful alternatives targeting sleep monitoring at home, especially when there is no other means to observe the targeted sleep conditions. In addition, the accuracy of each OCST method totally depends on a patient's self-management skills. Unlike PSG, in which medical experts check and rectify devices throughout the testing to ensure accurate biosignal measurement, OCST may sometimes fail to measure sleep-related biosignals because of sensors dropping off. We therefore should consider how to ensure stable biosignal

measurement throughout the night.

Considering all the above issues, we can conclude that OCST sacrifices accuracy for usability, to some extent, so physicians cannot evaluate OCST results in exactly the same way that they do for PSG results. This situation is especially noticeable in regard to PLMs home monitoring and sometimes results in over-detecting or overlooking PLMs.

2.3.4 Research toward Next-Generation OCST

Toward realization of OCST to enable more appropriate home monitoring of sleep-related biosignals, many approaches have been considered so far. We can roughly divide these approaches into two: one approach aims to achieve unaided measurement of the same biosignals as PSG at home, whereas the other approach aims to implement less invasive OCST by using alternative sleep-related signals other than those used in PSG.

Regarding the first approach, research has aimed to measure EEG alone [64–68], EOG alone [69], or the combination of EEG, EOG, and chin EMG [70] to enable more accurate observation of sleep conditions at home to capture sleep stage transitions. Note that research on this approach aims to achieve self-administered biosignal measurement at home by patients without any medical knowledge or any support from medical experts. The devices therefore look like objects familiar to patients such as earphones [64–66], hairbands [67, 68], eye masks [69], or full-face masks [70], none of which require any special knowledge for unaided setup. Other sleep-related signals like surface EMG of the bilateral tibialis anterior, however, have not yet been considered, so that physicians are still compelled to monitor PLMs at home by using alternative signals.

The second approach aims to implement less invasive OCST by using alternative sleep-related signals other than those used in PSG. Toward more appropriate OSA treatment, several approaches have been proposed [71–73]; each focuses on the mechanism of OSA itself and aims to measure OSA-related biosignals other than oxygen saturation. Note that these approaches assume unaided home use by patients without any medical knowledge by postulating the use of wearable devices for ECG recording [71, 72, 74], or by implementing

contactless respiration monitoring via Wi-Fi on a smartphone [73]. Aside from these approaches, other research aims to achieve audio-based snore sound recognition, which could provide a brand-new type of valuable information for OSA treatment, beyond PSG [75]. Regarding PLMD treatment, on the other hand, wearable devices using multiple accelerometers and placed around the lower extremities have been proposed for more appropriate acceleration-based PLMs evaluation [76]. Aside from this, PLMs home monitoring methods using a 3D depth sensor on the ceiling have also been proposed [77, 78]. Like the currently available acceleration-based PLMs monitoring devices, these PLMs evaluation approaches using alternative signals may be no better than surface EMG-based PLMs evaluation in PSG. They may also fail to detect comparatively faint PLMs occurring in the toes or ankles, which only involve relatively small partial body movements.

Overall, currently available OCST devices undoubtedly play a certain role in the treatment of sleep disorders, especially OSA. However, although the number of potential patients with PLMD may follow OSA, recent research still mainly focuses on OSA or common sleep-related conditions for all sleep disorders, such as EEG or EOG. In particular, for PLMs monitoring, there is no research on surface EMG measurement at home, and recent research focused only on alternative signals like acceleration [59–63, 76] or 3D depth sensor information [77, 78] may result in over-detecting or overlooking PLMs in principle. As a consequence, many patients with PLMD may still go undiagnosed, or physicians may be forced to determine a PLMD treatment plan based on limited information on the actual PLMs conditions.

PLMs occurring in the lower extremities could be observable by surface EMG of the bilateral tibialis anterior, as in PSG for definitive diagnosis. Therefore, we should develop a new type of surface EMG measurement device for unaided home use, which can be easily handled by non-expert users at their homes without any support from physicians or medical technicians throughout the use, including during setup and actual measurement. In addition, the device should be capable of distinguishing PLMs from other body movements and suppress measurement faults that might mislead physicians.

Chapter 3 Socks-Type Wearable Device for Surface EMG-Based PLMs Monitoring at Home

The current gold standard for periodic limb movements (PLM) evaluation targeting definitive diagnosis of periodic limb movement disorder (PLMD) is polysomnography (PSG) with surface electromyography (EMG) of the lower extremities. Because the intended users of such devices are physicians or medical experts, they are undoubtedly quite difficult for non-expert users without help. This is also because currently available surface EMG measurement devices are designed for experts who are knowledgeable about surface EMG measurement in the first place. That is, a designated user should be knowledgeable about the principles of surface EMG measurement itself together with essential related fields including biomechanics. Toward realization of surface EMG-based PLMs home monitoring, we should first develop easy-to-use devices targeting surface EMG measurement for unaided home use by non-expert users.

Meanwhile, recent technological development of functional materials such as conductive textiles [79–81] and conductive paste [82] has led to the development of practical wearable smart textile devices. These enable non-expert users to easily measure various biosignals, including electrocardiogram (ECG) [80,82,83] and surface EMG of the trunk and upper extremities [81], outside a hospital. This is possible, regardless of the user’s knowledge, by using an object familiar to non-experts as a setup adaptor for the measurement electrodes, together with embedded electrodes made of those functional materials. The measurement accuracy is generally lower than that of conventional gold standard methods with attendance by experts who can manually avoid measurement faults. Nevertheless, research has revealed that these could become useful alternative methods, especially for long-term or repetitive measurement of biosignals at a reasonable cost, such as managing the labor of bus drivers [84]. This study therefore considers the development of an easy-to-use device for surface EMG measurement targeting PLMs home monitoring by using similar approaches to

various related works [79–82].

This chapter thus proposes a sock-type wearable device targeting surface EMG-based PLMs monitoring for unaided home use by non-experts, while considering both biomechanical and human interface perspectives to ensure both accuracy and usability. First, 3.1 introduces the target movements (i.e., PLMs) in detail, and then 3.2 introduces the essential characteristics of muscle activity and surface EMG measurement to confirm the requirements for the proposed device. Next, 3.3 introduces related work on recently developed wearable devices for unaided biosignal measurement by non-experts. Lastly, 3.4 proposes the actual device.

3.1 Target Movements

3.1.1 Leg Movements Induced by PLMs

In the field of sleep medicine, PLMs are defined as involuntary movements that mainly occur in the lower extremities, typically involving extension of the big toe, resembling the Babinski reflex, in combination with the abduction or adduction of the toes [33] or partial flexion of the ankle, knee, or sometimes even the hip [31]. These movements can also start from extension of the big toe [85]. Figure 12 shows typical examples of leg movements induced by PLMs.

These movements are not constant but may vary among PLMs even in the same night: a PLM can comprise either of the above movements alone or a combination of two or more of them, which may vary even between two adjacent PLMs. It is also known, however, that PLMs can tend to involve flexion of the big toe alone [31].

3.1.2 Scoring Criteria of PLMs

For definitive diagnosis of PLMD, the current gold standard method for PLMs evaluation is PSG with surface EMG of the bilateral tibialis anterior (Figure 13) as described in 2.2.4.

Because all body movements inevitably activate related muscles in principle, this method mainly focuses on PLM-derived muscle activations occurring in the ankle. Physicians use this method to evaluate PLMs according to whether the measured surface EMG satisfies the criteria for PLMs, as defined in the

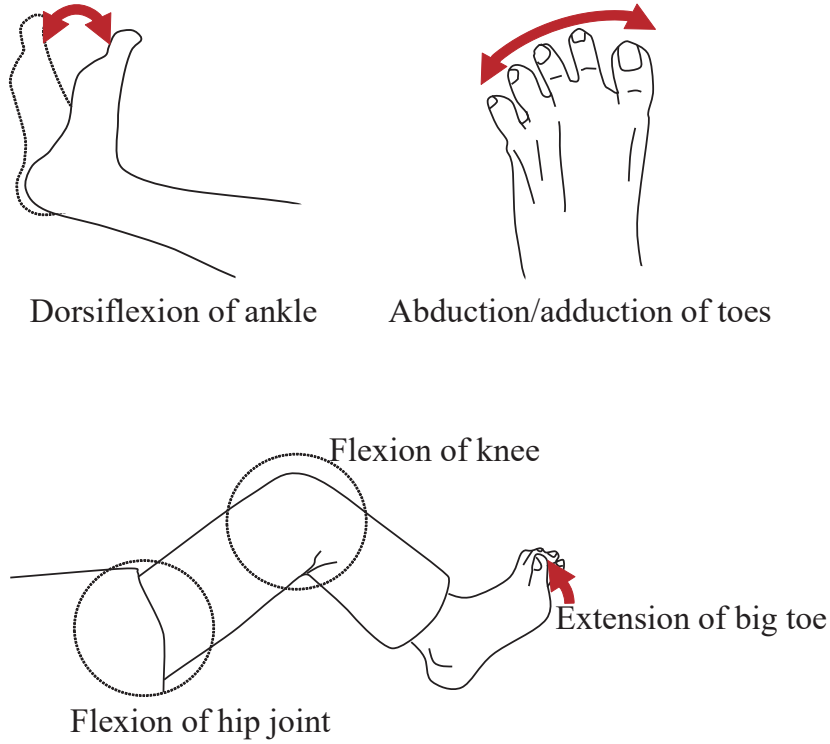


Figure 12: Typical examples of PLMs occurring in the lower extremities (originally shown in [33] and cited from [86] together with added annotations).

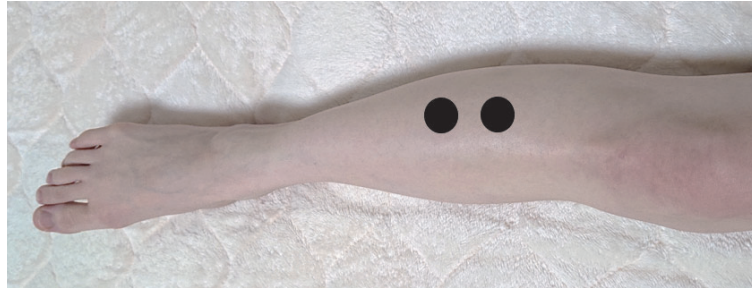


Figure 13: Electrode placement for PLMs evaluation in PSG. Each black dot indicates the location of a measurement electrode. This figure is based on [47]. Note that the scale may not be accurate.

American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events (hereafter, the AASM scoring manual) [47]. For a PLM, the AASM scoring manual regards a chain of muscle activations, which starts from resting and finishes in resting, as an “event.” It evaluates events one by one as a series of events. Thus, it defines two criteria (i.e., one for PLM event

detection and the other for a series of PLM events) and finally regards only certain consecutive PLM events satisfying both criteria as PLMs. Physicians therefore first evaluate surface EMG with regard to the amplitude and duration of muscle activation to extract candidate PLM events and then evaluate the inter-event intervals of several candidate events and the number of events in a series of PLMs.

Figure 14 summarizes the description defined in the AASM scoring manual [47]. PLMs must consist of a series of four or more consecutive movements, each lasting 0.5 to 10 s with inter-event intervals of 5 to 90 s and an amplitude greater than 8 μV above the resting baseline EMG signal [31]. According to the latest AASM scoring manual [47], physicians should additionally evaluate whether these detected candidate PLMs may be related to sleep-related respiratory activities such as apnea or hypopnea. For definitive diagnosis, they should only count candidate PLM events that are not associated with such activities measured in PSG.

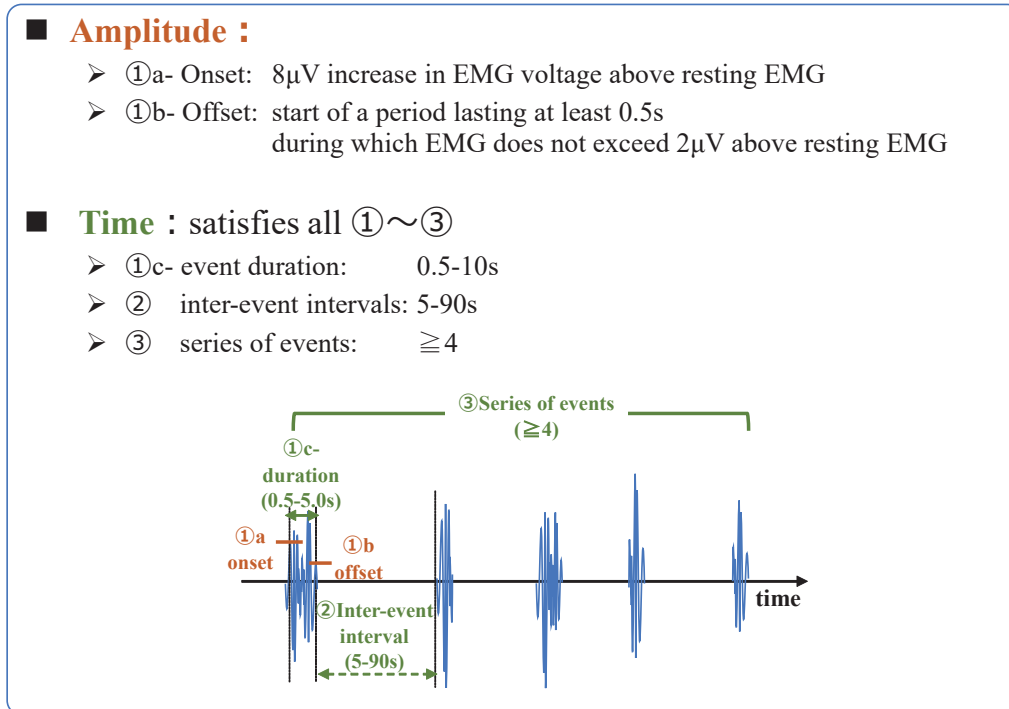


Figure 14: Illustrated criteria for PLMs evaluation, based on [47].

The definitive diagnosis of PLMD is determined in accordance with the PLM index (PLMI), which is defined as the number of PLMs divided by the observation time in hours [31]. The PLMI is generally considered abnormal when it is more than 15 per hour in adults, or 5 per hour in children [15,31,33].

Note that the AASM scoring manual gives, so to speak, add-on criteria for precisely measured surface EMG. In a clinical setting, fully attended PSG for definitive diagnosis of sleep disorders requires medical experts to manually ensure precise surface EMG measurement by on-demand equipment rectification, including replacement of measurement electrodes dropped from the designated place, as described in 2.2.4. Therefore, this research first ensures appropriate surface EMG measurement of the bilateral tibialis anterior and then applies the PLMs detection criteria defined in the AASM scoring manual.

3.1.3 Issues Toward Surface EMG-Based PLMs Home Monitoring

To achieve surface EMG-based PLMs home monitoring targeting a screening test for potential patients with PLMD or a follow-up observation for diagnosed patients with PLMD, ideally, we should appropriately measure the surface EMG of the bilateral tibialis anterior regardless of the environment and analyze it according to the AASM scoring manual, as much as possible.

We should therefore first develop a surface EMG measurement device for unaided home use targeting non-expert patients as its users. This device would detect certain leg movement events that at least satisfy the required duration of each event, inter-event intervals, and series of events. This is because we cannot currently guarantee the amplitude of surface EMG, which could be primarily due to the hardware configuration used for surface EMG measurement.

3.2 Essential Characteristics of Muscle Activity and Surface EMG Measurement

3.2.1 Mechanism of Muscle Activity

To appropriately address issues toward the development of a surface EMG measurement device for unaided home use by non-experts, this section first clarifies how myoelectricity originates.

The basic functional unit of the neuromuscular system is the motor unit,

comprising an α -motor neuron, including its dendrites and axon, and the muscle fibers innervated by the axon [87,88]. The motor neuron is located in the ventral horn of the spinal cord or brain stem, where it receives sensory and descending inputs from other parts of the nervous system, whereas the axon of each motor neuron exits the spinal cord through the ventral root, or through a cranial nerve in the brain stem, and projects in a peripheral nerve to its target muscle and the muscle fibers that it innervates [87–90].

As illustrated in Figure 15, the generation of an action potential by a motor neuron typically results in generation of action potentials in all the muscle fibers belonging to the motor unit via the axon of each motor neuron innervating muscle fibers, and this finally causes muscle activation by depolarization [87, 88, 90]. EMG recording of muscle fiber action potentials is therefore not the result of muscle activation but the main cause of muscle activation, while also providing information on the activation of motor neurons in the spinal cord or brain stem [87, 90]. This electrical activation begins from the axon’s innervation point to the muscle fiber (i.e., the neuromuscular junction) and propagates towards the end of the muscle fiber [90].

3.2.2 Surface EMG Measurement and Its Requirements

As shown in Figure 16, surface EMG measurement focuses on the above electrical activation, which also propagates on the surface of the skin. Because it measures the propagated electric potential from the skin surface covering the target muscle, we should ensure sufficiently low impedance between the measurement electrode and the skin. This requires stable placement of all measurement electrodes; if they do not adhere to the skin, changes in contact could cause a varying impedance between the measurement electrode and the skin, resulting in measuring artifacts.

Most conventional surface EMG measurement uses a differential amplifier to suppress the influence of common-mode noise derived from the body. Therefore, we should appropriately place at least three measurement electrodes for surface EMG measurement of one muscle: bipolar measurement electrodes for the target muscle and its body earth. Note again the mechanism of action potential generation in the muscle fibers: electrical activation in the muscle begins from

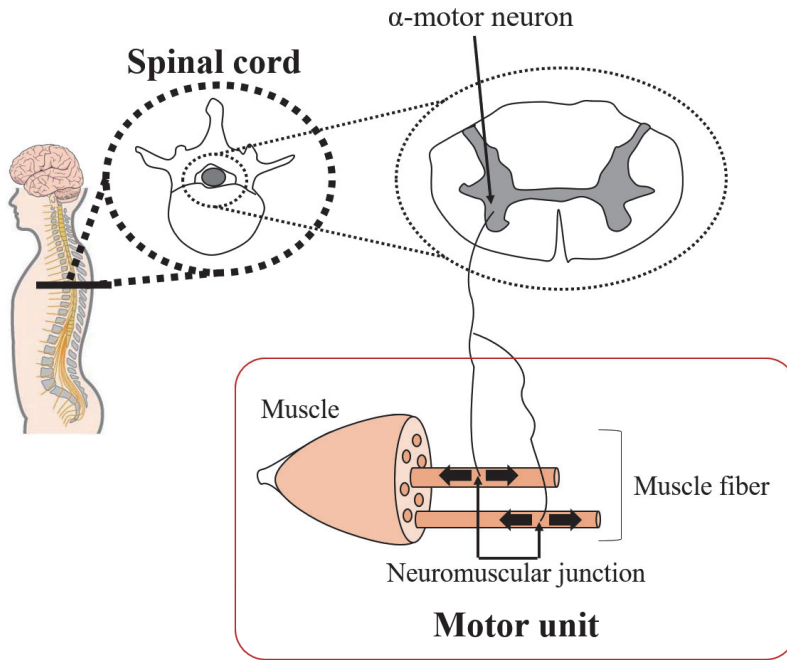


Figure 15: Principle of EMG. This figure is based on [88,90,91].

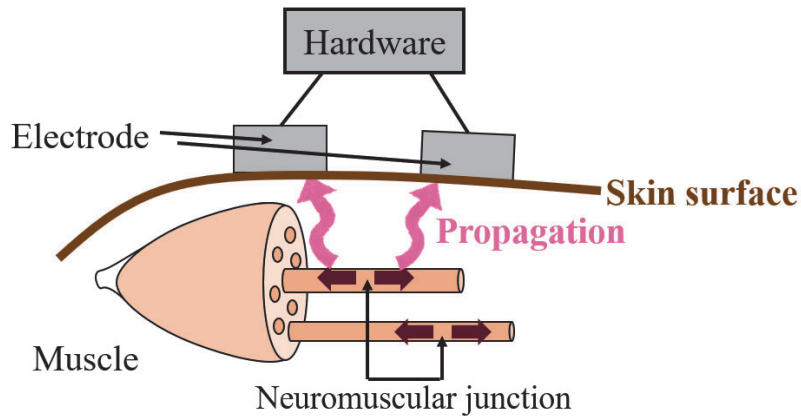


Figure 16: Principle of surface EMG measurement. This figure is based on [88,90,91].

the neuromuscular junction. We therefore should avoid placing a measurement electrode at an equal distance from neuromuscular junctions, which could cause measured signals to cancel each other out. Similarly, we should place the body ground at a certain location where it can avoid measuring surface EMG from

other muscles (i.e., crosstalk), either on the target muscle itself or a certain location far from other muscles (e.g., the knee cap).

Overall, we should satisfy the following two requirements when conducting surface EMG measurement.

- **Requirement A: Low contact impedance between the measurement electrodes and the skin.** To measure an EMG signal from the skin surface, the contact impedance between the measurement electrodes and the skin should be low enough.
- **Requirement B: Appropriate placement of the measurement electrodes.** All electrodes for surface EMG measurement (i.e., both the measurement electrodes and the body earth) should be appropriately placed at appropriate positions: the measurement electrodes should be on the target muscles, whereas the body earth should be at a certain point that is less influenced by other muscle activities. To avoid artifacts, the initial positions of the measurement electrodes should be stably maintained, without them dropping off or slipping on the target muscles.

3.2.3 Issues to Address for Unaided Surface EMG Measurement by Non-Experts

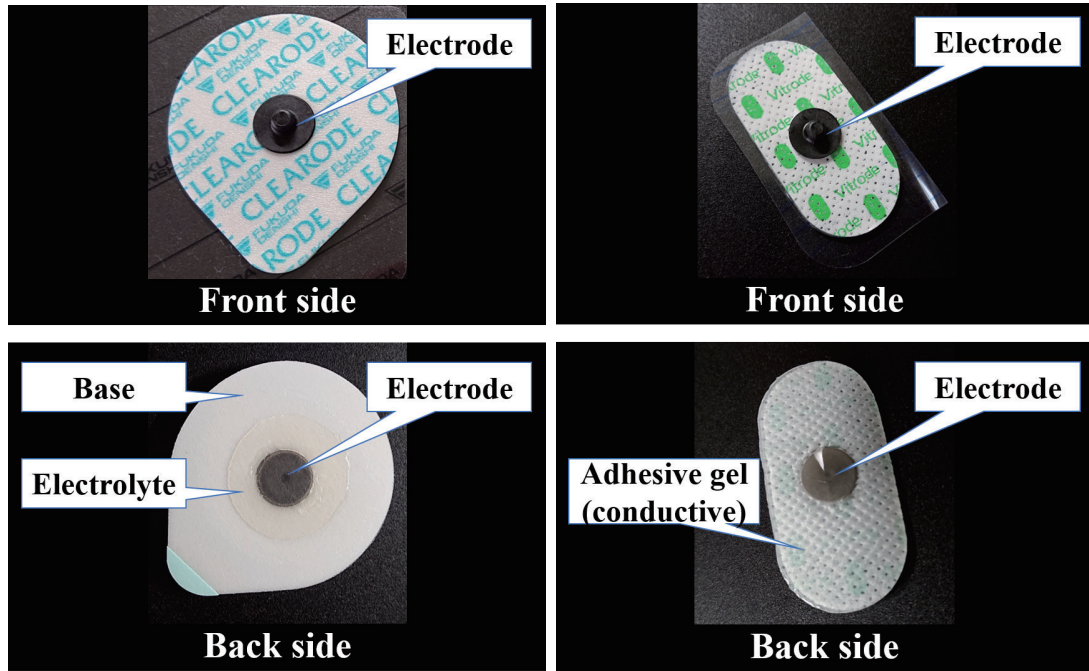
When non-experts conducting surface EMG measurement, they often encounter issues related to *requirement B*; issues related to *requirement A*, on the other hand, can be solved by using certain measurement electrodes with sufficiently low impedance.

Regarding the issues related to *requirement B*, we should understand well how the location of the target muscle together with its possible neuromuscular junction could relate to its muscle belly as well. It is quite difficult, however, for non-expert users to properly understand those issues, which require sophisticated knowledge of biomechanics and biosignal measurement. It is also difficult for them to set up all the devices for surface EMG measurement at home unaided, without any expert support.

Therefore, to put surface EMG-based PLMs home monitoring into practice in a daily life environment, we should first address the setup issues related to surface EMG measurement.

3.3 Wearable Devices for Biosignal Measurement

The recent development of functional materials has enabled the development of cutting-edge measurement electrodes with sufficiently low impedance, besides the traditional combination of Ag/AgCl electrodes and conductive gel (Figure 17); examples include conductive fabric (i.e., smart-textile) [79–81] as shown in Figure 18, and conductive paste [82]. These cutting-edge electrodes can improve usability in terms of preparation, as well: the impedance is low enough for biosignal measurement without requiring the typical preparation such as hair removal, so users simply have to place the measurement electrodes on the target location of the skin.



(a) Partial surface-gel type
(CLEARODE TEO-174DCR [92])

(b) Whole surface-gel type
(Vitrode F F-150ML [93])

Figure 17: Example of conventional electrodes.

To enhance this usability advantage, new types of wearable devices for biosignal measurement have been developed to fulfill the two requirements described in 3.2 [67, 69, 80–82, 97]. Regardless of the target biosignals,



(a) NISHIJIN electrode [94] (b) hamon® [95] (c) hitoe® [96]

Figure 18: Examples of cutting-edge biosignal measurement electrodes. The white arrow in each image indicates the electrode.

these devices use a fabric adaptor for unaided setup, which seems like a familiar object to non-expert users (e.g., a hairband [67], eye mask [69], or T-shirt [69, 80, 82, 97]), together with embedded measurement electrodes made of cutting-edge materials. Thus, just by the user wearing a fabric adaptor in a normal way, all electrodes for biosignal measurement embedded into the backside of the adaptor can be placed on the skin with appropriate inter-electrode distances, while firmly contacting the skin via the adaptor's pressure as well. In other words, unlike when using conventional electrodes for biosignal measurement, users do not necessarily have to know appropriate positions and inter-electrode distances for the target biosignal measurement. Several pilot studies requiring unaided setup at a reasonable cost, such as fatigue telemonitoring of bus drivers for labor management, used a T-shirt as a wearable device for ECG measurement, as shown in Figure 19. Those studies confirmed that there were no problem with unaided setup by non-expert users, and that the measured biosignal could be useful for the intended purpose as well [84].

Considering this achievement based on easy-to-use wearable devices with embedded measurement electrodes, we could also achieve unaided surface EMG measurement by non-experts for PLMs home monitoring, which would fulfill all the requirements of surface EMG measurement as described in 3.2, by designing new wearable devices for surface EMG measurement targeting PLM-related muscles. This should take human interface perspectives into account in addition to biomechanics. If a new device seems hard to use, then users are forced to learn how to precisely use it through trial and error, but this is not suitable for the



Figure 19: Example of easy-to-use T-shirt-type wearable device for unaided ECG measurement by non-experts (hitoe® [96]). Note that it additionally require a smartphone to receive and record signals transmitted from attachable hardware.

assumed situation in which physicians inevitably involve non-expert patients at many times, especially for follow-up observation. We therefore should develop an easy-to-use wearable device that users can easily understand at a glance, while enabling precise, stable surface EMG measurement throughout the night.

3.4 Proposed Method

3.4.1 Concept

Toward realization of P4 medicine [7] for potential/diagnosed patients with PLMD according to the actual severity of PLMs symptoms on a daily basis, including the night-to-night variability, we set a final research goal to develop a surface EMG-based PLMs home monitoring device that is easy to handle unaided, even by patients without any medical knowledge.

Figure 20 illustrates the ideal treatment of potential/diagnosed patients with PLMD by using this device for unaided surface EMG measurement by non-experts. The device enables physicians to conduct accurate PLMs home monitoring via the essential biosignals (i.e., surface EMG). This would contribute to revealing PLMs conditions outside a hospital, including its severity and night-to-night variability. It would even allow physicians to

better understand the relationship between medication and actual PLMs conditions, especially for diagnosed patients undergoing symptomatic treatment by medication.

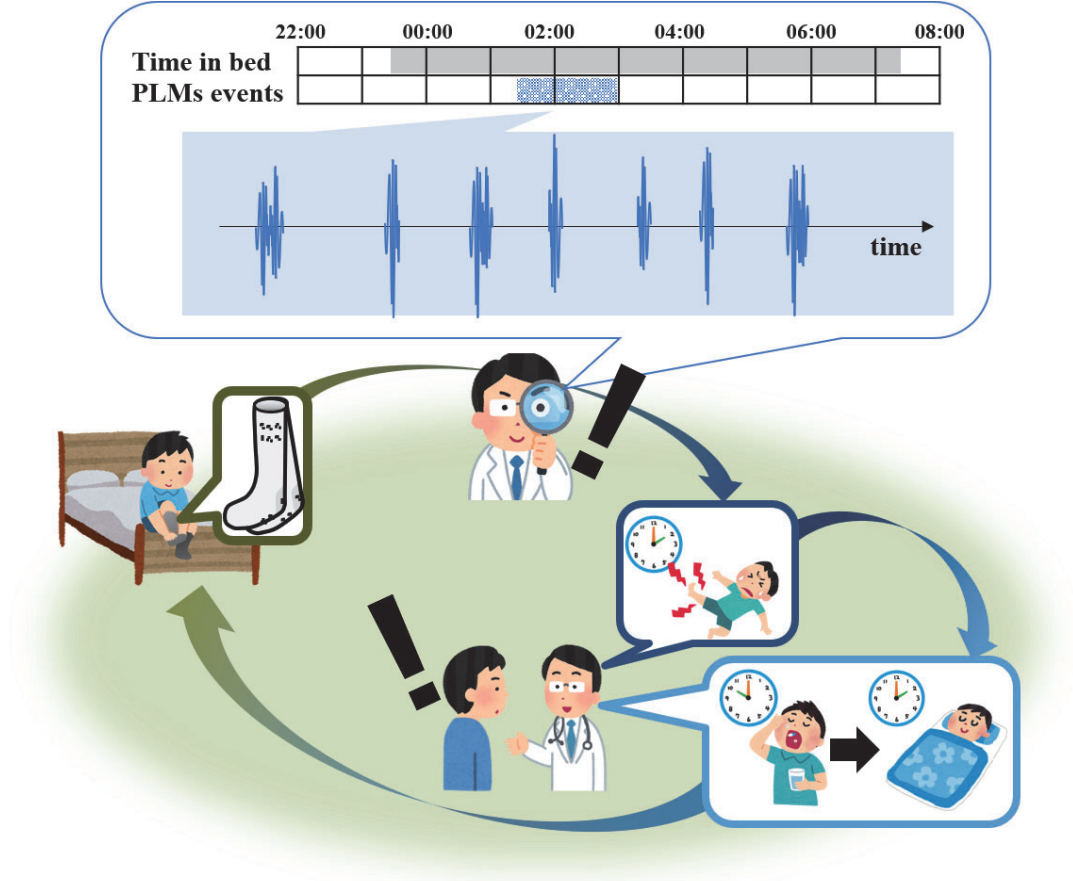


Figure 20: Ideal treatment for patients with PLMD realized by the proposed device.

3.4.2 Research Objectives and Requirements

The key enabler of this concept is an easy-to-use device for unaided surface EMG measurement by non-experts. Here, the term “easy to use” involves the following three characteristics:

- (α) Easy-to-use measurement electrodes with low enough contact impedance, which do not require cumbersome preparation such as hair removal.
(*Requirement A* in 3.2.2)
- (β) Easy-to-use measurement electrodes appropriately placed for surface EMG

measurement of target muscles in PLMs monitoring, which do not require patient effort in considering the appropriate position and inter-electrode distance.

(*Requirement B* in 3.2.2)

- (γ) Easy-to-use measurement electrodes to stably measure the surface EMG of target muscles throughout the night without dropping off or slipping on the target muscles.

(*Requirement B* in 3.2.2)

To satisfy these three requirements for “easy to use,” this research proposes a sock-type wearable device for surface EMG measurement, comprising embedded fabric electrodes and a fabric adaptor that looks like a sock. The first main feature of this device is the ready-to-use surface EMG electrodes satisfying requirements (α) and (β). Fabric electrodes with low enough impedance for surface EMG measurement are embedded on the inside of a sock-type fabric adaptor with an appropriate inter-electrode distance. Thus, all the user must do is wear the device like a normal sock. The device’s second main feature is stable surface EMG measurement of the target muscles via its own compression, which satisfies requirement (γ) and ensures the final accuracy of surface EMG-based PLMs evaluation using the device.

Note again that the device should be designed from both biomechanical and human interface perspectives to ensure both accuracy and usability. It should also be able to precisely discriminate PLMs by enabling precise, stable surface EMG measurement of the target muscles during sleep without disturbing the patient’s usual sleep throughout the night. Finally, it should be easy enough for non-experts to use unaided, by resolving issues related to its setup and stable measurement in conventional surface EMG measurement in consideration of the biomechanical and user interface perspectives. Because the proposed device primarily targets PLMs home monitoring, this research first clarified the target muscles for surface EMG measurement suitable for PLMs evaluation, before actually developing the device. After developing the device, on the other hand, it was important to evaluate its performance on PLMs home monitoring for an actual patient diagnosed with PLMD. Thus, taken together, the proposed

device was developed by fulfilling the following requirements step by step:

- (a) Target muscle selection for surface EMG-based PLMs home monitoring in advance of the device development.
- (b) Development of the proposed sock-type wearable device for unaided surface EMG measurement by non-experts and basic confirmation of its performance during voluntary movements.
- (c) Overnight surface EMG measurement by the proposed device for PLMs evaluation.

The following chapters correspond to each of the requirements: requirement (a) in Chapter 4, requirement (b) in Chapter 5, and requirement (c) in Chapter 6. Then, this dissertation summarizes all the contributions related to these requirements in 7.1 of Chapter 7.

Chapter 4 Surface EMG-Based PLMs Monitoring Targeting Sock-Type Wearable Device Development

This chapter aims to clarify the design of surface electromyography (EMG) measurement for periodic limb movements (PLMs) monitoring at home, in advance of actually developing the proposed easy-to-use device for unaided surface EMG measurement by non-experts.

This chapter first introduces the essential design concept of the proposed device, which is essential for selecting target muscles with a view toward the actual device development, in 4.1. That section also introduces related work investigating multiple muscles during PLMs, and the investigation in this research on target muscle selection for surface EMG-based PLMs home monitoring. Then, 4.2 describes a preliminary comparative evaluation on PLMs home monitoring between the proposed surface EMG-based method and the current de facto standard, an acceleration-based method for which the experiment used commercially available devices with medical approval. Finally, 4.3 discusses the results.

4.1 Method

4.1.1 Design Concept

As mentioned in 3.1, the major PLMs described in [31, 33, 85] induce several different motor movements at a time or sequentially. Assuming that this research should target several PLM-related muscle movements at a time, multi-channel surface EMG with multiple target muscles, which could also be a standard tactic in this case, would be effective to appropriately discriminate PLMs from voluntary movements by measuring as many probable PLMs as possible. However, this does not necessarily mean that multi-channel surface EMG of all possible PLM-related muscles is effective for the purpose here. Because each channel requires independent hardware, including a differential amplifier together with an analog-to-digital (A/D) converter to measure the

surface EMG signal, too many multi-channel surface EMG measurements may disrupt the setup by non-expert users, and also disturb usual sleep itself because of the increased hardware.

Single-channel surface EMG measurement, on the other hand, would not be sufficient either. Although PLMs monitoring for the definitive diagnosis of PLMD targets the bilateral tibialis anterior for its surface EMG measurement, it is not necessarily sufficient for PLMs monitoring in consideration of commonly understood movements in the field of sleep medicine, as described in 3.1. Physicians point out that PLMs typically involve extension of the big toe, but the tibialis anterior is not biomechanically related to that movement [98]; rather, it is the agonist of dorsiflexion of the ankle. We therefore should revisit PLMs from the perspective of biomechanics and investigate possible target muscles for PLMs home monitoring that could be used to detect PLMs occurring in the big toe as well. Taken together, surface EMG measurement with a few limited channels should be considered sufficient for PLMs monitoring.

For these reasons, as the very first step in this research before primary prototyping of the proposed device, this research focuses on two-channel surface EMG measurement targeting two individual muscles, which includes the tibialis anterior as one of the target muscles. This is because the most reliable PLMs evaluation method via polysomnography (PSG) uses surface EMG of the bilateral tibialis anterior. In that method, PLMs in an actual clinical site are defined as certain involuntary movements measured by the surface EMG of the bilateral tibialis anterior, which satisfy several criteria defined in the *American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events* (hereafter, the AASM scoring manual) [47] as described in 3.1. The tibialis anterior is therefore reserved for comparative evaluation on PLMs monitoring performance with respect to PSG, which will be essential for the device approval process in the future.

This approach can be expected to improve the accuracy of PLMs evaluation as compared to conventional one based on surface EMG of the bilateral tibialis anterior alone by suppressing misdetection or overlooking of PLMs, especially those occurring in the big toe.

4.1.2 Related Work

Because PLMs intrinsically activate multiple muscles in the lower extremities roughly at the same time, several studies have been conducted to clarify their activity patterns by measuring multi-channel surface EMG during PLMs [99, 100].

Although all previous studies reported that the tibialis anterior was more strongly activated than other PLMs-related muscles were [99, 100], or even that it was the most frequent starting muscle [99], several have pointed out that measuring the surface EMG of the tibialis anterior alone would not necessarily be sufficient for PLMs evaluation. Weerd et al. [100] noted that several PLMs do not activate muscles in a chain reaction (in order of the extensor digitorum brevis, tibialis anterior, biceps femoris, and tensor fasciae latae), and the extensor digitorum brevis is sometimes solely activated. The same possibility was pointed out in [59] as well: the extensor digitorum brevis sometimes shows better sensitivity than that of the tibialis anterior in detecting limb movements.

Aside from this, Provini et al. [99] found that muscle activation in the lower extremities often occurred on alternating sides, meaning muscle activation on the right side followed by that on the left side, and vice versa. They also found that antagonist muscles could be activated at the same time as PLMs, but there was no constant recruitment pattern from one PLM episode to another, even in the same patient.

These results suggest that PLMs do not necessarily activate the tibialis anterior alone but possibly activate several PLM-related muscles in a different manner from general voluntary movements. This indicates that adding another target muscle for PLMs evaluation could prevent overlooking PLMs that cannot be observed from the bilateral tibialis anterior alone.

4.1.3 Revisiting Leg Movements Induced by PLMs

To determine an additional target muscle other than the tibialis anterior for two-channel surface EMG measurement that would be sufficient for PLMs monitoring, the leg movements induced by PLMs were investigated via the following four step. In brief, this study first reconfirmed the PLM-induced movements by visual observation and listed PLM-related muscles from the

perspective of biomechanics, and then selected target muscle candidates in consideration of their anatomical locations and innervation.

Step 1: Reconfirmation of PLM-Inducing Movements by Visual Observation

For this step, a patient with diagnosed PLMD and perceivable PLMs was asked to capture a video of the lower extremities during actual PLMs.

The visually observable PLMs recorded in the video confirmed the aforementioned movements, including extension of the big toe and dorsiflexion of the ankle. They occurred concurrently or sequentially, as described in 3.1. It was additionally found, however, that most of those PLMs were followed by movements back to the original position. For instance, a PLM-like event truly induced extension of the big toe, but the extension did not continue for long, and the big toe returned to the original position via flexion. Note that flexion of the big toe is, so to speak, the biomechanical counterpart movement of extension of the big toe [101]. It was also confirmed that this movement back to the original position might not be perceivable by the patient. The target patient claimed to only perceive the PLM-induced leg movements (i.e., extension of the big toe, or dorsiflexion of the ankle). Although this consecutive muscle activation occurring in the ankle (i.e., dorsiflexion of the ankle followed by its plantar flexion) has been reported before [102], the similar phenomenon was visually confirmed to occur in the big toe as well.

Therefore, PLMs can possibly be considered as certain movements reported by physicians (described in 3.1), but they may be accompanied by the counterpart movements of PLM-induced leg movements, as shown in Figure 21.

Step 2: Biomechanical Motor Features of PLMs

From the perspective of biomechanics, we can observe arbitrary body movements as combinations of joint actions, namely, flexion/extension, abduction/adduction, or external/internal rotation, all of which are achieved by muscles and joints [101]. Because PLMs are also body movements involving related muscle activation, PLM-related muscles can be identified by investigating the PLM-related joint action units and their agonists and synergists.

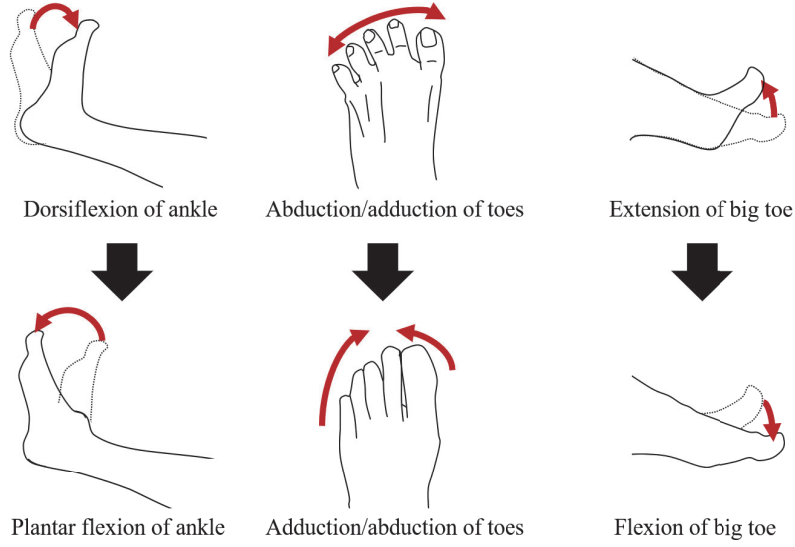


Figure 21: Subsequent leg movements after PLMs.

As described in 3.1, major PLMs occurring in the lower extremities can involve either one of or a combination of extension of the big toe and toes in combination with their abduction/adduction, or dorsiflexion of the ankle [31,33]. Table 4 lists probable target muscles corresponding to the aforementioned joint actions occurring in PLMs [98].

Among these muscles, the abductor hallucis and abductor digiti minimi have been measured in other studies [103], which primarily targeted restless leg syndrome/Willis-Ekbom disease, whose patients frequently also exhibit PLMD [15]. The abductor hallucis is also related to flexion of the big toe, which is the biomechanical counterpart movement of extension of the big toe [98]. Although several muscles annotated in Table 4, including the abductor hallucis and abductor digiti minimi, could be related to PLMs, they are not measured in the current PSG for PLMs monitoring.

Step 3: Anatomical Locations of PLM-Related Muscles

Considering the principle of surface EMG measurement as described in 3.2, we need to place two or more measurement electrodes only on the target muscle to measure surface EMG. This means that we can only target superficial muscles with sufficient presentation area to place two or more measurement electrodes. However, it is still not necessarily sufficient to measure the surface EMG. When

target muscles are anatomically close to influential muscles whose motor power is stronger than that of the target muscles, it becomes difficult to discriminate the activation of each muscle from only the measured surface EMG due to the crosstalk from those influential muscles. To ensure appropriate surface EMG measurement without crosstalk from nearby muscles, we should exclude certain superficial muscles that have only a small presentation area or are located near certain muscles considered influential.

Hence, muscle locations and their deep/superficial classifications were investigated for this step. Table 4 summarizes the results of the investigation based on [98, 104, 105]. The locations of plantar muscles (i.e., the abductor hallucis, adductor hallucis, abductor digiti minimi, interossei dorsalis, and interossei plantares) are subdivided into four layers, with the first layer being the most superficial [98]. As listed in Table 4, several muscles located in the leg or the first plantar layer are anatomically superficial muscles. Aside from these, we could regard the extensor digitorum brevis as a possible target for surface EMG measurement. Although the extensor digitorum brevis itself is an anatomically deep muscle, we can measure its surface EMG as reported in [100] because no muscles cover it.

Regarding the three superficial muscles located in the leg (i.e., the tibialis anterior, extensor digitorum longus, and extensor hallucis longus), their locational relationship was also considered. As seen in the cross-sectional anatomical chart of the calf shown in Figure 22, all these muscles are located next to each other [104]. However, the muscle power is quite different among the three muscles: the tibialis anterior is the largest and most powerful, with greater power than the other two muscles. Therefore, it could become quite difficult to discriminate the activity of the extensor digitorum longus or extensor hallucis longus from that of the tibialis anterior according to only the measured surface EMG, especially in a non-expert setup. For this reason, both the extensor digitorum longus and extensor hallucis longus were excluded as additional target muscle candidates.

Step 4: Innervation of PLM-Related Muscles

According to a neurologist, their field practically targets certain muscles

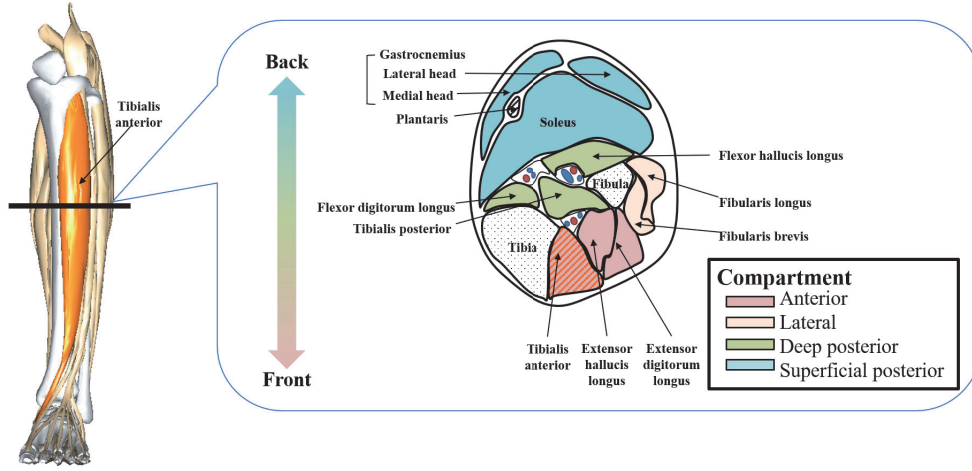


Figure 22: Cross-sectional anatomical chart of the left leg, from [106]. The figure of the leg on the left was generated by [107], whereas the cross-sectional anatomical chart (right) was adapted from [104].

whose innervated nerves differ from each other when measuring two or more channels of surface EMG for examination of the peripheral nervous system. This study therefore investigated innervation of the remaining target muscle candidates for surface EMG measurement.

Table 4 also summarizes the results of this investigation based on the nerves of the lower limb [108]. There are two different nerves in the lower extremity below the knee, namely, the tibial nerve and the common peroneal nerve. The tibial nerve around the ankle ramifies into the medial plantar nerve and lateral plantar nerve, whereas the common peroneal nerve around the knee ramifies into the superficial peroneal nerve and deep peroneal nerve [108].

At this point, the remaining target muscle candidates were the abductor hallucis and abductor digiti minimi. In addition to those, the extensor digitorum brevis could remain as a possible candidate because of its peculiar location. Considering the innervating nerves of those candidate muscles, however, left only the abductor hallucis and abductor digiti minimi, both of which are innervated by the tibial nerve, as additional target muscles to the tibialis anterior, which is innervated by the deep peroneal nerve from the common peroneal nerve.

Table 4: List of PLM-related joint actions and PLM-related muscles in the lower extremities (summarized by the present author from [98, 104, 108]).

Part	Movements	Step 2		Step 3			Step 4		Our target
		Related muscles	Location	Superficial	Near influential muscles	Innervation			
Big toe	Extension	Extensor hallucis longus	Anterior compartment of leg	Yes	Yes (tibialis anterior)	Deep peroneal nerve (from common peroneal nerve)			
		Extensor digitorum brevis	Dorsal	*	No	Deep peroneal nerve (from common peroneal nerve)			
	Abduction	Abductor hallucis	1st plantar layer	Yes	No	Medial plantar nerve (from tibial nerve)		Yes	
	Adduction	Adductor hallucis	3rd plantar layer	No		Lateral plantar nerve (from tibial nerve)			
Toes	Extension	Extensor digitorum longus	Anterior compartment of leg	Yes	Yes (tibialis anterior)	Deep peroneal nerve (from common peroneal nerve)			
		Extensor digitorum brevis	Dorsal	*	No	Deep peroneal nerve (from common peroneal nerve)			
	Abduction	Abductor digiti minimi	1st plantar layer	Yes	No	Lateral plantar nerve (from tibial nerve)			
		Interossei dorsalis	4th plantar layer	No		Lateral plantar nerve (from tibial nerve)			
	Adduction	Interossei Plantares	4th plantar layer	No		Lateral plantar nerve (from tibial nerve)			
Ankle	Dorsiflexion	Tibialis anterior	Anterior compartment of leg	Yes	No	Deep peroneal nerve (from common peroneal nerve)		Yes (reserved)	
		Extensor digitorum longus	Anterior compartment of leg	Yes	Yes (tibialis anterior)	Deep peroneal nerve (from common peroneal nerve)			
		Extensor hallucis longus	Anterior compartment of leg	Yes	Yes (tibialis anterior)	Deep peroneal nerve (from common peroneal nerve)			
		Peroneus tertius	Anterior compartment of leg	Yes	Yes (tibialis anterior)	Deep peroneal nerve (from common peroneal nerve)			

* Although it is an anatomically deep muscle, its surface EMG can be measured as reported in [100], because no muscles cover it.

4.1.4 Target Muscles

By looking back to PLM-induced leg movements as defined in the field of sleep medicine (described in 3.1) and considering the above investigation, the abductor hallucis was chosen as an additional target muscle to the tibialis anterior. Because the abductor hallucis is biomechanically related to the abduction and flexion of the big toe [98], certain PLMs solely involving extension of the big toe could be observed by measuring its flexion, which follows right after PLM-induced extension.

This study therefore considered that two-channel surface EMG targeting the abductor hallucis and tibialis anterior, as shown in Figure 23, would be suitable for comprehensive monitoring of PLMs that probably occur in the lower extremities below the knee.

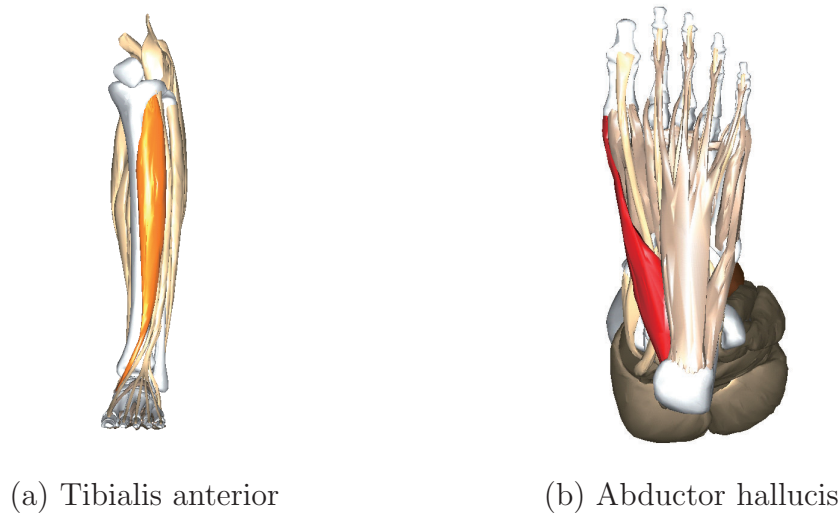


Figure 23: Target muscles in the left leg. These figures were generated by [107].

4.2 Experiment

4.2.1 Overview

To confirm the effectiveness of the proposed bilateral two-channel surface EMG measurement targeting the tibialis anterior and abductor hallucis for PLMs home monitoring, the surface EMG of those muscles was measured in a patient with diagnosed PLMD under medication for PLMs suppression. To avoid

compelling the burden of PLMD symptoms because of this experiment, the subject continued medication as usual. Instead, three different days were targeted in case no PLMs could be observed on one day because of successful PLMs suppression by the medication.

The aim of this experiment was to clarify the following: (1) whether the proposed surface EMG monitoring is useful for PLMs evaluation, and (2) whether the proposing monitoring can go further than the representative alternative of PLMs home monitoring using an acceleration-based device with medical approval. Therefore, both the bilateral two-channel surface EMG (i.e., of the bilateral tibialis anterior and abductor hallucis) and the acceleration-based partial body activity were measured.

Because this experiment is the very first stage of a preliminary validation of PLMs monitoring at home with limited resources, there was no choice but to conduct this experiment outside a hospital, without fully attended PSG. It was therefore conducted while capturing a video of the lower extremities, which was used to observe the actual PLMs conditions as a reference for this comparative evaluation.

For this reason, one PLMD patient was asked to wear six devices in total during sleep at home while capturing the video: four devices for the bilateral two-channel surface EMG measurement, one device for the acceleration-based PLMs monitoring, and one other device for acceleration-based sleep condition estimation. To facilitate this comparative evaluation, it used a conventional acceleration-based device with medical approval, which has been used for sleep evaluation at home in actual treatment of people with sleep disorders.

4.2.2 Target Participant

Because both the commercial surface EMG measurement device and the medically approved conventional acceleration-based device had to be on the target participant, comparatively large normal body movements (e.g., turning over) could have greatly affected the measurement conditions. Thus, the present study targeted one female patient with PLMD who rarely turns over in her usual sleep at home according to reports from her family.

The participant was previously diagnosed as having PLMD with an average

number of leg movements per hour during sleep (PLMI) of 42.82, which is much larger than the PLMD diagnostic criterion in adults (over 15 events/hour [15]). The participant was currently under medication with pramipexole (0.125 mg), taken at around 9:00 pm each night for PLMs suppression.

Although the medication truly suppresses the overall number of PLMs, the participant reported sometimes experiencing nocturnal awakening due to perceptible consecutive PLMs. The most recent results of acceleration-based measurement of PLMs over three nights at home (using PAM-RL, Philips Respironics, Murrysville, PA, USA) revealed an average of >5 PLM events/hour in both legs; the three-night average PLMI of each leg was 7.97 ± 2.64 events/hour in the right leg and 5.43 ± 3.52 events/hour in the left leg, which did not differ to a statistically significant extent ($p=0.10$). Note that the participant was <40 years of age, and it is very uncommon to observe more than 5 PLM events/hour among healthy subjects at that age [15]. In other words, although the frequency was below the diagnostic criterion because of the medication, the participant still suffered from PLMs that were unlikely to have been accidental.

4.2.3 Experimental Environment

To conduct this preliminary validation at the actual patient’s home under usual sleep conditions, the positions of her bed and furniture were not changed at all. Rather, several pieces of experimental equipment were set up around the bed. Figure 24 shows an overview of the experimental environment’s layout. A video camera was placed where it could capture a video of the lower extremities, regardless of the leg movement or turning of the body. To avoid disturbing the participant’s usual sleeping conditions, the video camera did not require lighting (FDR-AX60, Sony Corporation, Japan).

Aside from the video camera, several other pieces of equipment were set up for surface EMG measurement, including an integrated wireless signal receiver/transmitter and a laptop, described in detail below, on the cart near the bed.

4.2.4 Arrangement of Target Devices

The most recent results of acceleration-based PLMs measurement over three nights at the participant’s home (described in 4.2.2) revealed that she tends to

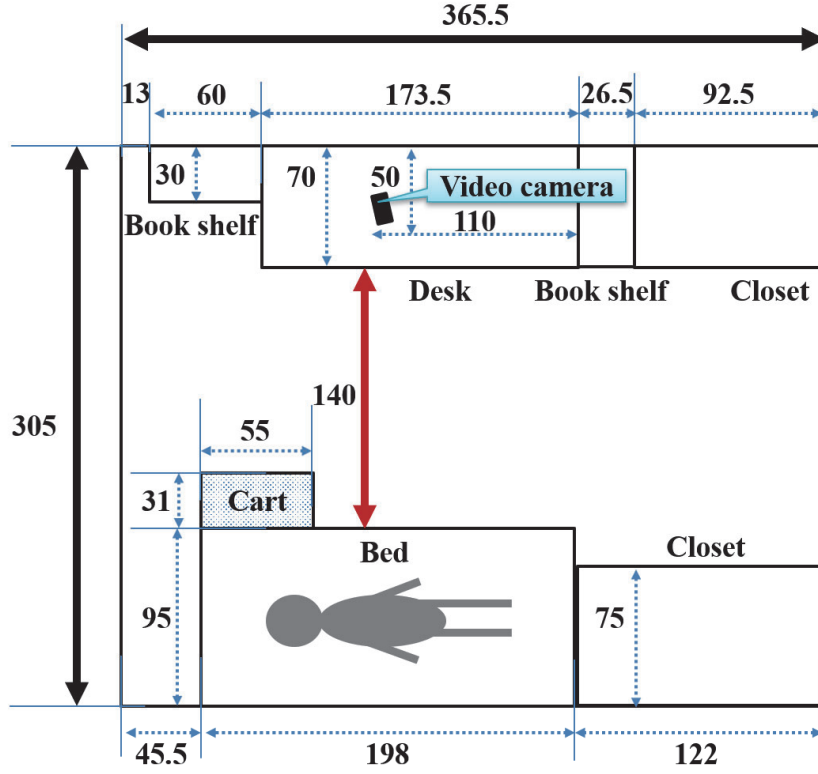


Figure 24: Overview of experimental environment (unit is cm). The mesh of blue dots indicates the location of the cart. Note that this figure is from [86], in which the experimental environment was the same as in the present experiment.

experience more PLMs in the right leg than in the left leg. The right leg was therefore targeted for the comparative evaluation of PLMs measurement in this preliminary experiment.

The participant wore both a conventional surface EMG measurement device and a conventional acceleration-based device, as shown in Figure 25. The surface EMG device was placed on the target muscles (i.e., the abductive hallucis and tibialis anterior) of both legs, while the acceleration-based device was put around the right ankle.

As a dependable device for evaluating the usual sleep conditions at home, a commercially available and medically approved wristband with a built-in accelerometer was chosen, namely, Actiwatch Spectrum Plus (Philips Respironics, Murrysville, PA, USA). For validation of PLMs along with the

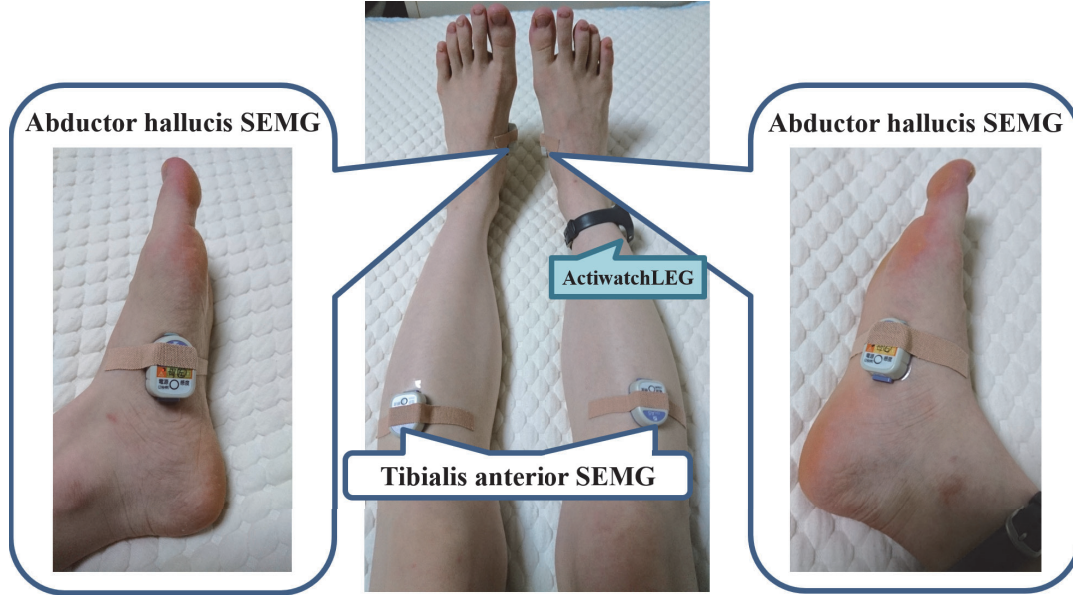


Figure 25: Arrangement of the target devices. Flesh-colored tape is kinesiology tape for stabilizing each device on the skin [109].

sleep status, the participant wore two Actiwatchs on her body, as shown in Figure 26. One for sleep evaluation was worn on the non-dominant left wrist (hereafter denoted as ActiwatchARM, as in Figure 26(a)). The other was used for acceleration-based validation of PLM-like events and worn on the right ankle (ActiwatchLEG, as in Figure 26(b)). After all devices were worn, it was confirmed that none of them slipped from their initial positions during or after leg movements. Note that the participant was asked not to put a blanket over the lower extremities to prevent measurement faults.

4.2.5 Overview of Data Collection

As described previously, the following three types of data were measured during sleep in this experiment: surface EMG of the bilateral tibialis anterior and abductor hallucis; acceleration-based body movements of the left hand and right leg, as measured by the acceleration-based devices (i.e., ActiwatchARM and ActiwatchLEG); and video as a reference for PLM-like events. The following sections describe the experimental conditions of the surface EMG measurement and the conventional acceleration-based method in detail.

For appropriate validation, a “sleep diary” was also collected to confirm the



(a) Actiwatch on the left wrist
(ActiwatchARM)



(b) Actiwatch on the right ankle
(ActiwatchLEG)

Figure 26: Arrangement of Actiwatches on the participant's limbs. Note that the participant additionally wore her own smartwatch (top device in (a)).

sleep conditions, including the subjective PLMs experience and environmental conditions during sleep. The participant was asked to keep a record of the times that she got into bed, got out of bed, and took medicine, as well as the details of her medication use (e.g., the name and amount). The participant was also asked to record her subjective evaluation of PLMs experiences to evaluate the probability of PLM-like events, as in her usual routine. Finally, the participant was also asked about the lighting conditions on the nights of measurement to confirm the effect of brightness.

Note that all the data measured in this experiment was recorded to a storage medium (i.e., a wire-connected laptop for surface EMG and built-in device memory for the acceleration-based device) and analyzed offline afterward.

4.2.6 Settings in Surface EMG Measurement

The surface EMG measurement settings followed the standards for reporting EMG data [110].

Hardware

To ensure high reliability for the evaluations, a commercially available wireless biosignal measurement device was used. It had a dedicated wearable amplifier designed for surface EMG measurement (WEB-1000 with surface EMG picker ZB-150H, Nihon Kohden Corporation, Japan). As shown in Figure 27, the WEB-1000 includes packaged equipment commonly used for biosignal measurement, comprising an integrated wireless signal receiver (ZR-100H) with a dedicated antenna (ZA-100H) and wireless signal transmitter (ZB-100H), and a laptop (CC-700H) with a dedicated software program. The laptop had the following specifications: OS, Microsoft Windows 7 Professional (64 bit); CPU, Intel ® Core™ i5-4210M (clock rate: 2.60 GHz); RAM, 4GB. The WEB-1000 allows a user to easily measure target biosignals by simply using a designated “picker,” a small wearable data-transmitting device designed for biosignal measurement, together with the equipment described above, as long as the user is knowledgeable in measuring the target biosignal.

This experiment used the designated picker for surface EMG measurement (surface EMG picker ZB-150H), shown in Figure 28. Its functionality comprised surface EMG data measurement by embedded tripole active electrodes with a built-in amplifier, and measured surface EMG transmission to the WEB-1000. Note that the inter-electrode distance between active electrodes in the surface EMG picker was approximately 3 mm.

In advance of the experiment, all components of the WEB-1000 required for surface EMG measurement were assembled, and their operation was confirmed without any trouble.

Electrode arrangement

To measure the surface EMG of the bilateral tibialis anterior and abductor hallucis, one surface EMG picker was placed on each target muscle as shown in Figure 25. It was necessary to reduce the risk of the picker dropping off the surface of the target location because of perspiration or the participant unexpectedly rolling over. Therefore, each picker was placed near the muscle belly of the target muscle by using commercially available double-sided tape designed for such devices after wiping perspiration from the skin surface

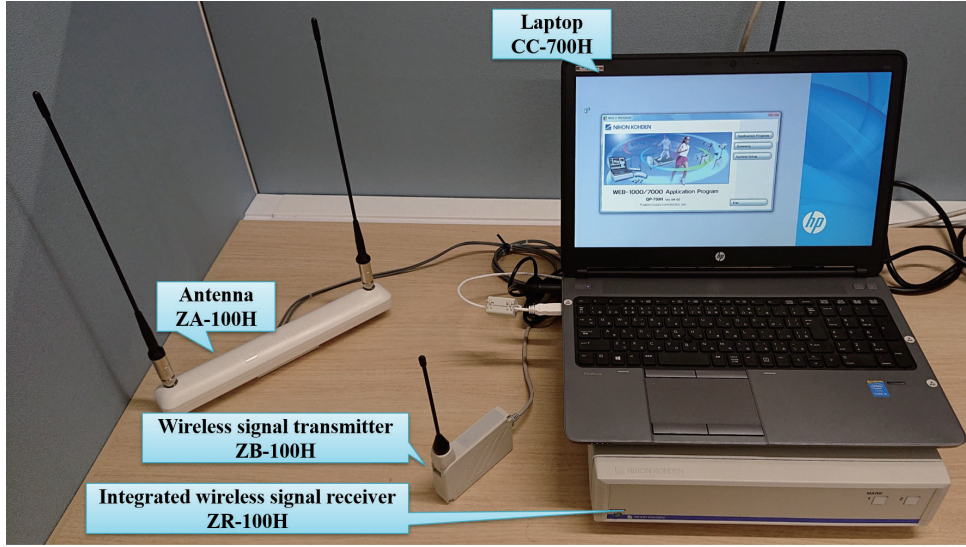


Figure 27: Overview of the WEB-1000 equipment.



(a) Front side (height)

(b) Front side (width)

(c) Back side

Figure 28: Enlarged view of the biosignal “picker” for surface EMG measurement (ZB-150H).

over the target muscles. Then, each picker was additionally stabilized by using commercially available adhesive tape, which was originally developed as kinesiology tape (Profits Kinesiology Tape with Strong Adhesive 50mm Width for Foot, Knee, and Calf, PIP Co., Ltd., Japan) [109].

Software

The digital signal measured by the above equipment was monitored via its dedicated software program (WEB-1000/7000 Application Program QP-700H, Ver. 04-03, Nihon Kohden Corporation, Japan) with a 1-kHz sampling rate

to satisfy the Nyquist frequency of the subsequent signal processing using a bandpass filter (BPF). As preset filter cutoffs, 5 Hz was selected for the low end and 500 Hz for the high end, both of which satisfied the surface EMG measurement requirements (i.e., 10-350 Hz) [110]. The default settings were used for all other configurable settings.

Signal Processing

Because surface EMG measured during sleep at home may contain noise or artifacts, it would have difficult to analyze the measured surface EMG signals as they were. Thus, to reduce the effects of noise and artifacts, the measured signals were post-processed using the following signal processing procedures: (1) BPF processing, (2) root mean square (RMS) calculation, (3) and peak envelope calculation. These procedures are described in more detail below. Note that all the signal processing was achieved through self-developed dedicated program code for MATLAB (MATLAB R2017a, The MathWorks, Inc., Natick, MA, USA).

1. **BPF processing:** a twentieth-order 10-450 Hz Butterworth BPF was used to suppress the effects of noise and artifacts in the measured surface EMG signal.
2. **RMS calculation:** the RMS of the BPF-processed surface EMG signal was calculated. The RMS calculation window was set to 50 ms and slid forward in 1-ms increments.
3. **Peak envelope calculation:** the peak envelope of the RMS-processed surface EMG signal was calculated from 100 sample intervals.

4.2.7 Settings in Acceleration-Based Method

Hardware

Because each PLM event lasts for <10 seconds according to the AASM scoring manual [47], each Actiwatch was set to a different resolution, called the “epoch length” in the Actiwatch settings. The sleep status was evaluated by the ActiwatchARM, whereas short-lasting movements, including PLMs, were evaluated by the ActiwatchLEG. The epoch length of the ActiwatchARM was thus set to 60 s, while that of the ActiwatchLEG was set to 15 s (the minimum epoch length). The default settings were used for all other configurable settings.

Data Analysis

The Actiwatch itself outputs data throughout its use. To obtain appropriate output data via the Actiwatch auto-analysis system (Actiware®, Philips Respironics, Murrysville, PA, USA), appropriate times for getting in and out of bed were manually set according to the participant’s sleep diary, and only the output data measured during sleep was used. Note that, before the data analysis, it was confirmed that both the ActiwatchARM and ActiwatchLEG were appropriately worn on the participant’s body during sleep according to the output data of the “off-wrist detector.”

A sleep time reference was provided by the ActiwatchARM’s “Interval Status,” the possible values of which were “Active,” “Rest,” “Rest-Sleep,” “Excluded,” and “N/A.” The Active, Rest, and Rest-Sleep values were transformed to numerical values (1, 0.5, and 0, respectively) to obtain a hypnogram-like state transition. In addition to the Interval Status, the momentary “Wake/Sleep Score” was also considered, because the time in bed did not necessarily reflect the actual total sleep time. Hence, the Wake/Sleep Score in the epoch-by-epoch data was used as an output from each Actiwatch, with values of 0 (sleep), 1 (wake), or NaN.

4.2.8 Results

Overall Sleep Conditions

Before analyzing the PLM-like epochs, the sleep conditions were first confirmed from the subsidiary data, namely, the sleep diary, recorded video, and ActiwatchARM data.

Table 5 lists the start time of surface EMG measurement, the time of getting into bed, and the time of getting out of bed according to the sleep diary. According to the participant’s main complaint described in the sleep diary, she habitually took 0.125 mg of pramipexole around 9:00 p.m. for PLMs suppression, but she forgot to take it at that time on the first night.

To summarize the sleep conditions, the participant was able to fall asleep each night of the experiment without experiencing difficulty in staying asleep, which eventually resulted in early morning awakening. This was also confirmed from the recorded video and the “Interval Status” of the ActiwatchARM,

Table 5: Summary of subjective sleep times and surface EMG measurements.

Night	Surface EMG measurement starting time	Getting into bed	Getting out of bed
1	01:37:05 a.m.	01:40 a.m.	07:22 a.m.
2	02:36:42 a.m.	02:40 a.m.	07:56 a.m.
3	02:04:10 a.m.	02:07 a.m.	07:49 a.m.

as shown at the tops of Figures 29 to 31. On the first night, however, the participant perceivably experienced difficulty in falling asleep because of perceivably severe consecutive PLMs, which were possibly caused by the missed dose of medicine. Hence, she additionally took 1 mg of eszopiclone together with 0.125 mg of pramipexole around 02:00 a.m. Note that eszopiclone is, so to speak, a sleep-inducing medicine. Regarding the second night, on the other hand, the participant experienced difficulty in falling asleep with no relevance to PLMs, so she only took 1 mg of eszopiclone around 03:00 a.m. as a sleep-inducing drug. This difficulty in falling asleep was confirmed in the recorded video. In addition, the “Wake/Sleep Score” of the ActiwatchARM, which could indicate fragmentary nocturnal awakening, also supported the above complaints of the participant.

The participant seemed to never experience eventual early morning awakening even though PLM-like events were observed in the video on all three nights of the experiment. Furthermore, these visually observable PLMs conditions varied each night in terms of both the number of PLM-like events and their observed times. Figures 29 to 31 depict the occurrence times of the PLM-like events that were visually observed in the video as red shaded areas.

Results of PLMs Monitoring by Proposed Method Using Two-Channel Surface EMG

Figures 29 to 31 show all the processed data from the experiment on each night. The surface EMG results confirm that the participant suddenly began repetitive muscle activation continuing for several dozen minutes on each night, and this activation occurred during visually observable PLM-like events.

Turning to the combination of activated muscles, the results confirm that the targeted muscles, namely, the tibialis anterior and abductor hallucis, were

not necessarily activated at the same time but could be activated alone as well. As representative examples, this study focused on the PLM-like events observed on each night, annotated as the grey shaded areas in each figure. Figures 32, 33, and 34 show enlarged views of those events observed on the first, second, and third nights, respectively. Comparing the surface EMG of the tibialis anterior and abductor hallucis in the same leg confirms the difference in their muscle activation. Both target muscles were repetitively activated during the PLM-like movements during the first half of the first night (Figure 32), whereas the left abductor hallucis was solely activated several times on the second night (Figure 33). On the other hand, only more frequent muscle activation in the right tibialis anterior can be confirmed for the third night (Figure 34).

Note that there is a limitation in this evaluation related to the PLMs reference obtained by visual observation. The reference video was recorded from the participant's left side, and this may make it difficult to visually determine abduction/adduction of the toes rather than extension/flexion or dorsiflexion/plantar flexion, which are both movements orthogonal to the abduction/adduction. In addition, it is not possible to visually confirm isometric exercise of a muscle, in which the muscle does not cause any movement. Taken together, the possibility of overlooking PLMs in the visual observation cannot be ruled out, but the results do indicate the minimum possible performance of each method in terms of the probable PLMs confirmed visually .

These findings suggest that PLMs could involve either one of or a combination of the extension of the big toe and the dorsiflexion of the ankle, as pointed out by physicians [31,33]. Moreover, the proposed two-channel surface EMG measurement targeting the abductor hallucis in addition to the tibialis anterior would precisely monitor those PLMs regardless of the combination of PLMs inducing movement.

Comparative Evaluation of PLMs Home Monitoring between Proposed Method and Conventional Acceleration-Based Method

As a preliminary validation of the potential performance of the proposed PLMs monitoring based on two-channel surface EMG as compared to conventional PLMs monitoring using an acceleration-based device, the

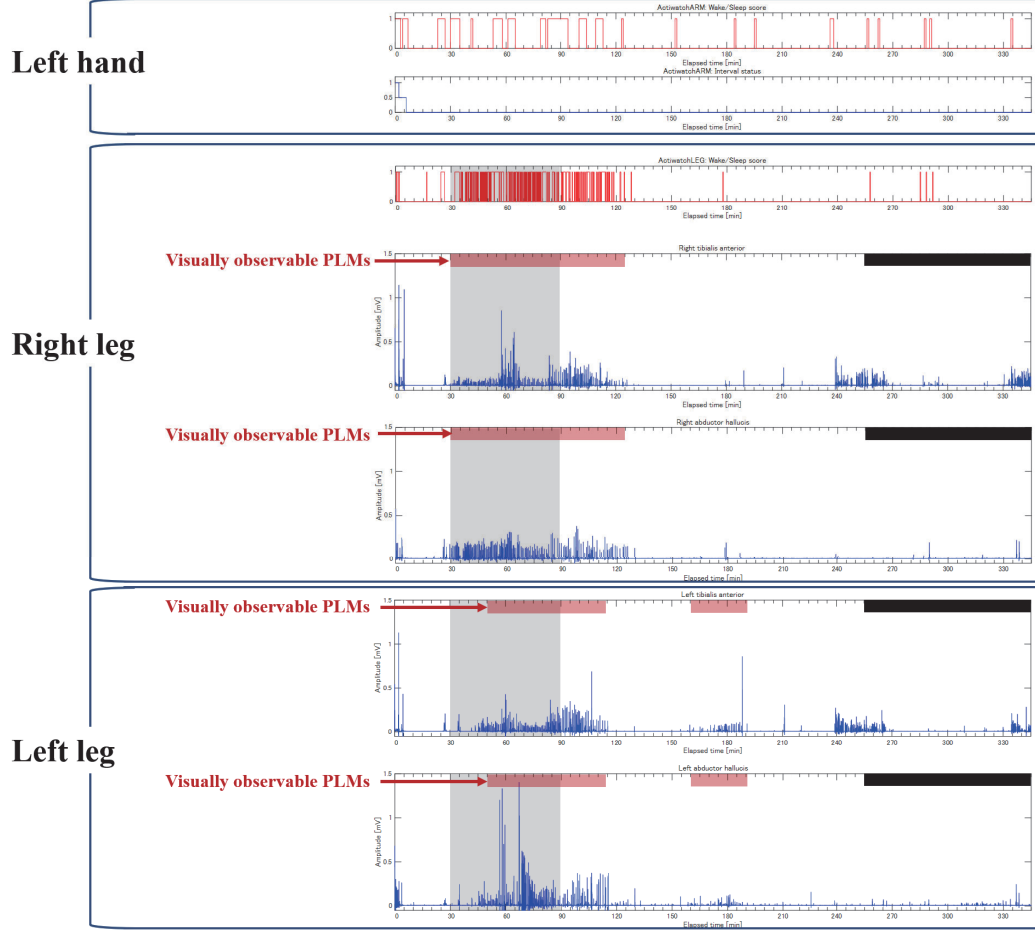


Figure 29: Overview of all data measured on the first night. The graphs from top to bottom show the “Wake/Sleep Score” of the ActiwatchARM, the “Interval Score” of the ActiwatchARM, the “Wake/Sleep Score” of the ActiwatchLEG, and the processed surface EMG signals of the right tibialis anterior, right abductor hallucis, left tibialis anterior, and left abductor hallucis. The occurrence times of visually observable PLM-like events according to the time-related criteria of the AASM scoring manual are depicted above each signal as the red shaded areas. A black shaded area above a signal indicates no recorded video because of a lack of SD card capacity.

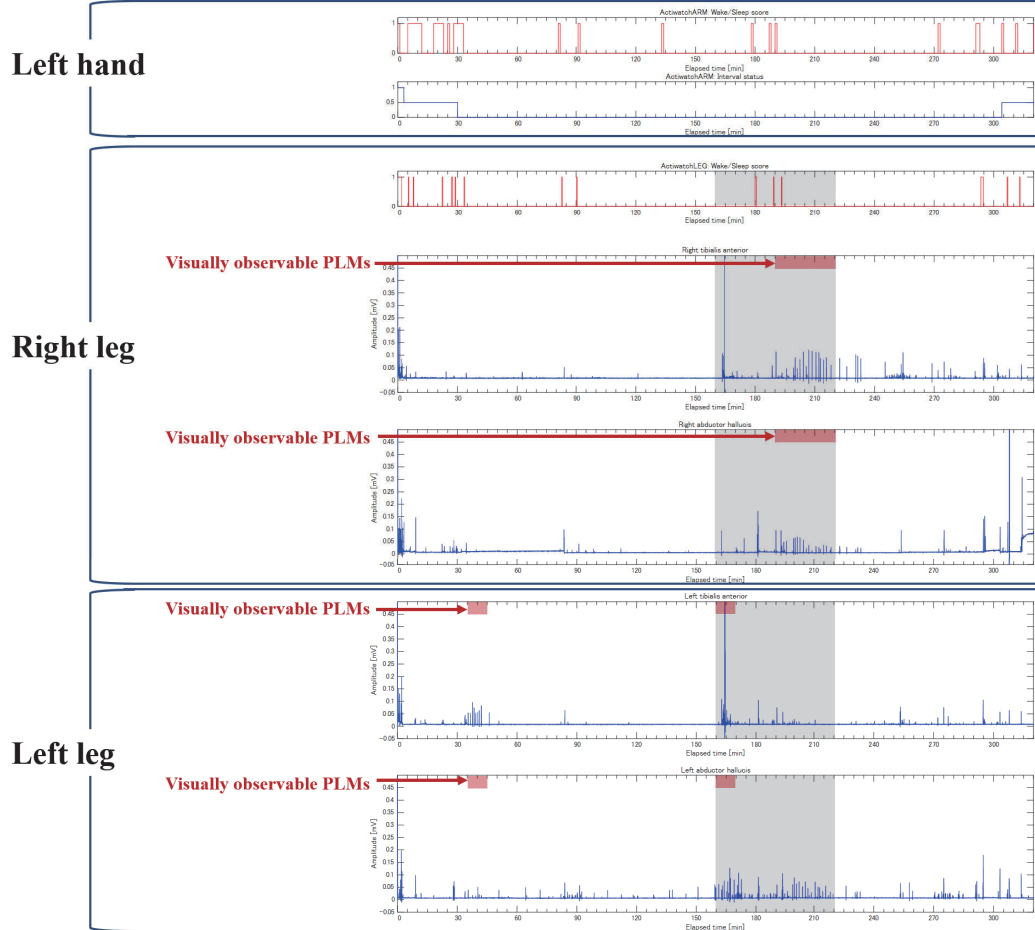


Figure 30: Overview of all data measured on the second night. The graphs from top to bottom show the “Wake/Sleep Score” of the ActiwatchARM, the “Interval Score” of the ActiwatchARM, the “Wake/Sleep Score” of the ActiwatchLEG, and the processed surface EMG signals of the right tibialis anterior, right abductor hallucis, left tibialis anterior, and left abductor hallucis. The occurrence times of visually observable PLM-like events according to the time-related criteria of the AASM scoring manual are depicted above each signal as the red shaded areas.

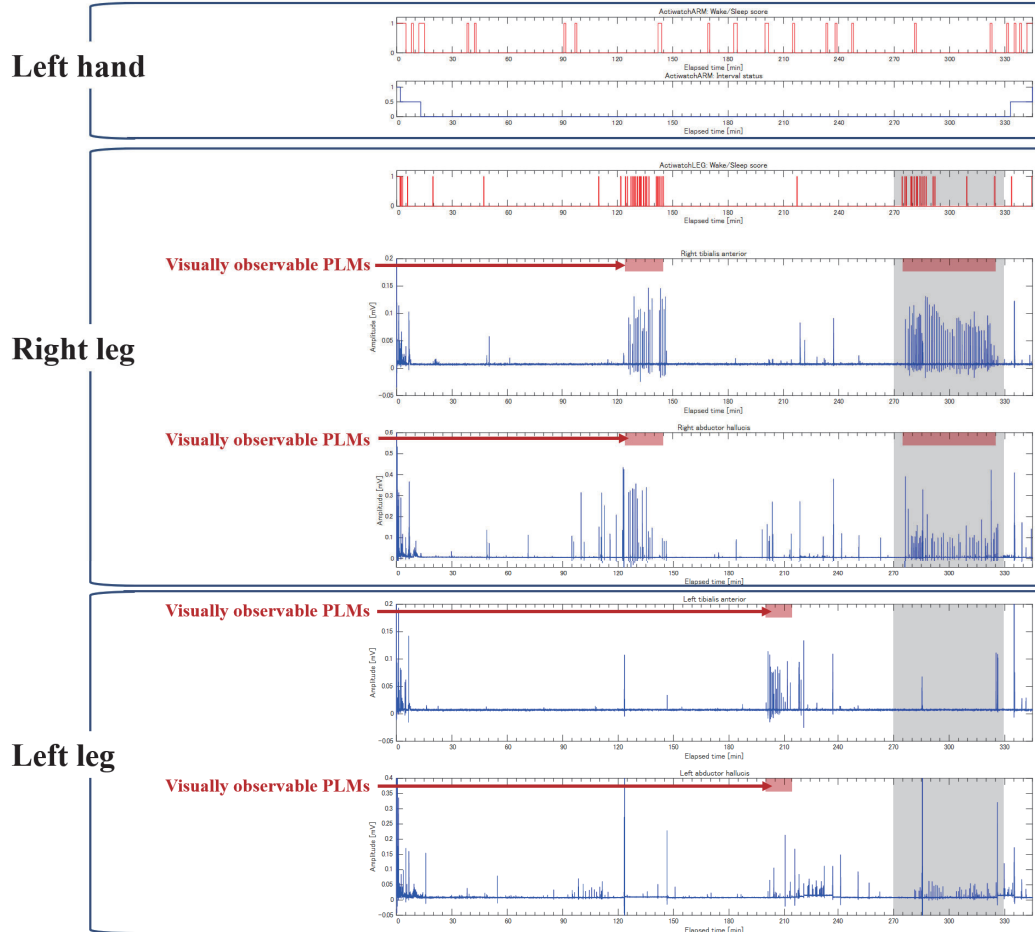


Figure 31: Overview of all data measured on the third night. The graphs from top to bottom show the “Wake/Sleep Score” of the ActiwatchARM, the “Interval Score” of the ActiwatchARM, the “Wake/Sleep Score” of the ActiwatchLEG, and the processed surface EMG signals of the right tibialis anterior, right abductor hallucis, left tibialis anterior, and left abductor hallucis. The occurrence times of visually observable PLM-like events according to the time-related criteria of the AASM scoring manual are depicted above each signal as the red shaded areas.

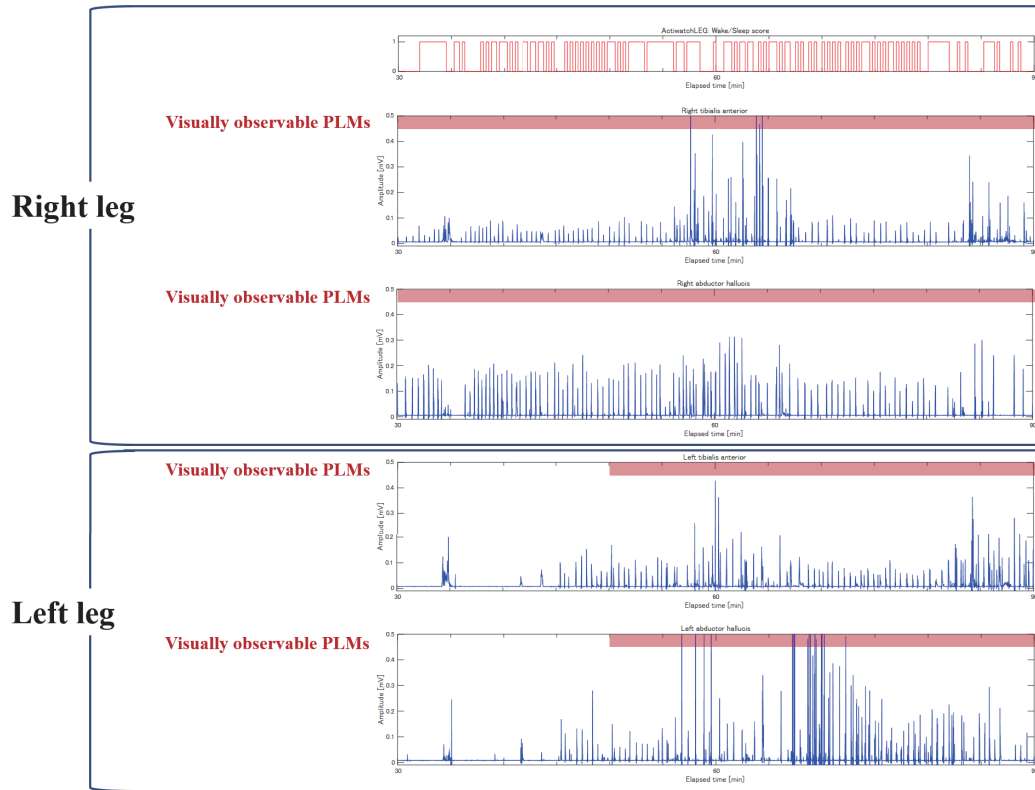


Figure 32: Enlarged view of leg data in the grey shaded area from the first night. The graphs from top to bottom show the “Wake/Sleep Score” of the ActiwatchLEG and the processed surface EMG signals of the right tibialis anterior, right abductor hallucis, left tibialis anterior, and left abductor hallucis, respectively. The occurrence times of visually observable PLM-like events according to the time-related criteria of the AASM scoring manual are depicted above each signal as the red shaded areas.

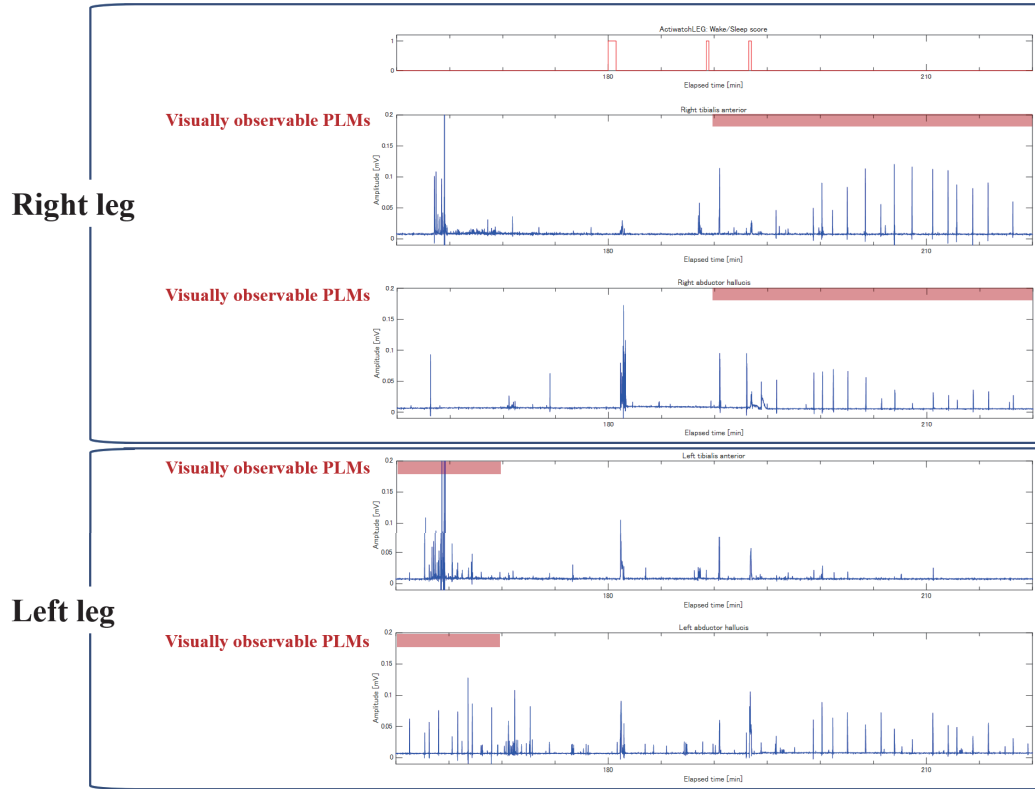


Figure 33: Enlarged view of leg data in the grey shaded area from the second night. The graphs from top to bottom show the “Wake/Sleep Score” of the ActiwatchLEG and the processed surface EMG signals of the right tibialis anterior, right abductor hallucis, left tibialis anterior, and left abductor hallucis. The occurrence times of visually observable PLM-like events according to the time-related criteria of the AASM scoring manual are depicted above each signal as the red shaded areas.

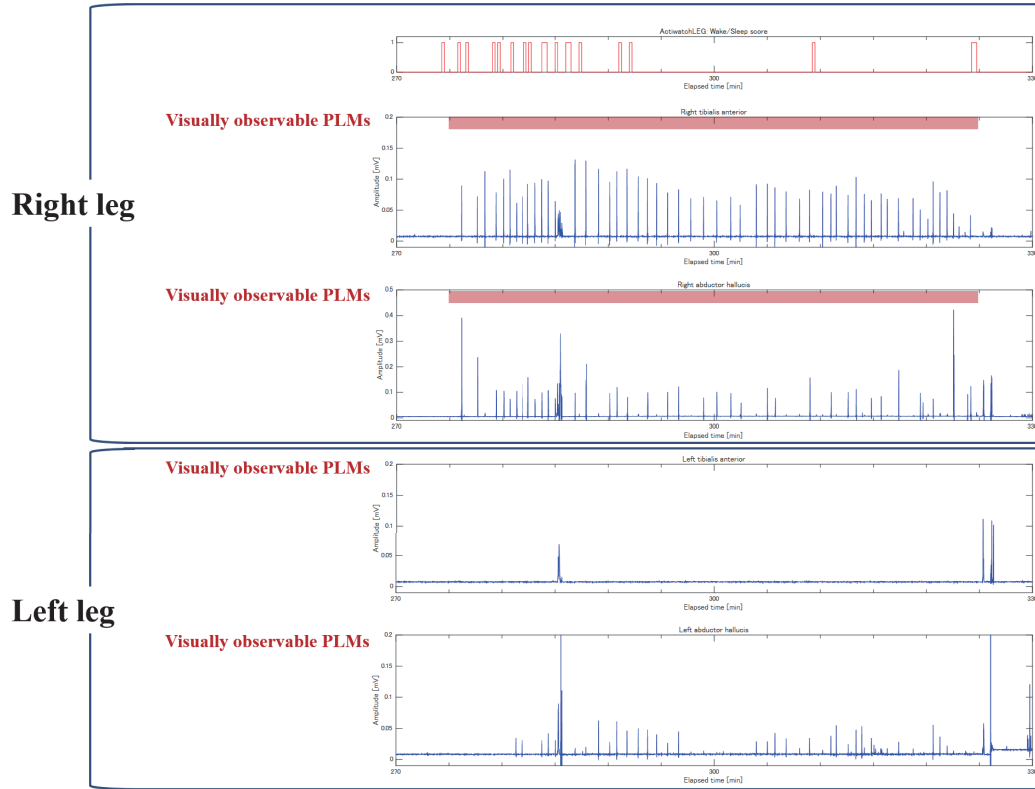


Figure 34: Enlarged view of leg data in the grey shaded area from the third night. The graphs from top to bottom show the “Wake/Sleep Score” of the ActiwatchLEG and the processed surface EMG signals of the right tibialis anterior, right abductor hallucis, left tibialis anterior, and left abductor hallucis. The occurrence times of visually observable PLM-like events according to the time-related criteria of the AASM scoring manual are depicted above each signal as the red shaded areas.

measured signals from each device were compared. This comparison used the “Wake/Sleep Score” of the ActiwatchLEG, which was originally intended to indicate fragmentary nocturnal awakening inducing partial body movements, to indicate the PLMs monitored by the conventional acceleration-based device. Note that this evaluation only targeted the lower extremities on the right side, because only one conventional acceleration device with medical approval could be used for the PLMs monitoring in this experiment.

The results in Figures 29 to 34 confirm that activation in the conventional device was concurrent with that in the two-channel surface EMG measurement, but not necessarily for all PLM-like events that were confirmed by surface EMG. Even for observation of muscle activation in the tibialis anterior, which is related to dorsiflexion of the ankle, the “Wake/Sleep Score” of the ActiwatchLEG did not necessarily show activation. This indicates that conventional acceleration-based PLMs home monitoring using such devices might overlook some PLMs, as described in 2.3.3 and pointed out in [61]. As defined in biomechanics, all body movements inevitably activate the related muscles in principle, so any body movements can be observed from their muscle activation, regardless of the voluntary/involuntary nature. As confirmed in this experiment, however, this does not necessarily mean that acceleration also occurs, especially for comparatively small or short-lasting partial body movements.

Overall, the proposed two-channel surface EMG measurement targeting the abductor hallucis in addition to the tibialis anterior could be suitable for surface EMG-based PLMs home monitoring. Its PLMs evaluation performance has the potential to enable more reliable home monitoring than by the conventional acceleration-based PLMs evaluation.

4.3 Discussion

Although this experiment targeted only one patient with PLMD, it confirmed that PLMs conditions can occur even with medication, and that these conditions can differ each night in terms of the observed times, the inter-event intervals, and even the combination of activating muscles. These results support

already-known PLMs features such as night-to-night variability [39], and that the muscle recruitment pattern can vary even in the same patient [99]. Considering these facts together with the experimental results, we need PLMs home monitoring methods that can be used to observe PLMs regardless of the induced combination of leg movements. The proposed PLMs monitoring based on two-channel surface EMG of the abductor hallucis and tibialis anterior could satisfy this requirement.

Regarding the conventional acceleration device, on the other hand, its performance on PLMs evaluation is not sufficient, because it can overlook PLMs even when targeting dorsiflexion of the ankle alone. The results did confirm, however, that the “Wake/Sleep Score” of an Actiwatch on the arm can be concurrently activated together with PLMs inducing muscle activation, which can be measured by the proposed two-channel surface EMG approach. The Actiwatch acceleration device used here has several built-in sensors for sleep condition evaluation, such as illuminance sensors. Therefore, combined use of a conventional acceleration device like that together with the proposed two-channel surface EMG method could play a certain role in evaluating sleep conditions, including PLMs home monitoring. Note that this combined use of devices targeting the upper extremities together with the lower extremities is not a brand new idea: several hospitals use this combination, as the participant experienced in the follow-up observation described in 4.2.2. The findings in this experiment suggest, however, that switching PLMs home monitoring from an acceleration-based method to a surface EMG-based method would perform better than the conventional configuration only using acceleration devices.

Toward realization of appropriate PLMs home monitoring based on surface EMG, this research developed a new wearable device for surface EMG measurement targeting the abductor hallucis and tibialis anterior. The device’s basic performance on surface EMG measurement was first confirmed, followed by its performance on PLMs monitoring.

Chapter 5 Surface EMG Measurement with Sock-Type Wearable Device

This chapter aims to actually develop the very first prototype of our proposing easy-to-use sock-type wearable device for unaided surface electromyography (EMG) measurement by non-experts targeting surface EMG-based periodic limb movements (PLMs) home monitoring based on our investigation conducted in Chapter 4.

This chapter first introduces the essential design concept of our proposing devices towards the actual development of its prototype in 5.1, and describe the very first prototype of our proposing device in detail step-by-step in 5.2. Then, 5.3 describes the basic performance evaluation between the proposed easy-to-use sock-type wearable device and the conventional measurement electrodes targeting surface EMG measurement during voluntary movements, and 5.4 discusses the results.

5.1 Design Concept and Requirements

Our final research goal is to develop a surface EMG-based PLMs home monitoring device that is easy to use unaided, even by the patients without medical knowledge. This device should be designed on the basis of both biomechanics and human interface perspectives to enable precise discrimination of PLMs from voluntary movements by appropriately and stably measuring surface EMG throughout sleep without disturbing the wearer's usual sleep.

This study therefore considers that the device must meet the following requirements, which is described as well in 3.4.2, to overcome the usual problems with conventional surface EMG measurement:

- (α) ensure low enough contact impedance in the measurement electrodes which does not require cumbersome preparation such as hair removal
- (β) enable surface EMG measurement of PLM-related muscles without needing medical knowledge for its preparation, including appropriate electrode placement on the target muscles while considering its appropriate inter-electrode distance

- (γ) enable overnight surface EMG measurement of the target muscles regardless of the changes in measurement conditions (e.g., perspiration and body movement)

To meet these requirements, this study developed a sock-type smart textile device with embedded fabric electrodes [106]. Requirement (α) was met by using fabric electrodes called NISHIJIN electrodes [80,83,106] for surface EMG measurement due to their usability and stability; the impedance of NISHIJIN electrodes is low enough for surface EMG measurement without the use of conductive paste [94], while their composition supports the absorption of water including perspiration.

Requirements (β) and (γ) were met by using a sock-type fabric adaptor with embedded NISHIJIN electrodes. Requirement (β) would be overcome by embedding NISHIJIN electrodes with a precise inter-electrode distance into the back side of a clothing-shaped fabric adaptor that is easy for non-expert users to handle. This means that users do not need to know the appropriate points for surface EMG measurement of the target muscles, and so as to its inter-electrode distance. Hence, they simply wear the device as they would a regular pair of socks; the device is positioned appropriately front-to-back by fitting its heel part to the heel, which prevents misplacement of the electrodes on nearby muscles. Requirement (γ) would be met by its own compression with which the device can prevent the measurement electrodes from dropping out or slipping on the target muscle due to perspiration or other body movement.

Because these three requirements are related to actual device development, a prototype was first developed and then evaluated its basic performance for surface EMG measurement targeting voluntary movements as a preliminary validation before conducting the actual PLMs monitoring during sleep.

5.2 Sock-type Wearable Device for Unaided Surface EMG Measurement by Non-Expert Users

5.2.1 Target Muscles

Given the experimental results presented in Chapter 4, the tibialis anterior (Figure 23(a)) and abductor hallucis (Figure 23(b)) were set as the preliminary

target muscles. These muscles are comparatively large superficial muscles [104]; thus for surface EMG measurement, which requires the placement of two or more measurement electrodes on the target muscle alone with a few centimeters of inter-electrode distance to prevent crosstalk from adjacent muscles, can be easily performed.

To perform surface EMG for these two target muscles, its body earth was set to the inside of the ankle, where few muscles are located, thereby preventing crosstalk from the other muscles.

5.2.2 Overview of NISHIJIN Electrodes for Measurement Electrodes

This study used NISHIJIN electrodes as the measurement electrodes. In a previous study, the usability of NISHIJIN electrodes in surface EMG measurement was demonstrated [94], and confirmed that it do not need extra preparation such as hair removal.

Each NISHIJIN electrode is composed of a combination of conductive yarn and non-conductive yarn; silver-plated nylon (AGposs ®, Mitsufuji Corporation, Japan [111]) was used as the conductive yarn for the weft, whereas polyester (SD110T96, Yamakoshi Corporation, Japan) was used as the non-conductive yarn for the warp [86]. Because both materials are capable of absorbing perspiration, which degrades electrode impedance in conductive yarn, the quality of the surface EMG measurement would be stable even when the wearer perspires.

The electrodes were fabricated using the conventional NUIWAKE technique of NISHIJIN brocade using a direct Jacquard loom.

5.2.3 Overview of Base Socks for Prototype

This study used a pair of ready-made stretchy socks (Dr. Scholl Medi-Qtto ® short socks for sleeping (M size), Reckitt Benckiser Japan, Ltd., Japan) as the fabric adaptor. Because these socks were originally developed to be worn during sleep to reduce leg swelling, they have specially sewn adaptor parts for the ankle, as well as for the leg part which is designed to provide graduated compression corresponding to the part of the leg that it covers; each specially sewn part has a specific “stitch” (i.e., ankle part has a “tuck stitch”), whereas the leg part has a weft-inlay stitch produces graduated compression.

These features enable the socks to remain fixed on the intended positions of the leg throughout the overnight sleep regardless of leg movement. Prior to prototyping, this study independently ascertained that they do not slip down during or after leg movements, including dorsiflexion/plantar flexion of the ankle or extension/flexion of the knee. A fabric adaptor using these socks can thus position the measurement electrodes appropriately over the target muscles and prevent slippage.

Figure 35 shows an overview of the base socks. The specially sewn ankle part has a “tuck stitch,” while the leg part has a weft inlay stitch that produces graduated compression. The socks also have a wide-ribbed stretchy belt at the top part in order to appropriately place the top part around the knee without applying too much pressure on it.

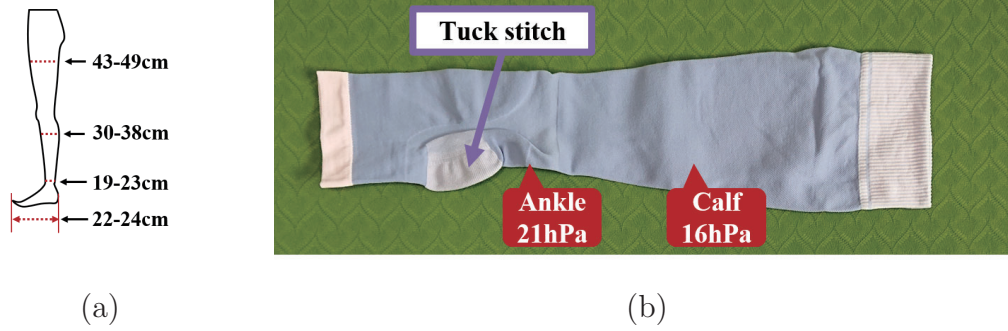


Figure 35: Overview of the base socks for the prototype. (a) Adaptive size of each part of leg in M size socks. (b) Overview of the base socks with its stitch and graduated compression. Note that Figure 35(a) is cited from [86], whose adaptive size is exactly the same as this.

5.2.4 Prototype

This study developed prototype socks by attaching NISHIJIN electrodes to the inside of each base sock. Figure 36 shows a flattened overview of the prototype socks inside out.

The size of an electrode defines signal measurement performance. This study set the size of NISHIJIN electrodes to around 1.3cm^2 , the size demonstrated to be feasible in our previous study [94]. The circumferences of the electrodes

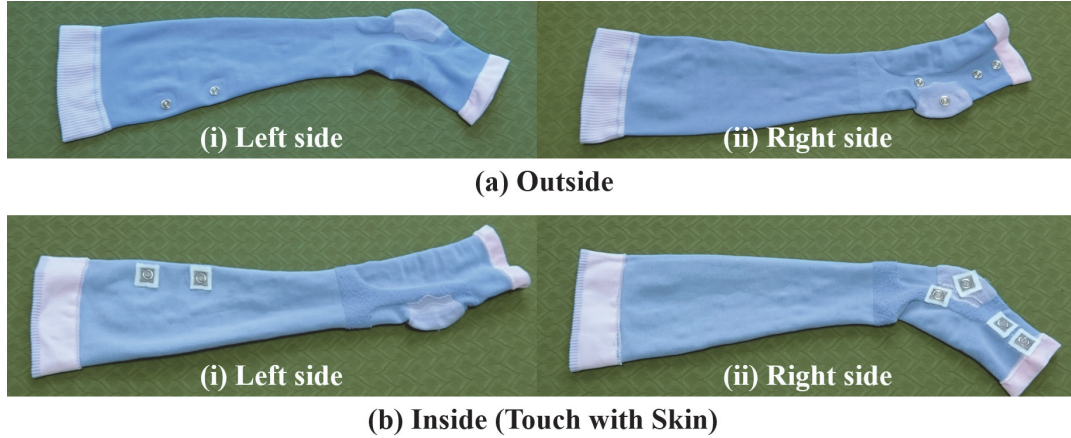


Figure 36: Lay flat overview of the prototype. This figure is cited from [106].

were heat sealed using a fusible tape to prevent fraying (Figure 37); all the electrodes were fixed to the fabric adaptor using double-sided fusible tape. To manage both stable fixation of the electrodes to the base socks and easy measurement of surface EMG, the male side of a rivet snap fastener made of nickel was additionally used; it consisted of a back side part with an eyelet with a prong that attached to the front side part, which had a convex shape. This arrangement enabled us to measure the surface EMG signals by attaching an alligator clip that was connected to the measurement circuit.

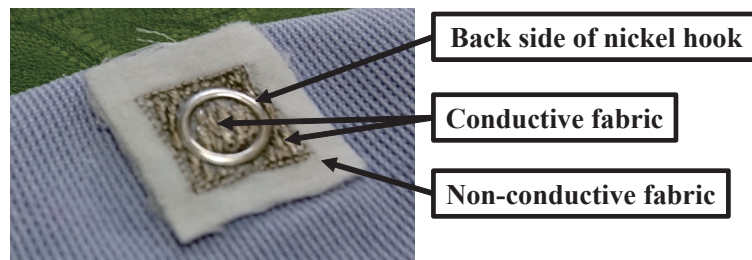


Figure 37: Enlarged view of NISHIJIN electrode. This figure is cited from [106], but annotations are newly added.

In accordance with the anatomical location of the target muscles, the electrodes were placed inside the sock-type fabric adaptor so that they would be located near the muscle belly, where the surface EMG could be measured the most clearly on the basis of the nature of EMG (described in 3.2), when the

wearer wear sock-type fabric adaptor as like a regular socks. The inter-electrode distance between each surface EMG measurement electrode when the device was worn was set to 20.0-30.0 mm, almost the same as that for the surface EMG measurement of the tibialis anterior in practical polysomnography [47].

To suppress both the crosstalk from nearby muscles and the common-mode noise in the surface EMG measurement, the common body earth of the tibialis anterior and abductor hallucis was set on the inside of the ankle, where few muscles are located and can prevent crosstalk from other muscles.

5.3 Evaluation

5.3.1 Overview

As a preliminary evaluation of this prototype, this study first tested its performance for surface EMG measurement during voluntary movement; two channel surface EMGs during voluntary movement was compared between conventional electrodes and the prototype in order to determine whether the surface EMGs of the target muscles measured with the prototype could distinguish the presence/absence of the target movement.

Because the target muscles of this prototype were the tibialis anterior and abductor hallucis, the following two types of voluntary movements were set as the target movements:

- **ankle dorsiflexion** corresponding to the tibialis anterior (Figure 38(a))
- **big toe flexion** corresponding to the abductor hallucis (Figure 38(b))

Instead of measuring the surface EMG of the target two different conditions (i.e., one using the prototype and the other using the conventional electrodes) at the same time, this study independently measured the surface EMG during the target voluntary movement by using either type of target electrodes. To conduct comparative evaluation focusing on the discrimination of the presence/absence of the target movements under this experimental condition, the interval between each voluntary movement was set to approximately 15 s.

5.3.2 Settings

Surface EMG Measurement Conditions

For surface EMG measurement, the electrodes were placed on the left lower

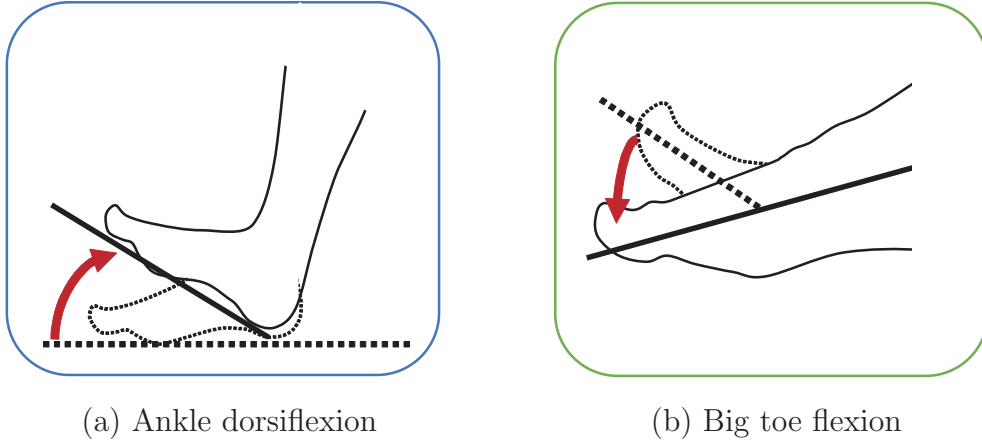


Figure 38: Target voluntary movements. Each target movement starts from dashed line and ends solid line.

leg, as shown in Figures 39(a) and 39(b).

For our prototype (shown in Figure 39(a)), conductive paste on the electrodes (Kenz ECG cream, Suzuken Co., Ltd., Japan) was used to reduce the possible influence of impedance between the skin and the electrodes, which depends on the skin condition. However, hair removal was not conducted as the preparation of surface EMG measurement.

As the conventional electrode, this study used Vitrode C electrodes (Nihon Kohden Corporation, Japan) [112], which comprises an Ag/AgCl electrode, conductive solid gel, and soft cloth tape. Vitrode C electrodes were placed as shown in Figure 39(b).

Hardware

After wearing our prototype, an alligator clip was attached to the convex part of the front side part of each rivet snap fastener, as shown in Figure 40. The clip was connected to the analog circuit via a lead wire. This study used equipment consisting of two analog circuits, an analog-to-digital (A/D) converter, and a laptop computer to measure the surface EMG signals, as shown in Figure 41.

- **Analog circuits:** two self-made analog circuits were used for analog signal processing of the measured surface EMG signals. Each had a single differential amplifier with a 50-Hz notch filter for measuring the surface EMG while suppressing the common-mode noise. To suppress both the

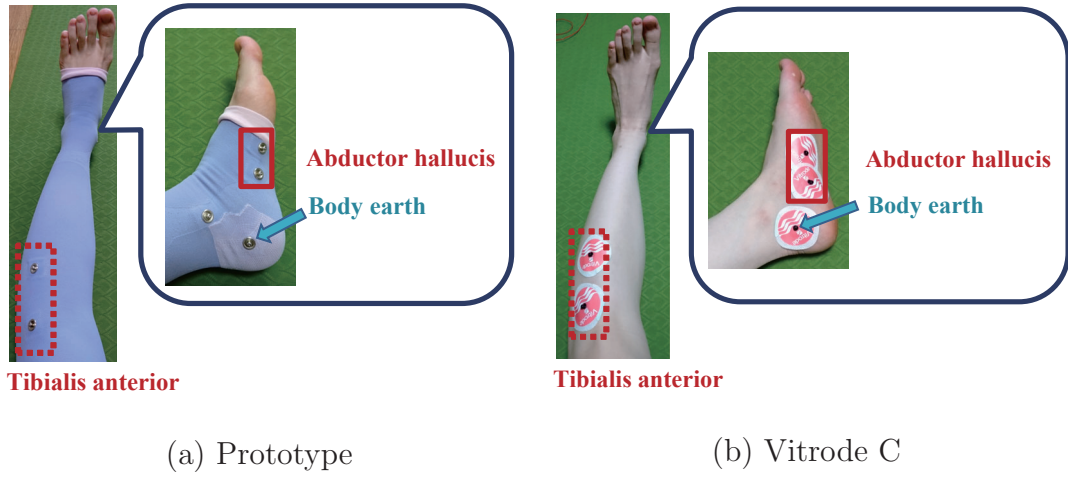


Figure 39: Overview of surface EMG measurement. These figures are cited from [106].

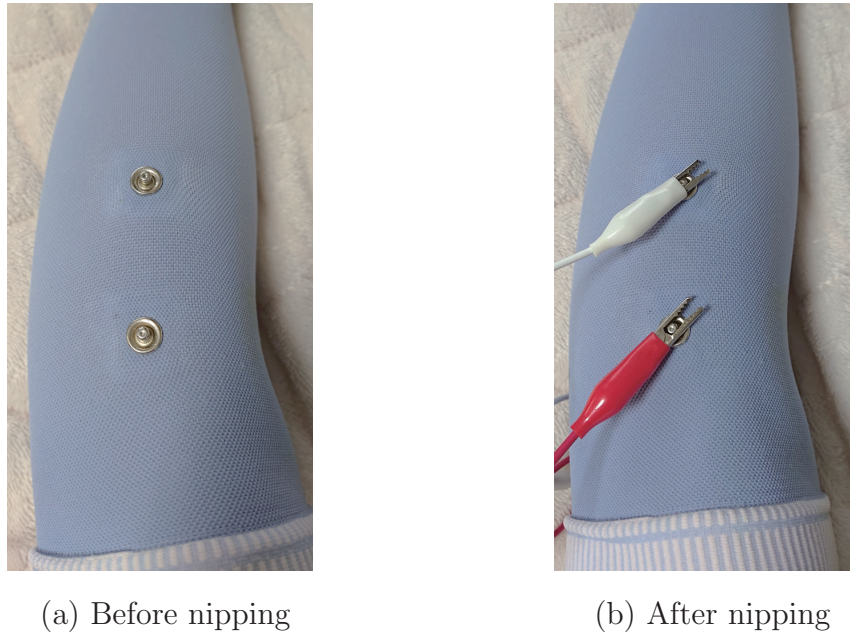


Figure 40: Example of alligator clip arrangement for surface EMG measurement.

crosstalk from nearby muscles and the common-mode noise, this study used the same body earth for both circuits; the body earth of one circuit was connected to the electrode placed on the inside of the ankle, while that of the other circuit was directly connected to the input of the body earth of the first circuit.

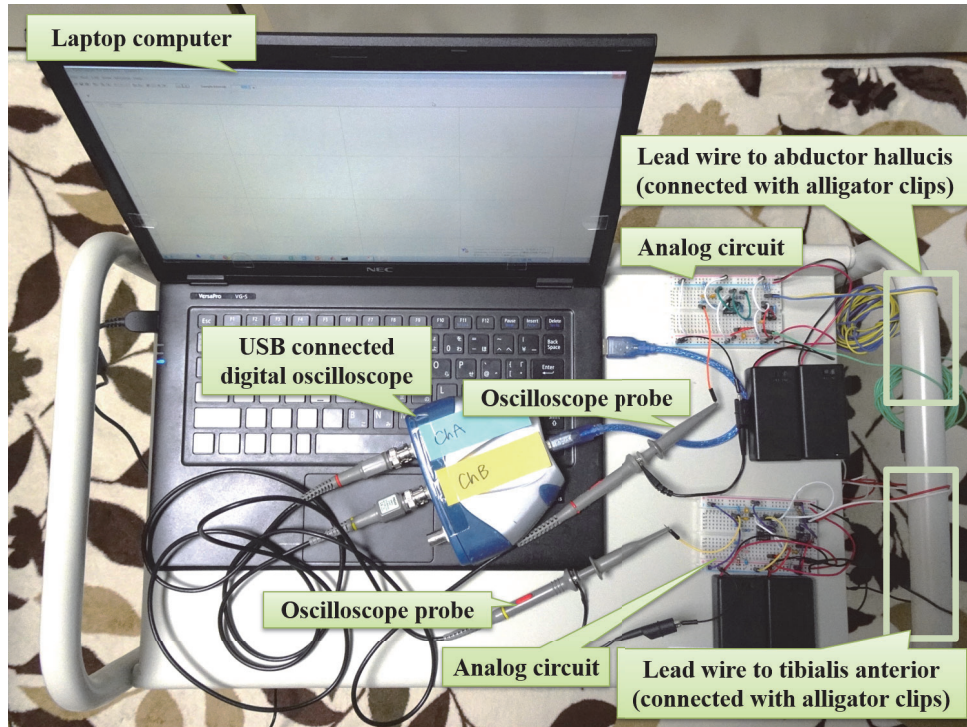


Figure 41: Overview of surface EMG measurement equipment on the cart.

- **A/D converter:** a USB-connected digital oscilloscope (DS1M12, EasySYNC Ltd., United Kingdom) was used to obtain digital signals from the analog circuits, which was done using a P6040 Oscilloscope Probe.
- **Laptop computer:** a laptop computer with the following specifications was used: OS, Microsoft Windows 7 Professional Service Pack 1 (64 bit); CPU, Intel ® Core™ i5-5200U (clock rate: 2.20 GHz); RAM, 4 GB.

Software

The digital signal measured with the USB-connected digital oscilloscope was monitored by using a dedicated software program (EasyLogger for DS1M12, EasySYNC Ltd., United Kingdom). Sampling rate of surface EMG measurement was set as 1-kHz. The default settings were used for all other configurable settings.

Signal Processing

Because measured surface EMG may still contain noise or artifacts due to the changeable measurement conditions, it is difficult to analyze the measured surface EMG as it is. This study therefore performed post-processing in

accordance with the following methods in order to reduce the influence of noise and artifacts: moving average filter, mean value subtraction (direct current removal), absolute value calculation, and peak envelope calculation.

5.3.3 Results

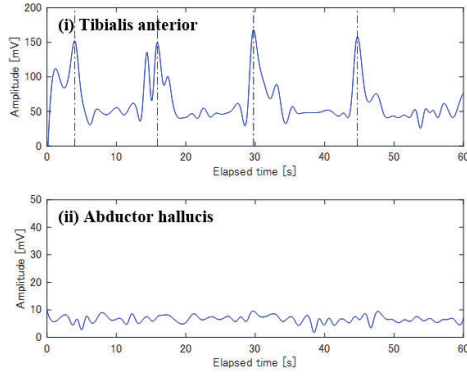
The processed surface EMG envelopes of the tibialis anterior and abductor hallucis measured with the prototype and Vitrode C electrodes are shown in Figures 42 and 43; Figure 42 shows the processed surface EMG during voluntary dorsiflexion of the ankle, whereas Figure 43 shows the one during voluntary flexion of the big toe, respectively. The black dashed lines shown in Figures 42 and 43 indicate detected movements.

Focusing on voluntary dorsiflexion of the ankle as shown in Figure 42, the processed surface EMG of tibialis anterior was activated along with voluntary movements while the one of the abductor hallucis was comparatively stable. During voluntary flexion of the big toe as shown in Figure 43, on the other hand, the processed surface EMG of the abductor hallucis was activated along with voluntary movements while the one of tibialis anterior was comparatively stable. These results demonstrate that the prototype performed surface EMG measurement as well as the conventional electrodes in terms of discriminating the presence/absence of the target movements such as ankle dorsiflexion (Figure 42) and big toe flexion after its extension (Figure 43).

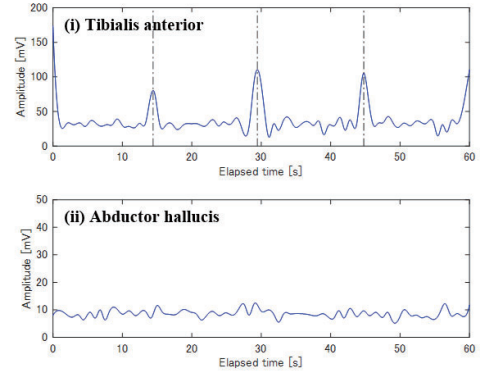
Note that this study this time did not evaluate the validity of the amplitude itself because the surface EMG measurements using the prototype and the conventional measurement electrodes (i.e., Vitrode C electrodes) were performed independently. However, the amplitude of the processed surface EMG measured with the prototype was sufficient to discriminate the presence/absence of the target movements, even though its amplitude values were differed from the ones obtained using the Vitrode C electrodes.

5.4 Discussion

The main advantage of the developed device over conventional electrodes is that it can be used by non-experts. Because all of the measurement electrodes are fixed to the stretchy socks, the user does not have to know the exact position

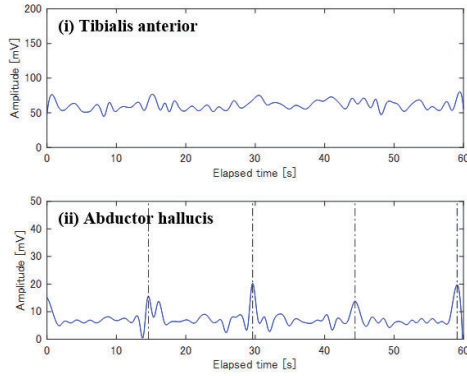


(a) Prototype

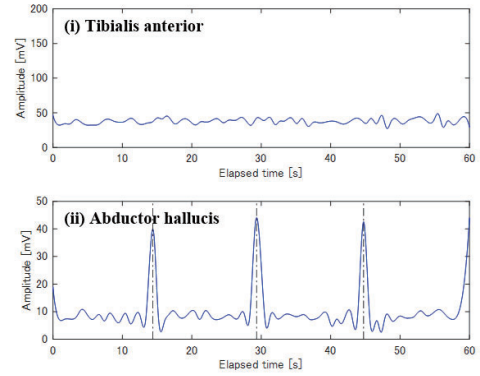


(b) Vitrode C

Figure 42: Processed surface EMG envelope during voluntary dorsiflexion of the ankle. Black dashed line indicates detected movements. These figures are cited from [106].



(a) Prototype



(b) Vitrode C

Figure 43: Processed surface EMG envelope during voluntary flexion of the big toe. Black dashed line indicates detected movements. These figures are cited from [106].

of the target muscles or appropriate measurement position together with its appropriate inter-electrode distance; they simply need to wear the prototype as they would a normal pair of socks by fitting their heel into the heel of the sock.

In addition to the device setup, this study also confirmed that the prototype kept the measurement electrodes at the appropriate position simply from the pressure applied by the fabric adaptors. Figure 44 shows the electrode marks

after surface EMG measurement with the prototype; they clearly show that the electrodes did not slide even though adhesive materials were not used in this prototype. This means that the proposed device is comparatively robust with regard to changeable measurement conditions including body movement and perspiration while maintaining comfortability. Because much adhesive tape or gel used to affix the electrodes in the conventional electrodes is weak against water, and it may slide and slip away from the target muscles due to perspiration. Moreover, the adhesive material itself can irritate the skin. The NISHIJIN electrodes used in this prototype, can absorb perspiration, and wet NISHIJIN electrodes can theoretically measure surface EMG more effectively than dry ones due to the reduced impedance. This means that using a combination of fabric electrodes and fabric adaptors, both of which can absorb perspiration, for surface EMG measurement should be effective for overcoming the problems inherent in conventional electrodes.

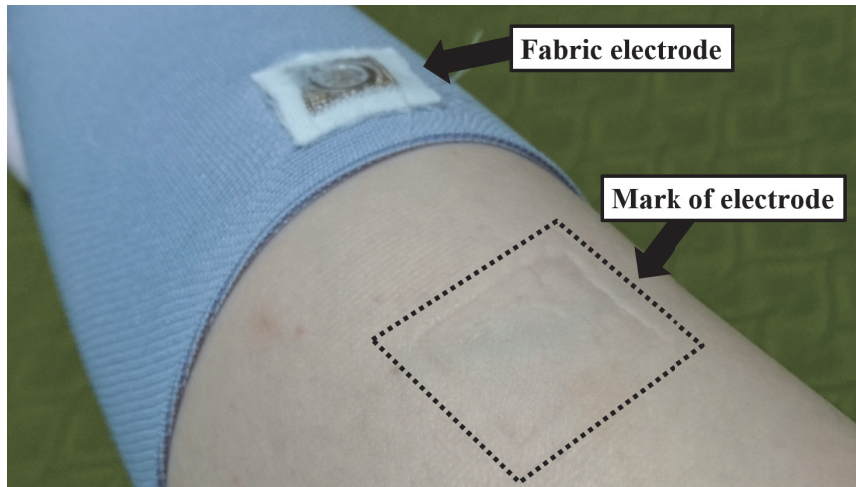


Figure 44: Mark of NISHIJIN electrode after the surface EMG measurement by the prototype. This figure is cited from [106].

As the first step in a preliminary validation of our proposed surface EMG-based PLMs home monitoring device, this study evaluated the performance of the prototype for surface EMG measurement targeting voluntary movements. To determine whether it would be effective for PLMs evaluation

at home, we need to conduct validation testing targeting diagnosed patients of periodic limb movement disorder with remaining PLMs by comparing its performance against the current de facto standard acceleration-based PLMs evaluation device.

Chapter 6 Surface EMG-Based PLMs Evaluation with Sock-Type Wearable Device

This chapter aims to verify the actual performance on surface electromyography (EMG) based periodic limb movements (PLMs) home monitoring using our proposing easy-to-use sock-type wearable device for unaided surface EMG measurement by non-experts, whose performance was confirmed to be sufficient to distinguish the presence/absence of muscle activity through the preliminary validation targeting voluntary movements in Chapter 5.

This chapter first introduces the remodeling of our proposing devices towards the overnight surface EMG measurement targeting the actual PLMs home monitoring while improving its usability in 6.1 [86]. Then, 6.2 describe the preliminary performance evaluation on PLMs home monitoring between the surface EMG-based method using the remodeled easy-to-use sock-type wearable device and the acceleration based method using the current de facto standard acceleration device with medical approval, and 6.3 discusses the results.

6.1 Remodeling of Sock-Type Wearable Device

6.1.1 Overview of Base Socks for Remodeled Prototype

Because our final goal is to develop easy-to-use sock-type wearable device for unaided surface EMG-based PLMs home monitoring, we should confirm whether our prototype can measure the surface EMG of target muscles sufficiently well for PLMs evaluation. Although the first version of our prototype, described in Chapter 5, was able to measure the surface EMG during voluntary movement, this form only with the fabric ankle adaptor may lead twisting in the leg part which finally results in the measurement fault such as measuring the surface EMG other than the target muscles. In addition, its wide-ribbed stretchy belt around the knee with comparatively loose compression was bit close to the muscle belly of the tibialis anterior; this could result in inaccurate surface EMG measurement due to slippage of measurement electrodes (e.g., wide-ribbed stretchy belt below the knee can be slipped away due to the friction against the bed covers during sleep).

To avoid those situations, a pair of ready-made stretchy socks (Dr. Scholl Medi-Qtto® long socks for sleeping (M size), Reckitt Benckiser Japan, Ltd., Japan [113]) were used as the new fabric adaptor. Figure 45 shows an overview of these socks; on the basis of its product description [113], the main difference between these socks and the ones used in our previous prototype [106] (described in Chapter 5) is the specially sewn knee adaptor parts, which prevent inaccurate surface EMG measurement due to slippage or twisting and make it easy to visually distinguish the front and back sides of the socks around the knee.

Because these socks were originally developed to be worn during sleep to reduce leg swelling, they have specially sewn adaptor parts for the ankle and the knee, as well as the leg part, which is designed to provide graduated compression corresponding to the part of the leg that it covers. Each specially sewn part has a specific “stitch” (i.e., ankle part has a “tuck stitch,” while the back of the knee part has a “soft stitch”), whereas the leg part has a weft-inlay stitch produces graduated compression. In addition, these socks also have a wide-ribbed stretchy belt at the top, so that they remain fixed at the top part on the thigh, thereby supporting appropriate placement of the knee adaptor. These features enable the socks to remain fixed on the intended positions of the leg throughout the overnight sleep, regardless of the leg movement. Prior to prototyping, this study independently ascertained that they do not slip down during or after leg movement, which could be induced by PLMs including dorsiflexion/plantar flexion of the ankle or extension/flexion of the knee while lying down. A fabric adaptor using these base socks should thus appropriately place the surface EMG measurement electrodes over the tibialis anterior without twisting of the leg parts by fitting the ankle and knee adaptors to their designated positions while the compression of the socks prevents slippage of the measurement electrodes.

6.1.2 Prototype

To achieve both stable fixation of the NISHIJIN electrodes to the base socks and easy measurement of surface EMG, this study used the large male side part of a rivet snap fastener made of brass (outer diameter of 21.0 mm). It consisted of a back side part with an eyelet with a prong that attached to the front side part (BELNAP® X cap Ligne 33 Prong 7320, YKK Snap Fasteners Japan Co.

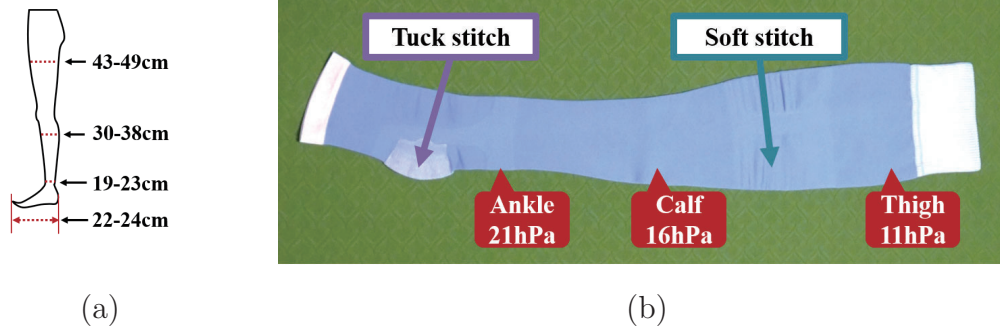


Figure 45: Overview of the base socks for the remodeled prototype. (a) Adaptive size of each part of leg in M size socks. (b) Overview of the base socks with its stitches and graduated compression. These figures are cited from [86].

Ltd., Japan [114]) and a front side part with a convex shape (BELNAP ® 33 Duo 6502, YKK Snap Fasteners Japan Co. Ltd., Japan [114]).

A square NISHIJIN electrode was set at the center of the eyelet (inner diameter of 19.0 mm), and riveted to the base sock and the front side part, as shown in Figures 46 and 47; the eyelet part on the back side had a prong piercing the NISHIJIN electrode as well as the base sock and connecting to the front side part. Surface EMG thus would be measured by attaching an alligator clip to the convex part of the front side part, as shown in Figure 47(c). Although metallic material was used to firmly fix the fabric electrodes and for conductivity, we can avoid beading around the snap fastener even if the wearer perspires by using water absorption materials for both the surface EMG measurement electrodes and the fabric adaptor. This would help suppress surface EMG measurement errors due to perspiration.

Figure 48 shows an overview of the remodeled prototype inside out. Given the anatomical location of the targeted muscle, a pair of NISHIJIN electrodes were attached for surface EMG measurement to the inside of the socks near the muscle belly of the tibialis anterior, where the surface EMG signals could be measured the most clearly. In addition, one NISHIJIN electrode was attached to the inside of the ankle (i.e., near the medial malleolus) for reference signal measurement, as this location reduces crosstalk from the peripheral muscles because there are relatively few superficial muscles in this area [104]. The

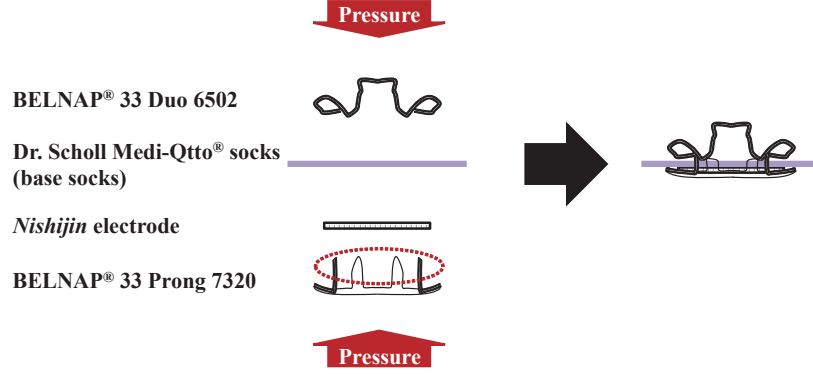


Figure 46: Cross sectional view of NISHIJIN electrode part before and after riveting. Applying pressure causes the prong part (red dotted circle) to pierce the NISHIJIN electrode and the base sock, and then becomes plastic deformation. This figure is cited from [86].

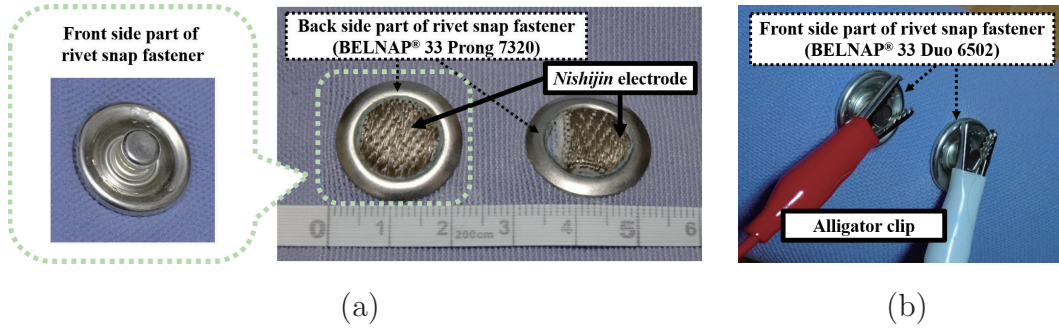


Figure 47: Enlarged views of NISHIJIN electrodes. (a) Front/back side of rivet snap fasteners with fabric electrodes for surface EMG measurement of the tibialis anterior. (b) Example of alligator clip arrangement for surface EMG measurement. These figures are cited from [86].

inter-electrode distance between each surface EMG measurement electrode when the device was worn was set to approximately 20.0 mm, almost the same as for surface EMG measurement of the tibialis anterior in conventional polysomnography [47]. In addition to these locations, the remodeled prototype also had a pair of NISHIJIN electrodes for surface EMG measurement of the abductor hallucis, which corresponds to abduction and flexion of the big toe [98] as a supplementary target muscle based on our investigation results described in Chapter 4.

To suppress both the crosstalk from nearby muscles and the common-mode noise in the surface EMG measurement, the common body earth of both the tibialis anterior and abductor hallucis was set on the inside of the ankle, where few muscles are located and can prevent crosstalk from other muscles.

The total weight of this remodeled prototype per leg was 52.0 g; 33.0 g for the base sock and an extra 19.0 g for the NISHIJIN electrodes and their attachments.

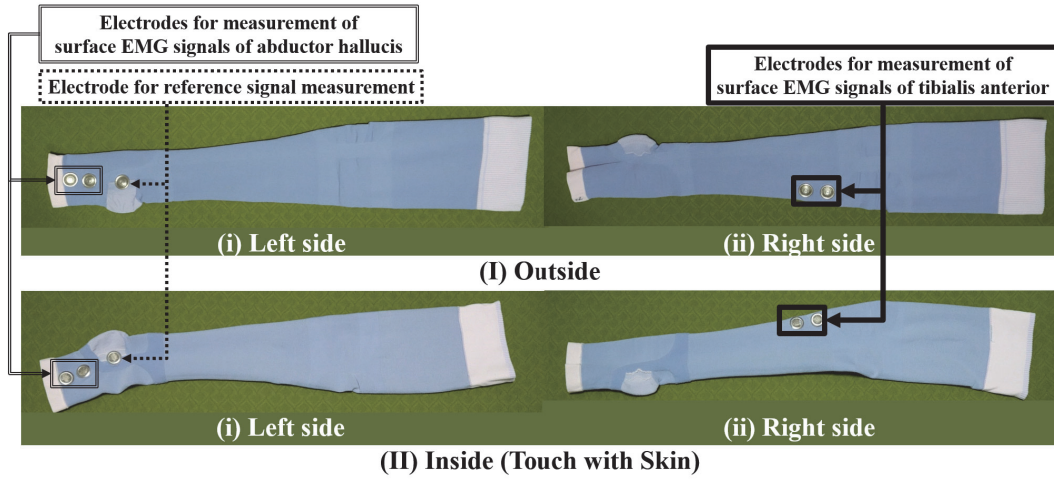


Figure 48: Overview of the remodeled prototype for the right leg inside-out. This figure is cited from [86].

6.2 Evaluation

6.2.1 Overview

As a preliminary validation of the remodeled prototype with regard to PLMs home monitoring performance, this study compared the measured data from the remodeled prototype with that from the de facto standard conventional acceleration-based device with medical approval. To validate two different devices, this study conducted a comparative evaluation against possible PLM-like events that were confirmed by visual observation.

Because this experiment is the very first stage of a preliminary validation of PLMs monitoring at home with limited resources, there was no choice but

to conduct this experiment outside a hospital, without fully attended PSG. It was therefore conducted while capturing a video of the lower extremities, which was used to observe the actual PLMs conditions as a reference for this comparative evaluation. For this reason, one PLMD patient with periodic limb movement disorder (PLMD) was asked to wear both our remodeled prototype and a conventional acceleration-based device with medical approval on the same leg during sleep at home while capturing a video of the lower extremities.

Of note, the experimental settings only allowed to measure two channel surface EMG. Looking back to the criteria of PLMs evaluation in PSG for the definitive diagnosis of PLMD we described in 3.1, it only targets the bilateral tibialis anterior; we consider that this indicates physicians possibly could not regard the certain movements involving the abductor hallucis alone as PLMs. Although our remodeled prototype is capable of measuring two channel surface EMG of the bilateral tibialis anterior and abductor hallucis, this study only employed the bilateral tibialis anterior as the target muscles of two channel surface EMG measurement in this experiment.

This case study validates the data on a night during which the participant experienced nocturnal awakening due to perceptible PLMs-like events that could also be observed on the recorded video by a physician.

6.2.2 Target Participant

Because the remodeled prototype needed alligator clips and lead wires to connect it to the analog circuits for surface EMG measurement, comparatively large normal body movements (e.g., turning over) could greatly affect the surface EMG measurement conditions. This study thus targeted the same female patient with PLMD described in Chapter 4 who rarely turns over when sleeping at home according to reports from her family.

6.2.3 Experimental Environment

To conduct this preliminary validation at the actual patient's home under usual sleep conditions, the positions of her bed and furniture were not changed at all. Rather, several pieces of experimental equipment were set up around the bed. Overview of the layout of the experimental environment is the same as Figure 24 in Chapter 4. A video camera was placed where it could capture a video of the

lower extremities, regardless of the leg movement or turning of the body. To avoid disturbing the participant’s usual sleeping conditions, the video camera did not require lighting (FDR-AX60, Sony Corporation, Japan).

Aside from the video camera, several other pieces of equipment were set up for surface EMG measurement, consisting of self-made analog circuits, an analog-to-digital (A/D) converter, and a laptop computer, as shown in Figure 41 in Chapter 5, on the cart near the bed (shown in Figure 24 in Chapter 4), in order to focus on evaluating the performance of our remodeled prototype as “measurement electrodes” for surface EMG measurement first of all.

6.2.4 Arrangement of Target Devices

The most recent results of acceleration-based PLMs measurement over three nights at home (described in Chapter 4) revealed that our target participant tends to experience more PLMs in the right leg than the left leg. This study therefore targeted the right leg for our comparative evaluation of PLMs in this preliminary experiment. The participant wear both our remodeled prototype and a conventional acceleration-based device, as shown in Figure 49(a); the participant first wore our remodeled prototype on the leg and then put the conventional acceleration-based device around the ankle.

As a dependable device for evaluating the usual sleep conditions at home, a commercially available and medically approved wristband with a built-in accelerometer was chosen, namely, Actiwatch Spectrum Plus (Philips Respironics, Murrysville, PA, USA). For validation purposes, the participant was asked to wear two Actiwatches, as shown in Figure 49: one for sleep evaluation (worn on non-dominant left wrist; hereafter ActiwatchARM, as shown in Figure 49(b)), and the other for acceleration-based confirmation of PLM-like events (worn on the right leg; hereafter ActiwatchLEG, as shown in Figure 49(a)). After all devices were worn, it was confirmed that none of them slipped from their initial positions during or after leg movements. Note that the participant was asked not to put a blanket over the lower extremities to prevent measurement faults.

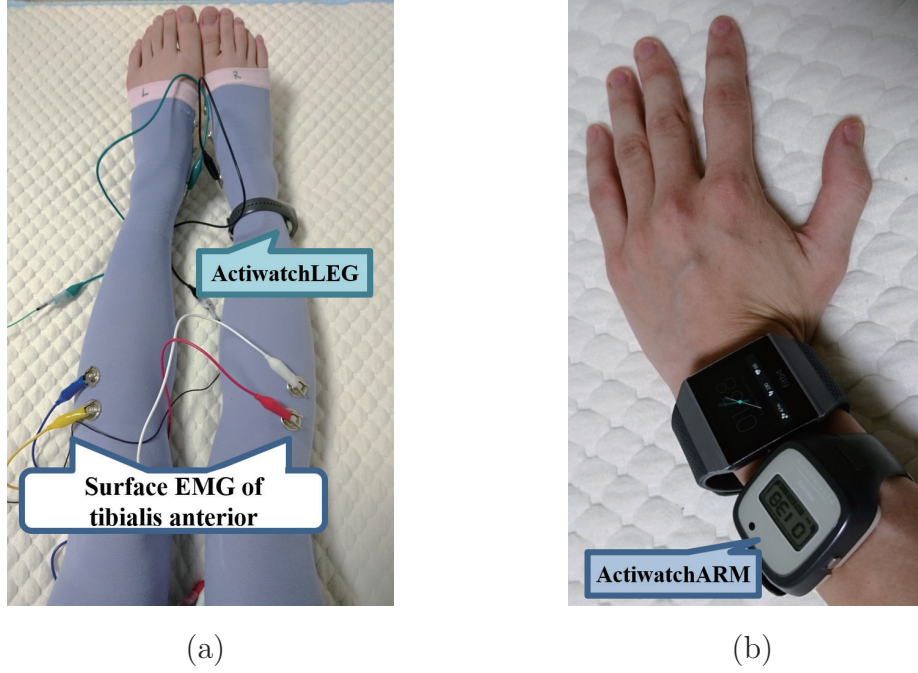


Figure 49: Arrangement of the conventional acceleration-based device and the remodeled prototype. (a) Remodeled prototype and with Actiwatch on the right ankle (ActiwatchLEG). (b) Actiwatch on the left wrist (ActiwatchARM, bottom device). The participant additionally wore her own smartwatch (device at top of Figure 49(b)). Note that these figures are cited from [86].

6.2.5 Overview of Data Collection

As described previously, the following three types of data during sleep were measured in this experiment: surface EMG of the bilateral tibialis anterior, as measured by our remodeled prototype; acceleration-based body movements of the left hand and the right leg, as measured by an acceleration-based devices with medical approval (i.e., ActiwatchARM and ActiwatchLEG); video for the reference of PLMs-like events. Experimental conditions of the surface EMG measurement and the conventional acceleration-based method were described in detail in the following sections.

For appropriate validation, a “sleep diary” was also collected to confirm the sleep conditions, including the subjective PLMs experience and environmental conditions during sleep. The participant was asked to keep a record of the times that she got into bed, got out of bed, and took medicine, as well as the details

of her medication use (e.g., the name and amount). The participant was also asked to record her subjective evaluation of PLMs experiences to evaluate the probability of PLM-like events, as in her usual routine. Finally, the participant was also asked about the lighting conditions on the nights of measurement to confirm the effect of brightness.

Note that all the data measured in this experiment was recorded to a storage medium (i.e., a wire-connected laptop for surface EMG and built-in device memory for the acceleration-based device) and analyzed offline afterward.

6.2.6 Video Analysis by Visual Observation

As a reference for the comparative evaluation, the recorded video was visually checked in the following three steps.

1. a record of all movements of the target leg along with the time of occurrence was made.
2. candidate PLM-like events were extracted on the basis of the *American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events* (hereafter, the AASM scoring manual) [47]; because the evaluation was done using recorded video, only the maximum duration of each PLM event was used (i.e., <5 s), the inter-event intervals (i.e., 5–90 s), and the minimum number of consecutive events comprising a series of PLMs (i.e., >4 PLM-like events).
3. a medical doctor visually checked the candidate PLM-like events extracted in the second step using a three-grade evaluation: “✓ (certain),” “△ (possible),” and “× (improbable).” This study only used certain PLM-like events judged “certain” as a reference for the subsequent comparative evaluation.

6.2.7 Settings in Surface EMG Measurement

Preparation

For the surface EMG measurement, the participant was asked to wear our remodeled prototype similarly to wearing a normal sock by fitting both the heel and the knee to the designated position of the fabric adaptor as shown in Figure 49(a). The participant was also asked to put conductive paste (Kenz ECG cream, Suzuken Co., Ltd., Japan) on the surface of the electrodes to

reduce potential impedance between the skin and the electrode just in case.

Hardware

After wearing our remodeled prototype, a convex part of the front side part was nipped with an alligator clip, as shown in Figure 47(b), which connected the analog circuit via a lead wire.

This study used the hardware as shown in Figure 50, which is the same one used in the experiment described in Chapter 5 except for the body earth connection; because this study targeted the bilateral tibialis anterior, the body earth was measured from the ankle of the corresponding leg.

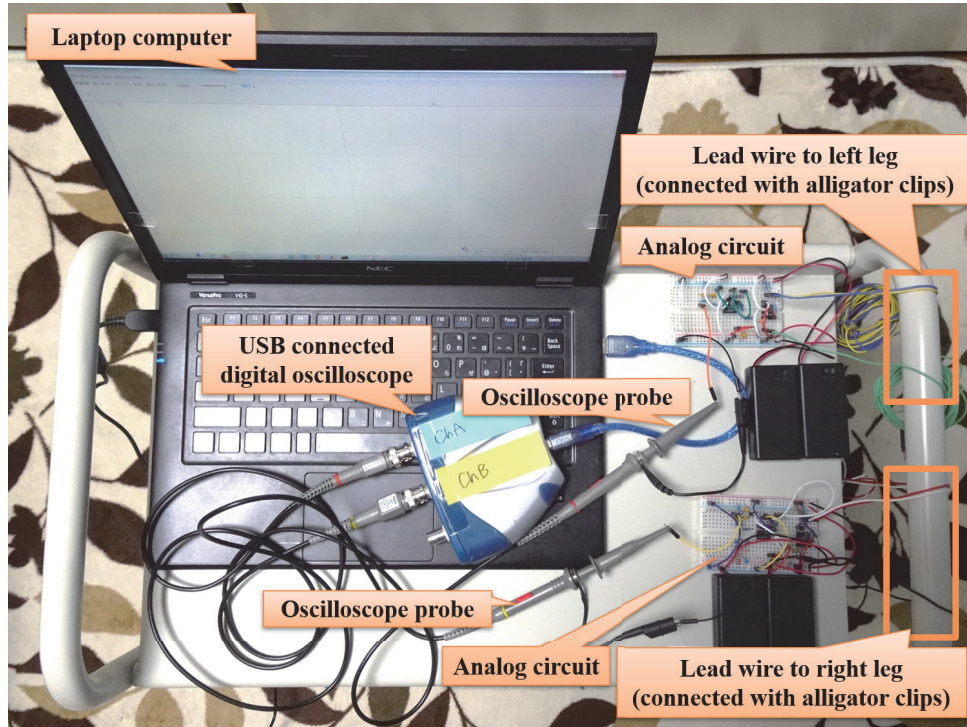


Figure 50: Overview of the surface EMG measurement equipment on the cart. Note that this figure is cited from [86].

Software

This study used the same software as described in Chapter 5; the digital signal measured with a USB-connected digital oscilloscope was monitored using a dedicated software program (EasyLogger for DS1M12, EasySYNC Ltd., United Kingdom) at a 1-kHz sampling rate to satisfy the Nyquist frequency of the

subsequent signal processing using a bandpass filter (BPF). The default settings were used for all other configurable settings.

Signal Processing

Because surface EMG measured during sleep at home may contain noise or artifacts, it is difficult to analyze the measured surface EMG signals as is. To reduce the influence caused by noise and artifacts, the signals were post-processed using the following signal processing procedures: (1) BPF processing, (2) root mean square (RMS) calculation, (3) peak envelope calculation, and (4) peak detection. This signal processing was performed using self-developed dedicated program code for MATLAB (MATLAB R2017a, The MathWorks, Inc., Natick, MA, USA).

1. **BPF processing:** a twentieth-ordered 10–450-Hz Butterworth BPF was used to suppress the effects of noise and artifacts in the measured surface EMG signals.
2. **RMS calculation:** the RMS of the BPF-processed surface EMG signals was calculated by setting the RMS calculation window to 50 ms and then sliding it forward in 1 ms increments.
3. **Peak envelope calculation:** the peak envelope of the RMS-processed surface EMG signals was calculated from 500 sample intervals.
4. **Peak detection:** the peaks exceeding 1.15 times the mean value of all processed data were detected. Only the peaks with a peak distance of >5 s were detected by using the inter-event intervals of PLMs [47].

6.2.8 Settings in Acceleration-Based Method

Hardware

Because each PLM event lasts for <10 seconds according to the AASM scoring manual [47], each Actiwatch was set to a different resolution, called the “epoch length” in the Actiwatch settings. The sleep status was evaluated by the ActiwatchARM, whereas short-lasting movements, including PLMs, were evaluated by the ActiwatchLEG. The epoch length of the ActiwatchARM was thus set to 60 s, while that of the ActiwatchLEG was set to 15 s (the minimum epoch length). The default settings were used for all other configurable settings.

Data Analysis

The Actiwatch itself outputs data throughout its use. To obtain appropriate output data via the Actiwatch auto-analysis system (Actiware®, Philips Respironics, Murrysville, PA, USA), appropriate times for getting in and out of bed were manually set according to the participant’s sleep diary, and only the output data measured during sleep was used. Note that, before the data analysis, it was confirmed that both the ActiwatchARM and ActiwatchLEG were appropriately worn on the participant’s body during sleep according to the output data of the “off-wrist detector.”

A sleep time reference was provided by the ActiwatchARM’s “Interval Status,” the possible values of which were “Active,” “Rest,” “Rest-Sleep,” “Excluded,” and “N/A.” The Active, Rest, and Rest-Sleep values were transformed to numerical values (1, 0.5, and 0, respectively) to obtain a hypnogram-like state transition. In addition to the Interval Status, the momentary “Wake/Sleep Score” was also considered, because the time in bed did not necessarily reflect the actual total sleep time. Hence, the Wake/Sleep Score in the epoch-by-epoch data was used as an output from each Actiwatch, with values of 0 (sleep), 1 (wake), or NaN.

6.2.9 Results

General Sleep-related Condition on the Target Night

This study first confirmed the general sleep-related condition including the environmental condition during sleep, dosages of medications, and a brief summary of the participant’s sleep status based on the participant’s sleep diary. According to the sleep diary, the participant turned off the light before going to bed, and only covered her body (and not her legs) with a blanket as asked. Regarding medication, the participant took pramipexole (0.125 mg) at approximately 9:00 p.m. for PLMs suppression as usual.

Information on the timing of the sleep conditions is shown in Table 6; Table 6 shows a summary of the subjective sleep status, including the time of getting into bed, the time of getting out of bed, and the time in bed (i.e., the interval between getting in bed and getting out of bed). According to the participant’s main complaint (described in the sleep diary), the participant

slept well right after getting in bed until approximately 4:00 a.m. The abovementioned experimental conditions were not associated with difficulty in falling asleep. However, the participant experienced perceivable consecutive severe PLMs around that time, and finally woke up to take an additional dose of medicine.

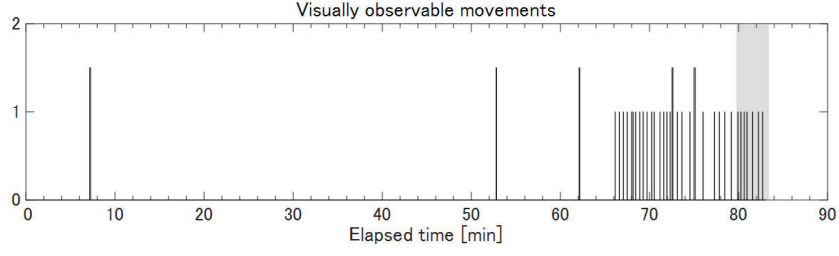
Table 6: Summary of subjective sleep time

Getting in bed	Getting out of bed	Time in bed
02:37 a.m.	04:00 a.m.	83 min

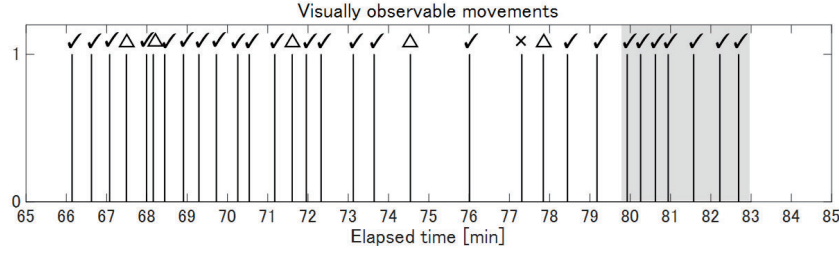
Visually Confirmed PLM-like Events

This study checked the recorded video to identify PLM-like events for the comparative evaluation. Figure 51(a) shows the movements involving the right leg detected by our visual observation of the recorded video: 0 indicates that there were no visually observable movements, 1 indicates the presence of PLM-like movements, and 1.5 indicates normal body movements. From the start until the middle part of sleep on that night, there were only two or three body movements that partially involved the lower extremities, all of which seemed to be normal body movements and not PLMs-like events. However, in the latter part of sleep on that night (i.e., approximately 3:43 a.m. [elapsed time, 66 min]), several PLM-like events were observed. A total of 31 PLM-like events that satisfied the aforementioned criteria were observed in the recorded video. Although most of those PLM-like events are comparatively small movements involving extension/flexion of the big toe, 7 PLM-like events that occurred in the grey shaded area in Figure 51 (i.e., after 3:57 am [elapsed time, >80 min]) were seemed to be larger PLMs-like movements involving dorsiflexion of the ankle compared to the other PLM-like movements than the ones that occurred earlier.

The medical doctor then checked these 31 possible PLM-like events. As shown in Figure 51(b), there were 25 “certain” PLM-like events, 5 “possible” ones, and 1 “improbable” one. This study used these 25 “certain” PLM-like events as references for the subsequent comparative evaluation.



(a)



(b)

Figure 51: Results of the PLMs visual confirmation. (a) Visually observable movements occurred in the right leg identified by authors. (b) Classification results of all the possible PLM-like events by a medical doctor. Note that these figures are cited from [86].

Comparative Evaluation of PLMs-like Events Measured by Target Devices

Before conducting the comparative evaluation of PLMs home monitoring between the surface EMG-based method and the conventional acceleration-based method, the measurement status of the surface EMG was confirmed to determine the target duration for the comparative evaluation. Information on the timing of surface EMG measurement including the start and end time is shown in Table 7. Of note, surface EMG measurement in this experiment ended at around 4:00 a.m. around when getting out of bed. Because the subjectively judged “time in bed” based on the sleep diary shown in Table 6 was shorter than the surface EMG measurement, the “time in bed” was set as the target of this analysis.

Figure 52 shows all of the processed data. The “Interval Status” and “Wake/Sleep Score” of ActiwatchARM suggest that the participant might have

Table 7: Summary of surface EMG measurement time

Starting time	Ending time
02:34:46 a.m.	04:01:19 a.m.

slept from 2:52 a.m. until approximately 3:57 a.m. [elapsed time, approximately 15 to 80 min] in contrast to the subjectively recorded time in bed (i.e., 83 min; from 2:37 a.m. to 4:00 a.m.). We could not specify the actual sleep condition with absolute certainty on the basis of only the ActiwatchARM output data because the sleep stage should in principle be determined by electroencephalography in accordance with the AASM scoring manual [47]. However, this study could at least specify that the participant was lying stably on the bed on the basis of the “Interval Status” of ActiwatchARM and visual confirmation of the recorded video. Likewise, the differences in the “Wake/Sleep Score” between the ActiwatchARM and ActiwatchLEG data were considered as reflecting the differences in movements between the arm and leg; for instance, a “Wake/Sleep Score” of 1 (i.e., “Wake”) from the ActiwatchARM data together with a “Wake/Sleep Score” of 0 (i.e., “Sleep”) from the ActiwatchLEG data suggests that the left arm moved while the right leg stayed still. Because the participant could not be visually confirmed as struggling to sleep (e.g., turning over in bed or groaning) around that time, this study assumed that the participant was most likely asleep until getting out of bed.

This study then evaluated the PLM-like events using data from each target device. Figure 53 shows an enlarged view of the shaded area in Figure 52 with regard to the PLM-like events reference data, ActiwatchLEG data, and surface EMG data. Focusing on the ActiwatchLEG data, there were only two observable momentary activations reflected in the “Wake/Sleep Score” during the experiment. However, the processed surface EMG signals of the right tibialis anterior showed seven activations between 3:57 a.m. and 4:00 a.m. [elapsed time, 80 - 83 min] when the comparatively larger PLM-like events were observed in the recorded video. Notably, the average inter-event interval of each muscle activation observed in the processed surface EMG data was 29.2 ± 8.13 s, which is in agreement with detection criteria for PLM events

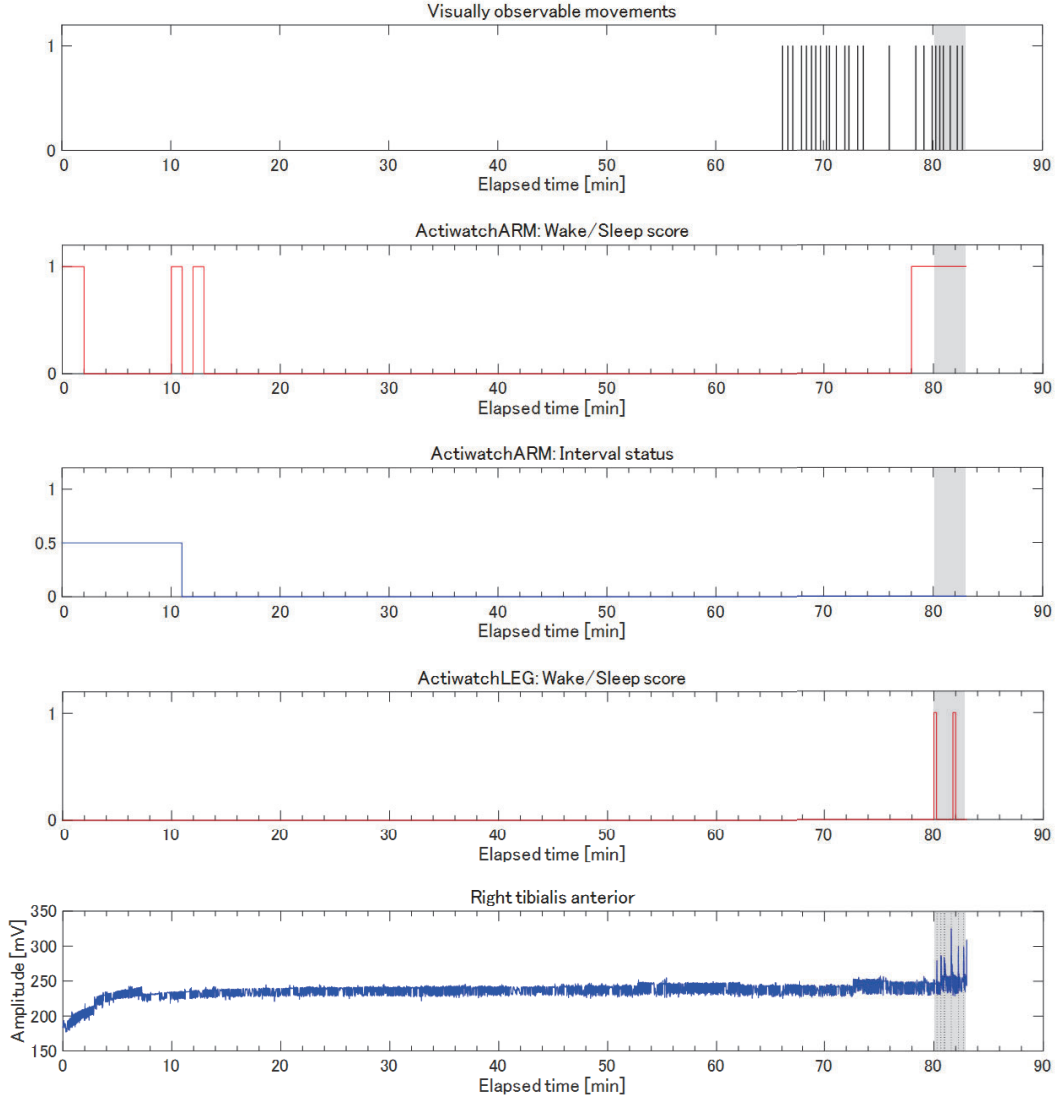


Figure 52: All measured data in this experiment. Graphs (from top to the bottom) show visually observable PLM-like movements in recorded video judged as “certain,” “Wake/Sleep Score” of from ActiwatchARM data, “Interval Score” from ActiwatchARM data, “Wake/Sleep Score” from ActiwatchLEG data, and processed surface EMG signals of the right tibialis anterior, respectively. Dashed lines in processed signals of the right tibialis anterior indicate detected peaks. Notably, the PLM-like events shown in the shaded area involved larger movements than the other PLMs-like events. Note that this figure is cited from [86].

defined in the AASM scoring manual [47]. These results, together with the aforementioned main complaints of the participant (i.e., nocturnal awakening and a tendency to experience more PLMs in the right leg than the left leg) as well as the visual confirmation of the recorded video suggest that the leg movements observed in both the ActiwatchLEG data and the surface EMG signals of the right tibialis anterior were likely actual PLMs, which ultimately resulted in nocturnal awakening, as the participant reported.

These experimental results also indicate that the “Wake/Sleep Score” from the ActiwatchLEG data was not necessarily reflect leg movements, even during PLM-like events involving the activation of the tibialis anterior muscle, which is in principle related to dorsiflexion of the ankle. Because all body movements inevitably activate the related muscles in accordance with biomechanics, we can observe such body movements on the basis of muscle activation measured in surface EMG, regardless of the voluntary/involuntary nature of the movements. However, this does not necessarily indicate that acceleration was also activated, especially when the movements are comparatively small. In other words, these experimental results indicate that the muscle activation of the tibialis anterior observed with surface EMG was associated with PLM-evoked dorsiflexion, but it could not be observed on the basis of acceleration. These findings suggest that the surface EMG-based PLM evaluation using our remodeled prototype will enable PLM-like events to be detected more reliably than with conventional acceleration-based devices, especially in terms of the number of detected PLM-like events, as well as the inter-event intervals of those movements.

6.3 Discussion

Although the experimental results indicate that our remodeled prototype would perform better in PLMs detection at home than the conventional acceleration-based method, its performance was still insufficient as shown by the comparison of the device data with the visual observations, as shown in Figure 52. The activation of the tibialis anterior, the targeted muscle in this experiment, corresponds to dorsiflexion of the ankle, but most of the PLM-like events observed in the recorded video only involved extension/flexion of the

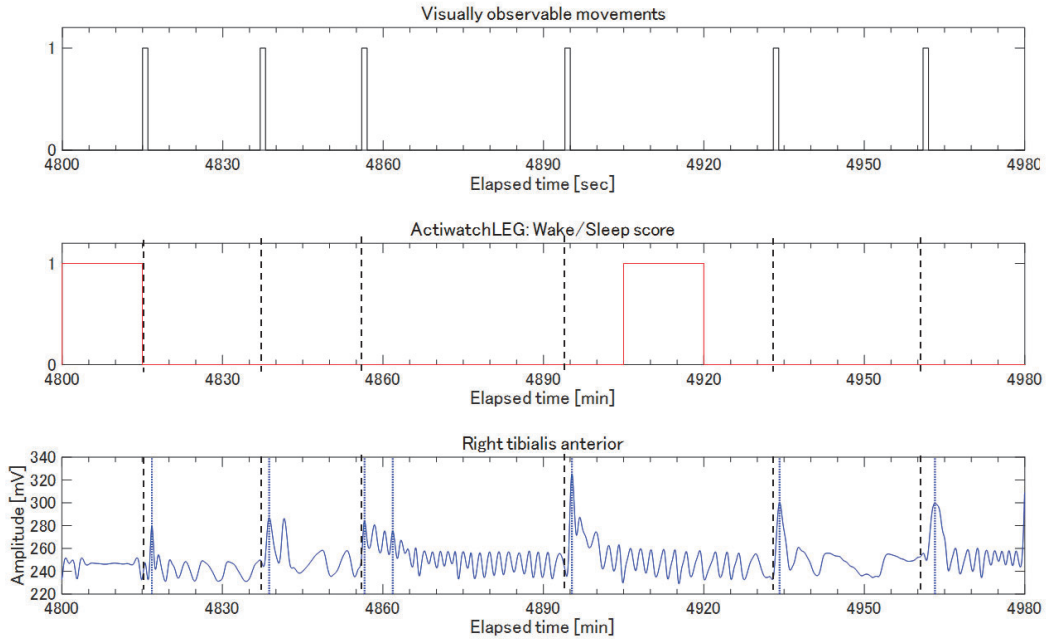


Figure 53: All measured data in the shaded area of Figure 52. From top to the bottom, visually observable PLMs-like movements in the recorded video judged as “certain,” “Wake/Sleep Score” from ActiwatchLEG data, and processed surface EMG signals of the right tibialis anterior, respectively. Blue dashed lines in the processed surface EMG signals of the right tibialis anterior indicate the detected peaks. Times at which events were observed are indicated by the black dashed line in the other data. Note that this figure is cited from [86].

big toe. Because physicians have also observed this tendency [31], using two channel surface EMG-based PLMs evaluation that targets the abductor hallucis in addition to the tibialis anterior, which is proposed in Chapter 4, would improve the PLMs evaluation performance.

The measurement of actual PLMs conditions with a home monitoring device has the potential to improve medication for suppressing PLMs. In this experiment, visually observable PLM-like events started at approximately 4:00 a.m., which is close to the half-life of pramipexole (approximately 7 hours [115]) considering the time that it was taken (described in the participant’s sleep diary as approximately 9:00 p.m.). If all of the PLMs-like events observed in this experiment were indeed actual PLMs that appeared as the effects of pramipexole wore off, the collection of several days of surface EMG-based PLMs monitoring data, as was obtained in this experiment, may enable physicians to improve the prescription of medicines, including advice on the best time to take them.

Chapter 7 Conclusion

In this doctoral research, the emerging genre of sleep technology was explored from the perspectives of sleep medicine, biomechanics, and user interfaces. Toward realization of appropriate treatments for patients with the targeted sleep disorder, namely, periodic limb movement disorder (PLMD) characterized by the occurrence of periodic limb movements (PLMs) during sleep, this research combined all those aspects and developed an easy-to-use wearable device for unaided surface electromyography (EMG) measurement by non-experts to enable PLMs home monitoring.

The following sections summarize the main contributions of this research, together with its limitations, issues to address, and possible prospects for future research.

7.1 Main Contributions

To improve the quality of life (QoL) in patients with lifestyle-related diseases while suppressing socioeconomic losses in a case of limited resources, it has become an urgent necessity to establish telemedicine and e-health to enable further self-administration. In this respect, easy-to-use self-administered devices that can be used unaided, regardless of the user's expertise, should be newly developed while ensuring adequate data quality and quantity. Given the emerging requirements for precise treatment of patients with lifestyle-related diseases, such devices would contribute to observing overall disease-related conditions outside a hospital on a daily basis, which physicians can observe only during an outpatient visit within a short period of time.

This thesis has proposed an easy-to-use sock-type wearable device targeting unaided surface EMG measurement by non-expert users. As a chronic disease requiring self-help effort to improve lifestyle habits, this research focused on PLMD. It is also considered as a sleep disorder causing sleep deprivation due to its inherent symptoms represented as the repetitive involuntary movements called PLMs. Because symptomatic treatment of PLMD via medication for PLMs suppression requires the actual PLMs conditions in terms of

severity, including its night-to-night variability, physicians require easy-to-use self-administered devices for unaided home use by non-experts which could enable precise PLMs home monitoring on a daily basis as well. In the realm described above, this research made three main contributions.

The first contribution was the design of surface EMG measurement targeting PLMs home monitoring. This research first clarified the issues to address in development of a surface EMG measurement device assuming unaided home use by non-experts, and then organized its requirements. The study then investigated all the muscles related to PLMs after revisiting the leg movements induced by them through visual observation. A two-channel surface EMG measurement targeting the bilateral tibialis anterior and abductor hallucis was proposed, and its performance was confirmed to exceed that of the current de facto standard method based on acceleration. This contribution is innovative because there was no previous work investigating PLM-related muscles from the perspective of device development in consideration of usability for non-experts, rather than from the perspective of medical or biomechanical investigation targeting the pathophysiology of PLMs.

The second main contribution, which was enabled by the first contribution, was the development of an easy-to-use wearable device for unaided surface EMG measurement by non-experts. By considering the issues related to conventional surface EMG measurement by non-experts, a prototype comprising of a sock-type fabric adaptor with embedded fabric electrodes was developed. It enables easy setup by non-experts and stable measurement of surface EMG, by simply wearing the device as a normal sock. It was then confirmed that the device's basic performance on surface EMG measurement was sufficient to distinguish the presence/absence of muscle activity through a preliminary validation targeting voluntary movements. This contribution is innovative because there was no previous work on developing a wearable device for unaided surface EMG measurement by non-experts with a target of PLMs home monitoring [81]. Considering the principle of surface EMG measurement, this is notable because it possibly allows more appropriate PLMs home monitoring than by the conventional acceleration-based method.

The third main contribution was evaluation of the developed device for unaided surface EMG measurement targeting actual PLMs home monitoring. Through a comparative evaluation with visual observation of PLMs by physicians, the developed device showed better performance in PLMs home monitoring than the current de facto standard method based on acceleration. This contribution is innovative because it justified the hypothesis that surface EMG-based PLMs monitoring would outperform the acceleration-based method. This study confirmed that PLMs home monitoring using the developed device would avoid overlooking PLMs involving the dorsiflexion of the ankle.

Overall, this research has enabled surface EMG-based PLMs evaluation, which uses the same biosignal as the gold standard method of polysomnography (PSG) with surface EMG of the bilateral tibialis anterior in a hospital laboratory, outside a hospital by enabling unaided surface EMG measurement regardless of expertise. The experimental results described as the third contribution indicated that the proposed method could perform better than the conventional acceleration-based PLMs evaluation at home. Furthermore, the experimental results described as the first contribution also indicated that the proposed surface EMG-based PLMs evaluation using the combined two-channel surface EMG measurement of the bilateral tibialis anterior in addition to the abductor hallucis could exceed the current PLMs evaluation performance of PSG, especially for certain PLMs occurring in the big toe. Although this evaluation only targeting one patient with PLMD is not sufficient to establish medical evidence, the results showed that the surface EMG-based PLMs evaluation performance was better than that of the current de facto standard acceleration-based PLMs evaluation. The proposed method therefore could improve PLMs home monitoring, which is an essential factor in providing appropriate symptomatic treatment based on actual PLMs conditions, by enabling physicians to conduct more appropriate PLMs evaluation outside hospitals.

These contributions can foment future research on revealing PLMs conditions outside a hospital, which can enable better understanding of the relationship between medication, including the dosing time, and the actual

PLMs conditions. These findings could allow physicians to explore new treatment strategies for patients with PLMD, like personalized medication considering the dosing time matters of therapeutic medicine together with each lifestyle, or even allowing a system integrator to develop more effective application software to establish and sustain better sleep habits.

7.2 Limitations

Note that there are limitations in this research. At this time, the present author was the targeted patient with PLMD in all the experiments described above. Because these experiments could be rephrased as self-investigation conducted by a patient with PLMD herself, they were not subject to review by an ethics committee.

However, the experimental results can be regarded as a case report targeting one patient with PLMD. Because both experiments described in Chapter 4 and Chapter 6 targeted PLMs home monitoring, all data was recorded during sleep. The results of visual observation of the recorded video also supported the sleeping conditions during the experiment. Note also that the experiment described in Chapter 5 originally aimed to simply clarify whether the presence/absence of movements could be confirmed from only the measured surface EMG as a preliminary performance evaluation of the developed device. Thus, this study did not discuss the performance in detail (e.g., the relationship between the surface EMG measurement performance and skin condition). For these reasons, although the current experimental results go no further than the results of one patient diagnosed with PLMD, they do confirm that both the proposed method and the developed device worked according to my hypothesis.

Of course, I understand that strict validation of actual PLMs home monitoring aiming to evaluate its validity with regard to clinical determination (i.e., whether the proposed device can precisely evaluate PLMs from the measured surface EMG) requires other experiments targeting multiple patients with PLMD. Hence, I will try to conduct such experiments after obtaining the approval of an ethics committee in the future.

7.3 Discussion on Future Issues to Address

Toward the realization of PLMs home monitoring under limited resources, we should consider a sophisticated service model standing on medical evidence while suppressing the cost of product realization as well as the workload of the primary users (i.e., non-expert users) together with its final users (i.e., physicians and other medical staff). Therefore, the following four future issues to address should be considered: standardization of a ready-made sock-type wearable device for unaided surface EMG measurement by non-experts, to enable highly cost-effective PLMs home monitoring; development of such an easy-to-use all-in-one small wearable hardware device for surface EMG measurement, to improve the usability and user experience for non-expert users; development of a fully automated PLMs detection algorithm in conformity with the *American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events* (hereafter, the AASM scoring manual) [47], to improve the usability and user experience for physicians and medical staff; and registration of medical approval in accordance with Japan’s pharmaceutical and medical devices act (PMD Act).

Assuming that we originally intend to incorporate new PLMs home monitoring using the proposing sock-type wearable device into the current clinical procedure described in 2.2.3 for a screening test or follow-up observation, we should ensure high cost-effectiveness. The current prototype, however, was specially designed for the target participant in terms of its electrode placement position and inter-electrode distance, so it would not be a reasonable model, especially for the screening test purpose. To enable stable surface EMG measurement regardless of physique at a reasonable cost, we should develop several sizes of ready-made sock-type wearable devices for surface EMG measurement by non-experts (e.g., S, M, L, or foot sizes like normal socks sold in a clothing store) instead of adopting build-to-order manufacturing. Investigating the location of target muscles together with the leg length targeting multiple people with various physiques would enable further standardization of the size and location of the measurement electrodes together with the inter-electrode distance. In addition, we should consider how to make

the setup much easier with a less expensive cost. Because the most important thing for ensuring precise surface EMG measurement is to avoid misplacement of the measurement electrodes on the target participant, we consider that “guideline patterns” knitted or printed on the outside of the leg parts would improve usability by avoiding a twist in the leg part of the sock without requiring high cost.

The second issue is also related to the usability improvement for non-experts. Although this research first focused on developing an easy-to-use self-administered wearable device for surface EMG measurement and confirmed its performance, the complete current configuration is not easy enough to use, especially with regard to its hardware comprising conventional alligator clips, lead wires, an analog circuit for surface EMG measurement, a stationary analog-to-digital (A/D) converter (i.e., a USB-connected digital oscilloscope), and a laptop computer. An ideal PLMs home monitoring device for unaided home use by non-experts should be easy to use throughout its whole use, while enabling stable measurement of surface EMG with adequate quality for PLMs monitoring. Thus, we should extend ‘easy-to-use’ to dedicated hardware for surface EMG measurement. Therefore, it is expected that a PLMs home monitoring device comprising a sock-type fabric device with embedded fabric electrodes and lead wires, and an all-in-one small wearable hardware device for surface EMG measurement comprising of analog circuit and an A/D converter together with a standalone data logger or wireless data transfer unit, would improve the usability for non-expert users. A simple setup, in which users simply wear the sock-type device and then attach the other device to it, would enable physicians to ask their patients to take the set of devices home for unaided surface EMG-based PLMs evaluation.

The third issue is related to usability improvement for physicians and medical staff. Considering the limited medical resources, it is quite important to ensure high-accuracy evaluation without compelling additional cumbersome work. To make an ideal PLMs home monitoring device more physician-friendly, we should also develop a fully automated PLMs detection algorithm in conformity with the AASM scoring manual [47], at least in terms of the

duration of muscle activation for one PLM event as well as the inter-event intervals between adjacent PLM events. In preliminary evaluation of the proposed sock-type smart textile device, the measured surface EMG signals are postprocessed in accordance with typical surface EMG signal processing in biomechanics [90], as described in Chapter 6. In the future, we must clarify the difference in surface EMG signal postprocessing between the typical surface EMG signal processing in biomechanics [90] and a PLMs detection algorithm for PSG in a clinical setting, such as MATPLM1 [116]. Then, we can consider a PLMs detection algorithm that is compatible with the AASM scoring manual and suitable for processing the surface EMG signals measured by the proposed sock-type device.

The fourth issue is registration of medical approval. Because medical devices should guarantee safety in use and clarify their benefits, we should ensure these aspects through a clinical trial targeting multiple patients with target disorders. Considering these remaining issues together with a possible registration class, a possibly realistic registration procedure for this device would comprise at least two steps. The first step would be the proposed device described in this thesis as a “measurement electrode for surface EMG,” while the second step would be the combination of the proposed device, the all-in-one small wearable hardware device for surface EMG measurement, and the scoring-manual-compatible PLMs detection algorithm, which would be called a “PLMs evaluation device.” In each step, we should ensure the performance of the proposed device against the gold standard method; regarding the field of sleep medicine, PSG would be the reference. We herein should remind that medicine stands on medical evidence; we should therefore involve multiple patients with PLMD in this performance evaluation for registration. After registration with the results of the performance evaluation, other physicians would be able to use the registered device for their target purposes as well. This would be expected to allow evidence gathering, enabling physicians to explore new treatment strategies for patients with PLMD, just as the pulse oximeter was integrated into the standard treatment procedure of patients with obstructive sleep apnea (OSA) in the latest *International Classification of Sleep Disorders third edition* (ICSD-3) [15].

7.4 Future Prospects

This research originally aimed to optimize the definitive diagnosis of PLMD together with its treatment from the perspective of the digital revolution in P4 medicine [7] (i.e., predictive, preventive, personalized, and participatory care), by newly developing an easy-to-use wearable device for unaided surface EMG measurement by non-experts. Such a device could contribute to ensuring the bottom layer of big data collection essential for physicians, namely, the data, information, knowledge, and wisdom (DIKW) pyramid [8].

Regarding the other fundamental factors of P4 medicine, medicine mainly plays an important role in “systems biology and systems medicine.” All the work mentioned here could contribute to revealing actual PLMs conditions, such as its severity and night-to-night variability, and its relationship with dosing time or menstruation as well.

Toward the realization of P4 medicine for patients with PLMD, we therefore should additionally consider how to empower “consumer-driven healthcare and social networks.” In other words, we should consider appropriate provision of information that can raise awareness of people’s own sleep, including disease-related conditions like PLMs. This focuses on the fact that physicians usually use a sleep diary throughout the treatment of patients with sleep disorders before and after a definitive diagnosis, and we should consider that a fully automated, integrated sleep diary would be one ideal realization. The main issue with the current sleep diary is maintaining motivation in patients. Because patients only perceive their general sleep conditions, like the bedtime and time in bed, they mainly record that information in their sleep diaries. Just manually recording the bedtime and time in bed, however, only for the purpose of showing physicians could be psychologically distressing for patients and could even possibly induce dropout. Recall that the original purpose of a sleep diary is to clarify the relationship of all possible sleep-related factors to reveal what could have happened in the body of a patient during sleep to enable appropriate treatment based on the possibly actual sleep conditions.

We therefore consider that automatically gathering and integrating sleep-related information into one sleep diary would be effective to ensure

this original purpose as well as self-review of one’s own sleep. For instance, considering dosing time matters [117], the bedtime and time in bed, actual PLMs occurrence, and menstrual cycles in the same timeline would help both physicians and patients to understand the relationships of those sleep-related factors together with their influence over the severity of PLMs. Such an integrated sleep diary could contribute to shared decision making and enable optimal patient care [118] beyond medical paternalism or excessive consumerism. I emphasize here that the key enabler of this ideal goal is still ‘easy-to-use’ for non-experts. We therefore should consider how to realize such fully automated data processing to enable a fully automated integrated sleep diary, as shown in Figure 54.

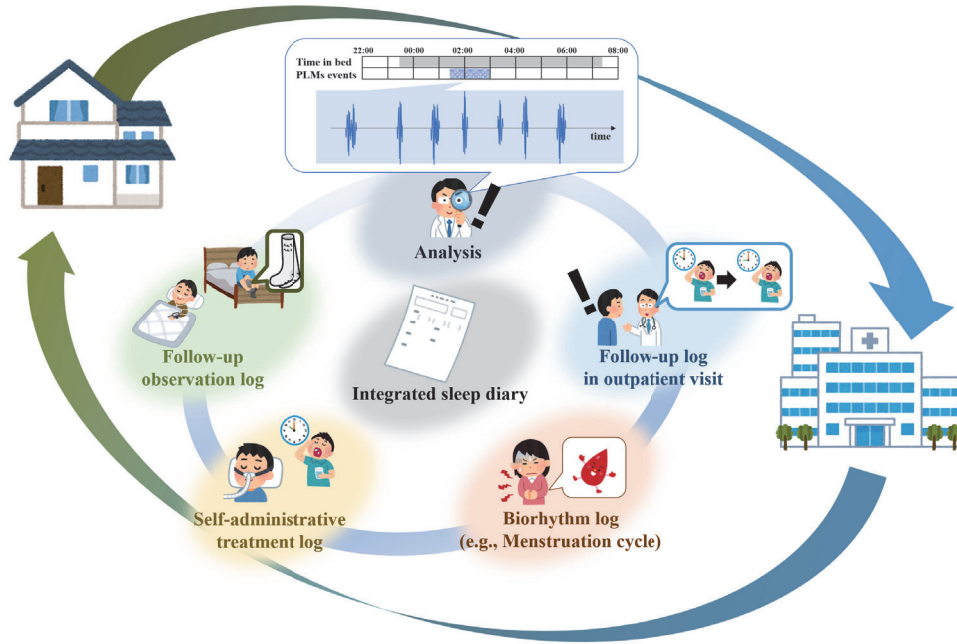


Figure 54: Concept of a fully-automated integrated sleep diary.

Overall, this research has enabled collecting data by newly developing an easy-to-use device for unaided surface EMG measurement by non-experts, from the perspective of informatics and engineering. This approach enabling data collection would undoubtedly be essential for establishing the DIKW pyramid,

especially for an academic discipline like medicine whose history stands on the shoulders of the giant.

We should remember that the basis of information is cognition and observation, which enable us to collect data based on them, and what we exchange via communication is the meaning of information (i.e., knowledge or wisdom in the DIKW pyramid) interpreted by each person. The implicit assumption herein is that the semantic interpretation has already been shared; that is, semiotically, “the code is well-defined” [119]. However, this premise cannot necessarily be satisfied in social information, so that we can consider that one fundamental mission of informatics is to find out how to fulfill it.

From this perspective, I can rephrase the achievement of this thesis as enabling non-expert patients to collect essential data without exactly knowing the “code” for it, meaning expertise in surface EMG measurement. Furthermore, the aforementioned ideal goal of a fully automated integrated sleep diary could become the shared code of sleep-related condition interpretation, including PLMs, between patients and physicians. Although both patients and physicians currently cannot precisely reason with or observe those sleep-related conditions because of the absence of perception or even the lack of verbalization or a method, a fully automated integrated sleep diary would provide the semantic interpretation.

7.5 Concluding Remarks

Like sleep deprivation caused by consecutive PLMs, not every disability is visible. Having a hint of those invisible disabilities, however, could give us the opportunity to consider how we deal with them, which might at least allow us to find a way to live with them. I strongly believe that a PLMs home monitoring system using the proposed easy-to-use sock-type wearable device for unaided surface EMG measurement by non-experts could contribute to revealing such invisible disabilities in sleep, namely, sleep deprivation due to PLMs, or even enable justifying treatment. This may contribute to setting both potential patients and diagnosed patients with PLMD free from those invisible disabilities by enabling appropriate treatment based on the actual PLMs conditions.

There is no doubt that the untiring efforts of physicians have radically improved our quality of life. At the same time, however, this can cause excessively one-sided demands from patients to physicians, and vice versa. I think that now is the time to remind and renew the view of Sydenham, “studying the patients.” As shown in the concept of P4 medicine [7], now that medicine is not alone, we know that it can be better with informatics, or even with engineering.

Medicine, informatics, and engineering thus go hand in hand toward the realization of a gentle, warm world for everyone. The heart of everything herein is that together we are one. We should empower patients by revealing sub-rosa phenomena in their bodies and lifestyles and allow physicians to approach deep inside their hearts to achieve the ideal aim of medicine, namely, “to cure sometimes, to relieve often, to comfort always.”

Nobody knows what may happen tomorrow. We therefore should come alive a life with all force in the present moment, without regrets, toward the final destination of life.

Because, you only live once.

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Appendix

A.1 List of Publications (Related with This Thesis)

A.1.1 Awards/Honors

1. Japanese Medical and Biological Engineering Symposium 2017 Poster Award, Japanese Society for Medical and Biological Engineering, (September, 2017).
2. Honorable mention, The 34th Telecom system technology award for student, The Telecommunications Advancement Foundation Award, The Telecommunications Advancement Foundation, (March, 2019).

A.1.2 Peer Reviewed Journal

1. K. Eguchi, M. Nambu, K. Ueshima, and T. Kuroda, **“Prototyping of Smart Wearable Socks for Periodic Limb Movement Home Monitoring System,”** Journal of Fiber Science and Technology, Vol.73, No.11, pp.284-293, 2017.
2. K. Eguchi, M. Nambu, T. Kamikawa, K. Ueshima, and T. Kuroda, **“Smart Textile Device with Embedded Fabric Electrodes Targeting Periodic Limb Movements Monitoring at Home: A Case Report,”** Journal of Fiber Science and Technology, Vol.75, No.11, pp.164-180, 2019.

A.1.3 International Conferences (Short Paper/Extended Abstracts)

1. K. Eguchi, M. Nambu, K. Murase, K. Chin, and T. Kuroda, **“Surface Electromyogram Measurement e-Textile for the Wearable Periodic Limb Movement Home Monitoring System,”** The 39th Annu. Int’l Conf. of the IEEE Engineering in Medicine and Biology Society (EMBC’ 17), Jeju Island, South Korea, (July 11-15, 2017).
2. K. Eguchi, M. Nambu, and T. Kuroda, **“Investigation of Two Channel Surface Electromyogram Measurement in Lower Extremities for Wearable Devices Targeting Periodic Limb Movements Detection at Home,”** Abstracts of XXII World Congress of International Society of Electrophysiology and Kinesiology (ISEK 2018), pp.286, Dublin, Ireland, (June 30-July 2, 2018).

3. K. Eguchi, M. Nambu, K. Ueshima and T. Kuroda, **“Overnight Investigation of Periodic Limb Movements Using Wearable Socks with Embedded Fabric Electrodes,”** The 40th Annu. Int’l Conf. of the IEEE Engineering in Medicine and Biology Society (EMBC’ 18), Honolulu, HI, USA, (July 17-21, 2018).
4. K. Eguchi, M. Nambu, and T. Kuroda, **“Preliminary Validation of Two Channel Surface EMG-based Periodic Limb Movements Home Monitoring for Developing Wearable Surface EMG Measurement Device Targeting Non-Experts,”** Abstracts of XXIII World Congress of International Society of Electrophysiology and Kinesiology (ISEK 2020) [Submitted].

A.1.4 Domestic Conferences (without Review)

1. 江口 佳那, 南部 雅幸, 村瀬 公彦, 陳 和夫, 黒田 知宏 : 日常環境下における周期性四肢運動の測定を目指したウェアラブル筋電計測布の検討, 信学技報, Vol.116, No.520, pp.33-36, (March, 2017).
2. K. Eguchi, M. Nambu, K. Murase, K. Chin, and T. Kuroda, **“Measurement Points Optimization for Wearable Surface Electromyogram Devices Targeting Periodic Limb Movements Screening at Home,”** 生体医工学シンポジウム 2017, pp.131, (September, 2017).
3. 江口 佳那, 南部 雅幸, 上島 一夫, 黒田 知宏 : ウェアラブル筋電計測布を用いた日常環境における周期性四肢運動検出の検討, 日本繊維機械学会 第71回 年次大会 研究発表論文集, pp.126-127, (June, 2018).
4. 江口 佳那, 南部 雅幸, 黒田 知宏 : **2チャンネル下肢表面筋電図による周期性四肢運動の終夜観察**, 第57回 日本生体医工学会大会 プログラム・抄録集, pp.368, (June, 2018).
5. 江口 佳那, 南部 雅幸, 上島 一夫, 黒田 知宏 : ウェアラブル筋電計測布を用いた周期性四肢運動の在宅検出に向けた初期検証, 日本繊維機械学会 第72回 年次大会 研究発表論文集, pp.119-120, (May, 2019).

A.2 List of Publications (Aside from Thesis Theme)

A.2.1 Awards/Honors

1. DICOMO 2017 Presentation award, Information Processing Society of Japan, (June 2017).
2. DICOMO 2018 Presentation award, Information Processing Society of Japan, (July 2018).

A.2.2 Peer Reviewed Journal

Corresponding Author

1. K. Eguchi, R. Aoki, S. Shimauchi, K. Yoshida, and T. Yamada, “**R-R Interval Outlier Processing for Heart Rate Variability Analysis using Wearable ECG Devices**,” Advanced Biomedical Engineering, Vol.7, pp.28-38, 2018.

Co-author

1. 角田 啓介, 江口 佳那, 吉田 和広, 渡部 智樹, 水野 理 : 心拍と呼吸を用いたコンテンツ視聴による気分変化の推定 : コメディ視聴における検討, 情報処理学会論文誌コンシューマ・デバイス&システム (CDS), Vol.7, No.1, pp. 44-52, 2017.

A.2.3 International Conferences (Full Paper)

Corresponding Author

1. K. Eguchi, R. Aoki, K. Yoshida, and T. Yamada, “**Reliability evaluation of R-R interval measurement status for time domain heart rate variability analysis with wearable ECG devices**,” The 39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC’ 17), pp.1307-1311, Jeju Island, South Korea, (July 11-15, 2017).
2. K. Eguchi, R. Aoki, K. Yoshida, and T. Yamada, “**R-R Interval Outlier Exclusion Method Based on Statistical ECG Values Targeting HRV Analysis Using Wearable ECG Devices**,” The 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC’ 18), pp.5689-5692, Honolulu, HI, USA, (July 17-21, 2018).

3. R. Aoki, K. Eguchi, S. Shimauchi, K. Yoshida, and T. Yamada, **“Consideration of Calculation Process Assuming Heart Rate Variability Analysis Using Wearable ECG Devices,”** The 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC’ 18), pp.5693-5696, Honolulu, HI, USA, (July 17-21, 2018).

Co-author

1. S. Shimauchi, K. Eguchi, T. Takeda, and R. Aoki, **“An analysis method for wearable electrocardiogram measurement based on non orthogonal complex wavelet expansion,”** The 39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC’ 17), pp. 3973-3976, Jeju Island, South Korea, (July 11-15, 2017).
2. M. Sasagawa, A. Nijima, K. Eguchi, R. Aoki, T. Isezaki, T. Kimura, and T. Watanabe, **“Lower Limb Muscle Activity Control by using Jamming Footwear,”** The 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC’ 19), pp.3302-3305, Berlin, Germany, (July 23-27, 2019).

A.2.4 International Conferences (Short Paper/Extended Abstracts)

Corresponding Author

1. K. Eguchi, K. Tsunoda, T. Yabuuchi, K. Yoshida, T. Watanabe, and O. Mizuno, **“Noise Detection Method for Wearable ECG Devices,”** The 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC’ 16), Orlando, FL, USA, (August 16-20, 2016).
2. K. Eguchi, S. Azuma, T. Indo, H. Takeyama, K. Chin, M. Nambu, and T. Kuroda, **“A Pilot Study of Predicting CPAP Adherence Based on the Statistical Values of Previous CPAP Usage Duration and Related Parameters,”** The 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC’ 19), Berlin, Germany, (July 23-27, 2019).

Co-author

1. Y. Kubo, K. Eguchi, R. Aoki, S. Kondo, S. Azuma, and T. Indo, **“FabAuth: Printed Objects Identification Using Resonant Properties of Their Inner Structures,”** Extended Abstracts of the 2019 CHI Conference on Human Factors in Computing Systems (CHI 2019), Glasgow, UK, (May 4-9, 2019).
2. Y. Kubo, K. Eguchi, and R. Aoki, **“3D-Printed Object Identification Method using Inner Structure Patterns Configured by Slicer Software,”** Extended Abstracts of the 2020 CHI Conference on Human Factors in Computing Systems (CHI 2020), Honolulu, HI, USA, (April 25-30, 2020) [Accepted].

A.2.5 Domestic Conferences (Reviewed)

Co-author

1. 久保 勇貴, 江口 佳那, 青木 良輔, 近藤 重邦, 東 正造, 犬童 拓也 : スライサーによる内部構造生成を利用した 3D プリントオブジェクト識別手法, 第 27 回インタラクティブシステムとソフトウェアに関するワークショップ (WISS2019) Web 予稿集, (September, 2019).
<https://www.wiss.org/WISS2019Proceedings/oral/8.pdf>

A.2.6 Domestic Conferences (without Review)

Corresponding Author

1. 江口 佳那, 青木 良輔, 吉田 和広, 山田 智広 : QRS 群電位特性を用いたウェアラブル心電計用の RRI 計測信頼度評価, 信学技報, Vol.116, No.412, pp.171-176, (January, 2017).
2. 江口 佳那, 青木 良輔, 吉田 和広, 山田 智広 : 日常環境を対象とした推定呼吸特徴量による自律神経活動の状態推定, 信学技報, Vol.116, No.435, pp.57-62, (January, 2017).
3. 江口 佳那, 青木 良輔, 吉田 和広, 山田 智広 : ウェアラブル心電計から計測された心拍の周波数特徴量解析を対象とした欠損 RRI の補完手法, マルチメディア, 分散, 協調とモバイルシンポジウム (DICOMO 2017), pp.888-897, (June, 2017).
4. K. Eguchi, R. Aoki, K. Yoshida, and T. Yamada, **“R-R Interval Outlier Processing for Heart Rate Variability Analysis using Wearable**

ECG Devices,” 生体医工学シンポジウム 2017, pp.132, (September, 2017).

5. 江口 佳那, 青木 良輔, 島内 末廣, 吉田 和広, 山田 智広: 着衣型ウェアラブル心電計を用いた実環境での心拍変動解析における RRI 異常値処理と心拍の時間特徴量の算出精度に関する検証, マルチメディア, 分散, 協調とモバイルシンポジウム (DICOMO 2018), pp.1698-1705, (July, 2018).

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1. 角田 啓介, 江口 佳那, 吉田 和広, 渡部 智樹, 水野 理: 心拍と呼吸を用いたコンテンツ視聴による気分変化の推定: コメディ視聴における検討, 情報処理学会研究報告, Vol.2016-CDS-16, No.4, pp.1-8, (May, 2016).
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