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Features as Indicators for Delirium

An Application on Single Wrist-Worn Accelerometer Data from Adult Intensive Care Unit Patients

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Abstract

Objective: The diagnosis of delirium in intensive care unit patients is frequently missed. Key symptoms to identify delirium are motoric alterations, changes in activity level, and delirium-specific movements. This study aimed to explore features collected by a single wrist-worn accelerometer as indicators of delirium.

Methods: The study included twenty-two patients in the intensive care unit. The data was collected with the GENEActiv accelerometer device and the activity level was calculated. Differences between the delirious and non-delirious patients were tested.

Results: Differences in activity level and rest-activity patterns were noticed between the delirious and non-delirious patients. However, the differences were not found to be significant.

Conclusion: Activity patterns revealed differences between delirious and non-delirious patients. Further study is required to confirm the potential of actigraphy in the early detection of delirium in the intensive care unit.

Keywords

Abstract

Mål: Diagnosen delirium hos intensivvårdspatienter missas ofta. Nyckel-symptom för att identifiera delirium är motoriska förändringar, förändringar i aktivitetsnivå och deliriumspecifika rörelser. Denna studie syftade till att utforska funktioner som samlats in av en enskild handledsburen accelerometer som indikatorer på delirium.

Metod: Studien omfattade tjugotvå patienter på intensivvårdsavdelningen. Data samlades in med GENEActiv accelerometerenheten och aktivitetsnivån beräknades. Skillnader mellan de delirious och icke-delirious patienterna testades.

Resultat: Skillnader i aktivitetsnivå och viloaktivitetsmönster noterades mellan de deliriösa och icke-deliriösa patienterna. Skillnaderna visade sig dock inte vara signifikanta.

Slutsats: Aktivitetsmönster avslöjade skillnader mellan deliriösa och icke-delirösa patienter. Ytterligare studier krävs för att bekräfta potentialen för aktigrafi vid tidig upptäckt av delirium på intensivvårdsavdelningen.

Nyckelord

Delirium, Accelerometri, Intensivvårdsavdelning, Patientövervakning

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Ya Ting Hu

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List of acronyms and abbreviations

AD   Alzheimer's Disease
AUC   Area Under the Receiver Operating Characteristic Curve

CAM   Confusion Assessment Method
CAM-ICU   Confusion Assessment Method for the Intensive Care Unit

DRS-R-98   Delirium Rating Scale-R-98
DSM-IV   Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

FN   False Negative
FP   False Positive

ICDSC   Intensive Care Delirium Screening Checklist
ICU   Intensive Care Unit

PD   Parkinson's Disease

RASS   Richmond Agitation-Sedation Scale
ROC   Receiver Operating Characteristic

SDGs   Sustainable Development Goals

TN   True Negative
TP   True Positive

UN   United Nations

Chapter 1

Introduction

1.1 Problem Statement

Delirium is an acute neuropsychiatric syndrome. The syndrome is charac-terised by deranged attention, concentration, cognition, and consciousness. Delirium often occurs in patients in the intensive care unit (ICU). Symptoms of delirium typically show a fluctuating course during the day with serious symptoms during the nighttime [1, 2].

At the moment, delirium is detected by screening tools which are done manually by hospital staff. The screening is limited to a few times a day. Due to its fluctuating nature, delirium may easily get unnoticed. The diagnosis is shown to be frequently missed [3]. Therefore, to improve the current situation it is necessary to develop a new supporting evaluation method to detect delirium in ICU patients. With improved early delirium detection in ICU patients, healthcare outcomes are improved and consequently increased healthcare costs are prevented. Requirements for the method are objectivity, continuity, and accuracy.

One approach for early detection of delirium in ICU patients is to look into motion. Key symptoms identifying a delirious state are namely motoric alterations, changes in activity levels, and delirium-specific movements. Devices that can continuously measure these types of motor activity in ICU patients are wrist-worn actigraphy accelerometer devices. A variety of clinical and research fields have applied actigraphs, including neurological and psychiatric disorders. The present paper discusses the validity of actigraphy, in particular, the GENEActiv [4] in a clinical setting. The study broadens the scope of applications for delirium detection in ICU patients.

1.2   Goal

The main goal of this project is to derive features in the accelerometry data that are indicators for delirium in ICU patients. This goal has been divided into the following three sub-goals:

1. Investigate the sensitivity and specificity of the use of GENEActiv for measuring activity in patients in the ICU.

2. Investigate whether activity levels from the accelerometer data is a suitable feature to distinguish between delirious and non-delirious ICU patients.

3. Investigate whether there are alterations in rest-activity patterns in delirious ICU patients as opposed to the control group.

1.3   Purpose

The United Nations (UN) Sustainable Development Goals (SDGs) are an urgent call for action by all countries in a global partnership. It is recognised that ending poverty and other deprivations must go hand-in-hand with strategies that improve health and education, reduce inequality, and spur economic growth while tackling climate change and working to preserve our oceans and forests [5]. This study contributes to the UN SGDs number 3, which is ensuring healthy lives and promoting well-being for all at all ages, by contributing to early delirium detection in the ICU to prevent worsening negative health outcomes of ICU patients.

1.4   Structure of the thesis

The structure of the thesis is as follows: Chapter 2 presents relevant background information about delirium, actigraphy for delirium detection, and actigraphy in other clinical use cases. It concludes with the research questions of our study. Chapter 3 presents the methods used to solve the problem. Chapter 4 shows the major results of our study. Lastly, Chapter 5 gives a brief discussion of the results and Chapter 6 presents the main conclusions of our study.

Chapter 2

Literature

This chapter provides basic background information about delirium. Additionally, the use of actigraphy for delirium detection is described. Moreover, related work about actigraphy in other clinical use cases that are related is briefly mentioned and discussed. The chapter is concluded with the main research questions which will be the focus of our study.

2.1 Delirium

According to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) [6] delirium is defined as

A disturbance of consciousness with inattention often accompanied by a change in cognition or perceptual disturbance that develops over a short period (hours to days) and fluctuates over time

Risk factors for delirium include age, dementia, previous history of delirium, medical conditions, post-surgical state, and mechanical ventilation [7, 3, 8, 9]. Consequently, delirium has been shown to often occur in the ICU with a prevalence of as high as 87% [10]. The diagnostic criteria for delirium by DSM-IV are as follows [6]:

- Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.

- A change in cognition or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia.

- The disturbance develops over a short period (usually hours to days) and tends to fluctuate during the day.

- There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

So delirium is an acute neuropsychiatric syndrome characterized by deranged attention, concentration, cognition, and consciousness [1, 2]. Other terms describing the acute mental status changes associated with delirium are ICU psychosis and sun-downing [11]. The first term refers to the changes in mental status often noticed in the ICU. The latter term sun-downing refers to the nighttime. It describes the apparent pattern experienced by patients, namely that they experience confusion more frequently during periods of decreased or inappropriate simulation [11].

2.1.1 Sub-types of delirium

Based on their psycho-motor behaviour, delirium is sub-categorised into three different delirium motoric sub-types [12, 13, 14, 15, 16, 17], namely:

1. **Hyperactive delirium** is characterized by having three or more of the following: anger or irritability, combativeness, distractibility, easy startling, euphoria, fast or loud speech, hyper-vigilance, impatience, laughing, restlessness, singing, swearing uncooperativeness, wandering, nightmares, and persistent thoughts. The psycho-motor activity is increased and agitation is very prominent.

2. **Hypoactive delirium** is characterized by having four or more of the following: unawareness, decreased alertness, sparse or slow speech, lethargy, decreased motor activity, staring, and apathy. Hypoactive delirium is more common and more easily overlooked. It is often unrecognized or misdiagnosed as sedation or depression [18]. As the psycho-motor activity is decreased, the chance of remaining undetected is increased. Consequently, this delirium sub-type has the worst prediction and diagnosis while having the highest prevalence among elderly patients [19, 20].

3. **Mixed delirium** is when the criteria of both hyperactive and hypoactive delirium are met. This delirium sub-type presents with alternating features of both. It shows a fluctuating pattern while at risk for complications associated with both sub-types.

The three sub-types do have some characteristics in common. Both hyperactive and hypoactive delirium show symptoms of inattentiveness, distractibility, and confusion about date, time, and/or place. Patients with either hyperactive or hypoactive delirium may experience hallucinations or delusions, and sleep disturbances i.e., day/night reversal. The occurrences of hyperactive, hypoactive, and mixed delirium sub-type in ICU are 1.6%, 43.5%, and 54.9%, respectively [21]. Since each delirium sub-type may have its pathophysiology, they may respond differently to treatments [19].

Serafim et al. [22] defines a fourth sub-type namely sub-syndromal delirium. Sub-syndromal delirium is characterized by less severe cognitive impairment. It meets some but not all the diagnostic criteria of delirium. It can be seen as a stage between delirium and a normal mental state, but it is officially not considered a sub-type of delirium by the DSM-IV [6]. Some patients have delirium but no sub-type. They show no motor features i.e., neither hyperactive nor hypoactive sub-type in the previous 24 hours. Different sub-typing scales have therefore been developed in clinical practices, but unfortunately, there is no golden standard yet [23].

Needless to say, patients in the ICU spend most of their time lying in bed. There is significantly less time moving e.g., sitting up may be the case but standing and walking hardly occurs [24, 25]. The activity levels of patients are therefore generally very low. Furthermore, certain symptoms of delirium are also shown to be less frequent in ICU patients. Franco et al. [26] defined three core domains of delirium, namely:

1. Attention and other cognitive deficits

2. Higher level thinking disturbances

3. Circadian disturbances

Higher level thinking disturbances refers to thought process, executive function, and semantic language. Circadian disturbances are noticed in sleep-wake cycle and also in motor activity alterations. Examples of motoric activity alternations are carphologia and floccillation. Carphologia is a lint-picking behavior at imaginary objects, clothes, or bed linens. Floccillation is plucking at the air. Both carphologia and floccillation are uncommon physical signs in patients. However, their presence is highly suggestive of delirium and unrelated to the delirium sub-type [27].

2.1.2 Consequences of delirium in ICU

Delirium has inauspicious consequences but also potentially preventable associated factors. Delirium may be prevented and treated by non-pharmacologic approaches, i.e., not primarily based on medication. Examples are management of sedatives, pain management, early mobilization, improving sleep, pharmacologic approaches, or a combination of the two approaches [28, 29, 21]. Ongoing efforts to develop and adopt proactive interventions to prevent or reduce the severity and duration of delirium are essential.

Delirium in the ICU is associated with a prolonged hospital stay, increased mortality, and the development of post-ICU cognitive impairment in adult ICU patients after ICU discharge. Delirium negatively impacts the health outcomes of patients and leads to an increase in ICU and healthcare-related expenditures. [30, 31, 32, 33, 34, 35, 36]. It is therefore of utter importance that delirium is detected and identified early. Patients should receive the needed treatment and care to prevent future complications. To detect delirium, routine monitoring is recommended. Based on past research it is shown to be feasible in clinical practice [37].

2.1.3 Detection of delirium in ICU

Delirium in ICU is diagnosed by psychiatrists and trained non-psychiatric clinical staff. At the moment, detection of delirium in ICU is done through subjective screening tools. Examples are the Confusion Assessment Method for the ICU (CAM-ICU) [38], the Intensive Care Delirium Screening Checklist (ICDSC) [39], and the Richmond Agitation-Sedation Scale (RASS) [40, 41]. Agitation and slowing down occur frequently, namely in more than 90% of delirious patients. Independent assessment of individual features of delirium should be emphasized as these may be promising indicators of prognosis [42].

The CAM-ICU is derived from the Confusion Assessment Method (CAM) Diagnostic Algorithm. It is primarily clinical based on the following key features [38]:

1. Acute onset and fluctuating course

2. Inattention

3. Disorganized thinking

4. Altered level of consciousness

Diagnosing delirium requires the presence of features 1 and 2 and either feature 3 or feature 4. The CAM-ICU can be found in Appendix A. The CAM is a validated instrument based on the DSM-IV criteria. It has been extensively used in several research studies in the field of delirium [43, 44]. A multi-center study of the CAM-ICU states that the specificity of the CAM-ICU as performed in routine practice seems to be high. However, sensitivity is shown to be low in healthcare settings which may hinder early detection of delirium [45, 46].

The RASS is a 10-point scale. Four levels of anxiety or agitation range from +1 to +4. One level denotes an alert and calm state (0). Five levels of sedation from -1 to -5, ranging from combative (+4) to unarousable (-5). The RASS can be found in Appendix A. It is a simple-to-use instrument with discrete criteria and sufficient levels for agitation evaluation. However, one limitation is that RASS heavily relies on patient auditory and visual acuity. Therefore it is not suitable for patients with very severe impairments [41].

Lastly, the ICDSC and the scoring system are available in Appendix A. The first four screening elements refer directly to the first two DSM-IV criteria. It is a user-friendly checklist with high sensitivity and reliability suitable for screening patients with delirium. However, it should not be used as a stand-alone diagnostic instrument [39, 47].

2.1.4 Drawbacks of current detection methods

Constant monitoring of patients in the ICU is expected to lead to better results than routine monitoring. Current clinical monitoring practices namely fail to capture important behavioral indices, such as mobility and agitation. The aforementioned screening tools have high sensitivity in research settings, but in healthcare settings their sensitivity is much lower [45, 48].

The possibility of constantly monitoring patients' activities is limited by the availability of staff for observing and documenting events. It is also not cost- and time-efficient. The previously mentioned screening tools heavily rely on manual and repetitive examinations by staff. This leads to increased work pressure. Moreover, these manual assessments have a chance of suffering from human error in data entry and the subjectivity of the observer.

Thus, the current method is very subjective and time-consuming. Moreover, patients cannot be monitored continuously throughout the day. Since the symptoms of delirium have a fluctuating nature, delirium often remains undetected [30]. Treatment interventions require accurate and timely prediction and detection methods.

2.2 Actigraphy

Actigraphy is an instrumental method where the evaluation is done through human activity and movement measurement. Actigraphy is recorded and measured continuously with the help of a small device called an actigraph, also known as a wearable accelerometer. An accelerometer is an electromechanical device that measures the acceleration forces of the body, which is the rate of change of the velocity. They measure in meters per second squared (m/s^2) or in G-forces (g). A single G-force on planet Earth is equivalent to 9.8 m/s^2.

Actigraphs are generally small, lightweight, portable devices that can be worn on the hip, ankles, arms, wrist, and other body movement collection points of interest. The devices are non-invasive, generally easy to use, and do not negatively affect the patient or hospital staff [49]. The devices are therefore generally well-tolerated and do not pose any safety or comfort concerns for the patient [50]. Moreover, they do not interfere with the current care procedures in the ICU. They allow for convenient data collection and various data analyses by providing continuous and patient-specific data streams.

Examples of actigraphy devices are ADXL322, Actiwatch, and ActivPAL. ADXL322 is from Analod Devices Inc. and it is attached to the thigh [51, 52, 53, 54, 55]. Actiwatch is from Cambridge Neurotechnology Ltd. and it is placed on the wrist [56, 57, 58, 59, 12, 60]. ActivPAL is from PAL Technologies Ltd. and is attached to the thigh and records activity [51, 52, 55, 61, 49]. Different devices can produce different output values due to their software design and evaluation. This makes it difficult to compare different studies [62]. The actigraph accelerometer device GENEActiv by Activinsights Ltd. provides the benefit of using raw unfiltered data [4]. It allows for flexibility by using different tools and statistical packages to analyze the data [63].

2.2.1 Actigraphy for delirium detection

Actigraphy accelerometer devices are non-intrusive, continuous, and able to collect data long-term. They have shown strong potential for monitoring patients for delirium detection [64]. From the three core domains suggested by Franco et al. [26], the circadian disturbance is the highest suggested one for the detection of delirium as it links back to the term sun-downing [11]. These include sleep-wake rhythm disruptions and motor activity alterations and optionally differentiating between different delirium sub-types [50, 26]. The other two domains are less easily to be quantified by actigraphy.

2.2.1.1 Rest-activity pattern alternations

The sleep quality of patients in the ICU may be affected by delirium [65, 66]. However, it is difficult to establish a direct relationship between the two due to other interfering factors. Current methods to measure sleep of patients in the ICU include electroencephalography [67, 68], sleep reports [69, 70], and actigraphy. However, actigraphy is not able to measure the different stages of sleep contrary to the other methods. It has not been validated yet for ICU patients and it is not considered to be a reliable method [70]. Both total time and efficiency of sleep have been shown to be overestimated by using actigraphy [71, 72]. Therefore instead of using actigraphy for measuring sleep, it is suggested to detect the rest and active periods of patients instead to measure their physical activity patterns.

The study of Jacobson et al. [59] has shown promising results linking back to the state of pathologic wakefulness found in delirious patients. The study included 13 postoperative patients of which 6 were delirious and 7 non-delirious. The Octagonal Basic Motionlogger by Ambulatory Monitoring, Inc. was used to collect data for 24 to 72 hours. The actigraphy returns the total count of wrist movements within an epoch of one minute. Only 24 hours of the collected data from each patient were used for further analysis. It was based on the highest Delirium Rating Scale-R-98 (DRS-R-98) score indicating the severity of delirium over a broad range of symptoms [73]. The results of the study indicated that there is a lack of recovery in the diurnal rest-activity cycle in delirious patients as opposed to non-delirious patients. Thus, the rest-activity cycle may be a good alternative for the sleep-wake cycle when using actigraphy to detect delirium and is something to look into further.

Also, Osse et al. [57] explored actigraphy as an objective quantification of motor activity patterns to detect delirium after surgery. The study included a total of 88 patients of which 38 were delirious and 32 non-delirious. The data was collected for 6 days with the Actiwatch. Only one day per patient was used for their analysis, namely the first day after surgery. From this analysis, they concluded that delirious patients had a significantly lower mean activity level than non-delirious patients both during the daytime and nighttime. During the daytime, the restlessness was significantly lower whereas the number of immobile minutes was significantly higher for the delirious patients.

The Actiwatch was also used in the study of Van Uitert et al. [60]. The study included 9 patients with a hip fracture scheduled for surgery. Instead of classifying the patients, the days were classified as delirious or non-delirious. There were 29 days labelled as delirious and 24 days labelled as non-delirious.

It was concluded that delirious patients had significantly lower sleep time than non-delirious patients. Sleep/wake cycle disturbances were also indicated for the delirious group. Delirious patients had more difficulty falling asleep and the total duration of sleep was also shorter. Delirious patients were also found to have more transitions between rest and activity compared to non-delirious patients. Another study with the Actiwatch included a total of 79 patients of which 23 were delirious and 46 non-delirious over 5 postoperative days [56]. The conclusions of the study were in line with the aforementioned studies. It was found that patients with delirium had lower activity values, lower restlessness, and a higher number of daytime immobility minutes.

In summary the average activity of delirious patients was shown to be significantly lower than non-delirious patients during the daytime, but higher during the nighttime. Delirious patients also show significantly reduced restlessness compared to non-delirious patients. Moreover, the number of immobility minutes was significantly larger for delirious patients.

2.2.1.2   Motor activity alterations

Studies have looked into detecting delirium based on motor activity alterations. Godfrey et al. [51] included 25 delirious and 9 non-delirious patients. It was concluded that the discriminating features between the two are the number of postural changes during daytime and the frequency of ultrashort, short, and continuous movements.

In a follow-up study by Glynn et al. [74], the majority of patients with full syndromal delirium showed clear signs of observable changes in motor behavior. However patients without a motor sub-type have shown to differ in the severity of delirium symptoms. These patients may even be classified as subsyndromal delirium. Greater awareness of motor activity alterations occurring in delirium can therefore assist in the early detection of emergent full syndromal delirium.

Quantitative aspects of movements are non-numeric evaluation of movement that will produce a description of movement. Qualitative aspects of movements are numeric evaluation of movement based on data acquired during analysis. The study of Leonard et al. [55] has shown that according to both quantitative and qualitative aspects of movement, motorically defined sub-types can indeed be distinguished. However the study did not include non-delirious controls. Therefore it was recommended to include both delirious and non-delirious patients in future research.

2.2.2   Actigraphy in other clinical use cases

Actigraphy has been predominantly used for studying human mobility [75, 76], sleep [50, 77], and activity patterns [78] in various populations. Several studies have shown their potential in other clinical use cases [79, 79, 64]. Examples are monitoring physical activity [80, 81, 82], energy expenditure [83], sedation or agitation [84, 85], sleep and fall detection, [79, 50, 86, 87] and sepsis sub-typing [82]. In this section, we will briefly discuss the clinical use cases in which symptoms, activity levels, and motoric behavior are most similar and/or related to the ones of delirium.

2.2.2.1   Neurological disorders

Neurological disorders are medically defined disorders that affect the brain, nerves, and the spinal cord, such as Alzheimer's Disease, dementia, and Parkinson's Disease [88].

Alzheimer's Disease The typical clinical syndrome of Alzheimer's Disease (AD) includes an amnestic type of memory defect with difficulty in both learning and recalling new information. There is a progressive language disorder beginning with anomia and progressing to fluent aphasia and disturbances of visuospatial skills manifested by environmental disorientation. The patient is typically unaware of these memories and/or cognitive compromises and all these cognitive deficits worsen progressively throughout time [89]. Symptoms of AD include apathy, diminished interest, reduced concerns, agitation, depression, delusions, and motor systems abnormalities [90].

Several studies have observed sleep-wake cycle disturbances due to the occurrence of daytime naps and/or nocturnal activity episodes in patients with AD when compared to controls [91, 92]. Apathy assessment in AD patients is currently based on structured interviews, but there is a need for an objective assessment of apathy. The study of Müller et al. [93] has shown that high apathy patients had significantly reduced locomotor activity and more episodes of inactivity (mostly due to naps) during the daytime. There was a correlation noticed between self-rated apathy and daytime activity, nap frequency, and cognitive executive deficits. Actigraphic locomotor activity assessment, therefore, has been found a useful, objective method to evaluate the severity of apathy in AD patients [93, 94, 95].

Dementia The patient's cognition, independence, and behavior are altered by dementia. Symptoms of dementia can include problems with planning and decision-making, language, and sometimes changes in mood or behavior.

Behavioral and psychological symptoms in dementia might influence the motor activity of patients. Therefore there is the potential for using actigraphy to assess daily motor activity and investigate apathy in patients with dementia. It was found that motor activity assessed by wrist actigraphy was significantly related to apathy and aberrant motor behavior [96, 97]. Apathy was found to be associated with a significant reduction in motor activity during the daytime.

Moreover, repetitive and stereotyped activity with no apparent purpose has been found during the evening, which is related to sundown syndrome or sundowning. The latter means that there is an increase in agitation and aberrant motor behaviors in the late afternoon, evening, or at night [97]. This may also explain the difference in activity levels between patients with and without dementia [98]. These results add to previous studies that have identified actigraphy as a validated method of measuring patterns of motor behaviors in dementia patients [99].

Parkinson's Disease Patients with Parkinson's Disease (PD) experience various movement-related abnormalities. With the use of current assessment tools, daily fluctuations in disease symptoms may be easily missed and therefore not fully captured or understood. Actigraphy has been used to evaluate symptoms of PD, such as sleep disorders and tremor, an involuntary rhythmic muscle contraction leading to shaking movements in the body [100].

So far, little is known about activity-related disease symptoms in patients with PD. Studies have shown that changes in physical activity captured by actigraphy were related to increased severity in disease symptoms over time [101, 102]. Also, the rest was found to be significantly higher in subjects with PD compared to the control group [103].

2.2.2.2   Psychiatric disorders

Psychiatric disorders, or mental illness, refer to a broad range of problems that disturb a person's thoughts, feelings, behavior, or mood. A person's ability to perform in life can significantly be affected by mental illness. Actigraphy has been used to study psycho-motor retardation in psychiatric disorders, such as depression, bipolar disorder, and schizophrenia.

Depression Actigraphy confirms the clinical impression that patients with depression display less daytime motor activity than healthy controls. It is noticed that activity levels increases throughout treatment. Depressed patients also appear to have increased night-time activity although this is not apparent in standard actigraphic measures of sleep duration or sleep efficiency [104, 105, 106].

Bipolar Disorder Several studies have shown that patients with bipolar disorder were found to have less stable and more variable circadian activity patterns than controls. There was evidence that bipolar patients were also less active than controls and there was an altered pattern of sleep in bipolar patients noticed. However, regarding the latter not all studies have shown agreeing results. A difference between bipolar and controls on sleep indices were not always noticed. Circadian activity disruption may therefore be a better indicator since it is shown to be apparent in bipolar patients even when not acutely ill [107, 108, 109, 110].

Schizophrenia Several studies have shown that patients with schizophrenia generally have lower motor activity levels, poorer sleep quality, and efficiency compared with patients without schizophrenia. Moreover, lowered motor activity and longer sleep duration in patients were associated with greater severity of negative symptoms [111, 112].

One study also showed that motor activity was significantly reduced in both schizophrenic and depressed patients. However, schizophrenic patients differed from both depressed patients and controls, demonstrating motor activity patterns marked by less complexity and more structured behavior [113]. The study by Wulff et al. has shown that significant sleep/circadian disruption occurred in all patients with schizophrenia. However, these cannot be explained as these severe circadian sleep/wake disruptions exist despite stability in mood, mental state, and newer antipsychotic treatment [114].

2.3   Research questions

Research using wrist-worn accelerometer devices for detecting delirium is currently limited despite the high prevalence of delirium in ICU patients. Further research was recommended to confirm the potential of actigraphy accelerometer devices in the early detection of delirium [64, 60]. The primary goal of our study was to look into indicators for delirium in ICU patients. The accompanying research questions of our study are as follows:

- Is GENEActiv actigraphy a useful and valid means for estimating activity levels in ICU patients?

- Is there a difference in the activity levels between delirious and non-delirious patients in the ICU during the day and night?

- Are there alterations in the rest-activity patterns in ICU patients with delirium as opposed to the control group?

Chapter 3

Methods

The purpose of this chapter is to provide an overview of the methods performed in this study. Section 3.1 focuses on the data collection techniques. The pre-processing techniques for differentiating between activity and no activity from the collected raw unfiltered data are described in Section 3.2. Section 3.3 explains the method used to calculate features of interest that were included. Finally, Section 3.4 describes the statistical tests regarding the data analyses.

3.1   Data collection

The study was conducted at Philips Research in Eindhoven, the Netherlands and the data collection was done at the Radboud University Medical Center in Nijmegen, the Netherlands. Patients of 18 years and older who were able to speak Dutch fluently and were expected to stay at least two days in the ICU were eligible for the study. Informed consent was obtained from all patients or substitute decision-makers in cases of cognitive impairment.

The RASS score at the start of measuring should be at least minus two before continuing with the CAM-ICU assessment. Patients with acute neurological and/or psychological problems, a known history of dementia and/or alcohol abuse, a recent trauma, motor limitations, or a history of neuro-psychiatric disorders were excluded. In total, thirty-one patients aged 51 years or older, admitted to the ICU were included in this study. The institutional medical ethics committee approved the study.

3.1.1   Demographics and medical data

Possible confounding factors such as postoperative complications, type of surgery, and type of medications were registered for all patients. This information, together with the exact time and scores of both the RASS and CAM-ICU assessments, start date, end date, inclusion date, and patient number, has been registered on paper by the nurses and experts. Afterwards, the papers have been scanned in and the data is manually entered for further data analysis.

The presence of delirium was assessed three times a day by well-trained ICU nurses with the use of the RASS and the CAM-ICU. An expert visits the patient once a day for a more precise diagnosis and to determine the delirium motoric sub-types (hypoactive, hyperactive, or mixed). Patients who were classified as negative by the expert during the whole duration of measurement were classified as *non-delirious*. So the control group of our study is always non-delirious. Patients with only positive delirium assessments performed by the expert were labeled as *delirious*. Patients who had both positive and negative assessments were labeled as *fluctuating*.

When comparing the delirious patients to the control group, the group labeled as fluctuating were assigned to either the delirious or control group. First, for each patient, we looked at which days had the most consecutive days with the same classification. Then based on the majority of consecutive days the patient was classified as either delirious or non-delirious for this specific duration of days. For these patients, the accelerometer data is then filtered based on these included consecutive days. The other days are discarded and the patient is classified into either the delirious or non-delirious group before continuing with the analysis.

3.1.2   Accelerometry data

The data was collected using the GENEActiv Original Smartwatch [4]. In total, the study used four GENEActiv watches. The smartwatch consists of an accelerometer that measures the motor activity of the patients involved in the experiment. The watch collects raw unfiltered data. The raw unfiltered data were recorded at a sampling frequency rate of 30-Hz for all patients. Only for one patient the frequency rate was set at 50-Hz.

Due to some of the treatments that certain patients have received, it was not always possible to place the watch on the (non-)dominant wrist for all of the participants. Therefore there are moments during which the same patient wore the watch either on the dominant or non-dominant wrist. This information is

taken into account while pre-processing the data. The number of days during which the GENEactiv watch was worn also differs per patient. In total, the study included data for a total of 78 days for all patients combined.

The collected data include a time stamp, raw acceleration (g) in the x-, y-, and z-direction, light level in lux, temperature in Celsius, and button (1 if pressed, and 0 otherwise). The open-source GENEActiv software allows for epoch compressed data extraction, for example, an epoch period of 1, 5, 10, 15, 30, or 60 seconds [4]. The epoch compressed data include the time stamp of epoch, the mean acceleration (g) in the x, y, and z-direction, the mean light level lux, the sum of button, the mean temperature in Celsius, the standard deviation in x-, y-, and z-direction, peak lux, and the sum of vector magnitudes. The latter is given by:

$$\sum |\sqrt{x^2 + y^2 + z^2} - 1g|$$

For each measurement in the epoch, the vector magnitude is created and 1g is subtracted. When the accelerometer is static and the earth's gravitation pull is the only acceleration, the result of this will be zero. The total number of measurements in the sum is then defined by multiplying the recording frequency by the epoch length. Measurements from different re-coding frequencies and epoch lengths are then compared with suitable scaling.

3.1.3 Video and annotations data

For several patients, there is also video data available. Of all the patients that have accelerometry data, there are only four patients for which video data is also available. The video data is manually annotated on movements of specific parts of the body and interference of other persons in the image, amongst others.

The annotation data consists of the frame number, date, time stamp, patient identification number, delirious (1 if delirious, and 0 otherwise), and the following binary variables (1 if movement, and 0 otherwise): ambiguous, left arm, right arm, left hand, right hand, head, left leg, right leg, another person in the image, another person in the region of interest, and trunk. Ambiguous indicates when it is not entirely clear what part of the body moved or what caused movement. The duration of one video is fifteen minutes and the total video recording duration is approximately 15% in comparison to the total duration of the collected accelerometry data. The video and annotations data have been primarily consulted to check the ground truth when working with the accelerometry data.

3.1.4   Small experiment with GENEActiv

Accelerometry data is generated and collected from a few small experiments where two GENEActiv devices are simultaneously worn on the wrist of both the dominant and non-dominant hand. The data is recorded at a sampling frequency rate of 30-Hz and contains the following variables: raw acceleration (g) in the x-, y-, and z-direction, the light level in lux, the temperature in Celsius, and button (1 if pressed, and 0 otherwise).

Examples of activities included in the experiment are amongst others non-movement, holding the arm in the air, putting the arm on a flat surface, forming a fist, and several repetitive movements. The experiment also includes video data which is manually annotated per second for the specific movements performed at each time point. The start and end have been filtered out due to movements during putting the device on and walking that are not of interest in the current study.

3.2   Data pre-processing

The data is collected and converted into the suitable file format required for doing the analysis. All the converted data files undergo data pre-processing which involved cleaning and preparing the data files along with data filtering.

For several accelerometer devices, the recording exceeded the manually listed end date. This can be explained by the nurse not having turned off the device afterwards. Also very large movements are noticed at the start and end of the data recordings indicated by spikes in the accelerations. This can be explained by devices that have not been turned off when the nurse is putting them on the patient's wrist. Some nurses may even have turned on the device already even before walking into the room of the patients. These moments are therefore manually removed accordingly.

Both duplicates of the data and empty files have been noticed. The study initially included thirty-one patients and in the end, we are eventually left with twenty-two patients due to files having been overwritten or the device not having been properly used.

A high pass second order Butterworth filter with a cut-off value of 0.2 is used to remove the extreme low-frequency data points in the acceleration in each x-, y-, and z-direction. This is done to remove the noise that was noticed in the data when there was no movement at all. So, the filtering process used sought to remove all data related to frequencies that are not commonly observed in human activity.

Then, for this study specifically, the vector magnitude is calculated as follows:

$$\sqrt{x^2 + y^2 + z^2}$$

where x, y, z is the acceleration in g-force in the x-, y-, z-direction, respectively. This helps in knowing the magnitude of the movement in all three directions without using a feature of each axis separately.

3.2.1 Binary class indicating activity

To decide whether there was an activity or not, we looked at the accelerometry data of which there were both video and annotation data available. First, the general time shift between the accelerometry data and video data is taken into account. From here, we decided on setting a threshold by first down-sampling the accelerometry data to one-second aggregates. The reason hereof is that the exact timestamps of the annotations and accelerometer data do not exactly align together.

By using majority-voting in both the accelerometry and annotations data, the final binary class was decided for each second of the data:

$$\hat{Y_i} = \begin{cases} 0, & \text{if } vm_i < t \\ 1, & \text{otherwise} \end{cases}$$

where $\hat{Y_i}$ denotes the predicted class (1 for activity, and 0 for no activity), vm_i denotes the vector magnitude at timestamp i, and t denotes the threshold. So for the accelerometer data, the class was set to be equal to zero when the vector magnitude was smaller than the set threshold indicating no activity. The class was set to one when the vector magnitude was equal to or greater than the set threshold, indicating that there was an activity and/or movement occurring at the specific time.

The same applies to the annotations data. For the experiment annotation data it depended on the activity label. For the patients annotations data the hand and arm were used as indicators of activity in the accelerometer data since the GENEActiv is worn on the wrist. Based on whether the watch was worn on the left or right wrist, the binary variables of left or right hand and arm were used as the class indicating whether there was a movement activity taking place or not:

$$Y_i = \begin{cases} 0, & \text{if } H_i = 0 \text{ and } A_i = 0 \\ 1, & \text{otherwise} \end{cases}$$

where Y_i denotes the actual class (1 for activity, and 0 for no activity), H_i denotes hand binary variable (1 for hand movement, and 0 no hand movement), and A_i denotes arm binary variable (1 for arm movement, and 0 for no arm movement) at timestamp i.

Evaluation metrics play an important role to achieve the "best" threshold during the training phase. Traditionally, for binary classification problems, the confusion matrix is used for the evaluation of the optimal solution [115]. The confusion matrix is shown in Table 3.1. Here the row represents the actual class while the column represents the predicted class. The TP and TN represent the number of positive and negative instances classified correctly, respectively. The FP and FN, on the other hand, represent the number of negative and positive cases that have been misclassified, respectively.

	Predicted Positive Class	Predicted Negative Class
Actual Positive Class	True Positive (TP)	False Negative (FN)
Actual Negative Class	False Positive (FP)	True Negative (TN)

Table 3.1: Confusion matrix for a binary classification problem.

In our case, the positive class denotes one for activity and the negative class denotes zero for no activity. So more precisely, FP is the number of cases that are actual moments of no activity but predicted to be a moments of activity. Likewise, FN is the number of instances that are actual moments of activity but predicted to be moments of no activity.

The most standard performance metrics for binary classification problems are the accuracy and error rate [116], which are generated from the confusion matrix in Table 3.1. The accuracy of the classification, and its complement represented by the error rate, evaluate the effectiveness of the classifier by the fraction of correct (or incorrect) predictions over the total number of instances to be evaluated, namely:

$$\text{accuracy} = \frac{TP + TN}{TP + FN + TN + FP}$$

$$\text{error rate} = 1 - \text{accuracy} = \frac{FP + FN}{TP + FN + TN + FP}$$

However, the use of accuracy as the sole measure of evaluation has revealed shortcomings in distinctiveness and distinguishability, informativeness, and bias [117]. This would be particularly problematic in imbalanced class distribution. In our study there are in general more moments of no activity than moments of activity and therefore more instances that are equal to zero than the number of instances equal to one.

So besides accuracy and the error rate, it is recommend to have a look at other evaluation metrics based on the confusion matrix. One of these are sensitivity, which is also called recall or TP-rate. Sensitivity is defined as the fraction of positive cases that have been correctly classified [115]:

$$sensitivity = \frac{TP}{TP + FN}$$

Moreover, specificity is defined to be the fraction of negative instances correctly classified:

$$specificity = \frac{TN}{TN + FP}$$

A more complex evaluation metric commonly used for binary classification problems is the Receiver Operating Characteristic (ROC) curve. The ROC curve is a graph with on the x-axis showing 1 – specificity and the y-axis showing sensitivity. The ROC curve is based on the trade-off between the TP-rate and FP-rate [118] and shows the relationship between sensitivity and specificity for every possible set threshold. To quantify the ROC curve, there is the area below it called the area under the roc (AUC). In our study the AUC may be of more interest than the accuracy.

3.3   Feature calculation

The feature included in this study is the activity level is calculated by taking the sum of the binary variable class, indicating either zero for no activity or one for activity. This is done for a specific window size divided by the number of total instances in this window multiplied by 100%. For the calculation of activity levels during daytime and nighttime, first, the activity level was calculated for each patient with a window size of 60 seconds (i.e., one minute). Based on the timestamp of the instance, it either belonged to daytime (7 am - 10 pm) or nighttime (10 pm - 7 am). Then the mean activity level was calculated per patient both per daytime and nighttime.

When we look at the activity level throughout the day per patient, the mean is taken per two hours. When we aim to compare the group of delirious patients to the control group, the activity level is taken for all patients in the delirious and control group combined. The values are then aggregated by taking the mean and the first and third interquartile range per two hours.

3.4 Statistical analysis

The sociodemographic data and clinical profiles of the included patients were analyzed using descriptive statistics. Daytime was defined as the time between 7 am and 10 pm whereas nighttime was defined as the time between 10 pm and 7 am.

The difference between the patients with delirium and the control group was analyzed with the use of the Mann-Whitney U test, also known as the Wilcoxon Rank Sum test [119]. The test is performed as a two-sided test with the following hypotheses:

- H_0: The two populations are equal i.e., there is no difference between the two groups in the population

- H_1: The two populations are not equal, i.e., there is a difference (with respect to the central tendency) between the two groups in the population.

The same test is performed to check the difference in activity level between the different sub-types during the daytime and nighttime. Analyses were performed in Python and a p-value smaller than 0.05 was considered to be significant.

Chapter 4

Results and Analysis

In this chapter, we present the results that try to answer the aforementioned research questions which were as follows:

1. Is GENEActiv actigraphy a useful and valid means for estimating activity levels in ICU patients?

2. Is there a difference in the activity levels between delirious and non-delirious patients in the ICU during the day and night?

3. Are there alterations in the rest-activity patterns in ICU patients with delirium as opposed to the control group?

There is evidence but it is not conclusive. This chapter will go into more detail, specifically Section 4.1, Section 4.2, and Section 4.3 discuss the results related to the first research question, Section 4.4 discusses the results related to the second research question, and lastly Section 4.5 addresses the last research question.

4.1 Experiment with GENEActiv

The raw accelerations in the x-, y-, and z-direction of the collected data during the experiment with GENEActiv watch 027021 on March the 29th, 2022 are shown in Figure 4.1. To the raw acceleration in each direction, a second order Butterworth filter with a cut-off value of 0.2 is applied and the result is shown in Figure 4.2. The vector magnitude is calculated based on the raw and filtered accelerations in the x-, y-, and z-direction, and the results are shown in Figure 4.3.

The vector magnitude is split into four parts for visualisation purposes due to a large number of different activities and/or motions included in the different parts of the experiment. The first part is shown in Figure 4.4. The first graph depicts the vector magnitude, the second graph depicts the activities that were included in this particular snippet of the experiment. The activities included here are as follows: none, finger, fist, arm up, trill, and arm down.

Both none and trill indicate that there is no activity and/or movement. The difference between the two is that for none the arm itself is laid on a flat surface whereas for trill the arm is held in the air. So for the latter, a very tiny sensation of activity can occur. The activity finger indicates movements of the fingers, either only one or together. The activity fist indicates the forming of a fist. Lastly, arm down and arm up are needless to say when the arm is moved down and up, respectively.

The class is either zero indicting no activity or one indicating activity. When we look at all the three graphs combined, we can see that for none activity the class is indeed equal to zero and the vector magnitude is almost zero. The same is noticed for the activity trill, although the vector magnitude values are slightly larger compared to the none activities. The same is noticed
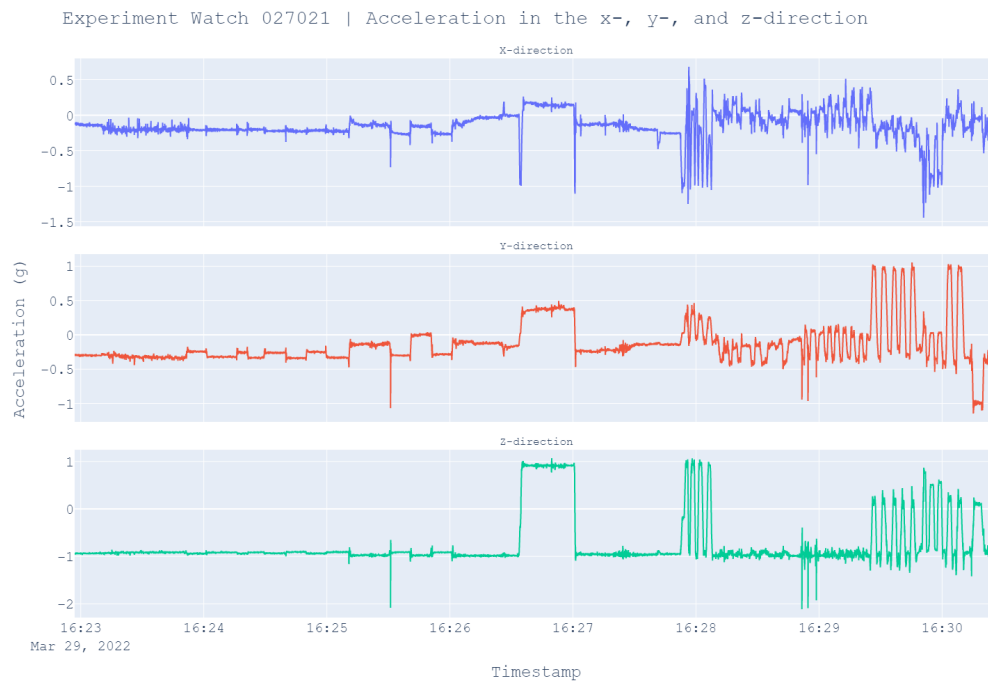

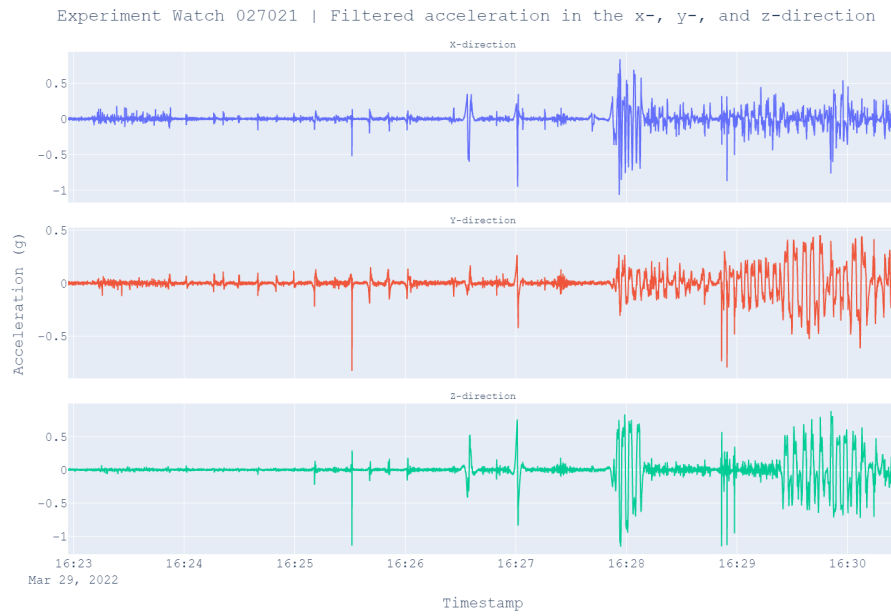Figure 4.1: Raw acceleration in the x-, y-, and z-direction of experiment 027021.

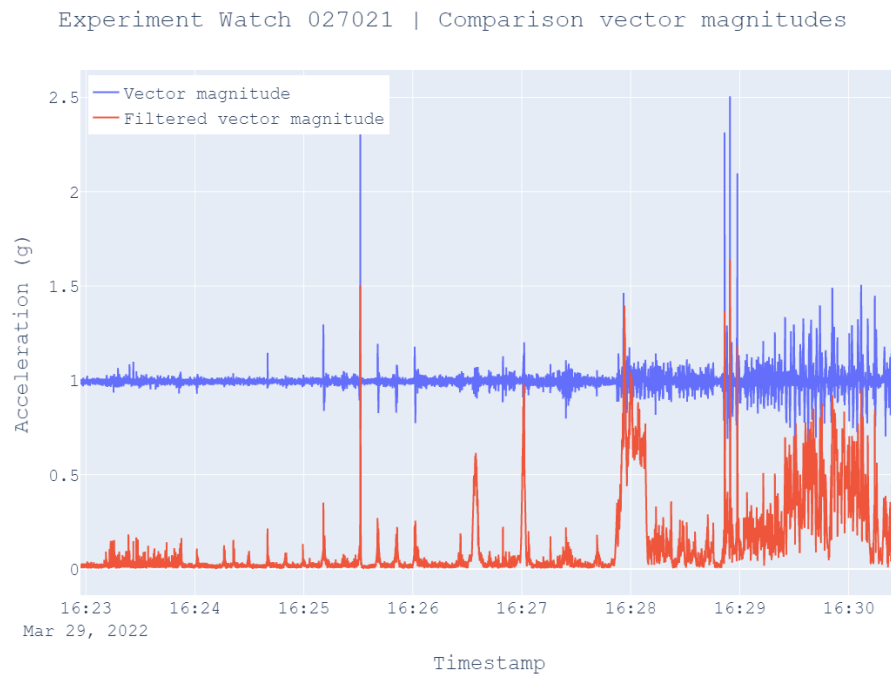Figure 4.2: Filtered acceleration in the x-, y-, and z-direction of experiment 027021.

Figure 4.3: Comparison of the vector magnitude of raw and unfiltered acceleration of experiment 027021.

for the activity fist and finger. Most of the classes here are equal to zero but a difference is noticed in the vector magnitude values. For arm down and arm up, the classes are mostly equal to one, and as expected the highest vector magnitude values are given during these activities.

To see the points on a one-second basis, we zoom in on the first two occurrences where the class is equal to one (Figure 4.5). We can see that the moment of starting forming a fist is missed by the classification. When approaching the end, however, the activity is noticed. The second time forming a fist is entirely missed by the classification. The later moment of forming a fist is similar to the first moment. We also zoom-in on the middle part (Figure 4.6). An activity such as moving an arm up is noticed, although one minute late. The behaviour is similar to forming of a fist as seen previously. Again here the activity thrill is classified as zero class and when looking at the vector magnitude values close-by, the difference between none and trill is indeed almost unnoticeable. The last part is shown in Figure 4.7. Similarly to before, the activities arm down and arm up are noticed in the classification but less times than the actual occurrence of the activity. Also here, the difference in vector magnitude values for trill and none is
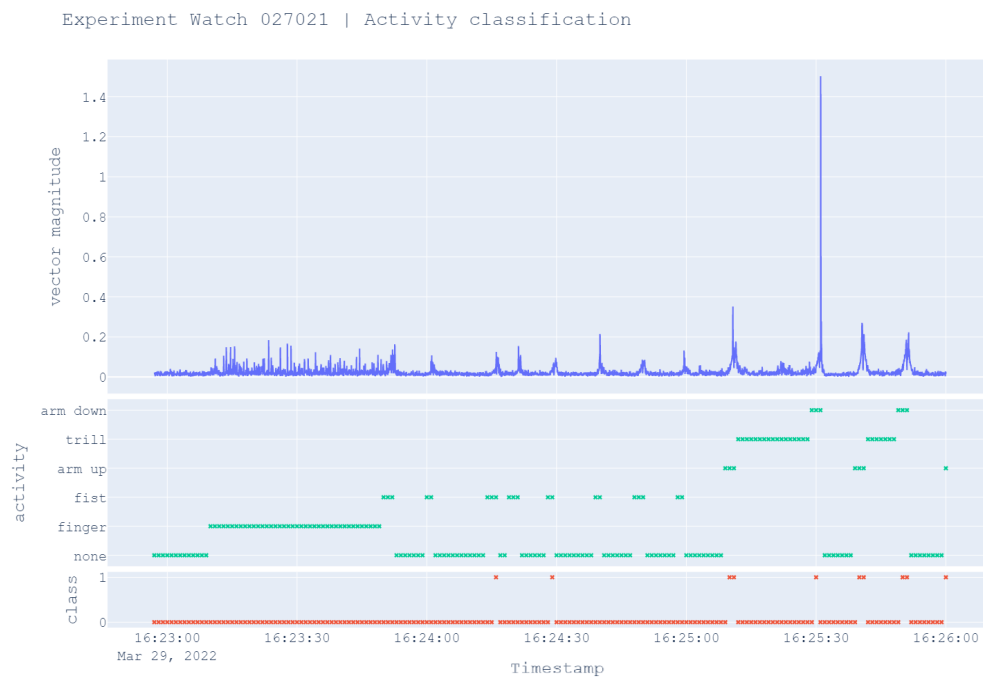

Figure 4.4: Comparison between the vector magnitude, activity, and class for experiment 027021 part 1.

indistinguishable and classified as zero. The second, third, and fourth part of the experiment are included in Appendix B.

The ROC curve for the binary classification of activity, which is zero for no activity and one for activity, is shown in Figure 4.8. Based on the analysis of the vector magnitude values it was chosen here to classify the actual class as zero for the activities none, finger, and trill, and one for the other activities. The highest accuracy reached is equal to 89.56% with false positive rate and true positive rate equal to 0.39 and 0.96, respectively. The ROC curve has an AUC equal to 0.942.

4.2   Patient characteristics

In total twenty-two patients were included in the data analyses of this study (Table 4.1). Of these twenty-two patients, eight patients were classified as delirious with a mean age of 73.3 ± 5.2, seven patients were classified as non-delirious with a mean age of 63.7 ± 8.8, and seven patients were classified as both delirious and non-delirious with a mean age of 73.7 ± 6.2. The delirious group consisted of four mixed, three hypoactive, and one hyperactive delirious patient whereas the latter group consisted of five mixed and two
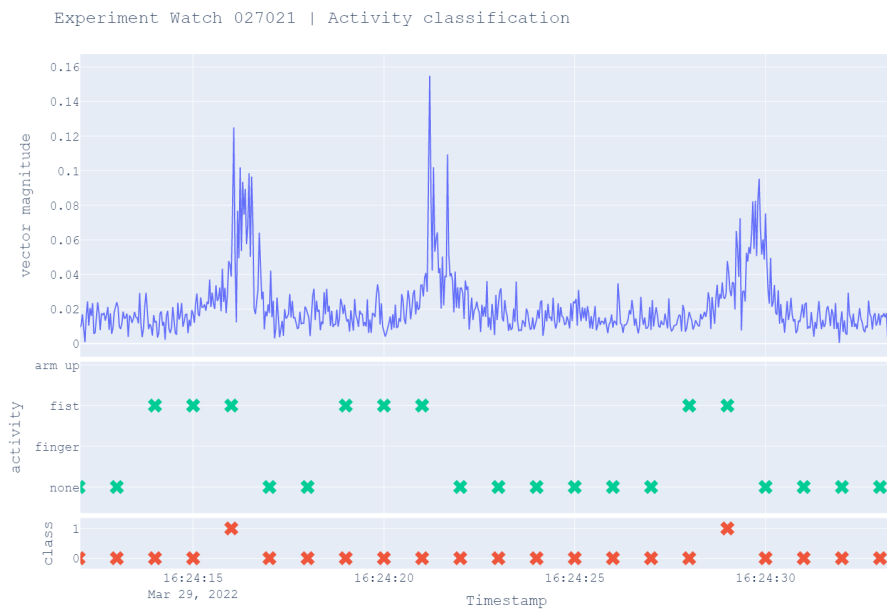
Figure 4.5:   First zoomed-in view of comparison between the vector magnitude, activity, and class for experiment 027021 part 1.
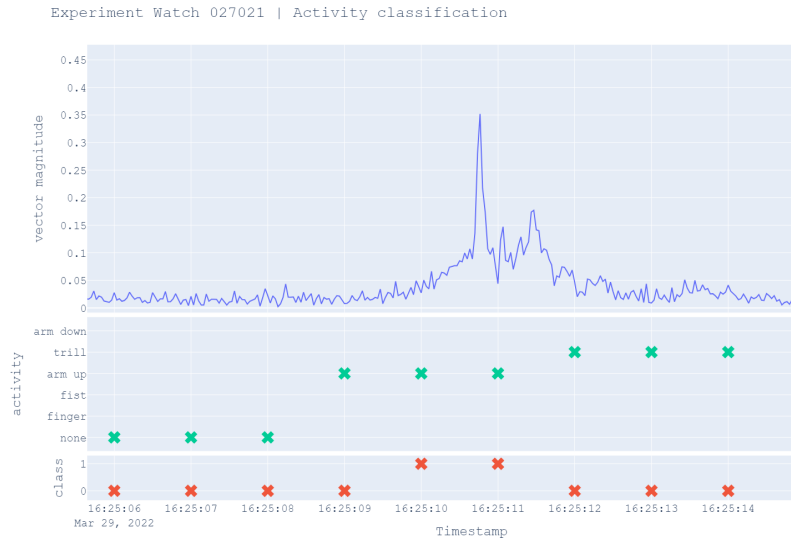
Figure 4.6: Second zoomed-in view of comparison between the vector magnitude, activity, and class for experiment 027021 part 1.
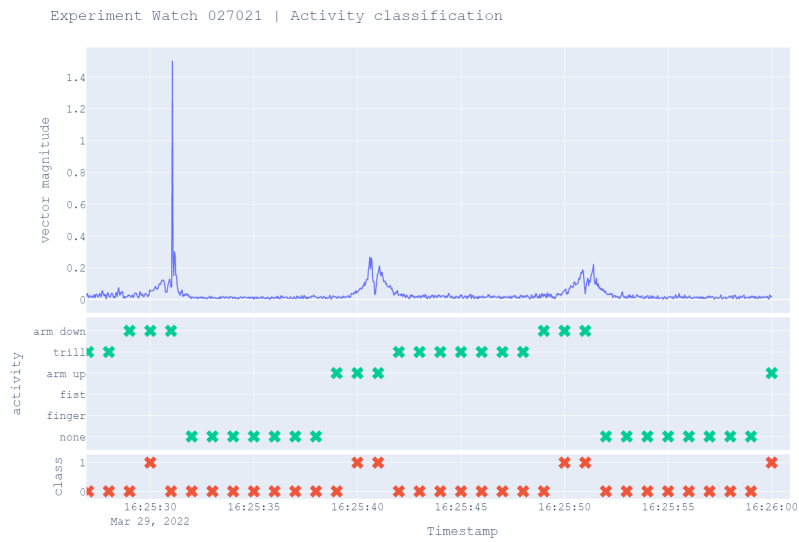
Figure 4.7: Third zoomed-in view of comparison between the vector magnitude, activity, and class for experiment 027021 part 1.

hyperactive delirious patients. The total duration of measurement recordings for the delirious, non-delirious, and both groups were 35, 25, and 42 days, respectively, with a mean of 5 ± 1 days per patient. The time from ICU inclusion to the start of the recordings is on average 7 ± 6 days per patient.
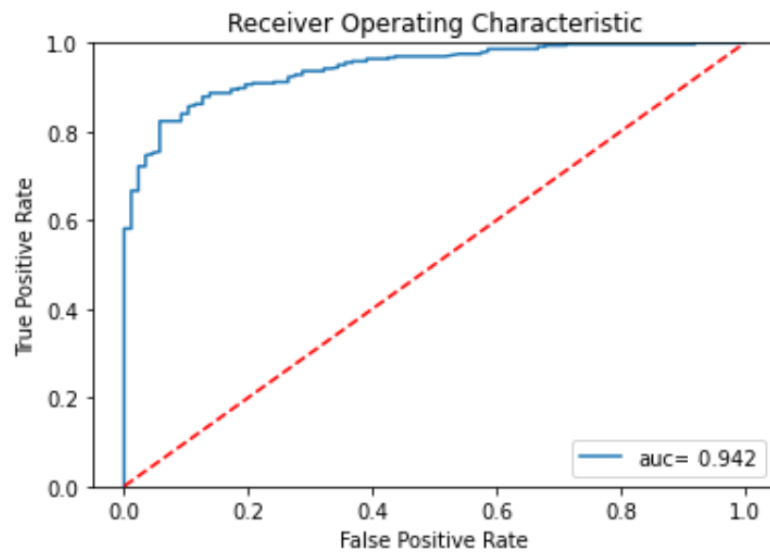
Figure 4.8: ROC curve of binary activity classification for experiment 027021.

The non-delirious group consisted of six patients who had a medical diagnosis and one patient with a surgery diagnosis. The delirious group consisted of five patients with medical diagnoses and three with surgery diagnoses. The group with both consisted of four patients with medical diagnoses and three with surgery diagnoses. The difference between the type of diagnoses indicates the type of nursing the patient receives. Medical nursing means taking care of a patient with an acute or chronic diagnosis, whereas surgical nursing is specific to surgery, pre-op, or recovery period. Acute refers to when a patient needs acute care e.g. is brought to the ICU after a critical incident.

All patients were right-handed, except for one patient. Physical restraints to the wrists were applied to one non-delirious patient, three delirious patients, and five patients of type fluctuating. From the delirious, non-delirious, and both patient groups seven, three, and three patients were in a state of sedation, respectively. Some of the patients also received mechanical ventilation, namely four in the non-delirious group, six in the fluctuating group, and all eight patients in the delirious group.

As a result of the pre-processing technique from the fluctuating group consisting of seven patients, five patients were added to the non-delirious group and two patients were added to the delirious group. Consequently, the non-delirious group ended up consisting of twelve patients whereas the delirious group consisted of ten patients.

Factor	Level	Value
N		22
Age, mean (SD)		70 (8)
Sex, n (%)	Female	7 (29.2%)
	Male	15 (68.2%)
Delirious, n (%)	No	7 (31.8%)
	Yes	8 (36.4%)
	Fluctuating	7 (31.8%)
Delirious[1], n (%)	No	12 (54.5%)
	Yes	10 (45.5%)
Sub-type of delirious, n (%)	Hypo	5 (22.7%)
	Hyper	1 (4.5%)
	Mixed	9 (40.9%)
	None	7 (31.8%)
Type of diagnosis, n (%)	Medical	15 (68.2%)
	Surgery	7 (31.8%)
	Acute	0 (0.0%)
Time from ICU inclusion to recording, mean days (SD)		7 (6)
Time of recordings, mean days (SD)		5 (1)
Dominant hand, n (%)	Left	1 (4.5%)
	Right	21 (95.5%)
GENEActiv, n (%)	026101	5 (22.7%)
	026100	5 (22.7%)
	027020	8 (36.4%)
	026104	4 (18.2%)
Physical restraint, n (%)		9 (40.9%)
Sedation, n (%)		13 (59.1%)
Mechanical ventilation, n (%)		17 (77.3%)

[1] After patients of both type were allocated to either the delirious or non-delirious group.

Table 4.1: Characteristics of study population.

4.3 Illustrative actigraphy examples

A snippet of the filtered acceleration data for patient 355 is shown in Figure 4.9. The acceleration for the x-, y-, and z-direction is depicted for fifteen minutes matching the video and annotations data of the patient.

A comparison between the vector magnitude, activities, and binary classification is shown in Figure 4.10. The GENEActiv was placed on the wrist of the left arm. The largest vector magnitude values occur around 06:46h

which is in line with the activity that occurred by the left arm. It is correctly classified as one by the basic classifier seen previously with AUC of 0.8. There are few occurrences of activity caused by the right leg, right arm, and head as well. The vector magnitude seems to capture some of these activities occurring between 06:41h - 06:42h and 06:47h - 06:48h. The ROC curve for the binary classification of activity, which is zero for no activity and one for activity, is shown in Figure 4.11. The annotations regarding the left hand and left arm are included to define the actual class. When either the left arm or left hand is equal to one, the actual class is equal to one and zero otherwise. The highest accuracy is equal to 95% and the ROC curve has an AUC equal to 0.84.

The same procedure has been applied to all patients. It was however noticed that the GENEActiv data was not always aligned with the video and annotations data. An example of a video snippet for which this was the case is shown in Figure 4.12. The vector magnitude shows higher values for moments when no activity in both the video and annotations is occurring.
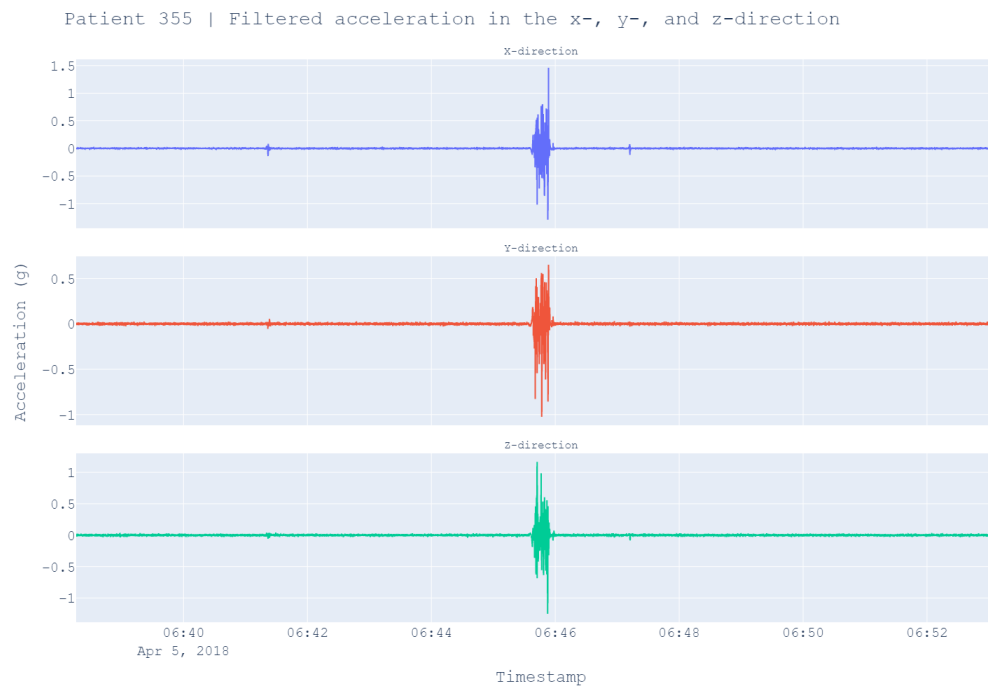

Figure 4.9: Filtered acceleration in the x-, y-, and z-direction of patient 355 during the video of 5 April 2018, 06:38:16h.
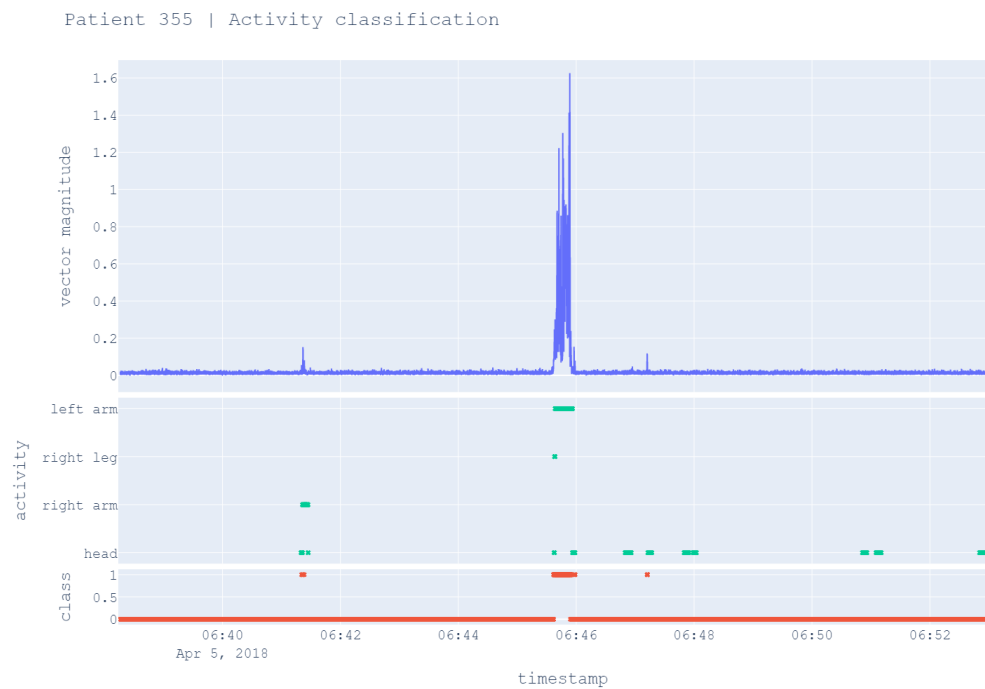
Figure 4.10: Comparison between the vector magnitude, activity, and class for patient 355 on 5 April 2018 06:38:16h.
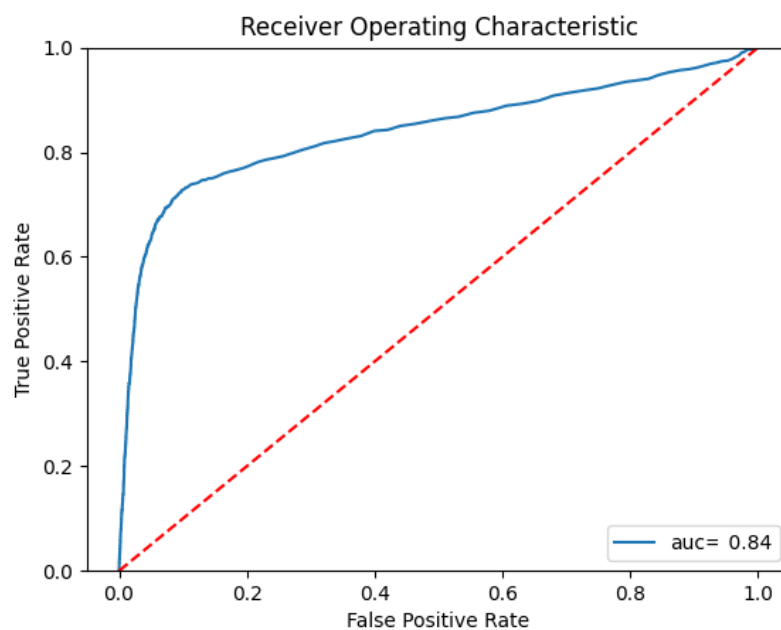
Figure 4.11: ROC curve of binary activity classification for patient 355.
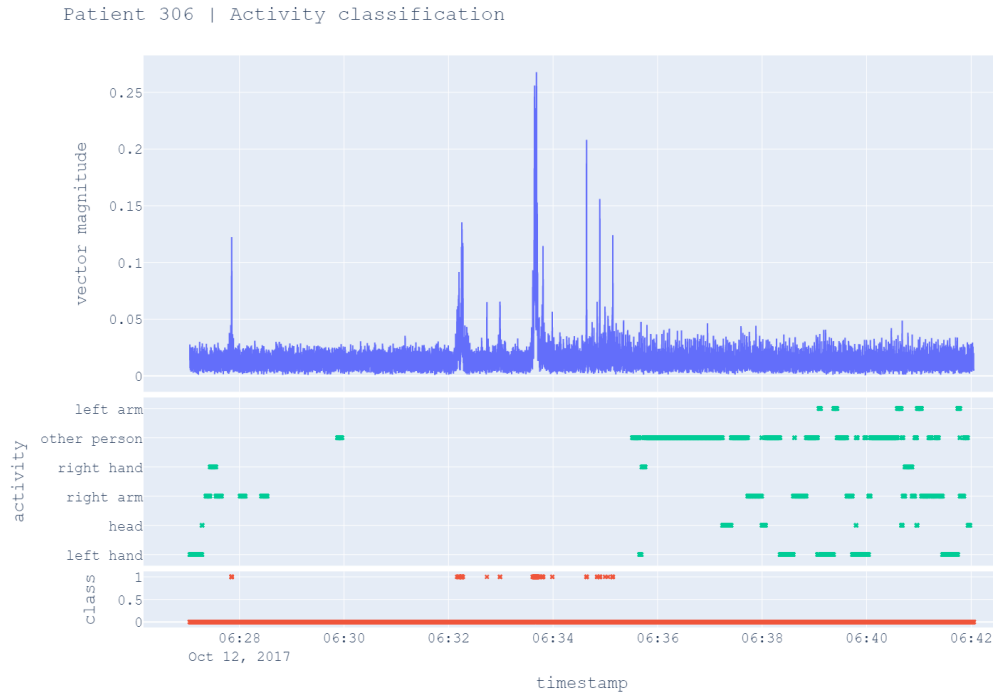
Figure 4.12: Comparison between the vector magnitude, activity, and class for patient 306 on 12 October 2017 06:27:30h.

4.4   Activity levels during day and night

In Figure 4.13 the minimum, maximum, median, and interquartile ranges are shown for the delirious and non-delirious patients. The mean activity level of the delirious and non-delirious groups during the daytime was 2.44 ± 4.22 and 5.52 ± 5.65, respectively. During the nighttime, the mean activity level of the delirious and non-delirious groups was 1.41 ± 3.13 and 3.39 ± 4.95, respectively.

Both the delirious ($U = 75, p = 0.064$) and non-delirious ($U = 101, p = 0.099$) groups showed no significant difference in activity levels between the daytime and nighttime. The activity level during the daytime was also not shown to be significantly different between the delirious and non-delirious groups ($U = 82, p = 0.156$). Also during the nighttime, there was no significant difference between the delirious and non-delirious groups ($U = 85, p = 0.106$).

In Figure 4.14 the minimum, maximum, median, and interquartile ranges are shown for the groups of patients who were classified as mixed, hypoactive, or have no delirium sub-type (indicated by none). Noted is that the study only

included one patient with hyperactive delirium and therefore it is not included here. There was no significant difference found between the activity level between daytime and nighttime for patients with mixed ($U = 53, p = 0.289$), hypoactive ($U = 21, p = 0.095$), or no delirium sub-type ($U = 39, p = 0.072$). Moreover between the patients without delirium sub-type and with mixed sub-type, there was no significant difference in the activity level for both daytime ($U = 34, p = 0.837$) and nighttime ($U = 36, p = 0.672$). Lastly, there was no significant difference between patients without delirium sub-type and patients with hypoactive sub-type both during the daytime ($U = 25, p = 0.268$) and nighttime ($U = 26, p = 0.202$).
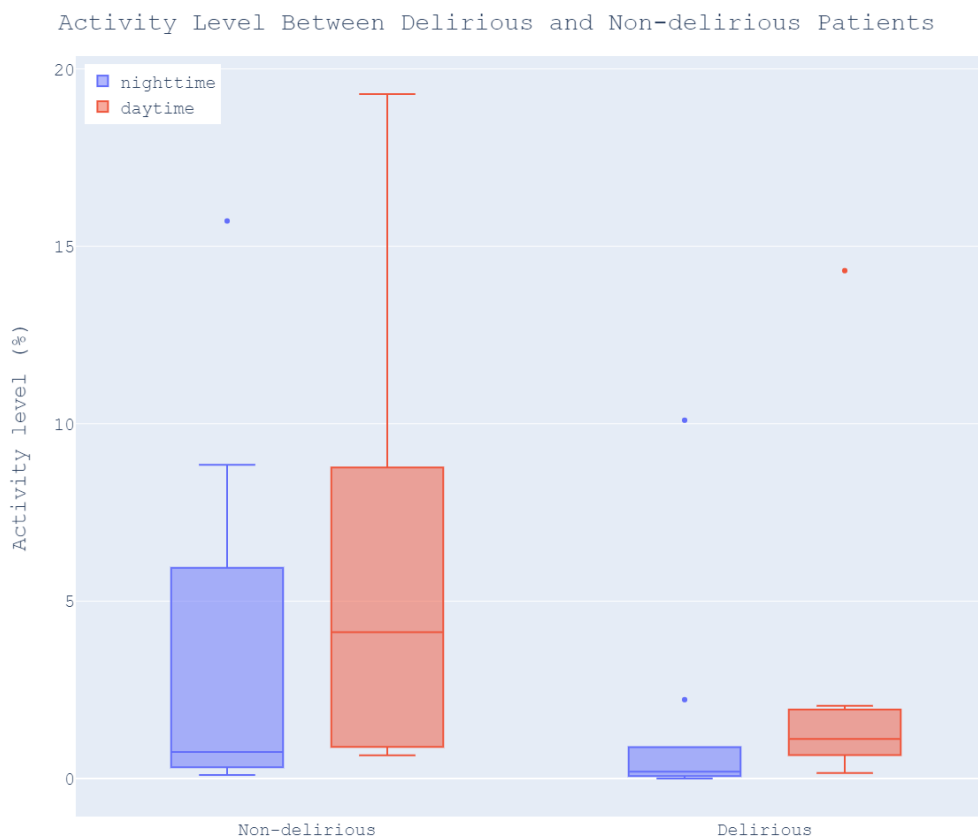
Figure 4.13: Box-plots of activity level in percentages during daytime (7am-10pm) and nighttime (10pm-7am) for the non-delirious and delirious patients.
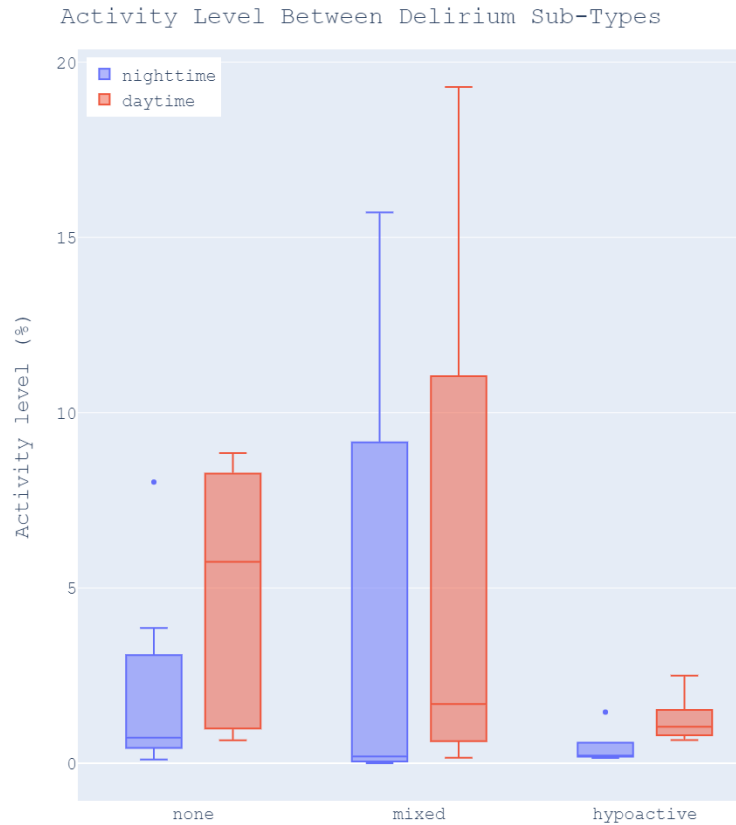
Figure 4.14: Box-plots of activity level in percentages during daytime (7am-10pm) and nighttime (10pm-7am) for patients with mixed, hypoactive, and no delirium sub-type.

4.5 Rest-activity patterns

To investigate whether there are differences in the rest-activity patterns between delirious and non-delirious patients, we look at the activity level (%) aggregated per two hours (Figure 4.15). The activity level is lower for the delirious patients compared to the non-delirious patients and this difference seems to be smaller during moments when patients are asleep and larger during the daytime and later in the evening. Overall, the activity level seems to be following a similar pattern for both delirious and non-delirious patients, namely that resting is mostly after 10 pm. Activity usually starts around 8 am and remains at 8 pm. It is noticed that there is more variation in activity level in the non-delirious group compared to the delirious group since there seem to be several patients with an even higher activity level throughout the daytime.
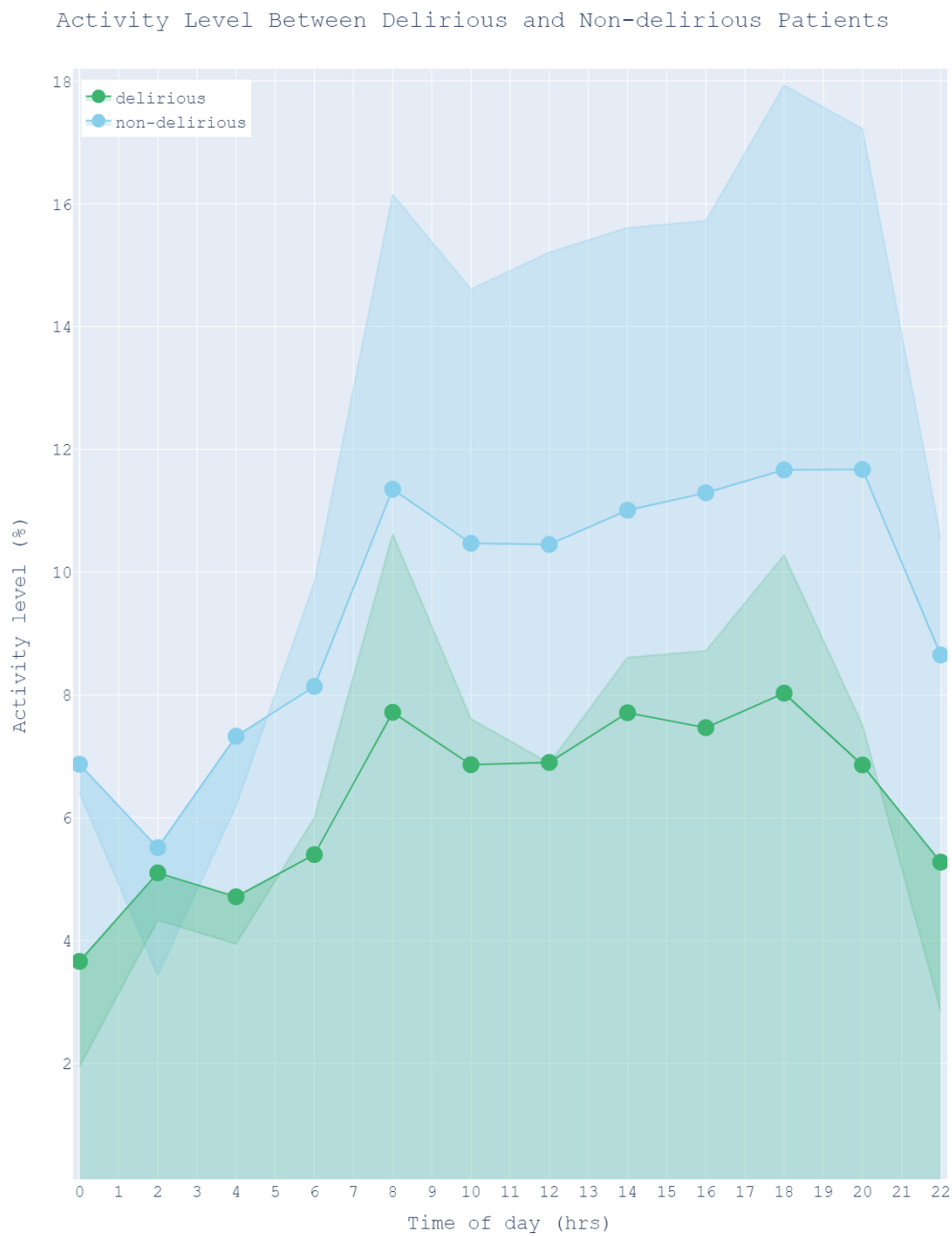
Figure 4.15: Activity level in percentages aggregated per 2 hours for delirious and non-delirious patients.

For patient 306, who is classified as both non-delirious and mixed delirious, the activity level is aggregated per 8, 4, and 2 hours. The results are shown in Figure 4.16. The patient was classified as non-delirious during the

first two days, namely October 6 and 7, 2017. Only until October the 8th did the expert visit the patient at 14:35h and classified the patient as delirious. Also for the next days, October the 9th at 7:40h, October the 10th at 8:10h, October the 11th at 7:40, and October the 12th at 9:00h, the patient was classified as delirious by the expert. The CAM-ICU assessments, however, were not always in agreement during these days as the outputs contained both zeros and ones for different moments during these days.

Figure 4.16: Activity level (%) per 8, 4, and 2 hours throughout the entire measurement duration of a patient diagnosed as both non-delirious and mixed delirious.

When comparing the three plots in Figure 4.16, it is noted that the greater the window size, the smaller the activity level. This is as expected as extremes are smoothed out by taking a larger window size. For all the three window sizes here it is however noticed that the activity level of this patient drastically changed during the midday between October the 8th and October the 9th. This may be caused by the patient going from a state of non-delirious to delirious since the classification of the patient also changed around the same time. Both the activity level during the daytime and nighttime increased for the next upcoming days. During the moment when the patient was classified as delirious, the activity level was not only higher compared to the previous days, but the activity levels were also more differences between the daytime and nighttime. More spikes are noticed for both daytime and nighttime, which may be caused by restlessness or other factors.

The activity level per two hours for non-delirious, hyperactive, hypoactive, and mixed delirious patients is shown in Figure 4.17. As seen by the y-axes the activity levels of the mixed delirious patient are the highest, followed by the non-delirious patient. The hypoactive delirious experiences the most lower activity levels. There is a clear difference in activity level of the non-delirious patient between the daytime and nighttime for all three days included. The activity level is higher during the daytime and during the three days the same pattern is repeated with one spike on the first day around 17:00h.

For the hyperactive delirious patient, the activity level is similar to the pattern noticed in the non-delirious patient. The activity levels are in general higher during the daytime and lower during the nighttime. For this specific patient, however, higher activity levels are noticed around 5 am. For the hypoactive delirious patient, there is also a clear difference in activity level between daytime and nighttime. Although during the daytime there are also occurrences of low activity levels noticed, for example, on May 24th, 2018 15:00h and 21:00h. Lastly, for the mixed delirious patient, the activity level is overall higher than the activity levels seen in the previous patients. There is however still a difference in activity levels between the daytime and nighttime, namely higher levels during the day. The patient was very active in the first few days and the overall activity level does seem to slowly decrease over the next few days.
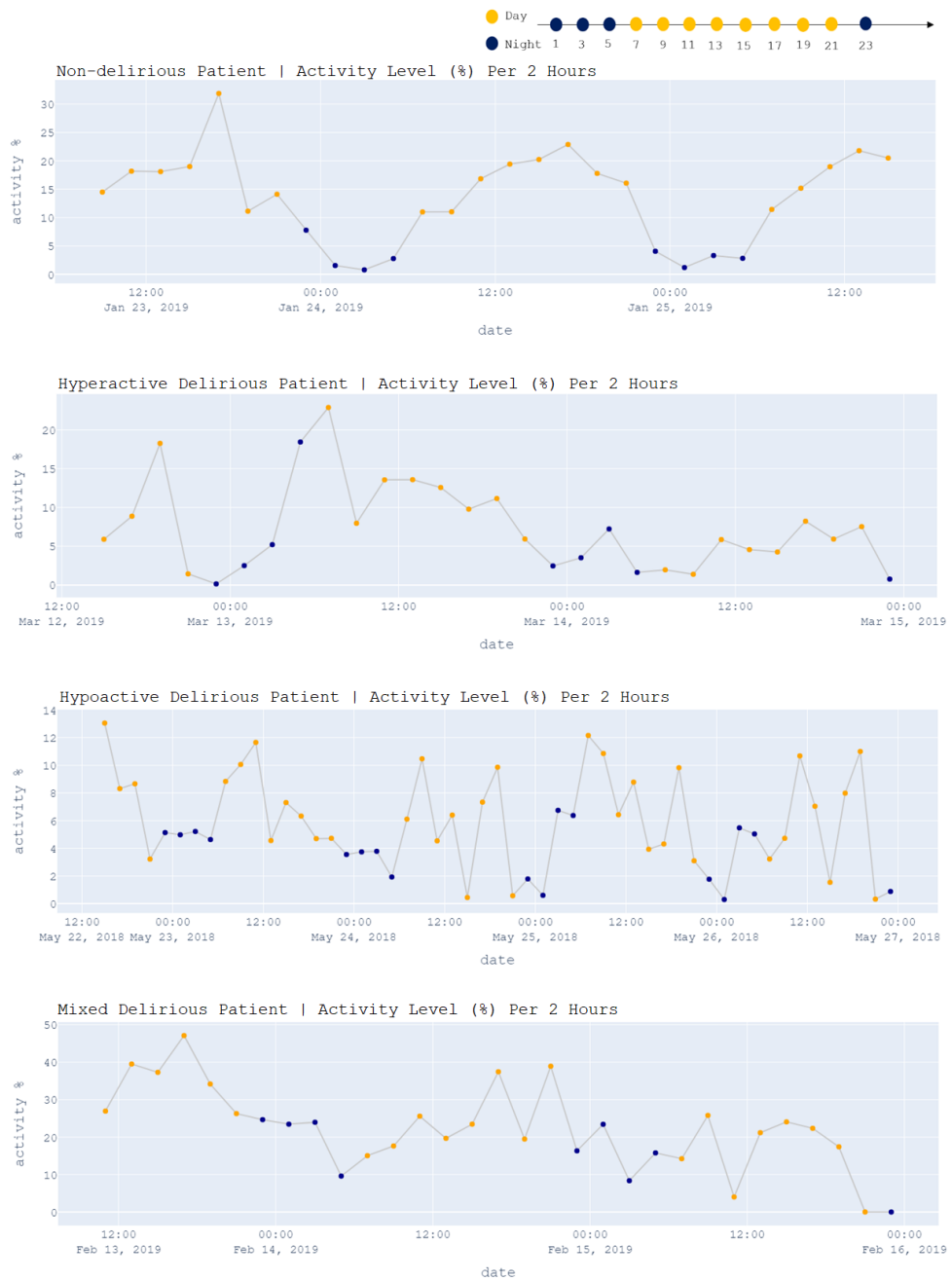
Figure 4.17: Activity level (%) per 2 hours throughout the entire measurement duration of 4 patients who are non-delirious, hyperactive, hypoactive, and mixed delirious.

Chapter 5

Discussion

In this study, we looked into motion-based features as indicators for early detection of delirium in ICU patients. The data was collected by the GENEActiv wrist-worn accelerometer device for several non-delirious and delirious patients in the ICU. An experiment with the GENEActiv accelerometer device was also included to investigate the overall sensitivity and specificity. The physical activity signals of the ICU patients were analyzed, and a binary classification was determined for activity. The performance was then analyzed after the preprocessing of the data. In addition, the Butterworth filter was used to eliminate the low-frequency noise from the signal while attenuating the high-frequency points.

The results show that delirious and non-delirious patients in the ICU have a difference in activity levels during both daytime and nighttime. In particular hypoactive patients have lower activity levels during both the daytime and nighttime compared to non-delirious patients. Moreover, the activity levels between daytime and nighttime show a larger difference for delirious patients than non-delirious patients. However, these differences appear not to be significant. Also between the different motoric delirium sub-types included in the study, the difference in activity levels both during and between daytime and nighttime was not found to be significant.

Although the current study successfully used actigraphy as an objective monitoring tool in ICU patients, some limitations should also be considered. Some of the accelerometers failed to record data. This problem caused no data for several participants to be recorded. There were also measurement errors in some of the collected data. Several ICU patients experienced physical restraints to prevent them from disrupting medical devices. This may significantly affect the patterns of physical activity of patients by limiting their

movements. Other factors that may have interfered with the results are the effect of the use of certain medications on a patient's activity levels. Several patients also experienced moments of sedation and mechanical ventilation. Moreover, the intervention of other people with the patient such as nurses and visitors could not always be excluded.

Furthermore, there is a limited number of patients. A study with more participants may give more insights from the analyses. Especially the mixed delirium motoric sub-type should be studied more elaborately due to the possibility of having both increased and decreased psychomotor activity. The sampling rate of 30-Hz also caused some limitations in studying movements of shorter duration. Also since the GENEActiv was placed on the wrist, movements in other body parts could not always have been taken into account. It is recommended for future studies look into the motoric behavior of different body parts. The severity of delirium was also not taken into consideration and the number of delirium assessments was limited which may cause an underestimation of delirium.

Thus there were data limitations due to the total number of patients included in the study, the inability to consider other body parts than the wrist, and missing data due to incorrect patient care management and/or incorrect use of the GENEActiv device by hospital staff.

Chapter 6

Conclusion

In conclusion, alterations in motor activity patterns and activity levels are an important symptom of delirium in patients in the ICU. Our data show that a difference in motor activity was observed between patients with and without delirium, however, the difference was not significant. Further study of the role of actigraphy in delirium detection is required.

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Appendix A

Screening Tools for Delirium

CAM-ICU Worksheet

Feature 1: Acute Onset or Fluctuating Course	Score	Check here if Present
Is the pt different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale (i.e., RASS), GCS, or previous delirium assessment?	Either question Yes →	☐
Feature 2: Inattention		
Letters Attention Test (See training manual for alternate **Pictures**) Directions: Say to the patient, *"I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand."* Read letters from the following letter list in a normal tone 3 seconds apart. **S A V E A H A A R T** **Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."**	Number of Errors >2 →	☐
Feature 3: Altered Level of Consciousness		
Present if the Actual RASS score is anything other than alert and calm (zero)	RASS anything other than zero →	☐
Feature 4:Disorganized Thinking		
Yes/No Questions (See training manual for alternate set of questions) 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? **Errors are counted when the patient incorrectly answers a question.** **Command** Say to patient: "Hold up this many fingers" (Hold 2 fingers in front of patient) "Now do the same thing with the other hand" (Do not repeat number of fingers) *If pt is unable to move both arms, for 2nd part of command ask patient to "Add one more finger" **An error is counted if patient is unable to complete the entire command.**	Combined number of errors >1→	☐

Overall CAM-ICU	Criteria Met →	☐ **CAM-ICU Positive** (Delirium Present)
Feature 1 plus 2 and either 3 or 4 present = CAM-ICU positive	Criteria Not Met →	☐ **CAM-ICU Negative** (No Delirium)

Figure A.1: CAM-ICU worksheet

Intensive Care Delirium Screening Checklist Worksheet (ICDSC)

- Score your patient over the entire shift. Components don't all need to be present at the same time.
- Components #1 through #4 require a focused bedside patient assessment. This cannot be completed when the patient is deeply sedated or comatose (ie. SAS = 1 or 2; RASS = -4 or -5).
- Components #5 through #8 are based on observations throughout the entire shift. Information from the prior 24 hrs (ie, from prior 1-2 nursing shifts) should be obtained for components #7 and #8.

1. **Altered Level of Consciousness** NO 0 1 Yes
   Deep sedation/coma over entire shift [SAS= 1, 2; RASS = -4,-5] = Not assessable
   Agitation [SAS = 5, 6, or 7; RASS= 1-4] at any point = 1 point
   Normal wakefulness [SAS = 4; RASS = 0] over the entire shift = 0 points
   Light sedation [SAS = 3; RASS= -1, -2, -3]: = 1 point (if no recent sedatives)
   = 0 points (if recent sedatives)

2. **Inattention** NO 0 1 Yes
   Difficulty following instructions or conversation, patient easily distracted by external stimuli.
   Will not reliably squeeze hands to spoken letter A: **S A V E A H A A R T**

3. **Disorientation** NO 0 1 Yes
   In addition to name, place, and date, does the patient recognize ICU caregivers?
   Does patient know what kind of place they are in?
   (list examples: dentist's office, home, work, hospital)

4. **Hallucination, delusion, or psychosis** NO 0 1 Yes
   Ask the patient if they are having hallucinations or delusions.
   (e.g. trying to catch an object that isn't there).
   Are they afraid of the people or things around them?

5. **Psychomotor agitation or retardation** NO 0 1 Yes
   Either: a) Hyperactivity requiring the use of sedative drugs or restraints in order to control
   potentially dangerous behavior (e.g. pulling IV lines out or hitting staff)
   OR b) Hypoactive or clinically noticeable psychomotor slowing or retardation

6. **Inappropriate speech or mood** NO 0 1 Yes
   Patient displays: inappropriate emotion; disorganized or incoherent speech;
   sexual or inappropriate interactions; is either apathetic or overly demanding

7. **Sleep-wake cycle disturbance** NO 0 1 Yes
   Either: frequent awakening/< 4 hours sleep at night OR sleeping during much of the day

8. **Symptom Fluctuation** NO 0 1 Yes
   Fluctuation of any of the above symptoms over a 24 hr period.

   TOTAL SHIFT SCORE: _____
   (0 – 8)

Score	Classification
0	Normal
1-3	Subsyndromal Delirium
4-8	Delirium

Adapted from: Bergeron et al. Intens Care Med 2001;27:859-64; Ouimet et al. Intens Care Med 2007;33:1007-13.

Figure A.2: ICDSC worksheet

Richmond Agitation Sedation Scale (RASS) *

Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	
+2	Agitated	Frequent non-purposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressive vigorous	
0	Alert and calm		
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to *voice* (**≥10 seconds**)	Verbal Stimulation
-2	Light sedation	Briefly awakens with eye contact to *voice* (**<10 seconds**)	
-3	Moderate sedation	Movement or eye opening to *voice* (**but no eye contact**)	
-4	Deep sedation	No response to voice, but movement or eye opening to *physical* stimulation	Physical Stimulation
-5	Unarousable	No response to *voice or physical* stimulation	

Procedure for RASS Assessment

1. Observe patient
   a. Patient is alert, restless, or agitated.   (score 0 to +4)
2. If not alert, state patient's name and *say* to open eyes and look at speaker.
   b. Patient awakens with sustained eye opening and eye contact.   (score −1)
   c. Patient awakens with eye opening and eye contact, but not sustained.   (score −2)
   d. Patient has any movement in response to voice but no eye contact.   (score −3)
3. When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum.
   e. Patient has any movement to physical stimulation.   (score −4)
   f. Patient has no response to any stimulation.   (score −5)

* Sessler CN, Gosnell M, Grap MJ, Brophy GT, O'Neal PV, Keane KA et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care patients. Am J Respir Crit Care Med 2002; 166:1338-1344.

* Ely EW, Truman B, Shintani A, Thomason JWW, Wheeler AP, Gordon S et al. Monitoring sedation status over time in ICU patients: the reliability and validity of the Richmond Agitation Sedation Scale (RASS). JAMA 2003; 289:2983-2991.

Figure A.3: RASS worksheet

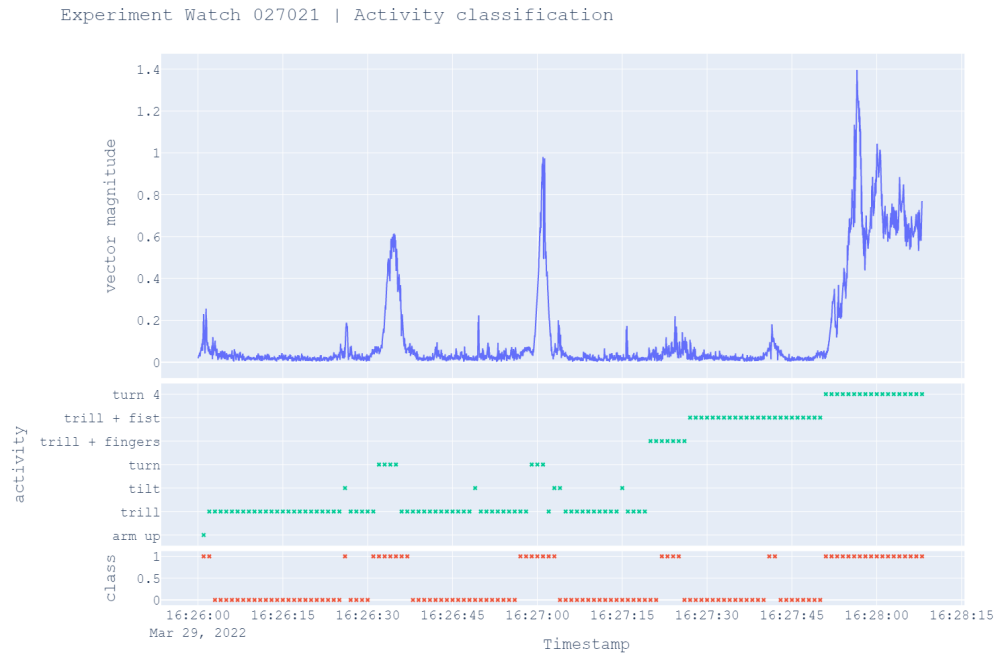# Appendix B

Experiment with GENEActiv

Figure B.1: Comparison between the vector magnitude, activity, and class for experiment 027021 part 2.
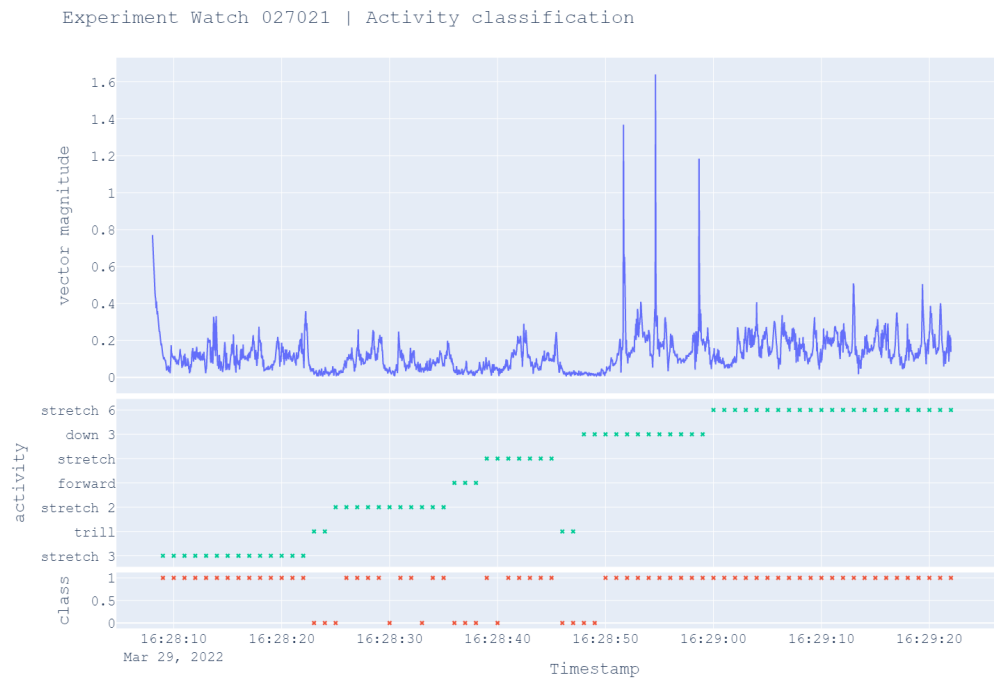

Figure B.2: Comparison between the vector magnitude, activity, and class for experiment 027021 part 3.
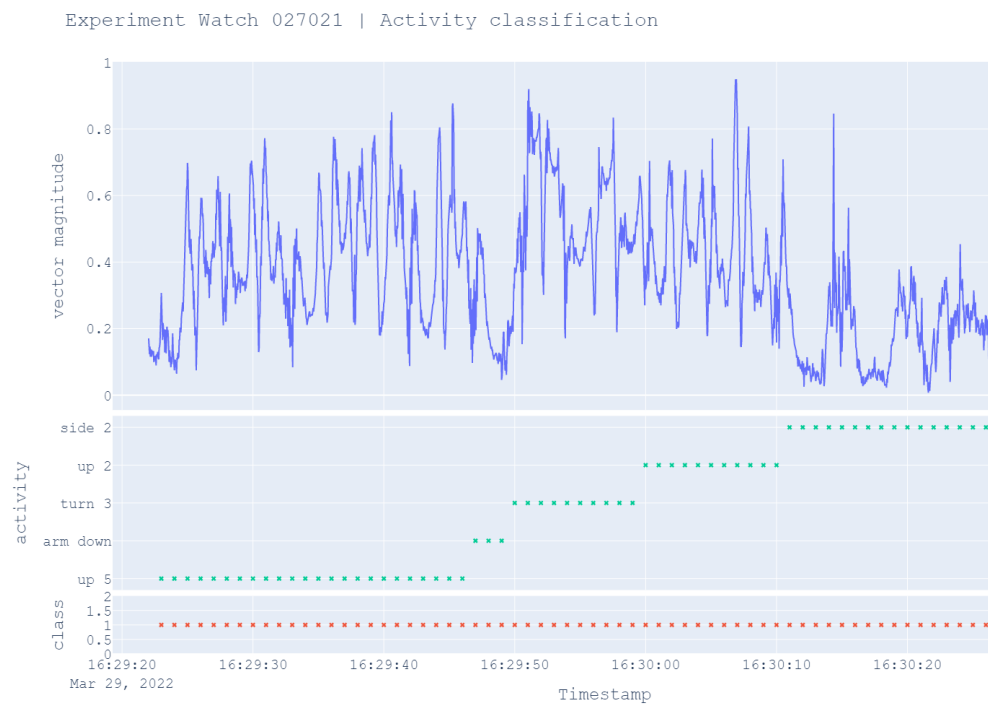
Figure B.3: Comparison between the vector magnitude, activity, and class for experiment 027021 part 4.

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