The Relationship Between Circadian Rhythms and Mood Symptoms in Bipolar Disorder and Borderline Personality Disorder

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Abstract

It is estimated that half of the health issues in the United Kingdom are linked to mental health for individuals under the age of 65, with the majority of these health issues being attributed to depression or anxiety. One of the most prevalent mental disorders is bipolar disorder, with patients experiencing mood instability with extended periods of depression, associated with feelings of unhappiness and dejection. They also experience periods of mania, associated with euphoria, delusions and overactivity. Borderline personality disorder is the most common personality disorder and is linked with disrupted mood and altered personal interactions. Current clinical practice in the management of bipolar disorder and borderline personality disorder involves self-reported monitoring and interviews with clinicians. This practice is based on research focused on clinical laboratory settings and single modality sensors to record data. Smartphones and mobile devices allow for at home monitoring in a natural setting and can acquire multiple signal modalities over very long periods of time, thus providing more information about the links between behaviour and physiology in mental health disorders. These objective measures could provide passive measures of sleep and circadian rhythms which could be used to determine the health of patients at home. This thesis explores the relationship between circadian rhythms, mood symptoms and depression within individuals and patient groups.

A longitudinal study of 141 individuals, including bipolar disorder, borderline personality disorder and healthy control participants, monitored behavioural, physiological and mood measures for a mean of 83 ± 31 weeks. Circadian features of activity and heart rate, in addition to measures of sleep were extracted from the signals through fitting of sinusoids and application of time varying hidden Markov models.

Internal desynchronisation of circadian rhythms were investigated through differences in the phase of the rhythms of a four day period. Significant desynchronisation between the rhythms of heart rate and both activity and sleep were seen in the patients groups. Borderline personality disorder participants had the greatest desynchrony with a three hour lag between heart rate and activity and one hour between heart rate and sleep.

The variability of circadian rhythms in healthy mood states, known as euthymia, were greatest in the borderline personality disorder patients, with bipolar disorder

participants also having more variable sleep. Significant correlations were seen between circadian variability and mood variability in borderline personality disorder participants. The variability in activity rhythms correlated strongly with negative mood ($\rho = 0.819$, $p = 0.04$) in addition to the variability in heart rate amplitudes and negative mood ($\rho = 0.852$, $p = 0.02$).

New features of circadian activity and sleep were extracted from longitudinal smartphone accelerometry using time varying hidden Markov models. Personalised regression models were developed which are capable of predicting levels of depression, with average mean absolute errors of depression scores (ranging from 0 to 27) of 0.80 ± 0.79 in bipolar disorder participants, 1.33 ± 1.03 in borderline personality disorder participants, and 0.39 ± 0.40 in healthy control participants. These errors are smaller than the thresholds for diagnosing episodes of depression ($0 - 5$ *no depression*, $6 - 10$ *mild depression*, $11 - 15$ *moderate depression*, and > 15 *severe depression*), with bipolar disorder and borderline personality disorder participants entering all levels of depression, but healthy controls remaining mainly in the *no depression* category. The personalised regression models developed were able to classify depression with an accuracy of 88% in bipolar disorder, 79% in borderline personality disorder, and 98% in healthy participants.

The results presented in this thesis show both bipolar disorder and borderline personality disorder to be associated with disrupted circadian rhythms. A major finding of this thesis is that the quantification of circadian rhythm disruption may be performed over a short-term high intensity period, reducing the need for multiple obtrusive devices to be worn over long periods of time, with shorter term monitoring have less barriers for adoption in to clinical practice. It was also found that the use of multiple modalities (acceleration and heart rate) allows for novel desynchronisation metrics to be performed, which are not possible from single sensor recordings, providing further insight into the levels of illness.

The findings also highlight the relationship between mood and circadian rhythms and show longitudinal monitoring of acceleration may act as an objective marker to aid monitoring of symptoms of depression. Due to the activity being recorded from smartphones, which are already in widespread use in current society, there is a reduction in the barriers to uptake for patients to begin using these monitoring tools. These markers of circadian activity may have a considerable impact in the future of clinical care through providing automated objective measures to compliment the current clinical practice and reduce some of the subjectivity in diagnosis and monitoring of depression.

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List of Abbreviations

AMoSS . . . . The Automated Monitoring of Symptom Severity study.

ANOVA . . . . Analysis of variance.

ANS . . . . . Autonomic nervous system.

ASRM . . . . . The Altman self-rating mania scale.

BD . . . . . Bipolar disorder.

BMI . . . . . Body mass index.

BPD . . . . . Borderline personality disorder.

BPM . . . . . Beats per minute.

BRIAN . . . . Biological rhythm interview of assessment in neuropsychiatry.

CBT . . . . . Cognitive behavioural therapy.

CLOCK . . . . The circadian locomotor output cycles kaput gene.

CRSD . . . . . Circadian rhythm sleep disorders.

CSM . . . . . Composite scale of morningness.

DSM . . . . . The Diagnostic and Statistical Manual of Mental Disorders.

ECG . . . . . Electrocardiogram.

EDA . . . . . Electrodermal activity.

EEG . . . . . Electroencephalogram.

EMA . . . . . Ecological momentary assessment.

EQ-5D . . . . . The Euroqol five dimensional questionnaire.

ESS . . . . . Epworth sleepiness scale.

FDR . . . . . False discovery rate.

fMRI . . . . . Functional magnetic resonance imaging.

FWER . . . . Family wise error rate.

GAD-7 . . . . The general anxiety disorder questionnaire.

GPS . . . . . Global positioning system.

HC . . . . . Healthy control.

HMM . . . . . Hidden Markov model.

HR . . . . . Heart rate.

HRV . . . . . Heart rate variability.

ICD . . . . . The International Classification of Diseases.

ISI . . . . . Insomnia severity index.

L5 . . . . . Least active five hours.

LASSO . . . . Least absolute shrinkage and selection operator.

M10 . . . . . Most active ten hours.

MAE . . . . . Mean absolute error.

MCTQ . . . . The Munich chronotype questionnaire.

MEQ . . . . . The morningness-eveningness questionnaire.

MESC . . . . . The morningness-eveningness scale for children.

MESOR . . . . The midline estimating statistic of rhythm.

MINI . . . . . The Mini-International Neuropsychatric Interview.

MOS . . . . . Medical outcomes study.

mRMR . . . . Minimum redundancy maximum relevance.

MSE . . . . . Mean square error.

MZirr . . . . . The irritable component of Mood Zoom using PCA.

MZneg . . . . The negative component of Mood Zoom using PCA.

MZpos . . . . The positive component of Mood Zoom using PCA.

NHS . . . . . The National Health Service.

PCA . . . . . Principal component analysis.

PER . . . . . The period gene.

PHQ-9 . . . . The patient health questionnaire.

PPG . . . . . Photoplethysmography.

PSQI . . . . . The Pittsburgh sleep quality index.

QIDS . . . . . The quick inventory of depressive symptomatology.

RMSE . . . . . Root mean square error.

RMSSD . . . . Root mean of successive differences.

RSS . . . . . Residual sum of squares.

SCN . . . . . Suprachiasmatic nucleus.

SPAQ . . . . . The sleep practices and attitudes questionnaire.

SRM-5 . . . . The social rhythm metric questionnaire.

STQ . . . . . The sleep timing questionnaire.

SVD . . . . . Singular value decomposition.

TIM . . . . . The timeless gene.

TKEO . . . . . Teager-Kaiser energy operator.

UK . . . . . United Kingdom

1 Introduction

1.1 Motivation

Maintaining good mental health is vital in order to sustain healthy relationships, to carry out work and study, and to adequately carry out daily tasks. Adverse changes to mental health may considerably reduce the capabilities of decision making and the ability to perform normal activities. These negative changes do not only affect the individuals suffering from these problems but also friends, family and society as a whole.

Mental disorders are attributed to more than one quarter of all measured disabilities and account for 45% of the leading causes of years lived with disability, accounting for 10% of the global (187 countries) burden of disease [1, 2]. The estimated loss of economic output over the next 20 years caused by mental health is estimated to be £12.5 trillion worldwide. Despite the huge impact mental health could have on the economy and society, treatment and care of people suffering from disorders is poor, especially in low income countries where only one in ten individuals receives any form of treatment [3].

The majority of the mental health issues in the United Kingdom (UK) are linked to anxiety and depression [4]. Within the UK alone, mental health disorders account for 23% of the burden for disease, significantly higher than the global

burden, yet mental health only accounts for 13% of the UK National Health Service (NHS) expenditure which amounts to £14 billion a year. The largest portion of this expenditure is on adults suffering from schizophrenia, bipolar disorder (BD) and personality disorders, with £5.6 billion spent on secondary (for example community mental health teams) and tertiary care (more specialised inpatient facilities). Costs to the NHS are predicted to increase to over £30 billion by 2026, thus increasing the need for care and monitoring of patients suffering for mental health disorders [5].

Mood and emotion are terms which are often used interchangeably and there still exists some debate as whether they refer to different experiences. The duration and causes of these experiences in an individual are the primary factors thought to differentiate mood and emotion [6]. Moods are thought to be longer lasting (from hours to days) and are influenced by many factors including mental state, physiology and the environment. Whereas emotions are thought to be much shorter term responses to stimuli and may only last for a few seconds. Mental health disorders are often associated with mood instability, especially in the case of BD, with many challenges involved in monitoring the current mental state. Currently, symptoms are self-assessed and are subjectively placed on mood scales, such as depression [7], mania [8] and anxiety [9], making it difficult to determine when the mental state of a patient is changing.

Diagnosis relies on the judgement of a clinician, along with the often biased self reported symptoms, thus making diagnosis of conditions and prescription of treatments extremely challenging. The ability to determine objective markers for the mental state of a patient would considerably improve patient monitoring, allow for better tracking of mood deterioration and increase the ability to manage mental health disorders. At present, management of mental health disorders such as BD and borderline personality disorder (BPD) involves trying to avoid transitions into negative mental states such as depression and mania. This is done by monitoring any warning signs that a patient's mental health may be deteriorating and providing interventions when these signs are detected to revert back to a healthy state, known as euthymia. Euthymia is the period when BD

patients are not experiencing depressive or manic symptoms, yet they are not considered to be completely symptom free and may experience mood instability and other symptoms. These warning signs often go undetected or are not noticed until too late due to lack of accuracy and frequency of the self-reported scores and minimal contact time with clinicians. Ambulatory monitoring of objective markers may allow for more reliable detection of early warning signs of deterioration and may allow for earlier interventions to occur, reducing the number of transitions into negative mental states.

One of the core symptoms associated both with BD and BPD is disruption to sleep [10]. Circadian rhythms, or daily cycles, are controlled by 24 hour clocks within the human body which set the timings of physiological processes within the body, such as body temperature and heart rate. They are also involved in the control of energy levels, thus controlling the sleep/wake cycle of individuals. Maintaining healthy circadian rhythms and regular sleep/wake cycles may be a key factor in preventing transitions into states of depression or mania in BD [11], with studies reporting levels of light received by BD patients altering their mood states [12]. BD patients have also been found to have altered levels of melatonin and cortisol compared to healthy subjects, with the levels of both melatonin and cortisol controlled by the circadian clock [13]. Lithium, a common drug administered to BD patients has also been found to alter the periodicity of circadian rhythms [14]. Although there is existing evidence circadian rhythms may provide significant insight into deterioration in mental state in BD, there is little work which attempts to measure these rhythms in a continuous and unobtrusive way. Therefore being able to passively monitor circadian rhythms may considerably aid with clinical practice of monitoring symptom severity in BD.

Data collected from smartphones and wearable medical devices can provide a wide range of physiological, physical and behavioural measures with minimal input from the patients being monitored, with the addition of mood data through user input to act as a control variable. The large data sets which can be obtained from these devices will allow for a wide range of features to be calculated, which

may be indicative of mental health disorders or the current mental state of the patient. Physiological features which differ in various psychiatric disorders have the ability to improve understanding of these disorders, with objective features providing early information about changing mental states of patients, allowing action to take place to revert from negative mental states.

This thesis aims to determine objective markers of circadian rhythm regularity and investigate how these rhythms differ in mental health disorders, specifically BD and BPD. It also aims to develop methods to objectively assess wearable and smartphone data for longitudinal monitoring of BD participants.

1.2 Thesis Outline

Chapter 2 gives a background to the assessment of mental health disorders. It describes the disorders studied in this work, how they are diagnosed, methods of management and how to determine symptom severity. It also reviews the relevant literature of the monitoring of mental disorders. Chapter 3 describes some of the background methodology developed in this thesis, including methods used to find objective markers of mood and for symptom assessment. Chapter 4 describes the data collection and Chapter 5 details the calculation of circadian features from the different data sources. Chapter 6 looks at circadian variability within mental health disorders and how they are linked to mood variability. Chapter 7 extends the circadian variability analysis to longer term recordings in order to track depression and deterioration in mood. Chapter 8 concludes the work and makes suggestions for future work.

1.3 Contributions

The following publications are associated with the work on this thesis:

- **Carr, O.**, Saunders, KEA., Tsanas, A., Bilderbeck, AC., Palmius, N., Geddes, JR., Foster, R., Goodwin, GM., and De Vos, M. (2018). Variability in phase

and amplitude of diurnal rhythms is related to variation of mood in bipolar and borderline personality disorder. *Scientific Reports*, 8(1):1649.

- **Carr, O.**, Saunders, KEA., Bilderbeck, AC., Tsanas, A., Palmius, N., Geddes, JR., Foster, R., De Vos, M., and Goodwin, GM. (2018). Desynchronization of diurnal rhythms in bipolar disorder and borderline personality disorder. *Translational Psychiatry*, 8(1):79.

- **Carr, O.**, Andreotti, F., Saunders, KEA., Bilderbeck, AC., Goodwin, GM., and De Vos, M. (2017). Linking Changes in Heart Rate Variability to Mood Changes in Daily Life. *Computing in Cardiology 2017*, 44:1.

- **Carr, O.**, De Vos, M., and Saunders, KEA. (2017). Heart rate variability in bipolar disorder and borderline personality disorder: a clinical review. *Evidence-based Mental Health*, 21(1):23-30.

- Palmius, N., Saunders, KEA., **Carr, O.**, Geddes, JR., Goodwin, GM., and De Vos, M. (2018). Group-personalized regression models for prediction of mental health scores from objective mobile phone data streams. *Journal of Medical Internet Research*. 20(10):10194.

- Saunders, KEA., **Carr, O.**, Bilderbeck, AC., Tsanas, A., Palmius, N., Goodwin, GM., and De Vos, M. (2018). Digital Data Capture in the Characterisation of Diurnal Correlates of Mood Instability. *Biological Psychiatry*, 83(9):S3.

- Andreotti, F., **Carr, O.**, Pimentel, MAF., Mahdi, A., and De Vos, M. (2017). Comparing Feature-Based Classifiers and Convolutional Neural Networks to Detect Arrhythmia from Short Segments of ECG. *Computing in Cardiology 2017*, 44:1.

2

A Background to Mental Disorders: Diagnosis and Monitoring

Some understanding of mental disorders has existed for thousands of years, with both the ancient Romans and Egyptians believing mental disorders were due to religious reasons, with a person with a mental disorder thought to be possessed by demons [15]. It was not until Hippocrates in the 5^{th} century who believed diseases and mental disorders were not punishments from the gods but were caused by environmental factors, diet, and life style, with human physiology affected by the disorders [16].

In the early 1400s, the first psychiatric hospital was founded in Spain [17]. From this date, the number of facilities for mental disorders grew rapidly. In the 1700s, Phillippe Pinel supported the development of the care of psychiatric patients through improving their living conditions, allowing more sunlight and time outside, and forbidding the use on restraints [18]. He also made significant contributions to the classification of different mental disorders and is thought by some to be the first person to describe schizophrenia. Psychiatrist Emil Kraepelin began to determine differences between different mental health disorders in the late 19^{th} and early 20^{th} centuries. Kraepelin is credited with defining the differences between manic-depressive disorder (which is now seen as a range of disorders including BD) and schizophrenia, with his notes still used to date [19].

At the beginning of the 20^{th} century, psychiatrists Sigmund Freud and Carl Jung developed psychoanalytical techniques used to treat symptoms of mental disorders [20]. The clinical methods of dialogue between patients suffering from mental health disorders and a psychiatrist became a central therapeutic treatment of mental disorders, with many of their methods and theories still used today in modern psychiatry [21].

World War I saw a considerable increase in mental health conditions which were commonly known as 'shell shock' (describing a type of posttraumatic stress disorder) [22]. With the increase in understanding of mental health, professions such as clinical psychology developed alongside psychiatry [23]. During World War II, new guidelines were created for categorising mental disorders, leading to the first development of Diagnostic and Statistical Manual of Mental Disorders (DSM) and later the International Classification of Diseases (ICD) adding sections on mental disorders in the sixth edition [24].

From the 1970s through to the 1990s, the development of drugs and treatments for mental disorders grew rapidly. Psychiatric medications, including lithium, came into use [25], along with antidepressants becoming some of the most globally used medications [26] and the development of cognitive behavioural therapy (CBT) [27].

The 21^{st} century led to the DSM and ICD developing criteria based classification guidelines for diagnosis of mental disorders [28]. The high comorbidity and unclear boundaries defined by the updated DSM-IV guidelines has led to redevelopments in the classification guidelines and the publication of the latest version of the DSM (DSM-5) in 2013 [29]. The major changes from the DSM-IV to DSM-5 include the introduction of further subcategories of disorders, with the diagnosis of bipolar and related disorders now including changes in mood, activity and energy levels. The requirements to be diagnosed with hypomania have been replaced from the previous need to meet both the requirements for mania and a major depressive episode to a new set of guidelines with mixed features. The diagnosis guidelines for personality disorders have not changed, although some of the criterion have been revised.

Current diagnosis of mental disorders, in addition to the longitudinal assessment of these disorders, are performed through subjective interviews and questionnaires, either self-reported or by clinicians, with doubts over the effectiveness of these methods of diagnosis [30]. The developments in technology has grown interest in finding objective physiological and behavioural measures which are able to assist in the diagnosis and monitoring of mental disorders. This chapter will first provide a background on some mental disorders which have the potential to benefit from the use of technology in the management of the conditions. Secondly, a background to some of the physiological and behavioural processes which, when measured, have the potential to aid with management of the disorders. Finally, a review of the current use of technology in psychiatry is performed and how it has been used to aid with diagnosis and monitoring of disorders.

2.1 Mental disorders

Mental disorders are disorders in which disturbances in the mood of a person is the primary feature of the disorder. Mood disorders often include periods of depressive, manic, hypomanic, and mixed episodes, with some of the most common mood disorders being major depressive disorder and BD. The mood disorders are commonly split into three separate groups: depressive disorders, bipolar disorders, and disorders based on etiology (for example substance induced mood disorder) [29]. The work presented in this thesis focuses on BD from the various types of mood disorders and attempts to determine markers of deteriorating mood and to identify changes in behaviour or physiology during the different episodes.

Personality disorders are identified by behaviour, cognition, or inner experiences which deviate from what is accepted by the culture of the individual [31]. Personality disorders develop in adolescence or early adulthood and remain constant over time, leading to high levels of stress and impairment of daily life [29]. The DSM-5 defines 12 different personality disorders, including BPD, which is the second group the work in this thesis focuses on.

The two disorders studied in this work, BD and BPD, are chosen due to the difficulties for doctors to distinguish between the two, even though they are thought to develop through very different processes. Both disorders are associated with mood instability and impulsive behaviour, with behavioural outcomes often appearing similar [32]. This work will aim to determine whether objective measures are able to capture differences between the disorders which are difficult to distinguish subjectively. The following sections will describe BD and BPD in greater detail.

2.1.1 Bipolar disorder

Formerly known as manic depressive illness, BD is characterised by recurring episodes of depression and elevated mood [33]. Approximately 1% of the global population suffers from a form of BD, with three quarters of those diagnoses with BD meeting criteria for at least one other condition (often anxiety or panic attacks) and under 50% of those diagnosed receive any form of mental health treatment [34].

The DSM-5 defines two types of BD: bipolar I disorder which an individual must have experienced at least one manic episode, and bipolar II disorder which an individual must have met the criteria for a major depressive episode and a hypomanic episode. A summary of the diagnostic criteria as defined by DSM-5 are listed in Figure 2.1 [29].

In addition to BD, less severe cycles of hypomania and lowered mood which last for at least two years and are experienced half that time are diagnosed as cyclothymia, together with BD forming the bipolar spectrum [35]. The bipolar spectrum refers to a range of conditions which include BD. Other conditions which involve depression and mood instability yet do not involve manic or hypomanic episodes are also included in the spectrum, for example some anxiety disorders, personality disorders and impulse control disorders. The bipolar spectrum groups together disorders which are thought to have similar mechanisms, however more recently there is a movement to avoid this grouping and maintain more narrow diagnostic definitions. Debate exists around whether these milder disorders should be included as a diagnosis of BD, in addition to the inclusion of unipolar depression

Diagnostic criteria for bipolar disorder (based on DSM-5)

Bipolar I disorder: have met the criteria for at least one manic episode
Bipolar II disorder: have met the criteria for at least one hypomanic episode *and* one major depressive episode

Depressive symptoms

- Depressed mood most of the day, nearly every day
- Reduced interest or pleasure in most activities
- Weight loss or reduced appetite
- Insomnia or hypersomnia
- Psychomotor agitation
- Fatigue and loss or energy
- Feelings of worthlessness or guilt
- Reduced ability to think or concentrate
- Recurrent thoughts of death

Manic symptoms

- Increased self-esteem
- Reduced need for sleep
- More talkative
- Racing thoughts
- Distractibility
- Increased goal-directed activity
- Increased involvement in activities with high risk of pain

Major depressive episode: At least five of the depressive symptoms are present during a two week period (which must include one of the first two points). Significant clinical distress in social or occupational functioning. The episode can not be attributed to a substance or medication.
Manic episode: A period of elevated or irritable mood for at least one week. At least three of manic symptoms during the week of elevated mood. The mood disturbance is severe enough to cause impairment or hospitalisation or there are psychotic features. The episode can not be attributed to a substance or medication.
Hypomanic episode: A period of elevated or irritable mood for at least four consecutive days. At least three of the manic symptoms during the week of elevated mood are present. The episode results in uncharacteristic changes in the individual. The change in mood and functioning is observable by others. The episode is not severe enough to require hospitalisation. The episode can not be attributed to a substance or medication.

Figure 2.1: DSM-5 criteria for diagnosing bipolar disorder.

with mild hypomanic symptoms [36]. This inclusion of these milder disorder would further increase the prevalence of BD, with BD already the third most prevalent mental disorder (following anxiety disorders and major depression) [37].

The key factors in the diagnosis of BD is the identification of mania or hypomania. Diagnosis is performed by a psychiatrist through interview and questionnaires, however determination of hypomania is difficult without prior knowledge of the individual, especially as elevated mood is often denied or not reported by the individuals [33]. Questionnaires and checklists have been developed in order to aid with identification of episodes of hypomania, achieving reasonable sensitivity yet low specificity [38, 39].

The acute treatment of BD attempts to revert individuals from episodes of depression or mania, whereas the long term treatment aims to prevent relapse into an acute episode through stabilising mood [33]. The primary treatment of BD is through administration of drugs, with psychotherapy also important in reducing relapse. The high prevalence of comorbid disorders adds to the difficulties in treating BD, with the usual practice to first stabilise the mood of the individual before treatment of the comorbid disorder [40].

Even between episodes of depression or mania when an individual is relatively well, known as euthymia, individuals with BD experience considerable mood instability, presenting a risk factor for a variety of negative psychiatric outcomes [41]. Monitoring of symptoms between episodes is an important step in the management of BD. The ability for automated objective monitoring of BD during euthymic periods could detect early deterioration of individuals and allow for preventative measures to take place [42].

2.1.1.1 Depressive episodes

The DSM-5 defines a major depressive episode as a continuous two week period with at least five of the criteria as defined in Figure 2.1 met. At least one of the symptoms must be either 'depressed mood most of the day, nearly every day' or 'reduced interest or pleasure in most activities'.

The average duration of a major depressive episode in BD has reported to last for 15 weeks, with 75% of individuals taking 35 weeks from the onset of the depressive episode to fully recover [43].

Episodes of depression have several increased risk factors in BD, primarily through the increased risk of suicide [44]. Depression is also associated with increased levels of insomnia [45] in addition to associations with heart disease [46], with increased cardiovascular morbidity found in individuals diagnosed with BD [47]. These factors suggest that monitoring of heart rate and measures of sleep could provide markers of deteriorating levels of depression in BD.

2.1.1.2 Manic episodes

Episodes of mania are defined by the DSM-5 as one week periods of abnormally and persistently elevated, expansive, or irritable mood and persistently increased goal-directed activity or energy [29]. Three or more of the criteria for mania, defined in Figure 2.1, must be met for an episode of mania, in addition to the mood disturbances being severe enough to cause impairment in social or occupational functioning.

The duration of manic episodes can vary greatly, with remission in 50% of participants in one study occurring by 12 weeks [48]. Full recovery can take a much longer time, with only 35% of individuals recovering to fully personal and occupational functioning two years after a manic episode [49]. The periods between episodes vary greatly with a recurrence within two years reported in 36% of participants, however 40% had no recurrence of manic episodes after five years [50].

2.1.1.3 Euthymia

Euthymia is the time when individuals are not experiencing a depressive or manic episode [51]. Even though appearing apparently well, sub-syndromal features of episodes of depression or mania and also mood instability often remain [52, 53]. Studies have found that individuals diagnosed with BD are only completely free from symptoms around 50% of the time [54], with others reporting evidence of cognitive impairment during euthymia [55].

Typically, people suffering from BD experience one or two cycles per year, with the average length of major depressive and manic episodes lasting for around 12 weeks [48]. It is most common for a period of depression to follow a manic episode, however major depressive episodes can also be triggered from external factors. Much

Diagnostic criteria for borderline personality disorder (based on DSM-5)

Borderline personality disorder: have a pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity beginning by early adulthood and is present in at least five or the criteria.

Criteria

- Frantic efforts to avoid real or imagined abandonment
- Unstable and intense interpersonal relationships, alternating between idealisation and devaluation
- Persistently unstable self-image
- Impulsivity in at least two potentially self-damaging areas (for example: spending, sex, substance abuse, reckless driving, binge eating)
- Recurrent suicidal behaviour, threats or self-mutilating behaviour
- Affective instability due to reactivity of mood
- Chronic feelings of emptiness
- Inappropriate, intense anger or problems controlling anger
- Paranoid ideation or severe dissociative symptoms

Figure 2.2: DSM-5 criteria for diagnosing borderline personality disorder.

faster cycling of episodes is also possible, with people who experience over four cycles per year diagnosed as having rapid-cycling BD [56].

2.1.2 Borderline personality disorder

BPD is a personality disorder which is characterised by extensive patterns of impulsivity and instability of mood, relationships, and identity, often associated with anger and aggression [57]. BPD affects 1 to 2% of the global population who suffer from severe psychosocial impairment. Extremely high rates of suicide exist in BPD, around 50 times higher than the general population, with up to 10% of individuals diagnosed with BPD committing suicide [58]. The diagnostic criteria, as defined by the DSM-5, are summarised in Figure 2.2.

Of the ten personality disorders listed in the DSM-5, BPD is the most prevalent [57]. Unlike BD and mood disorders in general, where individuals experience

episodes where they are acutely unwell but also periods when they are relatively well or euthymic, BPD and personality disorders reflect the normal personality of an individual. They often experience intense episodes of anger, depression or anxiety which can last for several hours to multiple days. BPD and personality disorders can be considered to have more continuous negative symptoms compared to BD who experience more temporary episodes. A common symptom of BPD is disturbance to sleep [59], thus making measures of sleep-wake cycles a potentially useful marker of symptom severity in BPD.

Treatment for BPD is reported to be difficult, with individuals often unresponsive to psychotherapy [60], which is not unexpected as psychotherapy attempts to alter the personality of a patient [61, 62]. No medication is prescribed to treat BPD, with therapy the only method of support. However, medications are prescribed if other conditions are present, such as depression or anxiety. Symptoms of BPD tend to improve over a lifelong course, with symptoms often peaking in late adolescence but with the affective symptoms tending to persist the longer [63]. The symptoms of many individuals improve over a number of years to the extent that they no longer meet the criteria to be diagnosed with BPD. However, 12% of individuals relapse and symptoms worsen [64]. Longitudinal monitoring of individuals with BPD may be able to detect or predict relapse of the disorder, in addition to tracking symptom severity during varying courses of treatment to determine their efficacy [58].

2.2 Assessment of mental health

Current assessment of symptoms of mental disorders are performed through face to face interviews with psychiatrists or mental health workers [60]. These interviews are often aided with questionnaires or checklists administered by the psychiatrist or self-reported by the patient [65, 66]. Unstructured interviews are commonly performed by clinicians in order to collect information used for diagnosing the patient. The lack of structure of these interviews means the ability of the psychiatrist performing the interview affects the quality of the information obtained and therefore determines accuracy of the diagnosis or the ability to assess the symptoms [67].

Structured interviews are considered to be more reliable through the reduced dependence on the interviewers [68]. The structured interviews follow a standard set of questions with the aim of obtaining more consistent assessments between interviewers. Semi-structured interviews have a general structure which interviews should follow, however they are allowed to deviate from the structure if required to aid with the assessment of specific symptoms or diagnosis [68].

The gold standard tool for diagnosis is considered to be the structured interview [69], however they are not always preferred due to their more formal dialogue with the patient, and are often more time consuming than the unstructured interviews [68]. The inherent subjectivity of interview based methods for diagnosis has led to a demand for objective measures of the disorders. The assessment of symptoms is another critically important aspect of mental disorders which also relies on subjective interviews to determine the severity of the disorders. The length of interviews and the requirement of highly trained psychiatrists to perform them reduce the frequency the assessments can occur, with regular assessments beneficial especially in the case of episodic disorders such as BD [70]. The self-reported questionnaires aid with the assessment of symptoms, but are also subjective in nature and are prone to recall bias, again pointing to objective markers for longitudinal monitoring in order to improve assessment methods [71].

The increase in use of smartphones and the development of wearable devices can be exploited to find objective markers to aid with the assessment of mental health. Self-reported measures are easy to collect through smartphones or websites but are subjective and require time and input from the patients filling them out [72]. Biological measures such as genetic factors may provide information useful in the diagnosis of disorders, however biological data remains difficult and obtrusive to obtain over longitudinal periods [73]. Developments in wearable devices capable of recording longitudinal physiological signals may aid with assessment of symptoms, with more detailed physiological data capable of aiding diagnosis [74]. Behavioural measures such as activity and smartphone or social media usage may also provide useful markers for symptom severity assessment [75, 76]. The current practice

and research in these areas for assessing mental health disorders, especially BD, will be discussed further in the following sections.

2.2.1 Self-reported measures

Current practice of the assessment of mental health involves the use of two methods of self-reporting, both based on questionnaires. The first method is the completion of clinically validated questionnaires which are used to score various diagnostic features of a disorder or to assess symptom severity. Examples of these questionnaires can be seen for depression [7], mania [8], anxiety [9], and quality of life [77] (all of which are described in more detail in Section 4.2.3), with another commonly used questionnaire being the patient health questionnaire (PHQ-9) used to score the nine DSM-IV criteria for depression [78]. Individuals rate various features of conditions through these questionnaires, retrospectively providing scores for the past week or two weeks. The questionnaires are typically completed electronically through text or email. Clinically defined thresholds for the questionnaires are able to provide an aide for assessment of symptoms [79].

Questionnaires which attempt to record higher frequency measures of the current mood and activity of individuals are also used to aid the assessment of symptoms of mental disorders. These questionnaires, often known as ecological momentary assessment (EMA), aim to reduce the effects of recall bias of self-reported measures and also aim to determine the processes which influence behaviour in real-world settings [80]. The correlation between the higher frequency questionnaires and the retrospective clinical questionnaires was found to depend on the time period between the entries. Increasing the frequency of self-reported measures also reduces the likelihood of missing the deterioration into an episode of mania or depression [81]. Studies have found that in research settings the compliance between daily and weekly questionnaires is similar, with 88% compliance for weekly questionnaires and 81% for daily [82].

More recently, an increase in smartphone application based questionnaires has occurred in research settings. A mobile platform, EmotionSense, for capturing mood

measures from surveys in addition to a range of behavioural signals recorded from the phone has been developed for research in psychology [83]. The MoodBuster application was designed to provide self-help treatments for depression through CBT [84]. The application requests daily mood entries and uses physiological signals to try and predict relapse into depression, with a six week trial study finding significantly reduced symptoms of depression in 24 participants.

The MONARCA study uses a smartphone application to monitor subjective mood measures in 78 BD patients [85]. In addition to the mood scores collected daily, a range of other measures are also collected. These include: the numbers of calls and texts received, duration of phone calls, screen usage and voice data during phone calls.

The StudentLife study of 48 university students collected passive data from mobile phones over a 10 week term-time period in order to quantify mental health through levels of stress, positive affect, and sleep patterns amongst others [86]. In addition to the passive data collection, EMA questionnaires were prompted on smartphones throughout the day, with variable numbers of questionnaires being asked, averaging eight per day. The results found as the term progressed levels of stress increased, whereas positive affect and quality of sleep diminished.

Daily mood scores were collected through text message using HealthySMS in a study designed to determine the relationship between daily mood scores and clinical screening questionnaires [87]. The results found the daily ratings can be used as a proxy for the clinical tool, reducing the time and effort required to fill out the longer clinical questionnaires.

A recent study of young people who had suffered from depression involved the design of a smartphone application jointly between the study participants and clinicians [88]. The designed application included a mood monitoring feature or 'well-being tracker', highlighting the need and desire of people suffering from mental disorders to regularly monitor their mood.

2.2.2 Genetic factors for mental health

The genetic makeup of an individual could be considered as the core objective markers for the majority of illnesses. Many mental disorder are well known to be genetic with increased prevalence with a family history of a disorder [89]. Both BD and BPD have been reported to have genetic contributions, however there exist considerable environmental impacts in the cause and onset of the disorders [73, 90, 58]. It remains unclear how much hereditary risk factors are linked to the diagnosis of either BD or BPD, with the relatively high prevalence of the disorders making it relatively common for more than one individual in a family to have a disorder. In addition, many individuals with BD or BPD have experienced some trauma, often in their childhood. The widespread presence of these external influences reduces the likelihood of the disorders being purely genetic. Preliminary candidate gene studies have also suggested a link between circadian genes and susceptibility to BD [91].

Although genetic studies may provide a range of tools which may be beneficial in the diagnosis of disorder through providing objective markers for the disorders, the genetic information itself is not useful for longitudinal symptom assessment. However, identifying the roles the specific genes associated with the disorders play in altering the mind or physiology of an individual may identify potential mechanisms to monitor. For example, the potential link between circadian genes and BD may indicate that monitoring of circadian rhythms through biological measures such as melatonin [92] or physiological signals such as body temperature [93] can provide more obtainable longitudinal objective measures which may be used to assess symptom severity.

2.2.3 Physiological markers of mental health

The physiology of the human body is the ability to adapt to constant changes in the environment around us [94]. Examples of how physiology may be used in the quantification of mental health can be seen through heart rate variability (HRV) which is used to quantify the balance of the nervous system, thus has potential markers of mental state [95]. In addition signals such as body temperature have a

considerable circadian component and therefore controlled by the timing systems within the brain, again providing potential measures of mental state [96]. The following studies investigate how physiology is altered in mental disorders and how changes in physiological signals may be used for diagnosis and assessment of symptoms.

2.2.3.1 Heart rate

Heart rate, or the number of heart beats per minute, varies due to the physical needs of the body. The rhythm of the heart is controlled by the sinoatrial nerve which is regulated by sympathetic and parasympathetic activity, the two main division of the autonomic nervous system (ANS) [97]. The balance of the ANS has also been shown to be linked with depression and emotions, thus making measures of heart rate potential markers of mental health [98, 99].

The central autonomic network is a vital component of the internal regulation system which is controlled by the brain [100]. It is thought to control levels of the ANS through sympathetic and parasympathetic activity and thus controlling heart rate. Studies have shown that exposure to short term and long term visual emotional stimuli can be detected through changes in HRV measures, identifying different pathways within the central autonomic network [101]. These findings suggest that measures of HRV may be used to infer the emotional state of individuals, thus potentially providing an objective tool for the monitoring of mental health.

The PSYCHE project developed a wearable 't-shirt' monitoring system for patients with BD. The wearable device recorded electrocardiogram (ECG), electrodermal activity (EDA), respiratory rate, voice, and acceleration signals [102, 103]. The main focus of the project involved using the ECG signals for the identification of mood states through quantification of HRV [95, 104]. The HRV measures developed provided measures of parasympathetic activity of individuals [105]. Sympathetic activity is not quantified due to the difficulties in separation from the parasympathetic components. During unstructured activity monitoring, detection of euthymic episodes was able to be achieved with an accuracy of 82.4% in the BD

participants [74]. Further work from the PSYCHE project aimed to forecast periods of non-euthymia in 14 BD patients, with forecasting one day in advance achieving prediction accuracy between euthymia or non-euthymia as high as 83.3% with an average accuracy of 69% [106]. The work also found that physiological information obtained from HRV in the current mood state also contained information which improves prediction of the following state [107].

Many other studies have investigated HRV in BD and BPD, however mostly in cross-sectional studies under controlled conditions, with a review and summary of previous studies conducted as part of this work [108]. Statistical comparisons of BD patients to healthy individuals are often made, for example HRV of 90 euthymic BD participants was compare to 62 healthy controls, with variability measures reduced in BD [109]. Whereas other studies have compared BD in episodes of depression or mania to control groups, including a study finding dysregulation of the ANS in 61 unmedicated BD participants with mania compared to 183 healthy controls [110]. Another study compared BD participants in depressive states with healthy controls and participants with unipolar depression, finding difference in HRV of BD participants compared to the other groups but no difference between unipolar depression and healthy individuals [111]. Differences in HRV measures have also been found in comparisons between BD participants in varying affect states [112], suggesting measures of heart rate or HRV for quantification of the ANS could aid with assessment of symptom severity in BD.

More recently complexity changes in HRV metrics been quantified with the aim of improved monitoring of mental health [113]. Non-linear complexity measures such as: detrended fluctuation analysis, entropy, fractal dimension, and recurrence quantification analysis have been applied to heart rate series and have improved the detection of individuals with depression compared to the traditional HRV measures [113].

2.2.3.2 Voice

Characteristics of voice or speech have been looked at as predictors of episodes in BD since the early 20^{th} century [114]. More recently, with the availability of voice data through mobile phone recordings, analysis into the changes in voice when depressed have been performed.

As part of the MONARCA project [115], which recorded location data, activity, voice recordings and EDA, a study into how real time calculation of voice features from phone calls can classify episodes in BD was performed [116]. The openSMILE library [117] was used to extract 6552 features from phone calls which were used to classify episodes of depression with an accuracy of 68% and episodes of mania or mixed mania with an accuracy of 74%. Fusing the voice data with other modalities in the MONARCA project improved performance of detection of episodes, with a state change detection method obtaining an accuracy of 97.4% when additional location and activity measures were included [118].

The state of the art methods used in the quantification of voice for detection of depression rely on features such as speech rate (slower in depression), cadence (reduced in depression) and prosody, with these features able to achieve an accuracy of 82.9% when predicting depression [119]. The ability to measure these features from ambulatory settings such as phone calls or normal conversation makes quantification of voice a potentially useful marker for depression with lower barriers for uptake.

2.2.3.3 Electrodermal activity

EDA is the measure of the electrical activity of the skin, often used as a measure of ANS activity [120]. A study as part of the PSYCHE project found differences in the ANS in BD participants using EDA to measure affective elicitation supporting the evidence of altered ANS during negative mood states [121].

2.2.3.4 Electroencephalogram

Electroencephalogram (EEG) records the electrical activity of the brain through non-invasive electrodes placed on the scalp. EEG is often used to measure the

activity of the brain when certain tasks are performed or when different activities are carried out.

The OPTIMI project also focuses on the physiological assessment of mental health, aiming to detect early signs of stress and depression through EEG, ECG, activity, voice, cortisol levels and electronic diaries [122]. EEG alone, with features including α-band power and β-band power were used to detect episodes of depression with an accuracy of 94.2%, suggesting EEG signals have the potential to be used for monitoring mental disorders, however the ability to obtain continuous signals of EEG in real-world situations is limited. In addition, the gold standard for EEG analysis is visual labelling from clinicians, with improvements needed in the objective assessment of signals.

2.2.3.5 Photoplethysmography

Plethysmography is the measure of change in volume. Photoplethysmography (PPG) is plethysmography measured optically and is most commonly used to measure blood volume changes using a pulse oximeter [123]. Two studies which used PPG to quantify ANS balance in 195 patients with varying mental disorder diagnoses and 113 healthy students were able to classify between the patient group and students with an accuracy of 99% [124, 125].

2.2.4 Behavioural markers of mental health

Behavioural indicators of mental health have existed for many years, however difficulties in recording and analysing data restricted their use. Behavioural markers are often described as observable behaviours of individuals and traditionally have been described and measured visually by clinicians. More recently these behavioural markers are measured automatically from signals recorded from individuals, for example activity or sleep levels from accelerometers or social activity from smartphone usage. Compared to physiological signals, which can still remain inconvenient and uncomfortable to record longitudinal data, behavioural signals can often be

obtained in a much more passive nature with smartphones being able to record a variety of different modalities of behaviour.

Measures of activity and sleep-wake cycles have been investigated as longitudinal measures of mental health since the early 90s [126], with levels of activity suggested as a potential tool for diagnosis of mental disorders [127]. However low compliance with the instrumentation needed and difficulties in continuous monitoring has not led to common use of behavioural measures in psychiatric assessments.

Within the last ten years the number of devices capable of monitoring long term activity has greatly increased, with a wide range of commercial products available [128, 129]. Arguably the most simple measure of activity is through acceleration, with numerous studies performing activity recognition form wrist-worn [130], body-worn [131], and smartphone accelerometers [132].

The following sections will give an overview of different modalities of behavioural measures in studies of mental health.

2.2.4.1 Activity

Physical activity is a common behavioural marker in the study of mental health often measured through the accelerometers in smartphones or wearable activity devices. As can be seen in Figure 2.1, many of the depressive and manic symptoms could result in a reduction or increase in activity levels respectively.

Before the widespread availability of activity recording devices, studies of activity relied on self-reported measures [133, 134, 135]. Self-reported activity is still common in modern research, with correlations found between activity levels reported daily and levels of depression and mania in 30 BD patients as part of the MONARCA study [71]. Self-reported measures provide a simple and easy to collect metric of activity for large studies, however reports suggest that self-reported levels of activity do not quantify the true levels activity [136]. Recent studies have found the differences between self-reported measures and recorded measures of activity to be minor [137].

A study of 12 BD participants in which acceleration was passively recorded through smartphones was able to achieve an average precision/recall value of 66%

in the prediction of changes in state of the BD participants [138]. In 10 BD participants, an accuracy of 70% for state prediction using movement features measured from accelerometers was reported [118]. This supported their previous findings in a preliminary study [139], in which increased movement was associated with improved mood state, and the opposite trend found when moving from manic to euthymic states with a 33% reduction in mood.

A further study of smartphone based acceleration in 9 BD participants was performed, in which correlations were found between the overall activity levels and the patients' states [140]. Additionally, stronger correlations were found when the acceleration data was divided into daily segments, such as morning or evening activity, compared to the total activity.

The acceleration of 5 BD participants was measured during phone calls, with an average accuracy of 81% when classifying episodes using time domain features and a 4% increase in classification accuracy was found when frequency domain features of acceleration were used [141].

However, other studies have found no associations between activity levels in BD and episodes of depression or mania. A 12 month study of 13 participants with BD found no relation between smartphone acceleration and clinical symptoms in a between-patient analysis [142].

2.2.4.2 Geographic location

Smartphone usage allows for the quantification of more geographic movements of participants in addition to the movements from accelerometers. Geographic movement may be determined through global positioning system (GPS) sensors in the smartphones, WiFi usage or cell tower identification in order to try and obtain information relating to travel patterns.

A three-fold increase in the time spent outside was found in euthymic BD participants compared to those in a depressive state [139], with further studies obtaining accuracy of 80% when using travel patterns to predict mood state [138, 118]. A study of 13 BD participants found a negative correlation between the

distance travelled and manic symptoms in between-patient analysis, with within-patient analysis showing similar results in addition to correlations with depressive symptoms [143].

Further studies found significant correlations between the number of cell tower IDs per day and depression scores, with fewer cell towers visited, thus less movement, being associated with increased depression [71, 144]. A significant positive correlation was found between the location clusters, or the number of locations visited, and self-reported energy scores in BD [145]. A study of 22 BD participants was able to classify depressive and non-depressive episodes with an accuracy of 85% using geographic movements of the participants [146], with further analysis of training on groups of similar participants improving the detection of depressive episodes [147].

2.2.4.3 Social activity

Social interaction has been used in studies of mental health through measuring the numbers of incoming and outgoing calls and text messages, with reduced social interaction reported in depression and increased interaction in mania [118].

During mild depression, the length and the number of phone calls was found to be increased compared to severe depression and euthymic states [139]. Both the number and duration of phone calls were also found to be positively correlated with levels of mania. Positive correlations were also found between the duration of phone calls and the level of depression [148]. Whereas no correlations were found between levels of depression and the number of incoming and outgoing text messages [71].

Other studies have found differing results, with negative associations between the number of text messages sent and the level of depression [143]. No correlations were found between call duration and either depressive or manic levels, and positive correlations were found between the number of outgoing calls and levels of mania [143].

In addition to calls and texts, application usage and screen time may also be a predictor of mental state. A study of 18 BD participants found negative correlations

with self-reported mood level and the time the phone screen is on and usage of social and entertainment applications [149].

The contradicting results reported in the current literature indicate further studies are required to determine the true links between social activity and depression in BD.

2.2.4.4 Sleep

Sleep disturbances have long been reported in psychiatric disorders [150]. The most common methods for determining sleep quality were through questionnaires and self-reported sleep and wake times [151, 152]. More recently, automated detection of sleep has been performed from activity data with reliable detection of sleep onset and offset achieved in real-world settings [153, 154].

Quality of sleep can be seen in the criteria for diagnosing both depression and mania, as can be seen in Figure 2.1. Sleep has widely been identified as a crucial factor in determining the deterioration of patients with unipolar depression and BD into depressive episodes [155]. The StudentLife study combined measures of activity, phone usage, light and sound in order to quantify sleep timings [86]. They found significant negative correlations between the duration of sleep and both levels of depression and levels of stress.

2.2.4.5 Circadian regularity

The disruption of biological, physical and social rhythms have been identified as a feature of depression for many years, with the disruption to social activities and daily tasks affecting the setting of the daily clock [156]. Studies of biological rhythms in depressed participants including: body temperature, cortisol, and melatonin have shown clear abnormalities in the rhythms compared to healthy controls, however when returning to healthy states the rhythms also revert to normal [157].

Although the causal direction between circadian rhythms and depression is not clear, maintaining regular circadian rhythms has been considered as both a prevention for depression and a therapy for reverting back to a healthy state [158, 159]. Strong associations between circadian and sleep regularity exist suggesting

improvements in sleep may result in improved circadian rhythms and therefore impact depression, however the causality may have varying directions [160]. Similarly, reports have indicated that regular social interaction, which has been shown to be a marker of mental health, may improve regularity of activity and also sleep [161].

The highly interrelated nature of social behaviour, sleep and physiology makes determining the causality between these markers and mental health difficult. The common pattern of increased regularity being linked to healthy states suggests circadian rhythms as an ideal marker for monitoring mental state as they often incorporate information from a variety of other factors.

A more detailed review on how circadian rhythms have been studied in BD and BPD can be found in Sections 2.3.2 and 2.3.3.

2.2.4.6 Aggregated data

Many studies aggregate various modalities in order to predict or classify symptoms of mental health, often improving upon the results obtained from single modality analysis.

The combination of social interaction measures, physical activity measures and geographic location in a study of 10 BD participants was able to classify episodes with an accuracy of 76% and was able to to achieve a precision and recall over 97% in state change detection [118]. The combination of smartphone sensors including light, acceleration and microphone signals in addition to patterns of communication were able to predict social rhythm metric (SRM) scores, a measure of lifestyle regularity, with an accuracy of 76% [145]. The addition of audio features from phone calls only slightly improved the results of emotional state classification compared to acceleration features alone [141]. The combination of voice features with social interaction and geographic location features resulted in an increase in sensitivity, specificity and accuracy of the classification of depressive states [116].

2.3 Sleep and circadian rhythms in mental health

Throughout the 1970s and 1980s some of the first studies highlighted the links between circadian rhythms, sleep disruption and mental health [162, 163, 164]. The links between sleep, circadian rhythms and the frequency of episodes in BD have been suggested [165], with many recent studies focusing on quantifying circadian rhythmicity in BD. Circadian rhythms in BPD is not as well studied, although circadian disruption has also been suggested [59].

The following sections will give a background to circadian rhythms and will give a detailed review of the literature involving circadian rhythms in both BD and BPD.

2.3.1 Background to circadian rhythms

All organisms require biological timing due to the constant need to adapt to the environment around them. Cycles in physiology or behaviour can vary greatly due to the required function, from variations over the course of seconds for the cardiac pace-making cells, up to variations in months for seasonal changes [166]. Circadian rhythms are related to the variations which take place over 24 hour periods and it is believed these rhythms evolved as a response to the light-dark cycle. The environmental cues that set the rhythms each day are known as zeitgebers, with the most important zeitgeber being light. Other zeitgebers exist, some of which include: temperature, eating and drinking, exercise, social interaction and medication [167].

The region of the brain which is believed to control the timing of the biological rhythms in humans is known as the suprachiasmatic nucleus (SCN), which is located in the hyopthalamus directly above the optic chiasm [168]. Photoreceptors in the retina, known as melanopsin ganglia, are light detecting cells which do not send information to the visual parts of the brain, instead sending the information to the SCN. This information of light through the SCN allows the entrainment of the circadian rhythms [169]. Entrainment is the synchronisation of the circadian rhythms to an external factor, such as the light-dark cycle [170]. Even without the external stimuli of light, the SCN is still able to maintain a regular rhythm. This is known as ‘free-running’ where circadian rhythms of approximately 24 hours

persist, in humans the average period of a free-running rhythm is thought to be slightly longer than 24 hours [171].

The SCN controls timings of circadian rhythms through the modulation of body temperature and controlling the production of hormones such as melatonin, which controls wakefulness, and cortisol, to increase blood sugar levels and aid metabolism [172]. The timing system can be seen as a genetic network through a series of negative feedback loops which regulate the transcription of genes. Some of the genes which are involved in the SCN timing are the circadian locomotor output cycles kaput (CLOCK), the period (PER), and timeless (TIM) genes [173, 174, 175].

Chronobiology, the study of circadian rhythms, has grown considerably since what is considered the first discovery in the 18^{th} century by Jacques d'Ortous de Mairan, who reported daily leaf movements of the mimosa which continued to show 24 hour cycles even in the absence of light [176]. Much more recently chronobiology has seen a rapid expansion, with research in genetic, endocrinology, psychology, amongst others and with the 2017 Nobel Prize in Medicine being awarded to Jeffrey C. Hall, Michael Rosbash and Michael W. Young for their discoveries of molecular mechanisms controlling the circadian rhythm.

2.3.2 A review of sleep and circadian rhythms in bipolar disorder

A review of the existing literature is given in the following sections. Studies involving chronotype, the preference of morningness or eveningness of individuals [177], and circadian rhythmicity, the stability or variations in circadian rhythms will be reviewed in BD and in BPD [178].

2.3.2.1 Questionnaire studies

By far the most common method of studying chronotype or circadian rhythms in BD is through the use of questionnaires. Ashman et. al. [179] used the SRM questionnaire in 9 BD participants with varying mood status and 9 healthy controls, finding a phase delay in morning activities in BD compared to controls and a reduction in activity levels. They also found a significant phase delay in depressed

BD patients compared to hypomanic and euthymic patients. Shen et. al. [180] also used the SRM questionnaire to study 206 BD patients and 208 controls finding that activity levels in the BD patients were significantly reduced compared to the controls. The lack of social rhythm regularity was also found to reduce the time to the first onset of major depressive, hypomanic and manic episodes.

Mansour et. al. [181] used the composite scale of morningness (CSM) questionnaire in a study of 75 BD patients, 81 schizophrenia patients and 349 controls, finding bimodally distributed CSM scores in BD. The CSM scores were lower in BD patients compared to the other two groups, with rapid-cycling BD showing the lowest CSM scores. A study by Ahn et. al. [182] also used the CSM questionnaire to study 92 euthymic BD patients, 113 schizophrenia patients and 95 controls. The results again showed lower CSM scores for BD patients in addition to BD patients having a greater preference for eveningness and later sleep times. Wood et. al. [183] studied 190 BD patients and 128 controls using the CSM questionnaire finding similar results to the previous studies. Lower CSM scores were found in BD which were stable over a two year period, with BD patients tending to prefer evening activities. No differences were found between BD-I and BD-II patients. They also found that individuals who had higher depressive mood scores were more likely to be evening types. Chung et. al. [184] used the CSM questionnaire with 106 BD-I, 43 BD-II and 108 major depressive disorder patients finding no difference in the CSM scores between the three subject groups. However, they found the BD-I patients had higher evening tiredness compared to BD-II patients.

Soreca et. al. [185] combined the CSM questionnaire with the Pittsburgh sleep quality index (PSQI) in a study of 29 euthymic BD patients and the effects of obesity. They found evening chronotypes were associated with significantly higher body fat, suggesting that chronotype could be a proxy for the unknown causes of the high obesity rates in BD. PSQI was also used by Giglio et. al. [186] in the study of 81 euthymic BD patients and 79 controls in addition to an interview about biological rhythms. They found increased eveningness in the BD patients compared to controls and also increased sleep latency (the time from wakefulness to falling

asleep) in the BD patients. Saunders et. al. [187] combined the PSQI with the Epworth sleepiness scale (ESS) and the Munich chronotype questionnaire (MCTQ) in a study of 119 euthymic BD patients and 136 controls. They found no difference in the chronotype of the two groups, however the BD patients had reduced sleep quality as determined by the PSQI through measures of: sleep latency, subjective quality, sleep disturbance, sleep medication and daytime dysfunction.

Baek et. al. [188] used the sleep practices and attitudes questionnaire (SPAQ) and the sleep timing questionnaire (STQ) in combination with the CSM questionnaire to measure sleep and chronotype in 200 euthymic BD patients and 270 controls. BD patients had lower CSM scores compared to the controls and higher seasonality scores. In addition, they found that BD-II patients had lower CSM scores than BD-I patients, with all BD patients having increased evening preference.

The circadian type inventory (CTI) was combined with the CSM in a study on 140 BD patients and 156 controls by Boudebesse et. al. [189]. They also found BD patients had reduced activity levels and a preference for eveningness compared to the controls. Seleem et. al. [190] used the CSM with the STQ to study sleep in 257 BD patients, 105 psychopathology patients and 55 controls over a mean of four years. BD patients showed increased sleep onset latency, wakening after sleep onset and evening preference compared to both other groups. BD patients also showed more instability in sleep and wake times, however this was dependent on mood state.

Brambilla et. al. [191] used the morningness-eveningness questionnaire (MEQ), the SPAQ and the medical outcomes study (MOS) sleep scale in 67 BD patients and 46 major depressive disorder patients. They found sleep disturbances were more associated with major depressive disorder than BD, with morningness types having less disturbed sleep in general. A family history of mood disorders was also associated with increased seasonal fluctuations in mood.

The biological rhythm interview of assessment in neuropsychiatry (BRIAN) was used by Rosa et. al. [192] in a study of 107 euthymic BD patients and 100 controls. It was found that there is increased circadian disruption in BD compared to the controls through both activity and sleep/social measures. Significant correlations

were also found between the rhythms and depressive symptoms suggesting a link between deterioration of BD and circadian rhythms. Duarte Faria et. al. [193] used BRIAN to assess rhythms as the output of a randomised clinical trial. 45 BD patients were split into two groups, one receiving a combined intervention of psycho-education and medication with the other group receiving the standard intervention of medication alone. The depressive symptoms of both groups improved, however there was no change in manic symptoms. The psycho-education showed no improvement in the rhythms of the patients, with only the standard intervention group improving in sleep, activity, social rhythms and total score of BRIAN. Duarte Faria et. al. [194] assessed 49 BD patients, 74 major depressive disorder patients and 94 controls using BRIAN. Significantly increased disruption of rhythms could be seen in the BD patients compared to the other two groups. No differences in rhythms were found in the different mood states of BD however for major depressive disorder patients rhythms were found to be more variable in depression compared to healthy states.

Pinho et. al. [195] examined severity of depression and biological rhythms through the BRIAN assessment on 260 BD patients and 191 controls. They found that the depressed patients had the greatest disturbances to their rhythms, followed by subsyndromal patients, euthymic patients and then the controls. They also found biological rhythm assessment to be an independent predictor of functioning. A study by Cudney et. al. [196] combined BRIAN with the PSQI questionnaire in 80 BD patients with euthymia or depression. They found that quality of life, measured through a questionnaire, was significantly associated with biological rhythm disturbances, independent of sleep disturbance, medication or severity of depression.

Kim et. al. [197] used the morningness-eveningness scale for children (MESC) in a group of 30 BD teenagers and 45 controls, with the BD patients having greater preference for eveningness compared to the controls. This result confirms the findings in adult studies.

Clinical interviews and sleep logs were used by Takaesu et. al. [198] in 104 BD patients and 104 patients with major depressive disorder were used to determine

circadian regularity. Significantly more circadian sleep/wake disorders were found in BD patients compared to the major depressive disorder patients.

2.3.2.2 Melatonin and cortisol studies

Studies involving the measurement of melatonin and cortisol are often used to study circadian rhythmicity, as the level of both melatonin and cortisol are known to be controlled by the SCN. Nurnberger et. al. [13] studied the effects of light therapy on the levels of melatonin in BD patients, unipolar patients and controls. They found significantly lower levels of melatonin in the BD patients when light was administered during night, also finding the peak time for melatonin during a normal dark night was later in BD patients. Novakova et. al. [199] also studied melatonin in 60 manic BD patients, 22 depressed BD patients and 19 controls. Elevated levels of melatonin were found in mania during daytime which was not seen in the other groups.

Van der Werf-Eldering et. al. [200] measured cortisol levels in a cohort of 65 BD patients to assess the links with cognitive function. They found associations between cognitive impairment and depressive symptoms, however there was no association between the cortisol measures and cognitive functioning or depressive symptoms. Cortisol levels were also studied by Girshkin et. al. [201] in 56 BD patients, 56 schizophrenia patients and 59 controls. No differences were found between the waking cortisol levels in BD patients and controls, although the levels in BD patients were higher than in schizophrenia. They also found that lower levels of waking cortisol in BD was associated with longer duration of illness.

2.3.2.3 Actigraphy studies

Actigraphy can provide information about the chronotype of an individual through levels of activity during different periods of the day, in addition to information about sleep or rest periods used in the quantification of circadian rhythms. As the gold standard for quantification of sleep comes from labelling of EEG signals to determine the sleep stages, studies which use actigraphy to measure sleep can not be interpreted as true sleep timings. The activity is able to determine periods of rest and

in some cases the orientation of individuals, therefore the majority of sleep measures presented in the literature should be interpreted as measures of rest or lying down.

Benedetti et. al. [202] monitored 48 hours of activity through a device worn on the non-dominant wrist which counted the number of zero-crossings of acceleration in one minute epochs. Sleep onset, sleep time, time asleep during the night, time awake during the night and sleep offset were calculated from the actigraphy data. The middle 24 hour period was selected and data averaged into 30 minute windows for analysis of variance (ANOVA). They found patients treated with lithium had increased activity levels in the evening and had later wake times.

Salvatore et. al. [203] monitored activity for 72 hours in 36 manic or mixed state BD patients and 32 controls. Activity was monitored using wristwatches worn on the non-dominant hand, recording zero crossings in 30 second epochs over three days. Analysis of circadian rhythms was performed using the cosinor method of fitting sinusoids to quantify the average, amplitude and acrophase. Sleep was also measured from self-reported markers. The recovered BD patients had advanced acrophase compared to the controls, increased nocturnal sleep and lower average daily activity, with all results independent of mania ratings, depression ratings and medication.

One week of activity was recorded in 42 BD patients by Gonzalez et. al. [204] through wearing a wrist worn device on the non-dominant wrist recording activity in 60 second epochs. Circadian rhythmicity was calculated through cross-correlation and the cosinor method, with correlation between the circadian measures and manic and depressive symptoms assessed. They found significant correlations between circadian rhythmicity and manic symptoms in BD, however no relationship was found between rhythmicity and depressive symptoms.

Krane-Gartiser et. al. [205] monitored 24 hour activity patterns of 18 hospitalised BD patients with mania, 12 hospitalised BD patients with depression and 28 controls. Wrist worn accelerometers were worn for 24 hours recording activity at one minute intervals. 64 minute periods were selected for analysis in the morning and evening with a range of measures calculated from the signals, including: mean, standard deviation, root mean square of successive differences, autocorrelation, Fourier

analysis measures, sample entropy and symbolic dynamic analysis. Patients with depression were found to have lower activity levels than the manic patients and the controls, the were also found to have increased variability in activity. Activity levels in mania and depression were lower in the morning compared to the controls, but no differences were found in the evenings.

McKenna et. al. [206] collected seven days of activity in one minute epochs from a left wrist accelerometer from 14 euthymic BD patients and 14 controls. The sigmoidally transformed cosinor method was used to quantify circadian rhythms. They found sleep efficiency, rhythm robustness, average of the cosine, and amplitude to width ratio of the cosine were abnormal in the BD patients, in addition to all sleep and circadian variables being associated with the levels of abnormality in functional magnetic resonance imaging (fMRI).

Faedda et. al. [207] studied the activity of children, which included 48 BD patients, 44 patients with attention deficit hyperactivity disorder and 42 controls who were monitored for three to five days through belt worn accelerometers which collect zero crossings in one minute epochs. Twenty-eight measures were calculated, including: nocturnal activity, sleep efficiency and circadian regulation. The results found BD patients to have reduced circadian amplitude and patients with mania or hypomania were hyperactive.

Grierson et. al. [208] studied 30 BD patients and 33 patients with major depressive disorder using 5 to 14 days of actigraphy. Sleep measures were calculated from the activity recordings of a wrist worn device and the cosinor method was used to determine the circadian profiles of the activity. The results found that patients who have suffered from mood disorders the longest had significantly reduced rhythmicity and lower activity levels. There was a delay in the acrophase in patients with mania, and more severe mood symptoms in BD were associated with reduced rhythmicity which was not seen in major depressive disorder.

2.3.2.4 Combined modality studies

A combination of seven days of activity and the SRM questionnaire were used by Jones et. al. [209] in 19 euthymic BD patients and 19 controls. Participants wore an accelerometer on their non-dominant wrist for seven days, collecting data in 15 second epochs. The most active ten hour periods and least active five hour periods were used to determine circadian metrics. The BD patients had more variable circadian rhythms than the controls and also had higher intradaily instability.

A combined heart rate and movement sensor was used by Faurholt-Jepsen et. al. [210] to study 18 BD patients in euthymia or depression, 20 major depressive disorder patients and 31 controls. Energy expenditure is calculated from activity and heart rate recordings with the 24 hour data split into four 6 hour periods starting at midnight. Statistical comparisons of the data in each quarter found BD patients to have higher sleeping heart rate than controls, with no significant differences found between BD patients and controls in fitness, activity and energy measures.

Rock et. al. [211] recorded 9 to 16 days of actigraphy combined with light levels and the MEQ in 19 euthymic BD patients and 21 controls. One minute epochs were used to measure activity from the non-dominant wrist. Built in device software was used to determine: sleep onset, wake time, total sleep, sleep onset latency and sleep efficiency. BD patients were found to have increased movement during sleep compared to the controls. The BD patients also had lower circadian amplitude and high activity levels during the least active sleep phase from 2am to 7am.

Bradley et. al. [212] recorded respiratory sleep analysis, three weeks of actigraphy, melatonin levels and the MEQ in 46 BD patients and 42 controls. The wrist worn accelerometer recorded acceleration at 30Hz for 21 days which was analysed to predict sleep measures, including: sleep onset, wake time, sleep efficiency, time in bed and sleep duration. The least active five hours and most active ten hours were also used for circadian analysis. The results found 50% of the BD patients to have abnormal sleep, with those with abnormal sleep having significantly lower melatonin levels compared to controls and BD patients with normal sleep.

From the multitude of studies investigating circadian rhythms and sleep in BD, it can be concluded that individuals with BD suffer from irregular sleep and wake times in addition to disrupted sleep. They also report suffering from circadian rhythm disruption, often through questionnaires, with more work required to confirm this with objective measures. Further work is required to determine the causality between the disruptions of sleep or rhythms and the severity of illness in BD.

2.3.3 A review of sleep and circadian rhythms in borderline personality disorder

There are far fewer studies on circadian rhythms in BPD compared to BD, with the majority of studies focusing on sleep.

Sansone et. al. [213] surveyed 76 individuals for BPD and also used the PSQI questionnaire. Statistically significant correlations were found between the symptoms of BPD and the PSQI questionnaire results, suggesting BPD symptomatology is indicative of poorer sleep quality. Sleep was assessed in a 16 year follow up in 118 BPD patients who recovered from symptoms and 105 BPD patients who did not recover by Plante et. al. [214]. Sleep was assessed using the PSQI questionnaire with the results finding the patients who did not recover had significantly worse sleep quality in addition to having longer sleep onset latency, increased use of sleep medication and increased experience of daytime dysfunction.

Selby [215] analysed sleep problems in $5,692$ individuals from the National Comorbidity Survey which assesses personality disorders and sleep. The results showed significant associations between BPD and all three chronic sleep problems which were assessed. These sleep problems were also linked to increased social, emotional, cognitive and self-care impairment. Oltmanns et. al. [216] analysed a sample of 633 individuals who completed a personality disorder questionnaire and the insomnia severity index (ISI) questionnaire. Symptoms from all personality disorders were correlated with insomnia symptoms, however after controlling for major depression, body mass index, race and gender, only BPD symptoms remained significantly associated with insomnia symptoms.

Huynh et. al. [217] recorded actigraphy in 18 BPD patients, 6 BD patients and 20 controls. A wrist watch was worn on the non-dominant hand which collected activity measures in one minute intervals and automated feature calculation was applied to determine: time in bed, time awake in bed, sleep onset latency, total sleep time, sleep efficiency, final awakening, sleep time and awake time. During weekdays, BPD patients spent significantly more time in bed compared to both BD patients and controls. On weekends, both BPD and BD spent more time in bed compared to controls. Wake times were over one hour later in BPD patients compared to controls and night to night variability in measures was also greater.

Activity was also measured by Bromundt et. al. [218] in 14 female BPD patients and 10 controls in their response to light therapy. Activity was measured with a wrist watch for approximately 42 days, with the same automated sleep features calculated as Huynh. Circadian measures were also calculated from the activity signal from the most active ten hour and least active five hour periods. Simultaneous skin temperature and melatonin measures were also recorded. The PSQI, MEQ and SPAQ questionnaires were administered during the study. They found that the BPD patients had significantly worse subjective sleep quality compared to controls, with the sleep patterns in BPD varying from regular to extremely irregular. Circadian rhythms of melatonin and skin temperature were in synchronisation in all controls and the majority of BPD patients. The light therapy phase advanced the activity, shortened sleep, decreased movement and increase skin temperature during sleep (an indicator of relaxation).

Lieb et. al. [219] studied diurnal cortisol levels in 23 unmedicated females with BPD and 24 controls. Cortisol levels were collected every two hours for 14 hours on three consecutive days in ambulatory conditions, in addition to cortisol levels being collected after awakening every 15 minutes for one hour. BPD patients had significantly higher levels of cortisol both at awakening and throughout the day. Cortisol levels were also studied by Wingenfeld et. al. [220] who measured cortisol levels at night (7pm to 7am) in 21 female BPD patients and 24 female controls.

They found a positive association between cortisol levels and the level of depression suggesting cortisol levels change with symptom severity in BPD.

Many other studies have been conducted on sleep in BPD through more detailed polysomnography analysis [221]. With the consensus of results reporting sleep disturbances in BPD patients similar to those seen in depression even without comorbid depression in the BPD patients. There is growing evidence that sleep disturbances worsen emotional dysregulation and increase suicidal tendencies, so monitoring and improving sleep in BPD is vital.

2.3.4 Summary

The current work on circadian rhythms in BD indicate a phase delay in BD rhythms, with the evening chronotype being a risk factor for BD. There is also evidence of disruption to the circadian rhythms in BD through measures of social rhythms, sleep/wake cycles and activity with these disruptions greater in depression compared to euthymia and mania [178, 222]. There is evidence that circadian rhythms may be used to determine the onset of BD and also used to monitor relapse of mood [223]. Although research on circadian rhythms in BPD is not as prevalent, the evidence suggests that circadian disruption is a symptom of BPD much like BD [59]. Therefore the further study of rhythms in both disorders is required, with circadian quantification having the potential to be used as objective markers for symptom severity in both cases.

The majority of studies rely on self-reported measures of circadian rhythm status and clear improvements are needed through development of methods to objectively quantify circadian rhythms. Novel signal processing techniques should be able to quantify different aspects of rhythms such as the timings or phase and the amplitudes of the rhythms in addition to their variability.

More work is needed to understand how circadian rhythms are altered when patients enter periods of depression or mania. Determining how circadian rhythms are altered during differing mood states could have significant clinical impact through providing objective markers for deteriorating mood. In addition, circadian

rhythms may provide a tool to measure the effectiveness of medications which aim to improve mood or mental state.

Future studies should be longitudinal in order to capture transitions to states of depression or mania in BD patients. This will allow for the quantification of circadian measures across these transitions and will provide details into the directions of causality. The devices used to obtain signals for circadian quantification should be unobtrusive and allow for data to be recorded at home in an ambulatory setting. This will reduce the barriers to uptake if the methods are to be used in clinical practice. Validation of circadian measures is also needed, this could be through smaller studies which collect simultaneous biological samples such as cortisol or melatonin to confirm the circadian measures match those from the biological samples. Validation of sleep measures are also required to determine whether actigraphy derived sleep times are true sleep timings or, more likely, recording timings of rest periods.

3 Methods

The algorithms and methods described in this chapter form the basis to the analysis performed in this thesis. This chapter aims to provide a background to hidden Markov models (HMMs), principal component analysis, regression and regularisation, and some traditional statistical tests which are implemented and developed in Chapters 5, 6 and 7.

3.1 Feature extraction

Raw physiological and behavioural signals contain a multitude of information which can be utilised to learn and help interpret human activity. Signal processing methods which can be applied to these time series are able to emphasise or detect regions and patterns of interest in the signals which are commonly known as features or biomarkers. Feature extraction aims to reduce the dimensionality of the data through finding a reduced set of features which describe the original data.

In addition to extracting features from raw time-series data, transforms may be applied to the data, for example the Fourier transform can be applied to determine frequency components of the signal from which features can be extracted.

The set of extracted features are often used for classification or regression models. Large numbers of features can have large computational requirements when

training the models and can also overfit to the training data. Feature selection algorithms are used to determine the most relevant features for a classification or prediction problem.

3.2 Regression analysis

The aim of regression analysis is to use a set of inputs to predict one or more continuous outcome variables. From a data set x_n consisting of N observations and y_m outcome values, the goal of regression is to predict the value of y from a new value of x. A simple approach would be to determine some function $f(\mathbf{x})$ which outputs a prediction of y for new values of x, however metrics are required to evaluate the performance of these predictions.

3.2.1 Model evaluation

The most common method of evaluating the predictions of a regression model is through the mean square error (MSE). The MSE calculates the mean of the squared error terms, $\mathbf{e}$, which is the difference between the predicted outcome and true outcome.

$$MSE = \frac{1}{N}\sum_{i=1}^{N} e_i^2 \tag{3.1}$$

The square root of the MSE is often found to quantify the root mean square error (RMSE).

A similar metric used to quantify prediction error is the mean absolute error (MAE) which also determine the average magnitude of error, however the MAE uses the absolute values of the errors.

$$MAE = \frac{1}{N}\sum_{i=1}^{N} |e_i| \tag{3.2}$$

There are many similarities between the MSE and MAE, as both are measures of average model prediction error. However, since the MSE squares the error terms before being averaged, a larger weighting is given to large errors compared to

the MAE. For this reason, the MSE is often preferred when large errors should be heavily penalised.

In addition to measuring the average error of the predictions, correlation may be used to measure the performance of predictions. The Pearson correlation coefficient is calculated as

$$R = \frac{\sum_{i=1}^{N}(p_i - \mu_p)(y_i - \mu_y)}{\sqrt{\sum_{i=1}^{N}(p_i - \mu_p)^2}\sqrt{\sum_{i=1}^{N}(y_i - \mu_y)^2}} \tag{3.3}$$

where $\mathbf{p}$ are the predicted outcomes and μ_p is the mean of the predicted outcomes. μ_y is the mean of the true outcomes.

The correlation coefficient has benefits to being used as a metric for prediction evaluation, primarily through easy interpretation of correlation coefficients which fall in the scale of -1 to 1. However, the scale of the predictions and true values can be hugely different, creating large errors, whilst still providing a very high correlation coefficient. Pearson correlation assumes linearity, there are no outliers in the data, and the data is normally distributed.

3.2.2 Linear regression

The most simple and commonly used method for predictive modelling is linear regression which assigns coefficients to each of the inputs or feature variables in order to predict the outcomes. The predicted outcome p is calculated as

$$p = \beta_1 x_1 + \beta_2 x_2 + ... + \beta_M x_M \tag{3.4}$$

where $\boldsymbol{\beta}$ represents the coefficients of the linear regression for the M different features. The coefficients assigned to the features determine their importance in the prediction of the outcomes through assigning them a weighting.

In order to determine the values of the coefficients which provide the best prediction of the outcomes, it is easiest to view this through linear regression using only one feature.

Figure 3.1 shows a line of linear regression in red which uses one feature ($\mathbf{x}$) to predict the true outcomes ($\mathbf{y}$). In order to find the best coefficient for the

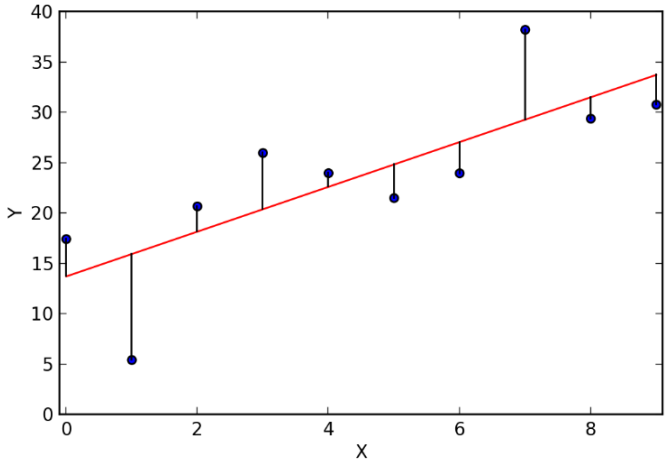


Figure 3.1: Residual errors between the true outcomes (y) and a linear regression from a single feature (x) shown as the red line.

feature (the gradient of the line) the error must be quantified and minimised. The predicted outcomes can now be defined as

$$p = \beta_1 x + \beta_0 \tag{3.5}$$

where β_0 is the offset (or y-intercept). The total error can be quantified from the sum absolute errors or sum of square errors or residual sum of squares (RSS). The sum of square errors is most commonly used due to the penalisation of large errors, therefore the sum of square errors can be written as

$$RSS = \sum_{i=1}^{N} (p_i - y_i)^2 = \sum_{i=1}^{N} (\beta_1 x_i + \beta_0 - y_i)^2. \tag{3.6}$$

Therefore minimising the function in Equation (3.6), known as the cost function, will find an optimal value of the coefficients β. This minimisation is performed using the gradient descent algorithm.

The gradient decent algorithm is an optimisation algorithm which iteratively updates parameters in order to find the local minimum of a cost function. If $F(x)$ defines a multi-variable cost function, with the current variables defined as a, after one iteration of gradient descent, the updated variable b can be defined as

$$\mathbf{b} = \mathbf{a} - \gamma \nabla F(\mathbf{a}) \tag{3.7}$$

where γ is a weighting factor, to determine the speed of the descent, and ∇, the gradient, is the direction of steepest descent. The iterations of gradient descent, as in Equation (3.7), continue until a threshold for convergence of the model parameters is met.

As the gradient descent algorithm can find the local optimum of multiple parameters which minimises the cost function, the cost function as in Equation (3.6) may be written in terms of multiple input features as opposed to a single feature. The predicted outcomes in Equation (3.6) may be replaced with Equation (3.4), with $M + 1$ parameters to optimise during gradient descent.

Confidence intervals may be calculated for the regression through the standard error in the β coefficients by calculating the error between predicted values and true values. For the example in Equation (3.5) the standard error of β_0 and β_1 are calculated as:

$$se(\beta_0) = \sqrt{\sigma^2\Big(\frac{1}{n} + \frac{\overline{x}}{std(x)}\Big)} \text{ and } se(\beta_1) = \sqrt{\frac{\sigma^2}{std(x)}} \tag{3.8}$$

where

$$\sigma^2 = \frac{\sum_{i=1}^{n}(y_i - p_i)^2}{n-2}. \tag{3.9}$$

3.2.3 Feature selection

With the development of machine learning algorithms, the numbers of features which are capable of being used for classification or regression have increased greatly. With these increases in sizes of feature sets, a number of problems arise through large numbers of irrelevant and redundant features. One problem is the increase computational requirements when there is a large number of features to be processed. Removing the redundant features reduces this computational burden. Interpretation of models becomes increasingly difficult as features are added, with increased complex interactions making it hard to determine how the models are operating. This is especially of importance in the medical field, as the clinicians often need to determine the mechanisms or symptoms of disorders in order to provide treatments.

The curse of dimensionality is also a factor which requires feature selection to improve model performance. As the numbers of features in a set increases, more observations are required to ensure there are several samples with similar combinations of features values. A typical guide is there should be at least five observations per number of features. Due to this phenomena, feature selection often increases the performance of prediction of classification algorithms through the reduction in dimensionality.

Feature selection methods also reduce overfitting of models. Overfitting occurs when a model is fit too closely to a subset of training data and does not generalise to test data. A model which is overfit to training data incorporates the noise of the training data and assumes this variation represents the structure of all data. Overfitting is often defined as a model including more adjustable parameters than are optimal.

Filter methods of feature selection are performed as a preprocessing step and are independent of the machine learning algorithms. They are based on statistical tests or correlations with the outcome values, for example Anova or Pearson's correlation.

Wrapper methods use a subset of features to train a model, with features either added or removed based on the performance of the previous iteration of the model. Common wrapper methods include forward or backward selection. Forward selection initially uses the most predictive feature and adds features at each step. Backward selection begins with all features and eliminates features at each step.

Embedded methods combine both filter and wrapper methods, with algorithms having built in feature selection methods through penalisation methods to prevent overfitting in the models. Two common methods are ridge regression and least absolute shrinkage and selection operator (LASSO) regression.

3.2.3.1 Ridge regression

For a regression with M features of length N, the RSS can be written as

$$RSS = \sum_{i=1}^{N} \left(\beta_0 + \sum_{j=1}^{M} \beta_j x_{ij}\right)^2 \tag{3.10}$$

Optimising this loss function will adjust the coefficients based on the training data. However if there is noise in the training data, the coefficients will not generalise well to future data. Regularisation attempts to shrink these coefficients towards zero in order to reduce overfitting of the data.

Ridge regression adds a shrinkage term defined by a tuning parameter λ as follows

$$\sum_{i=1}^{N}\Big(\beta_0+\sum_{j=1}^{M}\beta_j x_{ij}\Big)^2+\lambda\sum_{j=1}^{M}\beta_j^2=RSS+\lambda\sum_{j=1}^{M}\beta_j^2. \tag{3.11}$$

The tuning parameter controls how much the flexibility of the model is penalised, when $\lambda = 0$ the regularisation has no effect and when λ tends to infinity the coefficients will approach zero. Ridge regression uses L2 regularisation as the shrinkage term uses the 2-norm. Unlike standard least square regression, ridge regression requires standardisation of the features before performing ridge regression.

3.2.3.2 LASSO regression

LASSO regularisation is an alternative method to reduce overfitting in regression. The shrinkage term in the LASSO regression uses the 1-norm or L1 norm, the L1 norm penalises high coefficients more than in ridge regression, with LASSO regression defined as

$$\sum_{i=1}^{N}\Big(\beta_0+\sum_{j=1}^{M}\beta_j x_{ij}\Big)^2+\lambda\sum_{j=1}^{M}|\beta_j|=RSS+\lambda\sum_{j=1}^{M}|\beta_j|. \tag{3.12}$$

Comparing ridge and LASSO regression, it can be seen that ridge regression solves an equation where the sum of squares of coefficients is less than or equal to a value s, whereas LASSO regression is an equation where the summation of modulus of coefficients is less than or equal to s. Considering a problem with two coefficients, β_1 and β_2, ridge regression is determined by $\beta_1^2+\beta_2^2 \leq s$. Therefore the coefficients have the smallest RSS loss function for points that lie within a circle defined by $\beta_1^2+\beta_2^2 \leq s$. Similarly for LASSO, the regression is determined by $|\beta_1|+|\beta_2| \leq s$, where the coefficients have the smallest RSS loss function for points that fall within the diamond given by $|\beta_1|+|\beta_2| \leq s$. These two equations are described in Figure 3.2.

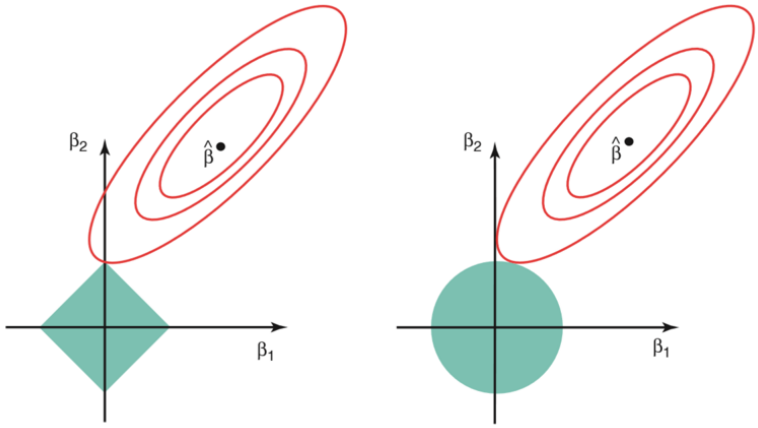


Figure 3.2: Examples of the regularisation in LASSO (left) and ridge (right) regression for a two dimensional problem. The green areas indicate the constraint functions and the red contours the RSS errors. The diagram shows how the intersection of the contours and constraint function occur on the axes for LASSO regression, but not for ridge regression. Credit: [224].

As the value of λ in Equation (3.12) increases the number of coefficients equal to zero in the regression increases. As λ becomes large enough all coefficients are set to zero excluding the intercept coefficient. As λ approaches zero, LASSO regression becomes traditional linear regression. The value of λ is often chosen through a grid search, with the value which minimises the MSE of the regression chosen for the optimal model.

The green areas in Figure 3.2 show the constraint functions for LASSO and ridge regression in addition to the RSS contours in red. Since ridge regression has a circular constraint, the intersection between the contours and constraint will rarely occur on an axis, thus the coefficients will be non-zero. Whereas for the LASSO regression, the constraint is corners on the axes, thus the contours will often intersect the constraint region at these corners, thus setting coefficients to be equal to zero.

These factors indicate a disadvantage of ridge regression as none of the coefficients will be set to zero, all features will be included in the final model. The LASSO regression forces a number of the coefficients to be zero when λ is large enough, thus results in feature selection and sparse models.

Increasing λ is beneficial in reducing variance in a prediction model through a reduction in overfitting over the model, however increasing λ too much starts

to remove important properties of the model resulting in a bias and therefore underfitting. A careful selection of λ must be made to obtain an accurate model.

3.3 Principal component analysis

Principal component analysis (PCA) is a method used to determine the underlying structure of data through finding the set of linearly uncorrelated variables known as the principal components. PCA is dependent upon eigen-decomposition of matrices as well as singular value decomposition (SVD) of rectangular matrices.

3.3.1 Eigenvalues and eigenvectors

Eigenvalues and eigenvectors are a set of numbers and vectors which describe the structure of a square matrix. Eigenvectors are used to describe the axes or directions on which matrix operations are based, with the corresponding eigenvalues used to determine the importance or weighting of the operations.

An eigenvector of the matrix $\mathbf{A}$ is defined as a vector $\mathbf{u}$ which satisfies the equation

$$\mathbf{Au} = \lambda\mathbf{u} \tag{3.13}$$

where λ is a scalar called the eigenvalue associated to the eigenvector. Traditionally, the set of eigenvectors are stored as each column of the matrix $\mathbf{U}$, with the eigenvalues stored in a diagonal matrix $\mathbf{\Lambda}$, where the diagonal elements are the eigenvalues and the remaining elements are zeros. This allows Equation (3.13) to be written as

$$\mathbf{AU} = \mathbf{\Lambda U} \text{ or } \mathbf{A} = \mathbf{U\Lambda U^{-1}} \tag{3.14}$$

This combination of eigenvalues and eigenvectors form the eigen-decomposition of the matrix $\mathbf{A}$.

3.3.1.1 Positive (semi-)definite matrices

In statistics, a positive semi-definite matrix is a matrix where the eigen-decomposition always exists. A matrix is defined as positive semi-definite if it can be obtained as the product of a matrix by its transpose, for example

$$\mathbf{A} = \mathbf{X}\mathbf{X}^{\mathbf{T}} \tag{3.15}$$

The eigenvalues of a positive semi-definite matrices are always positive or null, with the eigenvectors being pairwise orthogonal. Correlation matrices, covariance matrices and cross-correlation matrices are always positive semi-definite.

For PCA, we want to determine the factor scores of each of the components in a matrix $\mathbf{X}$ which explain as much of the variance of $\mathbf{X}$ as possible and are pairwise orthogonal. The factor score matrix can be defined as

$$\mathbf{F} = \mathbf{X}\mathbf{Q} \tag{3.16}$$

where $\mathbf{Q}$ is the matrix of coefficients. A constraint is set such that the sum of squares of the coefficients are equal to unity in order to keep the coefficients finite.

If $\mathbf{F}$ is an orthogonal matrix,

$$\mathbf{F}^{\mathbf{T}}\mathbf{F} = \mathbf{Q}^{\mathbf{T}}\mathbf{X}^{\mathbf{T}}\mathbf{X}\mathbf{Q} \tag{3.17}$$

is a diagonal matrix and if $\mathbf{Q}$ is an orthonormal matrix,

$$\mathbf{Q}^{\mathbf{T}}\mathbf{Q} = \mathbf{I}. \tag{3.18}$$

The solution can be obtained using Lagrangian multipliers, a method of finding local maxima or minima subject to a set of constraints [225]. The constraint in Equation (3.18) is multiplied with a diagonal matrix of Lagrangian multipliers $\mathbf{\Lambda}$

$$\mathbf{\Lambda} = \mathbf{Q}^{\mathbf{T}}\mathbf{Q} - \mathbf{I}. \tag{3.19}$$

The Lagrangian function can then be defined as

$$\begin{aligned}\mathcal{L} &= \text{trace}\Big(\mathbf{F^T F} - \mathbf{\Lambda}(\mathbf{Q^T Q} - \mathbf{I})\Big) \\ &= \text{trace}\Big(\mathbf{Q^T X^T X Q} - \mathbf{\Lambda}(\mathbf{Q^T Q} - \mathbf{I})\Big)\end{aligned} \tag{3.20}$$

The value of $\mathbf{Q}$ which maximise $\mathcal{L}$ is then found through the differential of Equation (3.20), giving

$$\frac{\partial \mathcal{L}}{\partial \mathbf{Q}} = 2\mathbf{X^T X Q} - 2\mathbf{Q\Lambda}. \tag{3.21}$$

Setting Equation (3.21) to zero results in $\mathbf{X^T X} = \mathbf{Q\Lambda Q^T}$ thus indicating that PCA is an eigen-decomposition problem. Where $\mathbf{\Lambda}$ is the matrix of eigenvalues and $\mathbf{Q}$ are the eigenvectors of the positive semi-definite matrix $\mathbf{X^T X}$. In addition, the variance of the factor scores is equal to the eigenvalues as

$$\mathbf{F^T F} = \mathbf{Q^T X^T X Q} = \mathbf{Q^T Q\Lambda Q^T Q} = \mathbf{\Lambda}. \tag{3.22}$$

3.3.2 Singular value decomposition

SVD generalises eigen-decomposition of a positive semi-definite matrix to any mxn matrix. If $\mathbf{M}$ is an mxn real or complex matrix, it can be factorised to the form

$$\mathbf{M} = \mathbf{U\Sigma V^T} \tag{3.23}$$

where

- the columns of $\mathbf{U}$ are the *left singular vectors* of $\mathbf{M}$ and $\mathbf{U}$ is the normalised eigenvectors of the matrix $\mathbf{M^T M}$
- the columns of $\mathbf{V}$ are the *right singular vectors* of $\mathbf{M}$ and $\mathbf{U}$ is the normalised eigenvectors of the matrix $\mathbf{MM^T}$
- $\mathbf{\Sigma}$ is a diagonal matrix of the *singular values*, the square roots of the eigenvalues of both $\mathbf{M^T M}$ and $\mathbf{MM^T}$

Therefore SVD can be used to solve the PCA problem, and is often used instead of PCA due to the computational speed. Further details of SVD calculations can be found in [226].

3.4 Stochastic processes

A stochastic process is defined as a system which has observations at certain times, with the observed outcome at each time being a random variable. In general, the probability of the observation at the current time depends on the observations at the previous times, with the more observations made enabling better prediction of future observations at later times.

3.4.1 Markov models

Markov chains are stochastic processes which describe a sequence of possible states. The probability of each event, or change in state, is dependent only on the previous state, therefore if $\mathbf{Q} = \{q_1, q_2, ..., q_T\}$, where $\mathbf{Q}$ is the sequence of states of length T, the joint distribution is given by,

$$P(q_1, q_2, ..., q_T) = P(q_1) \prod_{t=2}^{T} P(q_t|q_{t-1}) \tag{3.24}$$

thus,

$$P(q_t|q_1, q_2, ..., q_t - 1) = P(q_t|q_{t-1}) \tag{3.25}$$

A Markov model is defined by two parameters: the initial state distribution and the transition matrix. The initial state distribution is defined as $\pi_i = P(q_1 = S_i)$ where $\sum_{i=1}^{N} \pi_i = 1$, N is the number of states, q_t is the state at time t, and S_i is the i^{th} state. The transition matrix is defined as $a_{i,j} = P(q_{t+1} = S_j|q_t = S_i)$, which is the probability of transitioning from state S_i to state S_j. Each row of the transition matrix must sum to one, $\sum_{j=1}^{N} a_{:,j} = 1$ as the probabilities leaving each state (including self transitions) must sum to one.

In order to quantify circadian rhythms from activity using Markov chains, the states must be defined. For a two state model, the states may be defined as 'active' and 'inactive' and transitions between the two would have to be observed and calculated.

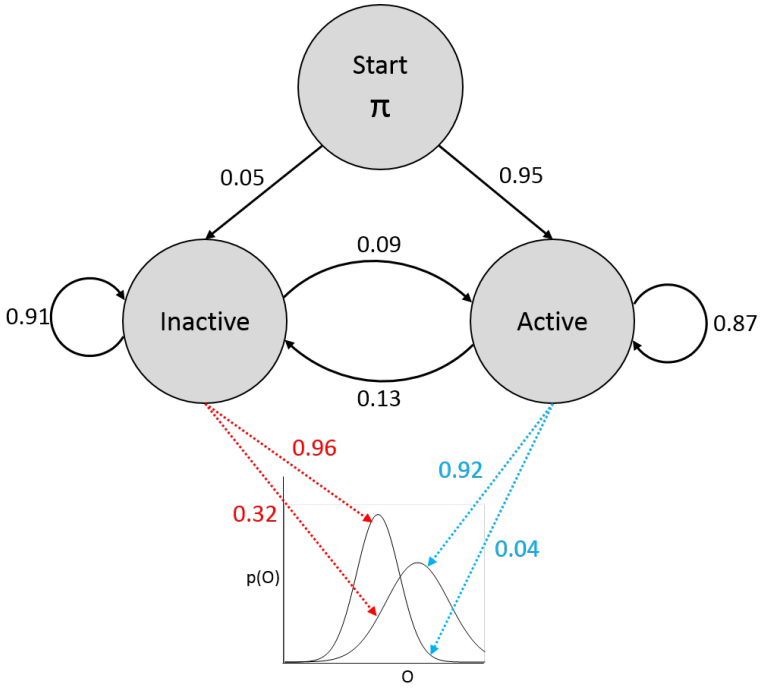


Figure 3.3: Example of a Markov model with two states, 'Inactive' and 'Active', initial state probabilities, π, and state transition probabilities, A. For a HMM, the observation probabilities , B, are also shown from their Gaussian distributions.

Figure 3.3 shows an example Markov chain for a two state, 'active' and 'inactive' model. There is a 5% chance of starting in the 'inactive' state, with a 91% probability of remaining 'inactive' (and 9% chance of transitioning to an 'active' state). Once 'active', there is an 87% chance of remaining 'active' (and 13% of transitioning to 'inactive'). Therefore the initial state distribution, $\pi = [0.05, 0.95]$ and the transition matrix, $A = \begin{bmatrix} 0.91 & 0.09 \\ 0.13 & 0.87 \end{bmatrix}$. The probability of being in the 'active' state after three time steps can be calculated as:

$$P(q_1, q_2, q_3) = A^3\pi' = \begin{bmatrix} 0.91 & 0.09 \\ 0.13 & 0.87 \end{bmatrix}^3 \begin{bmatrix} 0.05 \\ 0.95 \end{bmatrix} = \begin{bmatrix} 0.2435 \\ 0.6706 \end{bmatrix} \tag{3.26}$$

with the probability of being 'active' being 0.6706.

3.4.2 Hidden Markov models

In a Markov chain, the states must be directly visible. However, if only actigraphy data is available for quantification of circadian rhythms, the 'active' and 'inactive' states are not directly visible, but the measured accelerations are observed, a HMM

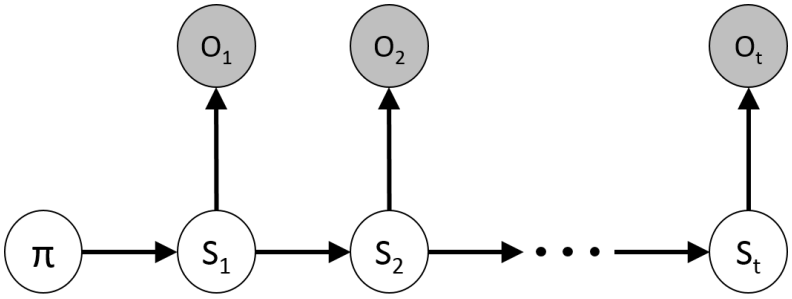


Figure 3.4: Graphical model of a HMM, with observation sequence, O, hidden state sequence, S, and initial state probabilities, π.

may be used to determine the hidden states. HMMs use a set of observations, $\mathbf{O} = \{O_1, O_2, ..., O_T\}$, at each time point, $\mathbf{t} = \{1, 2, ..., T\}$ to find the most likely sequence of hidden states, as shown in Figure 3.4. A HMM is characterised by the following parameters, with descriptions for the data used in this work:

1. N, the number of hidden states in the model. Here we use $N = 2$, for the 'active' and 'inactive' states, as two states will most closely measure the sleep/wake or rest/activity cycle. Individual states are denoted as $S = \{S_1, S_2, ..., S_N\}$, and the state at time t as q_t.

2. $\mathbf{A} = \{a_{ij}\}$, the state transitions probabilities, where

$$a_{ij} = P(q_{t+1} = S_j | q_t = S_i), \qquad 1 \leq i, j \leq N. \tag{3.27}$$

   A describes the probability of transitioning from an 'active' state to an 'inactive' state or the probability of remaining in an 'active' state and similarly for transitioning from 'inactive' states.

3. **B**, the observation probability distribution in state S_j, $B_{j,t} = \{b_j(O_t)\}$ where $b_j(O_t) = P(O_t | q_t = S_j)$. Here we assume a multivariate Gaussian distribution, as in Figure 3.3, but other distributions are permitted. The observation at time t, O_t, is an acceleration and $b_j(O_t)$ is the probability of seeing this observation in the 'active' or 'inactive' state.

$$b_j(O) = \mathcal{N}(O, \mu_j, cov_j), \qquad 1 \leq j \leq N \tag{3.28}$$

where μ_j is the vector of means and cov_j is the covariance matrix.

4. $\boldsymbol{\pi}$, the initial state probabilities where $\pi_i = P(q_1 = S_i)$ and $\sum_{i=1}^{N} \pi_i = 1$. The probability of initially being in the 'active' or 'inactive' state.

5. $\boldsymbol{\theta}$ is the parameter vector which fully specifies the HMM, $\boldsymbol{\theta} = \{\boldsymbol{\pi}, \mathbf{A}, \mathbf{B}\}$.

There remain three main problems to solve for HMMs to be used in applications with real-world data. These are:

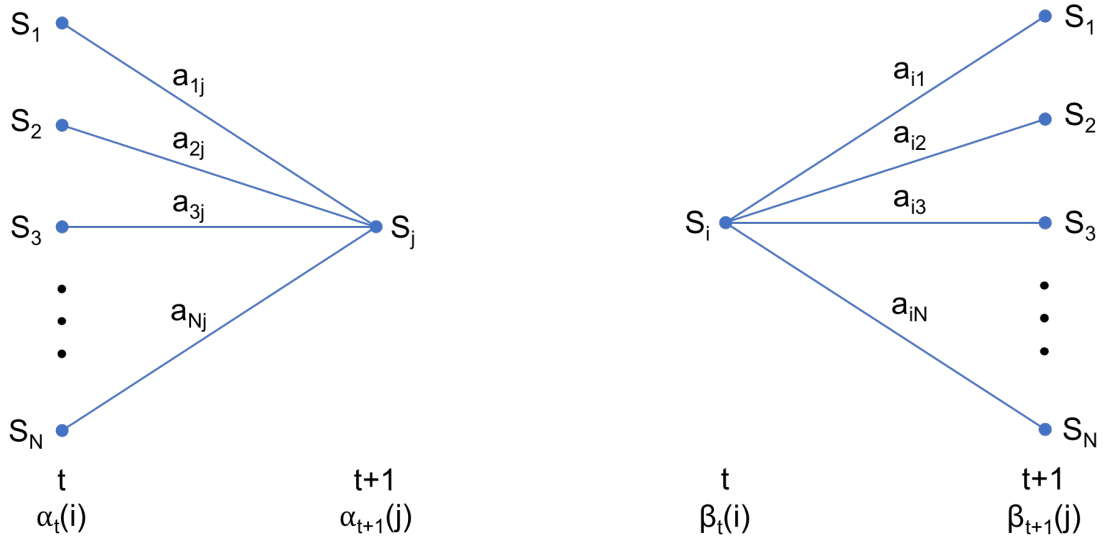
- Given the observation sequence $\mathbf{O} = \{O_1, O_2, ..., O_T\}$ and the model parameters $\boldsymbol{\theta} = \{\boldsymbol{\pi}, \mathbf{A}, \mathbf{B}\}$, calculate the probability of the observations sequence given the model, $P(\mathbf{O}|\boldsymbol{\theta})$.
- Optimise the model parameters $\boldsymbol{\theta}$ in order to maximise $P(\mathbf{O}|\boldsymbol{\theta})$.
- Find the sequence of hidden states given the observations $\mathbf{O} = \{O_1, O_2, ..., O_T\}$ and model parameters $\boldsymbol{\theta}$.

3.4.2.1 The forward-backward algorithm

The forward-backward algorithm gives a computationally efficient procedure to solve the first problem, calculating the probability of the observation sequence given the model, $P(\mathbf{O}|\boldsymbol{\theta})$. First, the algorithm calculates a set of forward probabilities by finding the probability of ending up in a particular state at each time point, $P(q_t|O_{1:t})$. The algorithm then calculates the probability of the remaining observation sequence given a starting state, $P(O_{t+1:T}|q_t)$.

The forward variable $\alpha_t(i)$ is defined as the probability of the partial sequence $O_1, O_2, ..., O_t$ and the state S_i at time t.

$$\alpha_t(i) = P(O_1, O_2, ..., O_t, q_t = S_i|\boldsymbol{\theta}) \tag{3.29}$$



(a) Depiction of the recursive calculation of the forward variable $\alpha_{t+1}(j)$. All possible paths from the states at time t to the state S_j at $t+1$, with transition probabilities are shown.

(b) Depiction of the recursive calculation of the backward variable $\beta_t(i)$. All possible paths from the state S_i at time t to all states at $t+1$, with transition probabilities are shown.

Figure 3.5: Recursive calculation of the forward and backward variables.

The forward variable $\alpha_t(i)$ can be solved iteratively, first by initialising $\alpha_1(i)$ using the initial state probabilities, $\boldsymbol{\pi}$, and the initial observation probabilities, $b(O_1)$.

$$\alpha_1(i) = \pi_i b_i(O_1) \qquad 1 \leq i \leq N \tag{3.30}$$

Figure 3.5 (a) shows how state S_j can be reached at time $t+1$ from the N previous states. The product of $\alpha_t(i)a_{ij}$ gives the probability of reaching state S_j at time $t+1$ via state S_i. Summing this product over the N possible states at time t will give the probability of reaching state S_j at time $t+1$ with all the previous observations. $\alpha_{t+1}(j)$ can then be obtained by multiplying by the observation probability, $b_j(O_{t+1})$, at time $t+1$.

$$\alpha_{t+1}(j) = \left(\sum_{i=1}^{N} \alpha_t(i)a_{ij}\right) b_j(O_{t+1}), \qquad 1 \leq t \leq T-1, \quad 1 \leq j \leq N. \tag{3.31}$$

Finally, $P(\mathbf{O}|\boldsymbol{\theta})$ can be calculated as the sum of the final values of the forward variable

$$P(\mathbf{O}|\boldsymbol{\theta}) = \sum_{i=1}^{N} \alpha_T(i). \tag{3.32}$$

The backward variable $\beta_t(i)$ can be calculated in a similar way. It is defined as the probability of the partial observation sequence from $t+1$ to T given state S_i at time t. The end initialisations of the backward variable are set to one

$$\beta_T(i) = 1, \qquad 1 \leq i \leq N. \tag{3.33}$$

Figure 3.5 (b) shows the possible states at time $t+1$ given being in state S_i at time t. To be in state S_i at time t and accounting for all future observations $O_{t+1}, O_{t+2}, ..., O_T$, all transitions from S_i to S_j have to be accounted for through a_{ij}, as does the observation O_{t+1} in state j through $b_j(O_{t+1})$ and the remaining observation sequence from state j through $\beta_{t+1}(j)$

$$\beta_t(i) = \sum_{j=1}^{N} a_{ij} b_j(O_{t+1}) \beta_{t+1}(j), \qquad t = T-1, T-2, ..., 1, \quad 1 \leq i \leq N. \tag{3.34}$$

The backward algorithm in combination with the forward algorithm, are used to solve the remaining problems: optimising the HMM parameters, and finding the most likely sequence of hidden states.

As the forward-backward algorithm computes products of probabilities, underflow can become a problem with longer signals. In order to deal with the problem of underflow, scaling is applied to the forward and backward variables, with the scaling applied to $\alpha_t(i)$ at each iteration step. The scaling coefficient is only dependent on the current time, t, and independent of state, S_i. The scaling factor used is c_t where

$$c_t = \frac{1}{\sum_{i=1}^{N} \alpha_t(i)}, \tag{3.35}$$

and $\alpha_t(i)$ is replaced by a scaled version $\hat{\alpha}_t(i)$ defined by

$$\hat{\alpha}_t(i) = c_t \alpha_t(i). \tag{3.36}$$

Similarly, the backward variable $\beta_t(i)$ can be scaled by the same coefficients

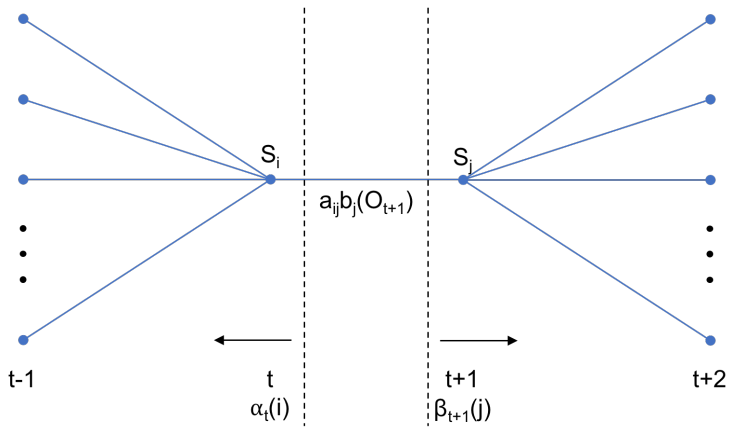


Figure 3.6: Diagram depicting the calculation of $\xi_t(i,j)$, the probability of being in state S_i at time t and state S_j at time $t+1$, for use in the Baum-Welch algorithm.

$$\hat{\beta}_t(i) = c_t \beta_t(i). \tag{3.37}$$

Equation (3.32) must now be altered to account for the scaled forward variable. This is now updated to

$$P(\mathbf{O}|\boldsymbol{\theta}) = exp\left(\sum_{i=1}^{N} \log\left(\hat{\alpha}_T\left(i\right)\right)\right). \tag{3.38}$$

3.4.2.2 The Baum-Welch algorithm

The second problem to solve is to determine and adjust the HMM parameters, $\boldsymbol{\theta} = \{\boldsymbol{\pi}, \mathbf{A}, \mathbf{B}\}$, to maximise the probability of the observation sequence. There are no known analytical solutions to this problem, but iterative procedures such as the Baum-Welch algorithm or other expectation-maximisation algorithms are able to locally maximise the probability of the observation sequence given the model parameters.

The probability of being in state S_i at time t and state S_j at time $t+1$ is defined as $\xi_t(i,j)$, where

$$\xi_t(i,j) = P(q_t = S_i, q_{t+1} = S_j|\mathbf{O}, \boldsymbol{\theta}). \tag{3.39}$$

The states leading to S_i at time t and the states following S_j at time $t+1$ are illustrated in Figure 3.6, it is now possible to rewrite $\xi_t(i,j)$ in terms of the forward and backward variables

$$\xi_t(i,j) = \frac{\alpha_t(i)a_{ij}b_j(O_{t+1})\beta_{t+1}(j)}{P(\mathbf{O}|\boldsymbol{\theta})} = \frac{\alpha_t(i)a_{ij}b_j(O_{t+1})\beta_{t+1}(j)}{\sum_{i=1}^{N}\sum_{j=1}^{N}\alpha_t(i)a_{ij}b_j(O_{t+1})\beta_{t+1}(j)} \tag{3.40}$$

The probability of being in state S_i at time t given the observation sequence is defined as $\gamma_t(i)$, where

$$\gamma_t(i) = P(q_t = S_i|\mathbf{O}, \boldsymbol{\theta}), \tag{3.41}$$

which can also be expressed in terms of the forward and backward variables

$$\gamma_t(i) = \frac{\alpha_t(i)\beta_t(i)}{P(\mathbf{O}|\boldsymbol{\theta})} = \frac{\alpha_t(i)\beta_t(i)}{\sum_{i=1}^{N}\alpha_t(i)\beta_t(i)}. \tag{3.42}$$

The normalisation term, $P(\mathbf{O}|\boldsymbol{\theta})$ makes $\gamma_t(i)$ a probability measure. Summing $\gamma_t(i)$ over time gives us a measure of the expected number of times that state S_i is visited, or the number of transitions from S_i

$$\sum_{t=1}^{T-1}\gamma_t(i) = \text{expected number of transitions from } S_i. \tag{3.43}$$

Summing of $\xi_t(i,j)$ over time gives a measure of the number of transitions from state S_i to S_j

$$\sum_{t=1}^{T-1}\xi_t(i,j) = \text{expected number of transitions from } S_i \text{ to } S_j. \tag{3.44}$$

From these definitions it is now possible to re-estimate the HMM parameters in $\boldsymbol{\theta}$:

$$\overline{\pi}_i = \text{expected number of times in state } S_i \text{ at time } (t=1) = \gamma_1(i) \tag{3.45}$$

$$\overline{a}_{ij} = \frac{\text{expected number of transitions from state } S_i \text{ to state } S_j}{\text{expected number of transitions from state } S_i} = \frac{\sum_{t=1}^{T-1}\xi_t(i,j)}{\sum_{t=1}^{T-1}\gamma_t(i)} \tag{3.46}$$

$$\bar{b}_j(v_k) = \frac{\text{expected number of times in state } S_j \text{ observing } v_k}{\text{expected number of times in state } S_j} = \frac{\sum_{t=1}^{T} 1_{O_t=v_k}\gamma_i(t)}{\sum_{t=1}^{T}\gamma_i(t)} \tag{3.47}$$

where $1_{O_t=v_k}$ is one when $v_k = O_t$ and is zero otherwise.

The re-estimated model can be defined as $\overline{\boldsymbol{\theta}} = \{\overline{\boldsymbol{\pi}}, \overline{\mathbf{A}}, \overline{\mathbf{B}}\}$ and it can be proven that $P(\mathbf{O}|\overline{\boldsymbol{\theta}}) \geq P(\mathbf{O}|\boldsymbol{\theta})$, so the observation sequence is more likely to have been produced by the new model than the previous model. This means the parameters can be iteratively re-estimated until a convergence criteria is met and the final model is the maximum likelihood estimate of the HMM. However, the Baum-Welch algorithm does not guarantee convergence to the global maxima, therefore the Baum-Welch algorithm should be run multiple times with varying start points in order to find the model with the greatest maximum likelihood.

3.4.2.3 The Viterbi algorithm

The Viterbi algorithm is a procedure to find the most likely state sequence, $\mathbf{Q} = \{q_1, q_2, ..., q_T\}$ for the given observation sequence $\mathbf{O} = \{O_1, O_2, ..., O_T\}$. $\delta_t(S_i)$ is defined as the highest probability along a single path at time t, which accounts for the first t observations and ends in state S_i,

$$\delta_t(S_i) = \max_{q_1,q_2,...,q_{t-1}} P(q_1\, q_2 ... q_t = S_i, O_1\, O_2 ... O_t|\theta) \tag{3.48}$$

and by induction

$$\delta_{t+1}(S_j) = [\max_i \delta_t(S_i)a_{ij}] \cdot b_j(O_{t+1}). \tag{3.49}$$

In order to obtain the state sequence, the argument which maximised Equation (3.49) for each t and j needs to be stored. This is done in a new variable, $\psi_t(j)$. The state sequence is initialised

$$\delta_1(S_i) = \pi_i b_i(O_1), \text{ and } \psi_1(i) = 0 \qquad 1 \leq i \leq N, \tag{3.50}$$

and both $\delta_t(j)$ and $\psi_t(j)$ are solved recursively

$$\delta_t(S_j) = \max_{1 \leq i \leq N} (\delta_{t-1}(S_i)a_{ij})b_j(O_t), \qquad 2 \leq t \leq T, \quad 1 \leq j \leq N \tag{3.51}$$

$$\psi_t(j) = \arg\max_{1 \leq i \leq N} (\delta_{t-1}(S_i)a_{ij}), \qquad 2 \leq t \leq T, \quad 1 \leq j \leq N. \tag{3.52}$$

The recursion terminates with

$$P^* = \max_{1 \leq i \leq N} (\delta_T(S_i)) \text{ and } q_T^* = \arg\max_{1 \leq i \leq N} (\delta_T(S_i)). \tag{3.53}$$

Backtracking is then performed to obtain the most likely sequence of hidden states

$$q_t^* = \psi_{t+1}(q_{t+1}^*), \qquad t = T-1, T-2, ..., 1. \tag{3.54}$$

Although there are similarities between the Baum-Welch algorithm and the Viterbi algorithm, they are used to calculate different aspects of a HMM. The Baum-Welch algorithm is an expectation maximisation function used to determine the most likely transition probabilities and observation probabilities. The advantage of the Baum-Welch algorithm is the guaranteed convergence to a local maximum, however convergence can be slow with high number of iterations being computationally inefficient. The Baum-Welch algorithm will also give a *point-wise* probability of each hidden state. The Viterbi algorithm is a more efficient algorithm to determine the hidden states, unlike the Baum-Welch algorithm the Viterbi algorithm calculates the most likely *sequence* of hidden states. However, the Viterbi algorithm requires the HMM parameters (from the Baum-Welch algorithm) in order to calculate the most likely state sequence.

3.4.2.4 Treating missing data

HMMs are easily adaptable to deal with missing data through slight alterations to the forward-backward algorithm. If the observations at time $t+1$ are missing (O_{t+1}), the forward variable is calculated as

$$\alpha_{t+1}(j) = \sum_{i=1}^{N} \alpha_t(i) a_{ij}, \qquad 1 \leq t \leq T-1, \quad 1 \leq j \leq N, \tag{3.55}$$

or by setting $b_j(O_{t+1}) = 1$. Similarly for the backward variable

$$\beta_t(i) = \sum_{j=1}^{N} a_{ij} \beta_{t+1}(j), \qquad t = T-1, T-2, ..., 1, \quad 1 \leq i \leq N, \tag{3.56}$$

with the transitions between states relying on the transition matrix probabilities alone and are no longer dependent on the observation probabilities.

3.5 Statistical testing

Statistical hypothesis testing is a common method for comparing the relationship between two or more sets of data. A null hypothesis (H_0) is generated which proposes there is no relationship between the data sets through a comparison of statistical measures between the two data sets. The two data sets are deemed to be statistically significant and the null hypothesis rejected if a probability threshold is met, known as the significance level, and the alternative hypothesis is accepted (H_1). The significance level is often set through the number of permitted type I or type II errors. Type I errors are rejections of true null hypotheses and type II errors are failures to reject false null hypotheses.

Statistical tests produce a p-value, which is the probability of an observed result or a more extreme result occurring under the null hypothesis. If a significance level was set at 5% (the most commonly used level for statistical significance), a p-value lower than 0.05 would indicate a rejection of the null hypothesis.

3.5.1 Selecting a statistical test

A number of considerations must be made before choosing a statistical test. Firstly, whether the test is one-tailed or two-tailed. One-tailed tests only test if significantly greater or significantly less than a value, thus providing greater power to detect effects in only one direction, however if the direction is not known, a two-tailed test should be used. Secondly the distributions of the data sets determine

whether parametric or non-parametric tests should be used. Parametric tests make assumptions about the distributions of the data, for example the data can be assumed to be Gaussian, whereas non-parametric tests make no assumptions about the distribution of the data.

3.5.1.1 One-sample t-test

The one-sample t-test tests whether the mean of a single data set (μ) differs from a specific mean (m_0). The null hypothesis assumes the difference between μ and m_0 is equal to zero and for a two-tailed test, the alternative hypothesis assumes the difference between μ and m_0 is not equal to zero.

The assumptions for this test are:

- the dependent variable is continuous
- the observations are independent of each other
- the dependent variable is approximately Gaussian
- the dependent variable contains no outliers

The test statistic can be calculated as

$$t = \frac{\bar{y} - m_0}{\sigma/\sqrt{n}} \tag{3.57}$$

where t is the t-statistic, $\bar{y}$ is the mean of the sample y, σ is the standard deviation of the sample and n is the size of the sample. The p-value is then calculated from comparing t to a t-distribution with $(n-1)$ degrees of freedom through reference tables. For a two-tailed test

$$p = 2Pr(T > |t|) \tag{3.58}$$

where T is the critical value of the t-distribution with $(n-1)$ degrees of freedom.

3.5.1.2 One sample Wilcoxon signed rank test

The one sample Wilcoxon signed rank test is the non-parametric version of the one sample t-test. As the test is based on the ranks, the median is used as opposed to the mean of the data.

The positive difference between each observation and hypothesised median value are determined and ranked from lowest to highest, with the sum of the ranks of positive differences denoted by W. The z-statistic is then used to determine the p-value through

$$z = \frac{W - n(n+1)/4}{\sqrt{\frac{n(n+1)(2n+1)}{24}}} \tag{3.59}$$

and reference tables to convert the z-value to the corresponding p-value.

3.5.1.3 Two-sample t-test

The two-sample t-test tests whether the mean of one data set (μ_a) differs from the mean of another data set (μ_b). The null hypothesis assumes the difference between μ_a and μ_b is equal to zero and for a two-tailed test, the alternative hypothesis assumes the difference between μ_a and μ_b is not equal to zero.

The assumptions for this test are:

- the dependent variable is continuous
- the independent variable consists of two categorical, independent groups
- the observations are independent of each other
- the dependent variable is approximately Gaussian
- the dependent variable contains no outliers

The test statistic can be calculated as

$$t = \frac{\bar{y_a} - \bar{y_b}}{\sqrt{\sigma_a/n_a + \sigma_b/n_b}} \tag{3.60}$$

where t is the t-statistic, $\bar{y_a}$ and $\bar{y_b}$ are the means of the samples y_a and y_b, σ_a and σ_b are the standard deviations of the samples and n_a and n_b are the sizes of the samples. The p-value is then calculated from comparing t to a t-distribution through reference tables.

3.5.1.4 Wilcoxon rank sum test

The Wilcoxon rank sum test (or Mann-Whitney U test) is the non-parametric equivalent of the two-sampled t-test, which does not require the assumption of normal distributions. The calculation of the U-statistic is as follows

- combine the data from both groups and rank the observations from smallest to largest (smallest assigned the value 1). When values of the observations are equal, assigned the midpoint of the unadjusted rank.
- calculate the sum of the ranks, R, for the two test groups.
- The U-statistic can now be calculated for each group as

$$U = R - \frac{n(n+1)}{2} \tag{3.61}$$

- the smaller value of U from the two groups is then used to determine the p-value from reference tables.

3.5.1.5 Paired t-test

A paired t-test is performed in a similar way to the one-sample t-test. A paired t-test is used when samples are dependent, for example when one sample is tested two times and tests whether two dependent samples are from populations with the same normal distribution. The mean and standard deviation of the differences between the pairs are defined as X_D and σ_D, with the t-statistic calculated as

$$t = \frac{X_D - \mu_0}{\sigma_D/\sqrt{n}} \tag{3.62}$$

where n is the number of pairs and μ_0 is the mean value to be tested against (usually set to zero). With the p-value found from reference tables.

3.5.1.6 Wilcoxon signed-rank test

The Wilcoxon signed-rank test is the non-parametric equivalent of the paired t-test with the test procedure defined as follows

- find the magnitude ($|d|$) and sign ($sgn(d)$) of the difference between each n pairs of samples
- exclude pairs where the magnitude of the difference equals zero, with the reduced number of pairs defined as n_r
- order the remaining pairs from lowest absolute difference to highest
- rank the pairs from smallest (1) to largest (n_r) with equal values labelled with the average rank, with the rank denoted as R_i
- calculate the test statistic W

$$W = \sum_{i=1}^{n_r} sgn(d) \cdot R_i \tag{3.63}$$

- W is compared to critical values in reference tables to determine the p-value

3.5.2 Correction for multiple testing

As the stated confidence intervals only apply to individual tests, when multiple simultaneous comparison are made the likelihood of type I errors increases. For example, if 200 simultaneous tests are made at a 5% significance level and all the null hypotheses are found to be true, there would be an expected 10 type I errors.

The family wise error rate (FWER) is the probability of making one or more type I errors among all tests. Instead of having a value, α, which controls the type I error probability of each individual test, the value, α, controls the overall FWER. A range of FWER correction methods have been developed.

There is no consensus on choosing which correction method should be used. FWER methods tend to be over conservative, reducing the level for significance to very small values, yet they have the lowest probability of type I errors. However,

when making multiple comparisons between highly correlated measures the FWER methods are often too stringent, therefore alternative methods such as the false discovery rate (FDR) controls for the number of errors in a less stringent manner.

3.5.2.1 Family wise error rate

The Bonferroni correction corrects for the increase in type I error through scaling the value α by a factor m, the total number of hypotheses or tests made. If p_i is the p-value for testing H_i, H_i is rejected if $p_i \leq \frac{\alpha}{m}$.

Another correction method is the Sidak correction which tests each individual hypothesis at a level $\alpha_{SID} = 1 - (1 - \alpha)^{\frac{1}{m}}$.

The Holm's step-down procedure or Holm-Bonferroni method is a more powerful version of the Bonferroni test which first orders the p-values from lowest to highest $(P_{(1)}...P_{(m)})$ and associated hypotheses $(H_{(1)})...H_{(m)}$ [227]. An index k is then defined as

$$P_{(k)} > \frac{\alpha}{m + 1 - k} \tag{3.64}$$

and all null hypotheses from $H_{(1)}$ to $H_{(k-1)}$ are rejected.

3.5.2.2 False discovery rate

As the FWER is too strict in many cases, especially in the case of large number of tests, the FDR corrections are designed to control the expected proportion of rejected null hypotheses (or 'discoveries') which are incorrectly rejected. FDR tests have increases power compared to FWER methods, however they have an increased number of type I errors [228].

If V is defined as the number of type I errors, the FWER is defined to be the probability of V being greater or equal to than one, $Pr(V \geq 1)$.

The FDR is defined as

$$FDR = E\Big(\frac{V}{R}|R > 0\Big)Pr(R > 0) \tag{3.65}$$

where R is the total number of discoveries. The FDR is the expected proportion of false positive findings from all of the rejected hypotheses multiplied by the probability of making at least one rejection [229].

3.6 Summary

This chapter has described the methods which will be used in the following chapters. Feature extraction techniques have been described in addition to the increasing need for regularisation and feature selection to avoid overfitting and aid with interpretation of models. The following chapters will aim to extract features of sleep and circadian rhythms and investigate their associations with mental health and depression. Regression analysis for prediction of outcomes from observable data is explained and will be implemented for the prediction of levels of depression.

PCA and HMMs have been described as methods to find latent structure or hidden states of the data. PCA will be applied to mood scores to measure the underlying latent structure of the mood of people with BD, BPD and healthy controls. In addition, HMMs will be used to estimate rest and active periods from acceleration data with features extracted to quantify sleep and circadian measures. Statistical tests will be applied to comparisons made in the data with correction for the multiple testing applied in order to determine the statistical significance of the results reported.

4
Dataset: The AMoSS Study

The data used in this work were collected as part of the Automated Monitoring of Symptom Severity (AMoSS) study[1] with the study set up by the Department of Psychiatry, Oxford, to determine whether objective measures of behaviour, activity, or physiology can aid with diagnosis and identification of deterioration of mental health disorders.

A total of 141 participants were recruited to the AMoSS study between January 2014 and January 2016, including 54 BD participants, 34 BPD participants and 53 healthy control (HC) participants. Participants were given a smartphone which passively collected data throughout the study. Participants also used a custom designed Android app on the smartphone to record daily mood ratings. Multiple other devices were worn by the participants throughout the duration of the study, recording behavioural and physiological signals.

4.1 Motivation and study objectives

Monitoring relapse in BD and BPD relies solely on subjective measures which are self-assessed through questionnaires [230]. The AMoSS study aims to find markers which will aid with the monitoring of mood instability during relapse and acute

[1]The AMoSS study was approved by the local NHS research ethics committee (REC reference 13/EE/0288) and all participants provided written informed consent.

episodes as well as between these episodes. Despite the fact that patients are often thought to be healthy between acute episodes, they frequently experience considerable mood instability [52, 231, 232]. Objective measures used to determine this mood instability may provide significant improvements in the management of these mental health disorders.

The AMoSS study attempts to utilise the growth in the large amount of available information which can be passively collected in daily life. In addition it aims to use state of the art machine learning applications and the ability to fuse multiple data sources recorded at varying intervals which may provide new diagnostic monitoring tools for tracking changes in mental health. The ability to make early interventions through early detection of deterioration could lead to reduction in healthcare costs and increased quality of life of patients [233]. The widespread use of smartphones and the passive nature of the data collection should result in low barriers to adoption of the methods developed through the study.

The primary and secondary objectives are defined in the AMoSS study protocol as described in Figure 4.1 [234].

As the AMoSS study was designed as an exploratory study no hypotheses were proposed to be tested, instead the study was designed to be hypothesis generating, with primary and secondary endpoints or study outcomes defined in Figure 4.2.

4.1.1 Participant Recruitment

Participants were recruited from Oxford, UK, and the surround areas. Healthy control (HC) participants were recruited through advertisements. BD participants were recruited through advertisement and many were recruited from the OXTEXT-1 study cohort [235]. BPD participants were also recruited through advertisement and previous studies.

Participants must be over 16 years old and could be any height, weight, and may also have other medical conditions. Participants could also be any gender, however due to the prevalence of females being diagnosed with BPD, a higher proportion of female participants were recruited to the BD and HC groups in order

AMoSS study objectives

1. Primary objectives
    - To measure objective differences in activity and physiological measures, between healthy controls and people with bipolar disorder and borderline personality disorder, and associate these with the symptom severity which is quantified using the patients' self-reported assessments.
2. Secondary Objectives
    - What are the minimal number of sensors required to obtain disease classification accuracy (sensitivity and specificity) of at least 90%?
    - Can we identify, in advance, patterns in the data that are associated with deterioration in mental state? This will be determined by exploratory analysis at the end of the study.
    - Acceptability of the overall monitoring approach, and regarding specific sensors for each participant. We will also obtain implicitly the acceptability of each sensor by the frequency that participants set specific sensors off.

Figure 4.1: The primary and secondary objectives of the AMoSS study.

to balance the cohorts. The inclusion and exclusion criteria, as defined in the AMoSS protocol [234], are shown in Figure 4.3.

Initial recruitment was for a 12 week period with participants having incentives to continue in the study for one year. Participants were given £15 on their first visit to the clinic and a further £15 for each month of data provided (for the first 12 week period), if participants completed one year they could keep the smartphone provided. After the full year many participants opted to continue providing data for the study without incentives.

Table 4.1 shows a summary of the demographics of the three cohorts in the AMoSS study. The groups are generally well matched, the BPD cohort has less participants than the BD and HC groups and the proportion of females is considerably greater. The HC cohort also has a lower body mass index (BMI) compared to the patient cohorts and the BPD participants were younger than

AMoSS study endpoints
Primary

- Comparison of physiological parameters between patient groups and controls to generate objective signals (effectively biomarkers) sensitive to diagnosis and change in mental state. Parameters will be collected non-invasively over periods of at least a week to generate time series for each participant. The optimal choice of measure or measures is not established, so is a primary objective of the study.
- Relationship between objective measures and the subjective clinical data collected simultaneously in the study.

Secondary

- Minimal number and type of sensors required to predict the longitudinal disease symptom severity when quantified using the standard clinical and self-reported scales.
- The experience of participants of using the sensors.

Figure 4.2: The primary and secondary endpoints of the AMoSS study.

the BD participants. The medications the patients were currently taking were recorded during their initial recruitment to the study and are shown in Table 4.1. Throughout the study the participants were able to alter their medication, however this information was not readily available for analysis in this work, therefore medication was not taken into account.

4.2 Data collection

An initial assessment of each participant was made by psychiatrists at the Warneford Hospital, Oxford, to screen the participants for comorbidity and to exclude cases of psychiatric disorders in the HC participants. During the screening, additional personality characterisitcs are collected in addition to occupational information.

Participants then began the 12 week periods of ambulatory monitoring, although all participants were relatively stable at the time of recruitment, participants were permitted to receive medical treatment and many of the participants were medicated. During the 12 week monitoring period continuous activity signals were recorded

Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Participant is willing to use a smartphone and a smart-watch.
- Male or female, aged 16 years or above.
- Diagnosed with bipolar disorder (BD), I or II, or Borderline Personality Disorder (BPD) by DSM-IV criteria or healthy control (screened with the MINI† to exclude BD and BPD or other severe mental illness).
- Suitable for True Colours self-monitoring and accepting of data collection from mobile phone.

Exclusion Criteria

- Anyone unable to give informed consent, who would have difficulty participating for logistical reasons or in a current severe affective episode.
- Any current psychiatric illness (including depression).
- Admission to a psychiatric hospital or crisis team support in the past month.

Healthy adults:

- A history of neurological disorder or head injury.
- Any previous or current major psychiatric illness (including depression).
- Any first degree relatives with history of borderline personality disorder or bipolar disorder.

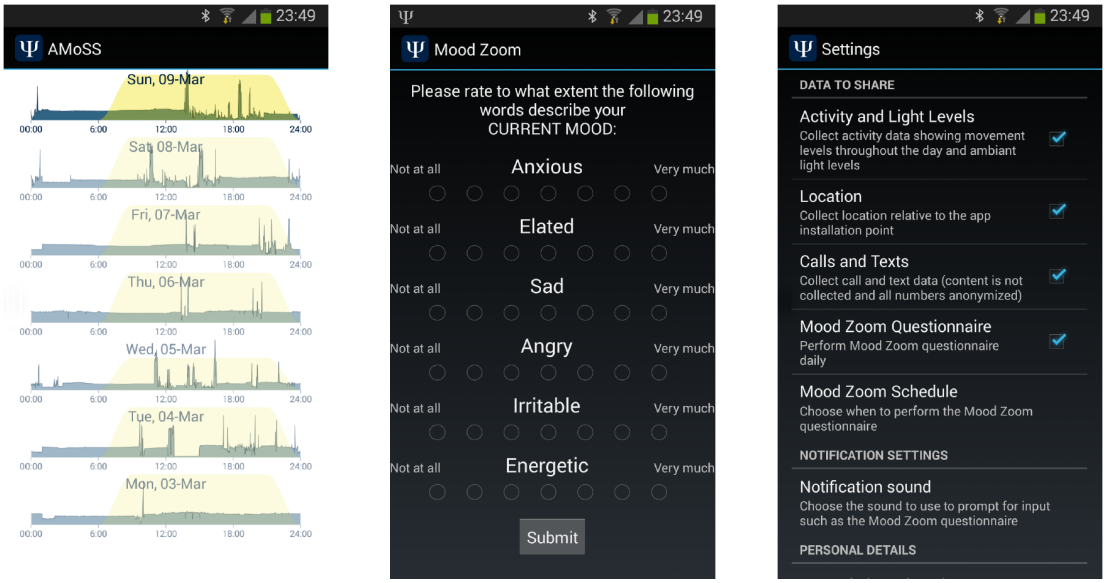
Figure 4.3: The inclusion and exclusion criteria for the AMoSS study. † A short structured diagnostic interview, the Mini-International Neuropsychiatric Interview (MINI) for DSM-IV psychiatric disorders.

from a Samsung Galaxy smartphone (Samsung, South Korea), shown in Figure 4.4 (a), and a Fitbit One activity tracker (Fitbit, US). The smartphone also collected GPS location in addition to light levels, call and text data and battery life. For a one month period participants additionally wore a GENEActiv watch (Activinsights Ltd, UK) which recorded tri-axial accleration, light levels and skin temperature. Participants were also prompted to fill out a daily mood questionnaire designed for

Table 4.1: Demographics of the participants recruited for the AMoSS study by cohort.

	Bipolar disorder	Borderline personality disorder	Healthy controls
Number of participants	54	34	53
Male/female	20/34	3/31	19/34
Age*	39.0 ± 12.9†	33.6 ± 10.1†	37.9 ± 12.9
Height (cm)*	170.8 ± 9.5	166.0 ± 6.9	169.9 ± 10.5
Weight (kg)*	79.9 ± 17.4	76.2 ± 18.5	71.3 ± 17.2
BMI*	27.3 ± 5.1†	27.6 ± 6.5‡	24.5 ± 4.5 †‡
Full-time employment	11	2	16
Part-time employment	9	6	5
Unemployed	4	11	4
Students	2	1	3
Retired	0	0	2
Unknown	1	2	0
Psychotropic medication	48	23	0
Lithium	20	0	0
Anticonvulsant	19	0	0
Antipsychotic	34	6	0
Antidepressants	17	23	0
Hypnotics	3	2	0

*Denoted by the mean $\pm$ the standard deviation. † and ‡ denote statistically significant differences at the $p = 0.05$ level.



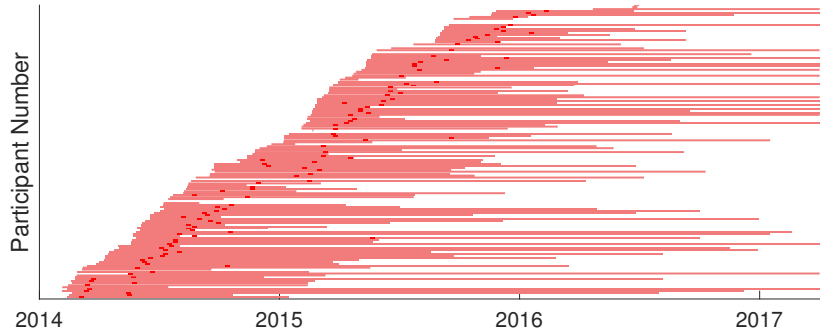
(a) Actigraphy levels

(b) Mood Zoom questionnaire

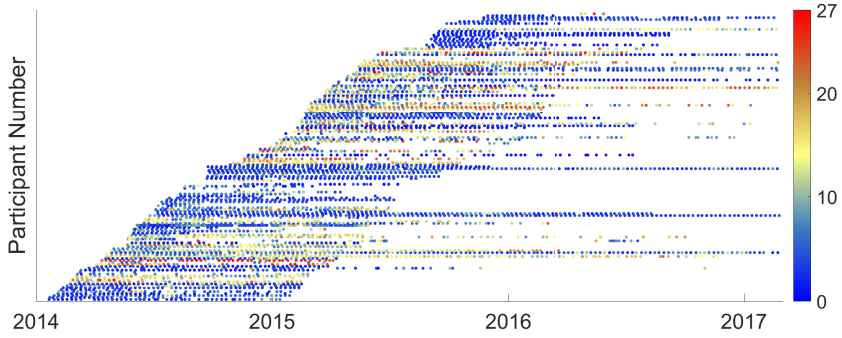
(c) App settings

Figure 4.4: Screen-shots of the data collection app on an Andriod smartphone. (a) shows the actigraphy levels over the past seven days, (b) shows the Mood Zoom questionnaire which is prompted to be filled out daily. (c) shows the settings which can be controlled by the participant to determine which data is collected and the times of the notifications.

the AMoSS study called Mood Zoom, with a screenshot of the questionnaire shown in Figure 4.4 (b). Weekly clinical questionnaires, known as True Colours, were also filled out by participants to quantify levels of depression, mania, anxiety and quality of life. Participants were asked to carry the new smartphone with them with the



(a) Time from entry to the study to the last data provided for each participant. Dark red indicates the high intensity monitoring week.



(b) Clinical depression scores provided for each participant. The colour indicates the level of depression on the QIDS score between 0 and 27.

Figure 4.5: Weeks of data recorded from participants with clinical scores of depression provided.

AMoSS app pre-installed. Although they were not required to use it as their primary phone, many participants switched to using the provided smartphone as their only phone, while others carried their previous phone with them. The exact numbers who switched to using the provided smartphone can not be quantified. The adherence throughout the study was good, with $80.1 \pm 31.2\%$ of Mood Zoom questionnaires completed and $83.8 \pm 49.1\%$ of the True Colours questionnaires completed.

For one week of the 12 week monitoring period, participants were asked to take part in a week of additional monitoring, known as the high intensity week. This week was selected at the convenience of the participant. During this week additional devices were given to the participants to record additional signals. Participants wore a Proteus patch (Proteus Digital Health Inc, Redwood City, US) which was attached to the torso and recorded continuous tri-axial acceleration, heart rate and

skin temperature signals. An ECG Holter device was also worn by participants, initially a Shimmer ECG (Shimmer Sensing, Ireland) which recorded four channels of ECG across the chest in a similar configuration to Eindhoven's triangle, and later in the study an ePatch (DELTA, Denmark) which was a small patch worn on the sternum recording two channels of ECG. Blood pressure recordings were made three times per day using an Omron home blood pressure monitor (Omron Corporation, UK). Participants were also prompted to fill out the Mood Zoom questionnaire 10 times per day during the high intensity week.

After the completion of the 12 week monitoring period, participants had the option to continue providing data for one year, with 76 participants providing data beyond a year. At any point during the study participants could select which data was being sent to the AMoSS study through a settings page on the AMoSS app, shown in Figure 4.4 (c). Figure 4.5 (a) shows the time period each participant provided data to the AMoSS study, with the high intensity week of recording marked in dark red. Participants provided data for a mean($\pm$ standard deviation) of 81.9 ± 45.7 weeks (104.4 ± 56.1 for BD participants, 67.4 ± 44.9 for BPD participants, and 68.9 ± 47.4 for healthy controls). Figure 4.5 (b) shows the scores submitted for depressive symptoms [7], one of the clinical questionnaires to quantify levels of depression, which is used to label the objective signals collected during the AMoSS study. A summary of the devices used and the data they record are shown in Table 4.2.

The demographics of the participants who had a compliance of at least 50% for the clinical questionnaires were compared to the demographics of those with a compliance of under 50%, with no statistically significant differences found between the two groups.

The work in this thesis focuses on the quantification of circadian rhythms using acceleration data and heart rate data, with both acceleration and heart rate data described in more detail in the following sections.

Table 4.2: List of devices used and the data recorded during the AMoSS study.

Device	Data	Description
Samsung Galaxy Smartphone	Acceleration Light levels GPS Calls and texts Battery level	Continuous monitoring of the entire study. Variable sampling rates for each modality
Mood Zoom	Mood scores	Prompted once per day or 10 times per day during the high intensity week
True Colours	QIDS (depression) Altman (mania) GAD-7 (anxiety) EQ-5D (quality of life)	Weekly clinical scores for the entire study
Fitbit One	Steps and floors Sleep analysis	Continuous for the study with one minute sample rate
GENEActiv	Tri-axial acceleration Light levels Skin temperature	Optional month within the study. Sampling rate set to 50Hz.
High intensity week only		
Shimmer ECG	Four channels of chest ECG	12 to 48 hours of ECG signals recorded at 256Hz
ePatch	two channels of chest ECG	72 hours of ECG signals recorded at 512Hz
Proteus patch	Tri-axial acceleration Heart rate Skin temperature	Continuous signals for up to one week. Acceleration recorded at approximately one recording per minute and heart rate at one recording every five minutes
Omron blood pressure	Blood pressure Heart rate	Prompted to record three measures three times per day

(a) Proteus patch **(b)** GENEActiv **(c)** Samsung Galaxy S4

Figure 4.6: Devices worn to record acceleration during periods of the AMoSS study.

4.2.1 Acceleration data

The use of acceleration as a measure of activity has grown greatly in the last decade, with the development of accelerometers providing signals which can be used to quantify many different aspects of activity.

Accelerometers detect changes in speed, or accelerations, primarily through piezoelectric effects which are detected in the devices (although other methods of measuring acceleration exist). This allows for acceleration to be measured

continuously with sampling rates high enough for detailed activity tracking.

Recent studies have used accelerometers to quantify levels of activity [236, 237], sleep [238, 239] and circadian rhythms [240, 241], in addition to being used to classify varying types of activity [242, 243]. Here, the acceleration signals will be used to quantify sleep and circadian rhythms through ambulatory recordings over multiple days. The measurements of acceleration from mobile devices change depending on the location of the device, with the the most common location for monitoring circadian rhythms being the non-dominant wrist [244]. However, no significant differences have been found between measuring from the wrist or the thigh [245].

The devices which record acceleration signals in the AMoSS study are shown in Figure 4.6. The Proteus patch (Figure 4.6 (a)) records acceleration signals in three orthogonal directions at a relatively low, variable sampling rate of approximately one recording per minute. It is not possible to classify detailed types of activity due to the low sampling rate, however the data is still able to capture longer term variations in activity, thus making it suitable for quantifying circadian rhythms. In addition, the tri-axial accelerometer recording allows the estimation of the orientation of the patch, and therefore the orientation of the participants, thus providing a proxy for sleep.

The Proteus patch was worn during the high intensity week in which simultaneous mood recordings were made 10 times per day. The week long acceleration signals and the corresponding mood scores allows for investigation of circadian rhythms and intra-daily mood variability.

The GENEActiv wrist worn accelerometer (Figure 4.6 (b)) records tri-axial acceleration at a much high sampling rate than the Proteus patch, with configurable sampling frequencies of 10, 25, or 50Hz. The GENEActiv records data from 10 days to 28 days (depending upon the sampling rate), so has the potential to be used to quantify circadian rhythms over longer periods than the Proteus patch. However, as the AMoSS study aims to identify objective markers of clinical episodes in BD and episodes must reach a clinical threshold for a minimum of two weeks, the two to four weeks of data provided by the GENEActiv device may not be sufficient to track how objective markers change with episodes of depression. Due to this lack of transitions

(a) Shimmer ECG **(b)** ePatch ECG

Figure 4.7: Devices worn to record heart rate during the high intensity monitoring week.

to negative mood states within the GENEActiv data and the fact GENEActiv is not recorded simultaneously with either physiological signals for comparison or with high intensity mood recordings, GENEActiv is not used in this work.

The Samsung Galaxy smartphone (Figure 4.6 (c)) is able to provide the most continuous and long-term acceleration signals from all devices in the AMoSS study. The Samsung Galaxy uses a three-directional accelerometer with a sampling rate which can be set up to 100Hz, with a resolution of 0.1mg able to record accelerations of plus or minus 2g. The high sampling rate and the data not being stored on the smartphone, but sent to remote servers, means quantification of sleep or circadian rhythms is possible over an unbounded period. Although the smartphone may be the most unobtrusive device and is able to record over the longest periods, the quality of the data recorded is often reduced compared to the body and wrist worn devices. This is due to the reliance on the participants to keep the smartphones charged and also to carry the smartphone with them at all times. Moreover, the time participants stop and start using the smartphone before and after sleep may also greatly vary between participants. However, if the signals recorded from the smartphone can be validated, the smartphone offers the greatest potential for monitoring of sleep and circadian rhythms from accelerometers.

4.2.2 Heart rate

The recent advances in wearable devices have increased the potential for longitudinal heart rate monitoring. Heart rate signals of at least 24 hours allow for the quantification of circadian measures and may be compared to the sleep-wake cycles and circadian rhythms of other modalities such as activity. In addition, measures of

heart rate and HRV are used to quantify ANS activity providing potential markers of mood or mental state in patients with mental health disorders [246, 247, 248].

Heart rate can be measured through a range of different methods. The most common method is through ECG which measures the electrical activity generated by the heart muscles which are detectable through the electrical activity in the skin. Another common method to determine heart rate is via PPG which sends light into tissue and records the absorption levels to determine the blood flow caused by the heart beats.

In the AMoSS study heart rate is only measured during the high intensity week through two devices. The Shimmer ECG (Figure 4.7 (a)) is a five lead ECG device which is worn around the waist with the five leads connected to the chest with electrodes. The Shimmer ECG records the raw ECG signal at 256Hz for up to 48 hours. The high quality signals recorded from the Shimmer device allow for multiple features to be calculated from the signal. R-peak detection algorithms must be implemented to determine the heart rate and may also be used to determine HRV features. The signals also allow for quantification of morphological features of the ECG such as P-wave and T-wave characteristics. However, the devices often run out of power or are removed before 24 hours of signal is recorded, preventing circadian analysis.

The ePatch device (Figure 4.7 (b)) was used as a replacement for the Shimmer ECG. The ePatch also records raw ECG signals, however no leads are used and two electrodes are located on the patch which is stuck to the chest. The smaller, leadless device is more comfortable for participants and is able to record for 72 hour periods. The high quality signals recorded at 512Hz allow for longer heart rate and HRV analysis and quantification of circadian rhythms.

The Proteus patch (Figure 4.6 (a)), which was also used to record acceleration, records heart rate for up to seven days. The Proteus patch measures the heart rate through electrodes located on the patch which is worn on the torso, however the raw ECG waveform is not provided by the patch, but a heart rate signal with a variable sampling frequency of approximately one sample per five minutes. Although the

Table 4.3: Clinical thresholds used to diagnose levels of depression [7], mania [8] and anxiety [9] from the scores of the True Colours questionnaires.

Questionnaire	Thresholds	Clinical Interpretation
QIDS	0-5	No depression
	6-10	Mild depression
	11-15	Moderate depression
	16-20	Severe depression
	21-27	Very severe depression
Altman	0-5	Unlikely mania
	6-25	Increased probability of mania
GAD-7	0-4	Minimal anxiety
	5-9	Mild anxiety
	10-14	Moderate anxiety
	15-21	Severe anxiety

Proteus patch does not allow for quantification of HRV or other measures, the more longitudinal heart rate signal gives a better recording for quantification of circadian rhythms compared to the shorter ECG signals.

4.2.3 Questionnaires

Four clinically validated questionnaires are prompted to be completed by participants once per week during the course of the AMoSS study. These questionnaires are used to determine the psychiatric state of the participants in an ambulatory setting and are completed via email or text. The set of clinically validated questionnaires are known as True Colours Self-Management System and is a monitoring system which is used by the NHS in Oxford [249, 250]. In addition to the clinically validated questionnaires, participants were also prompted by a smartphone notification to fill in a daily mood rating questionnaire called Mood Zoom in order to record higher frequency mood scores. However there were no mechanisms to ensure these questionnaires were completed, with participants often ignoring the prompts with a compliance rate of $83.8 \pm 49.1\%$.

4.2.3.1 QIDS

The 16 item quick inventory of depressive sypmtomatogoloy (QIDS-SR16 or QIDS) questionnaire consists of 16 questions which are used to determine the level of depression in participants [7]. The 16 questions have four possible answers, each assigned a score from 0 to 3. The scoring system converts the responses into the nine DSM-IV symptom criterion domains. The nine domains consist of: sad mood, concentration, self-criticism, suicidal ideation, interest, energy/fatigue, sleep disturbance (initial, middle, and late insomnia or hypersomnia), decrease/increase in appetite/weight, and psychomotor agitation/retardation. The final scores of the QIDS questionnaire are between 0 and 27, with different ranges of scores given different interpretations as shown in Table 4.3. A threshold score of 11 is often given as the lowest score at which the participant is labelled as depressed.

The QIDS questionnaire is available in full in Appendix A.

4.2.3.2 ASRM

The Altman self-rating mania scale (ASRM or Altman) questionnaire consists of five questions used to determine the levels of mania in participants [8]. The five questions are answered on a five point scale from 0 to 4, to measure: how happy/cheerfull, how self-confident, levels of sleep, how talkative, and how socially active participants have been over the past week, from 'no more than usual' up to 'all of the time'. The total scores of the Altman questionnaire range from 0 to 20.

4.2.3.3 GAD-7

The general anxiety disorder (GAD-7) questionnaire consists of seven questions answered on a scale from 0 to 3 corresponding to 'not at all' to 'nearly every day' used to measure anxiety [9]. The questions relate to: feeling nervous, worrying, relaxing, restlessness, irritability, and feeling afraid over the past two weeks, which were selected based on the DSM-IV symptom criteria.

4.2.3.4 EQ-5D

The Euroqol (EQ-5D) questionnaire consists of five questions used to measure the quality of life of participants [77]. The five questions relate to: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with a final question to rate overall health on a scale of 0 to 100.

4.2.3.5 Mood Zoom

The Mood Zoom app is a questionnaire designed for the AMoSS study and is part of the AMoSS app participants have on the smartphone. The questionnaire is designed to determine the mood of participants at a higher frequency than the True Colours questionnaires, with participants prompted to answer the Mood Zoom questionnaire once per day. Mood Zoom was designed to better quantify intra-daily mood variability, an important symptom of manic states in BD (as shown in Figure 2.1) and for diagnosis of BPD (Figure 2.2). Mood Zoom allows for day to day variations in mood to quantified which was previously not possible from the clinical questionnaires. A screenshot of the Mood Zoom app is shown in Figure 4.4 (b).

The questionnaire consists of six moods: anxious, elated, sad, angry, irritable, and energetic with participants required to fill out the mood score on a seven point Likert scale with scores from one to seven describing the current moods as 'not at all' to 'very much'. Participants could manually set the time at which the questionnaire would be prompted each day.

During the high intensity week of monitoring, the Mood Zoom questionnaire was prompted to be completed 10 times per day. The participants chose the start and end times of the 10 prompts, with the prompts evenly spaced between the two chosen times.

4.2.4 Labelling data

The weekly analysis presented here is based on quantifying features from calendar weeks of data (from Sunday midday to Sunday midday). The clinical questionnaires are prompted to be completed by email or text on a weekly basis, with the

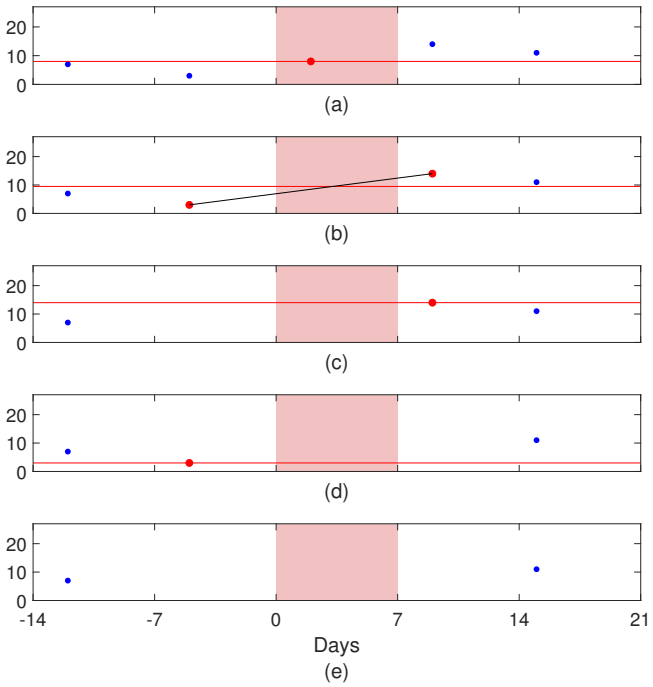


Figure 4.8: Plot to show the different methods used to label week of data with clinical questionnaire scores depending on available entries. The week of data for labelling in highlighted red, blue marks are the questionnaire scores which are not used for labelling, red marks are the scores used for labelling and the red line is the clinical score assigned to the red highlighted week. (a) uses the score submitted within the week of data. (b) uses interpolation of two scores within seven days preceding and succeeding the week, with the interpolated value in the centre of the week used. (c) and (d) use the nearest point within seven days of the week to be labelled. (e) has no clinical scores within seven days of the week to be labelled, so therefore left unlabelled.

questionnaires retrospectively scoring the previous week, however, participants do not always respond to the questionnaires or are often late in responding. Due to the variability in the clinical scores available to label the weeks of data, a set of rules are defined to assign a label to each week.

If any clinical questionnaire response is given during the week to be labelled the score from that entry is assigned to the week, as shown in Figure 4.8 (a) (if multiple entries are provided within the week, the last score is used as the questionnaires are retrospective over a week). If no score is available within the week, but scores are provided within one week prior to the start and one week after the end of the week to be labelled, linear interpolation is performed between the two nearest scores

and the interpolated score in the middle of the week is used, as in Figure 4.8 (b). If there is only an entry within one week after the week to be labelled this score is used, similarly if there is only one score within one week prior to the week to be labelled this score is also used, as in Figures 4.8 (c) and (d) respectively. If no scores are available within one week preceding or succeeding the week to be labelled, no score is assigned to the week, as in Figure 4.8 (e).

5
Quantifying Circadian Rhythms

The following publication is based on the work presented in this chapter:

- **Carr, O.**, Saunders, KEA., Bilderbeck, AC., Tsanas, A., Palmius, N., Geddes, JR., Foster, R., De Vos, M., and Goodwin, GM. (2018). Desynchronization of diurnal rhythms in bipolar disorder and borderline personality disorder. *Translational Psychiatry*, 8(1):79.

Sleep is commonly disturbed in psychiatric disorders and in the case of BD, sleep deprivation leads to mood elevation and mania [251]. This striking linkage is often used to claim that circadian rhythms are disturbed in mood disorders [252, 253]. However, a sleep effect does not automatically imply involvement of the circadian clock although sleep abnormalities appear to be associated with some other circadian measures in BD [212]. The relationship between mood and circadian function is of particular interest when patients are apparently well, because abnormal sensitivity to different aspects of sleep or the circadian cycle might explain why patients with BD show persistent mood instability in euthymia or have the potential to decompensate into mania or depression [52]. Accordingly, it is when patients are well and between episodes that interventions to stabilise mood must be developed and deployed.

Here, BD and BPD participants, together with HC participants, are studied in an observational protocol, which yielded intensive data over several days. As indicated, BD has long been of interest from a circadian perspective. BPD resembles

BD in that patients experience mood instability, but this variability of mood is greater [254]. Descriptions of sleep difficulties in BPD refer quite non-specifically to insomnia [221]. The BPD group are a relevant control group because the diagnoses are sometimes confused even though heritability and the clinical course are different from BD. The hypothesis is that disruption of the synchrony of circadian physiology would be disturbed in BD and we would test whether the effect is specific to the BD phenotype, as is often claimed or assumed, by comparison with BPD. In this chapter, the circadian rhythms of total activity, vertical acceleration and heart rate are quantified and the synchronicity between them analysed. In this work, the vertical acceleration metrics have been labelled as measures of sleep due to the changes in acceleration as the body position of participants change (lying down), however these metrics have not been validated against true sleep times and it is likely they are measures of periods of rest.

This chapter gives an overview of the methods used to quantify different aspects of circadian rhythms and applies them to some of the data sets described in Chapter 4. Circadian rhythms of activity, sleep and heart rate are quantified and desychronisation between the rhythms measured in the BD, BPD and HC participants.

5.1 Methods used to quantify circadian rhythms

A range of methods for quantification of circadian rhythms from behavioural and physiological signals have been developed, however there remains no standard method for this analysis with less work carried out on the quantification of circadian variability [255]. Some of the most common methods to quantify circadian rhythms from biological signals and the parameters used are identified in the following sections.

5.1.1 Fourier analysis

Fourier analysis is used to decompose a time series into separate oscillatory components. It is based on the work by Fourier which identifies that any time series

may be described as a sum of sine and cosine waves of varying frequencies. The spectral energy, R_j^2, for each frequency j/N can be calculated as $R_j^2 = a_j^2 + b_j^2$, where

$$a_j = \frac{2}{N}\sum_{i=1}^{N} x_i cos\Big(\frac{2\pi j t_i}{N}\Big) \tag{5.1}$$

and

$$b_j = \frac{2}{N}\sum_{i=1}^{N} x_i sin\Big(\frac{2\pi j t_i}{N}\Big). \tag{5.2}$$

N is the number of data points in the time series, where x_i denotes the the variable at time t_i, with angular values in radians. A periodogram can be calculated by computing the spectral energy from $j = 1$ to $(N-1)/2$. The spectogram is used to identify whether any spectral components appear in the circadian range, suggesting the signal exhibits circadian rhythmicity. An example of a Fourier periodogram computed from a week long acceleration signal is shown in Figure 5.1.

An assumption of Fourier analysis is that the signal must be stationary and the signal provided to analysis repeats to infinity with the same periodicity. The signal must be long enough to be representative of the frequencies which are to be captured and must contain at least one period of all components within the signal. For circadian analysis this must be at least 24 hours. However, the circadian component in the signal must be assumed to be stationary, therefore Fourier analysis is not able to capture any variations in periodicity within the signal. More complex analysis techniques could be implemented to avoid these assumptions, such as time-frequency analysis techniques which include short-time Fourier transforms and wavelet analysis.

5.1.2 Lomb-Scargale periodogram

The Lomb-Scargale periodogram is an adaption of Fourier analysis to allow for unevenly sampled data [256, 257]. This can be due to data being collected at irregular intervals or to device failure causing missing segments of data. The Lomb-Scargale method introduces a time delay, τ, such that the sine and cosine waves will be orthogonal at times t_j. The time delay, τ, is defined as

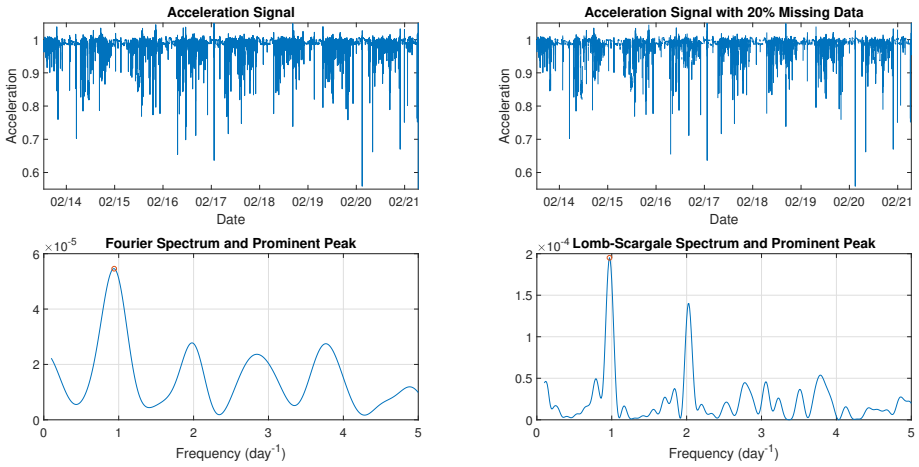


Figure 5.1: An example of an acceleration recording from the Proteus patch over seven days (top left) and the corresponding Fourier spectrum and prominent peak at one cycle per day (bottom left). The same acceleration signal with 20% of the recordings artificially removed is shown (top right) with the corresponding Lomb-Scargale spectrogram and prominent peak at one cycle per day (bottom right).

$$\tau = \frac{1}{2\omega} tan^{-1} \frac{\sum_{j=1}^{N} sin(2\omega t_j)}{\sum_{j=1}^{N} cos(2\omega t_j)}. \tag{5.3}$$

At frequency ω, the periodogram is estimated as

$$P(\omega) = \frac{1}{2}\left(\frac{\left[\sum_{j=1}^{N} x_j cos\omega(t_j - \tau)\right]^2}{\sum_{j=1}^{N} cos^2\omega(t_j - \tau)} + \frac{\left[\sum_{j=1}^{N} x_j sin\omega(t_j - \tau)\right]^2}{\sum_{j=1}^{N} sin^2\omega(t_j - \tau)} \right). \tag{5.4}$$

The periodogram may be used in the same way as with the Fourier analysis, with frequencies in the circadian range being identified from the signal. Figure 5.1 shows the Lomb-Scargale periodogram for the same week long acceleration signal with 20% of the data artificially removed to simulate missing data and therefore unevenly sampled data. The results from both the Fourier analysis and Lomb-Scargale analysis identify the same circadian component from the signal.

5.1.3 Cosinor method

The cosinor method was initially developed in the 1960s by Halberg in order to analyse short data series, as the periodograms require data to cover multiple cycles [258]. The cosinor method is a curve fitting method which attempts to fit a sinusoid

to data through least squares procedures, thus removing the limitations of data length and uniform sampling [259]. However, limitations in this method still exist, primarily through the sensitivity to outliers.

The model for fitting a single sinusoidal component can be written as

$$x_i = M + Acos(\theta_i + \phi) + e_i, \tag{5.5}$$

where M represents the midline estimating statistic of rhythm (MESOR) or mean level, A the amplitude and ϕ the phase. The parameter e_i represents the error at time t_i, with the error terms assumed to be normally distributed with zero mean. The angle at time t_i is represented by θ_i which is defined as

$$\theta_i = \frac{2\pi t_i}{\tau}, \tag{5.6}$$

with τ representing the period.

For the case of circadian rhythms and therefore this work, τ is often fixed to 24 hours. This allows Equation (5.5) to be written as

$$x_i = M + \beta y_i + \gamma z_i + e_i, \tag{5.7}$$

where $\beta = Acos\phi$, $\gamma = -Asin\phi$, $y_i = cos(2\pi t_i/\tau)$, and $z_i = sin(2\pi t_i/\tau)$. Equation (5.7) is therefore linear in terms of M, β and γ.

Subsequently, a standard ordinary least squares regression approach can be applied to determine the values of M, β and γ which minimise the sum of squares error, $\sum_{i=1}^{N} e_i^2$. The minimum occurs when the first-order derivative of the sum of squared errors is equal to zero, rearranging, summing and squaring Equation (5.7) gives

$$\sum_{i=1}^{N} e_i^2 = \sum_{i=1}^{N} x_i^2 - \sum_{i=1}^{N} M^2 - \beta^2 \sum_{i=1}^{N} y_i^2 - \gamma^2 \sum_{i=1}^{N} z_i^2, \tag{5.8}$$

from which the values of M, β and γ can be found by solving the resulting system of three equations with three unknowns obtained from differentiating Equation (5.8). This results in the following system of equations, where $\omega = 2\pi/\tau$,

$$\begin{bmatrix} \sum y_i \\ \sum y_i cos\omega t_i \\ \sum y_i sin\omega t_i \end{bmatrix} = \begin{bmatrix} N & \sum cos\omega t_i & \sum sin\omega t_i \\ \sum cos\omega t_i & \sum cos^2\omega t_i & \sum sin\omega t_i cos\omega t_i \\ \sum sin\omega t_i & \sum sin\omega t_i cos\omega t_i & \sum sin^2\omega t_i \end{bmatrix} \begin{bmatrix} M \\ \beta \\ \gamma \end{bmatrix} \text{ or } \mathbf{d} = \mathbf{Su}, \tag{5.9}$$

where the values of M, β and γ can now be found by solving $\mathbf{u} = \mathbf{S}^{-1}\mathbf{d}$. To obtain the original parameters in Equation (5.5), A and ϕ must be found. Using the values found for β and γ, it is possible to solve for A,

$$A = (\beta^2 + \gamma^2)^{1/2}, \tag{5.10}$$

and ϕ,

$$\phi = tan^{-1}(-\gamma/\beta). \tag{5.11}$$

5.1.4 Multiple-component cosinor

It is possible to extend the analysis of the single component cosinor to include multiple other frequencies,

$$x_i = M + \sum_{j=1}^{p} A_j cos(2\pi t_i/\tau_j + \phi_j) + e_i. \tag{5.12}$$

If all τ_j are assumed to be known, the system increases from 3 equations with 3 unknowns to $2p+1$ equations to estimate M and p pairs of (β_j, γ_j) or (A_j, ϕ_j). The parameters can be found using the same method as the single component cosinor, through the normal equation $\mathbf{d} = \mathbf{Su}$, which is rearranged to find $\mathbf{u}$.

5.1.5 Acceleration measures

One of the most common methods of quantifying circadian rhythms from accelerometer data is by finding the most active ten hours (M10) and least active five hours (L5) for each 24 hour period [126, 211]. Figure 5.2 shows four days of acceleration with the periods of L5 and M10 highlighted for each day. The circadian features calculated from each day include:

- L5, the total activity (or acceleration) within the least active five hours.

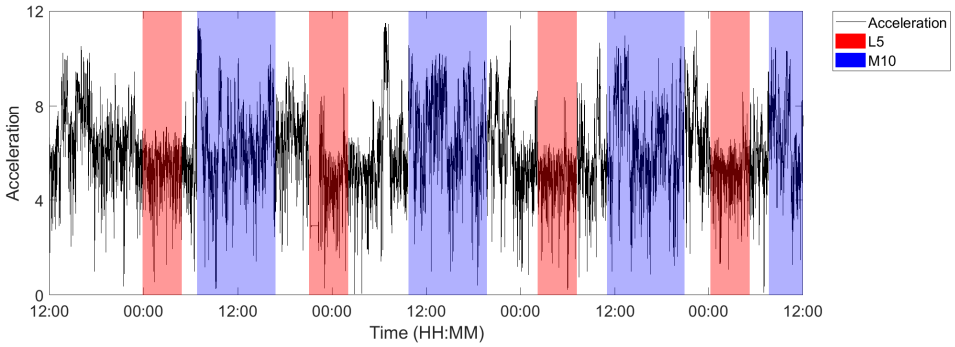


Figure 5.2: Highlighted periods of the least active five hour (L5) and most active ten hour (M10) periods over four days.

- L5 time, the time of onset of the least active five hour period.
- M10, the total activity (or acceleration) within the most active ten hours.
- M10 time, the time of onset of the most active ten hour period.
- Relative amplitude, the difference between activity levels with the L5 and M10 periods, calculated as $\frac{M10-L5}{M10+L5}$.

5.2 Estimating parameters of circadian rhythms

An ideal circadian or rhythmic process can be fully defined by four parameters, shown in Figure 5.3: the MESOR (mean level, M) which the oscillations cycle around, the period (τ) which is the time for a full cycle, the amplitude (A) defined as half the distance between the minimum and maximum values or the difference between the peak and MESOR for a symmetrical oscillation, and the phase (ϕ) which is the relative angular displacement between the oscillation and a reference point [260]. The acrophase can also be defined as the phase of the maximum value of the oscillation.

Two further parameters can be incorporated to fully characterise a circadian time series. The first is the waveform which defined the shape of the wave, the rhythms could have square, sawtooth or more complex forms than a simple sinusoid whilst having the same MESOR, period, amplitude and phase. The other parameter is the prominence, a measure of the signal to noise ratio or stationarity of the signal. A signal with higher prominence is a signal whose parameters stay constant over

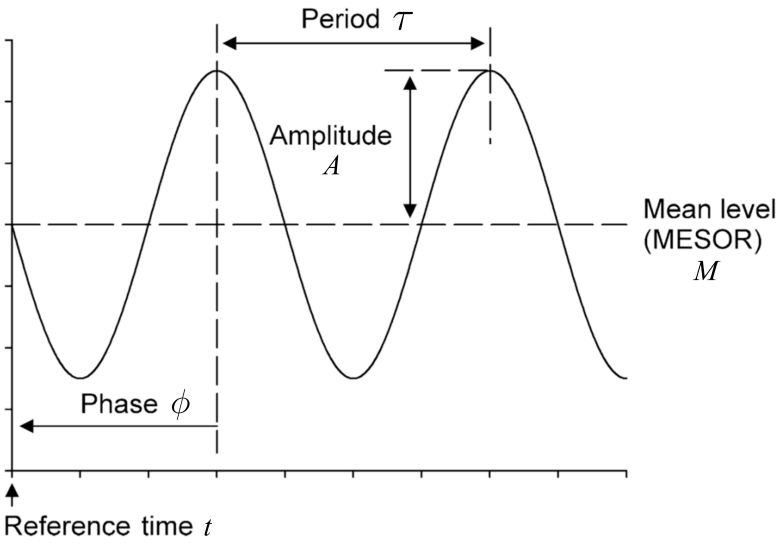


Figure 5.3: A diagram of the four main parameters used to quantify circadian rhythms, especially when using the cosinor method.

time.For example a circadian rhythm with a changing period, irregular waveforms, or change in MESOR over time would have a low prominence and would indicate a less stable rhythm.

5.2.1 Period

One of the first methods used to determine the period of a circadian rhythm is the inspection of an actogram [261]. An example of an actogram is shown in Figure 5.4, where the daily onsets and offsets activity can be seen, if the daily onsets of activity are vertically aligned over multiple days the period of the circadian rhythm is 24 hours. If the circadian rhythm is free running, linear regression of the daily onsets of activity can provide an estimate of the period of the circadian rhythm. Determining the period from actograms is limited, firstly due to the subjectivity of the activity onset and also no measure of variability of the period can be calculated. In addition, this method uses only the onset or offset times and ignores the majority of the data recorded.

The estimation of the period of circadian rhythms through periodograms has proven to give reliable measures. Comparisons of the many methods of analysis the frequency spectrums have shown the Lomb-Scargale periodogram to provide

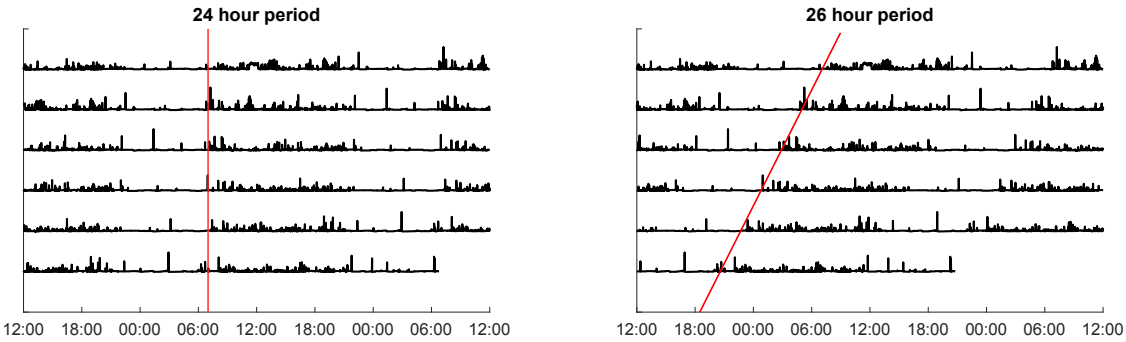


Figure 5.4: Examples of two actograms, the first plot shows an individual who has a circadian period of 24 hours and the second plot shows an individual with a circadian period of 26 hours.

the best estimations [255]. An example of the estimation of period is shown in Figure 5.1. The most common problem with the identification of the frequencies contained within the signal is the erroneous detection of harmonics which may contribute to frequencies around the circadian range, with the presence of infradian components potentially effecting the circadian range. In addition, signals may contain more than one circadian component which may have differing periods, high resolution in the circadian range is required to disentangle the circadian components of the multiple components.

Autocorrelation has also been used to determine the period of circadian signals. Autocorrelation measures the similarity of a signal with a shifted version of itself, the spacing between the peaks in the autocorrelation measure determine the period at which the signal is repeating, with the size of the peaks indicating the strength of the periodicity. This method of estimating the period of a signal has been extended to the maximum entropy spectral analysis, which uses autoregressive modelling to enhance the resolution of the frequencies detected in the signals.

5.2.2 MESOR

The central or typical value of a distribution is known as the central tendency. The classic methods used to calculate this central value are through finding the mean, median and mode of the data, with the mean being by far the most common method. When the data is not evenly sampled or the signal does not complete

an integer number of cycles the mean is not a suitable measure for the central tendency. In these cases a mean adjusted to the rhythm is more appropriate for determining the central value, an example of this is finding the MESOR using the cosinor method. Limitations of the cosinor method occur when there is insufficient data to fit the sinusoids or when the sinusoids are over-fit to the data.

5.2.3 Amplitude

The amplitude of circadian rhythms have traditionally be calculated as half the difference between the maximum and minimum values, $A = (x_{max} - x_{min})/2$ [262]. However this is highly affected by outliers, therefore the averages of the maximum and minimum values are used rather than the most extreme values. Alternatively the amplitude can be calculated from the functions fitted to the data, this typically results in more uniform and smaller predictions than using the minimum and maximum values, however both methods are still commonly used in circadian analysis.

5.2.4 Phase

Early measures of phase were calculated by comparing the mean value of a variable in the light phase of the light-dark cycle to the mean value in the dark phase to indicate diurnal or nocturnal activity [255]. Automated calculation of phase was then performed from actograms by detecting the onset of activity and using this time as a marker of phase. The cosinor method allows for calculation of phase, or acrophase, from the timing of the peak of the sinusoid, the phase can be reported in clock hours but is often stated in radians or degrees if there are non-24 hour components.

5.2.5 Waveform

The waveforms of circadian rhythms are often ignored in their quantification as they can not be defined from the MESOR, amplitude, phase or period. For example, a sinusoidal wave and a square wave can have these same four parameters, but their waveforms are very different. Increasing the complexity of the waveforms

used to model circadian rhythms often increase the complexity in calculating the previous parameters, especially the phase.

Analysing the spectral components of the signal could indicate the rhythmic components which should be included in the waveform, increasing the number of frequencies present as opposed to selecting only the most prominent frequency. Increasing the number of harmonics used in cosinor analysis will also increase the complexity of the waveform and improve the fit to the data, however the use of too many components will overfit the data.

In the case of more complex waveforms the phase is often calculated from the fundamental component alone and for waveforms which are not sinusoidal, the acrophase is calculated from the maximum value of the waveform.

5.2.6 Prominence

The prominence of a circadian rhythm is a measure of the strength and continuity and is often referred to as the signal-to-noise ratio. For the case of cosinor analysis a measure of prominence was introduced known as the *percent rhythm*, which quantifies the percentage of the variance accounted for by the fitted sinusoid. Other methods use sliding windows to calculate the frequency spectra of the signal and compare the similarity of the spectrums in each window. Changes in the period, waveform and MESOR of circadian rhythms calculated through the cosinor method can be used to give a measure of prominence through their calculation over time. The more stable these parameters are over time suggests a rhythm with high prominence, whereas more variable parameters are associated with less prominent rhythms [255].

5.3 High intensity monitoring

The analysis of circadian rhythms and their stability over time are often carried out over periods of weeks or even months, however recording high quality physiological or behavioural signals over this period is difficult. Wearable devices which are able to record high quality data often only record for shorter periods of time yet are impractical and inconvenient to wear for long periods. The ability to quantify

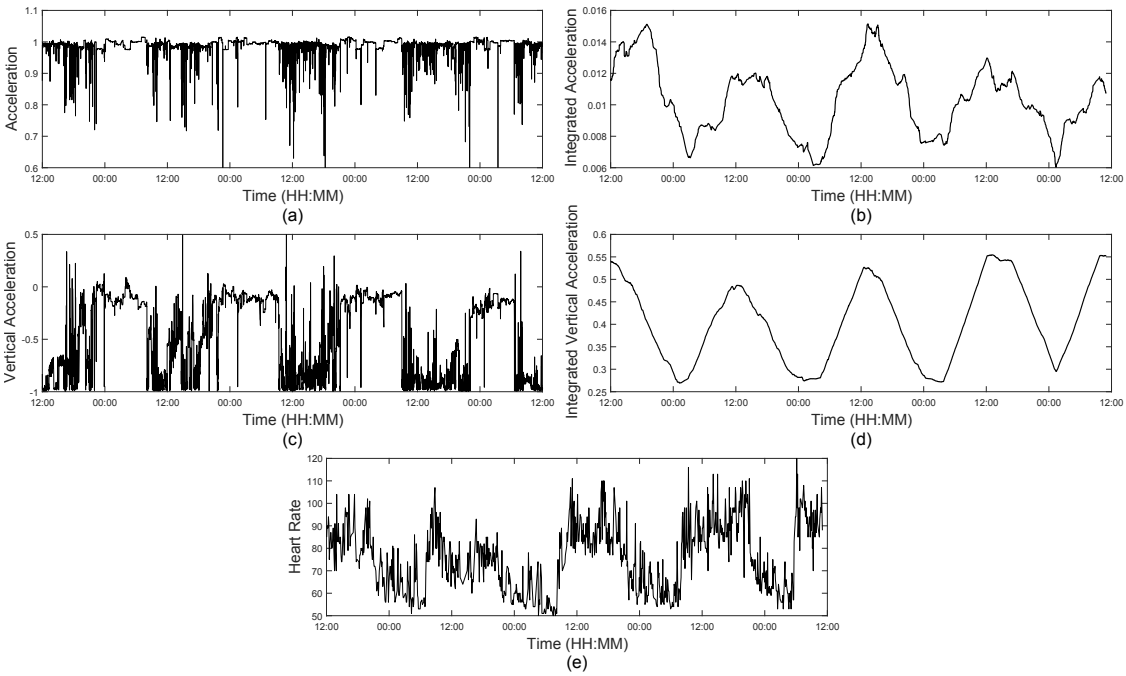


Figure 5.5: (a) An example of the raw total acceleration recorded from the Proteus patch over four days. (b) The integrated total acceleration signal over 6 hour windows. (c) A corresponding example of the vertical acceleration signal recorded from the Proteus patch. (d) the integrated vertical acceleration signal. (e) The corresponding heart rate signal recorded from the Proteus patch.

circadian rhythms and their stability from shorter time periods using these wearable devices could reduce the need for time consuming longitudinal recordings.

Here, the data collected during one week of high intensity monitoring is described along with the participant information from which it was collected, with the methods used to quantify the circadian rhythms of activity, sleep, heart rate and mood outlined.

5.3.1 Activity data

The collection of activity data is described in Chapter 4. In this work the total acceleration is used as a measure of overall activity of the participants, whereas the vertical component of acceleration is used as a measure of sleep (or lying down) due to the changes in acceleration caused by gravity when the orientation of the patch (and therefore the participant's body) changes. An example of the raw total acceleration signal and vertical acceleration signal are shown in Figure 5.5 (a) and (c).

5.3.1.1 Preprocessing

For consistency between participants and as many algorithms require evenly sampled data, both the total acceleration and vertical acceleration were resampled to one minute intervals. Initially, intervals between data points which are over five minutes in length are labelled as low signal quality. The signals are then resampled using linear interpolation to one minute intervals, with the previously labelled low quality segments removed from the signal.

The signal is then split into 24 hour periods from midday to midday as this emphasises the behaviour at night in order to focus on the sleep of participants. Missing data is then calculated for each individual day of recording, with days with over 20% missing data or days with a segment of missing data over two hours in length removed. Participants with a minimum of four consecutive days remaining were kept for analysis, with the first four available consecutive days are chosen for analysis.

As the high levels of activity often appear in short bursts, it is difficult to observe the rhythmicity of the acceleration signal. In order to highlight this rhythmic behaviour, the signals are integrated to show periods where activity levels are increasing or decreasing. The mean acceleration levels are subtracted from the signal and the signals are integrated over 6 hour windows which slide by one data point each iteration in order to preserve the same sampling rate. Figure 5.5 (b) and (d) show the integrated total acceleration and vertical acceleration signals respectively.

5.3.2 Heart rate

Recordings of heart rate were collected simultaneously to the activity data from the Proteus patch. The patch records heart rate in beats per minute (BPM) at a variable sampling rate of approximately one sample per five minutes.

5.3.2.1 Preprocessing

Preprocessing was performed in a similar way to the acceleration signals. Intervals between data points over 20 minutes in length are labelled as low quality sections. The value of heart rate at each recorded instance was compared to the value recorded

at the preceding time instance: if the value was over 150% or under 50% of the previous value the value at the current time was set to the mean of the preceding and succeeding values, with a mean of $0.9\% \pm 1.1\%$ of the data being adjusted for each participant. Values of heart rate which exceeded 200 BPM or are lower than 20 BPM are also labelled as low quality sections based on normal values of heart rate [263]. The recording was then resampled to five minute intervals using linear interpolation to ensure an evenly sampled signal. The segments labelled as low quality are then removed from the signal, the signal was split into days from midday to midday and days with over 20% missing data or days with missing segments over 2 hours in length are removed. An example of the processed heart rate signal is shown in Figure 5.5 (e).

5.3.3 Mood Zoom data

During the high intensity monitoring, mood scores obtained through the Mood Zoom questionnaire were collected 10 times per day. As the participants selected an initial and end time for the Mood Zoom prompts for the high intensity week and the 10 prompts were evenly spaced between these two selected times, the times of entries and their sampling rate varied between participants. The mood scores were resampled to 1 minute intervals through linear interpolation in order to standardise the recordings across all participants.

5.3.4 Participant demographics

From the participants recruited for the AMoSS study, 129 of them underwent the high intensity week of monitoring, during which acceleration in three directions and heart rate were recorded from the Proteus patch and the Mood Zoom questionnaire was prompted 10 times per day. Participants were included if they had four consecutive days of simultaneous acceleration and heart rate signals after preprocessing. Table 5.1 shows the demographics of the participants who underwent the high intensity monitoring and of the participants who were included and also excluded from the analysis of the circadian rhythms.

Table 5.1: Participant demographics for: i) the participants who underwent the high intensity week of monitoring, ii) the participants included in the analysis of circadian rhythms and iii) the participants which were not used due to data quality.

High intensity week participants			
	BD	**BPD**	**HC**
Age* **(years)**	39.0 ± 12.9	33.6 ± 10.4	36.6 ± 13.0
BMI* (kg/m^2)	27.3 ± 5.1†	27.7 ± 6.7‡	23.8 ± 3.8 † ‡
Male/Female	20/34	3/28	13/31
QIDS*	6.94 ± 4.86 † §	11.13 ± 4.81 ‡ §	1.75 ± 1.67 † ‡
Altman*	2.72 ± 3.22†	2.93 ± 2.54‡	0.88 ± 2.45 † ‡
Participants with over four days signal			
	BD	**BPD**	**HC**
Age* **(years)**	40.9 ± 11.4	34.3 ± 10.2‡	43.4 ± 14.6‡
BMI* (kg/m^2)	26.1 ± 3.9	25.9 ± 5.1	24.6 ± 4.2
Male/Female	4/14	2/12	4/16
QIDS*	6.65 ± 4.33 † §	11.33 ± 4.12 ‡ §	1.88 ± 1.36 † ‡
Altman*	1.65 ± 2.00†	2.70 ± 1.70‡	0.12 ± 0.33 † ‡
Non-participants (under four days)			
	BD	**BPD**	**HC**
Age* **(years)**	37.4 ± 13.9†	31.8 ± 9.6	29.8 ± 8.0†
BMI* (kg/m^2)	27.4 ± 5.3†	28.1 ± 8.5‡	22.2 ± 2.8 † ‡
Male/Female	16/20	1/16	6/21
QIDS*	7.33 ± 3.06 † §	11.04 ± 5.64 ‡ §	1.65 ± 2.55 † ‡
Altman*	4.00 ± 5.19	4.00 ± 5.66	1.75 ± 4.17

*indicates the mean and standard deviations are shown.

5.4 High intensity monitoring of mood

Previous work from the AMoSS study investigated how the multidimensional Mood Zoom questionnaire could be described in terms of latent variables through PCA [254, 264]. This analysis was performed on Mood Zoom questionnaire results collected longitudinally over the course of the entire AMoSS study, ranging from three months to over a year for some participants, during which the participants were prompted to complete one Mood Zoom questionnaire per day. PCA applied to time series attempts to reduce the dimensionality of multivariate data through finding the orthogonal components which describe the greatest amount of variance in the data. The first component is in the direction which describes the greatest amount of variance in the data, with each of the following components describing

the next greatest variance whilst being orthogonal to all previous components. PCA assumes all of the multivariate observations to be independent and normally distributed. For the case of Mood Zoom, PCA finds weightings for each of the six mood scores which contribute to each of the principal components, thus determining the latent structure of responses. Other methods to determine latent structure of time series exist, such as functional PCA or factor analysis, but this work focuses on the use of PCA for direct comparison to the previous studies [254, 264].

Here, the latent variable structure of Mood Zoom is found from the data collected during the high intensity week in order to determine whether the same information can be gained from short, intense periods of monitoring as compared to much more longitudinal monitoring.

The results of the longitudinal Mood Zoom PCA, which calculates PCA from the time series of Mood Zoom entries when one set of entries are completed per day, found that the first three components accounted for 85% of the variance in the Mood Zoom questionnaire, with the results shown in Table 5.2 [254]. The first three components were given different interpretations: the first being 'negative' mood (with high weightings for the 'Anxious', 'Sad', 'Angry', and 'Irritable' items), the second component being 'positive' mood (with high weightings for the 'Elated' and 'Energetic' items), and the third component being 'irritable' mood (with high weightings for the 'Angry' and 'Irritable' items but also high inverse weightings for the 'Anxious' and 'Sad' items).

PCA was applied to the pooled Mood Zoom data from the high intensity week for participants from of all subject groups. The PCA on the high intensity Mood Zoom recordings reveals a very similar structure of latent variables to the previous work which used longitudinal data. The first three components account for 77.44% of the variance in Mood Zoom, with the weightings of the components shown in Table 5.2. All three components had very similar weightings for all items when calculated from the high intensity data compared to the longitudinal data.

The latent variable structure of each of the subject groups were also found from the longitudinal Mood Zoom recordings, with the weightings for each of the Mood

Table 5.2: The latent variable structure of Mood Zoom questionnaire using PCA. The left results show the structure when calculated from one Mood Zoom entry per day over months of recordings with their interpretation. The right results show the structure when calculated over one week of 10 recordings per day. Bold entries highlight weightings greater than 0.4 in magnitude.

	One MZ entry per day [254]			Ten MZ entries per day		
MZ Item	**P1**	**P2**	**P3**	**P1**	**P2**	**P3**
Anxious	**0.55**	0.08	**-0.47**	**0.54**	0.20	**-0.71**
Elated	-0.11	**0.76**	-0.11	-0.37	**0.64**	-0.07
Sad	**0.52**	0.04	**-0.43**	**0.56**	0.03	**-0.57**
Angry	**0.42**	0.11	**0.46**	**0.50**	0.33	**0.48**
Irritable	**0.47**	0.12	**0.60**	**0.54**	0.32	**0.56**
Energetic	-0.13	**0.62**	0.02	-0.26	**0.78**	-0.19
Cumulative % variance explained	55	77	85	44.25	66.10	77.44
Interpretation	Negative	Positive	Irritable			

Zoom items for the first three components shown in Table 5.3 [264]. The first two principal components in the BD and BPD participants from the longitudinal data were consistent between the groups and were given the same two interpretations ('negative' mood and 'positive' mood). The HC participants had similar weightings for the first two components, however in the opposite order, with the 'positive' mood explaining 51.7% of the variance and the 'negative' mood explaining 26.5% of the variance. The third component is not consistent between the groups and no interpretation was given to this component.

The results of using 10 Mood Zoom entries per day for one week to find the latent variable structure is shown in the right of Table 5.3. In general, the BD and BPD participants show the same latent structure as the longitudinal analysis, with the first component being interpreted as 'negative' mood and the second being 'positive' mood. This structure was similar to the HC participants, where the first principal component was 'negative' mood and the second being 'positive' mood, the opposite order to the longitudinal analysis. For the high intensity analysis, the third component was consistent across all three subject groups with high weightings for the 'Angry' and 'Irritable' items, thus they can be given the 'irritable' mood interpretation as was given in Table 5.2. These results suggest that the greatest variability in the mood of BD and BPD participants over many days is through negative moods. The same results are seen in shorter within day analysis, as both the longitudinal and high intensity analysis found negative mood to explain the

Table 5.3: The latent variable structure of Mood Zoom questionnaire for each subject group using PCA. The left results show the structure when calculated from one Mood Zoom entry per day over months of recordings. The right results show the structure when calculated over one week of 10 recordings per day. The structure is similar for one and ten entries per day in BD and BPD participants across all components. The HC participants also have a similar structure for ten entries per day, although the first two principal components are ordered differently.

	One MZ entry per day [264]			Ten MZ entries per day		
MZ Item	**P1**	**P2**	**P3**	**P1**	**P2**	**P3**
Bipolar disorder						
Anxious	0.52	0.10	0.81	0.60	0.26	0.80
Elated	-0.19	0.72	0.07	-0.39	0.66	0.04
Sad	0.49	0.09	-0.05	0.60	0.08	0.58
Angry	0.45	0.17	-0.44	0.52	0.33	-0.53
Irritable	0.47	0.19	-0.38	0.59	0.34	-0.60
Energetic	-0.19	0.63	0.03	-0.30	0.82	0.17
Cumulative % variance explained	57.8	77.2	84.6	47.13	68.41	78.56
Borderline personality disorder						
Anxious	0.51	-0.01	0.39	0.65	0.23	0.88
Elated	-0.13	0.70	0.24	-0.50	0.68	0.16
Sad	0.48	-0.24	0.56	0.72	-0.09	0.79
Angry	0.48	0.24	-0.36	0.66	0.51	-0.52
Irritable	0.51	0.27	-0.49	0.67	0.51	-0.69
Energetic	-0.07	0.58	0.32	-0.31	0.86	0.30
Cumulative % variance explained	48.9	69.6	81.2	43.99	65.42	77.31
Healthy controls						
Anxious	0.18	0.57	-0.06	0.33	0.05	0.52
Elated	0.74	-0.23	-0.63	-0.20	0.61	-0.01
Sad	0.15	0.50	-0.02	0.36	0.03	0.25
Angry	0.12	0.37	0.03	0.31	0.14	-0.26
Irritable	0.12	0.46	0.05	0.35	0.11	-0.32
Energetic	0.61	-0.17	0.77	-0.14	0.67	0.16
Cumulative % variance explained	51.7	78.2	87.8	38.34	62.36	75.36

greatest variance. Similar results were found for the healthy controls in the high intensity data, with negative moods explaining most of the variance. However, longitudinal results indicate that positive moods have the greatest impact on mood variance over longer periods in healthy controls.

5.4.1 Circadian mood

PCA was applied to the high intensity Mood Zoom recordings, pooling all participant groups together (as in Table 5.2). The first three principal components, 'negative' mood, 'positive' mood and 'irritable' mood, were calculated for each participant. The mean and standard error were calculated at each time point for the separate participant groups in order to determine the average circadian rhythms of mood.

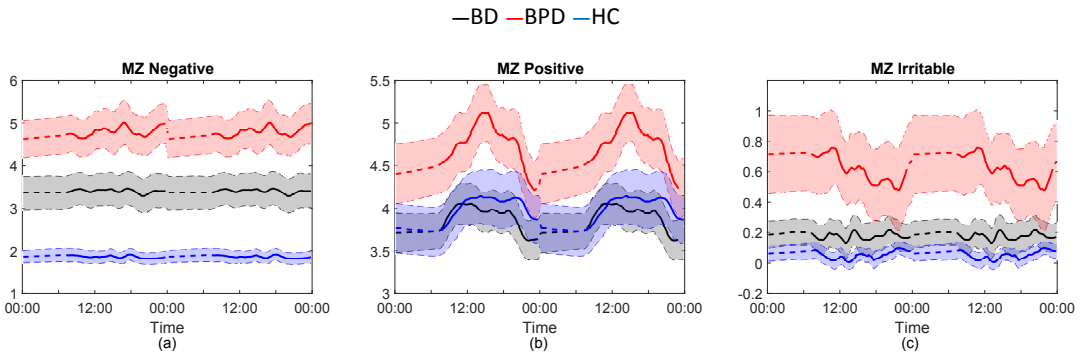


Figure 5.6: Circadian variability in the first three PCA components of Mood Zoom: negative mood (a), positive mood (b) and irritable mood (c). The signal is repeated over two cycles with the shaded region representing the standard error and the dashed line indicating the period in which no Mood Zoom recordings were made.

Figure 5.6 shows the mean circadian patterns repeated for two cycles for each subject group (shaded region represents the standard error). Negative mood was clearly higher in the patient groups than in controls (Figure 5.6 (a)) with BPD participants being the most variable, followed by BD participants and then HC participants; cyclicity was not markedly circadian in any group, although higher ultradian frequencies appeared to occur in BPD. For positive mood, lower frequency quasi-circadian changes were evident for all groups. Finally, for irritable mood there appeared to be higher frequency ultradian components for all three groups along with different mean levels as for negative mood.

5.5 Quantifying circadian rhythms

Figure 5.7 shows the behavioural and physiological data from a single subject (total acceleration, vertical acceleration and heart rate) to demonstrate circadian rhythms. Acceleration data were preprocessed and integrated to give a smooth measure of movement. There is an obvious first harmonic at around one cycle per 24 hours, corresponding to the circadian period.

The heart rate data were preprocessed to remove artefacts in the signal. An indicative example of the recorded data is presented in Figure 5.7 (e). The heart rate signals again exhibit natural sinusoidal behaviour, as do the integrated acceleration signals in Figure 5.7 (b) and (d).

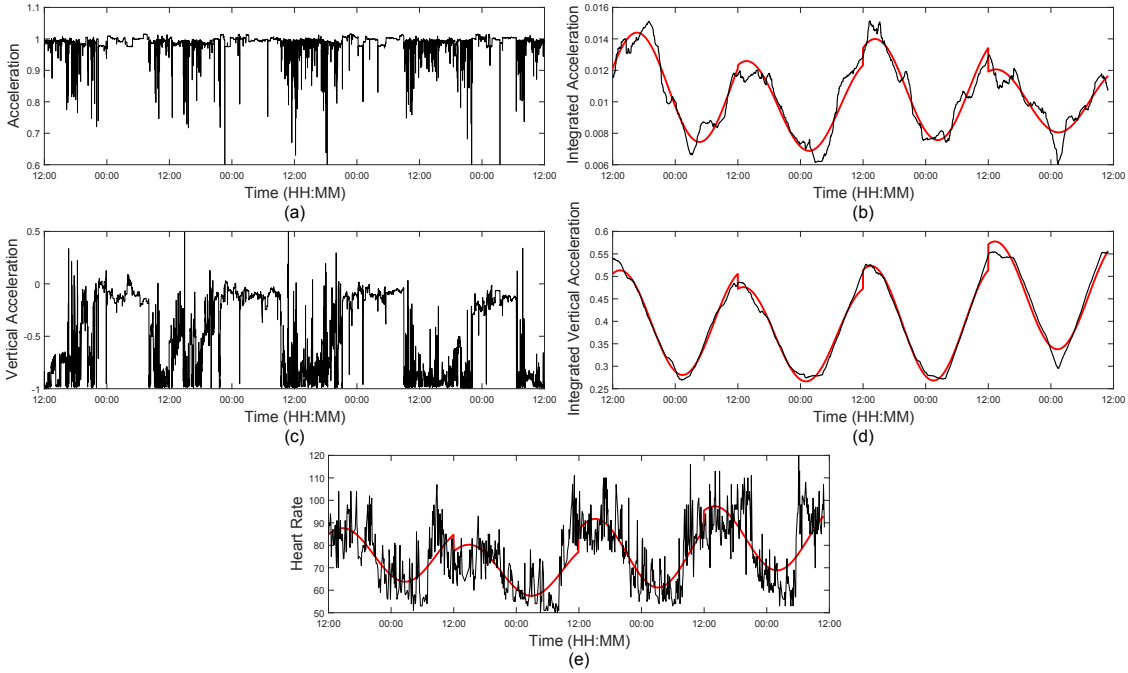


Figure 5.7: (a) An example of the raw total acceleration recorded from the Proteus patch. (b) The integrated total acceleration signal over 6 hour windows. (c) A corresponding example of the vertical acceleration signal recorded from the Proteus patch. (d) the integrated vertical acceleration signal. (e) The corresponding heart rate signal recorded from the Proteus patch. The cosinor fits to each 24 hour period (midday to midday) shown in red in (b), (d), and (e).

Circadian rhythms were quantified by using the cosinor method of fitting a sine wave to a 24 hour signal by quantifying the phase, MESOR and amplitude. A sine wave was fit to each of the four consecutive days of total acceleration, vertical acceleration and heart rate from midday to midday, thus giving four measures of phase, MESOR and amplitude for each signal. An example of the 24 hour sinusoids fit to the integrated total acceleration, integrated vertical acceleration and heart rate are shown in Figure 5.7 (b), (d), and (e) respectively.

5.6 Circadian desynchronisation

The signals of vertical acceleration will be referred to as measuring 'sleep', recognising that it is an imperfect estimate of just one element of sleep. The total acceleration will be referred to as activity.

The average circadian rhythms of participants were calculated by finding the

mean of the phase, MESOR and amplitude of the four fitted sinusoids, creating an average sinusoid for each participant. Average sinusoids for each subject group were then calculated by finding the mean of the phase, MESOR and amplitude across the participants. These subject group sinusoids are shown in Figure 5.8 for activity, sleep and heart rate (confidence intervals are not shown in the figure, variability measures are displayed in Table 5.4).

Internal desynchronisation of the rhythms were calculated by finding the time difference between the phases of each of the modalities (heart rate phase minus activity phase, heart rate phase minus sleep phase and activity phase minus sleep phase). This results in three sets of four time differences for each participant, the mean difference is then found for each participant and group differences are then calculated from the mean and standard deviation of all participant differences. Statistically significant differences are marked on Figure 5.8.

The average first harmonic sinusoidal fits for the circadian measures are shown in Figure 5.8 for each subject group, significant phase differences are marked with an asterisk and correspond to the within group phase differences in Table 5.4 . For the HC participants, data largely overlap, with a small phase lag (1.29 hours) between activity and sleep, as would be expected: heart rate is in phase with activity. In BD, the difference between activity and sleep was absent; instead there were significant phase delays in the heart rate signal of about 1 hour compared with sleep and activity. For BPD there was a 2 hour phase lag between activity and sleep and almost 3 hour delay between peak activity and peak heart rate. In addition the average heart rate level in BPD was substantially higher then HC, with BD intermediate, even with similar activity levels across all groups. These statistical differences between groups and within groups are quantified in Table 5.4. Also in Table 5.4, the average phase, MESOR and amplitude is compared for activity, sleep and heart rate across groups; the average values are broadly similar across groups, with the exception of the heart rate MESOR which was elevated in BPD compared with HC, although not statistically significant after FDR correction.

Table 5.4: Median and interquartile range of the participant averaged phases, MESORs and amplitudes of the daily sinusoid fits for each of the participant groups, and the difference between phases of each modality. Statistical significance pairwise comparisons across the three groups using the Wilcoxon statistical hypothesis test and FDR correction are shown.

Within group phase differences tested against zero mean						
	BD	**BPD**	**HC**	**BD (FDR)**	**BPD (FDR)**	**HC (FDR)**
HR-ACT*	0.72 ± 4.17	3.11 ± 3.08	0.46 ± 4.06	**0.017**	**<0.001**	0.246
HR-SLP*	0.56 ± 3.41	0.99 ± 1.66	-0.83 ± 2.11	**0.006**	**0.006**	0.051
ACT-SLP*	-0.16 ± 2.90	-2.12 ± 3.21	-1.29 ± 2.87	0.180	**0.005**	**0.004**
Group differences in phase, MESOR, and amplitude						
	BD	**BPD**	**HC**	**BD vs BPD (FDR)**	**BD vs HC (FDR)**	**BPD vs HC (FDR)**
Activity						
Phase*	14.09 ± 2.83	12.34 ± 3.57	12.82 ± 3.31	0.253	0.410	0.403
MESOR*	0.014 ± 0.004	0.013 ± 0.003	0.014 ± 0.004	0.276	0.418	0.418
Amplitude*	0.003 ± 0.002	0.003 ± 0.001	0.003 ± 0.001	0.294	0.401	0.380
Sleep						
Phase*	14.25 ± 1.68	14.46 ± 2.07	14.12 ± 1.31	0.398	0.483	0.391
MESOR*	0.35 ± 0.08	0.34 ± 0.07	0.36 ± 0.07	0.477	0.411	0.385
Amplitude*	0.11 ± 0.02	0.11 ± 0.03	0.11 ± 0.02	0.325	0.444	0.276
Heart rate						
Phase*	14.81 ± 3.21	15.45 ± 2.07	13.28 ± 2.37	0.384	0.086	0.051
MESOR*	75.24 ± 7.08	77.65 ± 5.69	74.48 ± 2.62	0.251	0.425	0.275
Amplitude*	8.10 ± 2.54	8.67 ± 3.45	7.41 ± 2.62	0.369	0.300	0.289

*indicates the mean ± standard deviation is shown

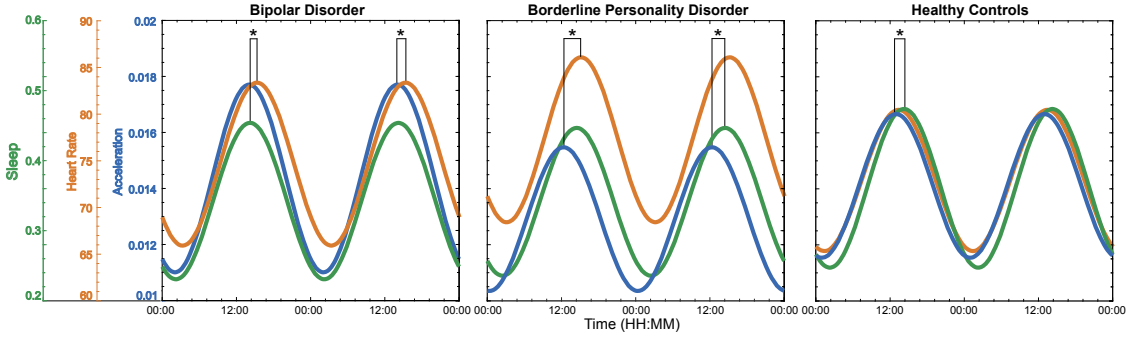


Figure 5.8: Statistically significant differences ($p<0.05$) between the phase of each pair of sinusoids, testing if the mean differs from zero, are marked with an asterisk. A significant difference suggests there is a phase lag between the two measures

5.7 Conclusions

The abnormalities in BD were modest in contrast with the widely held view that BD is, in some quite fundamental sense, a disorder of circadian function. In fact, the strongest evidence has hitherto related to variability in circadian function rather than formal evidence for phase changes or desynchronisation. Thus actigraphy studies

have shown less stable and more variable circadian activity in BD even in euthymia [208, 204, 209, 206], with additional disruptions to sleep patterns [265]. In the present study, there was 1 hour phase delay for heart rate in relation to activity, and only trend effects on the level of activity. Increased levels of nocturnal activity have been described in unmedicated young people with hypomanic experience [211]. The normality described here may in part reflect the impact of drug treatment. However, it is difficult to argue without measurement of melatonin or other circadian variables that circadian rhythm per se remains a problem or a potential target for management in such patients. Variability in day to day in sleep may be a different matter.

BPD is not commonly described as being associated with circadian disturbance, so the effects described here are of great potential interest and clinical importance. Abnormalities of the sleep wake cycle have been described before in patient samples including BPD as described in Chapter 2. The delay in sleep found suggesting sleep onset latency in BPD, which is often reported in the literature, as in Section 2.3.3. Clarification of the prevalence of circadian rhythm sleep disorders (CRSD) in BPD merits further study. It is striking but perhaps not surprising that no emphasis is placed on possible CRSD in the contemporary management of BPD. CRSD has been studied in small populations [266], but not systematically in large numbers of patients, with phototherapy or drugs like melatonin or agomelatine to phase advance (and so reset) the circadian cycle. Clinical experience suggests this is highly effective [266]. In a pilot study of a small group of BPD patients with variable sleep-wake profiles, some benefit of light therapy was observed over 3 weeks [218]. Previous sleep investigations in BPD have used polysomnography, with a view to comparing BPD with mood disorder and have identified sleep disorder as a broadly neglected element of the management in BPD.

Circadian mood variation is an important feature of severe depression [267], but has received limited attention in studies of euthymic BD and BPD patients. It has been shown that circadian rhythms of mood exist across the participant groups. The use of a simple smart-phone based questionnaire, allowed an uncomplicated

method of monitoring mood. Inspection of the average mood profile suggested that positive mood had a significant circadian component.

The cohort in the study is relatively small due to the technical limits of the devices used to record data. Accordingly improved devices will provide future opportunities to replicate and extend the present approach. The participant sample had to be very co-operative in wearing the devices and recording subjective data, so are a selected group in that sense.

Some limitations exist in the analysis performed in this chapter. The vertical acceleration metrics have been labelled as measures of sleep due to the changes in acceleration as the body position of participants change (lying down), however these metrics have not been validated against true sleep times and it is likely they are measures of periods of rest. The fact that PCA requires the multivariate time series to be independent was not met due to the similarities between the six mood items of Mood Zoom. PCA was used in order to directly compare to previous work carried out, however future work should focus on alternate methods of determining the latent structure such as functional PCA. No correction for weekdays and weekend recordings were made, which will have added to the variance of the recordings, and perhaps reduced the capacity to detect cross-sectional differences in the circadian behaviour of the groups. Consequently within group desynchronisation is emphasised as the major finding. It is also possible that environmental and behavioural differences existed between the groups, such as timings and composition of food, light exposure, social stress and other factors. These may have found expression in the measures we could make. Finally, most patients were medicated, but with differences between the BD and BPD groups.

Participants were not excluded from the study based on the scorers of their clinical questionnaires. A small number of BD participants scored over the QIDS threshold for depression, although no BD participants were considered to be in a depressive state as they had not met the criteria of being above the clinical threshold for two consecutive weeks. The majority of the BPD participants were over the QIDS threshold, although the responses to QIDS in BPD is less well understood,

the increase in levels of depression may have a causal effect on the desynchronisation of the rhythms rather than being a symptom of BPD. Time between episodes represents an at risk state to which the lived environment contributes, whether on medication or not. The point of intensive subjective or objective monitoring is to identify relevant differences that may serve as a future focus for disease management.

This chapter has demonstrated high intensity monitoring of mood follows the same structure as longitudinal daily monitoring. It also has demonstrated significant desynchronisation of circadian rhythms of activity, sleep and heart rate in both BD and BPD, confirming BD being associated with disrupted rhythms and indicating that BPD is also linked to circadian disturbances. Chapter 6 will investigate variability of mood and circadian rhythms over the same period and will explore the association between mood and circadian variability in the three subject groups.

6

Variability of Circadian Parameters

The following publication is based on the work presented in this chapter:

- **Carr, O.**, Saunders, KEA., Tsanas, A., Bilderbeck, AC., Palmius, N., Geddes, JR., Foster, R., Goodwin, GM., and De Vos, M. (2018). Variability in phase and amplitude of diurnal rhythms is related to variation of mood in bipolar and borderline personality disorder. *Scientific Reports*, 8(1):1649.

BD is associated with periods of elated and depressed mood interspersed by periods of euthymia. Major mood episodes can last for weeks to months [29, 33]. However, even when well, people with BD experience considerable inter-episode mood instability. Such instability is not unique to BD. It is also reported as a major problem by patients with BPD and is present in 14% of the general population [41]. Finding markers able to determine these periods of increased mood variability may allow for action to be taken to stabilise the mood of patients. Day to day variations in behavioural and physiological parameters may provide these markers, such as measures of activity, sleep or heart rate, as changes in these signals have all previously been associated with deterioration in affect state in BD and BPD, as described in Sections 2.3.2 and 2.3.3.

Chapter 5 quantified desynchronisation between circadian rhythms, finding significant internal desynchronisation in BD and BPD. The aims of this chapter are

to: i) develop a method of quantifying circadian rhythm regularity through day to day differences, ii) explore how circadian variability of activity, sleep, heart rate and mood are altered in BD, BPD and HC, and iii) to investigate the links between circadian variability and mood variability in BD and BPD participants.

Section 6.1 will give a background to mood variability, the methods used to quantify variability and the comparison of mood variability between BD, BPD and HC participants. Section 6.2 will describe the methods used to measure circadian variability and the results of the group comparisons, with Section 6.3 exploring the links between mood variability and circadian variability.

6.1 Mood variability

Mood instability is not well understood. One way to imagine its origin is to start from mechanisms that confer stability on biological systems. The best characterised example is perhaps the circadian or clock system present in all cells and particularly highly organized for regulation of brain function, with Chapter 5 and Figure 5.6 finding a circadian component of mood.

Mood instability in BD has been widely shown, with increased mood variability in euthymic BD patients compared to HC participants being shown through retrospective questionnaires, indicating BD is not restricted to episodes of depression and mania but is also associated with mood instability between episodes [52]. More recent studies have used more continuous daily monitoring of mood in BD with smartphones, again finding increased mood variability in inter-episodic periods [231, 232]. Patients with BPD are not as widely studied, however similar affective lability has been described in BPD [268]. Daily self-reported mood collected using Mood Zoom reveals increased mood variability in both BD and BPD [254]. In addition, mood variability measures were able to discriminate between the three subject groups, suggesting mood varies differently across the disorders.

6.1.1 Quantifying mood variability

As described in Section 5.4, the latent structure of the Mood Zoom questionnaire was found using PCA from one week of high intensity recordings. The results confirmed that the latent structure found for multiple daily recordings over a week is the same as the structure found from single daily entries over longer periods, as found in [254, 264]. Variability measures are calculated from the first three principal components of the Mood Zoom scores, interpreted as 'negative' mood, 'positive' mood and 'irritable' mood respectively. Mood variability can be calculated as a day to day variability from the time series of daily Mood Zoom entries throughout the study, or as a daily mood variability from the 10 Mood Zoom entries per day during the high intensity monitoring week.

A range of variability measures can be used to measure Mood Zoom variability. The standard deviation is the most common measure of variability however it is effected by outliers in the data, the Teager-Kaiser energy operator (TKEO) takes into account both the amplitude and the frequency of the signal variability, Shannon entropy gives a measure of the total uncertainty in the signal but gives little information about short term variability, and the root mean square of successive differences (RMSSD) measures short term variability through successive differences but only quantifies amplitude changes. As none of these measures outperform the others in all aspects it is useful to apply multiple measures in practice. The variability measures used are defined as:

$$std = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(x_i - \mu_x)^2}, \tag{6.1}$$

$$TKEO = \frac{1}{N}\sum_{i=2}^{N-1}(x_i^2 - x_{i-1}x_{i+1}), \tag{6.2}$$

$$entropy = \sum_{i=1}^{N} p(x_i)\log(p(x_i)), \tag{6.3}$$

$$RMSSD = \sqrt{\frac{1}{N}\sum_{i=1}^{N-1}(x_{i+1} - x_i)^2}, \tag{6.4}$$

Table 6.1: Comparing variability of all Mood Zoom recordings during the high intensity week across the three groups, and statistical significance pairwise comparisons across the three groups (BD, BPD, HC) using the Wilcoxon statistical hypothesis test and FDR. Values shown are the median plus or minus the interquartile range (iqr).

	BD (median±iqr)	**BPD** (median±iqr)	**HC** (median±iqr)	**BD vs BPD** (FDR)	**BD vs HC** (FDR)	**BPD vs HC** (FDR)
$\mathbf{MZneg_{std}}$	0.99±0.85	1.71±1.11	0.35±0.47	**1.57E-03**	**2.31E-02**	**1.79E-04**
$\mathbf{MZneg_{TKEO}}$	0.79±0.88	1.94±4.86	0.12±0.43	**1.37E-02**	**4.78E-02**	**6.62E-04**
$\mathbf{MZneg_{RMSSD}}$	1.07±0.64	1.69±1.46	0.42±0.62	**2.02E-03**	**2.23E-02**	**2.03E-04**
$\mathbf{MZpos_{entropy}}$	-6.67±122.65	6.67±3.91	-118.28±414.04	**4.34E-03**	**7.64E-02**	**7.76E-04**
$\mathbf{MZpos_{std}}$	0.91±0.70	1.42±0.56	0.62±0.52	**1.21E-03**	6.13E-01	**7.76E-04**
$\mathbf{MZpos_{TKEO}}$	0.39±0.77	1.40±1.04	0.23±0.54	**2.02E-03**	9.25E-01	**4.34E-03**
$\mathbf{MZpos_{RMSSD}}$	0.91±0.52	1.38±0.54	0.66±0.64	**1.87E-03**	7.35E-01	**1.87E-03**
$\mathbf{MZpos_{entropy}}$	-9.71±134.27	3.83±8.86	-65.57±143.14	**2.18E-03**	**4.14E-01**	**1.49E-03**
$\mathbf{MZirr_{std}}$	0.56±0.43	1.01±0.49	0.33±0.46	**1.87E-03**	**2.39E-02**	**2.98E-04**
$\mathbf{MZirr_{TKEO}}$	0.24±0.31	0.81±0.69	0.09±0.34	**1.25E-03**	**5.43E-02**	**4.78E-04**
$\mathbf{MZirr_{RMSSD}}$	0.71±0.44	1.15±0.41	0.40±0.59	**2.02E-03**	**4.34E-02**	**6.62E-04**
$\mathbf{MZirr_{entropy}}$	-23.90±92.84	-3.50±13.93	-188.99±547.87	**2.64E-03**	**5.27E-02**	**7.76E-04**

Statistically significant differences at the FDR=0.05 level appear in bold. "MZneg" denotes the negative principal component of Mood Zoom, "MZpos" denotes the positive principal component of Mood Zoom, and "MZirr" the irritability principal component of Mood Zoom computed using the PCA loadings [254].

where N is the total number of samples in the signal (number of Mood Zoom entries), x_i is the i^{th} value of the signal (i^{th} Mood Zoom entry) and μ_x is the mean of the signal (mean Mood Zoom entry). The entropy measure used in this work is the Shannon entropy, although many other variations in entropy measures exist, Shannon entropy is used for direct comparison to previous studies on mood variability [264].

The variability measures are calculated on the principal components of Mood Zoom for the four days corresponding to the heart rate and actigraphy recordings (the same time periods and scores as are used in chapter 5). The approximate sampling frequency is one entry per hour, however there is a nightly gap for each 24 hour period where no Mood Zoom entries are recorded, as the RMSSD and TKEO measures take into account adjacent entries, the values across the period at night are ignored for these two measures.

These four measures of variability are applied to the 'negative' mood (MZneg), 'positive' mood (MZpos) and 'irritable' mood (MZirr). The median and interquartile range of the variability measures are shown in Table 6.1 for the three subject groups. Differences in variability between groups were tested for using the Wilcoxon test, with FDR correction for multiple testing applied.

From Table 6.1 it can be seen that there were very large differences in all measures of daily Mood Zoom variability in negative mood, with BPD participants more variable than BD, who were more variable than HC participants. A similar pattern was observed for daily measures of irritability and, to a lesser degree, positive mood. All pairwise comparisons were found to be statistically significant, with the exception of comparisons of positive Mood Zoom variability between BD and HC participants.

Previous studies have shown that there are distinctive differences in the variability of subjective mood experienced by BPD, BD and HC groups [254]. These differences in variability were measured from one mood entry per day over a number of months for each participant, with the variability able to discriminate between the three subject groups. These results suggest monitoring of mood variability has the potential to aid with diagnosis of mental health disorders and such measures may be useful in determining the outcomes of treatments in BD and BPD. However single mood recordings per day require longitudinal studies in order to obtain enough measures to accurately determine mood variability.

The BPD participants can be discriminated from the other two groups through the intradaily mood variability measures, which confirms the clinical impression that mood is both more variable and at a higher frequency in BPD patients. High intensity monitoring was able to achieve similar results to that of longitudinal monitoring of single daily scores and thus can reduce the sampling interval required to acquire mood data in the future for variability analysis. The results found here could have considerable benefits as an aid for diagnosis through finding differences in the mood variability of BD and BPD with are notoriously difficult to distinguish. In addition the short, high intensity monitoring is a faster alternative to collect mood scores, which are typically only recorded once per day.

6.2 Circadian variability

Disruption of sleep is observed to be a prominent feature of psychiatric disorders in general and BD in particular [269, 270], which will operate through the homeostat, and the possible intrinsic variability in the circadian rhythm of the clock. The effects

of the clock are obvious in relation to jet lag, before the clock resets to local time after long haul travel [271]. More subtle disruption of the clock's circadian rhythm has been studied infrequently in psychiatric patients [272]. Thus, descriptions of sleep disturbance tend to be informal and do not distinguish between homeostat and clock mechanisms in its causation.

Stabilisation of circadian rhythms in BD is the objective of a number of current treatments [273]. Initial studies on BD measured circadian disturbance through alterations to the sleep-wake cycle using simple estimates of sleep onset and offset from diaries and questionnaires [179]. More recently, actigraphy and melatonin levels have been employed as more objective measures [272, 204, 178]. Longer term recordings of actigraphy allow a wider range of circadian measures to be calculated, for example the least active 5 hours of nocturnal activity (L5), most active 10 hour period (M10) or average daily activity [126]. These measures, in addition to quantifying the phase of 24 hours of activity through fitting a sinusoid, found BD participants to have less regular circadian rhythms compared to controls [209, 210]. There have been far fewer studies on circadian disruption in BPD but a relatively recent review by Fleischer et al. described evidence of altered circadian rhythms in BPD, along with considerable sleep disturbance [59]. Preliminary candidate gene studies have also suggested a link between circadian genes and susceptibility to BD [91].

Variability in circadian rhythms or sleep may contribute to mood symptoms in BD and BPD. Variations in circadian function can be quantified as activity in sleep-wake cycle variability [274]. In addition, subtle changes in temperature and ANS function also vary in a circadian cycle. Broadly speaking, sympathetic nervous system activity is activating (e.g. increasing heart rate), whereas parasympathetic nervous system activity imposes resting states in the body (e.g. returning the heart rate to a normal level) [94]. If circadian instability is related to mood instability, objective measures of variability in activity, sleep and heart rate should correlate with variability of subjective experience [29, 209]. A relation between objective

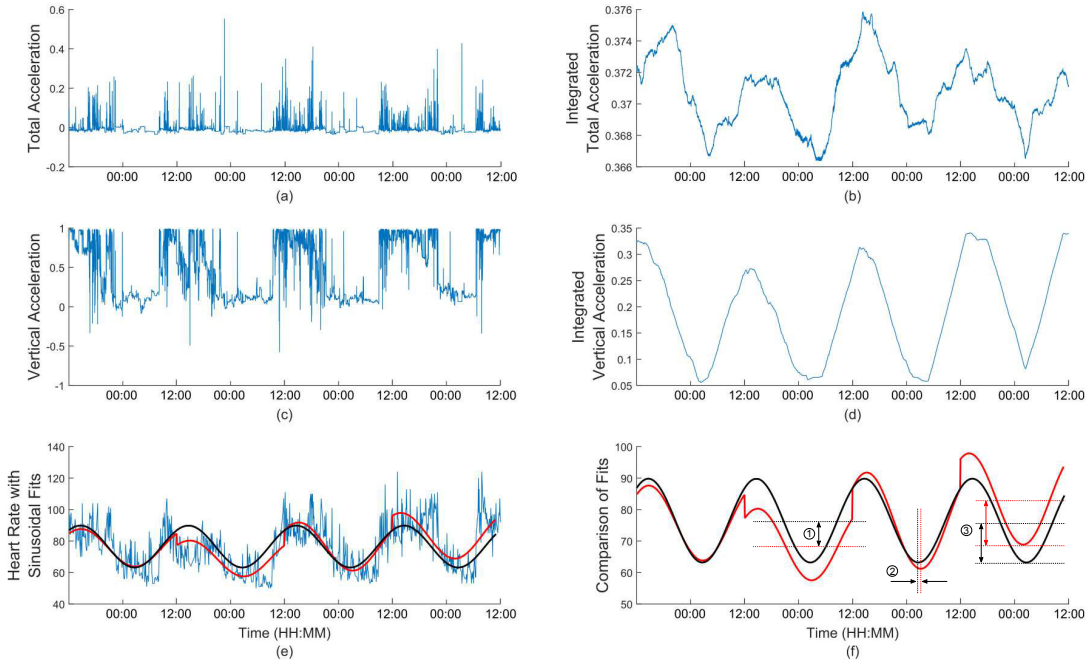


Figure 6.1: An example of data recorded for the Proteus patch for one participant. (a) total acceleration, (b) the integrated total acceleration, (c) vertical acceleration, and (d) the integrated vertical acceleration. (e) the heart rate with a sinusoid fit to each 24 hour period in red and to the total data in black. (f) the comparison between daily and total sinusoids with difference between MESORs (1), phases (2) and amplitudes (3) shown.

measures of circadian variability and symptoms of mood would provide a tool to aid with monitoring of mental health in patient populations.

6.2.1 Measures of circadian variability

Heart rate data was pre-processed to remove artefacts in the signal as described in Section 5.3.2.1. An indicative example of the recorded data is presented in Figure 6.1. The heart rate signals exhibited a natural sinusoidal behaviour (Figure 6.1 (e)). The acceleration signals did not show this pattern as clearly, therefore the signals were integrated to emphasise this sinusoidal behaviour (see Figure 6.1 (b) and (d)). Pre-processing and integration of acceleration signals is described in more detail in Section 5.3.1.1.

Quantification of circadian rhythms allows for the analysis of behavioural and physiological regularity within participants or subject groups. Here, the analysis of circadian rhythms has been extended from Chapter 5 through fitting of sine waves

to both the entire signal and to each 24 hour section of the signal for integrated total acceleration, integrated vertical acceleration and heart rate (see Figure 6.1 (b), (d) and (e)). Comparison of the daily sinusoids to the sinusoid fit to the entire signals allows for quantification of the deviation of the daily sinusoids from the total sinusoid to measure the variability in the cosinor parameters.

The circadian analysis was performed on the heart rate signal, in addition to the integrated total acceleration signal (a measure of total activity) and the integrated vertical acceleration signal (a measure of sleep or rest-activity, due to changing reference angle of the wearer). Sinusoids are fit directly to the raw heart rate signal from midday to midday in order to emphasise the night time behaviour, as shown in red. The sinusoids were fit with a fixed period of 24 hours and the amplitude and phase were optimised to give a least squares fit. Secondly, a sinusoidal fit was carried out on the entire signal to provide an average circadian pattern for the length of the signal, with an identical fitting method as the daily fits, shown in black in Figure 6.1.

6.2.1.1 Circadian variability features

Circadian features were calculated by comparing the daily sinusoid fits of heart rate, total acceleration and vertical acceleration to the total sinusoid fits to the same data. The similarity between the daily and total fits indicates the degree of circadian regularity during the period of measurement.

Differences between the fits were measured through differences in the MESOR (Figure 6.1 (f), ①), or average, the phase (Figure 6.1 (f), ②) and the amplitude (Figure 6.1 (f), ③); the timings of the minimum values of the daily sinusoidal fits are found (Td), as well as the amplitudes (Ad) and MESORs (Md), in addition to the timings of the minimum values for the total (or weekly) sinusoidal fit (Tw) and the corresponding amplitudes (Aw) and MESORs (Mw). The mean and standard deviations of the differences between the daily and total sinusoids are found, as well as the RSS error between the daily and total fits. Also the mean and standard deviation of the successive differences of daily sinusoid measures are calculated. All features are listed and calculated as:

- The mean of the difference in phase between the daily and total fits

$$\mu_T = \frac{1}{D}\sum_{i=1}^{D}(Td_i - Tw_i) = \text{meanPhase}, \tag{6.5}$$

where D is the total number of days (in this work $D = 4$). Similarly the mean difference in amplitude, μ_A (meanAmplitude), and MESOR, μ_M (meanMESOR), can be calculated from Ad and Aw, and Md and Mw respectively.

- The standard deviation of the difference in phase between the daily and total fits

$$\sigma_T = \sqrt{\frac{1}{D}\sum_{i=1}^{D}\Big((Td_i - Tw_i) - \mu_T\Big)^2} = \text{stdPhase}, \tag{6.6}$$

The standard deviation in amplitude, σ_A (stdAmplitude), and MESOR (stdMESOR), σ_M, can be calculated from Ad, Aw and μ_A, and Md, Mw and μ_M respectively.

- The RSS between the daily sinusoids and total sinusoid is calculated as

$$\text{RSS} = \sum_{i=1}^{N}\Big(SIN_i^{day} - SIN_i^{total}\Big)^2 \tag{6.7}$$

where SIN represents the fitted sinusoids and N is the length of the signal.

- The mean of the successive differences in phase are calculated as

$$\mu diff_T = \frac{1}{(D-1)}\sum_{i=1}^{D-1}(Td_{i+1} - Td_i) \tag{6.8}$$

with the mean of the successive differences in amplitude, $\mu diff_A$, and MESOR, $\mu diff_M$, calculated from A_d and M_d respectively.

- The standard deviation of the successive differences in phase is calculated as

$$\sigma diff_T = \sqrt{\frac{1}{(D-1)} \sum_{i=1}^{D-1} \Big((Td_{i+1} - Td_i) - \mu diff_T \Big)^2} = \text{diffPhase} \qquad (6.9)$$

  with the standard deviation of the successive differences in amplitude, $\sigma diff_A$ (diffAmplitude), and MESOR, $\sigma diff_M$ (diffMESOR), calculated from A_d and $\mu diff_A$, and M_d and $\mu diff_M$ respectively.

These new measures quantify regularity of circadian rhythms over longitudinal recordings. They encapsulate how the timings (phase) of the rhythms are shifting along with how both the average (MESOR) and range (amplitude) of recordings differ from day to day, as well as giving an overall measure of circadian regularity through the RSS between the daily and total sinusoids. In contrast, the standard measures reported in the literature are based on actigraphy measures defined almost two decades ago: these include most active and least active periods and transitions between rest and activity[126]. A cosinor method has also been used which quantifies phase, amplitude and MESOR, and can be generalised to other recordings (such as heart rate[260]). However, the new measures which find the difference from an average or total cosinor fit for each day allow for better measures of regularity on an individual participant level.

All the features are calculated for heart rate and acceleration data to give measures of the range of: heart rate and activity levels through the amplitude, the average heart rate and activity levels through the MESOR and the timings of the maximum or minimum heart rate and activity levels through the phase. As the vertical acceleration is a measure of sleep, the timings of the sleep can be indirectly measured through the phase and the amount of sleep or rest-activity, can be measured through the MESOR. The vertical acceleration measures step changes from when the participant is lying down and standing as can be seen in Figure 6.1 (c), therefore the amplitude measures are not calculated for the vertical acceleration or sleep signal.

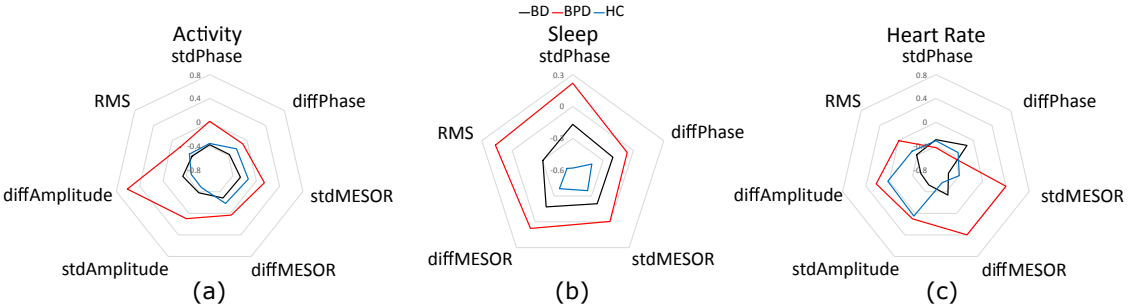


Figure 6.2: Standardised median circadian feature values across the three subject groups, separated into activity (a), sleep (b) and heart rate (c) features. stdPhase, stdMESOR and stdAmplitude denote the standard deviation of the differences between the daily and total sinusoid fit. diffPhase, diffMESOR and diffAmplitude denote the standard deviation of successive differences in the daily sinusoid fits. RSS is the residual sum of squares between the daily and total sinusoid fits. Measures were standardised by subtracting the mean and dividing by the standard deviation of each feature for the groups combined. Standardisation is only performed to visually compare measures in this figure.

6.2.1.2 Variability results

Circadian variability features were calculated from four simultaneous days of total acceleration, vertical acceleration and heart rate signals, the same participants and data as used in Chapter 5, with participant information shown in Section 5.1.

The patterns of circadian variability of participant groups are displayed in spider plots of the medians of the standardised circadian features for activity, sleep, and heart rate. Figure 6.2 shows standardised measures, obtained by subtracting the mean and dividing by the standard deviation of each feature for the groups combined. Standardisation is only performed to compare metrics visually in Figure 6.2. On inspection, variability of activity measures is increased in the BPD participants; BD and HC were not distinguishable and had very similar variability in activity measures, as shown in Figure 6.2 (a). For sleep, variability is greater in BPD participants for phase and amplitude measures; BD was also variable, but intermediate between BPD and HC participants, as can be seen in Figure 6.2 (b). For heart rate, all participants groups showed similar amounts of variability in the phase of the heart rate rhythms. BPD participants showed an increase in the MESOR variability compared with BD and HC participants; BD had less variability in the amplitude of heart rate compared to both BPD and HC participants, with the variability shown in Figure 6.2 (c).

Table 6.2: Comparing variability of circadian features of heart rate, activity and sleep across the three groups, and statistical significance pairwise comparisons across the three groups (BD, BPD, HC) using the Wilcoxon statistical hypothesis test.

Circadian features	**BD** (median±iqr)	**BPD** (median±iqr)	**HC** (median±iqr)
	Total Acceleration		
stdPhase	1.48±0.05	2.18±0.09	1.52±0.04
stdMESOR	7.1e-4±5.7e-4	9.3e-4±5.3e-4	8.5e-4±5.1e-4
stdAmplitude	6.4e-4±4.4e-4	9.0e-4±7.2e-4	6.5e-4±6.1e-4
diffPhase	2.29±0.08	3.15±0.16	2.75±0.08
diffMESOR	10.2e-4±6.9e-4	12.8e-4±6.3e-4	10.4e-4±8.2e-4
diffAmplitude	9.5e-4±7.2e-4	18.1e-4±14.3e-4	8.9e-4±10.3e-4
RSS	1.1e-6±1.2e-6	1.6e-6±1.4e-6	0.9e-6±1.1e-6
	'Sleep'		
stdPhase	0.93±0.03	1.17±0.05	0.67±0.02
stdAmplitude	0.017±0.016	0.019±0.017	0.015±0.010
diffPhase	1.298±0.048	1.462±0.104	1.057±0.023
diffAmplitude	0.03±0.02	0.03±0.03	0.02±0.02
RSS	0.001±0.001	0.001±0.001	0.001±0.001
	Heart Rate		
stdPhase	1.715±0.074	1.467±0.080	1.681±0.104
stdMESOR	1.768±1.756	3.196±1.837	2.036±1.422
stdAmplitude	2.03±1.94	2.80±2.06	2.74±1.33
diffPhase	2.69±0.10	1.94±0.09	2.24±0.11
diffMESOR	2.86±3.71	4.81±4.66	2.25±2.46
diffAmplitude	2.80±2.16	4.60±2.57	4.13±2.07
RSS	11.24±9.81	16.71±15.64	12.64±12.81

No statistically significant differences were found after FDR correction.

Non-standardised medians and interquartile ranges of the variability features are shown in Table 6.2. No statistically significant differences were found between groups after using the Wilcoxon test and FDR correction to determine group differences.

6.2.2 HMM Variability

In order to verify the circadian variability results, alternative methods of quantifying circadian variability were evaluated. The cosinor method used to fit sinusoids to data quantifies the underlying 24 hour rhythms in the data, but is unable to quantify or estimate parameters which have commonly been used in the literature, such as sleep timings and sleep quality measures [212, 211].

HMMs are capable of giving a more detailed estimates of certain aspects of

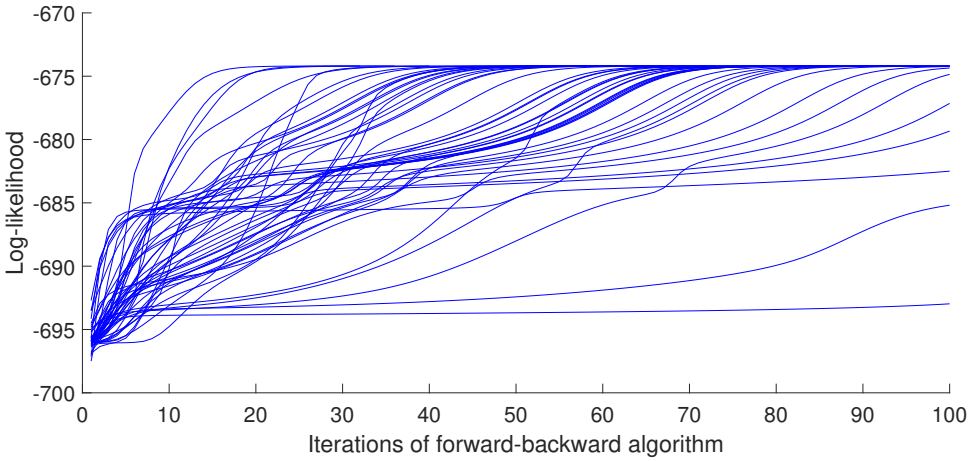


Figure 6.3: The log-likelihood after each iteration of the forward-backward algorithm for one participants with 50 different random initialisations of the initial HMM parameters.

circadian cycles such as the sleep-wake cycle and sleep timings. Here, HMMs with two hidden states are applied to the same four days of total acceleration data to which the cosinor analysis was applied. The Viterbi algorithm is used to determine the most likely sequence of the two hidden states which can be defined as an 'active' state and an 'inactive' state. The HMMs and the Viterbi algorithm used here are described in detail in Chapter 3.

6.2.2.1 Training the HMMs

The initialisation of the HMM parameters are set randomly. The initial probabilities of the two states, $\boldsymbol{\pi}$, are randomly set from a uniform distribution between 0 and 1 and are then normalised by dividing by their sum in order for the probabilities to sum to one. The values two by two transition matrix are also randomly set to be between 0 and 1, each row is then normalised by the sum of the values in that row to ensure the probabilities of leaving each state sum to one. Each data point in the signal is randomly assigned to one of the two groups, the mean and standard deviation of the two randomly assigned groups is found and used to define the two initial probability distributions of the observations.

As the Baum-Welch algorithm updates the HMM parameters the log-likelihood of the model parameters is calculted to determine the convergence of the parameter values. Figure 6.3 shows the log-likelihood of the Baum-Welch algorithm after each

iteration for one participant, the Baum-Welch algorithm has been run 50 times with random initialisation each time. From Figure 6.3 it can be seen that the majority of the initialisations reach a similar maximum log-likelihood before 100 iterations of the Baum-Welch algorithm, with 50% of initialisations reaching the maximum before 50 iterations. The maximum number of iterations allowed for the Baum-Welch algorithm was therefore set to 100 and a tolerance of 0.0001 was chosen. If the change in log-likelihood of one iteration compared to the previous iteration was less than the tolerance, the Baum-Welch algorithm stops optimising. Three random initialisations were made for each participant, with the forward-backward algorithm run on each of the initialisations. The optimised parameters with the highest log-likelihood from the three models was chosen as the final set of parameters, this was to try and ensure a fully optimised set of parameters is chosen whilst reducing the computational time.

6.2.2.2 HMM features

Once an optimised set of HMM parameters has been obtained, the Viterbi algorithm can be used to determine the most likely sequence of hidden states. Figure 6.4 shows an example of the Viterbi sequence of hidden states calculated from the four days of total acceleration signal recorded from the Proteus patch. Similarly to the cosinor method, the hidden state sequence is split into individual 24 hour periods from midday to midday, with an example day shown in Figure 6.4. Features are then calculated from each 24 hour period and are defined as:

- Number of inactive periods - the total number of transitions from an 'active' state to an 'inactive' state.
- Total inactive time - total hours spent in 'inactive' states during the 24 hour period.
- Estimated sleep time - total time of the longest 'inactive' period, which is assumed to be when the participant is sleeping.
- Estimated sleep onset - time of the start of the longest 'inactive' period.

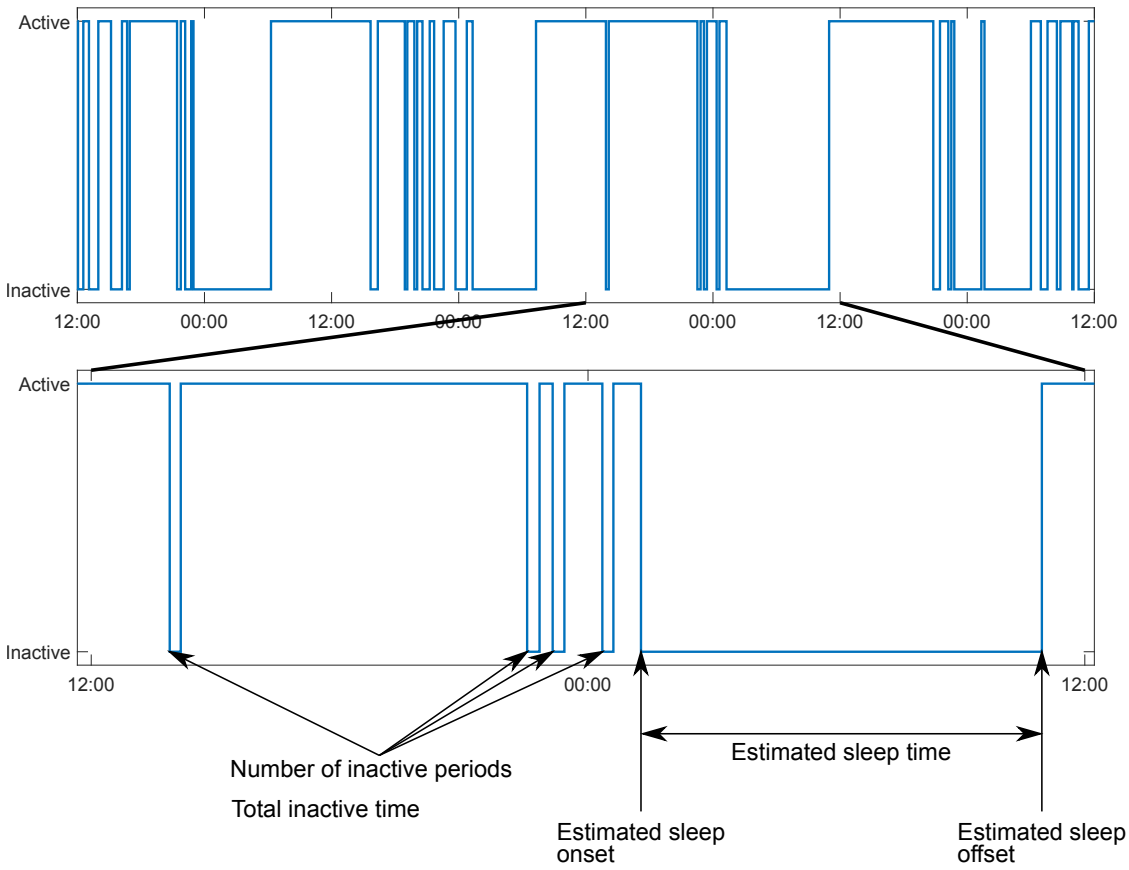


Figure 6.4: The five circadian/sleep features calculated for each 24 hour period of the Viterbi algorithm sequence of hidden states.

- Estimated sleep offset - time of the end of the longest 'inactive' period.

Features are calculated from the four days of acceleration signals. As the features mentioned above are calculated on 24 hour periods, the means and standard deviations of the features are found for the week, thus giving average measures of these features and also variability measures which provides a way of quantifying circadian regularity of activity (or sleep). Compared to the cosinor method of quantifying rhythms, detailed estimates of sleep or inactivity can be made through the prediction of sleep and wake times.

6.2.2.3 Variability measures

The standard deviation of the HMM features, or variability measures, are shown in Table 6.3. BPD participants have greater variability in the number of inactive periods, total inactive time, estimated sleep time, and estimated sleep offset

Table 6.3: Median and iqr of the HMM variability features for each subject group. Statistical pairwise comparisons are made across the three groups using the Wilcoxon statistical hypothesis test with FDR correction. Statistically significant differences are indicated in bold at the 5% significance level.

Variability of feature (median±iqr)	Subject Group			FDR		
	BD	BPD	HC	BD v HC	BPD v HC	BD v BPD
Number of inactive periods	1.25 ± 0.92	2.03 ± 0.79	1.48 ± 1.64	0.631	**0.044**	**0.007**
Total inactive time	1.09 ± 0.77	1.65 ± 1.31	0.92 ± 0.54	0.811	**0.002**	**0.003**
Estimated sleep time	1.17 ± 1.15	1.65 ± 1.43	0.99 ± 0.58	0.271	**0.005**	0.050
Estimated sleep onset	0.65 ± 1.17	0.83 ± 1.11	0.76 ± 0.67	0.921	0.720	0.635
Estimated sleep offset	1.10 ± 0.87	1.30 ± 1.09	0.68 ± 0.80	0.158	**0.002**	0.055

compared to HC participants. BPD participants are also more variable than BD participants in the number of inactive periods and the total inactive time. No significant differences are found between BD participants and HC participants.

The results show HMMs can provide an unsupervised method of quantifying circadian rhythms through signals recorded in an unobtrusive manner through their ability to detect detailed patterns of sleep, which cannot be seen using simpler methods such as the cosinor methods. The results further show the potential of circadian rhythms as a marker to track deterioration of mood disorders.

6.3 Linking mood and circadian variability

As reported in Sections 2.3.2 and 2.3.3, there is considerable evidence that episodes of altered mood are associated with significant changes in activity levels and sleep disturbances. These findings suggest measures of circadian activity and heart rate have the potential to be markers for mood variability, with increased mood instability associated with negative states in BD and BPD [33]. To assess the possibility of circadian rhythms and circadian variability being used as objective markers of mental health or mood instability, associations between the circadian variability measures calculated through the cosinor method (Table 6.2) and mood variability measures calculated from the standard deviation of the principal components of Mood Zoom (Table 6.1) are calculated through Spearman correlation. Only the standard deviation measure of mood variability is used due to the high correlation between the four variability measures. Features from HMMs are not used in this

analysis as many of them can be considered measures of sleep rather than circadian rhythm variability. Spearman correlation is used due to the non-parametric data and the fact it is robust to outliers.

When computing the correlation coefficients between circadian features and Mood Zoom features, outliers are removed by calculating the Cook distance of each point: if the Cook distance of a point is greater than three times the mean Cook distance the point was removed as an outlier. An average of 1.6 ± 0.4 participants are removed as outliers for the calculation of the correlation coefficient for each pair of mood and circadian measures. After outliers have been removed, Spearman correlation coefficients along with corresponding statistical significance (p-values) for each pair of circadian feature and Mood Zoom feature are calculated. Correction for multiple statistical hypothesis tests is performed using the positive FDR (significance at the 5% level), as defined by Storey, 2002 [229].

The correlation coefficients calculated between the seven circadian heart rate features, the seven circadian activity features and the five circadian sleep features and the standard deviation of Mood Zoom components are shown in Table 6.4. Statistically significant positive correlations were found in 15 of these pairs (after correction using FDR).

For total acceleration, BD show no consistent correlations with mood, and no trend even for small positive correlations. This contrasted with the BPD and HC groups where all mood dimensions were highly positively correlated with variation in the stdMESOR, a measure of variability of average daily activity levels. BPD showed equally strong effect for RSS, a measure of overall variability of activity levels, but not diffMESOR, a measure of variability of day to day variability in average activity levels. HC showed a strong effect for diffMESOR and trended positive for RSS.

For the sleep measure, negative mood variability was highly correlated with stdPhase, a measure of variability of sleep timings, in BPD. High positive correlations were found between variability of all moon dimensions and variability of sleep phases in BPD and similarly in BD with significant correlations between the

Table 6.4: Correlation coefficients between circadian features and Mood Zoom features for BD, BPD and HC participants.

Circadian features	BD Correlation Coefficient			BPD Correlation Coefficient			HC Correlation Coefficient		
	MZneg	MZpos	MZirr	MZneg	MZpos	MZirr	MZneg	MZpos	MZirr
Total Acceleration									
stdPhase	-0.258	-0.125	-0.100	0.610	0.615	0.364	0.214	0.113	0.174
stdMESOR	0.218	0.056	0.162	0.539	**0.797**	0.189	0.383	**0.660**	0.455
stdAmplitude	0.333	-0.152	0.036	0.308	0.678	-0.039	-0.030	0.116	-0.245
diffPhase	-0.212	-0.102	-0.049	0.473	0.532	0.168	0.152	0.230	0.030
diffMESOR	0.437	0.305	0.366	0.050	0.189	0.175	0.590	**0.667**	0.620
diffAmplitude	-0.181	-0.160	-0.220	0.341	0.741	-0.028	0.094	0.020	0.004
RSS	0.063	-0.195	-0.034	**0.819**	**0.881**	0.517	0.540	0.525	0.515
'Sleep'									
stdPhase	0.395	0.372	0.447	**0.615**	0.610	0.571	0.000	0.146	-0.025
stdAmplitude	0.567	**0.656**	**0.675**	0.055	-0.121	0.511	-0.414	-0.410	-0.428
diffPhase	0.515	0.388	0.468	0.573	0.368	0.462	0.117	0.150	0.092
diffAmplitude	0.321	0.301	0.335	-0.346	-0.423	-0.110	-0.325	-0.387	-0.277
RSS	0.368	0.558	0.528	0.552	0.357	0.714	-0.190	-0.081	0.016
Heart Rate									
stdPhase	-0.317	0.051	-0.166	0.495	0.532	0.374	-0.059	0.060	-0.013
stdMESOR	-0.368	-0.167	-0.600	0.259	-0.077	0.379	-0.253	0.026	-0.268
stdAmplitude	0.020	0.436	-0.191	**0.786**	**0.742**	**0.802**	0.061	-0.005	0.028
diffPhase	-0.196	-0.077	-0.082	0.511	0.517	0.648	-0.108	-0.018	-0.156
diffMESOR	-0.205	0.216	-0.432	0.434	0.098	0.654	0.408	0.350	0.417
diffAmplitude	0.0341	0.344	-0.080	**0.852**	**0.808**	0.714	0.044	-0.042	-0.002
RSS	-0.179	0.395	-0.077	**0.758**	0.522	**0.802**	-0.133	0.046	-0.100

Spearman correlation coefficients, with statistically significant correlations appearing in bold at the FDR=0.05 level. For circadian features, stdPhase, stdMESOR and stdAmplitude denote standard deviation of the difference between daily and total sinusoids measures. diff indicates the feature is the standard deviation of successive differences.

stdAmplitude and both positive and irritable mood variability. These correlations were not seen in HC participants.

For the heart rate measure in BPD, variation in signal amplitude was strongly positively correlated with measures of emotion. Neither the BD or HC groups showed even trend positive effects.

The absolute correlation coefficients between mood variability and circadian variability over four days are shown in Figure 6.5. For example, Figure 6.5 (i) shows the correlation coefficients between each of the circadian heart rate features and the standard deviation of irritable mood for the BD, BPD and HC participants, with BPD participants having large correlation coefficients, thus having a larger radius. The HC show little correlation, with a small radius close to zero at the centre and the BD participants have small absolute correlations, thus a small radius.

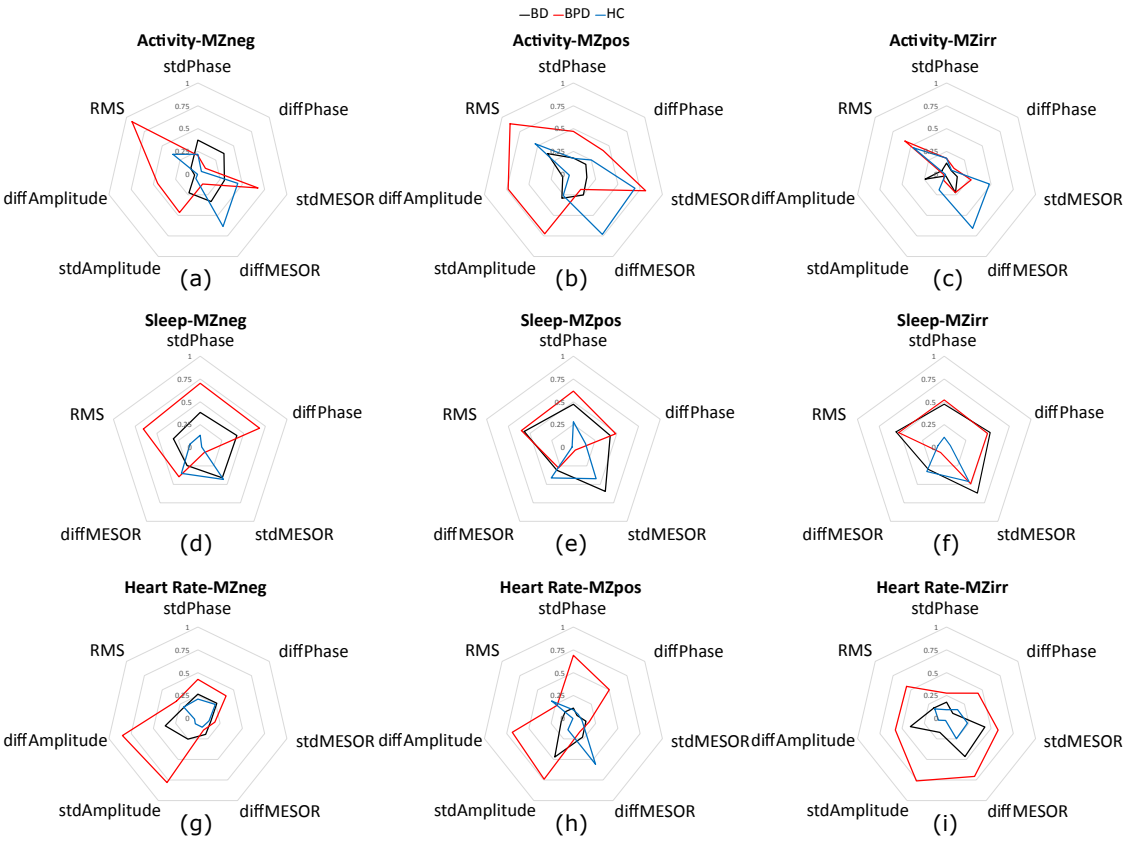


Figure 6.5: Absolute correlation coefficients between circadian variability measures and standard deviation of Mood Zoom measures to show how correlations vary across subject groups. Each spider plot represents a pair of circadian heart rate, acceleration or vertical acceleration with negative Mood Zoom, positive Mood Zoom or irritable Mood Zoom measures. stdPhase, stdMESOR and stdAmplitude denote the standard deviation of the differences between the daily and total sinusoid fit. diffPhase, diffMESOR and diffAmplitude denote the standard deviation of successive differences in the daily sinusoid fits. RSS is the residual sum of squares between the daily and total sinusoid fits.

Another example in Figure 6.5 (f) shows BD and BPD participants having larger correlations between sleep and irritable mood variability through a larger radius, whereas the HC show few correlations.

For BPD participants what is notable is the generally larger correlation coefficients compared to the other groups for most correlations, but especially in the case of irritability and heart rate. For BD participants, vertical acceleration (sleep) showed clearly greater correlations with Mood Zoom measures than the HC group (and comparable with BPD).

For HC participants, activity showed relatively large correlation coefficients with Mood Zoom measures comparable with BPD and greater than BD.

6.4 Conclusions

The results in this chapter demonstrate a convincing association between variability in subjective mood and variability in measures of circadian physiology for BPD. The ability to distinguish between patient groups and HC participants through mood variability (Table 6.1) and the increased variability of circadian measures in BPD (Table 6.2) are of considerable interest. The BPD group shows greater variation in both mood and in circadian physiology through all measures. By contrast, BD showed intermediate variation in mood (less than BPD, more than HC) and increased variability only in circadian measures of sleep (less than BPD, more than HC) and not total activity or heart rate. Direct associations between variation in subjective mood and objective measures of circadian variability were also demonstrated. Mood dimensions in both BPD and BD appeared more sensitive to variation in the phase and depth of sleep than HC. In addition, BPD showed clear evidence of an association between variability of heart rate and variation in irritability, a key symptom of the disorder. Mood variability in BD did not show this relationship. This may suggest that BPD, but not BD, should be thought of as a disorder linked with disorder of circadian rhythm, although both appear to be influenced by variation in sleep.

The variation in the phase, average levels and amplitude of circadian rhythms in BPD is a new observation. BPD was associated with the highest levels of variability in almost all the physiological measures as a trend and met conventional levels of significance for a number of individual measures versus BD and HC. In contrast BD was not generally more variable than HC on the measures of activity and heart rate; there were trend effects for sleep. However, variation in the physiological measures was less than the observed subjective variability.

It has been previously suggested that mood instability is an important feature of the phenotype of both BD and BPD [254]. Despite the apparently less discriminating difference in the variability of circadian signals, there appeared to be an important correlation between them. These correlations were most striking for both the BPD group in relation to activity and heart rate measures (Table 6.4). The present study

did not determine the direction of causation, so we cannot say that variation in circadian cycles drives mood variability. However, in the case of BD, this is the direction of effect suggested by observation of mood change in response to more obvious sleep disruption lasting many days. It would support the emphasis on sleep regularity on a day to day basis enshrined in the social rhythm metric [275] and other behavioural approaches to mood stabilization in BD [276]. More detailed measures of mood could be an important read out of the impact of effective treatment.

In relation to BPD, the observation that mood measures, especially irritability, are related to measures of sleep, activity and HRV appears to be new. Previous measures of sleep in BPD have emphasized poor sleep quality and in some studies delayed sleep timing, but not a direct effect of variability per se. Again sleep regularity may be as important an objective for psychosocial interventions for BPD as for BD. This is not reflected in current practice [217].

Variability in sleep was derived from the vertical component of the accelerometer worn on the chests of the participants. It is important that this signal was not the same as total acceleration. In fact, variability in total acceleration was not highly correlated with subjective parameters in the way that the vertical component was. However, it is of course not a measure of sleep per se and will include time lying down but not sleeping. The variability in the sleep cycle could nevertheless be driven either by variability in a hypothetical central clock or in the sleep homeostat.

The traditional measure of HRV derived from an ECG, is the most common analysis method used in the study of physiology in BD and other psychiatric disorders, with links to emotion [277]. While altered HRV has been reported in BD [278, 279], alterations to HRV in BPD are not as well defined [280, 281]. Furthermore, in previous studies HRV measures were recorded on very controlled five minute sections of ECG, based on timings between every individual heart beat, where the participants were known to be at rest [278, 279, 111, 282]. In contrast, the results presented in this study are over much longer periods when the participants are behaving as normal, therefore recording very different aspects of heart rate, representative of the spontaneous state and related to circadian changes in heart rate.

The increased variability in circadian measures of heart rate showed striking correlations with mood in BPD and much less so in BD and HC. Again, the direction of effect is not established by our observations, but it cannot be simply driven by activity or sleep. Instead it may support the idea that BPD really does show greater variability in the function of the central circadian clock. It is the first time that circadian irregularity has been shown to correlate with one of the core features of the BPD phenotype, mood instability. The absence of either greater variability in heart rate measures or a strong relationship with mood suggests that BD is much less likely to be well characterized by central instability of clock function, which we did not predict [29, 10, 283].

This was an exploratory study, therefore no detailed hypotheses were made for how mood variability might be linked to items of physiology, although, as previously explained, some link seemed plausible. A relatively large number of correlations were calculated between mood and circadian variability, and strong correlations were only found between certain measures of circadian variability and mood variability (Table 6.4). Moreover, the majority of correlations were found for the BPD group who had more variable mood than either BD or HC. Whether this is a result of stronger coupling between physiology and mood will require further work. However, the variability of circadian measures in BPD is less different (from BD and HC) than the mood variability.

Fewer complete and usable sets of data were collected than planned because the available equipment proved less than ideal. Study of circadian rhythms over longer periods could improve the findings reported here, as four days of data is a relatively short period and single abnormal days have large effects on fitting the data. The days of the week were not taken into account either, so participants may have been recorded over four working days, which might be relatively regular, or they may be recorded for two working days and two weekend days, which we would expect to be less regular. This added variability may have helped the correlation analysis and will have tended to amplify effects in BPD who had the highest emotional variability.

Participants were studied in a relatively stable state as outpatients. It would be interesting to study severe mania and depression for the BD group. However, inter-episode states in BD or BPD are 'at risk' states and the mood/circadian link is potentially important. Most interesting of all would be the transition from well to ill, but this presents a narrow observational window to a relatively rare event and so difficult to capture within the time frame of a prospective study.

Circadian analysis of other measures like temperature, metabolic or inflammatory biomarkers may provide further insight into the links between circadian function and mood, which could be closer to the brain mechanisms in BD or BPD.

The ability to detect a correlate of negative or unstable moods from objective measures, such as acceleration or heart rate, improves or complements the current methods of subjective report. With the right equipment, such measures could be largely frictionless. More continuous monitoring of participants suffering from mental disorders may lead to prediction of deteriorating mood states based on changes in circadian patterns of objective markers, therefore allowing for preventative action to be initiated as part of a clinical management plan. Improved methods for collecting circadian information over longer periods of time are required for confirmation and interpretation of circadian signals under a wider range of states of illness.

The work in this chapter has established for the first time that variability in circadian function is associated with variability of mood in BPD. It suggests that the associations are present for heart rate, total activity and the activity related to sleep. Any association between subjective experience and objective measures is unlikely to be simple or unidirectional. However, the results suggest that variable circadian function is more characteristic of the BPD than the BD phenotype and so treatment efforts might be explored which would regularize circadian function as a way to regulate abnormal mood in BPD. Improved regularity of sleep may be an important potential target for therapy in both BD and BPD.

Future work should focus on the development of machine learning techniques which utilise the mood variability differences and correlations between mood and circadian variability to aid diagnosis and to improve monitoring of mood. The

striking differences in mood variability between all three subject groups suggests that machine learning techniques would be able to predict which group an individual belongs to through a set of their mood variability recordings over a four day period. These methods were not applied in this work due to the relatively small group sizes, thus a lack of data to adequately train a machine learning model. With sufficient data, these models may become important tools in aiding with the diagnosis of disorders through more objective measures.

Chapter 7 will build on the findings in this chapter and will extend the evaluation of circadian variability to longitudinal signals and determine their associations with changing mood states in both BD and BPD.

7

Long-Term Smartphone Based Monitoring

Chapter 6 explored the link between circadian variability and daily mood variability over the course of a week of high intensity monitoring. However, with the goal of long term monitoring of mental state through tracking of depressive symptoms, longitudinal data is required. Body worn accelerometers which record for up to one week obtain reliable continuous signals, however it is not practical to collect long term signals from these devices. The widespread usage of smartphones in the current society allows for an unobtrusive and passive method of collecting activity levels of people suffering from mental health disorders.

This chapter explores whether longitudinal activity data recorded from mobile phones can be used as a suitable alternative for more specialised, body worn accelerometers by validating whether similar information can be obtained when tracking circadian rhythms. In addition it investigates the possibility of using long term circadian features obtained from mobile phone accelerometers in order to track and predict deterioration in mental state of BD and BPD participants.

7.1 Longitudinal Data

7.1.1 Actigraphy

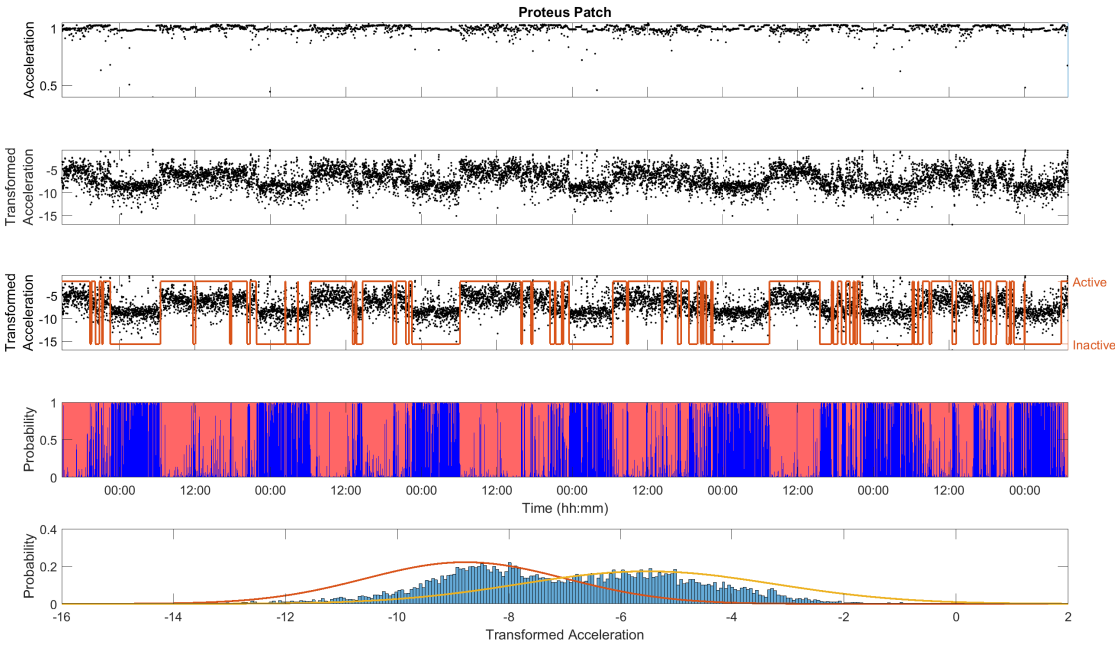
The collection of acceleration data is described in detail in Section 4.2.1, with the analysis of acceleration signals performed in Chapters 5 and 6 from the Proteus patch. However, it is not possible to obtain longitudinal recordings from the Proteus patch, therefore for longitudinal acceleration recordings it is required to use the smartphone data.

The feasibility of using the mobile phone signals for longitudinal monitoring of circadian rhythms is assessed through comparison of measures extracted from the simultaneous recordings of patch and phone signals. Figure 7.1 shows one week of simultaneous acceleration signal from the Proteus patch (a) and from the mobile phone (b). HMMs, as described in Section 3.4.2, are applied to both signals, with the most likely sequence of hidden states shown for both devices as well as the probabilities of being in each state at each time point in Figure 7.1. Although the acceleration signals are measured in differing ways, the predicted states appear visually similar in this example. This is further highlighted in Figure 7.2, where the two sequences obtained from the Proteus patch and mobile phone are directly compared.

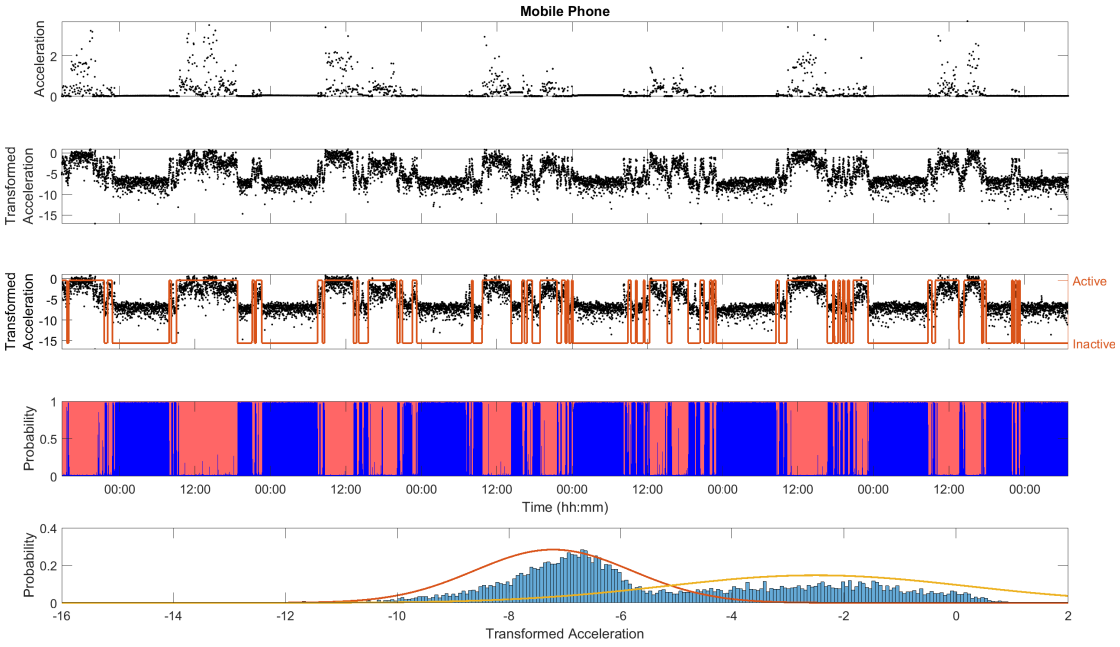
Table 7.1: Agreement between the hidden state sequences (active and inactive states) calculated from the Proteus patch and mobile phone acceleration signals.

	Accuracy ($mean \pm std$)	F1 Score ($mean \pm std$)	Cohen's Kappa ($mean \pm std$)
Viterbi sequence comparison (Proteus patch vs mobile phone)	0.65 ± 0.07	0.63 ± 0.08	0.31 ± 0.12

A total of nine participants had simultaneous Proteus patch and mobile phone acceleration recordings for a minimum of four days during the AMoSS study. Similarity and agreement measures were calculated between the sets of hidden state sequences through the accuracy, F1 score, and Cohen's Kappa. These results are shown in Table 7.1, with a mean: accuracy of 65%, F1 score of 0.63, and Cohen's Kappa of 0.31. There are considerable limitations to this comparison, primarily



(a) Proteus patch data and fitted HMM.



(b) Mobile phone data and fitted HMM.

Figure 7.1: A comparison of: accelerometer data recorded from the Proteus patch (a) and the mobile phone (b), the transformed data, the most likely hidden state sequences, the state probabilities, and the observation distributions for the states.

through the fact only nine participants had simultaneous phone and patch signals, thus reducing the statistical power of the study. In addition, neither of the estimates

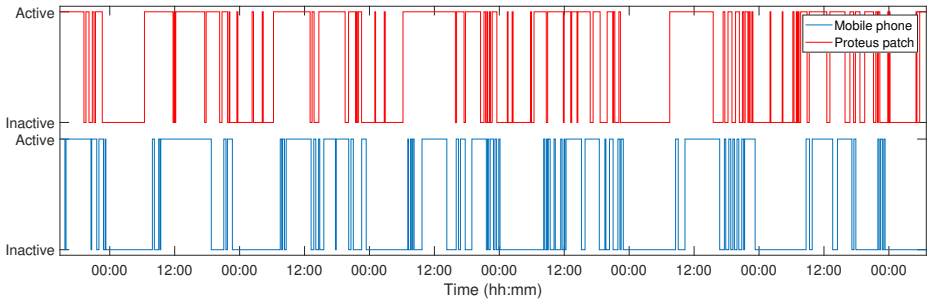


Figure 7.2: A comparison of the hidden state sequences from the Viterbi algorithm from the Proteus patch and the mobile phone acceleration signals from which the similarity measures are calculated.

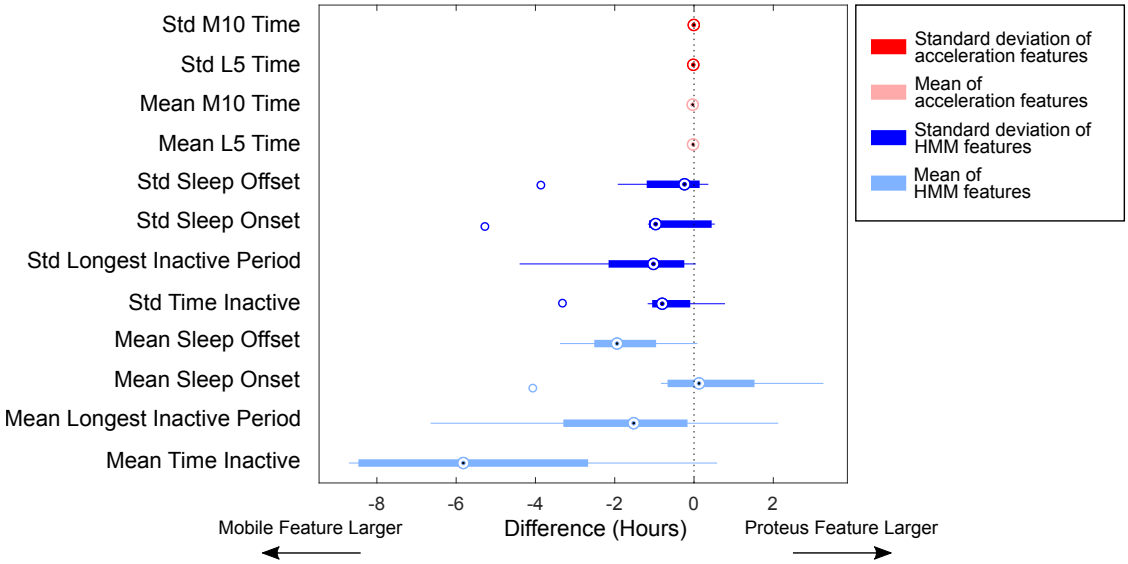


Figure 7.3: Differences in feature values when calculated from the Proteus patch and the mobile phone acceleration signals. Boxplots are shown for all features, however the acceleration features only vary by approximately 5 minutes. Outliers are shown as circles.

of sleep measures have been validated for either device, therefore the differences do not indicate which device provides more accurate estimates, only whether the devices may be interpreted in a similar manner. External validation of sleep measures is needed for both the mobile phone and the Proteus patch with true sleep times.

In addition to comparing the hidden state sequences, circadian features derived from both the raw signals and the hidden state sequences were compared between the two modalities. The differences in the mean and standard deviation of the features (L5 and M10 times from the raw acceleration signals and time inactive, longest inactive period, and estimated sleep onset and offset from the HMMs) are shown in

Figure 7.3. The features derived from the raw signals only varied by a maximum of 5 minutes between the two devices. In general there were only small differences in the HMM features (approximately ±2 hours), however the mean time spent inactive is much larger for the mobile phone estimation compared to the Proteus patch. A likely reason for this is that the participant may not carry the phone with them the entire time, so when the phone is left away from the participant, inactivity is assumed. The large difference in the mean time spent inactive may indicate this measure should be interpreted differently between the two modalities. For the patch, it is likely to represent the mean time at rest, whereas for the phone it is possible it is measuring when the phone is not being carried by the participant (in addition to periods at rest), hence the increased inactivity measure through the phone.

As the agreement between the Proteus patch acceleration data and the mobile phone acceleration data was adequate, it was decided the mobile phone signals would be able to provide reliable circadian measures when looking at long term changes in the circadian rhythms of participants.

A summary of the available data for the analysis of circadian rhythms of activity using mobile phone acceleration is shown in Table 7.2.

7.1.2 Data quality and labelling

Labelling the levels of depression, mania, and anxiety is carried out through the clinically validated questionnaires discussed in Chapter 4, including QIDS for depression, Altman for mania, and GAD-7 for anxiety. Weeks of acceleration data which have simultaneous labels from these questionnaires can be used and are shown in Figure 7.4 for each participant over the length of the study.

The main cause of loss of data for regression analysis is missing data or a reduction in data quality. A further cause of data loss is the lack of clinical labels available for the acceleration data. Table 7.4 shows the weeks lost due to missing labels (over 10%) and also to low quality data or missing data (over 50%). The likely causes for the missing data are participants not carrying the mobile phone with them 24 hours a day and also the phone running out of battery. The levels

Table 7.2: Weeks of mobile phone acceleration recordings with labelled weeks and participant demographics

	Bipolar disorder	Borderline personality disorder	Healthy controls	Total
Weeks of data for analysis				
Participants	54	35	54	143
Weeks	5638	2360	3719	11717
Weeks of labelled data				
Participants	52	33	52	137
Weeks	2105	1237	2082	5424
Weeks per participant*	37 ± 33	46 ± 31	44 ± 38	42 ± 36
Demographics for participants with any labelled weeks				
Gender	19 male 33 female	3 male 30 female	19 male 33 female	41 male 95 female
Age*	38 ± 19	34 ± 14	38 ± 20	37 ± 19
BMI*	26.8 ± 6.8	27.9 ± 10.5	23.8 ± 4.0	25.6 ± 7.4

*indicates the median and interquartile range are shown.

Table 7.3: Clinical questionnaire responses over and under the threshold values.

	Bipolar disorder	Borderline personality disorder	Healthy controls
Total weeks labelled	2105	1237	2082
Participants with labelled weeks	52	33	52
Weeks with QIDS < 11	1604	303	1995
Weeks with QIDS ≥ 11	501	934	87
Participants with QIDS ≥ 11	40	32	8
Weeks with Altman < 6	1800	1114	1996
Weeks with Altman ≥ 6	305	123	87
Participants with Altman ≥ 6	36	23	9
Weeks with GAD-7 < 10	1579	302	2040
Weeks with GAD-7 ≥ 10	526	935	42
Participants with GAD-7 ≥ 10	44	31	8

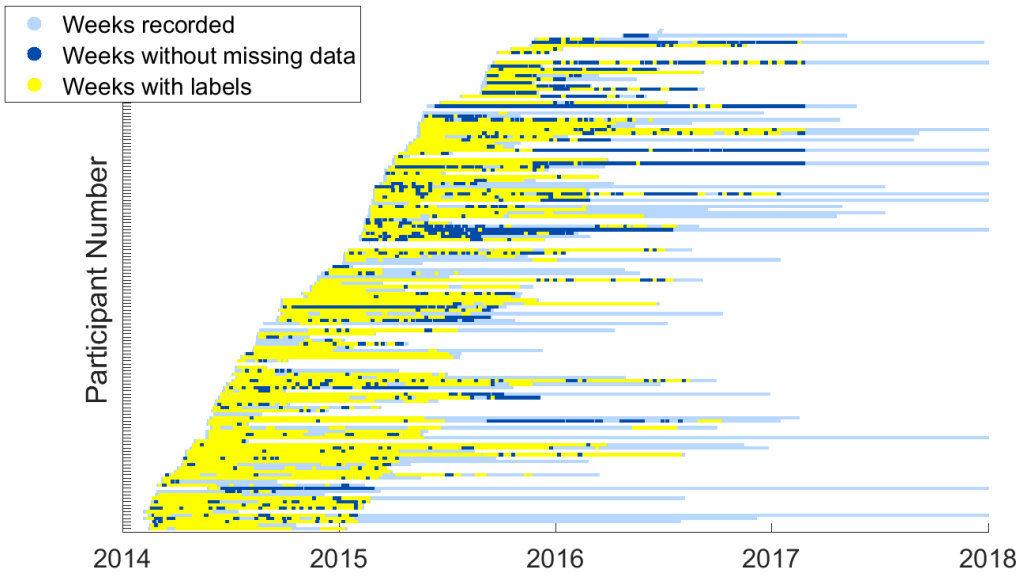


Figure 7.4: Weeks of mobile phone acceleration recordings are shown in light blue for each participant. The weeks which also have a corresponding clinical label assigned to them are shown in dark blue. Yellow indicates weeks in which under 20% of data was missing and which were labelled. These yellow weeks are the weeks used in the regression analysis of QIDS (depression score).

of depression are similar in the weeks of activity removed due to missing data and in the weeks used for the regression, with QIDS scores an average of 0.34 higher in the weeks used than weeks removed in BD participants, 0.16 lower in BPD participants and 0.21 higher in HC participants. This suggests the data quality is not affected by the levels of depression. The number of labelled weeks available and the demographic information of the participants are shown in Table 7.2.

The weekly questionnaires completed by the participants include: QIDS for assessing levels of depression, Altman for assessing levels of mania, and GAD-7 for assessing levels of anxiety. These questionnaires are generally completed simultaneously by the participants, thus giving three possible labels for each of the weeks indicated in Figure 7.4. A summary of these labels is shown in Figure 7.5, with the distribution of the responses shown for each questionnaire separated by the cohorts. Additionally, combined distributions are shown in the final row of plots. The clinically defined thresholds for each questionnaire is marked by the dashed line. A summary of this data is displayed in Table 7.3.

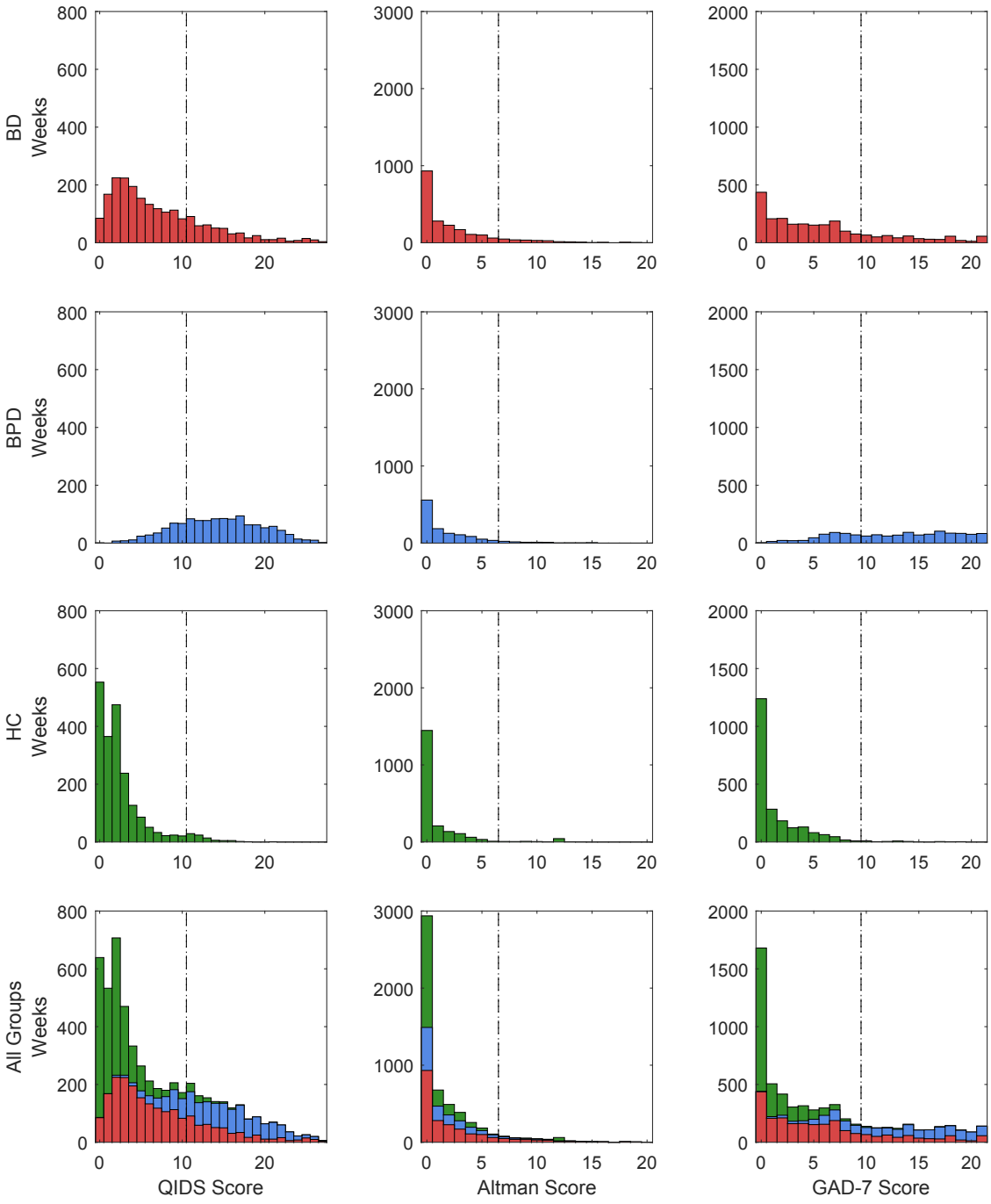


Figure 7.5: Distributions of the clinically validated questionnaire responses by participant groups. Rows correspond to the different groups, with the first column showing the QIDS scores for depression, the second showing the Altman scores for mania, and the third column showing the GAD-7 scores for anxiety. The final row shows the stacked distributions for all subject groups with the shading indicating the group responses. The dashed line in each plot marks the clinical threshold for each of the questionnaire scores.

Table 7.4: Weeks of data lost to missing labels and to low quality data.

	Bipolar disorder	Borderline personality disorder	Healthy controls	Total
Weeks with no QIDS label				
Weeks per participant	45.12 ± 37.62	41.10 ± 32.94	43.23 ± 37.73	43.26 ± 35.55
Weeks with missing data				
Weeks per participant	9.71 ± 15.19	9.36 ± 13.81	10.75 ± 15.19	10.02 ± 14.78
QIDS score	7.15 ± 5.55	14.35 ± 5.19	2.15 ± 3.13	6.73 ± 6.56
Weeks of data remaining				
Weeks per participant	31.38 ± 25.31	31.42 ± 23.71	29.04 ± 23.00	30.50 ± 23.92
QIDS score	7.49 ± 5.92	14.19 ± 5.15	2.36 ± 2.67	7.30 ± 6.59

7.2 Quantifying circadian rhythms

The traditional HMM is described in detail in Chapter 3, detailing the algorithms used to optimise the HMM parameters and to obtain the sequences of hidden states. In Chapter 6 the traditional HMMs are applied to the Proteus patch data in order to estimate inactivity and sleep timings. Here, the traditional HMM is extended to allow for time varying parameters in order to model the 24 hour varying circadian patterns of activity and sleep [241].

7.2.1 Time varying hidden Markov models

As the HMMs in this work are being used to quantify the circadian rhythms of the activity of participants, it would be reasonable to expect the transition probabilities to vary with time. For example, at night one may expect the probability of a transition from an 'inactive' state to an 'active' state to be low, however during the day one may expect this probability to be considerably higher. Due to these expected time dependent differences in behaviour, a co-variate can be added to the HMM to act as a circadian oscillator and allow the transition probabilities to vary with time.

To allow for time variance, a co-variate $\mathbf{Z}$ is included in the HMM, as in Figure 7.6. A combination of a 24 hour sine wave and cosine wave are used in order to ensure no repeating co-variate for a 24 hour period. $Z_t = \begin{bmatrix} Z_t^{sin} \\ Z_t^{cos} \end{bmatrix}$, where $Z_t^{sin} = sin(2\pi ft)$ and $Z_t^{cos} = cos(2\pi ft)$. The frequency, f, is one cycle per day. It is highly possible that higher harmonics exist in circadian rhythms of activity, however introducing these higher harmonics to the co-variate will increase the number of variables to be

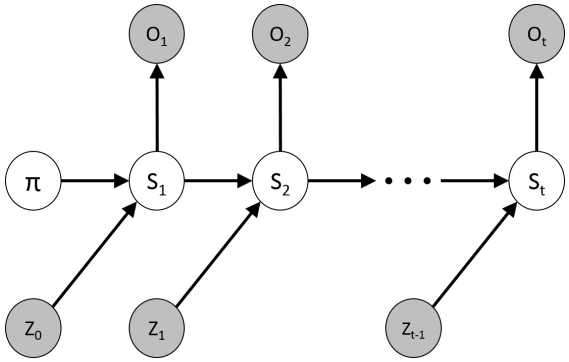


Figure 7.6: Graphical model of a time varying HMM, with co-variate, Z.

optimised exponentially. Therefore due to these computational limits, the analysis was restricted to single 24 hour sine and cosine waves.

From the definition of a HMM and it's parameters, as defined in Section 3.4.2, the joint likelihood of a time varying, or dependent, HMM with co-variates $\mathbf{Z}$ can be defined as

$$P(\mathbf{O}, \mathbf{Q}|\boldsymbol{\theta}, \mathbf{Z}) = P(q_1 = S_i|Z_1, \boldsymbol{\pi}) \prod_{t=1}^{T-1} P(q_{t+1} = S_j|q_t = S_i, Z_t, \mathbf{A}) \prod_{t=1}^{T} P(O_t|q_t = S_i, Z_t, \mathbf{B}), \tag{7.1}$$

or

$$P(\mathbf{O}, \mathbf{Q}|\boldsymbol{\theta}, \mathbf{Z}) = \pi_i(Z_1) b_i(O_1|Z_1) \prod_{t=1}^{T-1} a_{ij}(Z_t) b_j(O_{t+1}|Z_{t+1}), \tag{7.2}$$

where $\pi_i(Z_1) = P(q_1 = S_i|Z_1, \boldsymbol{\pi})$, the probability of being in state S_i at time t with co-variate Z_1 and initial state parameter. $a_{ij}(Z_t) = P(q_{t+1} = S_j|q_t = S_i, Z_t, \mathbf{A})$ is the probability of a transition from state S_i at time t to state S_j at time $t+1$ with co-variate Z_t and transition matrix parameter. $b_j(O_t|Z_t) = P(O_t|q_t = S_j, Z_t, \mathbf{B})$ is the observation probabilities for state S_j given co-variate Z_t and observation probability parameters.

7.2.1.1 Expectation-maximisation

The expectation-maximisation (EM) algorithm is a procedure used to estimate a set of parameters through maximisation of a likelihood function when some data is missing or unknown (eg. the hidden states in a HMM). The Baum-Welch

algorithm described in Section 3.4.2.2 is an example of EM for HMMs. With the introduction of co-variates to the HMM, it is no longer possible to use the Baum-Welch algorithm and other optimisation methods are required to solve the EM problem to estimate the new model parameters.

Marginalising over the hidden states in the joint distribution from Equation (7.1) will give the likelihood function

$$P(\mathbf{O}|\boldsymbol{\theta}, \mathbf{Z}) = \sum_{S} P(\mathbf{O}, \mathbf{Q}|\boldsymbol{\theta}, \mathbf{Z}). \tag{7.3}$$

However, the joint distribution $P(\mathbf{O}, \mathbf{Q}|\boldsymbol{\theta}, \mathbf{Z})$ in Equation (7.1) does not factorise and there are multiple variables not allowing explicit summation, the summation grows exponentially large with the length of the signal. The EM algorithm is able to provide a more efficient solution to maximising the likelihood function. A random initial selection of the model parameters is made denoted by $\boldsymbol{\theta}^*$ and the posterior distribution of the hidden states is found $P(\mathbf{Q}|\mathbf{O}, \boldsymbol{\theta}^*, \mathbf{Z})$. This distribution is then used to find the expectation of the logarithm of the likelihood function, as in Equation (7.1), to give the function $Q(\boldsymbol{\theta}, \boldsymbol{\theta}^*)$ defined as

$$Q(\boldsymbol{\theta}, \boldsymbol{\theta}^*) = \sum_{S} P(\mathbf{Q}|\mathbf{O}, \boldsymbol{\theta}^*, \mathbf{Z}) \log P(\mathbf{O}, \mathbf{Q}|\boldsymbol{\theta}, \mathbf{Z}). \tag{7.4}$$

From Section 3.4.2.2, we have defined $\gamma_t(i)$ as the probability of being in state S_i at time t and $\xi_t(i, j)$ as the probability of being in state S_i at time t and state S_j at time $t + 1$

$$\gamma_t(i) = P(q_t = S_i|\mathbf{O}, \boldsymbol{\theta}^*, \mathbf{Z}), \tag{7.5}$$

$$\xi_t(i, j) = P(q_t = S_i, q_{t+1} = S_j|\mathbf{O}, \boldsymbol{\theta}^*, \mathbf{Z}). \tag{7.6}$$

Substituting the joint distribution in Equation (7.1) into Equation (7.4) and using the definitions of $\gamma_t(i)$ and $\xi_t(i, j)$, $Q(\boldsymbol{\theta}, \boldsymbol{\theta}^*)$ is now given by

$$Q(\boldsymbol{\theta}, \boldsymbol{\theta}^*) = \sum_{i=1}^{N} \gamma_1(j) \log P(q_1 = S_j | \boldsymbol{\pi}, Z_1) + \sum_{t=1}^{T-1} \sum_{i=1}^{N} \sum_{j=1}^{N} \xi_t(i,j) \log P(q_{t+1} = S_j | q_t = S_i, Z_t, \mathbf{A}) + \sum_{t=1}^{T-1} \sum_{i=1}^{N} \gamma_t(i) \log P(O_t | q_t = S_i, Z_t, \mathbf{B}). \quad (7.7)$$

The maximisation step to find the updated model parameters $\boldsymbol{\theta} = \{\boldsymbol{\pi}, \mathbf{A}, \mathbf{B}\}$ involves the maximisation of Equation (7.7). As Equation (7.7) is split into three parts, each a function of $\boldsymbol{\pi}$, $\mathbf{A}$, and $\mathbf{B}$ alone, each part may be maximised separately.

Here, for model simplicity and computational limits, only the transition matrix is assumed to vary with co-variate $\mathbf{Z}$. This allows $\boldsymbol{\pi}$ and $\mathbf{B}$ (as well as $\boldsymbol{\gamma}$ and $\boldsymbol{\xi}$) to be calculated in the same way as Section 3.4.2.2 using the Baum-Welch algorithm, leaving only the transition matrix, $\mathbf{A}$, to be found. As the transition matrix is now time varying, the dimensions change from $(N \times N)$ to $(T \times N \times N)$ and a logistic link function is used between the co-variate $\mathbf{Z}$ and transition probabilities, given by

$$A_t(i,j) = P(q_t = S_j | q_{t-1} = S_i, Z_t) = \frac{\exp(c_{i,j}^0 + c_{i,j}^1 Z_t)}{\sum_{j=1}^{N} \exp(c_{i,j}^0 + c_{i,j}^1 Z_t)}. \quad (7.8)$$

Combining Equation (7.8) with the second part of Equation (7.7) gives the function f_{max} to maximise

$$f_{max} = \sum_{t=1}^{T-1} \sum_{i=1}^{N} \sum_{j=1}^{N} \xi_t(i,j) \log \frac{\exp(c_{i,j}^0 + c_{i,j}^1 Z_t)}{\sum_{j=1}^{N} \exp(c_{i,j}^0 + c_{i,j}^1 Z_t)}, \quad (7.9)$$

with the values of the coefficients $c_{i,j}^0$ and $c_{i,j}^1$ to be found by optimisation. The optimised coefficients are then put back into Equation (7.8) to determine the time varying transition matrix. Optimisation was performed using an interior-point algorithm, which provides a simple and computationally fast method of solving constrained problems, however the algorithm can often get stuck in local minima [284].

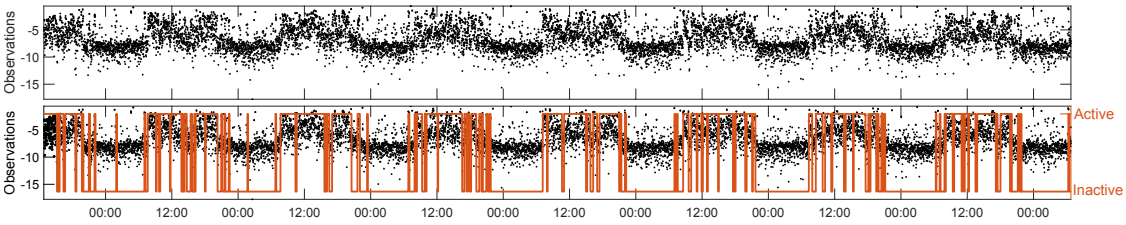


Figure 7.7: An example of the transformed acceleration data from the mobile phone which is used as the observation sequence for the HMM. The predicted 'active' and 'inactive' periods using the Viterbi algorithm are shown on the second plot.

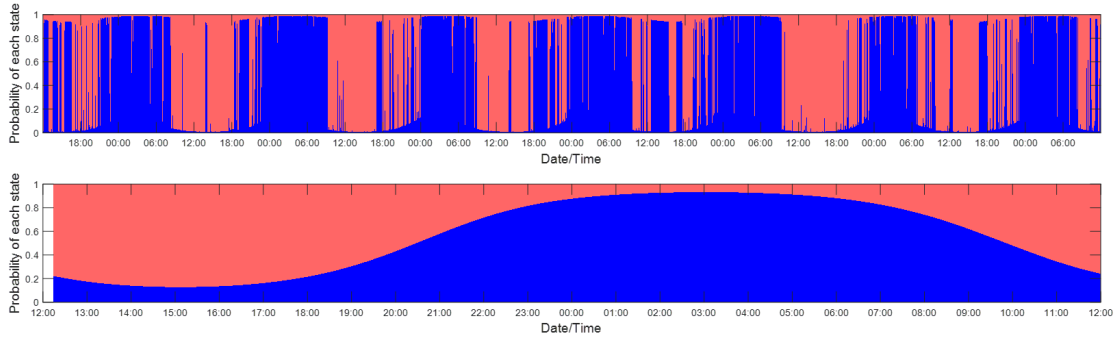


Figure 7.8: Example of the probabilities of the predicted states using the mobile phone acceleration data and the circadian profile from the time varying transition probabilities.

7.2.1.2 Viterbi algorithm features

A detailed description of the circadian features derived from the Viterbi sequence are described in Section 6.2.2.2 in Chapter 6. The time varying components of the HMMs here do not affect the output from the Viterbi sequence, therefore identical measures can be calculated.

7.2.1.3 Circadian profiles

Algorithm 7.1 Pseudo-code for the generation of the weekly circadian profiles from the time varying transition probabilities.

input transition matrix A, and prior probabilities π.

$Pr_1 = \pi$
for t=2 to T **do** ▷ Recursion
  for j=1 to N **do**
    $Pr_t(j) = \sum_{i=1}^{N} A_t(i,j) \cdot Pr_{t-1}(i)$
  end for
end for
output Pr

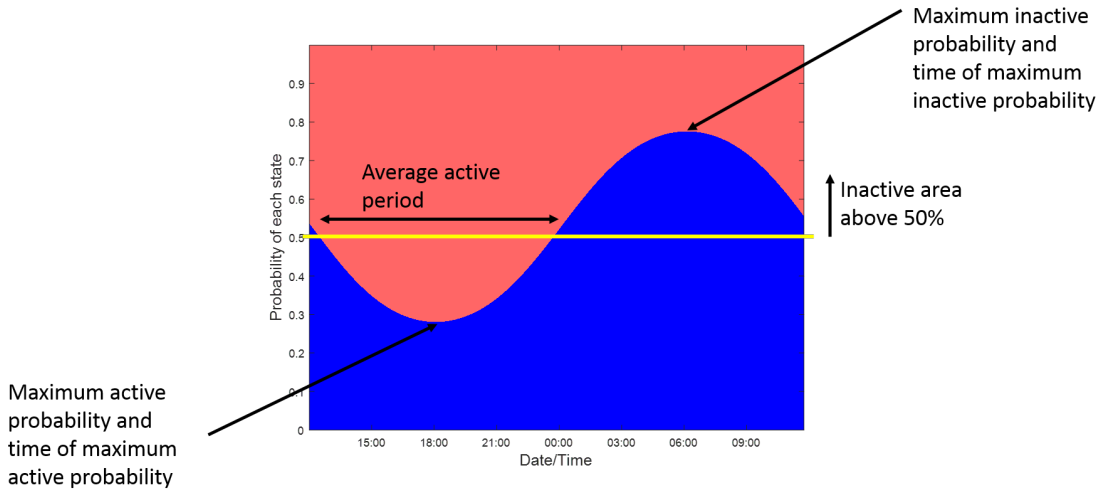


Figure 7.9: Circadian features calculated using the weekly circadian profile.

From the time varying transition matrix, the probability of the states throughout 24 hours can be calculated as in Algorithm 7.1. An example of this circadian profile is shown in Figure 7.8, with the blue area the probability of being 'inactive' and the red area the probability of being 'active'.

From this profile, calculated from one week, a number of features are calculated to quantify the average circadian rhythms. These are depicted in Figure 7.9 and include:

1. Average inactive period - length of time the probability of being in the 'inactive' state is greater than 0.5.

2. Inactive period onset - the time the probability of being 'inactive' becomes greater than 0.5.

3. Inactive period offset - the time the probability of being 'inactive' becomes less than 0.5.

4. Inactive area - area of the 'inactive' state greater than 0.5 probability.

5. Maximum inactive probability - highest probability of being in the 'inactive' state.

6. Maximum inactive time - time of the highest probability of being in the 'inactive' state.

7. Maximum active probability - highest probability of being in the 'active' state.

8. Maximum active time - time of the highest probability of being in the 'active' state.

9. Rhythm index - value between 0 and 1 indicating strength of the circadian rhythms, as defined in [241].

7.2.1.4 Confidence intervals

The Baum-Welch algorithm calculates the set of optimal parameters which maximise the likelihood of obtaining the observation sequence. To determine how well these parameters fit the data, confidence intervals can be used to indicate the variability these parameters have without significantly altering the likelihood.

The confidence intervals for the HMM parameters $\boldsymbol{\theta} = \{\boldsymbol{\pi}, \mathbf{A}, \mathbf{B}\}$ are calculated using a bootstrapping method which generates artificial observation sequences using the HMM parameters learned from the Baum-Welch algorithm, based on [285]. The bootstrapping method is as follows:

1. Find the set of parameters, $\boldsymbol{\theta} = \{\boldsymbol{\pi}, \mathbf{A}, \mathbf{B}\}$, which maximises the likelihood of the observation sequence, $\mathbf{O}$, of acceleration data.

2. Generate an artificial set of observations using the set of parameters from step 1, following the steps in Algorithm 7.2.

3. Estimate the HMM parameters, $\boldsymbol{\theta}^* = \{\boldsymbol{\pi}^*, \mathbf{A}^*, \mathbf{B}^*\}$, from the generated observation sequence, $\mathbf{O}^*$.

4. Repeat steps 2 and 3 M times in order to generate a set of HMM parameters, $\boldsymbol{\theta}^*_{\mathbf{1}}, \boldsymbol{\theta}^*_{\mathbf{2}}, ..., \boldsymbol{\theta}^*_{\boldsymbol{M}}$.

5. Calculate the confidence interval for parameters, $\boldsymbol{\theta}$, using the distribution of estimated parameters, $\boldsymbol{\theta}^*$.

Algorithm 7.2 Pseudo-code for the generation of artificial observation sequences using HMM parameters.

input transition matrix A, and prior probabilities π, means of observation distributions μ, covariances of observation distributions Σ.
$S_1 \sim Cat(\pi)$
$\mu_1 = \mu_{S_1}$, $\Sigma_1 = \Sigma_{S_1}$
$O_1^* \sim \mathcal{N}(\mu_1, \Sigma_1)$
for t=2 to T **do** ▷ Recursion
$trans = A_t(S_{t-1}, :)$ ▷ Probabilities from the state at t-1 to all states
$S_t \sim Cat(trans)$
$\mu_t = \mu_{S_t}$, $\Sigma_t = \Sigma_{S_t}$
$O_t^* \sim \mathcal{N}(\mu_t, \Sigma_t)$
end for
output O^*

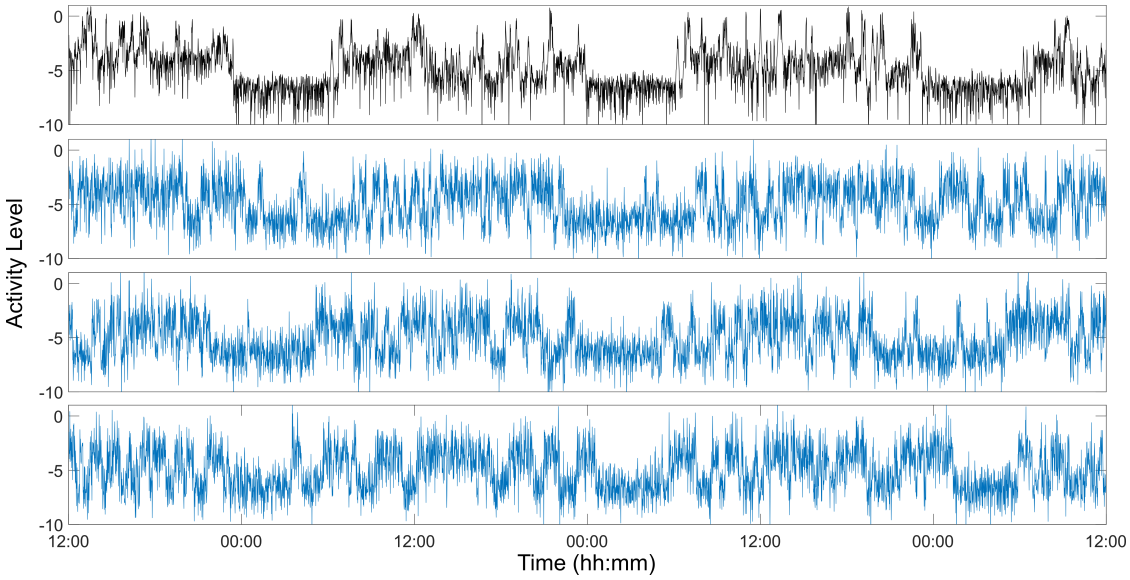


Figure 7.10: Recorded observation sequence (black) and three artificially generated observations sequences (blue) from the HMM parameters calculated from the recorded observation sequence.

Figure 7.10 shows an example of three days of an acceleration signal recorded from the mobile phone, with three artificially generated observation sequences calculated using the HMM parameters, $\boldsymbol{\theta}$, found from the Baum-Welch algorithm. These generated observation sequences are then used to calculate further HMM parameters, $\boldsymbol{\theta}^*$, to determine the variability in the original parameters, $\boldsymbol{\theta}$.

An example of confidence intervals for the time varying transition probabilities is shown in Figure 7.11, where the four possible transition probabilities are shown over a

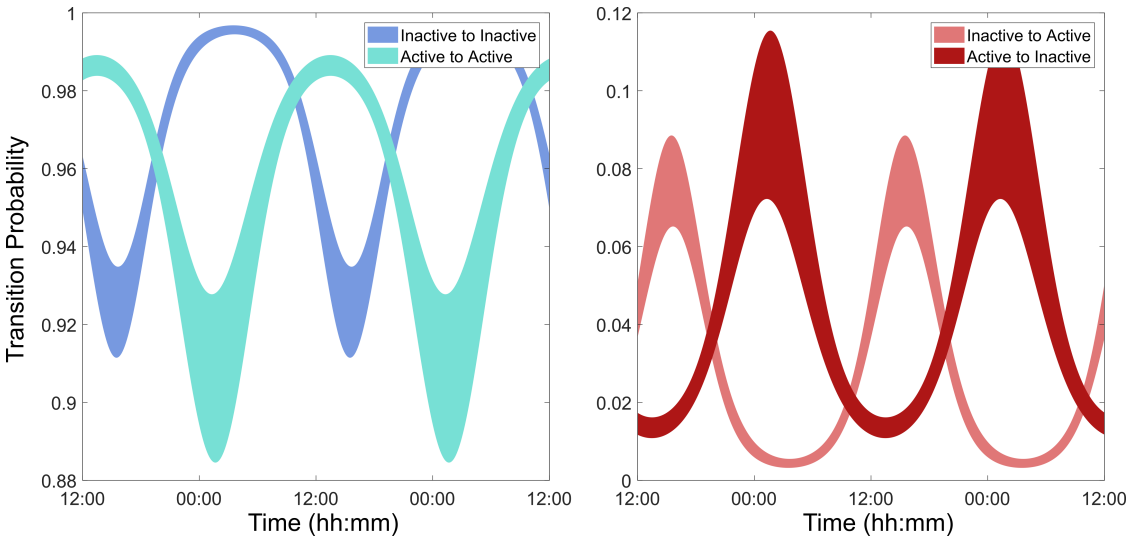


Figure 7.11: Confidence intervals of the time vary transition probabilities for the four possible transitions shown over a 48 hour period.

48 hour period for an individual with BD. The shaded regions indicate the mean plus and minus one standard deviation at each time point, calculated from the generated set of HMM parameters, $\boldsymbol{\theta}^*$. The small amount of variation in the transition probabilities at each time point indicate the original parameters, $\boldsymbol{\theta}$, fit the data well.

The full set of parameters and their confidence intervals are shown in Table 7.5 for each participant group which are also split into depressed and euthymic groups. The results show the confidence intervals are small relative to the parameter values, indicating the time varying HMMs fit the data well. There are small differences in observation distributions between the groups, but the transition probabilities are consistent across all groups.

7.3 Personalised regression

As the activity or sleep patterns of participants are highly individualised, in addition to great variability in how levels of depression are perceived, prediction of depression using circadian activity measures is performed on an individual basis. It is possible that prediction of depression would be improved from group regression of similar participants, however it is likely that a large amounts of data would be needed to cover the subgroups of participants. The downfall of individual regression is a

Table 7.5: The mean parameter value and mean confidence interval of the parameters which define the time varying HMMs by each subject group are shown. The parameters shown are: the probability of being active in the first state, the mean and variance of the observation distributions for the active and inactive states, the maximum self transition probabilities, and the minimum self transition probabilities.

	Bipolar disorder	Borderline personality disorder	Healthy control
Initial Active Probability, π_{active}	0.78 ± 0.14	0.82 ± 0.17	0.75 ± 0.16
Active Observation Mean, μ_{active}	-2.83 ± 0.17	-2.91 ± 0.16	-3.37 ± 0.18
Inactive Observation Variance, Σ_{active}	1.91 ± 0.15	1.81 ± 0.09	2.06 ± 0.15
Inactive Observation Mean, $\mu_{inactive}$	-5.57 ± 0.18	-5.36 ± 0.20	-6.27 ± 0.19
Inactive Observation Variance, $\Sigma_{inactive}$	1.62 ± 0.21	1.56 ± 0.17	1.56 ± 0.26
Max Active to Active Transition Probability	0.94 ± 0.03	0.94 ± 0.04	0.95 ± 0.03
Min Active to Active Transition Probability	0.72 ± 0.09	0.72 ± 0.09	0.84 ± 0.09
Max Inactive to Inactive Transition Probability	0.94 ± 0.04	0.95 ± 0.04	0.96 ± 0.05
Min Inactive to Inactive Transition Probability	0.84 ± 0.08	0.85 ± 0.09	0.81 ± 0.14

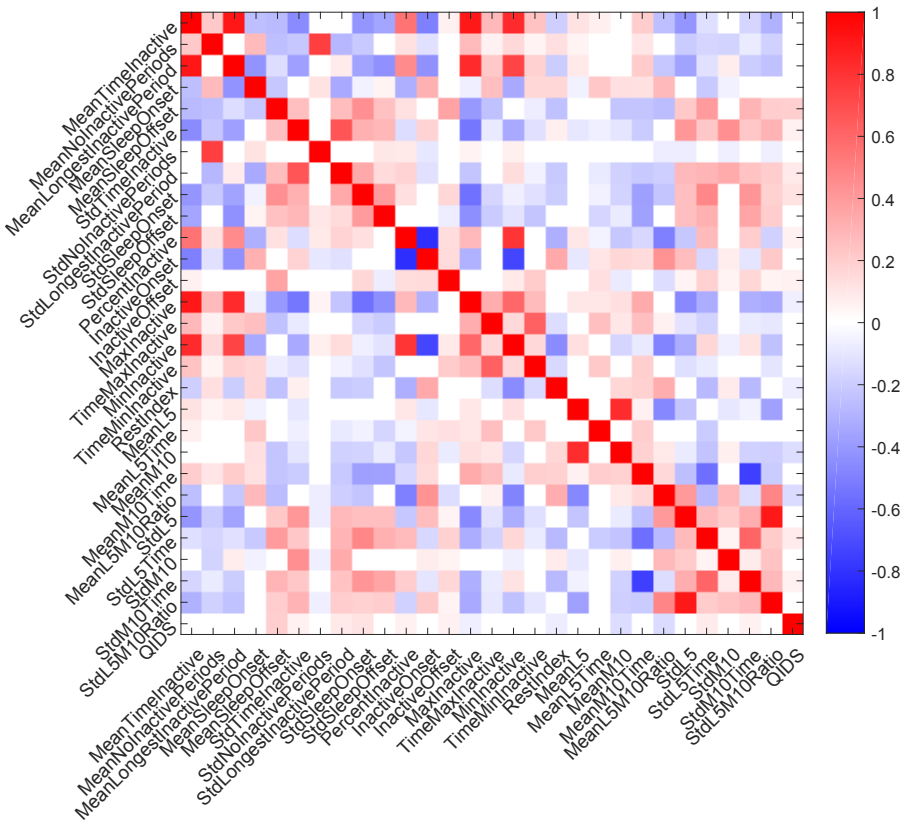


Figure 7.12: Correlation between each of the 28 features and also the QIDS score using Pearson correlation. The colour scale indicates the value of the correlation coefficient.

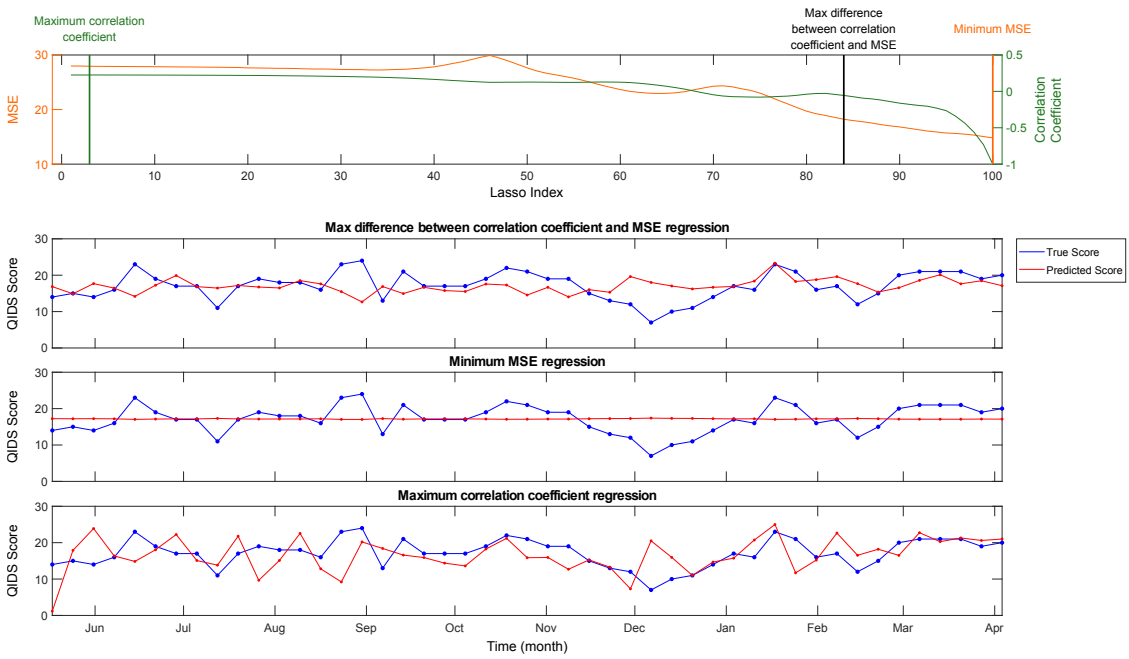


Figure 7.13: Example of errors in QIDS regression using the maximum difference between correlation coefficient and MSE, minimum MSE, and maximum correlation to select features from LASSO.

lot of longitudinal data is required, including transitions into depressive states, in order for a model to learn and predict further negative transitions. However, as a first step, prediction of depression is performed on an individual basis due to the relatively small numbers of participants, thus difficulty in grouping participants who behave in a similar manner.

Figure 7.12 shows the correlation between the 28 features calculated to quantify circadian regularity (and with the QIDS score for depression). As there are a large number of correlated features a regression algorithm with regularisation would be able to enforce sparcity of the coefficients. Therefore the regression is performed using LASSO, as described in Chapter 3, leaving one week out for testing and training on all remaining weeks, with five fold cross validation. MSE, MAE and Pearson correlation, ρ, are used to quantify the results of the regressions in addition to the number of features used in the regression, N.

The LASSO regression, as defined in Section 3.2.3.2, is performed by increasing the regularisation coefficient, λ, and producing a set of coefficients corresponding to each regularisation value. The typical method for selection of the optimal

regularisation value and coefficients is through minimising the MSE of the regression, in this case minimising the MSE of the QIDS prediction, and selecting the largest λ within one standard deviation of the minimum MSE. However, using this method to select the coefficients for regression when predicting QIDS scores from circadian measures of activity often results in the smallest regularisation coefficient being selected. This results in all or all but one of the coefficients being set to zero and the prediction only using the intercept terms, an example of this is shown in the third plot of Figure 7.13, where the red prediction is close to a flat line or average prediction.

Alternate methods for optimising regression or feature selection (such as minimum redundancy maximum relevance (mRMR) [286]) use the maximisation of correlation between a regression output and the true values. An example of using the maximum correlation to select the optimal regularisation coefficients from LASSO is also shown in the final plot of Figure 7.13. Although this results in improved tracking of the changes in QIDS scores compared to minimising the MSE, the changes are often large, resulting in large errors in the QIDS prediction.

In order to select a regularisation coefficient, λ, to provide results between these two extremes, a method was defined which finds the greatest differences between the standardised Pearson's correlation coefficient and the standardised MSE. The value of λ initially starts as zero and all features are included in the regression. The performance of the regression is measured and the value of λ is increased. This continues and the performance is measured at each value of λ until no features are selected in the model. The value of λ with the optimal performance measures is then selected for the final model. The three methods for selecting the regularisation coefficient are indicated in the first plot of Figure 7.13, with the results of the maximum difference between correlation and MSE shown in the second plot. The results of all further QIDS regressions are performed using this method.

7.3.1 Traditional features

As a baseline, regressions were performed using only the commonly used features derived from the raw acceleration signals (L5, L5 time, M10, M10 time, and the

L5/M10 ratio) as defined in Section 5.1.5. The MSE, MAE, Pearson correlation coefficient, and number of features used in the regression for the three methods of regularisation coefficient (λ) selection for LASSO are shown in Table 7.6.

The maximum difference method has a higher MSE compared to the minimum MSE selection, but has reduced MSE than selecting the maximum correlation. The maximum difference method also has lower correlation coefficient compared to the maximum correlation selection, but has high correlation coefficient compared to selecting coefficients using the minimum MSE. The maximum difference method is the method used to obtain the results shown in Table 7.6. Both the MSE and the MAE for the HC participants is much smaller than the other two groups. This is due to very little variation in the QIDS scores for HC participants with very few participants recording any QIDS scores above five. The BPD participants have the largest MSE and MAE, but also the largest correlation, with the BD participants being having MSE, MAE, and correlation coefficient between the other two groups. The mean number of features selected in all groups is similar, with four to five from ten possible features being the most common numbers used. Accuracy of depression classification is high across all groups, specificity is high in BD and HC participants with relatively low sensitivity. However, the BPD participants have a high sensitivity and low specificity.

As the BD participants vary between euthymic and depressive states, they have QIDS scores varying between periods of low and high scores, they will be the main focus of the regression analysis. The left column of Figure 7.14 shows the results of three regressions for three individuals with BD. The baseline trends of the QIDS predictions follow the true QIDS scores however there are large errors in most cases.

7.3.2 HMM features

The further 18 features calculated from the time varying HMMs were added to the ten traditional features used in Section 7.3.1 for the prediction of the QIDS scores.

The MSE, MAE, correlation coefficient, and number of features used after the introduction of the HMM derived features are also shown in Table 7.6. For the

Table 7.6: MSE, MAE, Pearson correlation coefficients (ρ) and number of features used (N) for each of the three subject groups using LASSO regression, when selecting the regularisation coefficients by finding the maximum difference between the standardised correlation coefficients and MSE. Accuracy, sensitivity and specificity are shown for the classification of depression by using the clinical threshold of 10 on the QIDS scale on the true scores and predicted scores. Results are shown for the regression against QIDS scores when only using the traditionally derived acceleration features and for when the HMM features are also included. The Wilcoxon signed rank test was used to determine improvements in the results between using the two sets of features, with statistically significant differences shown with an asterisk at the 5% significance level.

	Bipolar disorder	**Borderline personality disorder**	**Healthy controls**
Acceleration derived features only			
MSE	9.65 ± 14.90	14.05 ± 12.87	1.19 ± 3.68
MAE	0.74 ± 0.85	1.15 ± 0.97	0.36 ± 0.40
ρ	$0.11 \pm 0.39^*$	0.14 ± 0.28	$0.10 \pm 0.48^*$
N	$4.00 \pm 2.88^*$	$5.00 \pm 4.00^*$	$4.00 \pm 4.00^*$
Accuracy	0.86 ± 0.25	0.85 ± 0.25	0.98 ± 0.07
Sensitivity	0.41 ± 0.43	0.87 ± 0.28	0.30 ± 0.46
Specificity	0.73 ± 0.36	0.22 ± 0.31	0.96 ± 0.18
Addition of HMM derived features			
MSE	9.41 ± 14.16	12.68 ± 17.56	1.37 ± 4.83
MAE	0.80 ± 0.79	1.33 ± 1.03	0.39 ± 0.40
ρ	$0.20 \pm 0.47^*$	0.20 ± 0.44	$0.21 \pm 0.38^*$
N	$8.00 \pm 11.50^*$	$10.00 \pm 6.00^*$	$10.00 \pm 15.00^*$
Accuracy	0.88 ± 0.25	0.79 ± 0.27	0.98 ± 0.07
Sensitivity	0.48 ± 0.43	0.81 ± 0.31	0.35 ± 0.44
Specificity	0.76 ± 0.32	0.25 ± 0.33	0.95 ± 0.19

Values shown are the median $\pm$ the inter-quartile range

BD participants the mean number of features used in the regression increased from 4.07 to 9.45, this resulted in a slight reduction in MSE (13.79 to 13.12) but a slight increase in MAE (0.91 to 1.00), whereas the correlation coefficient increase from 0.09 to 0.20. Similar changes can be seen for the BPD and HC participants. For BPD participants, the mean number of features used increased from 5.14 to 9.38, the MSE reduced from 18.50 to 18.39, the MAE increased from 1.13 to 1.32 and the correlation coefficient increased from 0.15 to 0.19. For the HC participants, the mean number of features used increased from 4.68 to 12.27, the MSE increased from 3.53 to 3.84, the MAE increased from 0.42 to 0.44 and

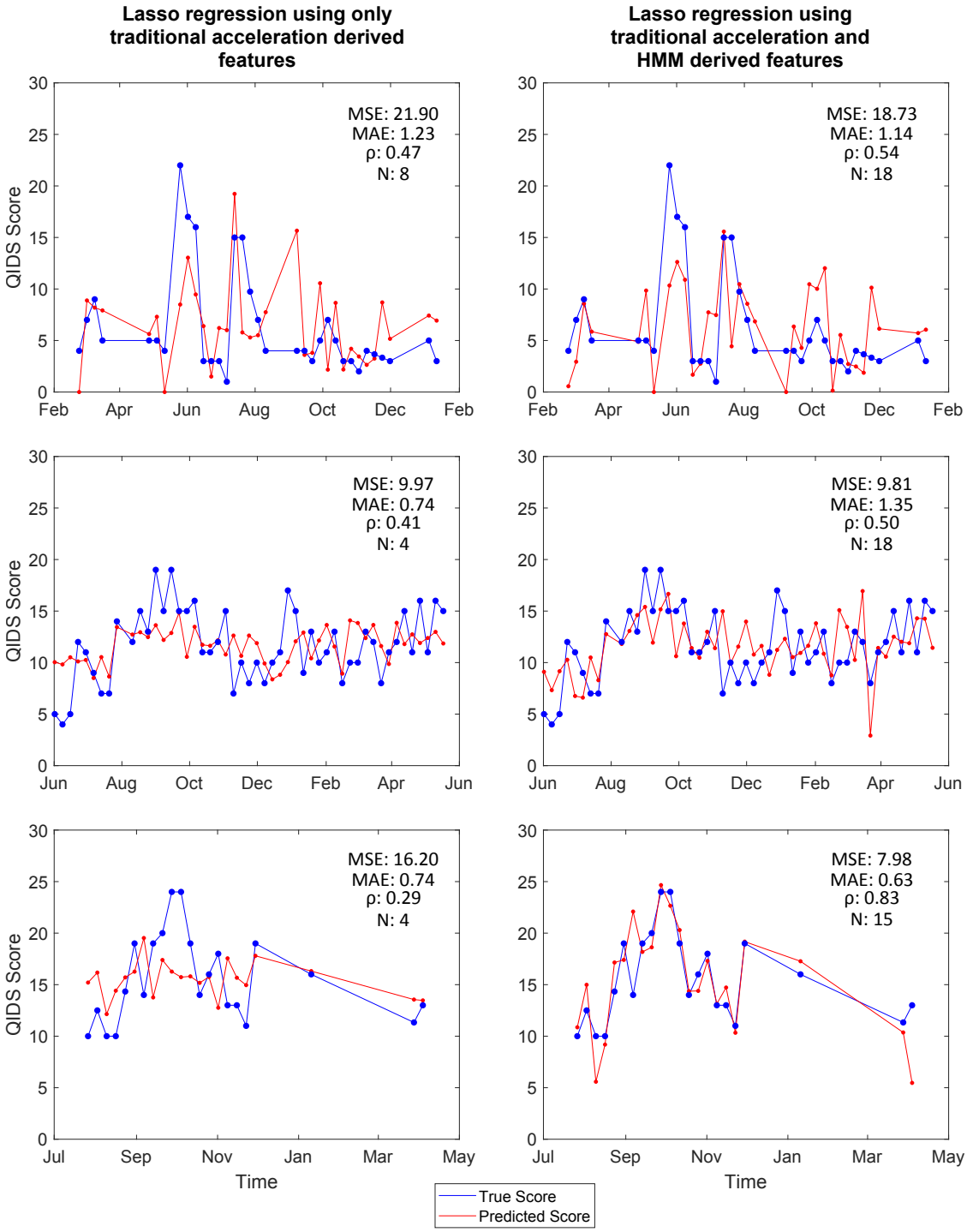


Figure 7.14: Three examples of LASSO regression for predicting QIDS in BD participants. The left column shows the results of the regression where only the traditionally derived acceleration features are used. The right column shows the results of the regression where the HMM derived features are also included.

the correlation coefficient increased from 0.07 to 0.19.

For BD participants, the accuracy, sensitivity and specificity of depression

classification all increased with the addition on HMM features. Specificity increased in BPD participants, whereas accuracy and sensitivity decreased, and sensitivity increased in the HC participants. These classification results suggest the LASSO regression classifies most of the BPD participants to be depressed the majority of the time, thus high sensitivity and low specificity. HC participants have very few periods of depression, thus high accuracy and specificity. Whereas the BD participants have more variable scores thus the intermediate values of sensitivity and specificity, with more episodes of depression to learn from potentially increasing sensitivity further.

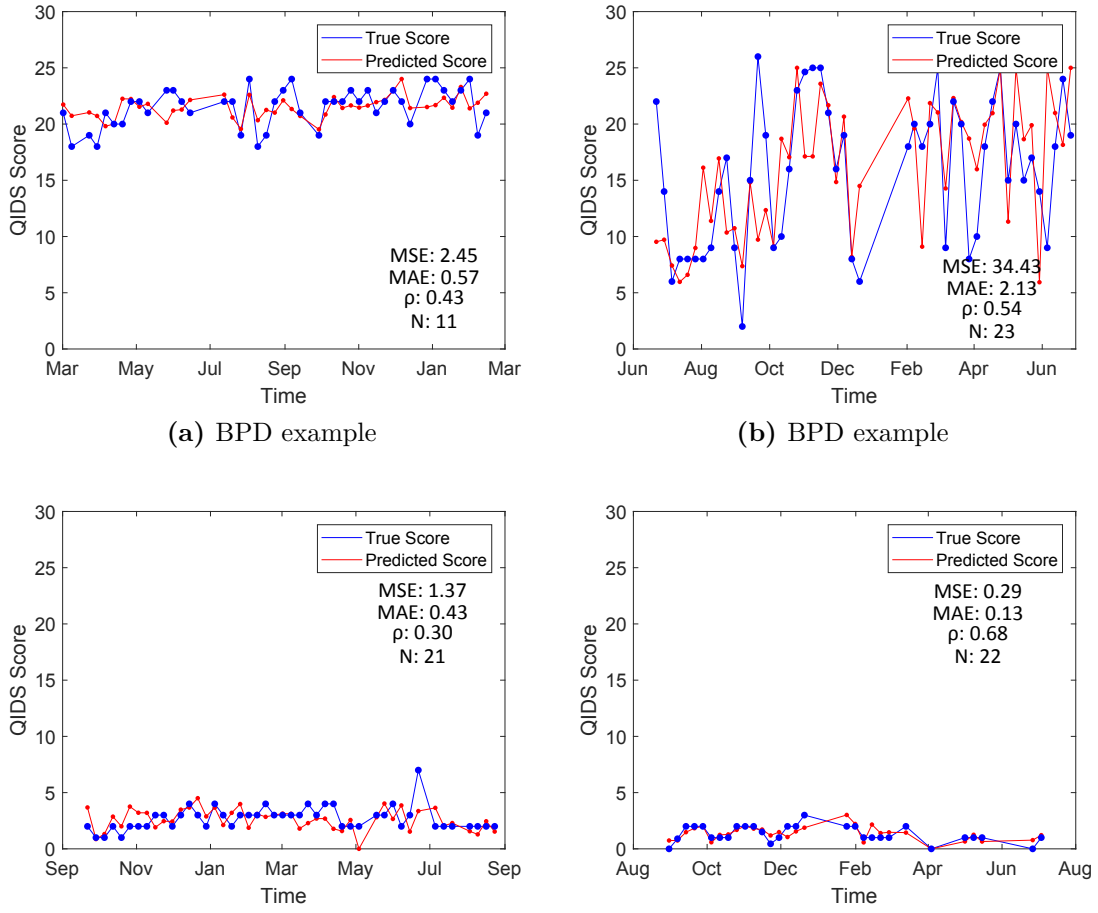
The right column of Figure 7.14 shows the regression results including the HMM features (compared to only the traditional features used in the left column). Improvements in the regression results can be seen through the MSE, MAE and ρ after the addition of the HMM features.

Two examples of the results of the LASSO regression for BPD participants using all features are shown in Figure 7.15 (a) and (b). The plot in (a) shows an example of a participant who has a very high QIDS score for the entire time of recording (one year), whereas the plot in (b) shows an example of a BPD participant with large variation in the QIDS score for over one year. The regression tracks the changes relatively well in both of these cases. The plots in Figure 7.15 (c) and (d) show two examples of HC participants, the HC participants have very little variation in QIDS scores, so the regression is easily able to predict this.

The full set of personalised regression results are shown in Appendix B for BD participants in Table B.1, BPD participants in Table B.2 and HC participants in Table B.3.

7.3.3 Feature importance

Figure 7.16 shows three plots of the LASSO coefficients for the regression of the same three BD participants shown in Figure 7.14. The features used in the regressions, in addition to the values of the coefficients vary greatly between the participants, thus highlighting the need for personalised prediction models. An example of how the regularisation is performed through variable shrinkage is shown in Figure 7.17.



(a) BPD example **(b)** BPD example

(c) HC example **(d)** HC example

Figure 7.15: Two examples of QIDS prediction for BPD and two for HC participants (blue true QIDS score, red prediction) using both the traditional acceleration features in addition to the HMM derived features.

The 20 plots show the β coefficients for each of the 28 features as the regularisation parameter changes. Each plot corresponds to the LASSO regression as one of the 20 weeks is left out for testing. The results remain consistent for the majority of the 20 weeks as each week is left out in turn, the vertical line indicates the index of the regularisation parameter which maximises the difference between the correlation coefficient and the MSE.

Although the features used for the prediction of QIDS in each personalised LASSO regression vary, a number of features are used in over 50% of cases. This can be seen in Figure 7.18 which shows the percentage of participants each feature is used for the QIDS prediction. The ordering of the features between the BD, BPD and

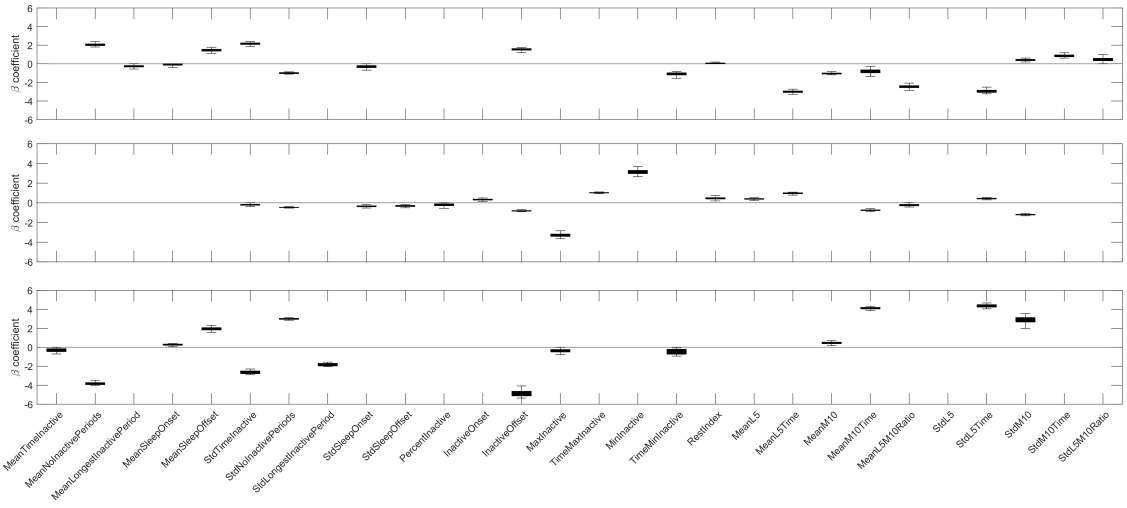


Figure 7.16: The distributions of the β coefficients calculated during the LASSO regression for the three respective participants shown in Figure 7.14.

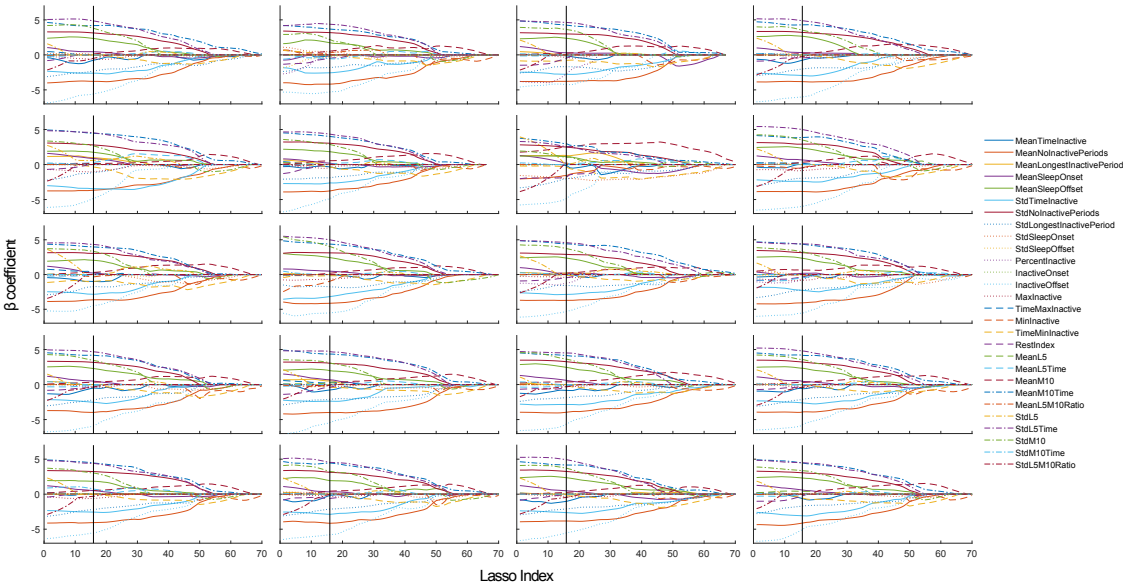


Figure 7.17: An example of the shrinkage of the features when performing leave one out LASSO regression. Each plot corresponds to the LASSO regression as one of the weeks from the participant is left out to be tested on. The vertical line indicated the index of the regularisation coefficient which maximised the difference between the standardised correlation coefficient and the MSE.

HC participants does not vary greatly suggesting the increased importance of some of the features, for example: rest index, standard deviation of the number of inactive periods, standard deviation of the longest inactive period, standard deviation of the L5 time, and the standard deviation of the M10 value. The distribution of the traditional acceleration features and of the HMM features are similar demonstrating

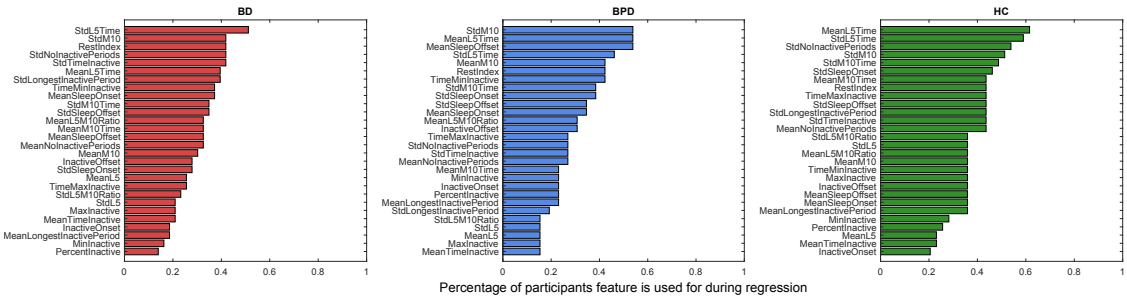


Figure 7.18: Features ranked by the percentage of participants in which they are used in the LASSO regression. The three plots show the rankings for the three different subject groups.

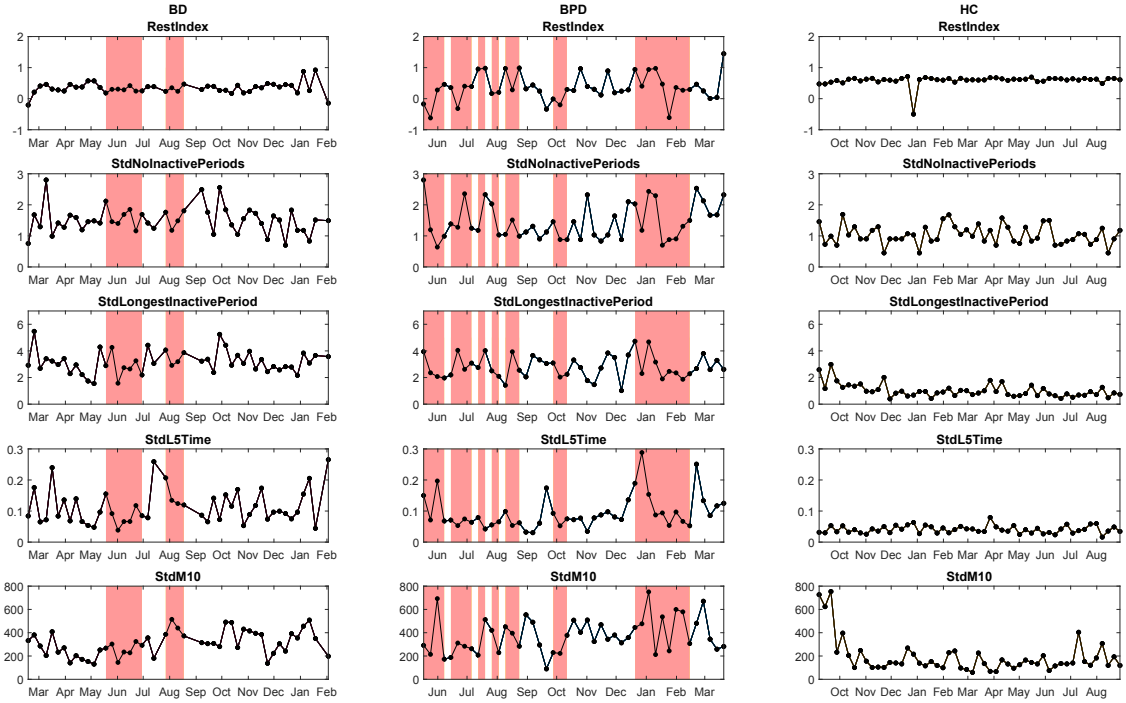


Figure 7.19: Three examples of how five of the most commonly used features vary longitudinally. The left column shows the variation of a BD participant, the centre a BPD participant and the right column a HC participant. The shaded red areas indicate periods where the QIDS score is above the clinical threshold.

the improved performance when combining the features.

7.4 Longitudinal variability

In order to try and understand what changes in someone's circadian activity are linked with changes in the levels of depression, the longitudinal variability of features may be able to provide some indications, although the direction may not be known.

Figure 7.19 shows the longitudinal variation of five of the most commonly used features, as determined by Figure 7.18, for one example of one BD participant, one BPD participant and one HC participant. Highlighted areas in red identify periods of depression over the clinical threshold. There appears to be no clear pattern or change in the features during the periods of depression, thus highlighting the need for multiple features for accurate prediction of depressive periods.

The HC participant has very stable features with time, which is consistent across the wide majority of HC participants, whereas the variability of the features in the BD and BPD participants is much more variable along with their QIDS scores. This suggests that either maintaining regular activity and sleep patterns could prevent the onset of depressive periods or entering depressive periods could cause disruptions to circadian rhythms.

7.5 Conclusions

This chapter has used mobile phone signal to calculate new features derived from rest-activity profiles in combination with more traditional circadian measures to predict levels of depression in BD and BPD. The features most predictive of depression have been determined and used to create personalised prediction models on a individual basis.

As discussed in Chapter 2, the assessment of mental health and diagnosis of depression if often extremely time consuming and is based on subjective measures, either from clinicians or self-reported questionnaires. The combination of some traditionally derived features from acceleration signals, in combination with novel features derived from active and inactive periods predicted from HMMs, has demonstrated the potential for objective markers to be used to quantify levels of depression and severity of mental health disorders.

The widespread use of smartphones in modern society allows for continuous and unobtrusive recordings of activity signals through accelerometers, from which circadian measures of activity and sleep may be derived. New features were derived from time varying HMMs which predict periods of rest and activity and were used

in combination with more traditional acceleration based circadian measures. These features, calculated on a weekly basis, were able to estimate levels of depression with small errors in the predictions. The median MSE error and MAE error in BD being 9.41 and 0.80 and in BPD being 12.68 and 1.33 respectively, which are well within the score ranges for identifying mood states from the QIDS questionnaire.

The importance of personalised prediction is highlighted through the large variation in the features selected for each participant. The reduction in available training data when performing personalised predictions emphasises the need for long term continuous monitoring of individuals. An additional way to increase the amount of training data available is to group individuals who share similar relationships between circadian rhythms of activity or sleep and levels of depression [147].

Many of the features which appear highly predictive of depression are based on sleep timings and variability, however the values differ when recorded from different devices (as shown in Figure 7.3), suggesting that validating these features with data labelled with true sleep and wake times may improve predictions further. In addition, many of the weeks of recordings during the study were omitted from the regression analysis due to limitations of data acquisition, as described in Table 7.4. Although mobile phones are common and their activity recordings are noninvasive making them an ideal candidate for longitudinal monitoring, they are not without problems. These could include: more missing data when devices are switched off, unwanted reduction in battery life, more noisy data through changing locations of devices. Improvements in the methods of data acquisition using mobile phones, or the development of mobile devices for long term, unobtrusive monitoring of activity could also greatly improve future performance.

8 Conclusions and Future Work

This final chapter provides a summary of the contributions of this thesis and how they could contribute to the field of circadian rhythm monitoring and mental health assessment. The limitations in the current work are discussed and potential directions for future work are suggested.

8.1 Summary of the work

This thesis has investigated the use of circadian rhythms as objective markers of BD and BPD, with the aim of providing a passive monitoring tool to aid the assessment of mental health symptoms. In particular, novel signal processing methods have been developed to quantify different aspects of the circadian rhythms of activity, sleep and heart rate from ambulatory signals recorded over both shorter and longer time periods using wearable devices and smartphones. The three main topics were: i) determining desynchronisation between different circadian rhythms (Chapter 5), ii) the association between circadian variability and mood variability (Chapter 6), and iii) the prediction of symptom severity from circadian rhythms of activity (Chapter 7).

In current clinical practice, diagnosis and symptom assessment of mental disorders, including BD and BPD, are performed by clinicians with the aids

of self-reported questionnaires, hence are inherently subjective. The time and resources needed to perform regular check-ups on patients means that infrequent visits result in missing deterioration of the mental state of individuals. Current prevalence of sleep disturbances and circadian rhythm disruption in BD and BPD are measured through questionnaires. Quantifying these disruptions in a long term passive way could provide a valuable tool to aid with the diagnosis and assessment of mental health in the future.

The desynchronisation of circadian rhythms was investigated in Chapter 5. Simultaneous acceleration and heart rate signals were recorded over four consecutive days from 18 BD participants, 14 BPD participants and 20 HC participants. Circadian rhythms of activity, sleep and heart rate were quantified using the cosinor method of fitting sinusoids to the signals, allowing the phase, amplitude and MESOR of each rhythm to be calculated. Although no differences were found between the three subject groups when comparing the average phase, amplitude or MESOR, significant internal phase differences between activity, sleep and heart rate were found in BD and BPD which were not seen in the HC participants.

The results confirm the previous literature which suggest disrupted circadian rhythms are important in BD. Although sleep disruption in BPD has been reported, little work into the circadian rhythms of BPD patients has been carried out. The desynchronisation of the rhythms was found to be greatest in the BPD participants, suggesting BPD is also associated with circadian disruption. The significant phase lag between the rhythms of sleep and activity indicates increased sleep onset latency in BPD, a feature previously reported in BPD through subject self-reported questionnaires [214].

The limitations of this analysis were the relatively small sample sizes, and variable scores of depression both between and within the subject groups. Future analysis should split the cohorts into groups of similar mood state (major depression, euthymia, hypomania and mania), this was not possible in this work due to the already small group sizes partially due to the quality of data recorded. Therefore, improvements in the technology to record the rhythms in large cohorts will give

further insight into the desynchronisation of the rhythms and may determine how the rhythms vary within mood states.

In Chapter 6, methods to assess the variability of the circadian rhythms were developed based on the results of Chapter 5. Mood variability over the same periods as Chapter 5 were investigated, in addition the associations between mood and circadian variability were evaluated. Increased variability in circadian parameters were observed in the BPD participants, further suggesting circadian disruption is a feature of BPD.

In order to determine intra-daily variability, mood scores were collected through the Mood Zoom app up to ten times per day during the week of high intensity monitoring. Previous studies have analysed the structure of the Mood Zoom scores using PCA in addition to quantifying the variability in mood from longitudinal recordings (once per day) over a number of months [254, 264]. The same structure of mood scores was found in the higher intensity, shorter term monitoring and the variability of the high intensity mood recordings was able to discriminate between the three subject groups in the same manner as the longitudinal study. These results show that shorter time period fine grained monitoring can act as an effective alternative to longer term studies when trying to distinguish between disorders.

Strong correlations between mood variability and circadian variability were found through a range of measures, especially for activity and heart rate features in BPD. The total variability in the activity rhythms measured by the RSS between the daily and total sinusoid fits and negative mood variability correlated strongly in BPD ($\rho = 0.923$), in addition to the variability in heart rate amplitudes and negative mood variability ($\rho = 0.848$). These findings indicate measures of circadian variability have the potential to act as objective markers of deteriorating moods, which are associated with increased mood variability.

Further evaluation of circadian variability measures to predict severity of depression in BD and BPD is performed in Chapter 7. Longitudinal recordings are required to capture information about the transition in mood state with the accelerometers in smartphones providing continuous measures of activity over a

number of months. Large amounts of missing data were observed in the acceleration data recorded from smartphones, this is expected as participants will not be carrying the phones at all times and often the phones run out of battery. This reduction in data quality and increased missing segments prevented the previous circadian metrics from being calculated. Time varying HMMs were used to determine the sequence of active and inactive periods through the Viterbi algorithm with circadian measures and estimates of sleep quantified from these sequences. Traditional circadian features found directly from the acceleration signals were also calculated, including the least active five hours and most active ten hours.

As behaviour and sleep patterns vary between individuals, in addition to the self-reported depression scores being highly subjective, individualised predictions of depression scores from circadian features were made. LASSO regression was used to predict current depression scores measured by the QIDS questionnaire using circadian features from HMMs in addition to the traditional features in order to determine feature importance. A MAE of 0.80 ± 0.79 and ρ of 0.20 ± 0.47 was obtained from the prediction of depression in 52 BD participants over a mean of 37 ± 33 weeks of circadian features and corresponding depression entries. A combination of the traditionally derived features and the novel HMM features were found to be important in the prediction of QIDS. The results presented here show that circadian and sleep measures can act as objective markers of symptom severity in BD and BPD. The current prediction of depressive scores uses features of a week to predict the score of that same week, thus further development is needed to incorporate future prediction of the onset of depression.

Overall, the results presented in this work met the endpoints of the study (Figure 4.1). Markers which are sensitive to changes in mental state were found through acceleration and heart rate recordings, with the variability in circadian measures correlated with mood variability scores over a four day period. More long term circadian markers from acceleration signals were also able to predict depression scores with high levels of accuracy. It was possible to predict longitudinal disease symptom severity from a single sensor (accelerometer in a mobile phone),

although the inclusion of more sensors may improve prediction of severity through depression scores. Desynchronisation of rhythms were also determined through two modalities recorded from a single sensor (acceleration and heart rate from the Proteus patch), suggesting it is possible to obtain markers of disease and symptom severity with only the addition of a single device.

8.2 Limitations and future work

The prediction of depression from circadian measures performs well on a large percentage of the participants in this work and the identification of desynchronisation and circadian variability in the patient groups gives insight into the disruption of rhythms in BD and BPD. However, the methods and results presented do suffer from a number of limitations which will be discussed below along with possible future directions of the work.

8.2.1 Validation of circadian and sleep measures

Many of the features used in Chapter 7 are based on sleep timings. As the participants were monitored in their daily lives the true sleep timings are unknown and there are no gold standard timings to compare to. Although the measures of sleep are not required to be consistent between participants as the predictions are made on an individual basis, the interpretation of the features between participants may not be consistent.

Quantifying accurate sleep timings in individuals will not only improve the interpretation of the results or predictions, it may also improve the results of the regressions. Validation of the measures of sleep require simultaneous accelerometer recordings and sleep labels. The most common method of acquiring sleep timings (sleep onset and wake time) is through self-reported timings and sleep diaries, this would allow for direct comparison of the estimated timings to the reported 'true' timings. Various accelerometers and other mobile devices claim to detect sleep and wake times along with other sleep measures which could be used to

validate the estimates, however these devices themselves need to be proven to be accurate through validation of their own.

Validation of circadian measures is difficult as there are no gold standard measures to compare to. A possible method of validation would be through the collection of biological signals such as melatonin or cortisol levels which are used to quantify circadian timings and phase. Regular collection of these signals is much more obtrusive than the passive acceleration recordings and would prove difficult in ambulatory settings.

One direction for future work would be to obtain accelerometer data with simultaneous sleep timings, which initially could initially be performed on a small number of participants. A greater number of participants would be required to ensure the measures are consistent across individuals and also to determine the measures can be validated in the different mood states of the participants.

8.2.2 Confounding factors affecting circadian rhythms

In addition to accurately determining sleep timings in individuals, which are used as the main predictors of depression in this work, it may also be important to determine any confounding factors which influence the sleep. The link between sleep and depression is not direct, with many other factors which can influence sleep, such as illnesses and work schedules. However, when sleep is altered by these external factors, it may lead to negative mood changes, thus further research is required into these complex interactions between all factors.

The diagnosis of depression is largely based on self-reported evaluation using questionnaires such as QIDS. The 16 questions in QIDS can be divided into subcategories, with one of the largest being linked to quality of sleep, therefore quantifying sleep alone may not be a good predictor of depression for everyone. The inclusion of other measures could improve the prediction, however many of the other aspects of QIDS are based on subjective measures such as fatigue and general interest and are not possible to measure objectively.

8.2.3 Feature extraction and forecasting

Although the current set of features are able to predict depression well in a large number of individuals, the development of new features may improve prediction further. These features may also be based on acceleration signals used to quantify other aspects of sleep, activity or circadian rhythms, or they may come from other modalities which are longitudinally recorded. An example of this could be the inclusion of geographic location features which have already been shown to be a predictor depression on the same data set [147]. Future work could perform a fusion of the features presented in [147] and the features in this work to determine the changes in predictions. Other modalities which are available in the AMoSS study include light levels and social activity data measured through calls and text messages sent and received from the smartphones.

As well as introducing new features for prediction of depression, alterations to the current feature extraction methods could be investigated. Increasing and decreasing the window length from one week may be beneficial in the prediction of depression. Also the method of labelling the weeks or feature windows with QIDS scores is not perfect. As the QIDS entries are not evenly spaced, or entries are often missing, the method described in Chapter 4 of labelling weeks through interpolation or the nearest entry may not be suitable in all cases. As the QIDS questionnaire is retrospective over the previous week, selecting weeks which end at a QIDS entry may provide a better labelling method than currently selecting consistent weeks of acceleration (from midday Sunday to midday Sunday) and trying to label these weeks.

The current method of QIDS prediction shows there is a relation between the current level of depression of an individual and the variability of their sleep and activity patterns. However, in practice this may not be of great use when attempting to monitor symptom severity of participants as it is important to prevent the transitions into negative states, whereas the current model can only predict if an individual is already in a depressive state. Therefore developing a predictive model of forecasting future levels of depression will have a greater impact in practice. A future direction could be to investigate whether circadian

and sleep features are able to predict levels of depression a number of days or weeks in advance. This would provide warning signs to clinicians and to try to prevent any negative transitions in mood.

In practice, future data is never available and models can only learn from previous data. The current regression uses future weeks in the training of the model. Forecasting by only training the model on weeks of data previous to the week of testing will determine how the model improves as more data is collected and will determine the number of weeks required to train an accurate model. Individuals must also experience at least one episode of depression in order for the model to learn from this episode and predict future episodes. Therefore many weeks or months of data may be required from each individual to train an accurate model.

The inclusion of time dependent models may also improve prediction and is a future area which should be investigated. As episodes in BD can be relatively rare and are required for the regression models to learn from, in addition to the range of different episodes individual can experience (depressive, manic, hypomanic and mixed), it may not be feasible to collect enough examples of these episodes for models to accurately learn from. Therefore other techniques of detecting transitions to negative mood states should be evaluated. An example of this could be through state change detection, or novelty detection. Novelty detection is a method of determining when a known pattern is becoming unknown [287, 288]. In this case, the model could learn the pattern of sleep and circadian rhythms in individuals during euthymia, with novelty detection able to detect changes in the sleep and circadian measures, indicating the transitioning into a different mood state. This may be able to provide the early warning signs needed to refer an individual to a clinician, and although it is not known which state the individual is transitioning to, the early referral to a clinician will allow the gold standard assessment to occur.

8.2.4 Transfer learning and clustering

As the time required to collect adequate data to learn an individualised model to predict depression for a BD patient may be very large, the incorporation of

readily available data may be able to reduce the acquisition time. Although it appears difficult to generalise models due to the subjective nature of the problem, it may be possible to cluster groups of individuals who exhibit similar behavioural patterns during euthymia, depression and mania. Further work into how individuals can be grouped with others would reduce the data needed for each individual and would give a more complete range of symptom manifestations to learn from. Grouping of individuals may be able to be performed from demographic information such as age, gender or employment status, or it could be based on grouping through behavioural patterns.

Transfer learning can be applied if clusters of participants who behave in similar ways can be determined. Trained predictive models for participants with sufficient data may be applied to participants with small amounts of data available, or little data for episodes of depression or mania. These transfers of already trained models may be able to improve monitoring of symptom severity in new participants, while there is not sufficient data to accurately train a fully personalised model.

8.2.5 Clinical collaboration

All future work in the computational analysis of mental disorders requires close collaboration with clinical professionals. This will not only provide a clearer insight into the types of features which are likely to be required for the detection or particular symptoms of mental health, but will also ensure the algorithms and models developed have a clinical use and will be able to contribute to the development of current practice in psychiatry and improve the healthcare of individuals suffering from mental disorders.

8.3 Conclusion

In summary, this thesis has shown desynchronisation between circadian rhythms in BD and BPD participants, in addition to increased variability of rhythms in BPD participants and correlations with their mood variability. This suggests BPD is more associated with disruptions to circadian rhythms than previously believed.

Further work and data is required to determine how desynchrony and variability of rhythms are altered within different mood states of participants.

Personalised regression is able to accurately predict scores of depression from circadian features in many individuals. Additional longitudinal accelerometry data is required from BD participants which cover multiple episodes of depression and mania in order to learn how circadian rhythms and sleep change within and leading up to these episodes. New data should also validate the measures of sleep used with labels of true sleep timings in order to improve the interpretability of features. Overall, the results presented in this thesis show promising indications that objective markers of sleep and circadian rhythms have the capability of improving the clinical care of mental health disorders.

Appendices

A

The Quick Inventory or Depressive Symptomatology (QIDS)

The QIDS questionnaire answered weekly as part of the AMoSS study is shown in the following section [7].

A.1 The QIDS questionnaire

Please circle the one response to each item which best describes you for **the past seven days**.

1. Falling asleep:

   0 I have never taken longer than 30 minutes to fall asleep.

   1 I take at least 30 minutes to fall asleep, less than half the time.

   2 I take at least 30 minutes to fall asleep, more than half the time.

   3 I take more than 60 minutes to fall alseep, more than half the time.

2. Sleep during the night:

   0 I don not wake up at night.

   1 I have a restless, light sleep with a few brief awakenings each night.

2 I wake up at least once a night, but I go back to sleep easily.

3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.

3. Waking up too early:

0 Most of the time, I awaken no more than 30 minutes before I need to get up.

1 More than half the time, I awaken more than 30 minutes before I need to get up.

2 I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.

3 I awaken at least one hour before I need to, and can't go back to sleep.

4. Sleeping too much:

0 I sleep no longer than 7-8 hours/night, without napping during the day.

1 I sleep no longer than 10 hours in a 24-hour period including naps.

2 I sleep no longer than 12 hours in a 24-hour period including naps.

3 I sleep longer than 12 hours in a 24-hour period including naps.

5. Feeling sad:

0 I do not feel sad.

1 I feel sad less than half the time.

2 I feel sad more than half the time.

3 I feel sad nearly all of the time.

6. Decreased appetite:

0 There is no change in my usual appetite.

1 I eat somewhat less often or lesser amounts of food than usual.

2 I eat much less than usual and only with personal effort.

3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

7. Increased appetite:

0 There is no change from my usual appetite.

1 I feel a need to eat more frequently than usual.

2 I regularly eat more often and/or greater amounts of food than usual.

3 I feel driven to overeat both at mealtime and between meals.

8. Decreased weight (within the last two weeks):

0 I have not had a change in my weight.

1 I feel as if I've had a slight weight loss.

2 I have lost 2 pounds or more.

3 I have lost 5 pounds or more.

9. Increased weight (within the last two weeks):

0 I have not had a change in my weight.

1 I feel as if I've had a slight weight gain.

2 I have gained 2 pounds or more.

3 I have gained 5 pounds or more.

10. Concentration/Decision making:

0 There is no change in my usual capacity to concentrate or make decisions.

1 I occasionally feel indecisive or find that my attention wanders.

2 Most of the time, I struggle to focus my attention or to make decisions.

3 I cannot concentrate well enough to read or cannot make even minor decisions.

11. View of myself:

    0 I see myself as equally worthwile and deserving as other people.

    1 I am more self-blaming than usual.

    2 I largely believe that I cause problems for others.

    3 I think almost constantly about major and minor defects in myself.

12. Thoughts of death or suicide:

    0 I do not think of suicide or death.

    1 I feel that life is empty or wonder if it's worth living.

    2 I think of suicide or death several times a week for several minutes.

    3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

13. General interest:

    0 There is no change from usual in how interested I am in other people or activities.

    1 I notice that I am less interested in people or activities.

    2 I find I have interest in only one or two of my formerly pursued activities.

    3 I have virtually no interest in formerly pursued activities.

14. Energy level:

    0 There is no change in my usual level of energy.

    1 I get tired more easily than usual.

    2 I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking or going to work).

    3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

15. Feeling slowed down:

    0 I think, speak, and move at my usual rate of speed.

    1 I find that my thinking is slowed down or my voice sounds dull or flat.

    2 It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.

    3 I am often unable to respond to questions without extreme effort.

16. Feeling restless:

    0 I do not feel restless.

    1 I'm often fidgety, wringing my hands, or need to shift how I am sitting.

    2 I have impulses to move about and am quite restless.

    3 At times, I am unable to stay seated and need to pace around.

B

QIDS Regression Results

Tables B.1, B.2, and B.3 show the regression results using circadian variability features from mobile phone accelerometers to predict QIDS scores for depression for each individual bipolar disorder, borderline personality disorder and healthy control participant respectively. A QIDS score greater than 10 is defined as depressed, with all clinical threshold described in Table 4.3.

Table B.1: Individual regression results and QIDS information for BD participants.

Participant number	Number of weeks	Mean QIDS	Std QIDS	Min QIDS	Max QIDS	MSE	MAE	ρ	N	Acc	Sen	Spec
Bipolar Disorder												
14003	42	4.98	1.84	1	11	3.66	0.61	0.07	9	0.98	0	1
14005	34	6.26	4.98	1	22	18.73	1.14	0.54	18	0.82	0.80	0.83
14008	47	6.67	3.78	2	15	16.90	1.42	0.22	16	0.74	0.11	0.89
14014	19	5.92	2.23	3	12	18.99	1.30	-0.25	13	0.84	0	0.89
14017	57	4.75	3.28	0	16	14.05	1.61	-0.07	17	0.91	0	1
14021	52	24.26	1.85	19	27	4.12	0.81	-0.11	14	1	1	-
14026	98	12.72	3.48	5	21	10.63	2.55	0.35	8	0.72	0.99	0
14027	11	6.36	1.50	4	9	3.35	0.38	-0.67	3	1	-	1
14028	52	8.82	1.92	6	14	7.35	0.96	0.00	13	0.73	0.13	0.84
14031	31	10.40	5.51	2	25	30.73	1.49	0.53	26	0.68	0.71	0.65
14032	8	7.50	3.40	3	13	4.33	0.26	0.79	6	0.88	0	1
14034	50	11.64	3.49	4	19	9.81	1.35	0.50	18	0.76	0.94	0.44
14036	23	4.60	1.63	2	8	2.33	0.45	0.60	16	1	-	1
14037	11	8.83	4.09	4	18	20.46	0.80	0.09	3	0.45	0	0.63
14039	44	5.90	4.26	0	17	27.36	1.75	0.09	20	0.84	0.17	0.95
14040	54	5.00	2.14	1	10	4.42	0.94	0.51	24	0.98	-	0.98
14041	55	14.45	0.94	12	17	0.76	0.37	0.49	20 1	1	-	
14042	10	10.24	6.34	2	19	50.18	1.31	0.27	4	0.70	0.80	0.60
14044	59	2.66	1.47	0	8	2.18	0.69	0.19	10	1	-	1
14045	87	2.92	2.48	0	12	5.59	1.62	0.29	2	0.98	0	1
14046	46	3.28	1.75	1	10	3.45	0.59	0.11	10	1	-	1
14047	45	11.00	5.56	2	21	36.85	2.46	-0.17	5 0.44	0.77	0	
14053	47	2.52	1.90	0	8	3.51	0.64	0.27	8	1	-	1
14055	21	5.05	1.36	3	8	2.38	0.34	0.33	14	1	-	1
14056	17	9.77	3.55	2	15	10.27	0.74	0.37	2	0.59	0.57	0.60
14059	28	4.29	3.18	0	12	9.26	0.78	0.25	3	0.96	0	1
14062	10	12.40	2.32	9	16	6.42	0.46	0.20	7	0.90	1	0.50
14065	21	8.40	4.09	3	19	17.11	1.08	0.09	4	0.76	0	1
14069	61	1.70	1.39	0	8	1.98	0.62	-0.02	3	1	-	1
14077	13	17.87	5.62	4	25	13.02	0.81	0.75	9	0.92	1	0.50
14081	12	7.63	2.46	2	12	9.43	0.59	-0.12	3	0.83	0	0.91
14083	26	4.63	2.66	0	12	8.48	0.75	0.32	10	0.96	1	0.96
14095	34	3.32	0.77	3	6	0.63	0.18	-0.12	4	1	-	1
14097	16	5.24	2.59	2	11	7.86	0.64	-0.19	3	0.88	0	1
14101	47	11.27	4.46	3	22	22.65	1.79	-0.05	7	0.53	0.73	0.29
14104	11	6.19	2.18	2	9	9.81	0.66	0.46	8	0.82	-	0.82
14105	30	11.97	7.30	0	26	51.75	1.86	0.07	1	0.63	1	0.15
14108	35	6.49	4.90	1	19	25.86	1.42	0.17	9	0.71	0.14	0.86
14109	8	12.00	3.25	7	15	13.98	0.59	-0.28	2	0.50	0.67	0
14115	21	12.27	5.88	3	23	27.50	1.32	0.44	1	0.71	0.93	0.17
14117	33	6.58	3.38	1	12	8.49	0.78	0.57	15	0.88	0.43	1
14119	74	3.57	3.04	0	15	9.41	1.65	0.00	4	0.95	0	1
14130	22	15.46	4.27	10	24	7.98	0.63	0.83	15	0.91	0.95	0.67

Table B.2: Individual regression results and QIDS information for BPD participants.

Participant number	Number of weeks	Mean QIDS	Std QIDS	Min QIDS	Max QIDS	MSE	MAE	ρ	N	Acc	Sen	Spec
Borderline Personality Disorder												
14010	50	14.80	4.17	6	22	21.37	1.87	-0.04	11	0.86	0.96	0
14011	20	18.24	3.41	12	27	12.80	0.92	0.28	12	1	1	-
14019	28	18.00	5.77	4	26	49.03	2.05	-0.02	6	0.86	0.96	0
14020	20	7.48	2.34	5	12	5.94	0.74	-0.38	3	0.85	0	1
14023	115	13.51	2.65	8	19	6.16	2.04	0.34	6	0.84	1	0
14024	48	10.83	3.87	4	19	12.19	1.33	0.43	10	0.56	0.71	0.42
14029	38	16.38	4.04	8	24	36.99	1.83	-0.01	20	0.79	0.91	0
14033	61	14.44	3.06	9	22	8.74	1.54	0.23	4	0.95	1	0
14043	12	10.00	2.36	7	16	5.64	0.41	0.17	3	0.58	0.67	0.56
14071	38	14.73	1.70	11	18	3.82	0.63	0.03	12	1	1	-
14073	46	19.13	3.00	11	25	7.15	0.94	0.47	11	1	1	-
14082	25	17.81	2.71	13	23	7.80	0.73	0.17	6	1	1	-
14084	67	7.60	3.82	2	18	10.68	1.80	0.51	6	0.79	0.07	1
14087	32	13.88	4.58	6	22	24.71	1.27	0.01	8	0.69	0.92	0
14091	27	11.87	3.76	6	23	7.84	0.79	0.65	13	0.67	0.89	0.13
14092	13	9.58	4.08	2	17	21.20	0.91	-0.23	4	0.38	0	0.50
14099	39	12.46	2.62	9	20	6.79	0.74	0.12	4	0.79	1	0
14100	44	21.50	1.73	18	24	2.45	0.57	0.43	11	1	1	-
14102	46	12.11	5.57	4	22	26.18	1.90	0.42	10	0.70	0.92	0.43
14110	35	13.36	5.09	4	22	22.74	1.44	0.33	2	0.69	1	0
14116	20	12.35	2.32	8	15	29.06	1.33	-0.27	14	0.65	0.73	0.40
14118	17	19.28	5.72	10	27	62.97	2.10	0.16	13	0.76	0.81	0
14121	45	10.57	4.66	4	20	20.54	1.78	0.26	6	0.58	0.71	0.46
14122	47	17.17	3.81	7	24	18.22	1.51	-0.06	12	0.96	1	0
14123	25	16.84	3.30	10	22	12.57	1.10	0.32	14	0.92	0.96	0
14128	49	15.79	6.40	2	26	34.43	2.13	0.54	23	0.71	0.85	0.44

Table B.3: Individual regression results and QIDS information for HC participants.

Participant number	Number of weeks	Mean QIDS	Std QIDS	Min QIDS	Max QIDS	MSE	MAE	ρ	N	Acc	Sen	Spec
Healthy Controls												
14001	38	2.29	2.37	0	8	7.77	0.83	0.25	22	1	-	1
14002	25	2.70	1.68	0	5	2.86	0.53	-0.02	3	1	-	1
14004	32	0.31	0.54	0	2	0.28	0.12	0.34	15	1	-	1
14006	16	1.30	1.00	0	3	1.37	0.27	0.01	6	1	-	1
14007	34	1.76	1.58	0	7	5.54	0.65	-0.22	20	1	-	1
14009	30	2.05	4.69	0	16	39.62	1.13	0.08	20	0.87	0.33	0.93
14018	52	0.74	1.14	0	5	1.80	0.55	-0.29	8	1	-	1
14022	42	4.03	2.73	0	11	7.76	0.96	0.09	5	0.98	0	1
14025	78	4.19	2.49	0	12	5.80	1.38	0.29	11	0.96	0	1
14030	42	1.17	1.59	0	7	2.77	0.50	0.43	25	1	-	1
14038	9	0.00	0.00	0	0	0.11	0.04	-	8	1	-	1
14052	50	2.00	0.00	2	2	0.81	0.20	-	28	1	-	1
14054	21	0.43	0.93	0	3	0.93	0.24	0.38	17	1	-	1
14060	31	1.44	1.44	0	5	3.95	0.47	0.09	19	1	-	1
14063	19	1.84	2.06	0	6	5.56	0.68	-0.09	6	1	-	1
14064	39	2.28	1.17	0	5	3.86	0.53	0.07	21	1	-	1
14066	46	2.70	1.05	1	7	1.37	0.43	0.30	21	1	-	1
14070	48	2.03	0.15	2	3	0.06	0.06	0.00	15	1	-	1
14075	74	0.36	1.05	0	7	1.03	0.39	0.25	8	1	-	1
14078	13	4.31	1.25	3	7	1.47	0.24	0.10	1	1	-	1
14089	17	0.88	1.54	0	4	1.13	0.22	0.71	9	1	-	1
14090	15	1.40	0.51	1	2	0.36	0.16	0.06	4	1	-	1
14094	61	1.03	1.37	0	8	1.70	0.59	0.29	2	1	-	1
14106	50	0.76	0.98	0	4	0.92	0.34	0.17	3	1	-	1
14107	9	14.67	2.12	10	17	6.35	0.39	-0.57	4 0.89	1	0	
14111	51	3.47	2.72	1	10	7.93	1.21	-0.16	4	1	-	1
14113	9	4.33	3.61	0	11	8.18	0.40	0.55	2 0.89	0	1	
14114	30	1.10	1.66	0	7	12.74	0.74	-0.05	23	0.97	-	0.97
14132	30	1.33	0.73	0	3	0.29	0.13	0.68	22	1	-	1
14133	11	2.00	0.00	2	2	0.43	0.09	-	10	1	-	1
14135	15	1.00	0.38	0	2	0.24	0.10	0.32	13	1	-	1
14137	52	0.10	0.30	0	1	0.53	0.15	0.38	19	1	-	1
14138	15	0.67	0.62	0	2	0.77	0.21	-0.03	12	1	-	1
14140	40	10.41	1.97	7	14	3.59	0.62	0.26	7	0.56	0.77	0.33
14144	11	1.82	1.17	1	4	1.08	0.22	0.46	1	1	-	1
14145	47	4.17	1.01	3	6	0.79	0.34	0.45	5	1	-	1
14147	8	1.13	0.83	0	2	0.30	0.09	0.73	6	1	-	1

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