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DEPARTMENT OF ENGINEERING MATHEMATICS

Investigating Diurnal Rhythm Disruption in T1D

Finding Patterns Using APS Data

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A dissertation submitted to the University of Bristol in accordance with the requirements of the degree
of Master of Science in the Faculty of Engineering.

Friday 29th August, 2025

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Declaration

This dissertation is submitted to the University of Bristol in accordance with the requirements of the degree of MSc in the Faculty of Engineering. It has not been submitted for any other degree or diploma of any examining body. Except where specifically acknowledged, it is all the work of the Author.

Ross Duncan, Friday 29th August, 2025

Contents

0.1 Acronyms	xiii
0.2 Notation and Terminology	xiii
1 Context	1
1.1 Problem Domain	1
1.2 Investigative Focus	3
2 Literary Review	5
2.1 The Research Gap: Circadian Rhythms and T1D	5
2.2 Glycaemic Control & Variability	5
2.3 APS System Data Use	6
2.4 Methods for Time Series Analysis	6
3 Execution	9
3.1 Dataset and Preparation	9
3.2 Grouping Similar Nights	11
3.3 Finding Time-Dependent Associations Between Variables	13
3.4 Glycaemic Variability (GV)	14
3.5 Glycaemic Stability as a Composite Score	15
4 Critical Evaluation	19
4.1 Cluster Analysis	19
4.2 Blood Glucose Analysis	21
4.3 Analysis of Glycaemic Variability	24
4.4 Stability Score (J) Analysis	27
5 Conclusion & Further Work	31
5.1 Conclusion	31
5.2 Further Work	32
A Circadian Rhythms - Supplementary Material	39
A.1 What are Circadian Rhythms?	39
A.2 Why are Circadian Rhythms Important to General Health?	40
B Data Selection Strategy	41
C Feature-Based Clustering	43
D Cross-Correlation Coefficient Results	47
E Finding Relationships by Machine Learning Modelling	49
F Law of Total Variance for Aggregated Data	51
G Intervals Out of Range	53
H Evening IOB and COB Relationship with Nocturnal BG	57

List of Figures

1.1	Defining the different types of disruptions to diurnal patterns [33]	2
3.1	Lagging COB and IOB values against BG to analyse relationships between passed values, in this case COB leads BG. E.g. COB (orange) are lagged $x + n$ intervals ($0 \leq n \leq 4$) to allow BG (blue) to be regressed against each lag (COB _{lagn}).	14
4.1	Silhouette scores by number of clusters for each approach used in a) features extraction, and b) dimensionality reduction technique. PCA_{14} with the $K = 4$ was the chosen model.	19
4.2	Two different projections of the same clustering outcome using K-Means of PCA_{14} using $K = 4$, where objects represent nights and colours are the cluster labels.	20
4.3	Time series profiles of each cluster using a DBA averaging of the variable means at each interval and a rolling average variance error (over 3 intervals), for COB (orange), IOB (green) and BG (blue).	21
4.4	Plots based on the unweighted standard BG mean at each interval showing (a) the profile over the nocturnal period and (b) the DTW distance between the mean profiles for BG.	22
4.5	Spearman correlation between mean scaled variables calculated at intervals for each cluster with the correlation on the y-axis, and lines showing values for each cluster (0 - blue, 1 - orange, 2 - green, 3 - red).	23
4.6	Comparison of P values for linear regression models for four passed lagged intervals of COB and IOB with BG.	24
4.7	Relationship between the number of total nights for a patient and the number of nights with excursions recorded. Markers (blue) represent a patient and size denotes the total number of excursions recorded for the patient.	25
4.8	Occurrence of excursions by cluster in the broad 17:00-11:00 period vs the nocturnal 22:00-06:00, for Intervals Above Range (blue) and Intervals Below Range (orange).	25
4.9	BG L1 excursions density (likelihood) over observed period, highlighting the nocturnal period. The violin plot uses a low kernel bandwidth to avoid smoothing and tails that extend greatly beyond the observed time range, hence the perceived sensitivity of the distribution to fluctuation	26
4.10	Time series showing the excursion means at each time interval (orange area) against DBA profile of scaled BG for each cluster, using marker size at each time point to highlight the mean of excursion counts at interval. The BG mean for the 17:00-11:00 is marked for reference as the dashed line, and the zero line as a dotted line for the BG mean axis. The 22:00-06:00 period is the focus while the shaded areas show the context of the broader BG profile. Grid lines are provided for the Excursion Mean axis	27
4.11	Average J scores at the intersection of cluster and patient. with colours blue to red representing the weight of the score.	28
4.12	Start 4.12a and end 4.12b of hierarchical analysis, highlighting consistency of high insulin where there is high J score.	30
4.13	J score components averages by cluster, highlighting the high component scores for cluster 1 in particular.	30
B.1	Counts of patients n and count of nights m based on varying thresholds of missing intervals permitted plus the max_length of the span of missing intervals in a night, where colours represent variants of the max_length threshold and marker/line styles distinguish between patient counts (primary y-axis) and night counts (secondary y-axis).	42

C.1	A heatmap based on the scaled values of all features used in the features-based clustering of nights in the sample. Actual values are displayed for reference, which are unscaled means of the feature for the cluster.	44
C.2	The distributions of nights between clusters for the $n = 16$ patients in the sample, with patients (A to P) along the y axis, and proportions (%) of nights illustrated using coloured bars on the horizontal axis (clusters: blue - 0, orange - 1, green - 2, red - 3), labelled with their proportion.	45
C.3	Intersection of night counts by patient and cluster with the patient (A to P) and cluster (0 to 3), with the count of nights provided as values and magnitude of the values by colour.	45
D.1	Each subplot shows the means of correlation coefficients for pairwise comparisons of variables, where one variable leads another by a number of interval lags, up to 5. Line colours represent the means of the coefficients for each cluster.	47
G.1	Relationship between the number of total nights for a patient and the number of nights with excursions recorded. Markers (blue) represent a patient and size denotes the total number of excursions recorded for the patient.	53
G.2	Occurrence of excursions by cluster in the broad 17:00-11:00 period vs the nocturnal 22:00-06:00, for Intervals Above Range (blue) and Intervals Below Range (orange).	54
G.3	L1 BG density of excursion amplitudes during the nocturnal period	54
G.4	L2 BG density of excursion amplitudes during the nocturnal period	54
G.5	BG L2 excursions density over observed period, highlighting the nocturnal period. The violin plot uses a low kernel bandwidth to avoid smoothing and tails that extend greatly beyond the observed time range, hence the perceived sensitivity of the distribution to fluctuation	55
G.6	L1 BG density of excursion amplitudes split by each cluster during the nocturnal period, with BG mean values are each interval overlaid.	55
G.7	L2 BG density of excursion amplitudes split by each cluster during the nocturnal period, with BG mean values are each interval overlaid.	56
H.1	Evening COB weighted mean against nocturnal J score for all nights in sample, with markers separated by colour and shape. Results of an overall linear regression is plotted with coefficients and p-value stated,	58
H.2	Evening COB weighted means against nocturnal J score by cluster, highlighting the relationships they have through OLS linear regression.	58
H.3	Evening IOB weighted mean against nocturnal J score for all nights in sample, with markers separated by colour and shape. Results of an overall linear regression is plotted with coefficients and p-value stated,	59
H.4	Evening IOB weighted means against nocturnal J score by cluster, highlighting the relationships they have through OLS linear regression.	59

List of Tables

3.1	Descriptive statistics of the irregularly sampled data for BG, IOB, and COB.	10
4.1	Results of linear regression between evening means (for the period 17:00-22:30) of COB and IOB relative to the composite score for each cluster.	28
4.2	Sample size of nights $m_{\text{bottom}50}$ and $m_{\text{top}25}$ as a proportion of the full sample of $m = 922$	29
D.1	Mean cross correlation coefficients by cluster	48
D.2	Standard deviation of means for cross correlation coefficients by cluster	48
E.1	COB Leading BG prediction performance averaged by night, showing MSE and R^2 scores	50
E.2	IOB Leading BG prediction performance averaged by night, showing MSE and R^2 scores	50

Abstract

Circadian rhythm is vital for optimising physiological processes and relies on regular diurnal patterns to maintain it. Considerable research has been done on the impacts of circadian rhythm disturbance in healthy adults and how it can lead to health problems (and, in particular, Type 2 diabetes). However, patients with Type 1 diabetes suffer rhythmic disturbances due to the need to control blood glucose levels, in part through exogenous insulin treatment. For example, glucose control during nocturnal periods can be challenging, leading to disturbance of sleep with insulin injections or carb intake. Artificial Pancreas Systems (APS) automate insulin delivery, reducing this burden, but are not a silver bullet. However, their data can produce useful insights into how such diurnal patterns are disrupted, thus leading to rhythmic disturbance.

The objective of this study was to identify patterns in blood glucose, insulin, and carbohydrate levels during fasting periods that distinguish between groups of nights with varying diurnal profiles. The study analysed these periods to identify where the diurnal patterns differ, based on blood glucose (BG), carbohydrates on board (COB) and insulin on board (IOB). Finally, it proposed a measure of the stability of a night using glycaemic variability (GV) metrics and analysed their relationship to COB and IOB.

Data from OpenAPS Data Commons was preprocessed and selected based on its level of completeness to night windows of 17:00-11:00. Nights were clustered into groups that exhibit different characteristics using a feature-based clustering method from COB/IOB features. These groups were compared using different lenses to highlight differences in diurnal patterns. The BG and GV of a nocturnal window (22:00-06:00) were analysed to highlight distinctive differences in the diurnal pattern. BG and GV-based measures were then compiled as part of a composite score to produce a single measure of stability, and used to identify further patterns between the groups.

Four groups of nights were identified, characterised as high-carb, high-insulin, low-carb/low-insulin, and common. The nocturnal BG profiles for each were significantly different, confirming that they represented different diurnal rhythms in all three variables. COB and IOB showed different relationships with BG, the strength of which was different between the groups. IOB demonstrated a stronger and more predictable relationship, but both COB and IOB showed a consistently weak time-dependent relationship using correlation- and regression-based approaches. An analysis of GV showed predictable target range level 1 excursions by group, but level 2 thresholds were personalised to the individual. The rate and occurrence of excursions to nights was significantly different for each group, providing interpretable evidence of diurnal differences. Finally, a stability score was proposed to indicate the instability of diurnal rhythms at night. The high-insulin group had a significantly different score distribution and also a stronger relationship between the score and COB than IOB. A hierarchical analysis method also showed that a higher stability score was characteristic of higher IOB. This offers insight into potential relationships between the level of disturbance in the nightly diurnal pattern (defined by GV) and insulin levels in the body.

The study demonstrates methods in which data from APS systems can be used to help understand differences in diurnal rhythms for patients with T1D. The methods have established ways to characterise and compare night periods using APS data and measure the stability of a night. This analysis opens up the possibility of new ways to study the impacts of circadian rhythm disturbance in these patients, which has the potential to inform decision making in their treatment and general health.

Ethics Statement: The project fits within the scope of ethics applications 11270, supported by an amendment request submitted by Isabella Degen and approved by the University of Bristol Ethics Committee, 29th July 2025.

Project Code: The full codebase for this project is stored and made available to the public via https://github.com/rdbrist/masters_project.

Supporting Technologies

Outlined here are the supporting technologies used and contributing to the output of the project.

- The insulin-need GitHub library was forked to form a basis of some preprocessing code to prepare raw data [35].
- `pandas`, `seaborn` and `matplotlib` public-domain Python libraries were used for data preparation and visualisation.
- `tslearn`, `tsfresh` and `scikit-learn` public-domain Python libraries were used to create machine learning models and other functions for data preparation.
- `numpy`, `scipy` and `statsmodels` public-domain Python libraries were used for computation, time series analysis and tests
- A University of Bristol OneDrive account (for Ross Duncan) was to store all the raw data used in the project.
- Code was authored in the PyCharm IDE.

Notation and Acronyms

Here details a reference for any notation and acronyms used as part of this document.

0.1 Acronyms

T1D	:	Type 1 Diabetes
APS	:	Artificial Pancreas System
CSV	:	Comma Separated Values (files)
DTW	:	Dynamic Time Warping
DBA	:	DTW Barycenter Average
DES	:	Data Encryption Standard
COB	:	Carbohydrates Onboard
IOB	:	Insulin Onboard
BG	:	Blood Glucose
GV	:	Glycaemic Variability
CGM	:	Continuous Glucose Monitor
mmol/l	:	Millimoles per Litre
mg/dL	:	Milligrams per 100 Millilitres

0.2 Notation and Terminology

Unit Measures

The unit convention used for blood glucose concentrations can differ between studies. Although much of the analysis uses scaled numbers (i.e. unitless values), other references to glucose will use mg/dL rather than mmol/l, reflective of the majority of the literature that has been used to contribute to the study and the underlying OpenAPS dataset convention.

Time and Duration

The notation for time in the study uses a 24-hour clock with a range [00:00, 23:59]. To differentiate time duration, this is annotated in the format 00hr00, with the first two numbers indicating the hours and the second two numbers indicating the minutes, e.g. 03hr15 would be a duration of three hours and fifteen minutes.

People With Type 1 Diabetes

There are many terms that have been used in studies of individuals with T1D. Sensitivity around the use of different terms is acknowledged and it is possible that the terms could be used at different stages in the project, e.g., 'candidate' or 'individual' could be appropriate at the data selection stage, 'subject' could also be helpful, and 'person with T1D' is a term also used in other studies. However, the term 'patient' is used consistently throughout the study, is distinct in its meaning (i.e., cannot be confounding) and is a term commonly used in studies of T1D data samples. It is hoped that, given its prevalence in T1D research, the reader is not offended.

Insulin Delivery Technology.

The technology used for automated insulin delivery can change depending on the resources. Hybrid closed-loop systems (HCL), Automated Insulin Delivery (AID), and Artificial Pancreas Systems (APS)

often interchangeable and used for the same thing. Although architecturally there might be subtle differences between them, for the purpose of this study (and aligning to the OpenAPS term) APS has been used consistently for the benefit of the reader. There is acknowledgement that when referring to other resources that use a different pseudonym, the reference might not be technically accurate; rather, it is a deliberate attempt to simplify concepts and acronyms that the reader may otherwise be confused by.

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Chapter 1

Context

1.1 Problem Domain

1.1.1 Type 1 Diabetes (T1D)

Type 1 Diabetes (T1D) is a condition that causes the glucose level in the blood to become too high due to the body not being able to effectively produce insulin, which is used by the body's cells to absorb blood glucose (BG) and turn it into energy. Although there is no cure, the core of any treatment regime is the use of exogenous insulin. When carbohydrates are consumed, they are broken down by the digestive system into sugar that enters the blood and insulin is required to help cells absorb this glucose, which otherwise would result in hyperglycaemia and can be dangerous to the body. On the other hand, a state of hypoglycaemia can occur when there is too much insulin in the blood and leads to insufficient BG, and can be exacerbated by factors such as missed meals or exercise. Managing this difficult balance, which in healthy people is something the body performs, can be disruptive and a cognitive burden. The aim of any person with T1D is to achieve good control of these diurnal rhythms involving carbohydrate intake, insulin dosing and ultimately glycaemic control, which are natural oscillating rhythms over the course of the day. For this reason, technological solutions have been sought that help reduce this burden and have progressed significantly in recent years [5, 78].

1.1.2 Technology in the Treatment of T1D

Recent developments in technology to support diabetes care have led to systems that can better deliver insulin so that circadian rhythm can be maintained and controlled. Technological advances in diabetes treatment have led to the commonplace use of Continuous Glucose Monitors (CGM) for continuous glucose monitoring in interstitial fluid, that is, a latent reading of BG. These have been integrated with insulin pumps that deliver insulin to the body through a small catheter, to create systems that manage insulin dosing based on a continuous feedback loop. Software algorithms use CGM data to help regulate insulin delivery in Artificial Pancreas Systems (APS) [16]. Providing algorithms with data to indicate the level of carbohydrate intake allows them to respond with more intelligence, making dosing more accurate to the timing of glucose metabolism as the body converts carbohydrates to BG. An APS uses a controller algorithm that runs on a connected device such as a smartphone or insulin pump. The algorithm predicts future glucose levels from the data and directs the pump to adjust insulin accordingly. Many APS are commercially available, but are costly and thus unavailable to some populations in countries where public health services do not cover provision. For this purpose, open source or "DIY" alternatives have been sought [78] to democratise their use and the benefits they provide. One such example is OpenAPS [41].

Carbohydrate intake can be entered into the OpenAPS platform by the user. There are complications with the carb counting process, such as accurate counting and timely recording, which requires the patient's dedication to maintain consistency and precision [6]. The efficacy of the most recent OpenAPS algorithm in predicting insulin need is based on the capture of accurate carbohydrate data. Many other confounders exist to accurately predict BG levels, such as meal timing, exercise, and stress, but an understated benefit of an APS for patients with T1D is the outcome in regulating physiological circadian rhythms. The fundamental aim of the APS is the control of BG, and the goal of control is minimising the chaotic peaks and troughs and imposing a more stable and predictable rhythmic pattern in the BG profile. Thus, the data an APS collects can be informative as to how such rhythmicity is undermined through variance in BG.

1.1.3 Importance of Circadian Rhythms in Patients with T1D

Appendix A provides background for the reader on circadian rhythm, its function, and health implications, while this section focusses on its importance in this study.

For people with a healthy pancreas, pancreatic beta cells that produce insulin have internal circadian clocks, leading to a natural circadian rhythm in insulin secretion [84]. During typical active and feeding hours, the body's cells are more sensitive to insulin, and insulin secretion is optimised to handle incoming glucose from meals. Insulin secretion typically peaks in the afternoon, although insulin sensitivity is generally higher at breakfast than at lunch and dinner [64]. During the sleep/fasting period, insulin secretion naturally decreases and insulin sensitivity generally decreases. This is part of a physiological adaptation to promote glucose saving for the brain during prolonged fasting. This physiological insulin resistance at night is normal. Similarly, glucose production in the liver (gluconeogenesis) and glucose uptake by muscles and fat cells are under circadian control. It is common for the body to experience a slight increase in BG in the early morning hours, even before eating, which is a circadian phenomenon that prepares the body for waking up (the "Dawn Phenomenon") [51], increasing glucose production by the liver and decreasing insulin sensitivity. In addition, glucose tolerance (or how well the body handles a glucose load) typically peaks in the morning and declines throughout the day, with its lowest level in the evening and at night. As such, the same meal consumed in the morning can cause a lower and less prolonged glucose spike than if consumed in the evening [53]. All of these examples highlight how closely linked and fundamental these circadian rhythms are.

The impact of circadian rhythm disturbance on people with T1D is significant, as patients with chronic rhythmic disturbance are at a higher risk of serious medical problems compared to nondiabetic individuals [1]. 'Stressors' such as artificial light during night hours and mistimed meals will affect circadian rhythms, and important physiological processes [49]. It is well evidenced that even though peripheral cellular circadian rhythms are driven by an internal biological clock, the phasing of these rhythms is affected by environmental factors such as the dark/light cycle, but also behavioural factors such as when a patient exercises [24], the regularity of their eating patterns [57] and the timing or regularity of sleep/wake cycles [63]. Therefore, these diurnal patterns are influenced by endogenous rhythms but also environmental and behavioural patterns [47]. A study of APS indicated that improved technology (allowing better personalisation of treatment) can help minimise the disruption of endogenous circadian rhythms by improving rhythmic coordination and the amplitude of changes in BG [30].

Figure 1.1 helps illustrate how disruptions in diurnal rhythmicity can be characterised. The suprachiasmatic nucleus (SCN) operates as the central pacemaker driven by the light/dark cycle, to which the peripheral processes synchronise. This can be affected by external stressors.

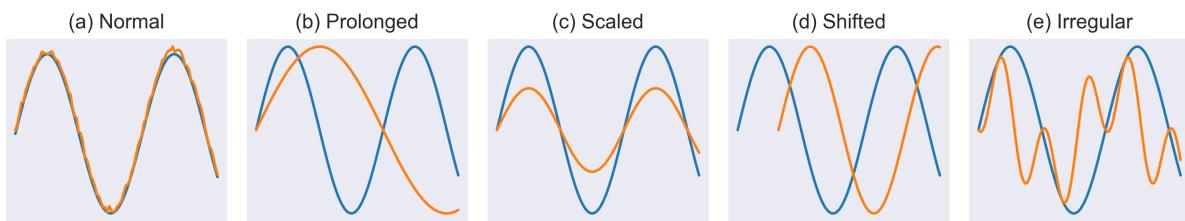


Figure 1.1: Defining the different types of disruptions to diurnal patterns [33] where the central rhythm (blue) and peripheral clock (orange) should align under optimal conditions (a)

- (a) In a **normal pattern**, peripheral processes align to the central rhythm without disruption.
- (b) A **prolonged rhythm** occurs when a peripheral process takes longer than normal to complete, typical in irregular sleep cycles, but also caused by irregular meal patterns. Patients with T1D who rely on fixed 24-hour insulin delivery patterns can suffer a lack of alignment and can lead to unexpected hyper or hypoglycaemic events.
- (c) A **scaled rhythm** occurs when peripheral pacemakers have their signal reduced or amplified. T1D patients may see the dampening of natural peaks/troughs in BG levels due to strict regulation, undermining important signals in insulin regulation with APS. The amplitude of hormonal rhythms can be influenced by physical or psychological stress, with effects on metabolic rhythms.

1.2. INVESTIGATIVE FOCUS

- (d) Less common in patients with T1D are **shifted rhythms** caused by frequent time zone changes, consistent shift work, and some unrelated medical disorders. Insulin rhythm misalignment is a key concern, where diurnal patterns (such as dawn phenomena) misalign to insulin delivery, leading to a glycaemic excursion.
- (e) An **irregular rhythm** results from a highly variable lifestyle: variable meal times, physical activity, sleep schedules, or stress are common causes resulting in extreme glycaemic variability, where isolating a single disruptor is too complex due to many different stressors, causing amplified and complicated impacts that make glycaemic control and patient condition difficult to manage.

Although the physiological impact of circadian rhythms on glucose metabolism is well understood, a significant research gap remains concerning how APS data can be used to identify and manage these disturbances in patients with T1D. The current literature focusses mainly on the link between rhythmic disturbances and the development of Type 2 Diabetes (T2D), leaving the influence on patient with T1D largely unexplored. Glycaemic variability (GV) is a key indicator of challenges in T1D management, and its direct relationship to glucose metabolism suggests that it is a strong measure of circadian rhythm disturbance. This study is motivated by the opportunity to use high-resolution data from APS systems to explore this disruption through the lens of GV.

1.2 Investigative Focus

BG data on its own are helpful in understanding diurnal rhythmicity, but its relationship with other key variables that APS systems offer could go further. Primary to the algorithm needs of these systems are Insulin On Board (IOB) and Carbohydrates On Board (COB). Background insulin needs are managed mostly by the APS, based on BG levels and COB, among other factors such as time of day. These variables provide other dimensions from which to understand GV that can be either a driver or an indicator of circadian disturbance, and have previously undergone rigorous statistical analysis by Degen et al. [19]. Grant et al. [30] also use the concept of GV as an indicator of rhythmicity, and from these studies this investigation draws its motivation.

The night is a unique period in the diurnal pattern, when a period of fasting normally resumes. The sleep/wake cycle is one of the most important physiological circadian rhythms and follows a pattern of absorption of remaining carbohydrates, absorption of the last daily preprandial insulin (bolus) and stabilisation of BG. The regulation of basal insulin for people without T1D is managed by the body. For those with T1D, disturbances in this natural circadian rhythm can occur in circumstances such as when carbohydrates are needed to counter nocturnal hypoglycaemic events, or if late meals, exercise, or irregular sleep times interfere with glucose metabolism and require reactive treatment during the sleep cycle. By studying patterns in GV and the relationship with COB and IOB before and during the fasting period, more can be understood about how to identify disturbances in the diurnal rhythms for patients with T1D. This study aims to answer the following research question: How can data from APS systems be used to help us understand disturbance of diurnal patterns in patients with T1D? Specifically, how can we use BG, COB and IOB data to understand nocturnal GV, its relationship with COB and IOB, and what it can infer about disturbance to circadian rhythmicity? To answer these research questions, this study aims to address the following research objectives.

1. To establish and characterise groups of similar nocturnal periods based on their BG, COB, and IOB patterns.
2. To determine the presence and nature of the relationships between COB/BG and IOB/BG within these nocturnal periods.
3. To identify how glycaemic variability metrics relate to COB and IOB, and how these relationships inform differences in diurnal rhythms.
4. To propose and validate a novel metric for nocturnal stability that can serve as an interpretable tool for indicating circadian rhythm disturbance.
5. To analyse the proposed stability metric to reveal novel insights regarding the state and influence of COB and IOB during the observed nocturnal period.

Chapter 2

Literary Review

2.1 The Research Gap: Circadian Rhythms and T1D

Having established that circadian rhythm disturbances can lead to negative clinical outcomes, it is natural to seek ways to identify "good" vs. "disrupted" patterns. An extensive literature search found significant evidence of the impact of disturbances in exogenous diurnal cycles and endogenous circadian rhythms and some more specific research on how APS can improve diurnal rhythmicity [30], but little research on how APS data can be used to understand the disturbances, their impact on the condition of T1D patients and the use of this in a clinical context. Academic research is overwhelmingly focused on the correlation and causation of rhythmic disturbances in the development of T2D [32, 90, 59], rather than on how such impacts can influence the health of patients with T1D. Much work has been done on glucose dynamics to produce predictive models [88], and Phillips et al. [55] incorporate multiple time series from wearable technologies to attempt to model circadian rhythmicity, which is a promising area of research. Impacts of circadian rhythmicity on glucose metabolism are well understood and documented, though complicated and varied. Spensnijder et al. [76] explain how gluconeogenesis, insulin sensitivity, neurone activity that regulates feelings of hunger and thirst are examples of glucose metabolism dependencies on these diurnal patterns. And, while there is much study on the effect of rhythmic disturbance on glucose metabolism and its resulting health risks, there is very little research on such impacts in patients with T1D. To address this gap, this review will now delve into the specific metrics, data and methods available to better understand these patterns, beginning with glycaemic control.

2.2 Glycaemic Control & Variability

2.2.1 Defining Glycaemic Control and Its Measurement

Glycaemic control is a vital concept in the management of T1D with the goal of achieving 'euglycaemia', i.e., the management of BG within a normal range. Short-term variability of BG is known to have detrimental effects, such as increasing oxidative stress and inflammation [46] if highly variable, so the importance of careful management of GV is obvious and the metrics used in measurement are evolving. CGM devices provide data on BG levels 24 hours a day. This permits measures of intraday variability that provide much clearer insight into daily glycaemic control and can highlight issues that the traditional method (HbA1c) cannot. In the past, glycaemic control has been assessed primarily through HbA1c [28], a term used for glycated haemoglobin, which is made when glucose sticks to red blood cells. As blood sugar cannot be used properly, more of it binds to blood cells and increases the volume of haemoglobin. Readings are taken quarterly, as red blood cells are active for 2-3 months, which is why the measurement reflects the level of control in that period. Principally a measure for predicting and preventing diabetes complications in a clinical setting, it has limitations [8]. It does not reflect GV, that is, daily fluctuations in glucose levels, and while it may indicate dangerous highs (hyperglycaemia), it does not indicate lows (hypoglycaemia) [17]. Patients can record normal HbA1c, but still experience significant GV.

2.2.2 The Rise of CGM and Glycaemic Variability Metrics

Intensive longitudinal data from CGMs can now bridge this gap. GV can now be measured with a range of metrics [65, 72], including but not limited to; Standard Deviation (SD), Coefficient of Variation (CV),

Time in range (TIR) and Mean Amplitude of Glycaemic Excursions (MAGE). SD and CV are commonly used statistical measures of variation, often used because they are easily understood by practitioners but have some limitations in the context of GV [4]. Time in range (TIR) is a good indicator of BG control, but the definition of the ideal range is highly individual. For adults in the UK, the target range is between 70-180 mg/dL and is termed the Level 1 target range. Several factors can influence this range, such as duration of the disease, comorbidities, pregnancy, and others [21]. For example, pregnant individuals are guided by a range of 63-140 mg/dL. A search of academic papers on guidance for fasting target ranges refers mainly to diagnosis levels rather than to guidance for those already with T1D. However, some important institutes assume a consistent Level 1 concentration range as a general guideline, which would be adjusted for individual needs [87]. MAGE is another important metric of GV and commonly used. It is a measure of the amplitude of glycaemic excursions originally proposed by Service et al. [71], and represents the magnitude of fluctuations in glucose levels beyond one standard deviation [65]. Different measures can offer different information: while TIR is commonly used as a measure of duration, MAGE is a measure of amplitude [4]. Each metric has its merits and their consideration depends on the clinical perspective required.

2.2.3 The Importance of Nocturnal Patterns

If the BG level drops below the target range during sleep for a 15 minute period or longer, this is considered a nocturnal hypoglycaemic event. Depending on the level of excursion and individual conditions, these can lead to complications such as seizures, coma, and even death. Nocturnal hyperglycaemic events, in which the BG level increases above the target range for a 15 minute period or longer, can lead to complications such as diabetic ketoacidosis (DKA) and cardiovascular disease. A characteristic of nocturnal hypoglycaemia events is that they are often asymptomatic, unlike with healthy people, which means that the patient may not be aware of the event [68]. Although the event may not directly cause sleep disturbance, creating irregularity in diurnal patterns where treatment intervention is required during an excursion and it is necessary to take quick-acting carbohydrates and persist in testing. These phenomena and the need for control and rhythmicity is what has led to the development of systems such as OpenAPS. As a result, data resources that help research have grown.

2.3 APS System Data Use

The rich real-world data available from OpenAPS Data Commons provide an opportunity to address the research gap. A community of OpenAPS users contributes data for the benefit of furthering research and development. Data are anonymised and available through OpenAPS Data Commons on request from its administrator [39]. A study looked at a sample of data ($n = 29$) available through the OpenAPS Data Commons dataset and used statistical and machine learning methods to analyse patterns between COB, IOB and BG, identify patterns that do not conform to expected norms [19], concluding that more research was needed on novel influences on BG than carbohydrate intake. Other research used its data to support the efficacy of OpenAPS against commercial APS systems, using GV measures [48] previously mentioned. Grant et al. [30] use a similar set of data to support their own research on the effectiveness of APS systems to improve the rhythmic coordination of glucose and insulin in patients with T1D. In the reviewed literature, missing data is found to have the potential to affect the precision and reliability of the analysis in the study of APS data and is recognised as an issue in their reliable operation [73, 75, 25], but these studies have focused mainly on the missingness of CGM data and its effect on reliable prediction.

2.4 Methods for Time Series Analysis

2.4.1 Clustering and Pattern-Finding

Analysing temporal patterns can be made simpler by clustering periods that exhibit similarity based on features extracted from the data, thus creating groups of data that can be characterised and compared. Clustering appears to be used for different applications in T1D research, which can be broadly categorised as; predictive modelling and risk stratification, APS optimisation, and clustering for pattern finding. The latter is often done to identify glycaemic patterns using methods such as K-means [42] and hierarchical clustering to stratify patients [14] or grouping similar time series [37], which can inform hidden and non-linear relationships in data that are not immediately apparent. Time series clustering can take

different approaches, which Aghabozorgi et al. [3] simplify into shape-based, feature-based, and model-based. Feature-based clustering is a whole time series clustering approach that vectorises static features of a time series, thus allowing standard clustering methods and distance calculations to be used in a lower dimensional space [85].

2.4.2 Distance and Correlation-Based Methods

Measuring distance between time series can be useful in comparing their shape to allow a better understanding of the nature of their patterns. When grouping time series, a distance measure is used to compare an object to cluster centroids to find its closest one, thus deciding the group it should belong to. They are also used to compare time series and help test whether they are significantly different in shape. Using distance metrics with time series can be more challenging than measuring the distance without the time dimension, given the natural distortions that exist in time series. Berndt and Clifford [10] describe how Dynamic Time Warping (DTW) can find patterns more accurately by accounting for these distortions, finding an optimal warping path that aligns points in two time series. Leveraging DTW, DTW Barycentre Averaging (DBA) proposed by Petitjean et al. [54] as a time series averaging method can provide a more robust average than simply taking the mean at each time point, supported by Python libraries such as `tslearn` [80]. Instead, the average is taken by iteratively aligning time series to a temporary average and updating that average, leading to a "barycenter" in the DTW space. This can be robust to time series distortions (such as erroneous or delayed CGM readings), providing more accurate patterns.

Finding associations between variables helps to understand their patterns and how they interact, providing information about the effect of variables on the diurnal patterns studied. These relationships can change direction and strength over time. Simple correlation measures such as Pearson or Spearman correlation can provide insight into linear and nonlinear relationships between variables [67]. Understanding diurnal rhythm disturbance using data available from APS could be supported by realising time-based associations between variables. Cross-correlation provides information on the relationship between two variables at various time lags and can be helpful in understanding any relationship over time [15].

2.4.3 Model-Based Methods

The cross-lagged panel model approach (CLPM) has a long history of use in measuring the causal effect of one variable on another at a later time [69] and the direction of the effect. Lucas [44] more recently argued that its simplicity means that it does not always produce correct results, with it being suited to panel data (where you have many subjects at a limited number of time points). A more appropriate method given the type of data in this study is Granger Causality, used by Degen et al. [19], where it was used to understand the directional relationship between COB, IOB and BG. Selig et al. [70] explore how the relationship (or association) of variables changes over time, defining a "lag as moderator" approach that can identify whether the association is stronger or weaker depending on the lag between them. In behavioural science, time-varying effect models (TVEM) have been used to model effects over time from one variable to another by incorporating time in the regression equation. Analysis of smoking cessation therapies [83] using TVEM shows promise in understanding time-dependent associations and with more granularity than regression approaches. An advantage over Granger Causality is that it does not need stationary time series.

Regression techniques may also help find relationships by using machine learning models to model them. These methods have the potential to go further than establishing correlation and can infer one variable is caused by other by establishing its ability to predict it. Linear regression is a technique to model two (or more) variables using a least-squares method and is argued by Toner and Darlow [79] that these can compete with more complex deep learning models in time series forecasting. Linear models are constrained in their ability to only find linear relationships between variables. Many other nonparametric regression models exist that have been used in predictive modelling in the diabetes domain, especially in the prediction of BG levels using models such as Support Vector Regression [31, 27], Decision Tree Regression [7] and Random Forest Regression [77].

Chapter 3

Execution

This chapter outlines the preparation and methods for the analysis carried out in the study. The dataset is summarised with an outline of the preprocessing performed prior to analysis, including considerations around missing data and data-selection principles. It then outlines the method of grouping similar nights, sets out how the analysis of patterns between variables will be approached, and describes GV measures and how they will be incorporated in the analysis. Finally, it outlines the method for the proposed stability score, used in the analysis.

3.1 Dataset and Preparation

3.1.1 Dataset Introduction

The OpenAPS Data Commons dataset is a source comprised of data donated by patients under free-living conditions from open source systems. This research project benefits from approved access to the OpenAPS dataset on which the analysis and results are based. Degen et al. [19] published their preprocessing methods used to establish the data set ($n = 29$) for their study, using criteria of > 29 days with hourly readings, to achieve a reliable analysis. This preprocessing strategy has been reengineered to meet the objectives of this research, using alternative data resampling and selection principles to maximise the data available for analysis. The data contributed are from OpenAPS, AndroidAPS and Loop platforms, from which OpenAPS are the most frequent. Data for each patient are contained in a zipped file that covers a period (or separate periods). Each platform has a different data structure, and so different preprocessing routines are required for each. For consistency, efficiency and maximum sample size, the OpenAPS platform was used. The latest dataset is $n = 231$ (as at 1st May 2025), but due to limitations in ethics approval is confined to $n = 186$ for this study (used previously in Degen et al.'s preprocessing [35]). The objective of the data preprocessing was to produce a time series for the variables described here.

Carbohydrates On Board (COB)

COB represents unabsorbed carbohydrates in the body, and carb intake is recorded by the patient on their device which the system deprecates over time, according to individualised settings. (For the oref1 algorithm, the system may also consider Unannounced Meal detection [40] depending on their settings). COB therefore naturally follows the shape of a sharp peak and then a slope and has a natural lower bound of zero. It is measured in grammes of carbohydrates (g). Given that the system user must enter the COB, the consistency of the data is not guaranteed (as discussed in Section 1.1.2).

Insulin On Board (IOB)

IOB represents active insulin in the body. It is an estimate of the amount of insulin that is still working to lower blood glucose levels. Insulin may be delivered through basal (background) or bolus dosing (at mealtime to cover carbohydrates or correctional, where it is necessary to lower blood glucose). An "easy bolus" function (that predates carb entry functionality) is available, which will supply an immediate bolus of insulin regardless of carbohydrate data [38]. Although IOB would also most naturally have a zero lower bound, this is not necessarily the case with APS systems, which will calculate IOB on the

Table 3.1: Descriptive statistics of the irregularly sampled data for BG, IOB, and COB.

	Count	Mean	Std Dev	Min	25%	50%	75%	Max
BG	1,028,030	138.28	50.47	29.00	102.00	127.00	164.00	489.00
IOB	1,002,671	1.61	2.33	-8.06	0.14	0.90	2.33	47.57
COB	965,094	8.55	18.42	0.00	0.00	0.00	8.00	223.00

basis of an algorithm that can allow a negative value to help with correctional system response. IOB is measured in units of insulin administered (U).

Blood Glucose (BG)

BG readings are taken by the CGM in APS. While readings indicate the level of glucose in the blood, CMGs actually measure the level of glucose in the fluid surrounding interstitial cells, having moved from the blood to the cells that absorb it; hence the term Interstitial Glucose (IG) used in some studies. Given this transition of glucose from blood to interstitial fluid, the IG readings are a reflection of BG up to 10-12 minutes earlier [89]. For the purposes of this study and to align with the terminology used in the data source, BG will continue to be used, acknowledging this discrepancy. BG readings are measured using milligrammes per decilitre (mg/dL) and are used in this study (again, to align with the data source), although other studies use alternative millimoles per litre (mmol/L).

3.1.2 Data Preparation

To arrive at useful variables for data analysis, the first task required extracting useful data. The data exist in Comma Separated Files (CSV) within zip files that contain all data for the patients. These CSV files are split between date-effective directories, also pertaining to different datasets within the patient's library. Due to data volumes resulting from high sampling frequencies, the files are further split into regular smaller file sizes. The files from which data are extracted are as follows, and others are ignored:

- `device_status` files contain the data for all time series variables analysed in the study and their timestamps.
- `profile` files detail the device configurations, including the time zone.

A preprocessing pipeline extracts and transforms the data from these files and generally consists of the following steps:

1. Raw data extraction: Each zip is read, locating the necessary `device_status` files and compiling them into a single file for all patients.
2. Raw data processing: The variables are extracted, and time series are de-duplicated into irregular sampled files.
3. Data resampling: Data are resampled at regular intervals.
4. Time zone offset: Timestamps are offset using a list of time zone offsets compiled from the `profile` files.

Following initial data extraction and in an irregular sample form, there are $n = 114$ patients in the sample, with data covering 10,193 days, comprising 1.06×10^6 time series records over a period of 06/02/2016 to 06/04/2021 (excluding clearly erroneous outlying dates). To get an initial sense of missing data, the record counts of BG, IOB and COB are 1.03×10^6 , 1.00×10^6 and 0.97×10^6 , respectively. Table 3.1 provides a statistical description of each variable. The frequency of COB values relative to other readings and its tendency to zero are evident, as are the negative values with IOB.

Data Resampling

Resampling the time series provides regular intervals to better support the data analysis and modelling undertaken in the study. It is also a helpful data reduction technique to facilitate reducing computational time in data processing. Two resampling frequencies were explored to consider their suitability in the analysis: 15 and 30 minute intervals. For the type of analysis carried out in this study, anything greater

than this (e.g. 1 hour) would lose the resolution necessary for observing patterns at a time series level. Several resampled statistics were created for each variable: mean, standard deviation (SD), minimum, maximum, count, aggregated after removal of missing values before calculation. All aggregates are based on the analysis requirements in the study.

Time Zone Offsetting

Timestamps used from the `device_status` files are time zone naive and relative to Coordinated Universal Time (UTC). The analysis in this study requires the capability to align time series such that a timestamp is considered ‘local time’, and so the naive timestamp was offset by the number of hours relevant to their time zone. (For example, a time component of the timestamp can be 09:00, but their local time is 03:00, that is, an offset of -6 hours).

A complicating (and thus limiting) factor is the existence of patients who changed time zones during data collection. The majority have data recorded in a single time zone only, but there are many that have changed time zone during the recording period, with no discernible way to determine the time-point that this occurred. Therefore, as part of data preprocessing, these patients have had to be omitted, thus limiting the available dataset. With only patients from a single time zone included, this results in $n = 83$.

3.1.3 Data Selection

Following analysis of the dataset and evaluation against criteria, a preprocessed data set was finalised that contained $n = 17$ patients, $m = 965$ nights. The criteria, as described in the appendix B along with detailed analyses, sought to maximise sample size while minimising the number of missing values in the data. The impact of 15 and 30 minute sampling was assessed against thresholds for the minimum number of nights per patient (to maximise the power of patient-based analysis), total missing values per night, and the number of intervals missing values spanned. The logic decided for selection was to use a 30-minute sampling, to include nights with a maximum of one missed interval, and for patients to have ≥ 30 nights. This significant drop from $n = 114$ to $n = 17$ is representative of the challenges in using real-world patient-generated data that have not been collected under controlled conditions. The rigorous selection process was intended to ensure the highest possible data quality for robust analysis.

3.1.4 Impact and Strategies for Missing Data

Strategies for handling missing data, such as imputation, can introduce bias and distort patterns, leading to inaccurate conclusions. This is particularly sensitive in a clinical setting where data is used to make decisions that affect health. Therefore, careful consideration was taken to avoid missing data where possible and, where necessary, to limit its impacts. The data selection approach prioritised this principle. Resampling of data reduces the number of missing values, but introduce the potential for bias in the resulting aggregate. This is something acknowledged later, with strategies for mitigation in different contexts. Following data selection, the dataset is left with some values that are missing for COB, unsurprisingly, given the initial data analysis. For each interval where only COB is missing, a decision was made to impute. Thresholds on ratios of missing values were set to qualify each night for selection. By minimising the threshold for missing COB values to 20%, the number of missing values was reduced to just 23 but now limiting the dataset to $n = 16$, $m = 922$. In only one instance did missing values span more than one interval, so it was possible to be confident that this would not sufficiently bias outcomes. COB missing values were imputed using linear interpolation prior to the next stage of clustering. The reason for choosing this approach was to avoid any additional peaks in COB, which is an important characteristic.

3.2 Grouping Similar Nights

The clustering of night periods into statistically similar subsets facilitates natural grouping based on the underlying patterns in the variables. The purpose was to find groups that represent different characteristics. There is no ground truth in this analysis with which to compare patterns or analyse outcomes. By segmenting data into similar groups and aligning their characteristics, further analysis could be explained by, or support, the patterns seen in each cluster.

3.2.1 Feature Extraction

Based on the interim pre-processed and selected dataset of $n = 16$, the data was clustered into separate groups. The method for clustering was feature-based, using aggregate features for each night from the available resampled time series variables. The features were selected based on the domain knowledge and desired outcomes for the clustering. An appraisal of the features, their values and their contribution to the clusters can be viewed in Appendix C. All of these have their basis in the COB and IOB mean and max variables taken at the resample intervals. The max variables helped define true peaks rather than those smoothed by averaging during resampling and provided more information in terms of extremes that might indicate patterns linked to BG in the subsequent analysis. For clustering, features based on the BG variable were omitted as a methodological choice. This facilitated the analysis of patterns and relationships between COB/IOB inputs and BG/GV outcomes, allowing for the objective categorisation of nights and avoiding circular reasoning.

To extract features, the `tsfresh` purpose-built library was used [22]. The library principally creates time series aggregation features for observed period (in our case, each night), such that these can be used in clustering, rather than creating features from each time interval and measuring similarity in this way. This was deemed to be more expedient and sufficient to deliver the required outcomes. Using its automated feature creation builds a significant number of standard features. The `EfficientFCParameters` parameter was used as a baseline to for further refinement (a set of features $F_{baseline}$ of features $\{f_{b_1}, f_{b_2}, \dots, f_{b_j}\}$), as it produced many features automatically ($|F_{baseline}| = 1589$), selecting those from its library that are efficient to produce. This number of default features would not help interpretability, which was deemed important in understanding the patterns behind the clusters. To improve the interpretability of the cluster, the `CustomFCParameters` parameter was used to create a refined set of 46 features (F_{select}) that would contribute information relevant to the desired clustering, as described in Appendix C.

3.2.2 Clustering

Clustering Method & Measurement

The clustering method chosen was K-Means clustering (using `KMeans` from the scikit-learn library). K-Means is an unsupervised learning algorithm that is used to partition N observations into K distinct, non-overlapping clusters. The algorithm aims to minimise the within-cluster sum of squares, effectively making the clusters as compact and well-separated as possible. It works iteratively by first randomly initialising the centroids of the K cluster. Then, in each iteration, it assigns every data point to the closest centroid (forming K preliminary clusters) and subsequently updates each centroid to be the mean of all data points assigned to its cluster.

To measure how well clusters are defined, a good indicator is the use of the Silhouette Coefficient [62]. This is a measure of how similar an object is to its own cluster compared to other clusters. A higher silhouette score indicates that the data point is well matched to its own cluster and poorly matched to neighbouring clusters. The silhouette score ranges from -1 to 1, where a score close to 1 indicates that the object is well clustered, a score close to 0 indicates that the point is on or very close to the decision boundary between two neighbouring clusters, and a negative score indicates that the point may have been assigned to the wrong cluster.

K-Means can face challenges with our high-dimensional feature set owing to the "Curse of Dimensionality". A high-dimensional space can have implications on the distance metric, with the concept of 'distance' becoming less meaningful and thus less helpful in separating clusters [2]. The algorithm can also be over-sensitive to unimportant features, given that it considers them all equal, so dimensionality was considered.

Dimensionality Reduction

The high dimensionality of the data (both $F_{baseline}$ but also F_{select}) raises the challenge of meaningful and interpretable clustering; thus, simplifying the dimensional space is preferred, and dimensionality reduction is employed. Two methods were analysed for their effectiveness in helping build clusters.

- Principal Component Analysis (PCA) [11] is a linear dimensionality reduction technique that transforms a high-dimensional dataset into a lower-dimensional space while preserving as much of the original variance as possible.
- t-Distributed Stochastic Neighbour Embedding (t-SNE) [82] is a nonlinear dimensionality reduction technique primarily used for visualisation of high-dimensional datasets and differs from linear

methods that try to preserve global variance, instead focussing on preserving local variance. t-SNE requires its **perplexity** parameter to be tuned, which moves the attention from global relationships to local, often through trial and error.

Following a review of these methods, PCA was preferred given that t-SNE is not designed for dimensionality reduction for the purpose of creating features, as it can lose global variance which may hold important information. However, it was deemed a useful tool for visualising the clusters found to see if the resulting PCA-based clusters hold relevance in the local-variance space.

Scaling

Scaling of data has several utilities throughout this study's workflow and analysis. Though some dimensionality reduction methods are less sensitive to unscaled data, PCA in particular requires data to be scaled to unit variance and preferably centred around zero, especially when interpreting the principal components. When clustering, the distance between objects can be affected by different feature scales. In particular, with the use of Euclidean distance in our implementation of K-Means, those features with larger scales would dominate others. Generally, throughout the analysis scaled values have been used, for technical consistency but also to help with unitless comparison. Each use case for scaling has been evaluated on its own merits throughout the pipeline, and the scikit-learn **StandardScaler** has been an acceptable choice in each circumstance.

3.3 Finding Time-Dependent Associations Between Variables

To analyse how COB and IOB impact BG, the strength of relationships between preceding COB/IOB and BG were analysed, based on the hypothesis that exists some lagged response in BG to these variables. Insulin absorption rates can be affected by a number of different factors, including dose, insulin mixtures, the site of (and exercise around) the injected area, temperature, and more. Onset of action can range from 5-30 minutes for fast-acting insulin, peaking between 15 minutes and 4 hours after bolus [20]. The rate of glucose metabolism depends on the glycaemic index of the type of carbohydrate among a number of other confounders [36], but can range from 30 minutes to several hours. The delayed impact on BG infers a relationship that would be important when considering disturbance of circadian patterns and can be analysed by shifting the COB and IOB values by intervals.

Analysis of the correlations between the variables was carried out to see how correlations between COB, IOB and BG relate to each other and over time. The first method looked to find patterns in correlation aligned at each interval and by cluster, with a method chosen on the data characteristics. Normality checks, initially with P values from a Kolmogorov-Smirnov (KS) test [13] by variable and cluster, showed no combination of cluster or lag could reject the null hypothesis with statistical significance (all were $P > 0.05$). Despite this, the skewness for the BG, COB and IOB means was 1.3, 3.0 and 3.4, respectively, with kurtosis of 2.5, 10.2 and 20.7, respectively, across the whole dataset, strongly suggesting that all were not normal, noting that COB also has 70% zero values and reinforcing the view of normality. The Pearson correlation was deemed unfit on the basis of normality and heavy presence of zero values for COB, and instead Spearman correlation was elected. The Spearman correlation was applied (as static correlations at each time interval) to understand how these correlations change over time and without making the data stationary, a design choice to help illustrate the changes in trends and behaviours over the period.

The second correlation analysis aimed to broaden the view of the relationships between variables by using cross-correlation, and quantified how much a change in one is related to a change in another at different point in time. For the analysis, five lags were chosen to see how the relationships change over a 2.5 hour period. Given that each night is effectively a separate time series, cross-correlation coefficients (CCF) were calculated for each night. The CCF mean was then calculated for lags for the whole sample to see if there were any overall patterns, and then by cluster to see if there were any differences in the behaviour of each. Given the significance of the CCF is domain dependent, the intention was for a descriptive examination of the results, highlighting any observable insights. A prerequisite of cross-correlation and further analysis is to make the time series stationary, which was done by differencing the previous values. An Augmented Dickey-Fuller (**statsmodels** test was used to test each time series for a unit root, the mean of the P value and the test statistic were taken to assess stationarity.

The objective of the final investigation is to see if there are patterns between variables that can be recognised using linear and nonlinear machine learning models, extending the concept of cross-lagging to identify patterns in lagged effects of COB on BG. Stationary data were continued for consistency, though

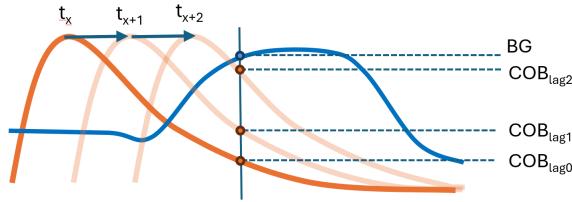


Figure 3.1: Lagging COB and IOB values against BG to analyse relationships between passed values, in this case COB leads BG. E.g. COB (orange) are lagged $x + n$ intervals ($0 \leq n \leq 4$) to allow BG (blue) to be regressed against each lag ($\text{COB}_{\text{lag}n}$).

it was less necessary for our nonlinear models given the robustness of those selected to non-stationarity. For this, data lags were created using a method described in Figure 3.1. The relationships between COB, IOB and BG for different clusters were first compared by looking at the statistical significance of a lagged variable to BG in a regression model for the observed period. Linear regressions of scaled COB and IOB with mean BG values were modelled using `statsmodels`, showing associations change over time and how they differed between groups. Then, nonlinear models were used to see how these compared, using R^2 and Mean Squared Error as metrics for comparison. The models used were `LinearRegressor`, `SVR`, `DecisionTree`, and `RandomForest` from the scikit-learn Python library. The models were tuned using the method described in Appendix E, where parameters and detailed results are published.

3.4 Glycaemic Variability (GV)

GV is a direct measure of control in the context of the observed time period. A high GV means a more chaotic period of variability, and greater and more frequent swings and excursions are a direct indicator of disturbance to circadian rhythmicity. As discussed in section 2.2, there are many ways that have been developed to measure glycaemic control. Those used within this study are elaborated here, outlining how they are implemented in the context of our dataset. It is important to remember that, given the resampling at 30 minute intervals, some modification is needed for this setting. However, the intention is for them to maintain the metric's value in the assessment of GV within the study's context.

3.4.1 Standard Deviation (SD) & Coefficient of Variation (CV)

SD is one of the most basic GV metrics and measures the average distance from the mean for the observed period. It is a simple calculation and provides a direct measure of the absolute magnitude of GV. CV is also a statistical metric that focusses on the diversity of glucose data and is one of the most used metrics for GV [61]. It is a unitless measure, often expressed as a percentage. SD and CV provide complementary measures of variability. SD measures the spread of BG around the mean in absolute terms and is unit-based, therefore providing direct interpretability and highlighting highly variable data. CV is relative to the average and therefore does not have the tendency to increase with the magnitude of the variable as does SD. This makes it comparable between different groups or patients, and even comparable to the variability of other variables when required, and research has provided guidance on optimal CV levels in patients with T1D [60].

3.4.2 Time In Range

Studying the number of excursions outside a target glucose range builds a concept of the frequency and extent of these excursions. Based on the assumptions given by other research (referenced in Section 2.2), such excursions can by association infer some form of disturbance of sleep. Setting accurate thresholds is not possible when generalising over patients. Section 3.4.2 outlines the importance of monitoring excursions from target ranges in T1D care. These levels provide interpretable measures of GV and can infer disturbance of the diurnal patterns of glycaemic control, especially when uncharacteristically high volumes of excursions are found.

Given that the intervals are at 30 minutes, the true definition of "time out of range" cannot be accurately measured, so instead a measure of excursion occurrence was used (i.e. the frequency of excursions) as well as the amplitudes beyond the threshold. Level 1 (L1) thresholds were set as 70-180 mg/Dl and level 2 (L2) thresholds set as 54-250 mg/Dl. Occurrences of excursions beyond these ranges

were given the names Intervals Above Range (IAR) and Intervals Below Range (IBR) for brevity. At each interval BG min and max values were used that capture the peaks and troughs without smoothing via the mean. In the knowledge that the OpenAPS system effectively manages nocturnal BG in patients, a lower number of excursions were expected in the nocturnal period compared to the broader period.

3.4.3 Mean Amplitude of Glycaemic Variation (MAGE)

MAGE is calculated as the mean of absolute differences between consecutive peaks and troughs in the glucose data. It is a measure of the magnitude of fluctuations in glucose levels and is often used to assess GV in patients with diabetes. MAGE is an algorithm that Satya Krishna et al. [65] formalise as:

$$\text{MAGE} = \sum \frac{\lambda}{n} \quad \text{if } \lambda > v \quad (3.1)$$

Where:

- λ each BG increase or decrease (nadir-peak or peak-nadir).
- n is the number of glucose measurements.
- v is one SD from the mean glucose data for the period.

The features extracted at each interval for the night were qualifying excursion amplitudes and a binary flag to denote an excursion, based on an implementation of MAGE provided in the `cgmquantify` library [9]. This omitted the final averaging step that MAGE would normally undertake to determine a metric for the whole observed period (hence the acronym AGE being used), given the desire to understand patterns across the period rather than using an overall mean for the night. This better facilitated the dual needs: (a) to represent and analyse variability over the time series, and (b) aggregation as a component (to include the averaging step for the observed period) for a composite score.

Identification and calculation of the amplitude of glycaemic excursions was based on the method used in the MAGE algorithm. The steps to identify and calculate the amplitude are as follows, since the data was already preprocessed into regular intervals.

1. Calculation of the SD of all glucose values in the observation period: In this case, the observation period is the overnight period. This is important as it provided a baseline for the amplitude calculation, and unlike arbitrary thresholds, it was based on the data itself, which means it was personalised to the patient. Therefore, it could be considered a true measure of variability relative to the patient, accepting that each will have their own ranges of glucose values.
2. Identification of peaks and nadirs: These were identified by looking for local maxima and minima in the glucose data, comparing each value with its neighbours, and identifying points that are higher or lower than each. The implementation identifies 'turning points' and uses iteration to find the next turning point at which the amplitude between the two could be calculated.
3. Identification of significant excursions: An excursion qualifies as significant if the absolute difference between one turning point and the next is greater than one SD. The amplitude was recorded at that time point.
4. Selection of non-overlapping excursions: It was important not to consider overlapping excursions, and so a maximum was used for two consecutive excursions (as was also implemented by Fernandes et al. [23]).

3.5 Glycaemic Stability as a Composite Score

As sections 2.2 and 3.4 describe, there are many ways to measure GV. The aim here was not to create a new measure, but to form a function providing a single metric that incorporates components of GV analysed here into a measure to compare our clusters with and effectively measure the 'stability' of a night. The objective was to see how this behaves against the model of our nights established by the initial clustering, derived from COB- and IOB-sourced features.

3.5.1 Composite Score Definition

Let the following notation be used:

G_t : Blood glucose reading at time t.

T : Total number of time intervals in the nocturnal period.

N : The set of all glucose readings during the nocturnal period, $\{G_1, G_2, \dots, G_T\}$.

G_{L1_lower} and G_{L1_upper} : Lower and upper thresholds for L1 excursions.

G_{L2_lower} and G_{L2_upper} : Lower and upper thresholds for L2 excursions.

G_i : is a peak or nadir.

The components here are described using their specific objectives:

Minimise BG mean. The average of BG means during the nocturnal period, calculated as

$$\hat{G} = \frac{1}{T} \sum_{t=1}^T G_t \quad (3.2)$$

A higher average BG can suggest potential dysregulation, although it is true that mean levels are specific to the physiology of the patient.

Minimise variance using SD. Based on the standard deviation of all BG readings in the period. High variability can indicate instability and potential physiological stress. The Law of Total Variance is considered in this calculation to make this more statistically robust, as described in Appendix F. The SD is calculated as

$$s_G = \sqrt{\frac{1}{T-1} \sum_{t=1}^T (G_t - \hat{G})^2} \quad (3.3)$$

Minimise GV using CV. The average of the interval CV values is used. This normalises variability to the mean, providing a robust measure of relative glucose fluctuations. The standard deviation is a measure of variability, but it does not account for the mean glucose level. The CV is defined as

$$CV = \frac{s_G}{\hat{G}} \quad (3.4)$$

which normalises SD by the mean glucose level, providing a relative measure of variability.

Minimise excursions outside the target ranges. The count of intervals where an L1 or L2 excursion occurred is used, indicating deviations from an acceptable L1 range, which can cause discomfort or impact restorative processes, to the more severe L2 range, which is very likely disruptive to the patient. The ranges provide a clinically relevant context for assessing glucose levels. The L1 excursion is defined as $G_{L1_lower} \leq G_t \leq G_{L1_upper}$, and the L2 excursion is defined as $G_{L2_lower} \leq G_t \leq G_{L2_upper}$. The number of intervals outside these ranges can be counted as follows.

$$L1_Excursions = \sum_{t=1}^T \mathbb{1}_{G_t < G_{L1_lower} \vee G_t > G_{L1_upper}} \quad (3.5)$$

$$L2_Excursions = \sum_{t=1}^T \mathbb{1}_{G_t < G_{L2_lower} \vee G_t > G_{L2_upper}} \quad (3.6)$$

Minimise the amplitude of glycaemic excursions. Focussing on excursion amplitudes, this is an average of the absolute amplitude values (above 1 SD from the mean). It captures significant rapid changes in glucose, which are often associated with physiological stress or symptoms that could disturb sleep, even if within clinical thresholds. Adapting Equation 3.1 to this context, stating $A_p = G_{i+1} - G_i$ and $\mathcal{A} = \{A_p | A_p \geq s_G\}$ based on the logic defined in Section 3.4)

$$MAGE = \frac{1}{|\mathcal{A}|} \sum_{A_p \in \mathcal{A}} A_p \quad (3.7)$$

All features are scaled using **StandardScaler** to make them unitless and thus remove any dominance based on range. Scaling is done using the mean and standard deviation of each feature over the whole sample:

$$X_{scaled} = \frac{X - \hat{X}}{s_X} \quad (3.8)$$

where X is the original feature value, \hat{X} is the mean of the feature over all periods, and s_X is the standard deviation of the feature over all periods.

Finally, the composite score J can be defined as a weighted sum of these components, where f is a feature used in the function of the set $\{f_1, f_2, \dots, f_k\}$, w_k is a weight applied to the feature and $0 < w \leq 2$:

$$J = \frac{\sum_{k=1}^K w_k \cdot f_k}{K} \quad (3.9)$$

Weights are included in the function to modify the calculation and give more dominance to the components. It was used in the analysis to give weight to two components (following scaling), which were *L2.Excursions* and *MAGE* by a factor of $w_k = 1.5$ based on the results described in the next section and their importance in: (a) highlighting extreme events that would be consequential to stability, and (b) highlighting rapid and consequential changes in BG that can have disruptive consequences, respectively. Through iteration and observations of the results, the weight of 1.5 was chosen as it provided a clear differentiation between clusters without completely overshadowing the other components, reflecting their clinical importance. Changes in weights have only had a subtle influence (without fundamentally changing the outcomes of) this study, yet remain a tool for further adaptation if the method is reused or expanded (see Section 5.2).

Chapter 4

Critical Evaluation

This chapter first describes the results of clustering and analysis of BG against these groups. Then comes analysis of the relationships between BG and COB/IOB through the lens of these clusters, and looks at the results of GV metrics as an indicator of circadian disturbance for further insight. Finally, an interpretable metric of night 'stability' is then proposed, combining common metrics of variability that have their own specific nuanced uses, and analyses how this can be used to interpret patterns and highlight nocturnal disturbance.

4.1 Cluster Analysis

4.1.1 Clustering Outcomes

At first addressing the set $F_{baseline}$, after reducing dimensions using PCA to components that cover 95% of the variance explained by the transformed data, a cumulative variance plot did not provide a discernible point on the curve to determine the optimal number of components to use, with 235 components covering 95% of explained variance. 97 components covered 80% of the variance, still more dimensions than would be ideal. However, PCA reduction on F_{select} reduced the components using a 95% threshold to 14 (PCA_{14} model). 80% of explained variance was reached in just 7 components.

Experimenting with K-Means and a range of $2 \leq K \leq 7$, silhouette analysis showed that clusters using 14 components were more distinct with a maximum silhouette score of 0.22 ($K = 2$), compared to $F_{baseline}$ of 0.13. Forcing a reduction of components to 2 (PCA_2 model) saw a rise in maximum silhouette scores for the range of cluster sizes to 0.42 for $K = 3$. The $K = 3$ PCA_2 model gave populations of clusters 0, 1, 2 that were $m = 107$, $m = 529$ and $m = 286$ nights, respectively, with cluster 0 showing extreme centroids of IOB mean and variance. Cluster 2 was high (but not extreme) COB mean and variance centroids, and cluster 1 had relatively low values for mean and variance for both. The difference from the $K = 4$ PCA_{14} model was that the four groups appeared to separate the other extremes of variance and mean for COB into their own group, rather than merging this with others. This was deemed important for

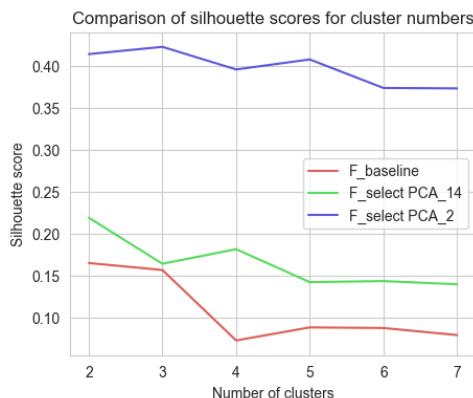
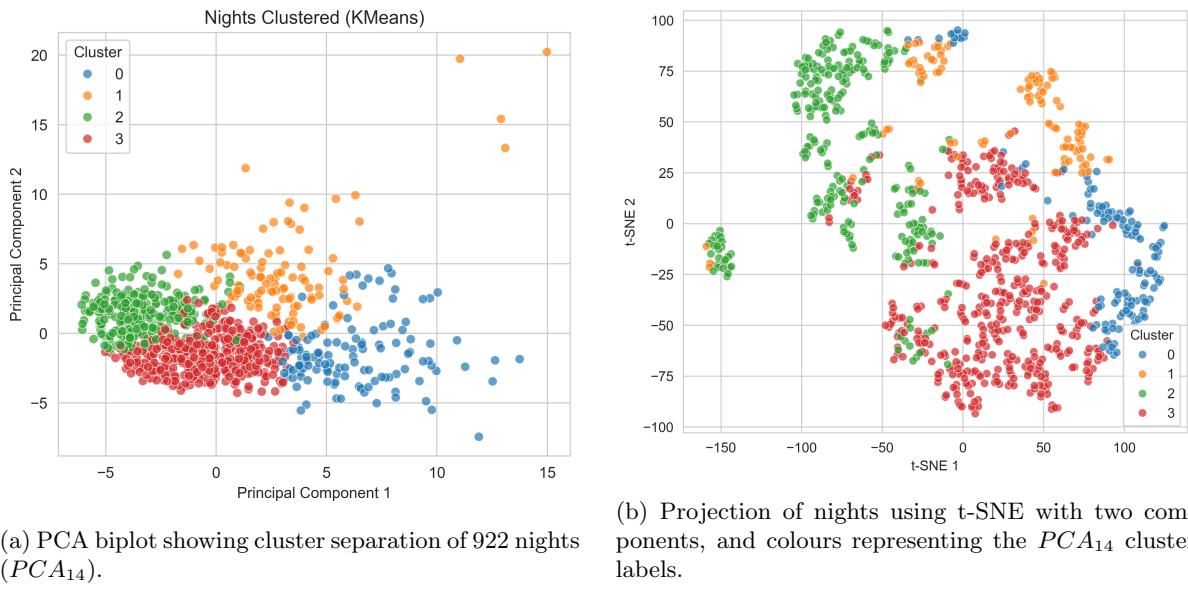


Figure 4.1: Silhouette scores by number of clusters for each approach used in a) features extraction, and b) dimensionality reduction technique. PCA_{14} with the $K = 4$ was the chosen model.

later comparisons in the study, so the PCA_{14} model with $K = 4$ was chosen, despite the lower silhouette score. Comparisons of the silhouette score for these approaches can be seen in Figure 4.1.



(a) PCA biplot showing cluster separation of 922 nights (PCA_{14}).

(b) Projection of nights using t-SNE with two components, and colours representing the PCA_{14} cluster labels.

Figure 4.2: Two different projections of the same clustering outcome using K-Means of PCA_{14} using $K = 4$, where objects represent nights and colours are the cluster labels.

Figure 4.2a shows the level of separation between clusters for PCA_{14} projected using the first two components (covering 45% variance). The clustering is not clearly distinct, reflecting the silhouette score. Generating a t-SNE visualisation validated the clustering decision, which shows (with a perplexity of 80,000 to preserve more local variance) that the patterns of the four clusters were largely maintained, as Figure 4.2b shows.

4.1.2 Cluster Time Profiles

The plot of the time profiles for the observed period for each cluster gave visual insight into the characteristics of each. Figure 4.3 shows the BG DBA profiles at each interval for IOB, COB and BG, with a shaded rolling average variance (over 3 intervals) error to give a perspective on the variance at each time-point. Similarly, the variance method gives a smoothed view, with less sensitivity to distortion and extremes. Given the profiles, prominent features, and cluster centroids derived from COB- and IOB-based features referenced in Appendix C, the clusters were characterised as follows. Note that no statistical analysis of BG is done at this point and was the subject of subsequent results, yet there are clear patterns to be observed.

Cluster 0 ($m = 124$) - 'high-carb'. This cluster had the highest peaks of COB, both evening and morning meals (maximum of 'COB max' is 115g), the highest averages (mean of 'COB mean' is 23g) and the high variance (SD of 'COB mean' is 34g). IOB follows a similar profile to COB, with peaks that appear synchronised. This, and the relatively low subsequent peaks and variance in BG, would suggest that insulin dosing is working well to keep BG within range, with a limited prenocturnal spike in BG. One notable feature in the BG of this group was an early dip in BG and IOB at 01:00. This was the first time such a nadir occurs across the clusters. This profile particularly dominated patient I and A with 73% and 50% of their nights respectively belonging to this cluster, therefore appearing more the norm for these patients, though unique in this respect.

Cluster 1 ($m = 106$) - 'high-insulin'. Labelled 'high-insulin', given the high dosing of insulin (maximum 'IOB max' of 15U, mean 'IOB mean' 3.6U) and variability (SD of 'IOB mean' of 3.9U), the IOB profile was visibly higher and more variable throughout the night. BG follows as a visibly more erratic profile with the highest peak of all clusters at 22:00. The morning peak of IOB was almost twice the height of the cluster with the next highest (cluster 0) at 15U. This was the least common night profile

4.2. BLOOD GLUCOSE ANALYSIS

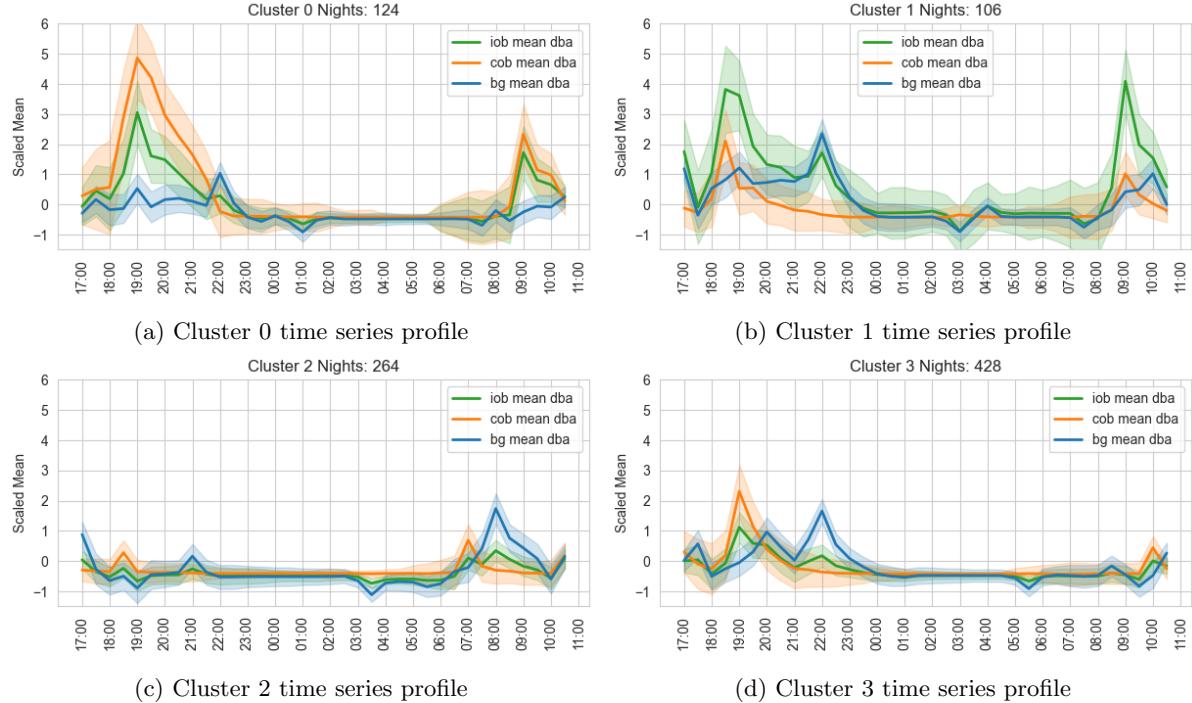


Figure 4.3: Time series profiles of each cluster using a DBA averaging of the variable means at each interval and a rolling average variance error (over 3 intervals), for COB (orange), IOB (green) and BG (blue).

given the sample size, and only the $n = 9$ patient had nights in this, and by its features was possibly the most restless.

Cluster 2 ($m = 264$) - 'low-carb/low-insulin'. The lowest and most stable COB and IOB profile with means of 3.5g and 0.7U respectively, and SD of 7.3g and 1 respectively. Two observable characteristics of BG to note were the lack of recovery following the nocturnal nadir at 03:30 and the considerable spike at 08:00, which was the largest observed in the morning period. Low BG levels after 03:30 and the subsequent spike could be symptomatic of low insulin levels at this point, rather than caused by carb intake.

Cluster 3 ($m = 428$) - 'common'. The most frequent profile and dominant night (i.e. majority) in 7 of 16 patients, this followed a pattern of moderate evening carb intake, limited insulin dosing and a notable peak of BG at the most common time of 22:00, fading then into a seemingly stable nocturnal period. The early morning nadir of BG occurs the latest of all clusters at 05:30 and the morning meal intake is the latest, at 10:00. The COB and IOB means were 7.4g and 1.0U respectively, and SDs of 14g and 1.3U. Patient and night membership of clusters can be seen in more detail in Appendix C.

4.2 Blood Glucose Analysis

4.2.1 BG Mean Profiles for Nocturnal Period

The nocturnal BG means for each cluster are illustrated in Figure 4.4a and show some common temporal segmentation, with 22:00-00:00 going through a period of stabilisation. There is a common nadir at 23:30 followed by an increase up to a period of stability that lasts 2.5 to 3.5 hours, before instability until the end of the period. During stable periods, in particular, a difference in the magnitude of BG is evident.

Glucose cluster profiles were compared using DTW as a metric of similarity. Figure 4.4b shows the DTW similarity between each pair of clusters, with lower values indicating more similar profiles. Clusters 1 and 3 were the most similar ($DTW = 182.31$), and cluster 2 was the most dissimilar to the others on average ($DTW_{avg} = 273.48$, with cluster 3 being a mixed result. The most dissimilar clusters were 2 and 3 ($DTW = 324.16$), due to the difference in absolute values and shape. Cluster 1 had the highest

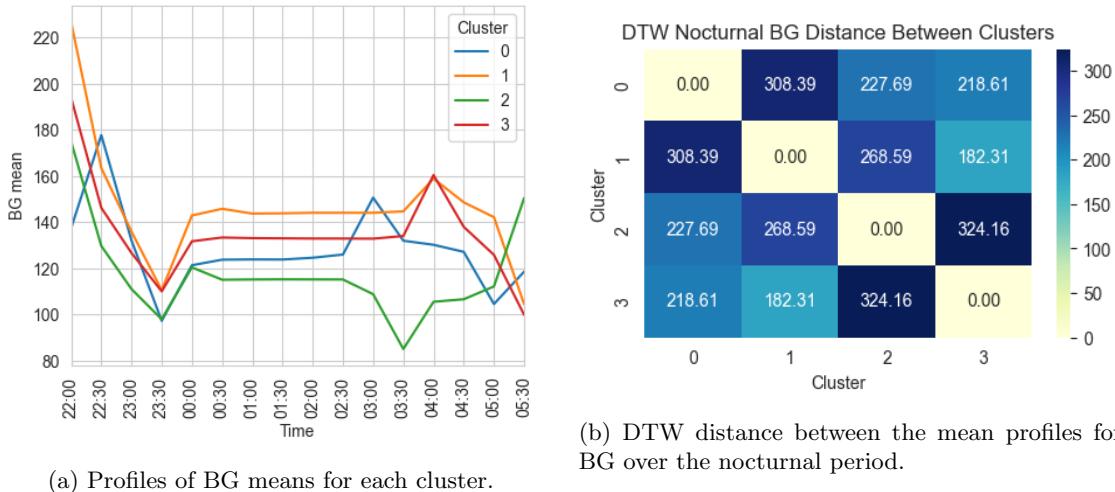


Figure 4.4: Plots based on the unweighted standard BG mean at each interval showing (a) the profile over the nocturnal period and (b) the DTW distance between the mean profiles for BG.

nocturnal glucose levels ($BG_{mean} = 146.54$), and cluster 2 had the lowest ($BG_{mean} = 117.44$). Given that the distance measure was based on unscaled values and the difference between these, it was not focused on the difference in the shape of the profile. The shapes of profiles 0 and 1 were visibly similar. Normalised BG profiles were assessed, which is more reflective of the difference in events than the difference in mean over the time series. Clusters 2 and 0 were the most dissimilar in shape ($DTW_{norm} = 2.24$), which aligned with the observed profiles. The notable differences appear to occur during the 02:30-06:00 segment, with preceding profiles looking predictably similar. The SD of the BG_{mean} for the segments were 33.3 between 22:00-00:00, 11.2 between 00:30-02:00 and 19.5 between 02:30-06:00. This highlighted some key characteristics across all clusters based on mean-average profiles for each. A Mixed Linear Model (`statsmodels.smf.mixedlm` as an extension of a repeated measures ANOVA test) was used to identify whether there was a significant difference in the means of the clusters, using cluster 3 (the 'common' and largest sample group) as control, which showed the nocturnal means of each other cluster as significantly different ($P < 0.05$). This validated that the clusters, based on COB/IOB input, were driving different BG outcomes.

4.2.2 BG Time-Dependent Association with COB and IOB

Using the mean of Spearman's correlation for IOB leading BG at intervals in each cluster gave a high correlation at lag 0 in the range [0.56, 0.74], the highest being cluster 2, and tapered for all clusters until lag 5, reaching a correlation range of [0.19, 0.28], with cluster 2 remaining the highest. Thus, IOB exhibited the same behaviour for each cluster. The correlations between COB and BG actually increased marginally over lags, though there was still a very weak monotonic relationship between the variables, reaching its highest for cluster 1 in lag 5 of 0.14. Figure 4.5 shows the Spearman correlation between each mean variable at intervals in the observed period and how the pattern of relationships changes. Seasonality was seen in the correlations which determined that the pattern is predictable and repeating, which was compared using Seasonal Strength calculated as $SS = 1 - \frac{Var(R_t)}{Var(S_t) + Var(R_t)}$, where R_t , S_t are residual and seasonal components of a seasonal decomposition, respectively. 0 indicates no seasonality and 1 demonstrates a high seasonal strength. COB with IOB in Figure 4.5c showed seasonality ($SS = 0.73$) with a generally stronger correlation in the evening and morning mealtime periods between COB and IOB, indicating a bolus response that is well-timed with carb intake. In particular, the relationship was weaker with the 'low-carb/low-insulin' cluster 2. This possibly indicated that carb counting has been imprecise or that a low-carb diet was being followed and that the weak correlation was a result, given that there was little need for bolus insulin. The lower correlated nocturnal period was expected during fasting as basal insulin plays its role and few carbs should be consumed. The 'high-carb' cluster 0 still exhibited a correlation of between 00:00-01:30 in the morning, which highlighted carb intake and bolus into the nocturnal period and behaviour outside an optimal diurnal pattern.

Figure 4.5a highlights an overall low, and sometimes negative, correlation between COB and BG with a lower seasonality ($SS = 0.45$). Without help from exogenous insulin, the expectation would be for

4.2. BLOOD GLUCOSE ANALYSIS

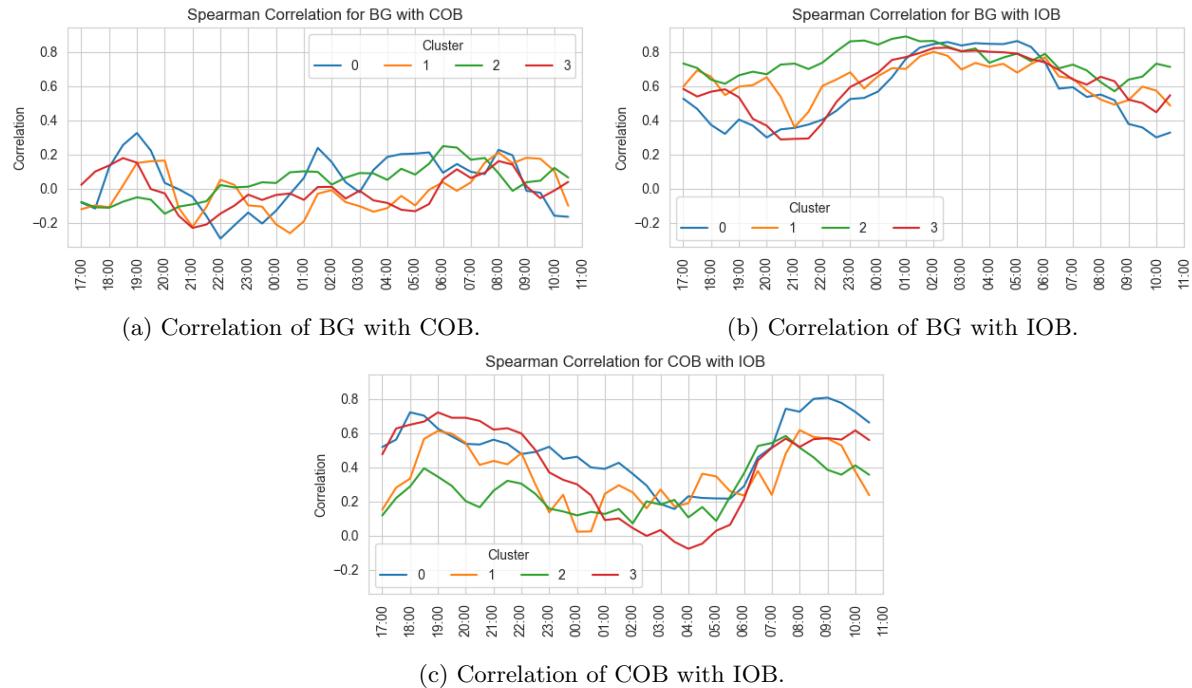


Figure 4.5: Spearman correlation between mean scaled variables calculated at intervals for each cluster with the correlation on the y-axis, and lines showing values for each cluster (0 - blue, 1 - orange, 2 - green, 3 - red).

BG to be highly correlated with COB, and observable with lagged values. It may infer that the insulin bolus was effective and that BG did not respond to COB, with a very weak effect size on the whole, or that there were other factors that influenced BG rather than COB, as Degen et al.[19] concluded in their findings. The prevalence of a negative correlation was likely due to BG falling in line with carb absorption, but much of the signal between these variables was overshadowed by noise and impacted by the prevalence of COB zero values. BG may have decreased due to insulin action, while COB decreased from a previous meal. This was highly likely at 22:00 for nights in the 'high-carb' cluster 0 and examples the disruptive impact on the nocturnal period of high-carbohydrate intake late into the evening.

For BG and IOB, there was an expected high correlation given the dependent relationship between insulin and BG, which Figure 4.5b supports. The correlation was also highly seasonal ($SS = 0.73$) and plateaued between the hours of 01:30-05:30 due to the basal insulin dosing and stable BG during this fasting period. However, the period before this showed differences in the effect size with cluster 2 between strong and very strong, with cluster 0 being only moderate. This suggested that the level of COB plays a role in the correlation of BG with IOB here, since the correlation with COB and IOB appears lower when the correlation with BG and IOB is high. The likely reason for this was the low carb intake characteristic in cluster 2 in the evening period that produces little need for insulin bolus.

The results of cross-correlation analysis showed no significant correlation over all lags for pairwise variables combinations when averaged over the whole sample, resulting in a range [-0.15, 0.10]. The standard deviations were high relative to the means, in the range [0.53, 1.72], indicating that the data are highly scattered. Breaking the analysis down by cluster, the results mostly agreed with that of the whole sample. The exception was where the most extreme mean CCFs appear, where COB leads BG, particularly cluster 0. This cluster moves from a negative correlation at lag 0 ($CCF_{mean} = -0.04$) to a positive correlation at lag 5 ($CCF_{mean} = 0.28$) which is distinct in the magnitude of change. Although it was important to note that the SDs of these means were still high at lags 0 and 5 ($CCF_{SD} = 1.67$ and $CCF_{SD} = 0.81$, respectively), should this trend be verifiable, it would suggest a clinically relevant observation of a delay in the impact of COB on BG, particularly in this 'high-carb' group. This relationship in a particular group can highlight where an impact on the diurnal rhythm for these types of nights is unique and warrants attention.

Broadening the methods to analyse time-based associations between COB/IOB on BG, regression analysis was used to create a richer understanding of the relationships and possibly infer causation.

Figure 4.6 shows mean P -value results from a linear regression of all intervals for each night. This

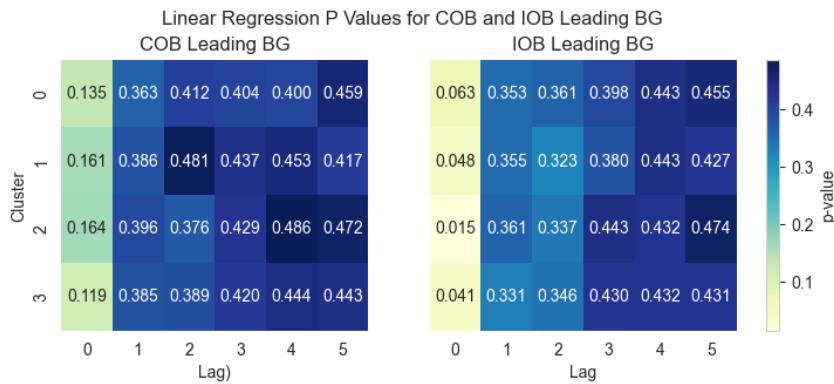


Figure 4.6: Comparison of P values for linear regression models for four passed lagged intervals of COB and IOB with BG.

was done at each lag for each cluster. Although a lag of 0 indicates the highest significance of the relationships for both COB and IOB, it was not possible to determine that COB had statistically significant relationships. For IOB at lag 0, only cluster 0 has $P > 0.05$. This suggested that any possible linear relationship between IOB and BG was more significant than between COB and BG. Lagged values lost significance the greater the lag for both COB and IOB generally, with subtle fluctuations that cannot be ruled out as chance. The weaker significance of the relationship of COB with BG could again reflect the results seen by Degen et al. [19] where more than half of the insulin need could not be explained by carbohydrates alone, with other confounders playing a role. The existence of nonlinear relationships between COB and BG was also considered, which required alternative regression models to capture them. Experimentation with nonlinear machine learning regression models that model more complex relationships produced similar, though less compelling, results as described in Appendix E. They offered some reinforcement to the observed stronger relationship between IOB and BG than with COB, and possibly reflected some of the lagged effects seen with COB leading BG, but lacked conclusive results.

4.3 Analysis of Glycaemic Variability

This section summarises the results obtained from the analysis of the different measures of GV outlined in section 3.4.

4.3.1 Target Range Excursions

The following analyses excursions beyond formal level 1 (L1) and level 2 (L2) thresholds for our clusters and notable patterns against COB and IOB.

The number of nights in the sample for a patient was proportional to the number of nights with L1 excursions, as Figure 4.7 illustrates. A linear regression between nights with excursions and total nights resulted in a strong correlation (with $P < 0.001$ and $R^2 = 0.91$), but the number of nights was not highly correlated with the number of excursions given a Pearson correlation of $R = 0.36$. This highlighted that the instance of excursions followed an alternative relationship, likely with a predominance by patient, rather than the sample size. A weaker but still significant relationship existed between total nights and nights with L2 excursions ($P < 0.004$ and $R^2 = 0.45$) and appeared to be more personalised at L2 thresholds, with two patients (B and M) having $40 < m < 50$ and disproportionately high nights with L2 excursions (23 and 19 nights, respectively).

Figure 4.8 shows the volume of occurrence of L1 excursions by cluster for intervals above range (IAR) and intervals below range (IBR). It is noticeable that the frequency of IAR, which are indicative of hyperglycaemic events, was greater than IBR, in general. In the nocturnal period, IBR had a higher prevalence, which makes sense during fasting. The regulation of BG then relies on basal dosing, which can have its effects altered by a number of factors, such as prior physical activity, insufficient carbohydrates before sleep, or excessive bolus insulin. Cluster 2 ('low-carb/low-insulin') saw the highest prevalence of IBR excursions, with IBR at a 0.56 ratio to IAR excursions, perhaps highlighting a difficulty in nocturnal glycaemic control and the impact it may have creating an irregular diurnal pattern. Cluster 0 ('high-carb') had a disproportionate number of excursions to the number of nights in the cluster during the

4.3. ANALYSIS OF GLYCAEMIC VARIABILITY

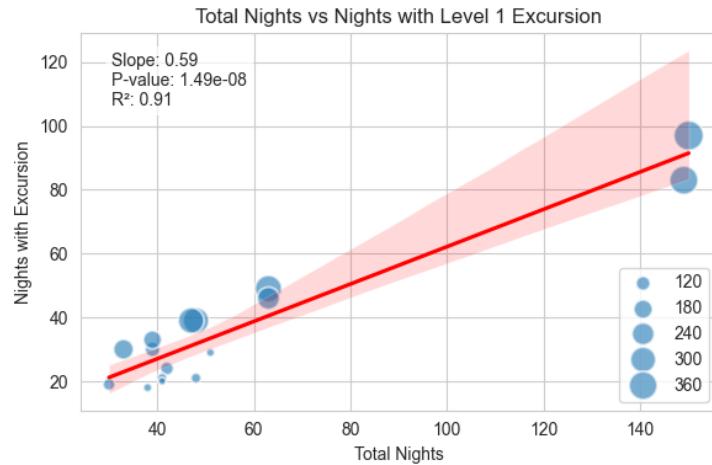


Figure 4.7: Relationship between the number of total nights for a patient and the number of nights with excursions recorded. Markers (blue) represent a patient and size denotes the total number of excursions recorded for the patient.

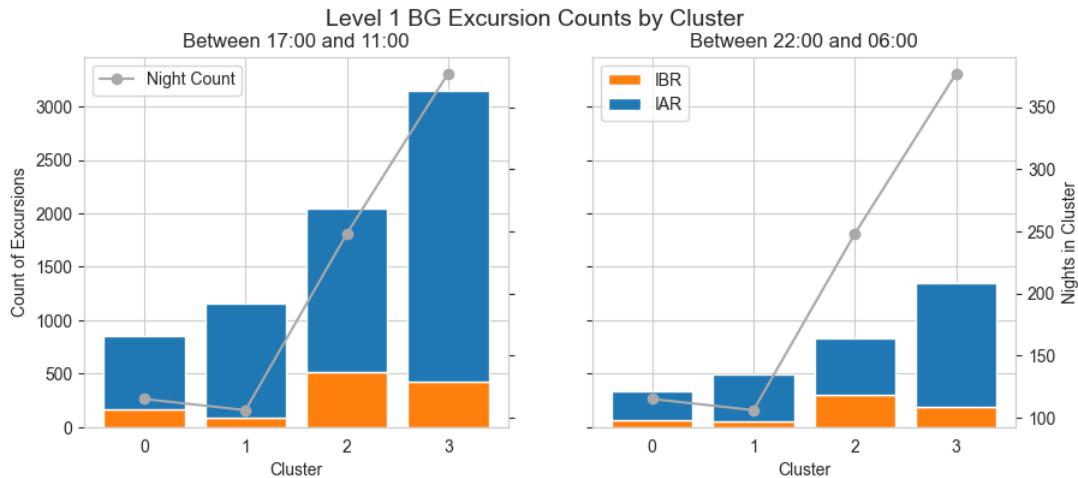


Figure 4.8: Occurrence of excursions by cluster in the broad 17:00-11:00 period vs the nocturnal 22:00-06:00, for Intervals Above Range (blue) and Intervals Below Range (orange).

17:00-11:00 period, which was also reflected in the nocturnal period, though less pronounced.

Figure 4.9 outlines a temporal pattern of excursion occurrence over the observed period. The temporal mean and interquartile range of excursion events highlighted the differences inferred in the violin plot. For each group, a bimodal distribution showed peaks and plateaus of the IAR excursion density centred around the evening and morning mealtime, in response to carb intake. Using a Gaussian Mixture Model (scikit-learn's `GaussianMixture`) to estimate the temporal means for each mode, the modal means for each cluster were found to be close, in the range 21:15-22:01. The morning modes were more variable, with a range of temporal means of 06:04-09:42. The earliest mean was cluster 3 and was due to the high spread of excursions over the morning period. The likelihood of IAR excursions was much higher in the evening period. Cluster 1 however had the latest mean at 09:42, presenting a high likelihood of IAR late in the morning, reflecting Figure 4.3b with its spike in morning BG. Recall in Figure 4.3b the significant spike in insulin from a bolus that responds to COB at the same time, yet the IOB did not regulate BG quickly enough, causing an increased probability of excursions. This was reinforced by the high correlation between BG and IOB seen at this time in Figure 4.5c.

Although the density of IAR L1 excursions in the nocturnal period was in the range 22.3-24.5%, the prevalence of IBR excursions ranged from 28.7-62.8% and follows less predictable distributions. The highest proportion of excursions for the nocturnal period (62.8%) was cluster 1 ('high-insulin'), and had a temporal IQR of 3hr30 ($Q_1 = 00:30$, $Q_3 = 04:00$). This was the latest IBR Q1 by 03hr15 with a

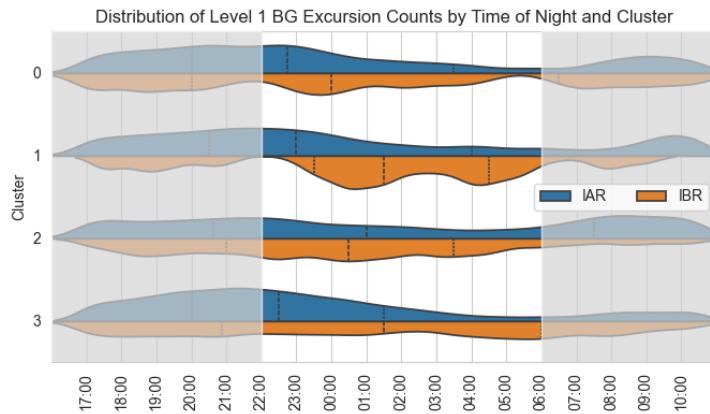


Figure 4.9: BG L1 excursions density (likelihood) over observed period, highlighting the nocturnal period. The violin plot uses a low kernel bandwidth to avoid smoothing and tails that extend greatly beyond the observed time range, hence the perceived sensitivity of the distribution to fluctuation

tighter IQR at just 03hr30 (a 01hr30 difference from the next temporal IQR of cluster 2). This cluster had a higher intensity of IBR excursions over a shorter period of time and during the nocturnal period. Ultimately, L1 IAR and IBR excursions largely follow distributions that could be anticipated given the understanding of the relationships between variables such as postprandial IAR dominance. However, the interesting distributions of the 'high-insulin' group showed a disproportionate number of IAR excursions to the number of nights, which was counterintuitive given its 'high-insulin' characterisation, with the large pre- and post-nocturnal peaks in IOB.

The density of excursion amplitudes (rather than occurrence) reflected a similar picture. For all nights in the sample, the IAR distribution is distinct and consistent over a count of 2397 excursion intervals, with $Q_1 = 14$ and $Q_3 = 74$ mg/dL; therefore 50% of the probability distribution of excursions above the L1 target range falls between 14 and 74 mg/dL. However, the maximum excursion was 221 mg/dL. IBR excursions number 608, with $Q_1 = 4$ and $Q_3 = 15$ mg/dL (absolute values). The maximum excursion was 31 mg/dL, making these excursions less pronounced than IAR. The IBR distribution also appeared multimodal, evidenced with statistical significance from a dip test with $P < 0.05$ that it was not unimodal, and a bimodality coefficient of 23 indicating a strong bimodal distribution. This bimodality was influenced by clusters 0 and 3 in particular, and possibly cluster 1 (detail of which can be seen in Appendix G, for reference).

The volume of excursions at L2 thresholds was obviously much reduced, totalling 494 for IAR and 131 for IBR for the nocturnal periods, a mean of 0.68 a night, compared to L1 excursions at 3.28. Cluster 2 - 'low-carb/low-insulin' - had most of the L1 and L2 incidence of IBR excursions as compared using observed vs. expected counts. A Chi-squared independence test revealed a statistically significant difference in the proportion of IBR excursions between clusters ($P < 0.05$) within the 22:00-06:00 time frame for L1 (and L2) excursions. Specifically in L2, cluster 2 demonstrated a statistically significantly higher proportion of IBR events (69%) compared to clusters 0, 1, and 3 (30%, 12%, 13%, respectively). For L2, the lack of signal in the data was evident, presumed to be due to the lower count of excursions to provide a pattern. Although the number of excursions was naturally much lower, much of the distribution was lost and the excursions tend to appear more random, apart from some cases such as IBR in cluster 3 which exhibited a well-defined distribution as shown in better detail in Appendix G. These results indicate that L2 thresholds present unique events, are more personalised to the patient, and offered particular information on diurnal differences.

4.3.2 Amplitude of Glycaemic Excursions (AGE)

An alternative to global target thresholds is to measure 'Amplitude of Glycaemic Excursions' (AGE, derived from the formal mean average 'MAGE' as described in Section 3.4.3), which calculates qualifying excursions beyond one standard deviation relative to the observed period. The personalisation of such a measure has benefits in identifying cases of disruption to diurnal rhythms, since it reflects variance relative to the patient's own mean and thus relative to their own circumstance, physiology, and behaviour. The excursions are summarised with the DBA BG profiles overlaid in Figure 4.10. Means of the excursion counts (marker size) and amplitudes (primary y-axis) were used to make the plots comparable irrespective

4.4. STABILITY SCORE (J) ANALYSIS

of different sample sizes. They show the tendency for excursions to occur at turning points in the BG mean profile, but also that they can occur relatively frequently at points where the BG profile seems stable.

The peak in mean for cluster 1 at 02:30 was the highest excursion mean seen during a 22:30-05:30 period and could be assumed to be similar to the results of IAR/IBR, which showed that L1 IBR has the highest proportion of excursions for the nocturnal period with the smallest spread based on a temporal IQR, visually aligned with the period of high variability we see in Figure 4.10b. However, amplitudes in this context are absolute values, and the type of excursion (peak-to-nadir or nadir-to-peak) is not evident in the metric, and so could not be compared. Cluster 1 was marked by the highest BG going into the nocturnal period and the highest average prior, yet it was also evident that the 04:00-05:30 period saw quite a reduction in excursions and excursion means, which could mean that the cause of any volatility by that point had subsided. The overall excursion mean was also the highest for cluster 1 (17.49, while for clusters 0, 2, 3 were 13.17, 14.50 and 13.69, respectively), as was the AUC for the Excursion Mean (calculated as mg/dL · hours for clusters 0, 1, 2, 3 as 98.6, 128.5, 107.4 and 102.1, respectively). Despite this, after first using a Shapiro-Wilk test that suggested that only cluster 1 is likely to have a normal mean AGE (MAGE) per night distribution ($P = 0.49$), a Kruskal-Wallis H-test indicated that there was no significant difference between the medians of the clusters and thus, insufficient evidence to suggest a difference between the clusters in this regard.

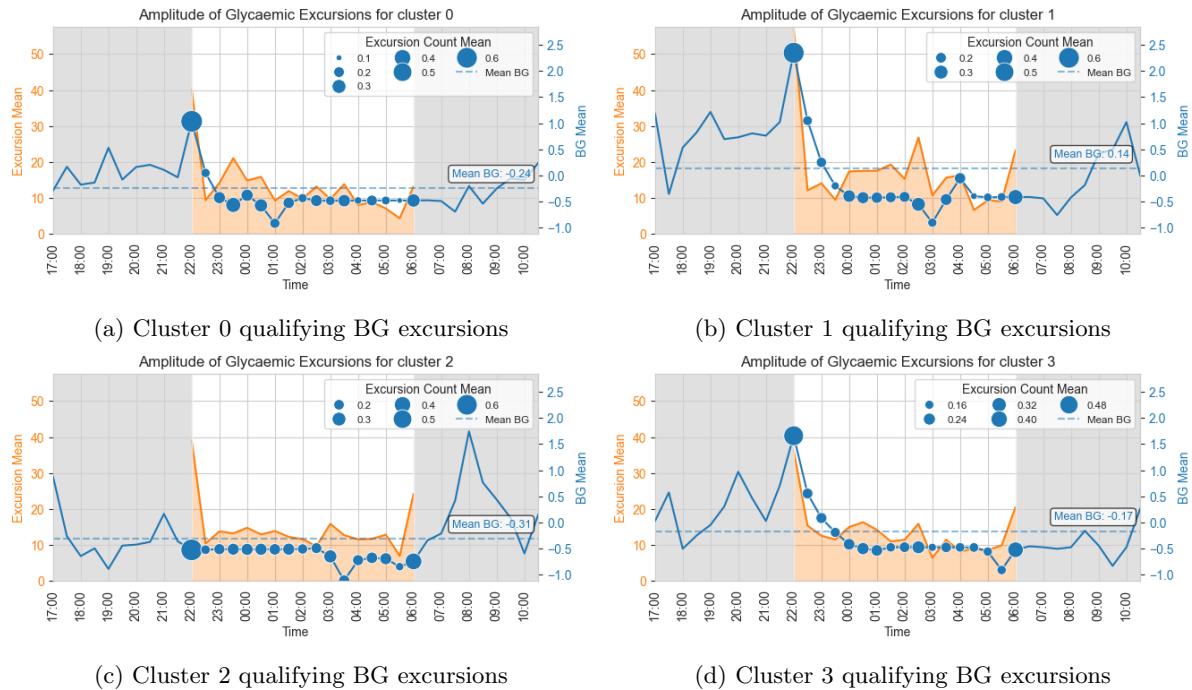


Figure 4.10: Time series showing the excursion means at each time interval (orange area) against DBA profile of scaled BG for each cluster, using marker size at each time point to highlight the mean of excursion counts at interval. The BG mean for the 17:00-11:00 is marked for reference as the dashed line, and the zero line as a dotted line for the BG mean axis. The 22:00-06:00 period is the focus while the shaded areas show the context of the broader BG profile. Grid lines are provided for the Excursion Mean axis

4.4 Stability Score (J) Analysis

This section reviews results from analysis of the J score from different perspectives, to identify patterns in the outcome of the composite score with COB and IOB, and previous results.

4.4.1 Overall Analysis

An initial view of the distributions of the J scores gave a mean of 0, an SD of 0.78, and a range of [-1.23, 3.03]. Lower/negative scores indicated a more stable night. The IQR was 0.93 ($Q_1 = -0.58, Q_3 = 0.35$),

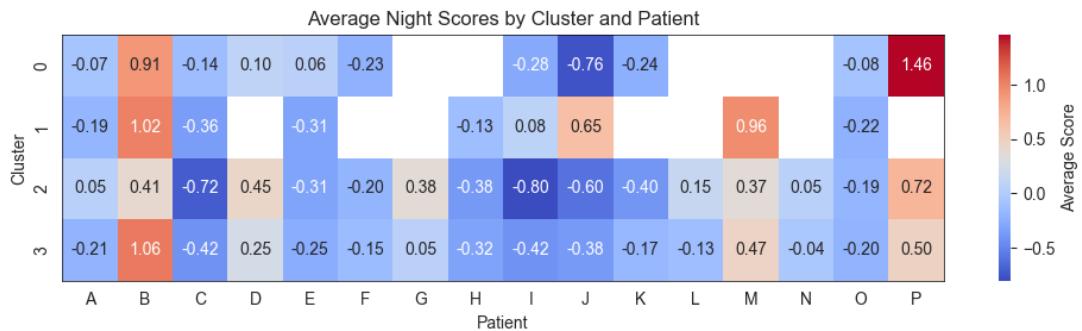


Figure 4.11: Average J scores at the intersection of cluster and patient. with colours blue to red representing the weight of the score.

and was therefore skewed, with a skewness of 1.33 (inferring that the scores were not normal) and a kurtosis of 1.86 (indicating a platykurtic distribution, thus defining the shape as not typically normal). The distributions by patient followed similar shapes with means in the range [-0.37, 0.87]. An average of the J score at the intersection of the cluster with the patient did not show any noticeable correlation patterns with the clusters in Figure 4.11. It highlighted how the patient scores in each group were not always variable as may be expected. For patient O for example, the means ranged by only 0.14 across each cluster, whereas patient J ranged by 1.41. The cluster distributions demonstrated skewness, but cluster 1 was deviant. Using a Kruskal-Wallis test to compare medians between clusters showed a significant difference ($H = 30.55$) and a post hoc Dunn test highlighted cluster 1 as a uniquely different distribution, with $P < 0.001$ in all pairwise comparisons.

4.4.2 Relationship Between Evening COB/IOB and 'Stability' of the Night

An early investigation of the relationship of lagged COB and IOB values with BG highlighted that its strength decreased as the data lagged, rather than showing an improvement using linear and nonlinear regression methods. Here, the analysis looked at whether there were discernible relationships between mean values in COB/IOB from the evenings, compared to the variability during the nocturnal period. The evening was defined as the period between 17:00 and 22:30, to widen the window for the carbs of the evening meal to be further absorbed. A weighted mean was used for the evening mean COB/IOB values so that it reflected more the true overall mean of the original high-frequency data, with the intention of removing any bias the original resampling introduced. Similarly to the previous analysis, the results

Table 4.1: Results of linear regression between evening means (for the period 17:00-22:30) of COB and IOB relative to the composite score for each cluster.

	Evening COB vs Score				Evening IOB vs Score			
	Slope	Intercept	R-value	P-value	Slope	Intercept	R-value	P-value
Cluster 0	-0.00	0.14	-0.13	0.14	0.12	-0.54	0.25	0.00
Cluster 1	0.02	0.16	0.22	0.03	0.07	0.11	0.15	0.12
Cluster 2	-0.01	-0.01	-0.10	0.11	0.17	-0.23	0.21	0.00
Cluster 3	0.00	-0.04	0.01	0.83	0.16	-0.34	0.24	0.00

showed that leading COB generally had less of a relationship than IOB, where IOB relationships were significant at $P < 0.05$ for clusters 0, 2, 3, while for COB they were all $P > 0.05$ except for cluster 1 that deviates. This relationship was inverse, presenting sufficient evidence of a relationship with COB ($P < 0.05$) and not with IOB. The COB correlation for cluster 1 also appeared different from the other clusters with a positive correlation coefficient ($R = 0.22$) compared to the negative or nearly neutral R values otherwise. Appendix H provides a visual representation of the results with better resolution, using scatter plots and broken down by cluster.

4.4.3 Hierarchical Analysis

Using hierarchical analysis, looking at an extreme example of a patient with the highest difference between their mean (J_{mean}) and maximum (J_{max}), a consistent pattern emerged in the data. The identified patient (patient N) had a $J_{\text{mean}} = 0.02$ and $J_{\text{max}} = 2.82$. Visual analysis (from Figure 4.12a) comparing the COB/IOB means for the patient's J_{max} night (m_{max}), with the COB and IOB averages for the rest of their nights gave two main observations. First, against a stable mean with no variation at night within a 95% CI, there were two COB intake events for m_{max} , one between 00:30-01:00 and another between 05:00 and 05:30. This indicated some disturbance at night since it would require the patient to be awake twice during this period. The second observation was that insulin remained above the mean for over half the night, as a bolus response to carb intake. This level of intervention would be typical of what we would recognise as an unstable night relative to glycaemic control and circadian disturbance, indicating that the J measure was fulfilling its objective.

Under the hypothesis that this phenomenon could be seen more broadly, patient N's sample nights were grouped between those with the lowest 50% of scores (m_{bottom50}) and the highest 25% (m_{top25}), reducing sample size but creating separation between groups. Some consistency in the differences was evident. COB and IOB means were different when comparing the means for the patient's two groups using DTW (with a Manhattan distance metric). The mean COB for nights with the highest 25% J scores (m_{top25}) were significantly higher than m_{bottom50} with a DTW distance of $DTW_{COB} = 0.29$, confirmed by a Mann-Whitney U test ($U = 61148, P = 0.003$). IOB saw much greater dissimilarity between the groups ($DTW_{IOB} = 3.59$, and $U = 27981, P < 0.001$). The patient sample had the following cluster membership: m_{bottom50} had $m = 19$ in cluster 2, $m = 12$ in cluster 3; m_{top25} had $m = 10$ in cluster 2 and $m = 6$ in cluster 3. The patient had some of the greatest differences in J , but had no nights in cluster 1, characterised by its higher peaks in carb intake in the evening and morning periods. The breakdown reflected the high number of nights within cluster 2 in the top 25% scores, a group characterised by a higher average BG during the nocturnal period and the highest spike in blood glucose heading into the night, peaking at 21:00.

Extrapolating the analysis to the other four patients with the largest sample of nights (since patient N was in the top five), the resulting sample was sufficient to see similar or alternative patterns using the same approach. The result was $DTW_{COB} = 0.98$ and $DTW_{IOB} = 3.33$ between m_{bottom50} and m_{top25} for this subgroup, highlighting similar characteristics for nights with the highest composite score: the greater the instability in BG overnight, the higher the general levels of insulin. A Mann-Whitney U test for difference in COB mean between m_{bottom50} and m_{top25} showed significance in this group ($P < 0.001$), with an increase of $U = 6.1 \times 10^4$ to $U = 2.6 \times 10^6$ as the sample increased. For IOB, the Mann-Whitney test showed stronger results in the difference between patient N and the broader group, increasing $U = 2.8 \times 10^4$ to $U = 1.7 \times 10^6$, all $P < 0.001$.

Finally, applying the same analysis to the entire sample of $m = 922$ (resulting in groupings for m_{bottom50} and m_{top25} as described in Table 4.2) and calculating DTW between the groups for COB and IOB, we saw the m_{bottom50} and m_{top25} reduce to $DTW_{COB} = 0.493$ and increase to $DTW_{IOB} = 5.978$, with $U = 1.3 \times 10^7$ and $U = 8.1 \times 10^6$, and $P = 0.013$ and $P < 0.001$ for COB and IOB, respectively. The relationship between high J and high IOB during the nocturnal period had therefore increased as the sample had increased. The Mann-Whitney P values allowed rejection of the null hypothesis that these differences between m_{bottom50} and m_{top25} were not different and accept that in both cases (of COB and IOB), a higher J score correlated with higher COB and IOB during the nocturnal period.

Table 4.2: Sample size of nights m_{bottom50} and m_{top25} as a proportion of the full sample of $m = 922$.

Cluster	Cluster m	% of $m = 922$	m_{bottom50}	m_{top25}	$m_{\text{bottom50}} \%$	$m_{\text{top25}} \%$
0	124	13.45	66	29	14.32	12.55
1	106	11.50	30	50	6.51	21.65
2	264	28.63	146	57	31.67	24.68
3	428	46.42	219	95	47.51	41.13

4.4.4 Between-Cluster Patterns in J Score

The components of the composite score provided interpretability. Figure 4.13 showed means of the weighted scaled components per night, illustrating their contribution. The differences in score were

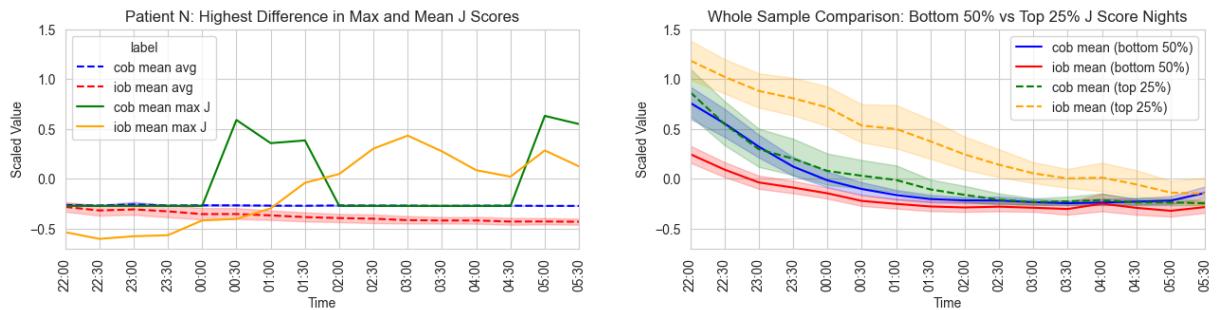


Figure 4.12: Start 4.12a and end 4.12b of hierarchical analysis, highlighting consistency of high insulin where there is high J score.

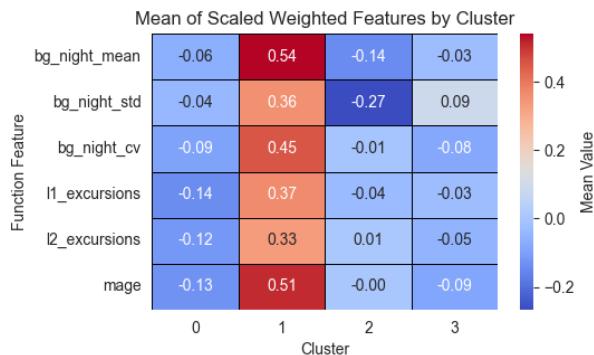


Figure 4.13: J score components averages by cluster, highlighting the high component scores for cluster 1 in particular.

striking across all components, although it was clear that these variables were not all independent. For example, the level of the BG mean would be a good indicator that someone is more prone to hyper- or hypoglycaemia events according to target ranges. If someone - due to their unique conditions - was prone to a higher mean BG, they would find it more difficult to keep it within the upper L1 target threshold, although it might be a manageable state according to their physician. Thus, L1 excursions should be interpreted in the context of the mean BG and similarly L2 excursions, though more severe and thus less likely to be acceptable. Although the main reflection here was that L1 excursions could be considered less influential given the sensitivity to the BG mean, (as reflected in the weights given in the function) this mattered little to the observed outcome: cluster 1 was associated with the highest J scores observed within each component.

The number of excursions against L1 and L2 hyperglycaemia was significantly higher in cluster 1, consistent with the association of cluster 1 with the highest J scores. Of interest here was that this number of excursions beyond arbitrary boundaries did not reflect that of the qualifying amplitude excursions that the MAGE variability metric incorporates. Cluster 1 has only 21.5% of total amplitude excursions of the four clusters, but 32.5% of the sum of the amplitudes, which means these excursions were larger in magnitude but less frequent. This is consistent with the association of cluster 1 with the highest J scores, as it indicated that although there were fewer amplitude excursions, they were more pronounced and disruptive and infers that the characteristics of a suboptimal night are more synonymous with cluster 1, as reflected in other analyses throughout the study.

Chapter 5

Conclusion & Further Work

5.1 Conclusion

In this study, a sample of $n = 16$ patients with T1D and $m = 922$ nights was analysed to identify patterns in nocturnal BG and its relationship to COB and IOB within a broader night period that could highlight disturbances in diurnal patterns and illustrate differences in groups of nights that exhibit similar characteristics. Using resampled data from OpenAPS Data Commons of BG, COB and IOB at 30-minute intervals during the observed periods, the nights were clustered into four groups that exhibited different characteristics of COB and IOB; high-carb, high-insulin, low-carb/low-insulin and 'common'. BG profiles across all groups were analysed and shown to be significantly different, validating the grouping. Time-dependent associations between COB/IOB and BG were analysed using Spearman's correlation at lagged intervals, showing a moderate to strong relationship at lag 0 for all groups with IOB, and a weak relationship by lag 5, and COB with BG was very weak from lag 0. The size of the effect in each interval highlighted an inverse relationship between the correlation of COB with IOB during the pre-nocturnal period and that of IOB with BG. A very strong effect size of the low-carb/low-insulin group of BG with IOB contrasting a weak correlation of COB with IOB shows levels of COB and IOB can have distinct effects on their relationships between the variables and where a dampening of one diurnal pattern can impact another. Cross-correlation analysis showed generally weak relationships but a unique phenomenon with the high-carb group, which saw high positive correlation at lag 5. Linear and nonlinear relationships with regression methods decreased as lagged intervals were introduced for each group, disproving the hypothesis that significant relationships exist between BG and lagged COB/IOB readings.

Analysis of glycaemic variability using different metrics provided additional insights. More extreme L2 target range excursions were more personalised and lost some of the distribution qualities that could be seen with the occurrence of L1 excursions, thus more likely to highlight irregular diurnal patterns and significant scaling of diurnal rhythms. L1 IAR excursions followed common distributions between each group, aligned with mealtime and postprandial hours and less likely during nocturnal hours (between 22 and 25%). L1 IBR excursions were most likely during the nocturnal period for the high-insulin group (with a probability density of 63%), although the high insulin spike in the evening did not cause a proportionately high volume of nocturnal IBR excursions as expected in this group, suggesting that despite the high evening bolus, this did not manifest in hypoglycaemic excursions as it was well managed. The low-carb/low-insulin group had a higher proportion of IBR to IAR excursions than other groups and a significantly higher proportion of IBR events (69%) compared to other clusters. These results showed L1 excursion can highlight general patterns in diurnal glycaemic activity, differentiating our groups of similar nights, and L2 events provide an indicator of unique disruptive diurnal events. Glycaemic excursions beyond one SD showed some visual patterns suggestive of higher rates of variability in cluster 1 over the night profile, but testing could not prove these clusters to be different using their excursion means.

The distributions of the stability score J for each group proved to be statistically different from each other. The high-insulin group was uniquely different. Investigation of the relationship between COB/IOB and the stability score provided a similar pattern of results as in the earlier analysis of time-dependent associations between variables and BG. Evening IOB means had a stronger association than COB means to the score. The high-insulin group was an exception, where the opposite relationships were true and COB was the dominant association. Analysis of the J score components gave an interpretable view that indicated some consistency in how the components characterise the high-insulin group. This again spoke to the unique diurnal rhythm and influences of the nights in this group and prompts interest for future

work. The correlation of the stability score with higher nocturnal COB (expected) and significantly higher IOB (unexpected) particularly highlighted a relationship between glycaemic variability and insulin levels that warrants further research to help better understand the causal effect and direction of this association. Irrespective of this, this gave weight to the proposal that the use of this score, or the use of GV measures, can be a possible indicator of disturbance of diurnal rhythms. Caution should be taken not to interpret such a stability score as the cause of circadian disruption, rather as a proxy indicator, and a potential tool to identify nights and/or patients that have suffered from such disruption and lead to targeted advice.

As the understanding of circadian rhythm disruption and the implications of this to the health of T1D patients become better evidenced, tools will be needed to help clinicians assess the impacts of the disease on their patients. The increasing adoption of technology and particularly APS systems to help manage the condition produces a wealth of data that is shown to provide insights into how these rhythms can be disrupted, and possibly indicate causal effects that can influence decision making. More research is needed to be able to understand such effects.

5.2 Further Work

Expanding the dataset. A larger sample (both of individuals and of nights) would provide more statistical power and precision to the results. From the raw data, $n = 33$ individuals that could not be used due to having multiple timezones, so incorporating them would increase the number of individuals. Seeking ethical approval to expand the dataset to the current available in OpenAPS Data Commons would also increase the sample size, but possibly the greater gain would either be to create pre-processing for the other platform types (AndroidAPS and Loop) which would offer a further $n = 71$ possible individuals. Beyond this, other datasets are available such as Tidepool [50] that offer anonymised data for research, at greater volumes, and have been used in similar studies [30].

Augmenting Methods Used. In retrospect, some methods of execution in the experiments used could have been augmented to improve their outcomes. When attempting to find time-based associations between variables, the investigation would benefit from a broader scope. Reichardt and Gollob [29] outline the principles of causal effects and their application and importance in longitudinal data (i.e., data consisting of values taken over time), especially that longitudinal models should consider autoregressive effects. The effect of prior BG on itself could augment this analysis. Additionally, the use of machine learning regression techniques holds much potential with these datasets to both describe relationships, but also to predict them. Refining the methodology by adapting the approach (changing the training set to incorporate more data points, using a multivariate approach, limiting the models and focussing more on model tuning) may yield better results.

Nocturnal Period Definition. The nocturnal period of 22:00-06:00 was chosen with the intention of isolating the fasting period. This period is of course variable based on factors such as individual behaviour, chronotype, and cultural setting. The BG profiles highlighted this period as more unstable period regarding BG than intended, in order to highlight true nocturnal instability, and output of GV calculations incorporate a bias of the postprandial BG spike which, in retrospect, can undermine the view of real nocturnal variation. To minimise this bias, a nocturnal period of 00:00-06:00 could be chosen, which may change some of the patterns seen and draw different conclusions, more sensitive to the sleep/fasting period. Under a 30 minute resampling regime, this leaves fewer data points and less power in the analysis, so 15 minute sampling or less could also be considered to improve resolution and understand the nature of variability, and disruption, better.

Adapting the Stability Score, Broadening Analysis. There are certain ways in which the composite score can be adapted to enhance outcomes. The pattern finding objective needed to separate the influence of variables in order to avoid data leakage in the analysis, which is the reason for clustering based on COB/IOB-derived features and to include only BG-derived features in the function. Based on an improved understanding of the relationship of COB, IOB, and other control variables to the stability of a night, it may be relevant to include the other variables. The duration of sleep and/or the timing or intensity of exercise would all be relevant factors to compare the results with or include as components in the function. The weighting of components would be other parameters to consider, to see if the score infers different patterns and relationships based on changes to them.

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Appendix A

Circadian Rhythms - Supplementary Material

This appendix provides a deeper context to what circadian rhythms are and their importance in hormone pathways, metabolism, and general health, referenced in Chapter 1.

A.1 What are Circadian Rhythms?

Circadian rhythm is a natural internal process that regulates the sleep-wake cycle and is repeated roughly every 24 hours. The term "circadian" comes from the Latin "circa" (meaning "around") and "diem" (meaning "day"). It can be considered the biological clock of the body: a complex system primarily governed by a small cluster of nerve cells in the brain called the suprachiasmatic nucleus (SCN), located in the hypothalamus, and optimises bodily function over a 24-hour period. When eyes detect daylight or artificial light with similar properties, signals are sent to the SCN, which helps reset the internal clock to local time. "Entrainment" is the alignment of a person's endogenous circadian rhythm to an external rhythm [18], with light patterns considered to be the principal environmental cue (or "zeitgeber", translated from German as "time giver") to align with the diurnal oscillations of the organism [26]. The light/dark cycle provides a basis for the body to set its rest-activity cycle. This cycle is indirectly responsible for when people eat, which is another significant cue, but there are other important cues, such as exercise, social interactions, and temperature. The SCN can be considered the central clock, but there are also peripheral clocks that produce circadian rhythms in local tissue processes.

Although circadian rhythms influence a wide range of physical, mental, and behavioural changes beyond sleep [56], the sleep-wake cycle is the most well known and primary function. The body prepares for sleep as it gets dark (releasing melatonin) and prepares for wakefulness as it gets light (releasing cortisol). The circadian rhythm drives hormone release such as melatonin, cortisol, and insulin, which follow distinct 24-hour patterns of release in perfectly healthy individuals [52]. They play a role in controlling core body temperature, which typically drops during sleep and rises during the day. They influence the digestive system, which becomes more active during certain times of the day in anticipation of meal intake. Cognitive function and alertness will peak and drop throughout the 24-hour cycle, aligning with the demand for physical and mental activity, and the effectiveness of the immune system can vary with circadian rhythm [66].

Although the main rhythm comes from the SCN, signals such as insulin and glucose (often in response to feeding) act as important zeitgebers for peripheral circadian clocks in tissues like the liver and adipose tissue (fat) [81]. Research shows that insulin can directly regulate clock genes in adipose tissue and liver cells, leading to a phase shift in their circadian oscillations. This means that post-meal insulin spikes can help synchronise these peripheral clocks with feeding times. This is why consistent meal timing is often recommended for metabolic health [45], as it helps align the peripheral clocks [86]. Changes in glucose levels can also signal to peripheral clocks. For instance, the liver adjusts its glucose production and utilisation on the basis of circulating glucose, and these metabolic processes are tightly controlled by the liver's clock. Misalignment between the central clock and peripheral clocks (and between different peripheral clocks) can lead to circadian misalignment, which is a major contributor to insulin resistance, impaired glucose tolerance, and increased risk of metabolic diseases.

A.2 Why are Circadian Rhythms Important to General Health?

Given that the purpose of circadian rhythm is to optimise bodily function, its regulating effect is undermined when disrupted. Reasons for disruption will be based on personal circumstance and - if non-recurrent - may have certain immediate but short-lived consequences as the body's circadian rhythm will realign using the types of entrainment aforementioned. Longer-term recurrent disturbance may have more destabilising effects leading to more chronic problems in metabolism and brain function. A key pathway is glucose homeostasis [34], as 'dysglycaemia' (highly relevant to those with T1D) plays a consequential role in such problems [43, 58]. Although these rhythms are important for achieving good quality sleep, prompting cognitive activity and alertness and inducing metabolic processes among other functions, disrupting rhythms can lead to problems such as sleep problems [74] (insomnia, excessive daytime sleepiness), fatigue and decreased alertness, digestive problems, mood disturbances (e.g., increased risk of depression) and an increased risk of chronic health problems such as obesity, diabetes, and cardiovascular disease in the long term [12].

Appendix B

Data Selection Strategy

This section provides more detailed information about the data selection strategy and the logic by which decisions have been made.

An initial principal from the outset was the maximisation of data in order to provide power to the results and for generalisation. A more frequent sampling rate is preferable to provide better resolution and identify nuance in the data when particular windows are analysed. The smoothing effect of aggregation when reducing time interval frequency has the potential to lose nuance and risk not identifying certain patterns or phenomena. Of the two sampling rates (15 and 30 minutes), the analysis was completed at 15-minute intervals to assess the viability of this method.

The data selection process follows the logic below and prescribes criteria for both the patient (n) and the nights (m) that are sampled for analysis. The criteria are as follows.

1. The patient has a single time zone so that there are no shifts in the time series, which would distort the modelling and comparison.
2. The patient has all input variables (COB, IOB, or BG) in their dataset.
3. The patient has a minimum threshold of nights that contain continuous data in a window of 17:00 to 11:00 (the following day) that captures overnight fasting and preceding/successive meal intake and behaviour. The purpose here is to establish night samples of sufficient size to balance the need for meaningful unbiased aggregation by patient (where necessary in the analysis) and to provide an overall sample size of nights to find patterns when grouping.
4. Thresholds for an acceptable number of missing values are set for each variable separately, based on our understanding of the data and acceptable tolerance.

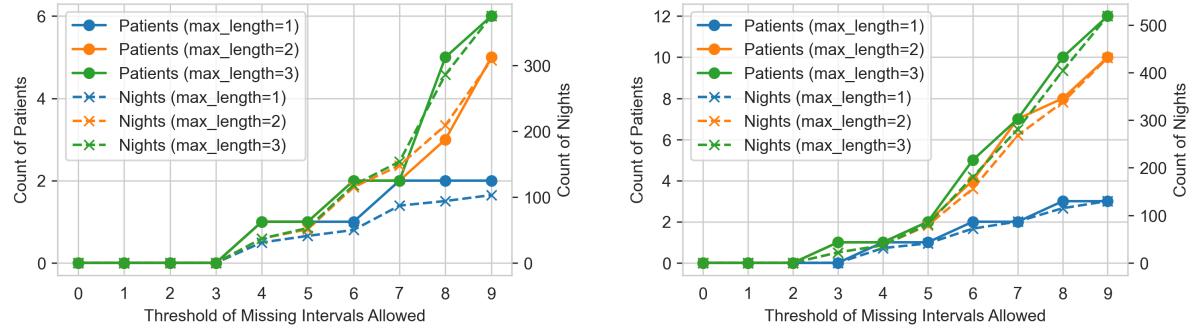
Figure B.1 supports the decisions made with respect to data selection. Figure B.1a shows the number of nights and patients that increase as thresholds are relaxed for both the number of missed intervals allowed and the span of continuous intervals that can be missing in a single night (represented by max_length), up to a maximum of 3. Accepting a threshold of ≤ 9 missing intervals per night period and a number of consecutive missing intervals max_length ≤ 3 (the most relaxed thresholds), a sample resulted of $n = 6$ and $m = 375$. Relaxing the threshold for the number of 'complete' nights per patient from ≥ 30 to ≥ 20 (Figure B.1b) still did not provide satisfactory results, with only $n = 12$ and $m = 519$ using max_length of with the same thresholds.

Resampling at 30 minute intervals using similar thresholds greatly increased the patient and night sample size bringing it to within acceptable ranges for the intended analysis. However, given the lower sampling rate, any max_length > 1 would introduce gaps in data too large to consider acceptable, and any number of missing intervals > 1 could mean that analysis of the nocturnal period (22:00-06:00) would have an unacceptable proportion of missing data points. This would risk the introduction of bias, especially in circumstances where the missing data followed a regular pattern. The following options were then assessed at this sampling rate:

- **Option 1: Only use complete nights.** Defined as having no missing intervals, with a threshold of $m \geq 30$, which creates a sample of $n = 4$, $m = 240$.
- **Option 2: Relax nights per candidate constraint.** Consider only $m \geq 10$ 'complete' nights, which result in $n = 22$, $m = 559$ nights.

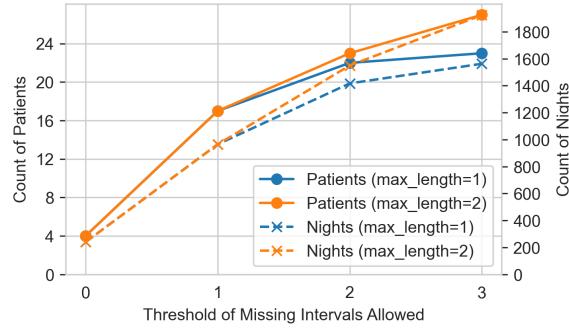
- **Option 3: Relax the missed intervals constraint.** Consider also nights with a single missed interval but ≥ 30 nights, which results in $n = 17$, $m = 965$.

Option 3 has been adopted to produce the final dataset for the study. This accepts that missing values still exist at intervals for the resampled data, which is summarised in Section 3.1.



(a) 15-minute sampling and a minimum of $m \geq 30$ per patient, aligning with Option 1 in Section 3.1.3

(b) 15-minute sampling and a minimum of $m \geq 20$ per patient.



(c) 30-minute sampling and a minimum of $m \geq 30$ per patient, aligning with Option 3 in Section 3.1.3

Figure B.1: Counts of patients n and count of nights m based on varying thresholds of missing intervals permitted plus the max.length of the span of missing intervals in a night, where colours represent variants of the max.length threshold and marker/line styles distinguish between patient counts (primary y-axis) and night counts (secondary y-axis).

Appendix C

Feature-Based Clustering

Features derived from COB and IOB resampled variables were selected based on the analysis requirements. Principally, this was to understand how patterns in these features distinguished nights that had similar characteristics in terms of constants, extremes, and temporal events that may infer differences in diurnal rhythmicity. In summary, these were

Average (Mean, Median): Provides an understanding of the centre of the data, grouping similarly high or low COB/IOB nights.

Range (Minima, Maxima): Identifies extremes in the data, grouping similar highs or lows in COB/IOB.

Variance (Variance, SD, RMS): Simple statistical measures of variance, grouping nights according to how extreme the changes in COB/IOB were.

Count above x: Specifically used for COB to reinforce (using an arbitrary level), nights with a high occurrence of carb intake passed a significant peak.

Entropy: The measurement of variability, predictability, and complexity in the variable is designed to indicate high levels of disturbance.

Figure C.1 provides the centroids of these features for each of the clusters defined using the method in Section 3.2.2. The colours represent scaled values of the features to make them comparable and highlight patterns in how the clusters differentiate. The values themselves are unscaled values of each feature, providing a more helpful reference in actual terms.

The resulting clusters have night distributions per patient as illustrated in Figure C.2. There is some observable predominance of nights in a single group for some patients, with 7 out of 16 patients having greater or equal to 60% of their nights in a group, and 4 patients with more than 70% of nights in a group. Figure C.3 then provides a more detailed view of the night counts by patient and group, helping to illustrate the magnitude of the nights and the dominance of individuals in each group, given the range of night samples for each patient.

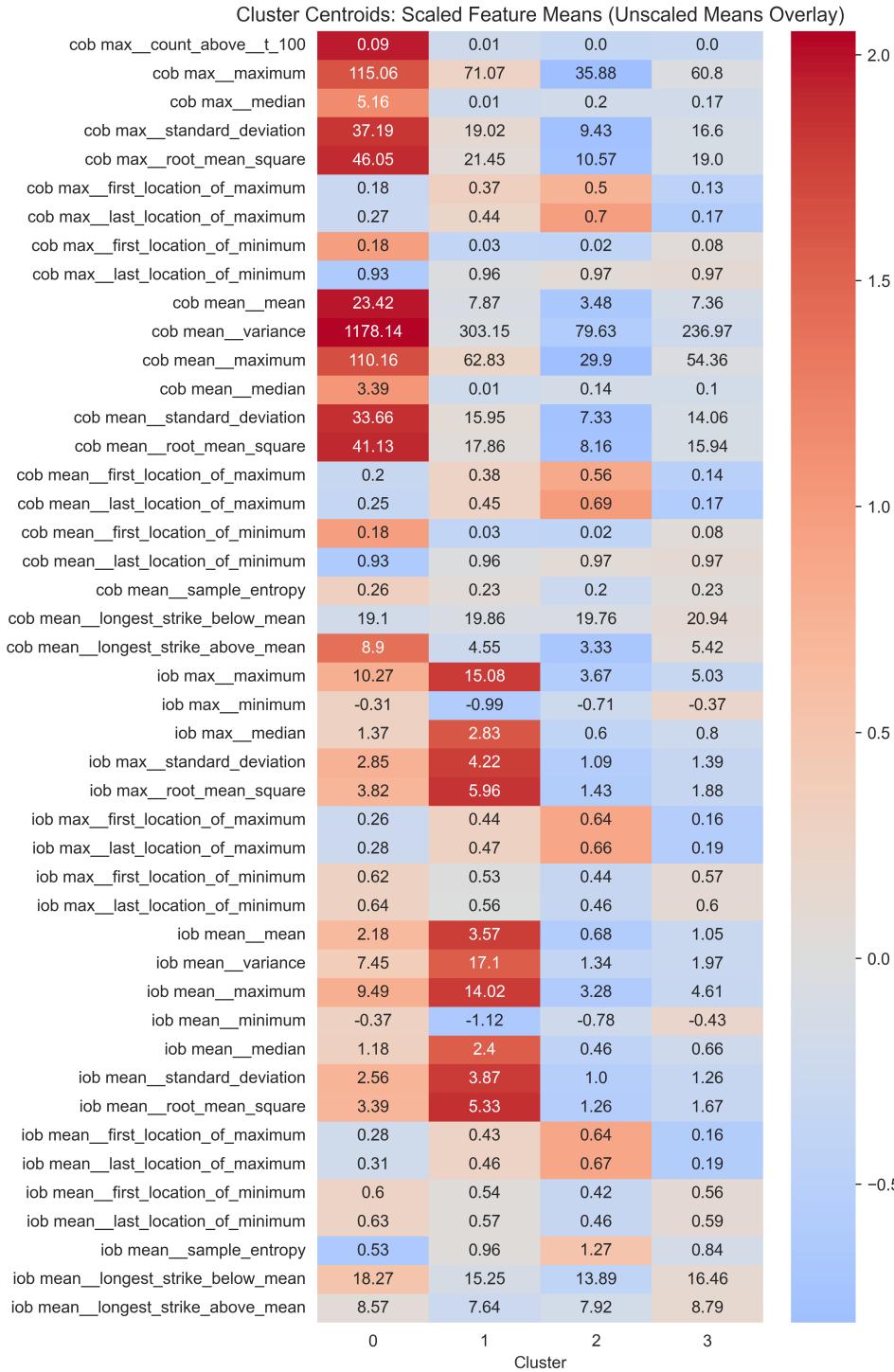


Figure C.1: A heatmap based on the scaled values of all features used in the features-based clustering of nights in the sample. Actual values are displayed for reference, which are unscaled means of the feature for the cluster.

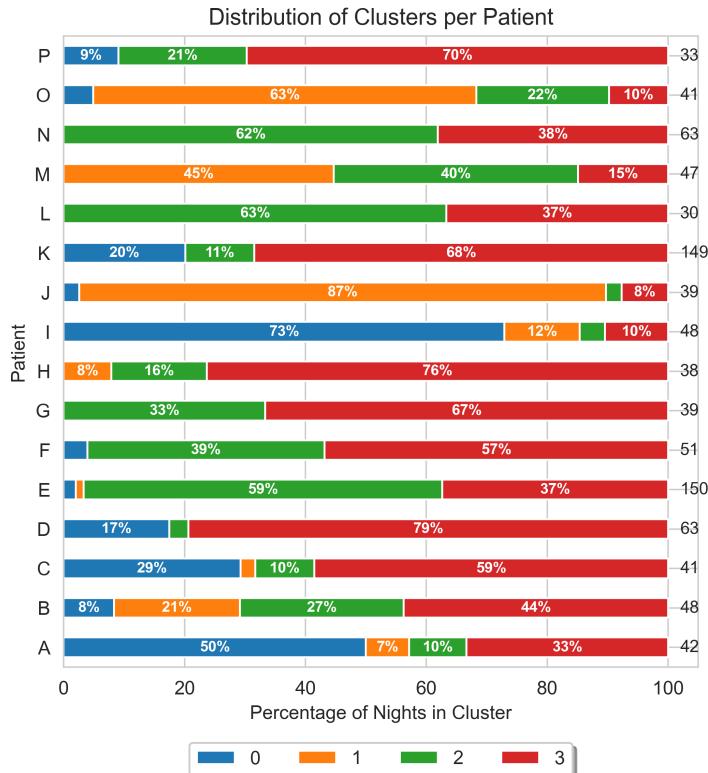


Figure C.2: The distributions of nights between clusters for the $n = 16$ patients in the sample, with patients (A to P) along the y axis, and proportions (%) of nights illustrated using coloured bars on the horizontal axis (clusters: blue - 0, orange - 1, green - 2, red - 3), labelled with their proportion.

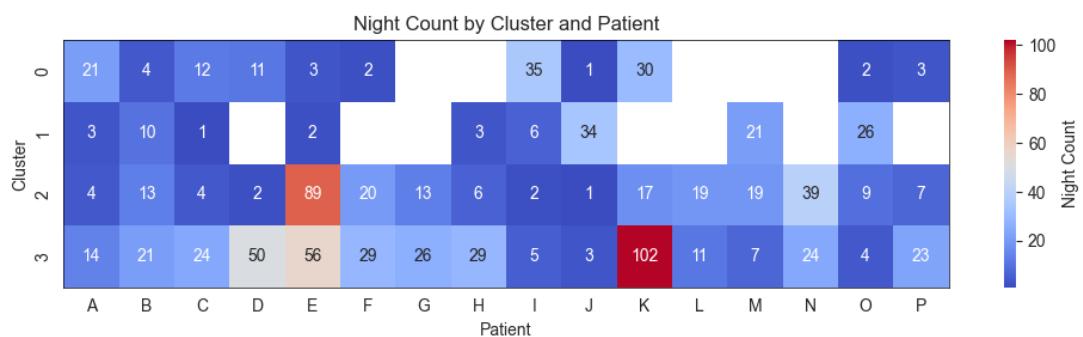


Figure C.3: Intersection of night counts by patient and cluster with the patient (A to P) and cluster (0 to 3), with the count of nights provided as values and magnitude of the values by colour.

Appendix D

Cross-Correlation Coefficient Results

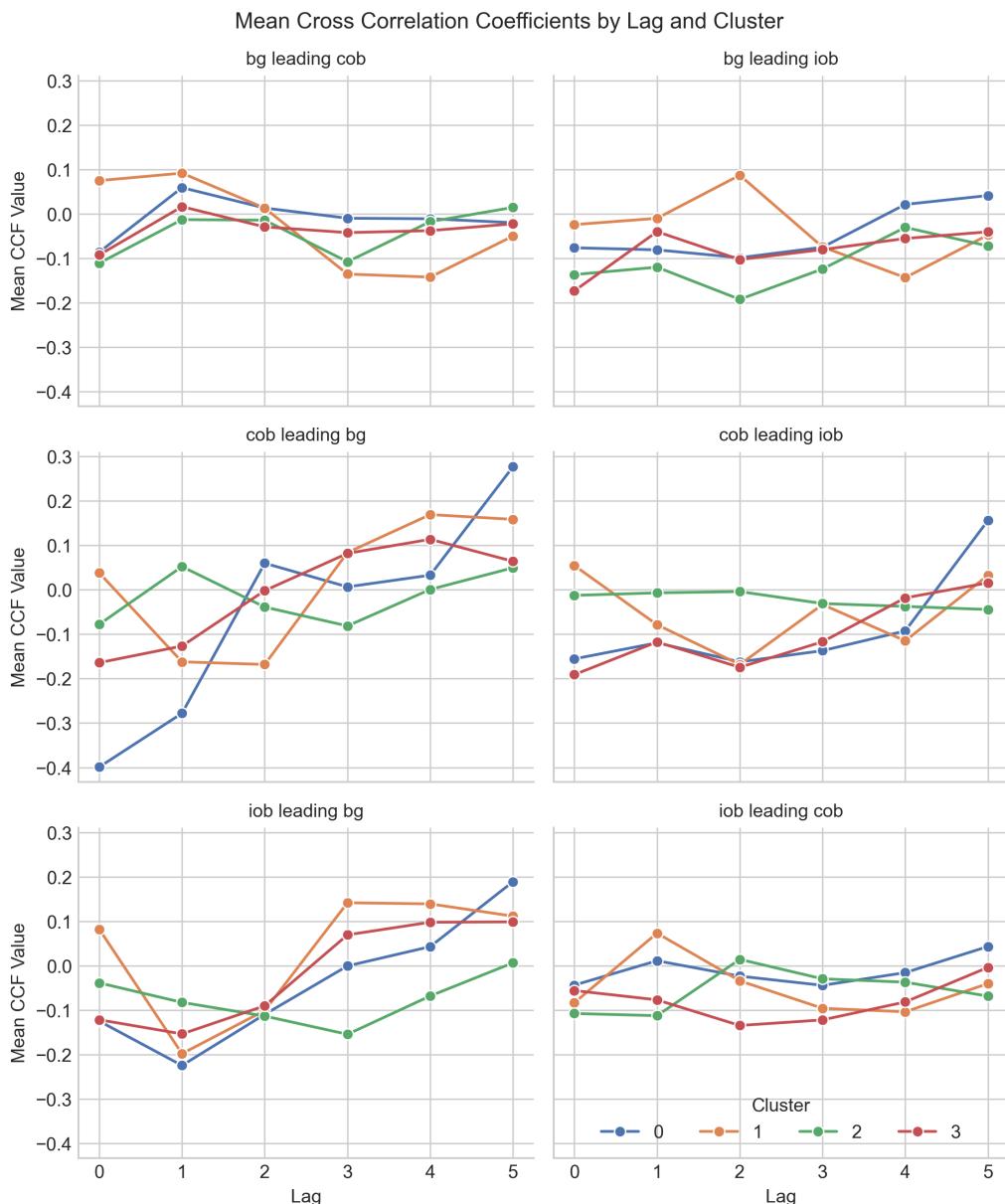


Figure D.1: Each subplot shows the means of correlation coefficients for pairwise comparisons of variables, where one variable leads another by a number of interval lags, up to 5. Line colours represent the means of the coefficients for each cluster.

Table D.1: Mean cross correlation coefficients by cluster

Cluster	Leading Variable	Lagging Variable	0	1	2	3	4	5
0	bg	cob	-0.09	0.06	0.01	-0.01	-0.01	-0.02
		iob	-0.08	-0.08	-0.10	-0.08	0.02	0.04
	cob	bg	-0.40	-0.28	0.06	0.01	0.03	0.28
		iob	-0.16	-0.12	-0.16	-0.14	-0.09	0.16
	iob	bg	-0.12	-0.22	-0.11	-0.00	0.04	0.19
		cob	-0.04	0.01	-0.02	-0.04	-0.02	0.04
1	bg	cob	0.07	0.09	0.01	-0.14	-0.14	-0.05
		iob	-0.02	-0.01	0.09	-0.07	-0.14	-0.05
	cob	bg	0.04	-0.16	-0.17	0.08	0.17	0.16
		iob	0.05	-0.08	-0.17	-0.03	-0.11	0.03
	iob	bg	0.08	-0.20	-0.10	0.14	0.14	0.11
		cob	-0.08	0.07	-0.03	-0.10	-0.10	-0.04
2	bg	cob	-0.11	-0.01	-0.01	-0.11	-0.02	0.01
		iob	-0.14	-0.12	-0.19	-0.12	-0.03	-0.07
	cob	bg	-0.08	0.05	-0.04	-0.08	0.00	0.05
		iob	-0.01	-0.01	-0.00	-0.03	-0.04	-0.04
	iob	bg	-0.04	-0.08	-0.11	-0.15	-0.07	0.01
		cob	-0.11	-0.11	0.01	-0.03	-0.04	-0.07
3	bg	cob	-0.09	0.02	-0.03	-0.04	-0.04	-0.02
		iob	-0.17	-0.04	-0.10	-0.08	-0.06	-0.04
	cob	bg	-0.16	-0.13	-0.00	0.08	0.11	0.06
		iob	-0.19	-0.12	-0.17	-0.12	-0.02	0.02
	iob	bg	-0.12	-0.15	-0.09	0.07	0.10	0.10
		cob	-0.06	-0.08	-0.13	-0.12	-0.08	-0.00

Table D.2: Standard deviation of means for cross correlation coefficients by cluster

Cluster	Leading Variable	Lagging Variable	0	1	2	3	4	5
0	bg	cob	0.94	0.76	0.74	0.56	0.64	0.58
		iob	0.96	0.78	0.80	0.62	0.65	0.69
	cob	bg	1.67	1.24	1.17	1.02	0.97	0.81
		iob	1.06	0.84	0.69	0.97	0.71	0.88
	iob	bg	1.41	0.99	1.01	0.86	0.93	0.72
		cob	0.84	0.58	0.66	0.72	0.60	0.71
1	bg	cob	1.33	0.72	0.77	0.74	0.67	0.50
		iob	0.88	0.73	0.64	0.68	0.65	0.49
	cob	bg	0.85	0.82	1.01	0.85	0.73	0.56
		iob	0.93	1.03	0.74	0.74	0.62	0.79
	iob	bg	1.10	0.73	0.93	0.77	0.62	0.53
		cob	1.88	1.56	0.71	0.78	0.72	0.61
2	bg	cob	1.72	1.19	0.80	0.76	0.63	0.71
		iob	1.57	1.14	0.83	0.78	0.62	0.61
	cob	bg	1.58	1.02	0.90	0.68	0.59	0.66
		iob	1.38	0.88	0.82	0.69	0.70	0.58
	iob	bg	1.57	1.03	0.81	0.67	0.59	0.63
		cob	1.58	1.05	0.73	0.76	0.66	0.60
3	bg	cob	1.18	0.81	0.59	0.48	0.38	0.42
		iob	1.41	0.98	0.66	0.55	0.51	0.50
	cob	bg	1.95	1.23	1.09	0.94	0.84	0.79
		iob	1.69	1.13	0.83	0.70	0.76	0.70
	iob	bg	1.70	1.11	1.00	0.90	0.76	0.75
		cob	1.29	0.77	0.55	0.53	0.49	0.54

Appendix E

Finding Relationships by Machine Learning Modelling

This section elaborates on results of experimentation to identify if machine learning regression methods (from scikit-learn) can help to identify relationships between COB/IOB and BG in any different way to the previous methods used. Finding relationships between lagged values of COB/IOB and the ability to predict BG from this would support other findings in the study, and the strength of such relationships. Reinforcing such patterns would define a relationship between COB and BG for lagged intervals and ultimately help establish that BG levels are driven in part by preceding COB/IOB.

The following models were used in the study from the scikit-learn Python library.

- Linear Regression (OLS - `LinearRegressor`)
- Support Vector Regression (SVR - `SVR`)
- Decision Tree Regression (DTR - `DecisionTreeRegressor`)
- Random Forest Regression (RGR - `RandomForestRegressor`)

The methodology used was to fit a model for each night with the leading variable as inputs X in order to predict BG (Y). The chosen metrics for comparison were R^2 and Mean Squared Error (MSE). R^2 is a measure of how well the model fits the data, with values closer to 1 indicating a better fit. MSE is the average squared difference between the predicted and actual values, with lower values indicating better performance. 5-fold cross-validation (CV) was used to aggregate metrics for each night and evaluate the results of different models, without partitioning. The models were tuned using a 5-fold CV randomised search on different parameters on a zero-lag dataset to arrive at those providing the best performance: **SVR** {kernel: rbf, gamma: 1.0, epsilon: 0.5, C: 1000}, **DTR** {min_samples_split: 2, min_samples_leaf: 1, max_features: sqrt, max_depth: 5}, **RFR** {n_estimators: 300, min_samples_split: 10, min_samples_leaf: 1, max_features: log2, max_depth: 5}. The predictive power of the models was not expected to be high given the small number of values used to train the models, rather that there may be some interesting patterns that provide an opportunity for further investigation.

As the results in Table E.1 and E.2 show as expected, the aggregate results show models did not perform well. This suggests that the relationship between COB/BG and IOB/BG is not well captured by these models. The negative values of R^2 indicate that the models do not fit the data well and that they cannot explain the variance in the data. This will be due to the methodology used and the need for more data to produce predictive results. However, as a comparative analysis, there are two salient points relevant to the results in the analysis of correlation. The first is that, unsurprisingly, the results for IOB are better than those for COB, aligning with the previous analysis with OLS, with R^2 higher and the MSE values lower. This suggests that the relationship between IOB and BG is stronger than that between COB and BG, which aligns with other findings. This suggests the relationship between IOB and BG is stronger than that between COB and BG, and that linear regression models can capture this relationship as effectively as nonlinear regression models. The second is that we do see some lagged effect of COB leading BG as we have in other analysis, yet the results are too subtle to be conclusive.

Table E.1: COB Leading BG prediction performance averaged by night, showing MSE and R^2 scores

Model	Lag Cluster	MSE						R^2					
		0	1	2	3	4	5	0	1	2	3	4	5
DTR	0	0.24	0.24	0.24	0.23	0.21	0.20	-1.61	-1.35	-1.70	-1.81	-2.27	-1.75
	1	0.26	0.28	0.30	0.30	0.27	0.26	-0.74	-0.90	-1.41	-1.31	-0.95	-1.07
	2	0.27	0.26	0.25	0.25	0.23	0.22	-0.85	-0.91	-1.01	-1.22	-0.91	-0.91
	3	0.22	0.23	0.22	0.21	0.21	0.20	-1.11	-1.25	-1.31	-1.42	-1.37	-1.44
OLS	0	0.19	0.18	0.17	0.18	0.18	0.16	-0.65	-0.46	-0.59	-0.79	-0.85	-0.89
	1	0.30	0.28	0.26	0.26	0.25	0.25	-1.84	-0.55	-0.65	-0.91	-0.76	-0.77
	2	0.25	0.25	0.23	0.31	0.30	0.21	-0.63	-0.85	-0.71	-1.95	-3.60	-0.66
	3	0.20	0.19	0.19	0.18	0.18	0.17	-0.82	-0.63	-0.65	-0.76	-0.84	-0.96
RFR	0	0.18	0.18	0.18	0.18	0.17	0.16	-0.58	-0.57	-0.72	-0.83	-0.91	-0.79
	1	0.23	0.24	0.25	0.25	0.24	0.23	-0.37	-0.44	-0.73	-0.79	-0.57	-0.67
	2	0.23	0.22	0.22	0.22	0.22	0.21	-0.50	-0.51	-0.60	-0.73	-0.65	-0.63
	3	0.18	0.18	0.18	0.18	0.17	0.17	-0.54	-0.59	-0.66	-0.82	-0.76	-0.78
SVR	0	0.58	0.43	0.65	0.46	0.31	0.37	-3.90	-3.38	-5.69	-4.73	-5.12	-4.92
	1	0.60	0.52	0.48	0.50	0.53	0.46	-2.53	-2.16	-3.00	-3.34	-2.81	-2.96
	2	0.49	0.53	0.42	0.36	0.36	0.36	-2.29	-2.45	-3.00	-2.41	-1.95	-3.75
	3	0.42	0.46	0.36	0.35	0.38	0.34	-3.06	-4.33	-3.26	-3.19	-3.66	-3.83

 Table E.2: IOB Leading BG prediction performance averaged by night, showing MSE and R^2 scores

Model	Lag Cluster	MSE						R^2					
		0	1	2	3	4	5	0	1	2	3	4	5
DTR	0	0.23	0.29	0.29	0.29	0.29	0.27	-1.61	-2.20	-2.53	-2.96	-3.37	-2.86
	1	0.32	0.45	0.43	0.40	0.43	0.42	-1.34	-2.27	-2.81	-2.56	-2.34	-2.78
	2	0.23	0.38	0.36	0.41	0.39	0.37	-1.04	-2.62	-2.77	-3.55	-3.03	-3.58
	3	0.22	0.30	0.29	0.30	0.28	0.28	-1.58	-2.61	-2.56	-3.32	-2.96	-3.61
OLS	0	0.15	0.18	0.17	0.18	0.17	0.16	-0.31	-0.47	-0.68	-0.72	-0.73	-0.99
	1	0.23	0.27	0.26	0.25	0.25	0.24	-0.36	-0.78	-0.72	-0.80	-0.73	-0.85
	2	0.15	0.22	0.22	0.22	0.21	0.21	-0.10	-0.46	-0.54	-0.67	-0.57	-0.66
	3	0.15	0.17	0.17	0.17	0.17	0.17	-0.39	-0.48	-0.58	-0.72	-0.68	-0.81
RFR	0	0.15	0.18	0.18	0.17	0.18	0.16	-0.38	-0.61	-0.82	-0.97	-1.11	-0.81
	1	0.21	0.27	0.26	0.26	0.26	0.25	-0.24	-0.67	-0.83	-0.78	-0.70	-0.89
	2	0.15	0.24	0.23	0.24	0.23	0.22	-0.12	-0.69	-0.79	-0.99	-0.83	-0.94
	3	0.14	0.19	0.18	0.19	0.18	0.17	-0.36	-0.71	-0.76	-1.02	-0.88	-1.07
SVR	0	0.47	0.41	0.39	0.44	0.41	0.35	-4.91	-2.99	-3.44	-5.34	-10.54	-4.53
	1	0.45	0.70	0.82	0.61	0.68	0.45	-2.44	-3.25	-7.59	-3.33	-3.57	-2.83
	2	0.29	0.38	0.41	0.42	0.38	0.34	-1.57	-2.08	-3.15	-3.05	-2.81	-2.82
	3	0.30	0.32	0.32	0.36	0.35	0.36	-2.21	-2.57	-2.76	-4.59	-4.32	-5.13

Appendix F

Law of Total Variance for Aggregated Data

The Law of Total Variance states that the total variance of a random variable (X) can be broken down into two parts; the expected value of the conditional variance (variance within groups) and the variance of the conditional expected value (variance of the group means). In the context that it is used in Section 3.5, it accounts for both variability within each 30min interval and the variability between the 30min interval means, by calculating the 'overall' variance based on the following:

$$\text{Var}(X) = E[\text{Var}(X|Y)] + \text{Var}(E[X|Y]) \quad (\text{F.1})$$

The variance of the aggregated data is the sum of the expected variance within each group and the variance of the group means. The theoretical formula for the overall standard deviation of the aggregated data is as follows:

Let X be the original high-frequency blood glucose readings.

Let Y represent the 30-minute time interval groups.

Let g_i be the mean blood glucose for the interval i .

Let s_i be the standard deviation of blood glucose for the interval i .

Let s_i^2 be the variance within the interval i (which is s_i squared).

Let n_i be the number of original readings that were aggregated into the interval i .

leading to the formula for variance:

$$\text{Var}_{\text{overall}} = \frac{\sum_{i=1}^K n_i \cdot s_i^2}{\sum_{i=1}^K n_i} + \frac{\sum_{i=1}^K n_i \cdot (g_i - \bar{G})^2}{\sum_{i=1}^K n_i} \quad (\text{F.2})$$

And standard deviation:

$$\sigma_{\text{overall}} = \sqrt{\text{Var}_{\text{overall}}} \quad (\text{F.3})$$

Where:

K is the total number of 30-minute intervals in the night period.

\bar{G} is the overall mean of all blood glucose readings during the night.

Appendix G

Intervals Out of Range

The visualisations in this section support the descriptive findings outlined in Section 4.3.1 and help to understand the distributions and behaviours of excursions from target range levels, predominantly supplementing with equivalent views of the distributions of L2 excursions.

Figure G.1 shows a similar correlation between the number of nights that a patient has in the sample against the number of L2 excursions than those of L1, though with a wider error bar representing the 95% CI. It is possible to see that this could result in quite a different correlation if it were not for the total nights and excursions that patients K and E have, thus highlighting the need for a greater sample of patients. This plot draws attention to the high proportion of L2 excursions to the number of nights for patient B, which could be a possible avenue for further analysis.

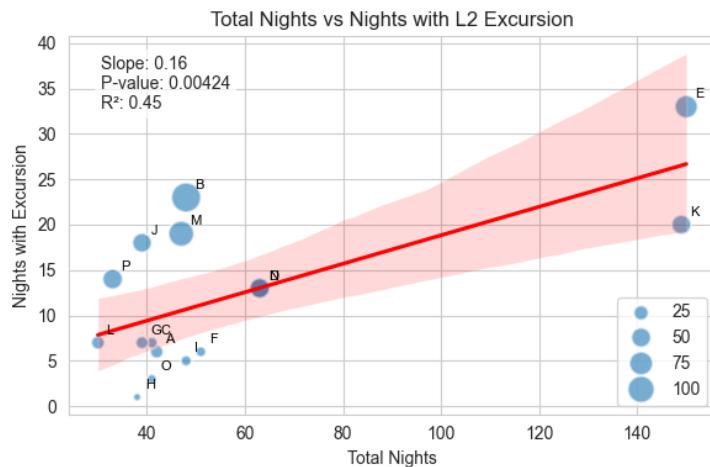


Figure G.1: Relationship between the number of total nights for a patient and the number of nights with excursions recorded. Markers (blue) represent a patient and size denotes the total number of excursions recorded for the patient.

Figure G.2 provides a reflection of the volume of L2 excursions, similar to Figure 4.8 in the analysis. This provided the cue for testing for proportionate difference in the analysis as it was evident that cluster 2 has a disproportionate number of IBR excursions to other clusters. Similarly, cluster 1 appeared to have a disproportionate number of total excursions in general to the number of nights in the cluster.

Figures G.3 and G.4 provide a perspective of the density of the L1 and L2 excursion values for the whole sample. Bimodality is evident in IBR and a very clear distribution of the IAR excursion is evident as COB is absorbed following the evening carb intake and a similar trend exists with L2. However, for L2, the probability of IBR excursions is noticeably greater in the initial part of the evening, reflecting the influence that cluster 2 is having on the density, with its high number of IBR excursions peaking density at around 00:00 (as seen in Figure G.5).

Figures G.6 and G.7 provide a more detailed breakdown of the density of excursions by cluster and overlay the BG profiles. There were no perceivable patterns between the average BG and the density of excursion, which may have been expected.

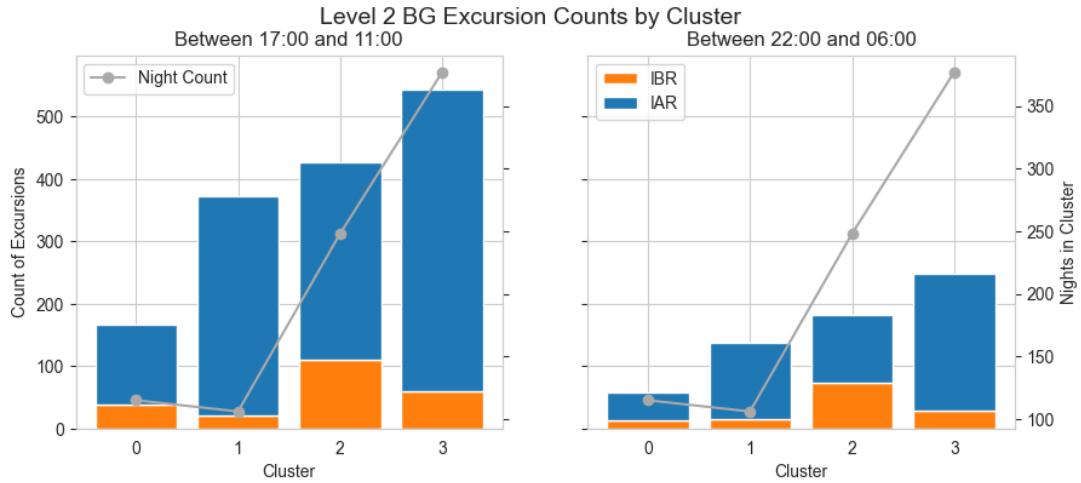


Figure G.2: Occurrence of excursions by cluster in the broad 17:00-11:00 period vs the nocturnal 22:00-06:00, for Intervals Above Range (blue) and Intervals Below Range (orange).

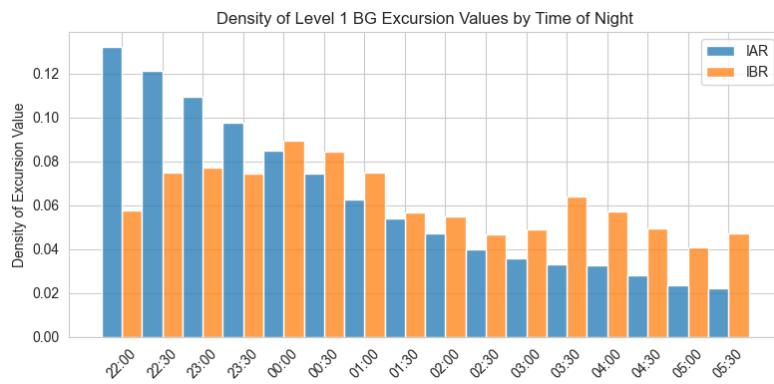


Figure G.3: L1 BG density of excursion amplitudes during the nocturnal period

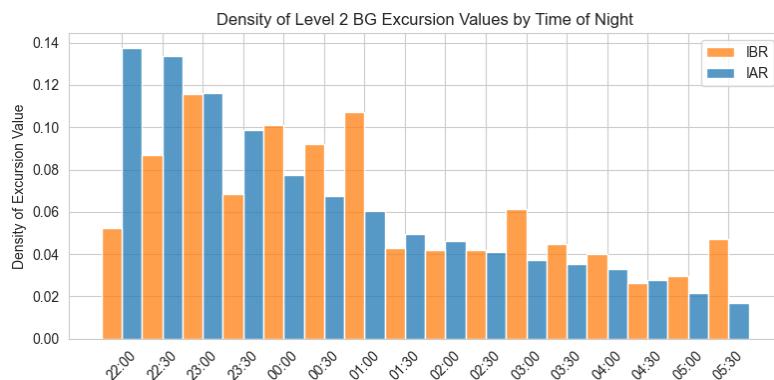


Figure G.4: L2 BG density of excursion amplitudes during the nocturnal period

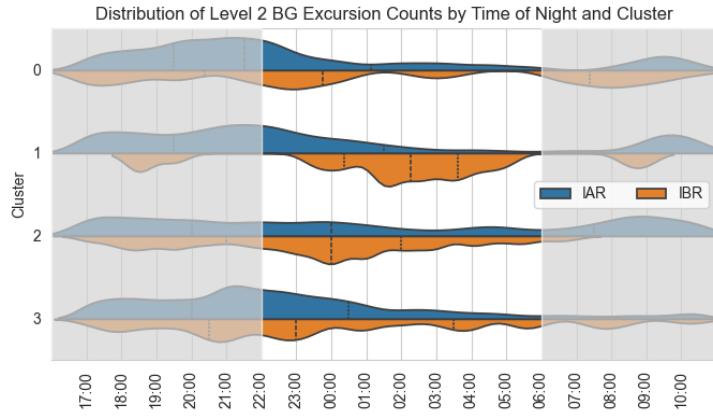


Figure G.5: BG L2 excursions density over observed period, highlighting the nocturnal period. The violin plot uses a low kernel bandwidth to avoid smoothing and tails that extend greatly beyond the observed time range, hence the perceived sensitivity of the distribution to fluctuation

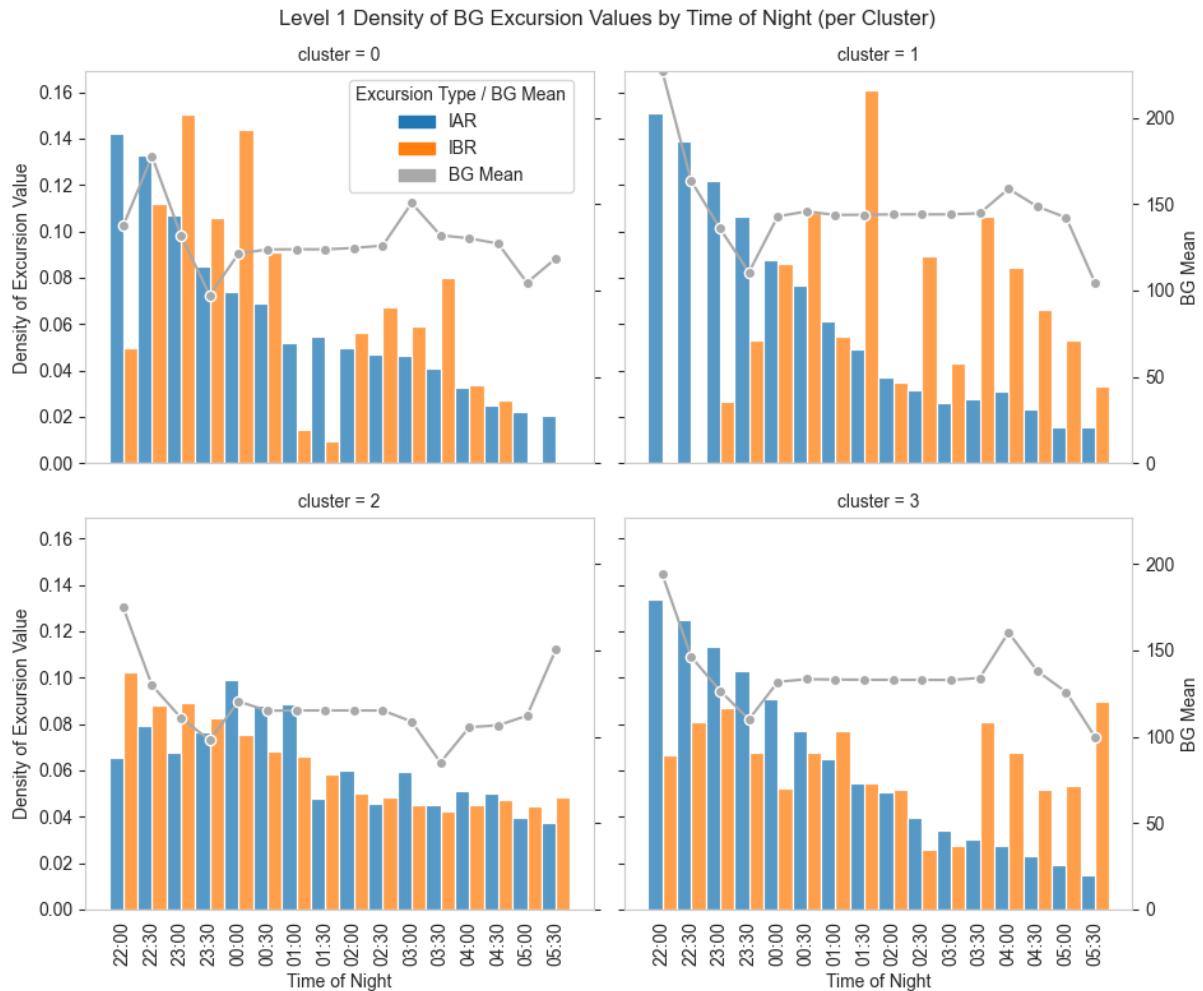


Figure G.6: L1 BG density of excursion amplitudes split by each cluster during the nocturnal period, with BG mean values are each interval overlaid.

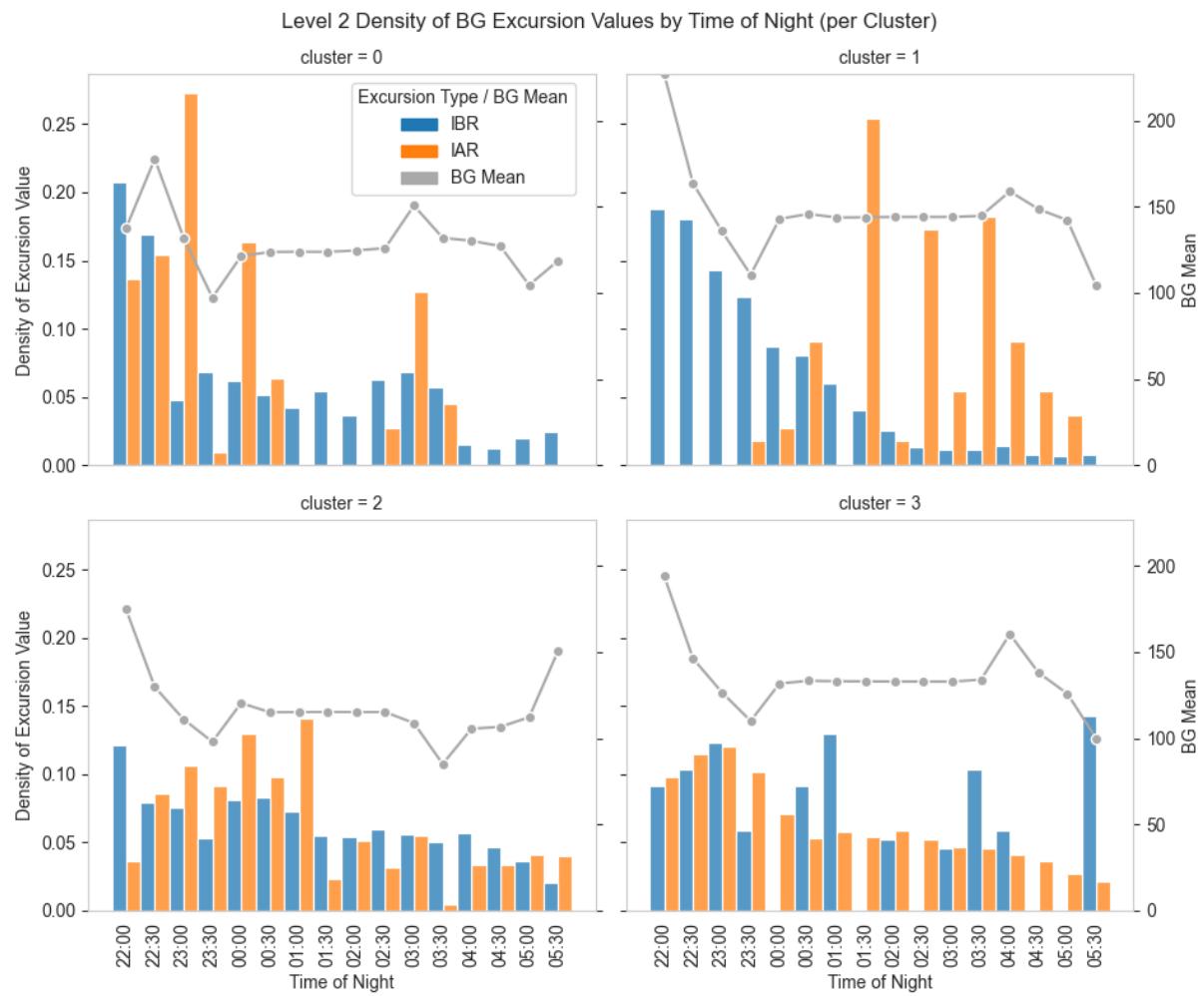


Figure G.7: L2 BG density of excursion amplitudes split by each cluster during the nocturnal period, with BG mean values are each interval overlaid.

Appendix H

Evening IOB and COB Relationship with Nocturnal BG

This section provides a visualisation to support Section 4.4.2 of the weighted mean of COB and IOB in the evening (defined as the period between 17:00-22:30) and the J score for all nights in the sample, and broken down by clusters.

Comment on Evening COB and J Score

Figures H.1 and H.2 give an impression of the relationships between the evening COB average and J . Figure H.2c shows the number of points where the evening COB mean is close to, or equal to, zero. Although characterised as a 'low-carb/low-insulin' cluster, it may infer a persistence of non- or late recording of carbohydrates, which is known to be a risk with carb counting as outlined in Chapter 1. Alternatively, it may simply reflect a low carb diet or the absence of meals where none are consumed. Cluster 0 is characterised as 'high-carb' and this is evident in Figure H.2a. With $P = 0138$ we cannot reject that the relationship occurred by chance, despite an apparent trend in the spread of the points. The only linear relationship of significance is for cluster 1 (Figure H.2b) and demonstrates a positive correlation between the evening COB and J .

Comment on Evening IOB and J Score

The more significant relationship ($P < 0.001$) is evident between the evening IOB and J , and is synonymous with other results in this study, as shown in Figure H.3). The direction of the relationship is also distinct in that the higher the average evening IOB, the higher the J score and thus the higher the inferred overnight instability. Looking at the cluster plots, Figure H.4b shows cluster 1 as the only relationship where we cannot discount that it did not occur by random chance. This may be due to the power of the regression given the small sample size of the cluster, but conversely that such a relationship does not exist. The R and slope coefficients are all quite similar for clusters 0, 2 and 3, inferring the relationships to be similar in all three clusters between evening IOB and J .

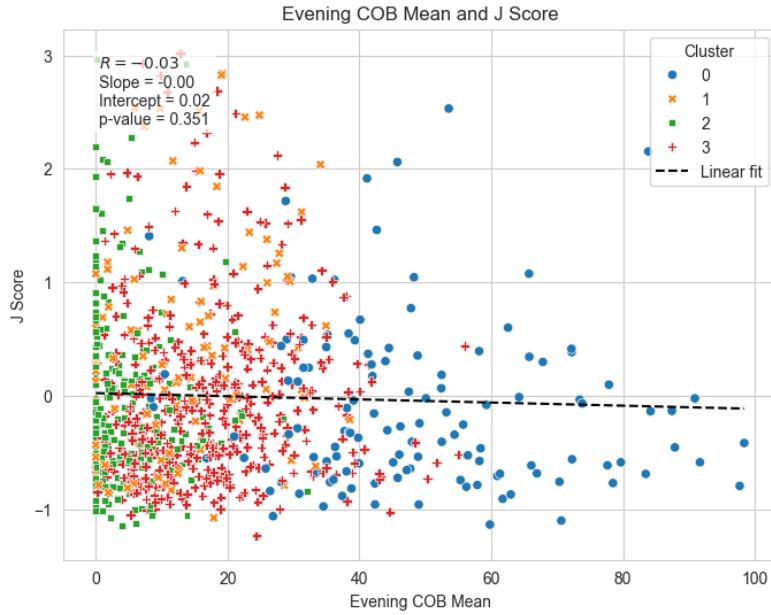


Figure H.1: Evening COB weighted mean against nocturnal J score for all nights in sample, with markers separated by colour and shape. Results of an overall linear regression is plotted with coefficients and p-value stated,

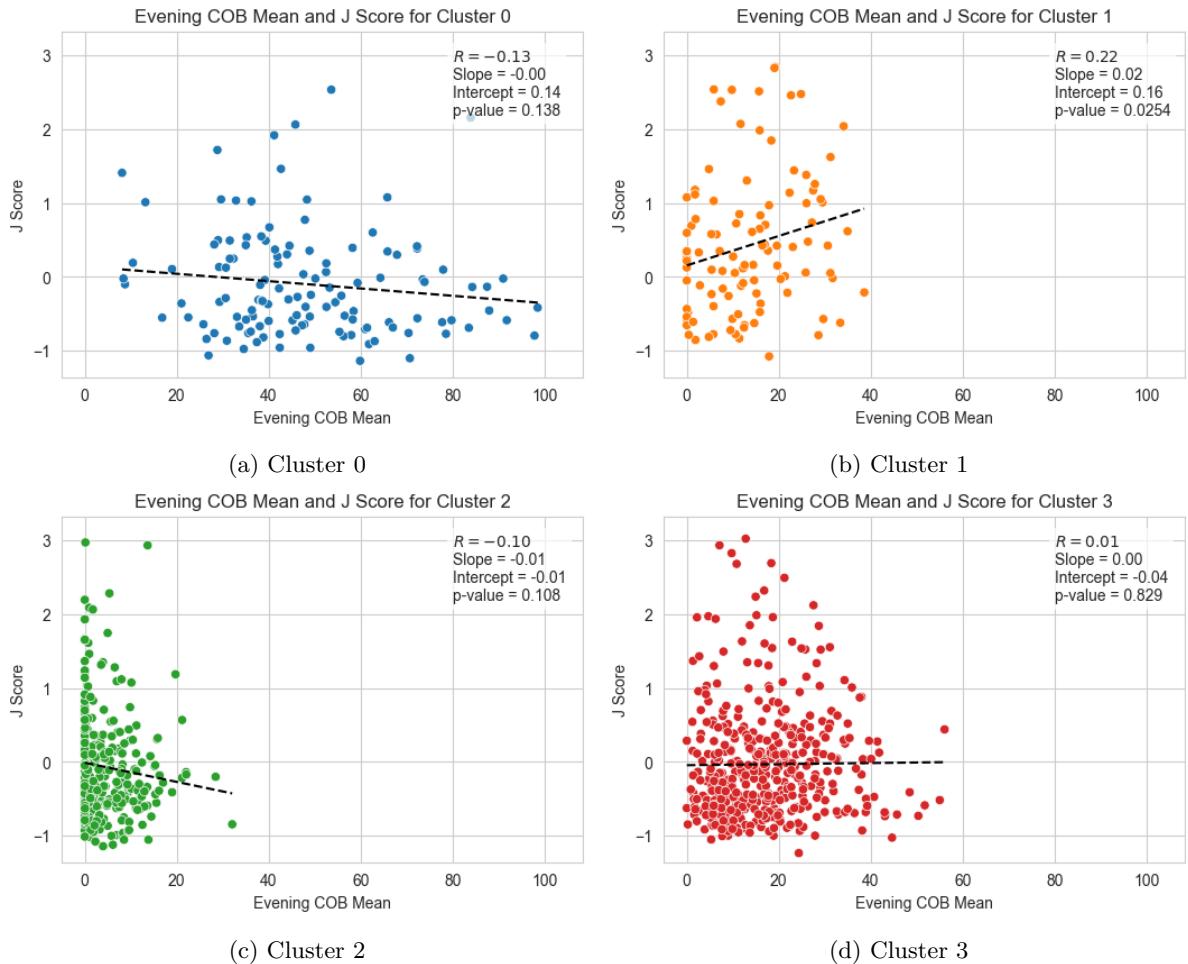


Figure H.2: Evening COB weighted means against nocturnal J score by cluster, highlighting the relationships they have through OLS linear regression.

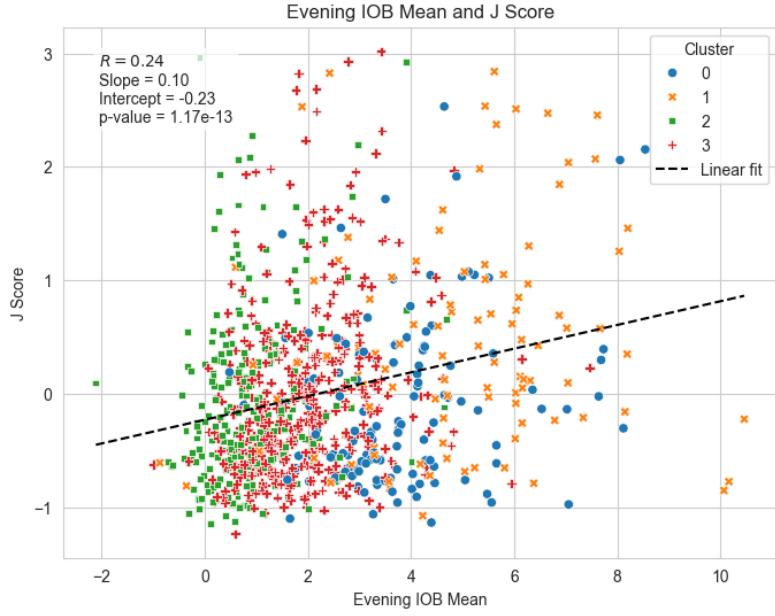


Figure H.3: Evening IOB weighted mean against nocturnal J score for all nights in sample, with markers separated by colour and shape. Results of an overall linear regression is plotted with coefficients and p-value stated,

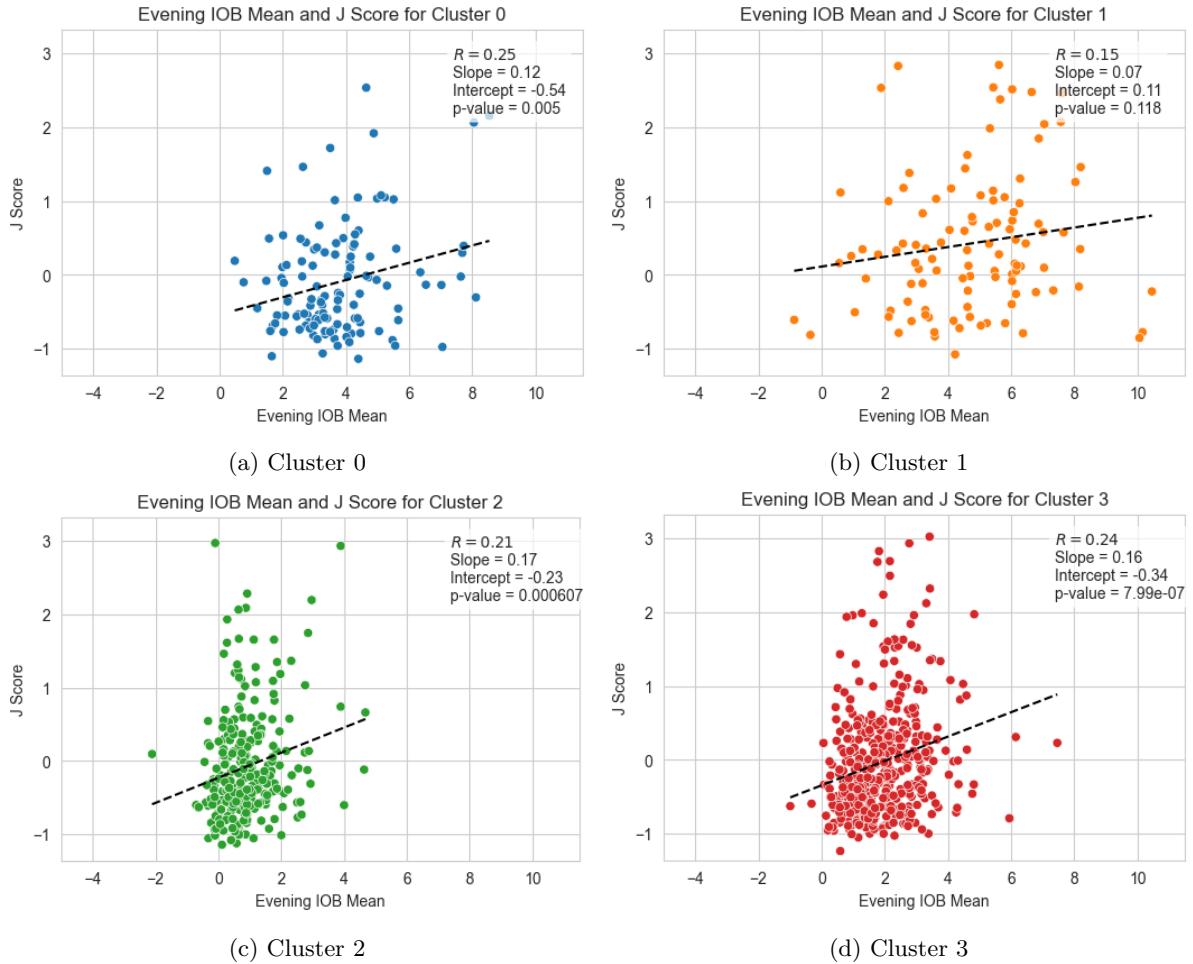


Figure H.4: Evening IOB weighted means against nocturnal J score by cluster, highlighting the relationships they have through OLS linear regression.