Nonparametric Time Series Summary Statistics for High-Frequency Actigraphy Data from Individuals with Advanced Dementia

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Abstract

Actigraphy data has been widely used to measure activity and the circadian rhythm of individuals across the health sciences, in particular with people with advanced dementia. Modern actigraph devices can record continuous observations on a single individual for several months at a sampling frequency of the order of one hertz. Such rich and lengthy data sets provide new opportunities for statistical insight, but also pose challenges in selecting from a wide range of possible summary statistics, and how the calculation of such statistics should be optimally tuned and implemented. In this paper, we build on existing approaches, as well as propose new summary statistics, and detail how these should be implemented with high frequency actigraphy data. We test and validate our methods on an observed data set from 40 participants: 26 of which are from individuals with advanced dementia, and 14 of which are individuals without dementia. We study four metrics: Interdaily stability (IS), intradaily variability (IV), Hurst parameter estimation via detrended fluctuation analysis (DFA), and a novel nonparametric estimator which we call the proportion of variance (PoV), which calculates the strength of the circadian rhythm using spectral density estimation. We perform a detailed analysis indicating how the time series should be optimally subsampled to calculate IV, and recommend a subsampling rate of approximately 5 minutes. In addition, we propose the use of Hurst parameter estimation separately for daytime and nighttime, to further separate effects between individuals. We compare the relationships between all these methods and show that they effectively capture different features of the time series.

Keywords: Circadian rhythm; Variability; Hurst exponent; Periodogram.

1 Introduction

Actigraphy is a method for monitoring physical activity over time. An actigraph device is worn (generally on the wrist) for a continuous period of time with minor impact on daily life; the device contains an accelerometer which measures acceleration of the individual, and sometimes a light and temperature sensor is also included. The device is designed to be lightweight, waterproof, and user-friendly. Actigraphy data has been widely used to study the pattern of 24-hour rest-activity rhythm, also known as circadian rhythm, of humans for almost half a century (Ancoli-Israel et al., 2003). Of primary interest here is the increased use of actigraphs with people with advanced dementia at the end of life (Kok et al., 2017; Khan et al., 2018). However,
data analysis of activity data from this population where circadian rhythms are significantly dysregulated is challenging, putting into question the validity of conclusions extracted from these analyses.

Several measures have been proposed to quantify the circadian rhythm that can be broadly classified into two groups: parametric and nonparametric measures. Cosinor is a traditional parametric method for calculating the amplitude and phase of the circadian rhythm (Halberg et al., 1967). This procedure fits actigraphy data by a regression model of continuous cosine functions with a rhythm-adjusted mean, where the period is assumed to be known (Cornelissen, 2014). The coefficient of determination ($R^2$) can be used to assess the proportion of variance explained by the model (Fossion et al., 2017). The inverse-logistic or expit model, is another parametric approach that uses the summation of multiparameter-extended cosine functions and residuals which follow a mean-zero weakly stationary stochastic process (Krafty et al., 2019). This approach takes into account that the circadian rhythm is generally not an exact sinusoidal pattern within a fixed time interval. These established methods can be very useful for characterising circadian rhythms, however they are model-based and suffer the usual disadvantages of parametric methods: namely the bias and lack of robustness that results when model assumptions are not met by the application data source of interest.

Nonparametric measures are model-free and require little to no user expertise to implement. Two such important and widely-used measures are interdaily stability (IS) and intradaily variability (IV). These were first proposed by Witting et al. (1990) to study how the circadian rhythm changes for patients with aging and Alzheimer’s disease. IS measures the strength of the circadian rhythm, while IV measures the fragmentation of the data by measuring the variation of hour-to-hour data relative to sample variance. In Witting et al. (1990) and other such early studies, both IS and IV were calculated from data with an hourly sampling interval due to the limitations of sensor processing in the actigraph device. However, storage capacity has now been increased and actigraphy data can be recorded with much higher temporal sampling intervals (Gonçalves et al., 2014). This is important as IV values change significantly as a function of the temporal sampling rate, although we note that the rate only has a very small effect on IS in general. In this paper we study the effect of temporal sampling on IV in detail, and propose an optimal rate, together with a simple method that ensures no data is thrown away in calculating the statistic.

IS and IV have been used as summary statistics for actigraphy data of patients suffering from Alzheimer’s disease or related dementia in several studies. A number of studies have reported that patients with dementia have significantly lower IS than those without dementia (Witting et al., 1990; Harper et al., 2001; Satlin et al., 1995; Hatfield et al., 2004), and this can be associated with cerebral microbleeds (Zaurbier et al., 2015), occipital periventricular and frontal deep white matter hyperintensities (Oosterman et al., 2008), and loss of medial temporal lobe volume (van Someren et al., 2019). On the other hand, these patients have significantly higher IV (Witting et al., 1990; Harper et al., 2001; Hatfield et al., 2004; Hooghiemstra et al., 2015) which was positively correlated with the ratio of phosphorylated tau$_{81}$ (pTau) to cerebrospinal fluid amyloid $\beta$ 42 (A$\beta$ 42) for the biomarker collection assessing preclinical Alzheimer disease (Musiek et al., 2018), and medial lobe atrophy (van Someren et al., 2019). More broadly, dementia can affect the disruption of circadian rhythm which is linked with dementia biomarkers (Smagula et al., 2019).

Another nonparametric method is detrended fluctuation analysis (DFA), which was introduced to study fractal scaling behaviours and determine long-range autocorrelation in nonstationary time series (Peng et al., 1993). With DFA, the Hurst exponent $H$ (proposed by Hurst (1951)) is estimated to quantify such characteristics. Generally, the value of this parameter is between zero and one, and this can be divided into three cases: (1) $0.5 < H < 1$ for persistent time series whose increments have positive long-term autocorrelation, (2) $0 < H < 0.5$ for anti-persistent time series whose increments have negative long-term autocorrelation, and (3) $H = 0.5$ for a Brownian process with uncorrelated “white noise” increments. However, to apply the DFA method to both stationary and nonstationary time series, some research studies have defined $H$ to be
between zero and two (Ihlen, 2012). The conventional Hurst value for nonstationary time series (such as a random walk) increases by one, i.e. \(1 < H < 2\), while the Hurst value for stationary time series (such as correlated noise) is less than one, i.e. \(0 < H < 1\). Pink noise or 1/f noise refers to time series with Hurst value of 1.

The DFA method has been commonly applied to time series with monofractal structure which is defined by a single Hurst exponent. However, there might be some temporal fluctuations (multifractal structure) in the time series and this requires a group of generalized Hurst exponents to explain them. Such fluctuations can be analysed by a method called multifractal detrended fluctuation analysis (MFDFA) (Kantelhardt et al., 2002).

For its part, both DFA (or monofractal DFA) and MFDFA have been widely used to estimate the Hurst exponent(s) in many research fields. Indeed, a few research studies collected actigraphy data from patients with dementia and analysed their fractal scaling behaviours using DFA (Hu et al., 2013, 2016; Huber et al., 2019). Some of their findings were that the degree of disrupted fractal regulation was strongly negatively correlated with two important circadian neurotransmitters of the suprachiasmatic nucleus (Hu et al., 2013), and the timed bright light therapy reduced the rate of decay of the Hurst exponent over time (Hu et al., 2016). In this paper we will further explore the use of monofractal DFA on actigraphy data, including a novel comparison of comparing Hurst exponents during daytime and nighttime respectively.

Finally, spectral analysis can be used to decompose variability in actigraphy data across different frequencies of oscillation. The simplest nonparametric estimator is the periodogram (Percival & Walden, 1993). Some studies have preferred a modified version named the chi-squared periodogram (Sokolove & Bushell, 1978) to characterise circadian rhythms (Gnidovec et al., 2002; Emens et al., 2010; Zuculo et al., 2017). For people who do not suffer from dementia or sleep disorders, both methods usually provide that the highest point in the spectrum generally occurs around the frequency of \(1/24\) hour\(^{-1}\) (known as the fundamental frequency), and further peaks occur at harmonic frequencies, which are positive integer multiples of the fundamental frequency. Harmonic peaks occur as the circadian rhythm is not perfectly sinusoidal. For individuals with disrupted sleep cycles, the spectrum will have relatively low energy at the fundamental and harmonic frequencies, and relatively high and noisy levels at other frequencies. In this paper, we propose a novel nonparametric estimator from the periodogram which calculates the ratio of variability at fundamental and harmonic frequencies versus the whole spectrum. We call this method proportion of variance (PoV), and we will analyse this to our dataset and compare with other methods in order to assess the efficacy of spectral analysis methods for actigraphy data.

The main objective of this paper is to provide detailed methodology for calculating four different non-parametric time series summary statistics—IS, IV, Hurst exponent, and PoV—to high frequency actigraphy data. The relationship among all statistical measures will be illustrated and analysed on a mixed dataset involving participants suffering from advanced dementia and participants who do not.

2 Materials and Methods

The studied dataset contains data from two groups of participants: a group of 26 individuals suffering from advanced dementia and a group of 14 individuals who do not have dementia. The 26 individuals with advanced dementia took part in a group intervention to improve quality of life when living in care homes (Froggatt et al., 2020). Fifteen of them received a non-invasive treatment during the period of data collection, while the remaining 11 participants were allocated to a control group receiving treatment as usual (see protocol details in Froggatt et al., 2018). Participants were recruited from eight nursing homes between the end of 2017 and May 2018. The study end date was 30/11/2018. To evaluate the feasibility objectives of the main study, eight nursing homes (six intervention and two control) with eight residents per home was
considered reasonable in terms of sample size. Being a permanent resident in a nursing care home, lack of mental capacity, and a FAST score of 6-7 reflecting advanced dementia status were part of the inclusion criteria (see full details in [Froggatt et al., 2018]). The original trial was approved by the Wales Research Ethics Committee 5 Bangor Research Ethics Committee (reference number 17/WA/0378) on 22 November 2017. Potential participants were screened by the principal investigator and the senior care team, and eligible participant’s written consent was provided by a personal consultee. For those without a personal consultee, the consent was requested to a nominated consultee following care home procedures. Following this, researchers discussed the study with consultees and gained assent from residents to take part in the study. The 14 participants without dementia were all members of the research team and colleagues that provided actigraphy data as part of piloting the use of actigraphs for the main study.

Although the treatment is not expected to have had a significant effect on actigraphy readings of those with dementia (Froggatt et al., 2020), we nonetheless study the differences between control and treatment groups as a useful indicator of the performance and stability of our time series metrics. In other words, we only expect small-to-mild differences between control and treatment groups, and we should not see large differences in our summary statistics which would likely be spurious, whereas we do expect large differences between participants with and without advanced dementia.

For each participant across the study, the actigraphy data was recorded by a wrist-worn accelerometer called GENEActiv for a maximum of 28 days. This device measures acceleration in the unit of gravitational force (g-force). The sampling period was set to five seconds. Raw data output from each sampling time consists of three non-negative values representing the magnitudes of projected vectors of acceleration on three axes in Euclidean space. The Euclidean norm was calculated from these magnitudes. Because the accelerometer is affected by the gravitation of Earth, this effect is removed. Thus, we calculate what is known as the Euclidean norm minus one (ENMO) (Van Hees et al., 2013), which results in the time series used for implementing our nonparametric time series methods in this paper. Before applying the statistical methods, date ranges including missing data were excluded. We apply four different nonparametric time series methods (implemented by RStudio software version 1.0.136) to the ENMO data which we now describe. R Software for implementing each method, on any actigraph time series, is publicly available at www.github.com/suibkitwanchai-k/Actigraphy_Project.

### 2.1 Interdaily stability (IS)

The first statistical method is interdaily stability (IS), which is a nonparametric measure for the strength of the circadian rhythm in actigraphy data. The circadian rhythm is driven by a circadian clock with approximately 24-hour time period. For each individual, we define \( \{X_t\} \) as a time series of ENMO data with length \( N \). The interdaily stability is the ratio of the average square-error of hourly means from the overall mean to the variance of \( \{X_t\} \), i.e.

\[
IS = \frac{\frac{1}{24} \sum_{s=1}^{24} (X_s - \bar{X})^2/24}{\frac{1}{N} \sum_{t=1}^{N} (X_t - \bar{X})^2/N},
\]

where \( \bar{X}_s \) is the sample mean of ENMO data during the \( s \)-th hour of the day (\( s = 1, 2, ..., 24 \)) and \( \bar{X} \) is the overall sample mean. This equation calculates IS by aggregating data on an hourly basis in the numerator into 24 bins. The original motivation for this is that the time series itself is sampled on an hourly interval (Witting et al., 1990) such that more bins are not possible. However for high frequency data, such as the 5-second data in our study, the hourly aggregation becomes an arbitrary choice, and IS could instead be calculated by
aggregating over shorter time intervals and into several more bins. According to Gonçalves et al. (2014), however, the interdaily stability is insensitive to this choice, and we found the same in our study. Therefore we keep to the choice of hourly binning in (1). In contrast, the value of intradaily variability (IV) depends strongly on the sampling period as we now discuss.

2.2 Intradaily variability (IV)

Intradaily variability (IV) is used to estimate circadian fragmentation in the data. In our implementation, we ensure all data in the high frequency time series is used, even if subsampling is applied. Specifically, we let

\[
\{Y_{k}^{[j]}\} = \{X_{(k-1)\Delta+j}, k=1,2,\ldots,[N/\Delta]\} \quad (2)
\]

be a finite sequence obtained from subsampling the time series of ENMO data \(\{X_{t}\}\) with length \(N\) by an arbitrary positive integer \(\Delta\) not greater than \(N\), and \(j\) is the index of the \(j^{th}\) time series data derived from this subsampling \((1 \leq j \leq \Delta)\). For each \(\{Y_{k}^{[j]}\}\), the intradaily variability is calculated by the ratio of variation in consecutive time intervals to the total variance, i.e.

\[
IV[j] = \frac{\sum_{k=2}^{M} (Y_{k}^{[j]} - Y_{k-1}^{[j]})^2 / (M - 1)}{\sum_{k=1}^{M} (Y_{k}^{[j]} - \overline{Y^{[j]}})^2 / M}, \quad (3)
\]

where \(M = [N/\Delta]\) is the length of \(\{Y_{k}^{[j]}\}\) and \(\overline{Y^{[j]}}\) is its overall mean. The final IV value is then the average of all IV values obtained from (3), i.e.

\[
IV = \frac{\sum_{j=1}^{\Delta} IV[j]}{\Delta}. \quad (4)
\]

This implementation, which averages across different start points of the time series, ensures all data is used regardless of the choice of \(\Delta\). Note that this procedure was also proposed in Zhang et al. (2005) for calculating integrated volatility in financial time series, which is a very similar metric to IV.

In Witting et al. (1990), the subsampling period is set to 60 minutes. However, for higher frequency time series it can be adjusted to any other appropriate time (Fossion et al., 2017; Gonçalves et al., 2014). In the next section we shall investigate in more detail the relationship between IV and the choice of \(\Delta\). We shall show that there is a natural trade-off to be balanced in that overly low values for \(\Delta\) lead to noise contamination from high-frequency jitter, whereas large values for \(\Delta\) fail to capture the differences in fragmentation for individuals with and without advanced dementia. Another consideration we make is the correlation between IV and other statistical measures and whether this metric responds as it should in response to other summary statistics.

2.3 Hurst exponent

The Hurst exponent is a parameter which measures the degree of long-range dependence of a time series, which is the rate of decay of its long-lag autocorrelation. Detrended fluctuation analysis (DFA) was proposed to estimate this parameter in Peng et al. (1994). The range of Hurst exponent \(H\) was defined to be between zero and two. Noise-like time series have Hurst exponent between zero and one \((0 < H < 1)\), while...
random walk-like time series have Hurst exponent between one and two \((1 < H < 2)\). A higher Hurst exponent indicates that the time series data is more persistent and has higher degree of positive long-term autocorrelation. Here we summarise Hurst parameter estimation using DFA in the following steps (see also Ihlen (2012)):

1. For a time series of ENMO data \(\{X_t\}\) with length \(N\), we construct a new time series \(\{Z_t\}\) which is the cumulative sum of \(\{X_t\}\) with mean centering, i.e.

\[
Z_t = \sum_{u=1}^{t} (X_u - \bar{X}),
\]

where \(1 \leq t \leq N\).

2. We divide \(\{Z_t\}\) into equally-sized non-overlapping segments with length \(S\) (scale parameter). \(S\) is equal to \(2^i\), where \(i\) is varied from 4 to 8 in increments of 0.25. The least squares regression line is fitted to the time series data in each segment. The local root-mean-square deviation at segment number \(K\) with length \(S\) is calculated as

\[
\text{RMSD}_{S,K} = \sqrt{\frac{\sum_{j=\lfloor S(K-1)+1 \rfloor}^{\lfloor SK \rfloor} (\hat{Z}_j - Z_j)^2}{S}},
\]

where \(\hat{Z}_j\) is the predicted value from the regression line and \(1 \leq K \leq \lfloor N/S \rfloor\).

3. For each \(S\), the overall root-mean-square deviation \((F)\) is calculated as

\[
F(S) = \sqrt{\frac{\sum_{i=1}^{\lfloor N/S \rfloor} \text{RMSD}_{S,i}^2}{\lfloor N/S \rfloor}}.
\]

4. The Hurst exponent is estimated by the slope of linear regression line of data points on the plot between \(\log_2(S)\) (x-axis) and \(\log_2(F)\) (y-axis).

5. This method does not work well if the estimated Hurst exponent is greater than 1.2. In such cases, the data has to be differenced before applying steps 1–4 (i.e. create a new time series \(\{U_t\}\) of length \(N - 1\), where \(U_t = X_{t+1} - X_t\) for \(1 \leq t \leq N - 1\), and use \(\{U_t\}\) instead of \(\{X_t\}\) in Step 1). The Hurst exponent is then re-estimated by the slope of the linear regression line plus one.

In our analysis, Hurst exponents from all participants are estimated using the DFA method. We also calculate these parameters separately for daytime (from 6 a.m. until 9 p.m.) and nighttime (from 9 p.m. until 6 a.m.) readings. This is done to examine whether there is a difference between daytime and nighttime readings for any given participant, and to see whether this difference is more pronounced in any of the participant groups, thus providing more statistical insight from this type of analysis.

### 2.4 Proportion of variance (PoV)

The power spectral density (PSD) or power spectrum describes the distribution of variability in a time series as a function of frequency. The PSD can be defined as the Fourier transform pair of the autocovariance
The periodogram is an asymptotically unbiased estimate of the PSD and is generally defined as
\[
I(f) = \frac{1}{N} \left| \sum_{t=1}^{N} X_t e^{-i2\pi ft} \right|^2,
\]
(8)
where \(N\) is the length of time series of ENMO data \(\{X_t\}\), and \(f\) is the frequency in cycles per second (Hertz). \(i \equiv \sqrt{-1}\) represents the imaginary unit and \(|\cdot|\) denotes the absolute value. For \(\{X_t\}\) with real-valued data, the periodogram is real-valued and symmetric, i.e. \(I(f) = I(-f)\). In addition, as \(\{X_t\}\) is a discretely observed time series from sampling, then its periodogram is only defined for positive and negative frequencies \(f\) that are less than half of the sampling rate, which is also called the Nyquist frequency. For our data, which is sampled every 5 seconds or 1/5 Hertz, the Nyquist frequency is therefore equal to \(f = 1/10\) Hertz. The total area under the spectral line of the periodogram is approximately equal to the variance of \(\{X_t\}\).

The periodogram can be used to assess the strength of the circadian rhythm by evaluating its spectral value at frequency \(f = 1/24\) hours \((f = 1/86400\) Hertz). However, because the total variance of ENMO data will vary across individuals, directly comparing the spectral values of the periodogram at just one frequency will be a noisy and unreliable measure of circadian strength. Instead, we propose a new method by calculating the proportion of variance (PoV) explained by the periodogram at or near the fundamental frequency (also called the first harmonic) of circadian rhythm \((f = 1/24\) hour\(^{-1}\)) and its three following harmonics. This is obtained by finding the ratio of area under the spectral line around these frequencies to its total area. Specifically, we use the range of frequencies between \(1/24.5\) hour\(^{-1}\) \((1/88200\) Hertz) and \(1/23.5\) hour\(^{-1}\) \((1/84600\) Hertz) along with their positive integer multiples from two to four. In the simplest case of considering only the fundamental frequency and ignoring higher order harmonics, the PoV value from each individual is calculated as
\[
\text{PoV}^{(F)} = \frac{\int_{1/84600}^{1/86400} I(f)df}{\int_{1/10}^{1/10} I(f)df},
\]
(9)
where \(f\) is the frequency in units of Hertz or second\(^{-1}\). The denominator in (9) is equivalent to the sample variance of \(\{X_t\}\), and therefore PoV\(^{(F)}\) can be interpreted as the proportion of variance in the time series explained by frequencies between \(1/24.5\) hour\(^{-1}\) and \(1/23.5\) hour\(^{-1}\). In the case of considering the first four harmonics, the PoV value for each individual is calculated as
\[
\text{PoV}^{(H)} = \frac{\sum_{k=1}^{4} \int_{k/84600}^{k/86400} I(f)df}{\int_{1/10}^{1/10} I(f)df},
\]
(10)
where again \(f\) is frequency (in Hertz). The number of harmonics used can be amended if necessary, but we found 4 to be a good value to use in practice.

There are several alternatives to using the periodogram, including smoothed and multi-tapered approaches. However, these techniques smooth across frequency leading to a loss in data resolution. Since our statistic in (10) is already implicitly smoothing across frequencies near the peak frequency to account for noise and variability, then we found no such further smoothing is required.
3 Results and Discussion

In the left column of Fig. 1 we display three examples of time series of ENMO data, one from each of the different groups (control, treatment, and individuals without dementia). The ENMO values from individuals with advanced dementia (control and treatment groups) are largely between 0 and 0.2g with occasional spikes above this range, and this is consistent with other participants in the study from these groups. The plot from the individual without dementia shows higher ENMO values and the daily circadian pattern is more clearly observed. In the right column of Fig. 1 we display the 24-hour time average plots of ENMO data from these three individuals. The individual without dementia has high ENMO values with large variation during daytime (from 6 a.m. until 9 p.m.) and significantly lower and less variable values during nighttime (from 9 p.m. until 6 a.m.). The average plots from individuals with advanced dementia show relatively low ENMO values in both periods and no clear circadian cycle.

Figure 1: Time series plots of ENMO data (left) and their 24-hour time average plots (right) from three participants from the study: one from each of the control group (black), the treatment group (red), and the group of individuals without dementia (green).
3.1 Interdaily stability (IS)

We used IS to evaluate the strength of the circadian rhythm in the ENMO data. The bar chart in Fig. 2 displays IS values from all participants in the study. All participants without dementia except the 7th and 14th individuals have higher IS values than all participants with advanced dementia. The corresponding box plot in Fig. 2 shows that participants in the treatment group have slightly higher mean IS value than in the control group, but this was not found to be significantly different (p-value = 0.4130). However, the mean IS value from the group without dementia was found to be significantly higher than from the combined control and treatment group (p-value < 0.001). All p-values in this paper were calculated using the nonparametric Mann-Whitney U-test at a 5% significance level. The findings from a parametric t-test were found to always be the same in terms of significance. Table S1 of the supplementary material presents mean, standard deviation, minimum and maximum values of all our summary statistics across all participant groups.

![Figure 2: The left panel displays IS values across all participants and the right panel is a box plot collating these values across the control group, the treatment group, and the group of individuals without dementia.](image)

3.2 Intradaily variability (IV)

We used IV to assess the circadian fragmentation in the ENMO data. First we attempted to find the best subsampling interval with which to calculate IV in (2) – (4). To do this, we subsampled the ENMO data with a sampling period ranging from 5 seconds ($\Delta = 1$) to 60 minutes ($\Delta = 720$), in intervals of 5 seconds, and calculated IV with each sampling period. Due to the high sampling frequency of our data, the conventional subsampling interval, which is hourly subsampling, might not be appropriate. The left plot of Fig. 3 shows the relationship between the average IV values and the subsampling interval for the three different groups of participants. IV values increase as a function of the subsampling interval for each group, and there is a noticeable dip at very low time intervals indicating that IV values here may be unreliable due to high frequency variability in the data. In the right plot of Fig. 3 we display the same results as the left plot, but this time the values for the treatment group and the group of individuals without dementia are represented as percentages of the control group values across the subsampling interval. Here we see that lower subsampling intervals are more effective at separating the groups. This indicates a clear trade-off in selecting the optimal subsampling interval, and we recommend a 5 minute subsampling period ($\Delta = 60$) as indicated by the horizontal dashed line in Fig. 3.
Figure 3: The left panel displays line plots of average IV values against the subsampling interval for the three different groups of individuals; the right panel displays line plots of the percentage of average IV values from the treatment group and the group of individuals without dementia, compared with those from the control group. The orange horizontal dashed lines refer to 5 minutes and indicate our recommended subsampling interval.

To further justify the recommendation of 5-minute subsampling, we also studied the effect of subsampling on the relationship between IV and our three other statistical measures. In Figures S1–S3 of the supplementary material, we show plots of the Pearson’s correlation coefficient, which is used to determine the linear association between IV and the other measures. Because IV is used to assess the circadian fragmentation, then the measurement of strength of circadian rhythm, as measured by IS or PoV, should have an associated negative correlation. Similarly, there should be a negative correlation between IV and the Hurst parameter. The results revealed such negative correlations were achieved with 5-minute subsampling, indicating that IV performed as expected at this subsampling interval. However, at higher or lower subsampling intervals, the correlations were weak or even positive, suggesting IV was not an effective measure at these rates, which is consistent with the findings of Fig. 3.

Using our recommended subsampling interval of 5 minutes, IV values were calculated for each participant. These are presented in Fig. 4. Participants from both control and treatment groups were found to usually have higher IV values than participants without dementia, as expected, but there is more overlap between groups than with IS. We also observed that participants without dementia have a larger spread of IV values than participants with advanced dementia. The mean IV value from the group of individuals without dementia is less than that from the combined control and treatment group (p-value < 0.001), but there is no significant difference in the mean IV value between control and treatment groups (p-value = 0.3565).

3.3 Hurst exponent

The Hurst exponent from each individual was estimated using detrended fluctuation analysis (DFA). Specifically, this parameter was estimated by the slope of the linear regression line between scale and overall root-mean-square deviation in log-log coordinates, as described in the Materials and Methods section. In Fig. 5, the regression lines from three individuals from the different groups are presented. We evaluated the $R^2$ value as a measurement of goodness of fit and found that approximately 99% of the variability of the data can be explained by the linear regression model in each case. From this figure we can see that the participant
Figure 4: The left panel displays IV values across all participants, with the same ordering of individuals as the bar plot representing IS values; the right panel is a box plot collating IV values across the control group, the treatment group, and the group of individuals without dementia.

![Intradaily variability (IV)](image)

Figure 5: Data points and their linear regression lines for the estimation of Hurst exponents (slopes) from three participants, one from each of the control group, the treatment group, and the group of individuals without dementia.

![Data points and linear regression lines](image)

without dementia has a higher slope, and hence higher Hurst exponent, than the participants from the control and treatment groups. We found this figure to be generally representative of the differences between Hurst exponents across all participant groups.

Using DFA we found that all time series in the study had an estimated Hurst exponent less than 1.2. This means the direct algorithmic approach provided in the Materials and Methods section can be used on all time series without having to difference the time series first (as outlined in Step 5). Fig. 6 shows Hurst values from all participants. Unlike the first two nonparametric measures, the difference of Hurst values
The left panel displays Hurst values across all participants, with the same ordering of individuals as the bar plot representing IS values; the right panel is a box plot collating Hurst values across the control group, the treatment group, and the group of individuals without dementia.

among all groups of participants is less clear from the bar plot when plotting on the full range of possible $H$ values between 0 and 2. However, the box plot on the right illustrates that the Hurst values from the group of participants without dementia are likely to be higher than those from the other groups ($p$-value < 0.001). In addition, individuals from the treatment group have a significantly higher mean Hurst value than those from the control group ($p$-value = 0.0037). All Hurst values from these two groups of individuals were between 0.7 and 1. This means that there exists long-term positive autocorrelation in these ENMO time series. In addition, each time series was considered to be a stationary time series of correlated noise since their Hurst values do not exceed 1. For individuals without dementia, the set of ENMO data was found to be a combination of both stationary and nonstationary time series due to the Hurst values ranging between 0.8 and 1.2—these higher values are consistent with time series that exhibited smoother and less jittery trajectories.

We also calculated separate Hurst exponents from daytime and nighttime readings of the ENMO data. The summary statistics are presented by two box plots in Fig. 7. The left and right box plots are for daytime and nighttime readings respectively. The daytime readings had a similar distribution of Hurst values to the entire time series analysed in Fig. 6. The nighttime readings however provided a rather different distribution. The Hurst values were more similar across the groups and indeed there was no longer a significant difference of mean Hurst values between participants in the treatment group and the group of individuals without dementia ($p$-value = 0.0697). Table 1 shows means and standard deviations of Hurst values from both daytime and nighttime readings. The mean values from participants in control and treatment groups were not significantly different between daytime and nighttime readings. Participants without dementia, by contrast, had a significant difference of mean Hurst values between daytime and nighttime readings, with daytime values being higher.

### 3.4 Proportion of variance (PoV)

In Fig. 8, we display the power spectral density, as estimated from the periodogram, from one participant from each of the control group, the treatment group, and the group of individuals without dementia. The
Figure 7: The left panel is a box plot collating Hurst values from daytime readings and the right panel is a box plot collating Hurst values from nighttime readings across the control group, the treatment group, and the group of individuals without dementia.

Table 1: Mean and standard deviation (in parentheses) of Hurst values from daytime and nighttime readings across the control group, the treatment group, and the group of individuals without dementia; p-values indicate the significance of differences of mean Hurst values between daytime and nighttime readings for each group of participants.

| Group                | Daytime       | Nighttime     | p-value |
|----------------------|---------------|---------------|---------|
| Control              | 0.8183 (0.0625) | 0.8102 (0.0706) | 0.8977  |
| Treatment            | 0.8757 (0.0549) | 0.8958 (0.0573) | 0.3046  |
| Without Dementia     | 1.0086 (0.1002) | 0.9443 (0.0657) | 0.0395  |

periodogram for the participant without dementia had its highest peak at frequency $1/24$ hour$^{-1}$, which we call the first harmonic or fundamental frequency, and the next highest peaks were at the following higher orders of harmonics. These features were found in all other participants without dementia. Thus, ENMO data from participants without dementia was roughly periodic with a time period of approximately 24 hours or one day, corresponding to the time period of circadian rhythm. However, actigraphy data from individuals with advanced dementia was often distorted and this resulted in a much less clear pattern of circadian rhythm. In particular, the periodograms showed that the ENMO time series were less periodic, and the time period of their circadian rhythm was not well represented by the periodogram. In Fig. 8, the periodogram for the participant in the control group does not show clear and sharp peak at some of the harmonics including the fundamental frequency. Although the highest peak can be observed at the fundamental frequency for the participant in treatment group, this peak has small spectral values compared with the peak from the participant without dementia. These characteristics were generally representative of the participants from each respective group, however we note that there was variability across participants with advanced dementia in terms of the location of dominant peaks in the spectrum—the idea behind our PoV statistic is to smooth over such noisy characteristics to obtain a stable metric.

First we used (9) to calculate $\text{PoV}^{(F)}$, which is the ratio of area under the spectral line around the first harmonic to the total area. This was used to indicate how well the variance is captured by sinusoidal cycles with period of 23.5-24.5 hrs. In Fig. 9 the PoV values from participants without dementia were typically
Figure 8: The power spectral density estimated by the periodogram for three participants, one from each of the control group, the treatment group, and the group of individuals without dementia.

Figure 9: The left panel displays PoV values explained by the periodogram at the fundamental frequency across all participants, with the same ordering of individuals as the bar plot representing IS values; the right panel is a box plot collating these PoV values across the control group, the treatment group, and the group of individuals without dementia.
greater than those with dementia. In addition, the box plot verifies that the mean PoV value from participants without dementia was significantly higher than from participants with advanced dementia (p-value < 0.001). Overall we saw that this metric explained on average 7.58% of the variance for participants without dementia but typically less than 5% for participants with advanced dementia.

To try and explain more of the variability, we then calculated PoV\(^{(H)}\) from (10) which included periodogram values from the first four harmonics. The results are presented in Fig. 10. Participants without dementia still had significantly higher PoV values than participants from control and treatment groups (p-value < 0.001). We observed that more variability was captured by this metric, in particular in the group of individuals without dementia where now an average of 11.21% of the variance was captured by this statistic, showing the benefits of including harmonics.

Figure 10: The left panel displays PoV values explained by the periodogram at the first four harmonics across all participants, with the same ordering of individuals as the bar plot representing IS values; the right panel is a box plot collating these PoV values across the control group, the treatment group, and the group of individuals without dementia.

### 3.5 Comparison of statistical measures

This section explores the relationship of results from all four proposed nonparametric methods. Scatter plots between all possible pairs of the four statistical measures—IS, IV, Hurst exponent, and PoV (with four harmonics)—are shown in Fig. 11. We see that the statistics of participants from control and treatment groups are largely non-separable by any pair of these measures. However, the summary statistics of participants without dementia are mostly distinct from participants with advanced dementia. Participants without dementia tend to have higher IS, Hurst parameter and PoV, but lower IV.

In Table 2, we show the Pearson’s correlation coefficient across all participants for all four measures. IV is negatively associated with all other measures, and all other pairwise associations are positively correlated. Such associations across groups are expected given the clear differences between actigraphy time series of participants without dementia and those with advanced dementia. Therefore, to explore relationships between groups, we also separately summarise the Pearson’s correlation coefficients for participants with and without advanced dementia in Tables 3 and 4, respectively. From these tables we can see that the relationships between all pairs of measures remains the same within these groups, albeit with lower correlations in
general. This demonstrates that these statistical measures have power in separating within group behaviour and are useful statistics that should be considered when performing larger studies, for example to see if certain treatment interventions are effective when circadian rhythms are used as primary outcome.

Figure 11: Scatter plots showing relationships between all possible pairs of the four statistical measures—IS, IV, Hurst exponent, and PoV from the first four harmonics. Participants from the control group, the treatment group, and the group of individuals without dementia, are represented by black, red and green dots respectively.

Table 2: Pearson’s correlation coefficients between pairs of statistical measures for all participants

|     | IS     | IV     | Hurst  | PoV    |
|-----|--------|--------|--------|--------|
| IS  | -0.7754| 0.7354 | 0.9428 |        |
| IV  | -0.7754| -0.7666| -0.7236|        |
| Hurst| 0.7354 | -0.7666| 0.6700 |        |
| PoV | 0.9428 | -0.7236| 0.6700 |        |
Table 3: Pearson’s correlation coefficients between pairs of statistical measures for participants with advanced dementia (combined control and treatment groups)

|       | IS    | IV    | Hurst | PoV   |
|-------|-------|-------|-------|-------|
| IS    | -0.3481 | 0.1484 | 0.9829 |
| IV    | -0.3481 | -0.6028 | -0.4063 |
| Hurst | 0.1484 | -0.6028 | 0.1678 |
| PoV   | 0.9829 | -0.4063 | 0.1678 |

Table 4: Pearson’s correlation coefficients between pairs of statistical measures for participants without dementia

|       | IS    | IV    | Hurst | PoV   |
|-------|-------|-------|-------|-------|
| IS    | -0.4335 | 0.5089 | 0.7723 |
| IV    | -0.4335 | -0.4410 | -0.2205 |
| Hurst | 0.5089 | -0.4410 | 0.3081 |
| PoV   | 0.7723 | -0.2205 | 0.3081 |

4 Conclusion

This paper proposes four nonparametric summary statistics (IS, IV, Hurst exponent, and PoV) for the study of circadian rhythm and other attributes found in actigraphy data. As a proof-of-concept, we computed each summary statistic on a dataset containing a mixed group of participants, some with advanced dementia, and compared these results with data from individuals without dementia. The analysis shows that these statistics can collectively summarise different features in the data: both the inter-daily features of the circadian cycle (IS and PoV), as well as the intra-daily fragmentation and correlation structure (IV and Hurst exponent). Using these statistics there are clearly different values obtained for participants without dementia and those with advanced dementia, therefore there is a potential for these nonparametric statistics to be used as primary outcomes related with circadian rhythms, or as diagnostic benchmarks and thresholds, which would naturally require more studies and analyses to precisely establish practical clinical guidelines.

Some of the participants with advanced dementia also received a group intervention during the study. In our analysis we only detected a mild effect from this treatment, where each metric showed evidence of participants having improved circadian rhythms or sustained periods of activity, but not statistically significantly so. There was one exception where Hurst values (whether daytime, nighttime, or aggregated across both) did show significant difference between control and treatment groups. Specifically, the Hurst exponent was found to be significantly higher for the treatment group which indicates a smoother pattern of behaviour in activity over longer time scales, which is a feature we also found in the group of participants without dementia. Overall, the fact that participants with and without dementia displayed clear differences to each other, but participants from the control and treatment groups did not, were both expected results and validates our statistical measures in terms of their efficacy and reliability in summarising key features of actigraphy data. Ultimately to determine the scope for using these summary statistics in a clinical trial setting requires much further study.

The actigraphy data we studied is high frequency—sampled every 5 seconds—and this is typical of modern instruments and studies. In this paper we paid careful consideration as to how statistical methods
should be adapted to high frequency sampling. A key finding is that IV should not be calculated from hourly subsampling, as has been historically performed in the literature. Hourly subsampling leads to IV values that are unable to effectively separate groups of participants, and have unexpected correlations with other summary statistics. Instead, we propose subsampling every 5 minutes, which improved the behaviour and increased the power of this statistic. We note that subsampling at even higher frequencies eventually worsens performance due to contamination from high-frequency variability. Finally, we note that we proposed a simple aggregation method to ensure no data is lost in the subsampling procedure. We are not aware of other such detailed studies of calculating IV from actigraphy data in the literature.

The high frequency nature of the data also allowed us to propose a new metric, proportion of variance (PoV), which is a nonparametric spectral-based estimate of circadian strength. As the data is high frequency, there are many frequencies at or near the circadian frequency which can be smoothed over to obtain a stable estimate of circadian strength. A key finding is that the inclusion of harmonics, which are integer multiples of the circadian frequency, increased the proportion of variance explained by this statistic and led to improved performance. This statistic is therefore a nonparametric alternative to the parametric cosinor method. We note however that PoV performs similarly to IS with high correlation in these values across participants, and it is therefore possible that only one of these metrics is required, which future studies may reveal.

Finally, the high frequency nature of our data allows for Hurst exponents to be calculated to quantify the memory or long-term autocorrelation structure of the time series. A variety of established techniques exist to estimate the Hurst exponent, including the DFA method used here. What our analysis revealed however, is the potential for utilising the richness of continuity of actigraphy data to obtain separate daytime and nighttime values, and how this may yield further insight as to the difference between individuals who have disrupted sleep cycles and activity rhythms, and those that do not. In particular, we expect individuals without dementia to have significantly higher Hurst exponents at daytime than at nighttime, and this is what our analysis revealed.

This paper we believe is the first to jointly consider three existing nonparametric metrics—IS, IV and Hurst exponent—for analysing actigraphy data, together with proposing a novel nonparametric alternative to cosinor analysis based on aggregating information in the periodogram. We provide guidelines on implementation, and an indication of their performance on a high frequency dataset from people suffering from advanced dementia living in care homes. In future work we will seek to further refine these methods, as well as explore opportunities for building new statistical analysis methods, as richer and larger datasets become available.
5 Supplementary Material

Table S1: Mean, standard deviation (SD), minimum and maximum values of the four statistical measures used in this paper for different groups of participants. The dementia group refers to the combined control and treatment groups.

| Statistical measures | Groups          | Mean   | SD    | Min.   | Max.   |
|----------------------|-----------------|--------|-------|--------|--------|
| IS                   | Control         | 0.0294 | 0.0193| 0.0033 | 0.0634 |
|                      | Treatment       | 0.0392 | 0.0252| 0.0046 | 0.0824 |
|                      | Dementia        | 0.0351 | 0.0230| 0.0033 | 0.0824 |
|                      | Without Dementia| 0.1470 | 0.0536| 0.0619 | 0.2572 |
| IV                   | Control         | 1.6046 | 0.1372| 1.4235 | 1.8563 |
|                      | Treatment       | 1.5185 | 0.1855| 1.0361 | 1.7753 |
|                      | Dementia        | 1.5549 | 0.1693| 1.0361 | 1.8563 |
|                      | Without Dementia| 1.0281 | 0.3012| 0.3758 | 1.4868 |
| Hurst exponent (overall) | Control    | 0.8156 | 0.0870| 0.7223 | 0.9461 |
|                      | Treatment       | 0.8782 | 0.0500| 0.8081 | 0.9654 |
|                      | Dementia        | 0.8517 | 0.0608| 0.7223 | 0.9654 |
|                      | Without Dementia| 1.0046 | 0.0983| 0.8426 | 1.1738 |
| PoV\(^{(H)}\)       | Control         | 0.0277 | 0.0180| 0.0035 | 0.0611 |
|                      | Treatment       | 0.0387 | 0.0261| 0.0058 | 0.0834 |
|                      | Dementia        | 0.0341 | 0.0233| 0.0035 | 0.0834 |
|                      | Without Dementia| 0.1121 | 0.0356| 0.0541 | 0.1692 |

Figure S1: Line plots showing Pearson’s correlation coefficients between IV and IS for the ENMO data with subsampling interval for calculating IV varied from 5 seconds to 60 minutes. The control group, the treatment group, and the groups of individuals with and without dementia are represented by black, red, blue, and green lines, respectively. The orange horizontal dashed line refers to 5 minutes and indicates our recommended subsampling interval for calculating IV.
Figure S2: Line plots showing Pearson’s correlation coefficients between IV and Hurst exponent for the ENMO data with subsampling interval for calculating IV varied from 5 seconds to 60 minutes. The control group, the treatment group, and the groups of individuals with and without dementia are represented by black, red, blue, and green lines, respectively. The orange horizontal dashed line refers to 5 minutes and indicates our recommended subsampling interval for calculating IV.

Figure S3: Line plots showing Pearson’s correlation coefficients between IV and PoV from the first four harmonics for the ENMO data with subsampling interval for calculating IV varied from 5 seconds to 60 minutes. The control group, the treatment group, and the groups of individuals with and without dementia are represented by black, red, blue, and green lines, respectively. The orange horizontal dashed line refers to 5 minutes and indicates our recommended subsampling interval for calculating IV.
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