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Approaches for Assessing Circadian Rest-Activity Patterns Using Actigraphy in Cohort and Population-Based Studies

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Abstract

Purpose of Review To review methods for analyzing circadian rest-activity patterns using actigraphy and to discuss their applications in large cohort and population-based studies.

Recent Findings We reviewed several widely used approaches, including parametric analysis (i.e., cosinor model and wavelet analysis), nonparametric analysis, data adaptive approach (i.e., empirical mode decomposition), and nonlinear dynamical approach (i.e., fractal analysis). We delved into the specifics of each approach and highlighted their advantages and disadvantages.

Summary Various approaches have been developed to study circadian rest-activity rhythms using actigraphy. Features extracted from these approaches have been associated with population health outcomes. Limitations exist in prior research, including inconsistencies due to various available analytical approaches and lack of studies translating findings to the context of the circadian system. Potential future steps are proposed. The review ends with an introduction to an open-source software application—*ezActi2*—developed to facilitate scalable applications in analyzing circadian rest-activity rhythms.

Keywords Accelerometer · Behavioral rhythm · Data adaptive approach · Fractal regulation · Sleep-wake

Introduction

Circadian rhythms reflect internal adaptations to the environmental light-dark cycles across solar days. The rhythms are cell-intrinsic [1], attuned to the physical environment by suprachiasmatic nucleus (SCN), the central clock pacemaker [2, 3]. Intact circadian function is key for optimal performance of virtually all biologic and physiologic processes, and perturbed circadian regulation has been prospectively linked to various age-related conditions [4, 5•].

Laboratory assessment of the endogenous circadian rhythms, i.e., the internal clock driven by the SCN, is stringent and costly. Alternatively, actigraphy allows a non-invasive and cost-effective assessment of the functional manifestation of the circadian control under naturalistic settings in terms of rest-activity patterns, enabling scalable applications in population and large cohort study settings. Actigraphy measures body movements through accelerometer sensors [6], commonly worn on the wrist, waist, or ankle. These sensors detect accelerations in X, Y, and Z directions [7], which are commonly integrated into a one-dimensional signal (i.e., activity counts) within a fixed length of time window (i.e., epoch). The term "actigraphy signal" refers to this one-dimensional signal throughout this review.

Actigraphy has been used since 1950s in biomedical research [8–10]. Although actigraphy can be used for measuring sedation level [11], estimating energy expenditure [11], and measuring step counts [12], it has been most

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commonly used to estimate sleep and circadian rest-activity patterns. The American Academy of Sleep Medicine recognized actigraphy as a useful research tool to study sleep in 1995 [9, 13]. Polysomnography remains the gold standard for sleep staging and assessment, but its cost and bulky equipment limit its widespread use [14•], especially in large cohort and population-based settings. Actigraphy provides a low-cost and easy-to-use alternative to measure multiple sleep parameters in free-living conditions with minimal interference. Several established algorithms are available for sleep-wake identification from actigraphy [14•, 15–17,18•].

Various features from actigraphy, such as strength, phase, stability, fragmentation, and multiscale or fractal correlation of the rest-activity patterns, shown links with disturbances or dysregulation of the endogenous circadian function [19–21]. In the following sections, we will introduce these previously well-established methods for analyzing circadian rest-activity patterns. We will start with a brief overview of terminologies that will be used throughout this review. Subsequently, for each method, we will briefly describe the methodological considerations and then review recent cohort studies that have adeptly employed these specific methods to establish links between circadian rest-activity patterns and various health outcomes in human participants. We will compare and discuss the strengths and limitations of each method and discuss potential applications of these measures. Lastly, we will introduce ezActi2 software, which is an open-source application that implements most of our reviewed methods to facilitate the analysis of circadian rest-activity rhythms using actigraphy data.

Overview of Terminologies

Prior to going into the details of each algorithm, to facilitate the understanding of technical terms that may not necessarily be well-known across a broader research community, in Table 1, we provide an overview of terminologies employed in this article.

Parametric Analysis of Circadian Rest-Activity Rhythms

Cosinor Model

The rhythms of many biological processes appear to be sinusoidal, i.e., smoothly rising to the peak, gradually decreasing to a minimum value, and then increasing again. This phenomenon inspired a mathematical approach, cosine curve fitting, that had been heavily used in chronobiology [22]. This approach fits a cosine curve of a known frequency

Table 1 Terminologies

Key terms	Definition/description
Cosine	Cosine is a mathematical concept commonly used in geometry and trigonometry to compare angles and distances between points. Mathematically, it is defined as the ratio of the length of the side adjacent to an acute angle of a right triangle to the length of the hypotenuse. In the context of circadian biology, cosine function is used as a smooth and periodic curve to model the shape of cyclic near 24-h oscillations in physiological output such as rest-activity data.
Fractal	Fractals are "self-similar" patterns that repeat themselves on different spatial scales. In other words, they look roughly the same at any level of magnification. Fractal temporal processes represent processes with self-similar statistical properties on different temporal or time scales, such as rest-activity time series.
Harmonic	A harmonic in physics means an oscillation with a frequency that is an integer multiple of the fundamental frequency. In the context of circadian biology, the fundamental frequency is usually assumed to be one cycle per 24 h. For instance, a component with the frequency of one cycle per 12 h will be considered a harmonic (i.e., the frequency is twice the fundamental frequency).
Linearity	In mathematics, a linear system possesses the properties of additivity and homogeneity. Additivity means that if one applies multiple signals to the system separately and adds the outputs together, it is the same as if one adds the multiple signals together and applies the summed signal to the system. Homogeneity means that if one scales the input signal by a constant factor, the new output will also be a scaled version (with the same scaling factor) of the original output. In the context of circadian biology, the circadian system is considered linear that takes input signals that are modelled by basic mathematical functions (such as a cosine function) scaled and summed together. This is simplified, and physiological systems are usually nonlinear that do not behave similarly as a linear system.
Noise	In the context of signal processing, noise refers to unwanted and random fluctuations that can disrupt or distort the information carried by a signal. Such interference can happen during measurement, transmission, and processing. In the context of rest-activity data, noise may include environmental physical vibrations, electromagnetic inference, and errors from the senor or circuit.
Stationarity	In the context of signal processing, a stationary system refers to a system or a process whose statistical properties remain constant over time. Usually, one examines the stationarity in a "wide sense," which means that the first-order moment (i.e., mean) and second-order moment (i.e., variance) remain constant over time. In the context of circadian biology, the cosine models are characterized by a constant mean and variance over the entire observation period, which is in keeping with a stationary system. However, it is commonly not true for these physiological oscillations whose means and variances keep changing over time, implying an intrinsic non-stationarity.

(e.g., one cycle per 24 h) to the data using a regression model. The approach can be easily extended to include multiple cosine components with different frequencies, typically utilizing a harmonic structure (i.e., the frequency of each additional component is an integral multiple of the "base" frequency; Table 1). The model outputs various variables, including the rhythm-adjusted mean or MESOR (Midline Estimating Statistic of Rhythm; reflects the average level of the rhythm), amplitude (reflects the strength of the rhythm), and acrophase (reflects the peak time of the rhythm). For more details on the mathematical basis of the cosinor fitting, see Supplemental Materials.

Criticism exists in applying the cosine curve fitting to actigraphy signals, as these data are often non-sinusoidal. Moreover, the approach is mathematically a truncated version of the Fourier series, which theoretically are comprised of an infinite set of harmonics to perfectly reproduce the original data. It needs more harmonics to be considered to acquire a better fit. This leads to complexity both methodologically and interpretation-wise, as the number of parameters to be estimated will increase exponentially with the number of harmonics.

To better adapt to the square wave–like shape of the actigraphy signal, a sigmoid transform-based modified cosine curve fitting was introduced by Marler and colleagues [23]. Instead of fitting the original actigraphy data by a typical cosine curve, they regressed the signal using a cosine curve nonlinearly transformed by a sigmoidal function (such as the Hill function, anti-logistic function, or the arctangent function). Although the approach may better adapt to the shape of actigraphy or rest-activity patterns, it increases the computational complexity as two more parameters in the sigmoidal transform need to be estimated, and the optimization process is complicated as it needs to be based on a nonlinear least squares regression.

Moreover, considering the non-negative nature of rest-activity data (along with many other biological and physiological time structures), Doyle et al. proposed to use the gamma distribution to replace the default Gaussian distribution for modeling regression residuals in the original cosinor model [24]. This approach is advantageous in modeling data acquired from acute care populations, in which signals are sometimes noisy and of poor quality.

Across population-based studies, lower amplitude has consistently been associated with negative outcomes, including Alzheimer's dementia [25••], hypertension [26], insulin resistance and type 2 diabetes [27], and frailty [28•]. However, findings for other measures are less consistent. For example, in the Rush Memory and Aging Project (MAP) cohort, while earlier acrophase was not associated with Alzheimer's dementia [25••] or overall frailty, it was associated with worsening fatigue symptoms [28•]. Conversely, in a cross-sectional study of 2450 older men, Xiao et al. found late acrophase associated with greater odds of type 2 diabetes [27]. Yet, later acrophase showed a trend association with lower odds of hypertension in a study of 6726 adults [26].

Wavelet-Based Analysis

Cosinor analysis is essentially a variant of the Fourier transform, which fundamentally assumes that the analyzed data are stationary. Furthermore, harmonics are considered a linear combination of two or more cosine/sine waves, which contradicts the nonlinear nature of actigraphy signals. Although this method can capture global features that persist over the entire signal, it is limited when the signal's characteristics vary over time. Therefore, the challenge remains in reliably analyzing signals that are noisy and nonstationary.

Wavelet analysis has been introduced as a time-frequency domain analytical approach to better decompose a nonstationary signal. Wavelets are small oscillations within a signal that can be isolated and analyzed separately. In contrast to the Fourier analysis that decomposes a signal into a set of sine and cosine functions of fixed frequency, wavelets are in different shapes and sizes that are localized in both frequency (or scale, how the wavelet is "stretched" or "squished") and time (or location, the position of wavelet in the time-series). By decomposing a signal into a set of wavelets at different scales, wavelet analysis can provide a multi-resolution representation of the signal, in which the larger-scale features are represented by wavelets with lower frequency oscillations and longer durations, and wavelets with higher frequency oscillations and shorter durations represent the smaller-scale features.

There are two wavelet transform types: discrete wavelet transform (DWT) and continuous wavelet transform (CWT; also known as analytic wavelet transform). We provided a technical summary of the two different types in Supplemental Materials.

In the context of circadian rest-activity analysis, Fossion et al. [29] studied two weeks of actigraphy data of individuals with regular and irregular circadian cycles using CWT. In all cases, they found a high-intensity ridge (dominant circadian rhythm) around a period of $T = 1440$ min (i.e., 24 h) for all the time points. However, for $T < 1440$ min, the intensity of T varied in time, meaning the time and amplitude variability of the circadian rhythm. For example, during the nighttime, the intensity was higher for Ts close to 1440 min, while during the daytime (higher activities), the intensity was higher for lower Ts. The scalogram of an older male adult with regular circadian cycle showed only a single circadian ridge. In contrast, the scalogram of a young male adult with an irregular circadian cycle showed multiple high-intensity ridges. They also applied DWT to the same data to decompose the actigraphy data of the same

participants. They identified (with visual inspection) the 10th scale, which had a period of approximately 24 h, as the circadian cycle. They found that the young male adult with an irregular circadian cycle had the highest variation (standard deviation) in all circadian parameters (e.g., period, amplitude, and acrophase).

Although wavelet analysis has been used in some chronobiological animal studies [30, 31], to the best of our knowledge, it has not been applied to large human cohort studies. This could be because the results of wavelet analysis need visual inspection (for the specific component corresponding to the circadian cycle) and interpretation (unlike some other methods that provide numerical values as output). Also, selecting wavelets or wavelet functions requires intensive experience and expertise, limiting its use in a wider research community.

Nonparametric Analysis of Circadian Rest-Activity Rhythms

Nonparametric analysis of circadian/behavioral rhythms is an alternative approach to traditional parametric methods (e.g., cosinor analysis) [32]. In the context of actigraphy, nonparametric analysis usually adopts a 24-h period to compute interdaily stability (IS), intradaily variability (IV), the mean activity levels of the most active 10 h (M10), and the least active 5 h (L5), as well as the relative amplitude (RA). IS measures the consistency of activity rhythms across days. It ranges from 0 to 1, with greater values indicating greater stability. IV measures the fragmentation of activity rhythms within a day, with greater values indicating greater fragmentation. M10 and L5 represent the activity levels during the most active 10 h and the least active 5 h, respectively. The mid-time of the M10 and L5 windows represent the M10 phase and L5 phase, respectively. Relative amplitude can be calculated based on M10 and L5. See Supplemental Materials for the mathematical details of IS, IV, and RA.

Other measures have been proposed based on nonparametric methods. For example, Ortiz-Tudela et al. proposed an integrated measure, the circadian function index (CFI), to represent the robustness of the behavioral rhythms [33]. CFI was calculated as the average of IV (inverted and normalized), IS, and RA, with greater values indicating a more robust circadian rhythm.

Compared with parametric measures of circadian rhythms, nonparametric analysis yields several strengths, including the ability to capture irregular non-sinusoidal patterns of activity and provide insights into the dynamics of the rhythm (e.g., the stability and fragmentation of the rhythm). Moreover, it has been argued that nonparametric analysis yields higher sensitivity in detecting individuals with diseases compared to parametric analysis [34]. Nonparametric analysis has been commonly applied to actigraphy data in large cohort studies. Across demographic populations, researchers found lower IS and greater IV to be associated with adverse outcomes, including cardiovascular diseases [35,36••,37], neurodegeneration [25••,38,39•], and other diseases [40••,41].

Nevertheless, nonparametric analysis has some limitations, such as assuming the shape of the rhythm is unknown, which limits the ability to detect specific features (e.g., amplitude) of the rhythms. In addition, because nonparametric analysis is designed for assessing circadian rhythms with a period of approximately 24 h, it may not be appropriate for analyzing irregular rhythms or rhythms that deviate from 24 h (e.g., ultradian/infradian).

Data Adaptive Approach for Circadian Rest-Activity Rhythms

For wavelet analysis, the selection and determination of the mother wavelet heavily depend on experience and expert knowledge of signal processing, which are usually beyond the field of a circadian biologist. Such complications ask for a data-adaptive approach which, ideally, is an assumption-free algorithm. The empirical mode decomposition (EMD) is a data-driven method that can more accurately capture the underlying characteristics of the rhythms during irregular sleep-wake periods [42, 43]. In addition, compared with cosinor-based analysis, EMD allows to examine the irregularity of cycle lengths and amplitude.

EMD processes time series signals without making the assumption of linearity or stationarity. EMD analysis starts by identifying the local maxima and minima of a signal. Then the upper and lower envelopes are connected and averaged. The average is subtracted from the original signal to obtain a residual which will be subjected to the same sifting process as described above until the residual meets specific criteria to be considered a narrow-band signal, which will then be considered the first intrinsic mode function (IMF). This process will be repeated after removing the first IMF from the original signal to obtain all subsequent IMFs, including a final residual that cannot be decomposed further, which usually represents a non-stationary trend [50, 51].

Limitations of EMD include mode mixing and sensitivity to noise. The mode mixing issue occurs when two or more intrinsic modes are captured in a single component, resulting in difficulty separating the two modes and interpreting the results [44]. Mode mixing can be caused by intermittency, noises, or artifacts in the signal and can be resolved by several variations of EMD. For example, the ensemble EMD method reduces mode-mixing by iteratively adding

white noise to the original signal that functions as random disturbances, which will be eliminated by averaging [45]. Similarly, uniform phase EMD introduces cosine-type disturbances during the sifting process to avoid mode mixing; it also helps avoid mode splitting and reduce residual noise that may exist in the ensemble EMD [46].

EMD and its variants can be applied to rest-activity rhythm data [47]. For example, in Wang and colleagues' study [22], the amplitude of actigraphy extracted using EMD correlated with the quantity of vasoactive intestinal peptide-expressing SCN neurons. In another study, Musiek et al. found that lower EMD amplitude of actigraphy data was associated with increasing age and male gender [38]. We have also previously used uniform phase EMD to analyze actigraphy data and found reduced amplitude and increased cycle length variation associated with a greater risk of incident frailty in older adults [28•].

Nonlinear Dynamics for Circadian Rest-Activity Patterns—Fractal Analysis

In addition to the visually identifiable rhythmic near 24-h patterns, rest-activity signals demonstrate seemingly "erratic" fluctuations, especially at shorter time scales [48]. The apparent random fluctuations also prevail in many other physiological outputs, such as heart rate and neuronal activity [49]. Nonlinear dynamic analyses have revealed that these physiological fluctuations are not random, but display fractal temporal patterns, which in mathematics, describes self-affine objects with small-scale patterns resembling large-scale structures. The fractal physiological fluctuations are believed to origin from the complex feedback interactions of different processes functioning at different time scales, reflecting system integrity, and adaptability.

The circadian system is a crucial hub of the regulatory network that generates and maintains fractal patterns in physiological signals. For example, in rats, lesioning the SCN, the central circadian pacemaker, led to the disappearance of fractality in motor activity at time scales between approximately 4 and 24 h [50]. Additionally, restoring a 24-h rest-activity pattern in SCN-lesioned rats by time-restricted feeding did not bring back the perturbed fractal patterns [51], further directly evidencing that fractal offers information regarding the endogenous circadian regulation complementary to the traditionally used rhythmic metrics. Possible evidence for a similar role of the SCN functioning beyond the generation of ~24-h rhythms in humans comes from a recent study showing that aging and Alzheimer's disease (AD) significantly perturb fractal activity regulation at large time scales between approximately 2 and 8 h [21]. For a more comprehensive review of fractals in physiology and the role of the circadian system in fractal neurophysiological patterns, readers can refer to a review by Pittman-Polletta et al. [52].

The detrended fluctuation analysis (DFA) [53] has been widely used to assess fractal patterns in physiological outputs, including rest-activity signals. The DFA calculates the fluctuation amplitude, $F(n)$, as a function of timescale n. See Supplemental Materials for a step-by-step summary for generating the outcomes.

Based on the fractal patterns of rest-activity data, intriguing findings have been obtained in cohort and population-based studies. For example, in a 3.5-year-long randomized control trial, degradation in fractal activity patterns was associated with cognitive decline in older adults with dementia [54]. In a longitudinal study of > 1000 participants in the Rush MAP cohort, degraded fractal patterns in rest-activity signals predicted incident Alzheimer's dementia, incident mild cognitive impairment, and faster cognitive decline, independent from many other known AD risk factors including age, education, physical activity, sleep disturbance, as well as circadian rest-activity rhythms [55]. The fractal degradation was also independently predictive of multiple physical functional declines, including frailty and disability, and death in the MAP cohort [56]. In addition, in the Knight Alzheimer's Disease Research Center "sleep & tau cohort" [44], fractal rest-activity patterns correlating with in vivo AD pathology independent of traditional rest-activity rhythms have also been consistently demonstrated [57••].

Discussion

Assessing circadian biomarkers in humans, such as melatonin, cortisol rhythms, or core body temperature [4] that can better reflect or reveal endogenous rhythms generated by the central circadian pacemaker—the SCN, is costly and requires specialized laboratory circadian protocols, such as constant routine and forced desynchrony protocols [58, 59]. Wearable devices such as actigraphy has become a popular alternative in prospective cohort studies, which can be used to extract multidimensional features in free-living conditions, many of which have been associated with metrics for endogenous circadian functions [19–21]. For instance, Wang and colleagues found that the number of vasoactive intestinal peptide immunoreactive neurons in the SCN was positively correlated with the normalized amplitude of the 24-h rest-activity patterns [19]. However, despite these correlational studies, it is yet to systematically examine to what extent the rest-activity rhythms can precisely predict/reflect the endogenous rhythms. It is well-accepted that external factors, such as work or study schedules and physical exercise, can influence these rest-activity patterns [60]. Therefore, while these wearable sensors provide useful screening tool for circadian disorders, researchers should exercise caution

Methods	Strengths	Weaknesses	Contexts to be used
Parametric analysis			
Cosinor model	• Mathematically simple with analytical solution • Computationally flexible to allow (theoretically) infinite number of harmonics	• Only allows predefined constant cycle length(s) • Computational complexity grows exponentially with more harmonics	• Traditionally the first choice for laboratory-based studies in which rhythms are minimally interfered by environmental factors • When regular rhythms are expected (i.e., relatively constant amplitude and phase across cycles)
Wavelet analysis	• Can handle non-stationary signals	• Requires expertise and experience in choosing wavelet function • Requires expertise in interpreting the scalogram	• When rhythms are expected to change over time
Non-parametric analysis	• No assumption of sinusoidal shape	• Only allows one predefined constant cycle length	• Traditionally a compliment of parametric analysis • When the consistency, fragmentation, or the levels of activities are the primary variables of interest
Data adaptive approach			
EMD and its variants	• No assumption on the shape of base function • Can handle non-stationary signals	• The original EMD suffers from mode mixing/separation issues (while uniform-phase EMD offers a reasonable solution)	• When rhythms are expected to change over time • Can be a first choice for irregular rhythms as EMD approaches have no assumptions on base functions
Nonlinear approach			
Fractal analysis	• Captures multiscale patterns independent of rhythmicity • Minimally masked by the signal magnitude	• Not immediately obvious in translating back to rhythmicity	• Can be used to infer the functional status of the circadian network based on ambulatory data

Fig. 1 Strengths, weaknesses, and applicable contexts of different approaches for analyzing circadian rest-activity rhythms

when using them to infer endogenous circadian functions, since the features captured with these sensors reflect both endogenous circadian rhythms and exogenous circadian entrainment. Recent advances in wearable sensors such as photoplethysmography and temperature sensors may offer opportunities to extract new features using multi-sensors data that are potentially better associated with endogenous circadian rhythms as well as various health outcomes.

We have reviewed various types of rest-activity rhythm analysis methods in this work, including parametric analysis (i.e., cosinor model and wavelet analysis), nonparametric analysis, data adaptive approach (i.e., empirical mode decomposition), and nonlinear dynamical approach (i.e., fractal analysis). A major challenge is therefore how to select an appropriate method in real-world applications. Each method has its own strengths, weaknesses, and applicable contexts, as summarized in Fig. 1.

Note that various features and inconsistent analytical approaches used in actigraphy data have led to mixed findings. For example, in the Study of Osteoporotic Fractures cohort, cosinor analysis revealed that lower amplitude or less robustness of rhythm was associated with increased risk of incident dementia or MCI [61]. In contrast, Posner et al. used nonparametric analysis in the same cohort and only found earlier sleep/wake times to be associated with increased dementia risk [62]. In a recent study of the Osteoporotic Fractures in Men cohort, all three were associated with increased odds of cognitive decline [63]. However, our recent study of the MAP cohort observed an association of AD risk with lower amplitude and increased fragmentation but not with the robustness of the rhythms or phase [25••]. Moreover, in cardiovascular health, Xu et al. found a connection between lower relative amplitude (from nonparametric analysis) and the cardiovascular disease [64•]. Similarly, Hoopes et al. employed nonparametric analysis on actigraphy data, discovering that higher IS and higher RA correlated with lower nocturnal systolic blood pressure, exclusively in women [65]. However, cosinor analysis allowed researchers to investigate other characteristics of rest-activity rhythms, suggesting that lower pseudo F statistic was associated with hypertension [26] and coronary artery disease [66], in addition to lower amplitude. These inconsistent findings hinder our understanding of circadian rhythms in the context of different health outcomes and translation of the findings into clinical practice.

Though the multidimensional features we reviewed in this work may provide complementary or overlapping information, their collective ability to better assess circadian function remains uncertain. This creates additional barriers in practice. For example, it is difficult to establish a cutoff level for circadian degradation using different methodologies, making it challenging to screen for sleep-wake or circadian disorders. A potential solution is to develop a construct encompassing all rest-activity rhythms characteristics. For example, in a prior proof-of-concept study, we established a biological age biomarker by leveraging different rest-activity rhythms features to predict chronology age. We have shown its ability to profile the chronological aging process and its prospective association with the risk of Alzheimer's dementia [67••]. With the advance of the model machine learning models, it is possible to integrate these multidimensional features to estimate the overall functioning of the circadian system or to predict different outcomes. Future endeavors leveraging the expertise of chronobiologists, mathematicians, computer scientists, and engineers will uncover valuable but hidden information within motor activity time series.

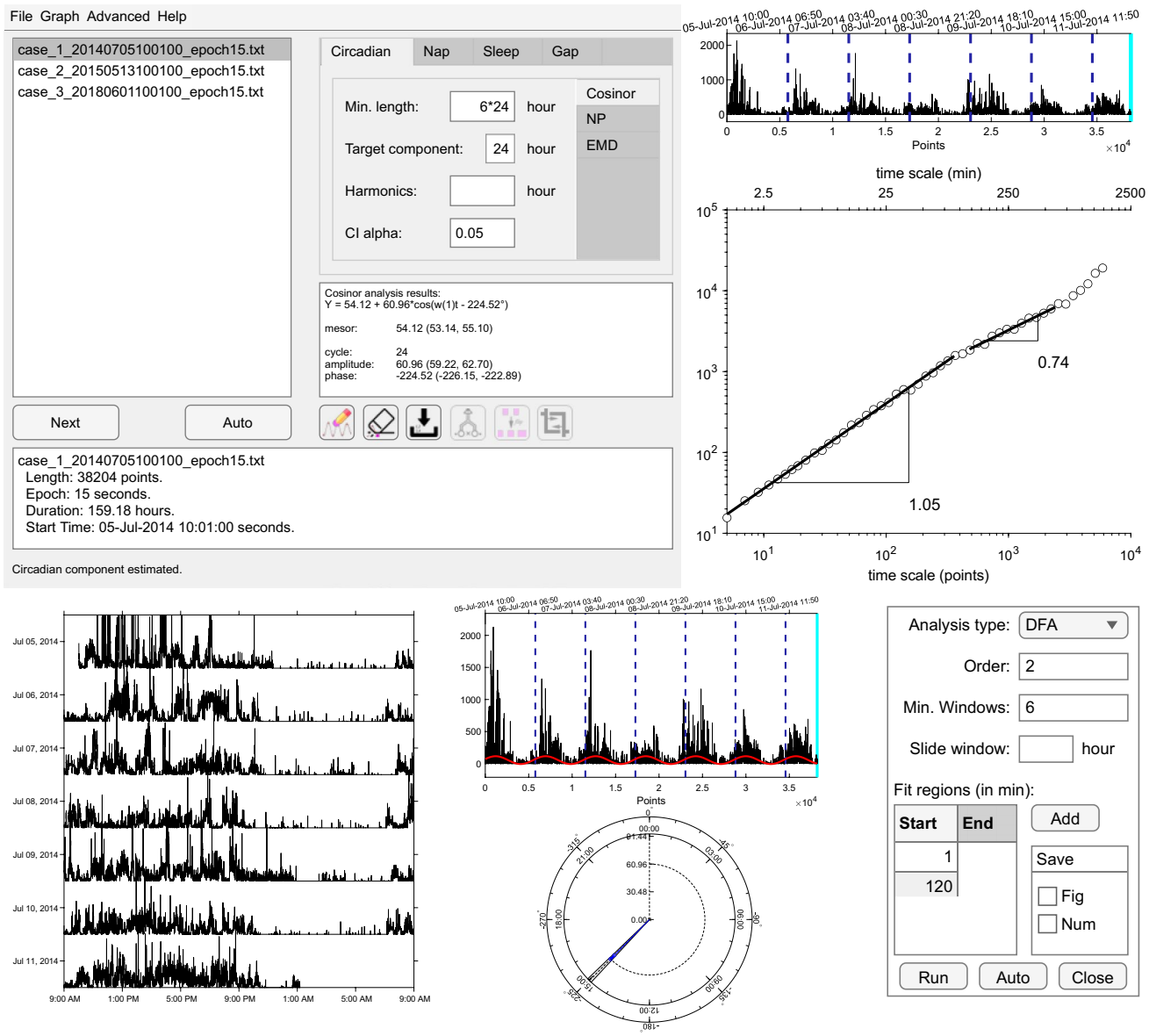

Fig. 2 MATLAB-based App for circadian rest-activity rhythms analysis—ezActi2

Though algorithm details and mathematical formulas for the reviewed circadian rest-activity metrics have been specified, we realize that it would be challenging for researchers without strong programming backgrounds to conveniently calculate these metrics from raw actigraphy data. Therefore, we developed a software application, ezActi2 (Fig. 2), in the MATLAB platform (R2022a and later versions, The MathWorks Inc., Natick, MA) that enables all the above-mentioned algorithms (except the two modified versions of cosinor models and wavelet analysis). We believe that such an application will ease and facilitate these analyses in a wider community within and beyond the network of sleep and circadian biologists/physiologists and clinicians. For example, activity counts exported from actigraphy devices/software can be imported in ezActi2 to implement cosinor model, nonparametric analysis, uniform phase EMD, and fractal analysis conveniently. Researchers can then export metrics of interest (e.g., amplitude, acrophase, IS, IV) from the software. The ezActi2 has been tested and validated through many projects across our collaborative networks. It is open-source and freely available on GitHub (https://github.com/pliphd/Actigraphy). We also plan to introduce it in greater detail in a follow-up paper.

Conclusion

Using actigraphy to assess sleep-wake and rest-activity rhythms has become a popular alternative to endogenous circadian biomarkers and polysomnography in cohort studies due to its lower cost and accessibility. Although various analytical approaches (e.g., parametric, nonparametric, data-adaptive, and nonlinear dynamics) have their strengths and weaknesses, they have led to mixed findings, making it challenging to compare results and understand the relationships between circadian rhythms and health outcomes. A potential solution is to develop a measure encompassing all characteristics of rest-activity rhythms, such as multidimensional digital phenotyping of circadian age, to enhance disease prediction and management at individual and population levels.

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Declarations

Ethics Approval N/A.

Human and Animal Rights and Informed Consent N/A.

Conflict of Interest S.H. reports receiving consulting fees from Achaemenid LLC, unrelated to this project. Other authors declare no competing interests.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Sassone-Corsi P. Molecular clocks: mastering time by gene regulation. Nature. 1998;392(6679):872–4.
2. Li JZ, Bunney BG, Meng F, Hagenauer MH, Walsh DM, Vawter MP, et al. Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. Proc Natl Acad Sci U S A. 2013;110(24):9950–5.
3. Rijo-Ferreira F, Takahashi JS. Genomics of circadian rhythms in health and disease. Genome Med. 2019;11(1):82.
4. Leng Y, Musiek ES, Hu K, Cappuccio FP, Yaffe K. Association between circadian rhythms and neurodegenerative diseases. Lancet Neurol. 2019;18(3):307–18.
5.• Sletten TL, Cappuccio FP, Davidson AJ, Van Cauter E, Rajaratnam SMW, Scheer FAJL. Health consequences of circadian disruption. Sleep. 2020;43(1):zsz194. **This article concisely summarizes how circadian disruption affects health outcomes**.
6. Acebo C, LeBourgeois MK. Actigraphy. Respir Care Clin N Am. 2006;12(1):23–30.
7. Sadeh A. Chapter 6 Actigraphy. In: Guilleminault C, editor. Handbook of clinical neurophysiology. Elsevier; 2005. p. 67–72. (Handbook of Clinical Neurophysiology; vol. 6). Available from: https://www.sciencedirect.com/science/article/pii/S1567423109700310. Accessed 9 May 2023
8. Martin JL, Hakim AD. Wrist actigraphy. Chest. 2011;139(6):1514–27.
9. Tryon WW. Activity measurement in psychology and medicine. New York London: Plenum Press; 1991. p. 247. (Applied clinical psychology)
10. Acker J, Golubnitschaja O, Büttner-Teleaga A, Richter K. Wrist actigraphic approach in primary, secondary and tertiary care based on the principles of predictive, preventive and personalised (3P) medicine. EPMA J. 2021;12(3):349–63.
11. Mandigout S, Lacroix J, Perrochon A, Svoboda Z, Aubourg T, Vuillerme N. Comparison of step count assessed using wrist- and hip-worn actigraph GT3X in free-living conditions in young and older adults. Front Med. 2019;6 Available from: https://www.frontiersin.org/articles/10.3389/fmed.2019.00252. Accessed 9 May 2023
12. Practice parameters for the use of actigraphy in the clinical assessment of sleep disorders. Sleep. 1995;18(4):285–7.
13. Agnew HW Jr, Webb WB, Williams RL. The first night effect: an EEG study of sleep. Psychophysiol. 1966;2(3):263–6.
14.• Haghayegh S, Khoshnevis S, Smolensky MH, Diller KR. Application of deep learning to improve sleep scoring of wrist actigraphy. Sleep Med. 2020;74:235–41. **This study compares different actigraphy modes of operation and their performance in estimating sleep**.
15. Haghayegh S, Khoshnevis S, Smolensky MH, Diller KR, Castriotta RJ. Deep neural network sleep scoring using combined motion and heart rate variability data. Sensors. 2020;21(1):E25.
16. Haghayegh S, Khoshnevis S, Smolensky MH, Diller KR, Castriotta RJ. Performance comparison of different interpretative algorithms utilized to derive sleep parameters from wrist actigraphy data. Chronobiol Int. 2019;36(12):1752–60.
17. Haghayegh S, Khoshnevis S, Smolensky MH, Diller KR, Castriotta RJ. 1196 Machine learning derived-interpretative algorithm better differentiates sleep and wake epochs and estimates sleep parameters from wrist actigraphy data. Sleep. 2020;43:A457–8.
18.• Gao C, Li P, Morris CJ, Zheng X, Ulsa MC, Gao L, et al. Actigraphy-based sleep detection: validation with polysomnography and comparison of performance for nighttime and daytime sleep during simulated shift work. Nat Sci. Sleep. 2022;14(14):1801–16. **This article compares the performance of two widely-used scoring algorithms in estimating daytime and nighttime sleep using actigraphy**.
19. Wang JL, Lim AS, Chiang WY, Hsieh WH, Lo MT, Schneider JA, et al. Suprachiasmatic neuron numbers and rest-activity circadian rhythms in older humans. Ann Neurol. 2015;78(2):317–22.
20. Hu K, Harper DG, Shea SA, Stopa EG, Scheer FAJL. Noninvasive fractal biomarker of clock neurotransmitter disturbance in humans with dementia. Sci Rep. 2013;18(3):2229.

21. Hu K, Van Someren EJW, Shea SA, Scheer FAJL. Reduction of scale invariance of activity fluctuations with aging and Alzheimer's disease: involvement of the circadian pacemaker. Proc Natl Acad Sci U S A. 2009;106(8):2490–4.
22. Halberg F, Tong YL, Johnson EA. Circadian system phase—an aspect of temporal morphology; procedures and illustrative examples. In: The cellular aspects of biorhythms: symposium on rhythmic research sponsored by the VIIIth International Congress of Anatomy Wiesbaden 8–14 August 1965. Springer; 1967. p. 20–48.
23. Marler MR, Gehrman P, Martin JL, Ancoli-Israel S. The sigmoidally transformed cosine curve: a mathematical model for circadian rhythms with symmetric non-sinusoidal shapes. Stat Med. 2006;25(22):3893–904.
24. Doyle MM, Murphy TE, Miner B, Pisani MA, Lusczek ER, Knauert MP. Enhancing cosinor analysis of circadian phase markers using the gamma distribution. Sleep Med. 2022;92:1–3.
25.•• Li P, Gao L, Gaba A, Yu L, Cui L, Fan W, et al. Circadian disturbances in Alzheimer's disease progression: a prospective observational cohort study of community-based older adults. Lancet Healthy Longev. 2020;1(3):e96–105. **This study used several different circadian rest-activity rhythm measures (including parametric and nonparametric analyses) from actigraphy, studied for the first time their longitudinal changes with aging, and linked them to the development of Alzheimer's disease in a bi-directional manner**.
26. Yeung CHC, Bauer C, Xiao Q. Associations between actigraphy-derived rest–activity rhythm characteristics and hypertension in United States adults. J Sleep Res. 2023:e13854.
27. Xiao Q, Qian J, Evans DS, Redline S, Lane NE, Ancoli-Israel S, et al. Cross-sectional and prospective associations of rest-activity rhythms with metabolic markers and type 2 diabetes in older men. Diabetes Care. 2020;43(11):2702–12.
28.• Cai R, Gao L, Gao C, Yu L, Zheng X, Bennett D, et al. Circadian disturbances and frailty risk in older adults: a prospective cohort study. 2023. **Findings from the Rush Memory and Aging Project that link disturbances in circadian rest-activity rhythms based on a data-adaptive approach with incident frailty and longitudinal change in frailty symptoms**.
29. Fossion R, Rivera AL, Toledo-Roy JC, Angelova M, Fossion R, Rivera AL, et al. Quantification of irregular rhythms in chronobiology: a time- series perspective. Circadian rhythm-cellular and molecular mechan IntechOpen. 2018; Available from: https://www.intechopen.com/chapters/60261. Accessed 9 May 2023
30. Poon AMS, Wu BM, Poon PWF, Cheung EPW, Chan FHY, Lam FK. Effect of cage size on ultradian locomotor rhythms of laboratory mice. Physiol Behav. 1997;62(6):1253–8.
31. Chan FH, Wu BM, Lam FK, Poon PW, Poon AM. Multiscale characterization of chronobiological signals based on the discrete wavelet transform. IEEE Trans Biomed Eng. 2000;47(1):88–95.
32. Gonçalves BSB, Adamowicz T, Louzada FM, Moreno CR, Araujo JF. A fresh look at the use of nonparametric analysis in actimetry. Sleep Med Rev. 2015;20:84–91.
33. Ortiz-Tudela E, Martinez-Nicolas A, Campos M, Rol MÁ, Madrid JA. A new integrated variable based on thermometry, actimetry and body position (TAP) to evaluate circadian system status in humans. PLOS Comput Biol. 2010;6(11):e1000996.
34. Marín-García A, Fossion R, Müller MF, Ríos-Herrera W, Rivera AL. A non-parametric model: free analysis of actigraphic recordings of acute insomnia patients. R Soc Open Sci. 2022;9(2):210463.
35. Sommer R, Yu L, Schneider JA, Bennett DA, Buchman AS, Lim ASP. Disrupted rest-activity rhythms and cerebral small vessel disease pathology in older adults. Stroke. 2021;52(7):2427–31.
36.•• Yang L, Feng H, Chen J, Kwok Wing Y, Benedict C, Tan X, et al. Association of circadian rest-activity rhythms with cardiovascular disease and mortality in type 2 diabetes. Diabetes Res Clin Pract. 2023;1(197):110262. **A representative population-scale study using the UK Biobank that links circadian rest-activity rhythms with cardiometabolic outcomes**.
37. Abbott SM, Weng J, Reid KJ, Daviglus ML, Gallo LC, Loredo JS, et al. Sleep timing, stability, and BP in the Sueño ancillary study of the Hispanic Community Health Study/Study of Latinos. Chest. 2019;155(1):60–8.
38. Musiek ES, Bhimasani M, Zangrilli MA, Morris JC, Holtzman DM, Ju YES. Circadian rest-activity pattern changes in aging and preclinical Alzheimer disease. JAMA Neurol. 2018;75(5):582–90.
39.• Xiao Q, Sampson JN, LaCroix AZ, Shadyab AH, Zeitzer JM, Ancoli-Israel S, et al. Nonparametric parameters of 24-hour rest–activity rhythms and long-term cognitive decline and incident cognitive impairment in older men. J Gerontol Ser A. 2022;77(2):250–8. **Findings based on nonparametric analysis of actigraphy from the MrOS study suggest a link between rest-activity rhythms and cognition in men**.
40.•• Gao L, Li P, Gaykova N, Zheng X, Gao C, Lane JM, et al. Circadian rest-activity rhythms, delirium risk, and progression to dementia. Ann Neurol. 2023. **Another representative population-scale study based on the UK Biobank that links circadian rest-activity rhythms with post-operative delirium**.
41. Sohail S, Yu L, Bennett DA, Buchman AS, Lim AS. Irregular 24-hour activity rhythms and the metabolic syndrome in older adults. Chronobiol Int. 2015;32(6):802–13.
42. Huang NE, Shen Z, Long SR, Wu MLC, Shih HH, Zheng QN, et al. The empirical mode decomposition and the Hilbert spectrum for nonlinear and non-stationary time series analysis. Proc R Soc -Math Phys. Eng Sci. 1998;8(454):903–95.
43. Wang YH, Young HWV, Lo MT. The inner structure of empirical mode decomposition. Phys Stat Mech Its Appl. 2016;15(462):1003–17.
44. Huang NE, Shen Z, Long SR. A new view of nonlinear water waves: the Hilbert spectrum. Annu Rev Fluid Mech. 1999;31:417–57.
45. Wu Z, Huang NE. Ensemble empirical mode decomposition: a noise-assisted data analysis method. Adv Adapt Data Anal. 2009;1(01):1–41.
46. Wang YH, Hu K, Lo MT. Uniform phase empirical mode decomposition: an optimal hybridization of masking signal and ensemble approaches. Ieee Access. 2018;6:34819–33.
47. Liao M, Guo Y, Qin Y, Wang Y. The application of EMD in activity recognition based on a single triaxial accelerometer. Biomed Mater Eng. 2015;26(s1):S1533–9.
48. Hu K, Ivanov PC, Chen Z, Hilton MF, Stanley HE, Shea SA. Non-random fluctuations and multi-scale dynamics regulation of human activity. Phys-Stat Mech Its Appl. 2004;337(1–2):307–18.
49. Iyengar N, Peng CK, Morin R, Goldberger AL, Lipsitz LA. Age-related alterations in the fractal scaling of cardiac interbeat interval dynamics. Am J Physiol. 1996;271(4 Pt 2):R1078–84.
50. Hu K, ScheerFA JL, Ivanov PC, Buijs RM, SA S. The suprachiasmatic nucleus functions beyond circadian rhythm generation. Neurosci. 2007;149(3):508–17.
51. Li P, To T, Chiang WY, Escobar C, Buijs RM, Hu K. Fractal regulation in temporal activity fluctuations: a biomarker for circadian control and beyond. JSM Biomark. 2017;3(1):1008.
52. Pittman-Polletta BR, Scheer FAJL, Butler MP, Shea SA, Hu K. The role of the circadian system in fractal neurophysiological control. Biol Rev Camb Philos Soc. 2013;88(4):873–94.
53. Peng CK, Havlin S, Stanley HE, Goldberger AL. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. Chaos Woodbury N. 1995;5(1):82–7.
54. Hu K, Riemersma-van der Lek RF, Patxot M, Li P, Shea SA, Scheer FA, et al. Progression of dementia assessed by temporal correlations of physical activity: results from a 3.5-year, longitudinal randomized controlled trial. Sci Rep. 2016;6:27742.

55. Li P, Yu L, Lim ASP, Buchman AS, Scheer FAJL, Shea SA, et al. Fractal regulation and incident Alzheimer's disease in elderly individuals. Alzheimers Dement J Alzheimers Assoc. 2018;14(9):1114–25.
56. Li P, Lim ASP, Gao L, Hu C, Yu L, Bennett DA, et al. More random motor activity fluctuations predict incident frailty, disability, and mortality. Sci Transl Med. 2019;11(516):eaax1977.
57.•• Gao L, Li P, Gaba A, Musiek E, Ju YES, Hu K. Fractal motor activity regulation and sex differences in preclinical Alzheimer's disease pathology. Alzheimers Dement Diagn Assess Dis Monit. 2021;13(1):e12211. **Findings from the "Sleep and tau" cohort that, for the first time, link fractal patterns in actigraphy with in vivo Alzheimer's disease pathology**.
58. Dijk DJ, Czeisler CA. Paradoxical timing of the circadian rhythm of sleep propensity serves to consolidate sleep and wakefulness in humans. Neurosci Lett. 1994;166(1):63–8.
59. Duffy JF, Dijk DJ. Getting through to circadian oscillators: why use constant routines? J Biol Rhythms. 2002;17(1):4–13.
60. Wittmann M, Dinich J, Merrow M, Roenneberg T. Social jetlag: misalignment of biological and social time. Chronobiol Int. 2006;23(1–2):497–509.
61. Tranah GJ, Blackwell T, Stone KL, Ancoli-Israel S, Paudel ML, Ensrud KE, et al. Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. Ann Neurol. 2011;70(5):722–32.
62. Posner AB, Tranah GJ, Blackwell T, Yaffe K, Ancoli-Israel S, Redline S, et al. Predicting incident dementia and mild cognitive impairment in older women with nonparametric analysis of circadian activity rhythms in the Study of Osteoporotic Fractures. Sleep. 2021;44(10):zsab119.
63. Rogers-Soeder TS, Blackwell T, Yaffe K, Ancoli-Israel S, Redline S, Cauley JA, et al. Rest-activity rhythms and cognitive decline in older men: the osteoporotic fractures in men sleep study. J Am Geriatr Soc. 2018;66(11):2136–43.
64.• Xu Y, Wang X, Belsky DW, McCall WV, Liu Y, Su S. Blunted rest-activity circadian rhythm is associated with increased rate of biological aging: an analysis of NHANES 2011-2014. J Gerontol A Biol Sci Med Sci. 2022:glac199. **Recent findings from the National Health and Nutrition Examination Survey suggest a link between blunted rest-activity rhythms and biological aging**.
65. Hoopes EK, Patterson F, Berube FR, D'Agata MN, Brewer B, Malone SK, et al. Actigraphy-derived rest–activity rhythms are associated with nocturnal blood pressure in young women. J Hypertens. 2021;39(12):2413–21.
66. Moon C, Benson CJ, Albashayreh A, Perkhounkova Y, Burgess HJ. Sleep, circadian rhythm characteristics, and melatonin levels in later life adults with and without coronary artery disease. J Clin Sleep Med. 2023;19(2):283–92.
67.•• Li P, Sun H, Gao C, Gao L, Yu L, Yang J, et al. Circadian age, chronological age, and Alzheimer's dementia. In: Alzheimer's Association International Conference; 2022 Aug 1. CA: San Diego; 2022. **Pilot results that imply the potential by integrating multiple circadian rest-activity rhythms measures for a homogenous biomarker of circadian health, namely circadian age that may represent the biological age of the circadian control**.