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Integrating wearable data into circadian models

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Abstract

The emergence of wearable health sensors in the last decade has the potential to revolutionize the study of sleep and circadian rhythms. In particular, recent progress has been made in the use of mathematical models in the prediction of a patient's internal circadian state using data measured by wearable devices. This is a vital step in our ability to identify optimal circadian timing for health interventions. We review the available data for fitting circadian phase models with a focus on wearable data sets. Finally, we review the current modeling paradigms and explore avenues for developing personalized parameter sets in limit cycle oscillator models to further improve prediction accuracy.

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Introduction

Chronic sleep deprivation and circadian disorders have reached critical levels around the world by recent estimates. For instance, a large chronotype survey found that approximately 69% of the respondents reported social jet lag of 1 h or more [1]. Circadian disruption and misalignment with the external environment has been linked to a host of negative mental and physical health outcomes [2,3].

In mammals, the core circadian clock has been localized to a region of the hypothalamus known as the suprachaismatic nucleus (SCN). To remain entrained to the external environment, the SCN must receive temporal information from external forces known as zeitgebers (time-givers). In mammals, the most important zeitgeber is the daily light cycle. The master clock, in the SCN, then coordinates a population of peripheral clocks producing physiological rhythms throughout the body.

The sleep and circadian research communities have made tremendous progress in elucidating the core mechanisms driving and connecting sleep and circadian rhythms. Translation of these scientific advances into improvements in circadian and sleep health of the populace has proved difficult [4]. For example, it has been found that the efficacy of a number of treatments vary in a circadian manner [5,6]. Application of this knowledge will require the ability to accurately predict the circadian phase of patients [7,8].

Circadian phase prediction is an inherently difficult problem. Circadian phase in humans can only be measured indirectly through the use of a peripheral marker rhythm driven by the core clock [9]. However, each of these peripheral rhythms has the potential to be obscured (masked) by behavioral rhythms such as the sleep–wake cycle [10]. This challenge has been met by the development of a series of laboratory protocols designed to isolate the circadian signatures from marker melatonin/core body temperature rhythms [10]. Although these protocols have been essential to determining many core circadian clock properties, the labor, expense, and significant patient burden make them impractical for use on large populations or children [4,11].

Personalizing circadian phase predictions will require novel data collection and mathematical modeling approaches. The advent and mass popularization of wearable technologies has provided an avalanche of data. However, this infusion of data will require careful integration into the accumulated body of knowledge using novel mathematical modeling techniques. Here, we will review the various data collection methods available and recent advances in building mathematical models.

Data overview

Phase assessment gold standards

The constant routine protocol is the current gold standard for human circadian phase estimation [10,12]. This protocol calls for participants to be held in a constant light environment free from time cues while a circadian marker is monitored. This constant environment

prevents the core circadian rhythms from being masked by exogenous periodic cycles and the sleep—wake cycle. Early circadian studies used the core body temperature as the circadian marker, although in recent years this has been replaced primarily by melatonin and other less invasive markers [13,14]. Melatonin rhythms may be collected from blood, saliva and urine samples, although using melatonin comes with the additional complication that even low levels of light suppress melatonin rhythms [14,15,12]. Thus, melatonin samples must be collected under dim light conditions of less than 30 lux-although many researchers strive for less than 5 lux [16]. Usually, samples are collected every 30—60 min and are used to estimate the onset of melatonin secretion which typically occurs just before bedtime. This time point is called the dim light melatonin onset (DLMO). Recently, positive progress has been made on an effort to move this protocol outside the laboratory by using self-collected melatonin samples from saliva, although compliance with this protocol could prove difficult in children and other groups [17].

These circadian phase assessment protocols may be applied to measure the effect of a light stimulus on the circadian phase. Plotting the timing of the stimulus (e.g. bright light) against the shift in circadian phase provides a phase response curve (PRC). PRCs are often used for treatment planning in clinical settings to determine the optimal timing to shift the circadian phase in the appropriate direction [18]. Several phase response curves to light have been found using a variety of light stimuli [13,19,20]. Moreover, several valuable data sets for the effect of light schedules of different duration's and intensities on the circadian phase have also been collected [21—23]. To date, PRC data have been the primary data used to fit and validate circadian prediction models [24,25].

Wearable data

A huge variety of wearable health and fitness trackers have entered the market place in the last decade. Generally, commercial versions of these devices will provide a time series of accelerometer and heart rate estimates based on photoplethysmography [26]. Wearable devices offer an objective alternative to self-reported data to measure circadian patterns of various clock outputs such as heart rate, sleep/wake patterns, activity, and wrist body temperature. Moreover, some of these devices have the ability to collect data on exposure to zeitgebers (e.g. ambient light exposure), although these are generally not found in commercial devices [4,27,2,28,26,29].

From a circadian phase estimation prospective, each of these sensor measurements should add additional information and improve circadian phase predictions. However, incorporation of these time series measurements has proved challenging. These variables are typically highly correlated with one another, and any circadian signatures within the time series can potentially be masked by the sleep—wake cycle or other biological rhythms [10]. Moreover, with the exception of the light intensity variable, each of these physiological processes is both an input and output of the master circadian clock. Each of these factors must be accounted for to build an accurate circadian phase prediction system.

The large size of wearable data sets has the potential to override some of these difficulties. The incorporation of commercial devices will likely be required to make maximal use of this big data potential for circadian phase predictions. The diversity of commercial devices on the market has proved a challenge to their validation. Moreover, the algorithms used in processing the raw sensor data are typically closed source and updated more quickly; then, they could be validated for research purposes [26]. However, recent progress has been made in extracting the raw accelerometer and heart rate data from a subset of these devices [26]. Development of open-source methods for the extraction and processing of raw sensor data from commercial devices is a crucial step toward incorporating these data into circadian phase estimates [26,4].

The relationship between the physiological variables measured by wearable devices and the gold standard for circadian phase estimation, DLMO timing, is still somewhat unclear. However, recent studies have found significant correlations between many of these time series and DLMO measurements [30,31]. In particular, measurements of the body temperature at the wrist and mid sleep time have been found to be correlated with the DLMO and have been applied to estimate circadian phase [32,30,31,33,34]. It remains to be seen how these correlations can be used to refine circadian phase estimates. In the best case scenario, these relationships in combination with a lengthy time series could eliminate the need for DLMO estimation all together. However, the majority of the correlation results above were obtained under regular entrainment conditions for healthy adults. Before generalizing these results to larger populations, additional validation will be required across larger demographic ranges and environmental conditions.

Predicting phase from wearables

The lengthy time series data collected by wearable devices have allowed for machine learning techniques to be used in sleep and circadian prediction [35,26,36,30,37]. For example, artificial neural network (ANN) approaches have provided some of the most accurate predictions of circadian phase [35,36]. The ANN approach is appealing because of the success of

these techniques in predicting a variety of complex time series data [38]. Furthermore, these techniques do not require a mechanistic model and are therefore well-suited to deal with the modeling of complex phenomena. However, the predictions of ANN models have been found to perform poorly when applied to the more challenging problem of circadian phase prediction for shift workers [35].

Limit cycle oscillator models

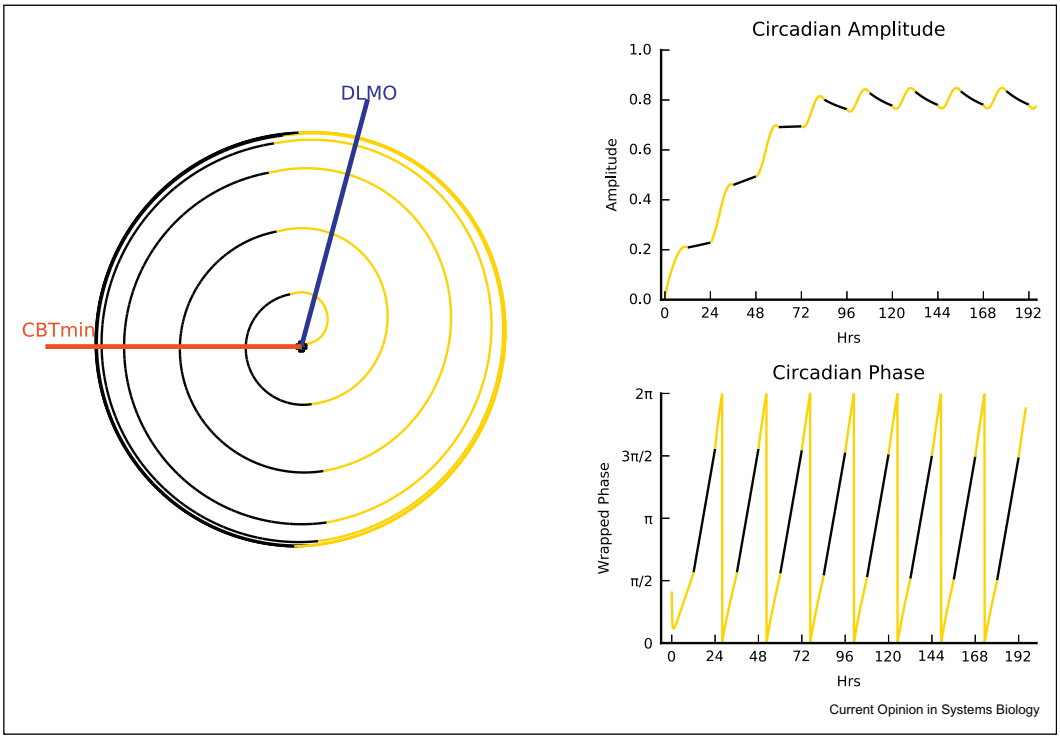
Mathematically, the circadian clock is an example of an attracting limit cycle oscillator (LCO), meaning its solutions contain a stable closed trajectory comprising a self-sustained oscillator (Figure 1). The most widespread LCO models for human circadian rhythms are based on progressive modifications of a Van der Pol nonlinear oscillator model [39,25,40,41,18]. Recently, a class of models based on a systematic reduction of phase oscillators was proposed and fit to human phase response curve data [24,42]. These models are based on the network level physiology of the core clock, and therefore, the parameters are endowed with physiological interpretations [24]. By comparison, the lack of a physiological foundation for the Van der Pol–based models makes parameter and variable interpretations more problematic. Each of these LCO models can take the light levels recorded by a wearable device and generate a circadian phase prediction as seen in (Figure 2).

A LCO model was recently applied to the prediction of circadian phase using wearable data for medical shift workers and compared against direct measurements of circadian phase [8]. These predictions were found to be accurate to within ± 1 hour for 70–80% of subjects in the study. This is comparable with the accuracy of predictions made for diurnal subjects in previous studies [43,44]. Being able to more accurately predict the circadian phase of shift workers from wearable data will help to facilitate the delivery of light therapy in the treatment of shift-work disorder.

Parameters for limit cycle oscillator models

LCO models have parameters $(\vec{\theta})$ which must be estimated using experimental phase response data (D_k). Optimization over a least squares cost function leads to a maximum likelihood estimation of the best-fit $(\vec{\theta}^*)$ parameter set.

Figure 1



This figure shows an example simulation for a LCO model. The individual is started from a low amplitude rhythm (near 0) and then is entrained to a regularly repeated light schedule with a period of 24 h. The yellow color shows light exposure times, and the dark shade shows periods of darkness on all plots. On the left, the phase plane plot shows a parametric plot of the phase and amplitude variables growing toward a limit cycle solution (closed trajectory). Two circadian phase markers used in human circadian rhythms are shown (CBT_{min} is the minimum of the core body temperature rhythm, and the DLMO is the dim light melatonin onset). The right plots show the amplitude (top) and phase plotted against the time variable [24].

$$\overrightarrow{\theta}^{*} = \arg\min \frac{1}{2} \sum_{k=1}^{N} \left(\frac{D_k - M_k(\overrightarrow{\theta})}{\sigma_k} \right)^2 \quad (1)$$

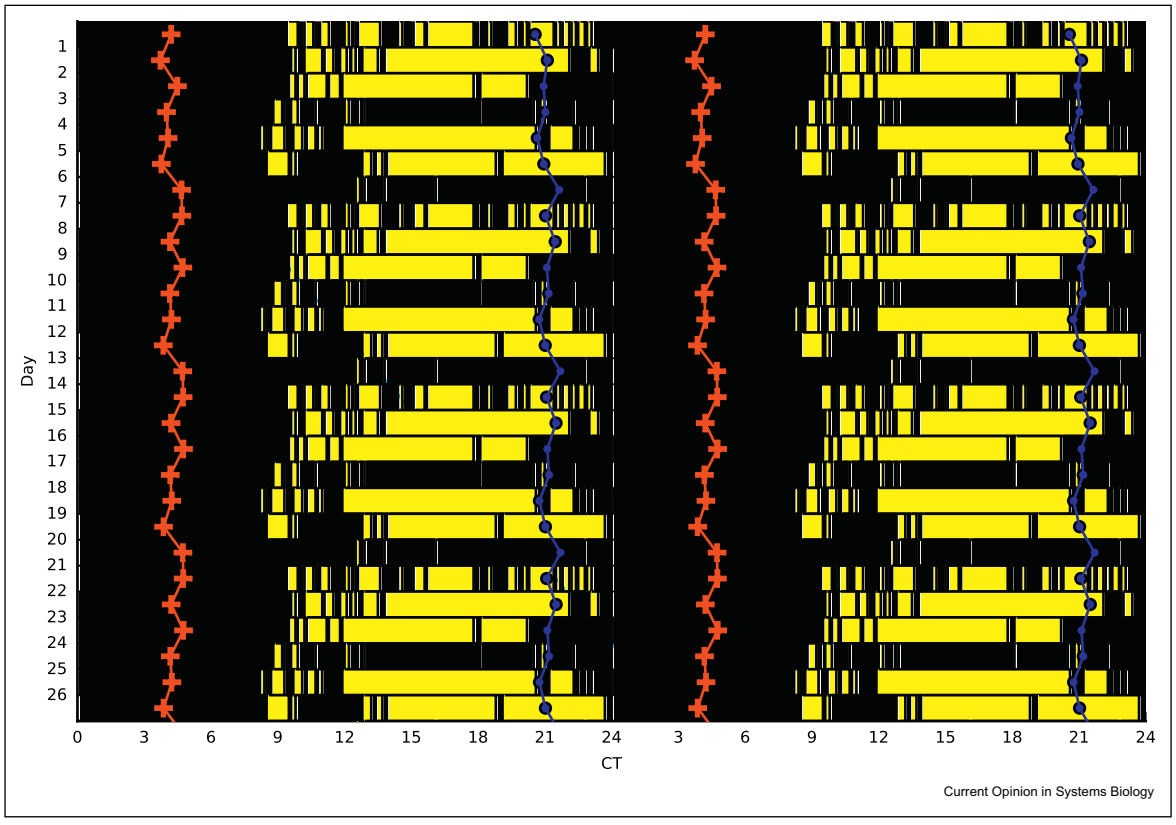
These best-fit parameter sets have been applied to generate circadian phase predictions from the model [8,44,43]. This use of a single set of best-fit parameters ignores the inherent experimental, parameter and model uncertainty [46]. Significantly, parameter uncertainty results from the variation in the circadian parameters among the individuals used to construct the experimental curve. These uncertainties may be partially accounted for by adopting a Bayesian approach and generating an ensemble of parameters which are consistent with the experimental data rather than a single best-fit set [24,47]. From a clinical prospective the generation of statistical parameter ensembles could assist in the classification of circadian and sleep disorders. Whether these states are identifiable as distinct regions in parameter space remains to be seen, however the development of low-dimensional models whose parameters can be tied to clock physiology should help in this regard [24].

Parameter estimation for circadian models

The intrinsic period (τ) parameter is influential in predictions, is variable across the human population, and can be measured directly using a forced desynchrony protocol [48–51]. Forced desynchrony decouples the sleep and circadian cycles, allowing the unmasked circadian cycle to be measured for long enough (10–20 days) to accurately assess the period [52,53].

Surveys can also be used to study circadian heterogeneity in larger samples than laboratory approaches, and the results of chronotype surveys have been found to be related to key circadian parameters [54,55,11,56]. Beyond the circadian period parameter, other parameters in circadian models have also been found to vary [57]. A striking example of this is provided by a recent study, which found that evening light intensities varying from dim reading light (10 lux) to bright indoor light (400 lux) caused equivalent suppression of melatonin rhythms in healthy young adults [57].

Figure 2



Wrist light level measurements recorded by an Actiwatch Spectrum wearable device [45]. The light recordings span one week but are repeated four times for illustration. The yellow blocks indicate light levels over 10 lux, and black areas indicate light levels below 10 lux. Red crosses show model predictions of the core body temperature (CBT) minimum circadian marker, and blue circles show model predicted DLMO timing [24].

The large data sets produced by wearable devices could be used to estimate key model parameters. A methodological challenge is how best to integrate the wearable device data alongside the laboratory and survey data. Some promising results have been found using a particle filter approach to integrate across these heterogeneous data sources [58]. Particle filters provide optimal state estimation by integrating a dynamical model with noisy observations [58]. As wearable data sets become more widely available, additional mathematical and computational tools will need to be developed to optimally perform this integration.

Conclusion

Here, we have reviewed the various data sources available for circadian phase prediction of which large-scale wearable data is an important component. In addition, we reviewed recent advances in mathematical and computational models for integrating wearable data into phase predictions.

Circadian phase prediction is a difficult problem, and a solution will require advancements in a number of fields. The first challenge will be to develop inexpensive methods for circadian phase measurement/validation which are suitable to be deployed on a massive scale outside the laboratory. Secondly, the challenge of incorporating and processing the heterogeneous and noisy measurements collected by wearable devices must be faced. Finally, new models and paradigms will need to be developed which can integrate laboratory, survey, and wearable data into predictions. Each of these data sources provide a complementary picture, and optimal circadian phase prediction will require that each of these are integrated into the predictive model.

Conflict of interest statement

Nothing declared.

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