Circadian Phase Prediction from Non-Intrusive and Ambulatory Physiological Data

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***Abstract*— Chronotherapy aims to treat patients according to their endogenous biological rhythms and requires, therefore, knowing their circadian phase. Circadian phase is partially determined by genetics and, under natural conditions, is normally entrained by environmental signals (*zeitgebers*), predominantly by light. Physiological data such as melatonin concentration and core body temperature (CBT) have been used to estimate circadian phase. However, due to their expensive and intrusive obtention, other physiological variables that also present circadian rhythmicity, such as heart rate variability, skin temperature, activity, and body position, have recently been proposed in several studies to estimate circadian phase. This study aims to predict circadian phase using minimally intrusive ambulatory physiological data modeled with machine learning techniques. Two approaches were considered; first, time-series were used to train artificial neural networks (ANNs) that predict CBT and melatonin dynamics and, second, a novel approach that uses scalar variables to build regression models that predict the time of the minimum CBT and the dim light melatonin onset (DLMO). ANNs require less than 48 hours of minimally intrusive data collection to predict circadian phase with an accuracy of less than one hour. On the other hand, regression models that use only three variables (body mass index, activity, and heart rate) are simpler and show higher accuracy with less than one minute of error, although they require longer times of data collection. This is a promising approach that should be validated in further studies considering a broader population and a wider range of conditions, including circadian misalignment.**

***Index Terms*— Circadian phase, chronotype, circadian rhythms, machine learning, mathematical models, physiological data.**

I. Introduction

MANY aspects of human physiology, metabolism, and behavior exhibit patterns that repeat approximately every 24 hours and are, therefore, called circadian. The master pacemaker that controls the circadian rhythms of sleep and wakefulness, core body temperature, and hormone secretion is the hypothalamic suprachiasmatic nucleus (SCN) that is entrained by exogenous factors [1]. In addition, virtually every cell of the body contains a circadian oscillator that contributes to the daily rhythmicity of a large variety of physiological and metabolic activities [2].

Individuals have different circadian phases, also called phases of entrainment, that are determined by internal and external factors and result in different preferences for sleep-wake and other physiological and behavioral schedules known as chronotypes [3], [4]. Chronotypes range from morning to evening types, with evening types having routines 2-3 hours later than morning types [5].

Circadian misalignment occurs when there is a mismatch between the environment's time and the body's internal time, and it can generate health issues such as sleep, digestion, and hormone secretion problems, obesity, and decreased cognitive performance [6], [7]. Light is one of the most influential exogenous factors for circadian entrainment that, currently, can be disrupted by multiple artificial lights coming from different devices. On the other hand, natural rhythms can sometimes be restored by light therapy [8]. Other external stimuli that can affect circadian phase are work schedules, social commitments, night light, and noise pollution. The combination of all these factors can generate a misalignment called social jetlag [7].

There is an increasing interest in developing accurate methods to determine circadian phase, not only to diagnose circadian misalignment and prescribe treatment but also to optimize the administration of many drugs and treatments at the optimal time of day [9].

The main physiological variables that have been considered to be good predictors of circadian phase are the following:

- **Melatonin concentration,** which is the "gold standard" to determine circadian phase because it is a reliable marker and a stable indicator, although it is affected by light exposure, some foods and drinks, stress, certain diseases and several drugs such as beta-blockers [10]–[13]. In individuals entrained to the light-dark cycle, melatonin levels begin to increase before sleep and peak during the first part of the night. Therefore, melatonin concentration can be measured in blood plasma, saliva, or urine, when the person is at rest in a dim light environment, and the time at which the amount of melatonin exceeds a certain threshold is known as the Dim Light Melatonin Onset (DLMO) [14].
- **Core body temperature (CBT),** which follows a circadian pattern, and its minimum can be considered a phase marker. There are three main ways to measure it: rectal and esophageal probes that are cheap but uncomfortable and delicate to ambulatory measurement and telemetry temperature

Manuscript received December 26, 2019. This work was supported by FONDECYT grant No. 1181094. (Corresponding author: M. Rodriguez-Fernandez).

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pills that are expensive but allow less intrusive ambulatory procedures. One of the limitations of CBT as a marker of circadian phase is that it can be affected by different stimuli known as masking effects, such as sleep onset, postural changes, activity levels and calorie intake [15].

Both of these markers have been well studied, but measuring them is expensive and laborious, and their measurement requires constant routine conditions to reduce masking effects on CBT and light-controlled conditions for melatonin concentration. Therefore, measuring these variables is not practical for large studies [16].

Due to the difficulties in measuring circadian markers such as DLMO and CBT, questionnaires have been developed to obtain an approximation of the sleep-wake schedule preferences. The Morningness-Eveningness Questionnaire (MEQ) of Horne and Ötsberg has been used since 1976 in various studies all over the world [17] and consists of a test of 19 questions about time preferences for performing physical and mental exercises, sleepiness, and hunger feeling and, based on the answers, it gives a score and obtains a rating for the chronotype between 16 (extreme eveningness) and 86 (extreme morningness). Another relevant test is the Münich Chronotype Questionnaire (MCTQ) created by Roennenberg et al. [18] that was translated into different languages and consists of 15 questions about sleep-wake schedules for working days and free days. The result of this test is the midpoint of sleep on free days (MSF) corrected for the sleep debt accumulated throughout the working days as an indicator of the chronotype (MSFsc). Although these questionnaires have been validated and used in multiples research studies, they are not measures of circadian phase and often do not correlate with melatonin phase [19].

Mathematical approaches have been developed to estimate circadian phase using less cumbersome physiological variables that also exhibit circadian rhythmicity, such as heart rate variability (HRV), skin temperature, breathing rate, physical activity, and external factors, such as light exposure [20], [21]. Kolodyazhniy et al. [22] developed a multiple linear regression model using skin temperature from eleven sensors, motion acceleration, and ambient light to predict the center of gravity of the area under the 24-hour melatonin curve from ambulatory data of 16 subjects using a multichannel monitoring system. The results showed statistically significant improvement over traditional approaches based on single predictors. One year later, the same authors generated an improved model adding nine more subjects following the same protocol and using a nonlinear regression model based on artificial neural networks (ANNs) that considered the same features decreasing the mean error ± SD from 12±41 minutes to -3±23 [20]. In an independent study, Gil et al. [23] developed different autoregressive moving average with exogenous inputs (ARMAX) models to predict DLMO using intervals between successive heartbeats (RR intervals) and light exposure showing a prediction error of 2±39 minutes (mean ± SD). The year after, the same authors published another study [21] also using ARMAX models but adding new predictors such as spectral and temporal HRV features and distal and proximal skin temperature, achieving an error of 17±28 minutes (mean ± SD). This is considered an improvement since the mean is the bias of the model, while the SD is the real measure of precision. Bonmati-Carrion et al. [24] found a strong correlation of the wrist temperature increase onset with DLMO and a small error range (between -58 to 96 minutes). More recently, Woelders et al. [25] used the Kronauer's limit cycle model for the human circadian system to predict DLMO using light exposure and activity under free-running conditions, obtaining an SD of 66 minutes. Stone et al. [26] consider the ANN developed in [20] to be the most accurate model to date and extended this study to shift workers, obtaining a mean error ± SD of 6±50 minutes for participants that have fixed sleep schedules of 8 sleeping hours and 16 wake hours. However, the model did not generalize to predict circadian phase during night shift work where it obtained a mean error of 318 ± 337 minutes. Komarzynski et al [27] recently developed a multivariate linear regression model to predict the core temperature bathyphase using as predictors the sex of the participants, a chronotype questionnaire score, the center-of-rest time and chest surface temperature bathyphase obtained during daily routines, achieving an error of less than 1 hour for 78.8% of the subjects.

The present study aims to build improved models for predicting circadian phase using data from minimally intrusive physiological sensors. We used certified instruments and built two types of models that predict the two most widely accepted circadian phase markers, DLMO and CBTmin. The first set of models uses ANNs for predicting two different time series as outputs, namely, the DLMO cosine curve and CBT data. The second type of model was obtained using multiple regression aiming to predict circadian phase markers directly (DLMO and CBTmin) from scalar features mostly obtained from the time series.

II. Materials and Methods

A. Participants

Data collection took place between January and July of 2019 at the Institute for Biological and Medical Engineering, Pontificia Universidad Católica de Chile. Nineteen healthy males between 18 and 35 years old were recruited through social media and flyers posted at the University. Exclusion criteria included diagnosed diseases or sleep problems, consumption of more than 3 units of alcohol per week, more than 3 cups of coffee or 3 cigarettes per day, and shift work or travel across time zones in the last month prior to the study.

Informed written consent was obtained from all the participants. This study was approved by the Scientific Ethics Committee of the School of Medicine of the Pontificia Universidad Católica de Chile on June 21st, 2018 (Project 170706006).

B. Physiological data collection

All participants completed one week of ambulatory data collection. During data collection, subjects kept their usual sleep-wake cycle and work schedules. Fig. 1 shows the

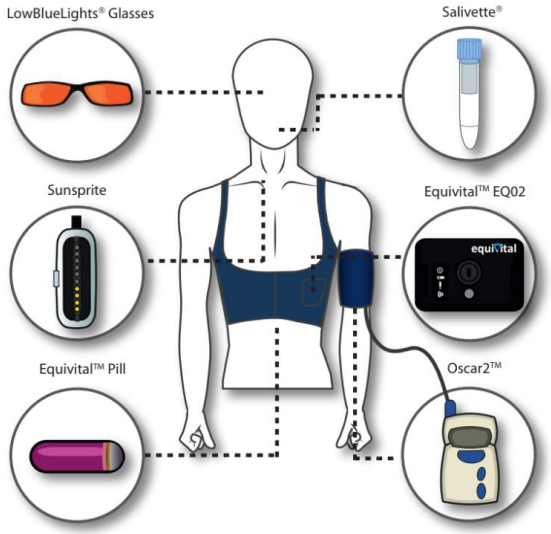

Fig. 1. Equipment used during the data collection protocol.

equipment used during the study, which is described as follows:

• **Equivital™** is a wireless physiological monitoring system able to record breathing rate (BR), under-arm skin temperature, electrocardiogram (ECG), activity and body position via a compact and unobtrusive sensor belt and a Sensor Electronics Module (SEM) that has a single connection port to interface with the sensor belt. It has FDA 510K clearance and is CE marked. The sampling rate is 256 Hz for the ECG, 26 Hz for the triaxial accelerometer, and 0.25 Hz for the other physiological variables.

• **VitalSense® Core Temperature** is an ingestible and disposable capsule that, once activated by the Equivital Core Temperature Pill Activator and swallowed, wirelessly transmits temperature measurements to the nearby Equivital SEM every 15 seconds within a 12-48 hour period, depending on each individual gastrointestinal transit time. The capsule dimensions are 8.5 mm diameter and 23 mm long, it weighs 1.6 grams and the nonreplaceable battery lasts for 240 hours from the time of activation. The accuracy is ±0.1ºC for temperatures between 32 and 42ºC, and the nominal transmission range is 1 m.

• **SunSprite** is a solar-powered wearable device that measures and tracks the amount of sun (UV index) and visible light (illuminance in luxes) that a person receives at a rate of one sample per minute. Participants were instructed to clip the Sunsprite with its flexible magnetic attachment to a collar, sleeve, pocket, or a lapel on the front of their body between their eyes and pockets and to keep it uncovered for the entire week.

• **Systolic, diastolic and mean arterial pressure (MAP)** was measured during 24 hours by an ambulatory blood pressure monitor (ABPM), Oscar 2TM (SunTech Medical®), at one sample every 15 minutes during the day and every 30 minutes at night (sleep-wake schedules were programmed for each subject according to their self-reported usual schedules). The ABPM measures pressure by the oscillometric method, which senses pressure waves in the artery when occluded by the sphygmomanometer cuff pressure. This device was validated by the British Hypertension Society (BHS), the European Society of Hypertension (ESH) and meets the standards of the Association for the Advancement of Medical Instrumentation (AAMI) [28].

• **Saliva samples** were collected in Salivettes® under dim light conditions (<10 lux) at home, starting 6 hours before the usual sleep time, while wearing 100% blue light-blocking glasses (LowBluelights®). One hour after the dim light started, the subjects collected the first sample and continued hourly until sleep time, for a total of six samples per participant. Detailed instructions about the protocol for saliva sample collection, described in [14], were given to the participants. Compliance with the protocol was assessed by interviews at the moment of returning the samples to the laboratory and with the light sensor [29]. The subjects stored the samples at their home at 4°C until bringing them to the laboratory. In the laboratory, samples were centrifuged and stored at -80°C until further analysis. Melatonin concentrations were determined using commercial Melatonin direct Saliva ELISA KITs (IBL International GMBH). Standards and all samples were incubated in duplicate wells of microliter plates and analyzed by spectrophotometry.

Table I shows the schedule for the use of each piece of equipment. Equivital system and Sunsprite were used over the whole week, core temperature pills were taken on Friday and saliva samples on Sunday evening. ABPM (Oscar2) was used for 24 hours any day between Monday and Friday.

TABLE I
SCHEDULE FOR DATA COLLECTION AND EQUIPMENT USE

Equipment	Mon	Tue	Wed	Thu	Fri	Sat	Sun
Equivital™ EQ02	■	■	■	■	■	■	■
Sunsprite	■	■	■	■	■	■	■
Oscar2™				■	■		
VitalSense® Pill					■	■	
Glasses and Salivettes®							■

C. *Chronotype questionnaires*

Volunteers were requested to answer two online questionnaires about their chronotype. First, participants responded to the Spanish version of the Morning-Evening Questionnaire (MEQ) [17], [30] which takes into consideration variables such as mental and physical activity, sleepiness, and hunger feeling. Second, they responded to the Spanish version of the Münich Chronotype Questionnaire (MCTQ) [18], [31] that considers sleep-wake schedules in working and free days to obtain MSFsc.

D. *Data gathering, preprocessing and consolidation*

Raw accelerometer data, RR intervals from ECG, CBT, skin temperature, heart rate (HR), and breathing rate (BR) were extracted from the Equivital SEM by the Equivital Manager software. These data were acquired at different sampling rates greater or equal to one sample per minute, and a dataset at one sample per minute was generated by downsampling when needed using a moving average filter. Additionally, outliers were removed by filtering the data according to realistic

physiological responses, such as HR > 30 beats per minute, BR > 6 breaths per minute, RR intervals > 200 ms, and CBT > 34°C. The data that did not comply with these restrictions were considered a sensor error and removed from the dataset.

Two features were extracted from the accelerometer's data, the angle and the magnitude of the acceleration vector. The position angle of the person with respect to a horizontal baseline (between 0° and 90°) was calculated following [32] and corrected by using the complementary angle. The Equivital monitor has a tri-axial accelerometer that gives information about coordinates of the three axes X, Y, Z (see Fig. 2), and with this information, the angle was calculated as follows:

$$\theta = 90 + tan^{-1}\left(\frac{x^2+y^2}{z}\right) \quad (1)$$

Fig. 2. Representation of three axes for the calculation of the angle of the position.

The magnitude of the acceleration vector was used to compute the Vector Magnitude Count (VMC) [33]:

$$VMC(t;H) = \frac{1}{H} * \sum_{h=0}^{H-1} r(t+h) - \bar{r}(t;H) \quad (2)$$

where H is the time frame that was analyzed, in this case, a one minute window, r is the vector's magnitude obtained by $r^2 = x^2 + y^2 + z^2$ and $\bar{r}$ is the mean of r in the selected time frame.

On the other hand, RR intervals were processed in Matlab software, using a script based on the work of León, H. [34]. Time frames of five minutes were analyzed and features such as the HR, standard deviation of HR (SDHR), RR mean, Root Mean Square of the Successive Differences in RR (RMSSD), numbers of intervals that differ in more than 50 ms (NN50), percentage of intervals that vary less than 50 ms (pNN50), frequency analysis (high frequency (HF), low frequency (LF) and LF/HF ratio), SD1 and SD2 from Poincaré analysis, cardiac sympathetic index (CSI=SD2/SD1) and cardiac vagal index (CVI=log10(SD1 x SD2)) were obtained [35]. Means of RR, SDHR, RMSSD, NN50, pNN50, LF/HF, CSI, and CVI were used to create the time series dataset.

Sunsprite data was downloaded from the Sunsprite official page after synchronizing the mobile application and added to the dataset. Blood pressure data from the AMBP was extracted by USB cable using the software Accuwin Pro 4 (SunTech Medical).

DLMO was determined from the melatonin curve by linear interpolation of the times before and after the melatonin crosses a certain concentration level. Different methods have been suggested for defining this threshold, namely, establishing a fixed value or making it subject-dependent. When considering a fixed value, some subjects may never reach the fixed threshold ("low secretors") and some may always be above it; therefore, a dynamic threshold was preferred. The dynamic threshold was computed as the mean of melatonin values comprising the non-ascending part of the profile and the first value in the ascending part, plus two standard deviations (SD) of the mean, using software developed by Danilenko et al [36].

In this study, we used the DLMO cosine wave for the time-series models as in [23] instead of the melatonin concentration because we have just 6 hours of melatonin data and not 24-hour melatonin profiles similar to those in other studies [20], [25], [26]. A DLMO cosine wave was obtained for each subject with a cosine wave of a 24-hour period, amplitude of 1 and DLMO as the phase shift, so when the curve takes the value of 1, it is the time of the DLMO [23]. This signal was calculated as follows:

$$\text{DLMOcosine wave} = \cos(2\,\pi/24 * \text{t} - \text{DLMO}) \quad (3)$$

where $2\pi/24$ is the frequency in radians, t is the time in hours, and DLMO is the time when the onset of the melatonin concentration is reached.

The dataset included data from 19 subjects, 17 time series per subject, 15 regarded as inputs for modeling (HR, BR, skin temperature, angle position, VMC, light exposure, mean of RR, SD of RR, SD of HR, RMSSD, NN50, pNN50, LF/HF, and CSI, CVI) and 2 regarded as targets to be predicted (CBT and DLMO cosine curve) with approximately ten thousand data points per time series.

Constant features for each subject, namely, age, rest HR, body mass index (BMI), MSFsc and MEQ score, were lumped with other scalar features derived from the time series to generate a dataset of scalar inputs. The targets to be predicted were the time of the minimum CBT and the DLMO. The time series-based features are presented below:

- **Time of the minimum CBT (CBTmin):** The first 4 hours of data were deleted in order to allow the pill to reach the intestinal tract [37]. To obtain the minimum from the signal avoiding outliers and spurious data, a two harmonic regression, with 24- and 12-hour periods, was fitted to the experimental data [38]. The time at which the minimum of the fitted curve is obtained was considered as CBTmin.
- **Time of the minimum mean arterial pressure (MAPmin):** The same protocol used for the CBT was applied to obtain the MAPmin.
- **L5 and M10 of VMC, MAP, CBT and HR:** L5 is the midpoint of the five hours with the lowest average value of the corresponding feature and M10, the midpoint of the ten hours with highest mean. This was calculated by taking a moving window of 5 or 10 hours throughout the entire data of the selected feature and obtaining the mean, then selecting the mean of the lowest or highest value, respectively. In case more than 24 hours of data for one feature were collected, such as VMC, L5 and M10 were calculated as the mean of the L5 or

M10 for each day of the week, and they were also calculated separately for working days and free days.

• **Interdaily stability (IS) and intradaily variability (IV) of the VMC:** The IS gives stability over different days, and the IV gives information about the fragmentation of the rhythm. These features were calculated for working and free days following the equations presented in [39].

This dataset has 30 scalar features per subject.

E. Correlation matrices

Normality of the distribution of data was determined using the Kolmogorov-Smirnov test. Scalar features were shown to be normally distributed, so the Pearson's correlation test was used to assess the correlation among them. Conversely, the time-series were not normally distributed, so the Spearman's correlation test was used to assess correlations in this case. The Pearson's correlation coefficient (r), the Spearman's rank correlation coefficient (r_S) and their respective p-values (P) were calculated in pairs. A $P<0.05$ was considered statistically significant.

F. DLMO cosine curve and CBT prediction

For predicting the DLMO cosine curve and the CBT time series, ANNs were trained using as inputs a subset of 15 available time-series. To build parsimonious models requiring fewer physiological variables to be measured, a maximum number of 8 features was considered.

Before training, a data conditioning stage was considered. First, the missing data from the predictors and the CBT time series was linearly interpolated. Then, a Savitsky-Golay filter [40] of order 3 was applied in batches of 15 samples. Finally, the input variables and the CBT were normalized by time series.

The ANN configuration consisted of a two-layer feed-forward network with sigmoid hidden neurons and linear output neurons. The input layer considers lags determined by evaluating the performance of a set of candidate models, which were built following a combinatorial design using short-term lags, 1, 5, 10 and 15 minutes, and long-term lags, 30, 60, 90, 120, and 240 minutes, both backward and forward in order to explore how short-term and long-term lags contribute to explaining the time series. The best performer among the candidates considered forward and backward lags of 2 and 4 hours for each of the inputs when the target was DLMO, and backward lags of 15, 30, 60, and 90 minutes when the target was the CBT time series. The number of hidden neurons was selected depending on the number of inputs as the floor of one-third of the number of inputs of the net. The ANNs were trained using the Matlab Neural Net Fitting application with the scaled conjugated gradient algorithm [41].

To validate the models, two methods were used: i) the subset method, using 70% of the data to train, 15% to validate, and 15% to test; the data were divided at random; ii) 4-fold cross-validation repeated 10 times in each model to obtain the average performance of the model; in this case, the data were divided by subject, leaving 75% of the subjects to train and 25% of the subjects to test.

In both cases, DLMO cosine curve and CBT time series, the best models were selected by exhaustive search among all possible combinations by comparing the root mean squared error (RMSE) between the original signal of the test set and the output of the NN and choosing those with the smallest value. This criterion was applied to both validation methods.

To quantify the prediction of circadian phase from the DLMO cosine wave, the output of the ANN was adjusted to one harmonic regression, and the maximum was calculated to obtain the phase of the DLMO from the ANN. The DLMO obtained from the ANN was compared with the experimental DLMO for each subject, and the mean error ±SD was calculated [23].

On the other hand, to compare CBT from the ANN model with the original signal, CBTmin was calculated with a two-harmonic regression for both signals, and the mean error ± SD was computed.

G. DLMO and CBTmin prediction

Different regression models that aimed to predict the two most commonly used markers of circadian phase, DLMO and CBTmin, were developed. Features derived from the CBT and DLMO were not considered as predictors since the goal was to obtain models that require minimally intrusive methods for data collection. From the remaining scalar features, predictors were selected by a hybrid method combining a filtering method and a wrapper method. The filtering method was used to reduce the number of features relying on general characteristics of the data, and the wrapper method selects features based on the results of the regression models [42].

First, the variables were filtered by a correlation-based feature selection (CFS) method. This method is capable of detecting relevant variables and dismissing redundant, irrelevant, and noisy features using the following measure [43]:

$$\mathrm{Ms} = \mathrm{k} * \frac{\mathrm{rcf}}{(\mathrm{k}+\mathrm{k}*(\mathrm{k}-1)*\mathrm{rff})^{1/2}} \quad (4)$$

where Ms is a vector with the results of multiple combinations of k features, k is the number of features that have to be selected from the total of variables, rcf is the mean of all correlation indexes between the response and the predictors, and rff is the mean of the correlation indices between the predictors. The numerator indicates how predictive the subset of k features is, and the denominator how much redundancy exists between the k features [43]. Therefore, the highest value of Ms considering k=10 was selected.

After the filtering stage, a wrapper method was used to select features based on model performance. For that, an exhaustive search optimization algorithm was applied in order to find the best model considering all possible combinations of the 10

preselected variables. Despite the high computational time required, an exhaustive search is recommended when feasible since it can guarantee that the optimal model is found [44]. To avoid overfitting, only combinations of up to 4 features were considered.

Since specific knowledge about which algorithm would perform better on the data at hand is lacking, the Matlab Regression Learner app was used to train and validate different methods for regression divided into five groups: linear regression models (just linear, considering interactions and stepwise), regression trees (fine, medium, coarse), support vector machines (linear, cubic, Gaussian), Gaussian process regression models (squared, Matern 5/2, exponential, rational quadratic), and ensembles of trees (boosted and bagged). The performance of these models was obtained by applying the RMSE between the predicted feature and its experimental value. The models were fitted to the data of all the participants simultaneously, and validation was performed by 5-fold cross-validation and repeated 20 times for each of the models to obtain robust results [44]. The model with the smallest RMSE in cross-validation was selected for each of the predicted features [45]. The mean error ± SD in minutes was calculated between the model predictions and original data, the mean represents the bias, and the SD is a measure of the precision of the models [21].

III. Results

One of the 19 participants was not used due to data collection problems leading to missing melatonin and CBT data. Two subjects did not have MSFsc because they could not choose sleep times freely on free days, one subject did not have an identifiable DLMO, and one subject had trouble with light data collection. The percentage of data loss for each sensor was: ECG = 4%, breathing rate = 15%, skin temperature = 15%, CBT = 4%, accelerometer = 4%, light = 6%, and BP = 16%. The 18 participants considered had an average of 7 ± 3% missing data that could be reconstructed by the linear interpolation and the Savitsky-Golay filter described above.

The age of the subjects was 24.77 ± 3.51 years old, and BMI was 24.54 ± 3.16 kg/m^2.

DLMO results ranged from 20:38 to 00:49 hours (mean± SD, 22:18±1:19), CBTmin from 03:26 to 07:46 hours (05:47±1:34) and MSFsc from 03:34 to 06:43 hours (05:06±1:02). DLMO and CBTmin were normally distributed. The MEQ score ranged from 29 to 59 (45.8±7.6), and MEQ chronotype classification was as follows: 1 moderate morningness, 14 intermediate, 2 moderate eveningness, and 1 extreme eveningness.

VMC, HR and most of the signals obtained exhibit periodic patterns throughout the entire week of data collection that are related to an underlying circadian rhythm (see Fig. 3).

L5 and M10 of VMC vary within subjects, particularly between working and free days and between subjects (Fig. 4).

A. Correlation matrices

Pairwise correlations among the 17 time series showed significant but weak correlations of melatonin with many variables, the strongest being with CBT (r_S=-0.27; P<.001),

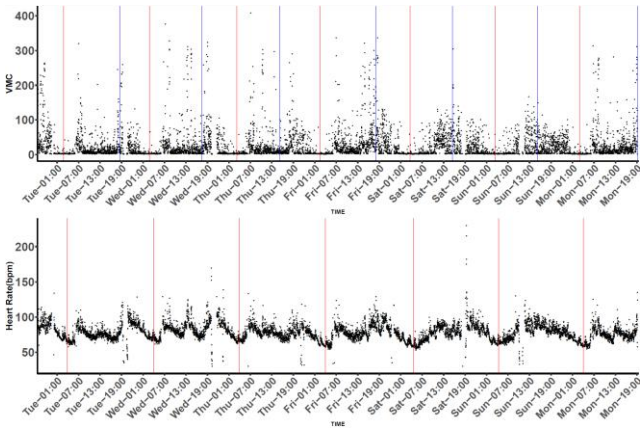

Fig. 3. The upper panel shows VMC and the lower panel the HR of a representative subject. The daily L5 of VMC and HR are marked in red and the daily M10 of VMC in blue.

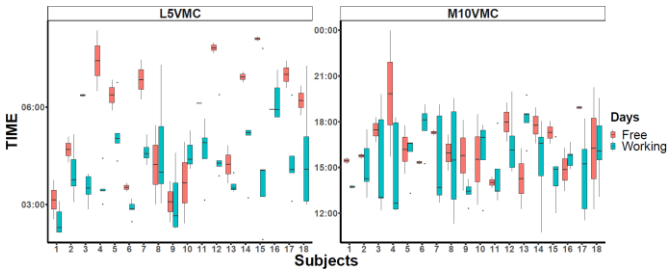

Fig. 4. Boxplots of L5 (left panel), and M10 (right panel) of VMC separated by working (blue) and free days (red).

mean RR (r_S=0.19; P<.001) and HR (r_S=-0.16; P<.001). CBT showed significant correlations with all the variables measured, the strongest being with the mean RR (r_S=-0.70; P<.001), HR (r_S=0.67; P<.001) and the position angle (r_S=0.63; P<.001).

The correlation of the scalar features showed a significant positive correlation of DLMO with CBTmin (r=0.57; P=0.02), the L5 of CBT (r=0.51; P=0.04), the L5 of the HF/LF of the RR (r=0.56; P=0.02), and the L5 of HR during working (r=0.69; P=0.002) and free days (r=0.56; P=0.02). CBTmin showed significant and stronger correlations than DLMO with the same features, namely, L5 of CBT (r=0.94; P<.001), the L5 of the HF/LF of the RR (r=0.64; P=0.006), L5 of HR during working (r=0.83; P<.001) and free days (r=0.86; P<.001), and with MSFsc (r=0.73; p=0.002), L5 of VMC (r=0.75; P<.001), and IS during free days (r=0.56; p=0.02). Surprisingly, the correlation between the scores of the two chronotype questionnaires, MSFsc and MEQ, was not found to be significant (r=-0.38; p=0.14). The correlation matrices can be found in the Supplementary Material (Fig. S1 and S2).

B. DLMO cosine curve and CBT prediction (ANNs)

The features selected for the best ANNs with each validation method are presented in Table II. Both ANNs obtained for DLMO prediction use 8 features derived from the accelerometer, the light sensor and the ECG. The ANN obtained for predicting the CBT profile using subset validation uses 8 features derived from the ECG, breathing rate, skin temperature and accelerometer, while the best ANN obtained using the cross-validation method uses only 7 features, derived

TABLE II
FEATURES FOR DLMO COSINE WAVE AND CBT PREDICTION WITH ANNS

DLMO cosine wave (subset)	DLMO cosine wave (CV)	CBT (subset)	CBT (CV)
Position angle	Position angle	Position angle	Position angle
Light	Light	Skin temp	Skin temp
Mean of RR	Mean of RR	BR	VMC
SD of RR	SD of RR	HR	Mean of RR
SD of HR	SD of HR	Mean of RR	SD of HR
NN50	NN50	NN50	CSI
pNN50	LF/HF	pNN50	CVI
LF/HF	CVI	LF/HF	

from the same sensors except for the breathing rate.

Fig. 5 shows the fit of the ANN estimation of DLMO cosine wave for a representative subject, and Fig. 6 shows an example of CBTmin estimation.

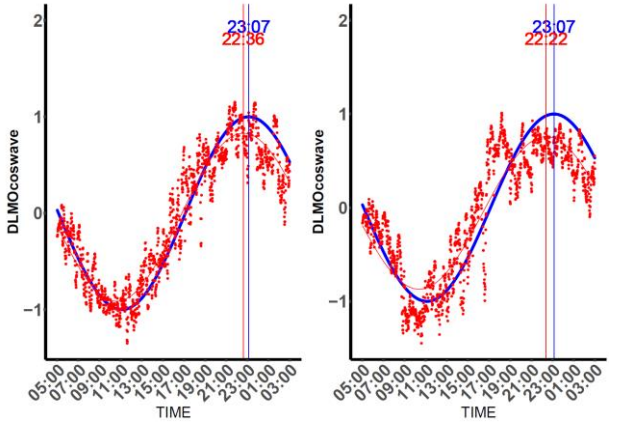

Fig. 5. Experimental DLMO cosine wave (blue lines) vs model prediction (red markers) with the best ANN obtained considering subset validation (left) and cross-validation (right). Predicted series were fitted to a cosine wave for calculating the predicted DLMO (red lines).

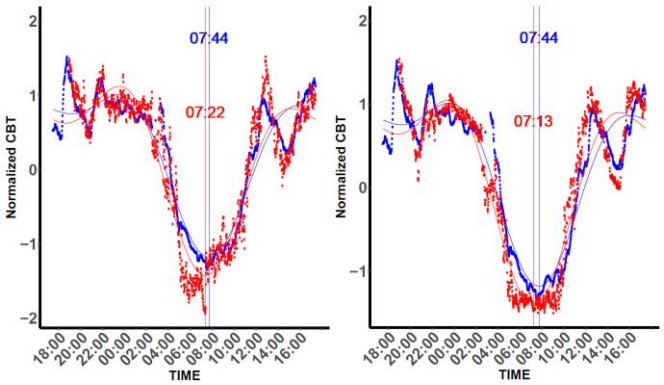

Fig. 6. Experimental CBT (blue markers) vs model prediction (red markers) with the best ANN obtained considering subset validation (left) and cross-validation (right). Experimental and predicted series were fitted to a cosine wave for calculating CBTmin (blue and red lines, respectively).

Table III presents the prediction error (difference between DLMO and CBTmin obtained from the ANNs and the experimental values) for each of the subjects and the mean and SD obtained by the best ANNs with each of the aforementioned validation methods. The missing data is due to subjects that were out of the training process either because they did not have data for the model output or because they did not have enough data for any of the predictors needed by the model.

TABLE III
MINUTES OF ERROR (XEXP-XPREDICT) WITH ANNS

Subject	DLMO (subset)	DLMO (CV)	CBTmin (subset)	CBTmin (CV)
1	-3	5	-55	-119
2	43	69	5	7
3	-	-	-22	-12
4	-52	-121	-11	-8
5	17	42	22	31
6	-26	-52	-24	-11
7	-33	-50	-4	-1
8	-66	-97	-25	-54
9	34	59	-24	7
10	24	41	-22	-22
11	-	-	-45	-50
12	-7	-3	-62	-39
13	-	-	2	-20
14	-24	-58	-44	-55
15	31	45	-51	-45
16	-2	-14	16	-13
17	48	57	-	-
18	9	44	-43	-43
Mean	-0.5	-2.2	-23	-26
SD	35	61	25	34

C. DLMO and CBTmin prediction (regression models)

The correlation-based feature selection method found ten different predictors for each of the responses to be predicted (see Table IV). After an exhaustive search, the best regression models of up to four features among the ones in Table IV were selected by their performance for each response variable and are presented in Fig. 7.

TABLE IV
FEATURES CONSIDERED FOR DISCRETE VARIABLES PREDICTION WITH REGRESSION MODELS

DLMO	CBTmin
BMI	MSFsc
MEQ	L5HRwd
MSFsc	L5HRfd
L5HRwd	L5LFHFaw
L5HRfd	L5VMCwd
L5LFHFaw	M10VMCfd
L5VMCaw	ISwdSD
M10VMCfd	ISfd
ISwdSD	IVaw
IVaw	IVwd

BMI is the body mass index; MEQ is the score obtained from the Morning-Evening Questionnaire; MSFsc is the corrected midpoint of sleep on free days obtained from the Münich Chronotype Questionnaire; L5 is the mid-point of the five hours with the lowest average value of the corresponding feature and M10, the mid-point of the ten hours with highest mean. HR is the heart rate; LFHF is the ratio between the Low Frequency (LF) and the High Frequency (HF) bands of the RR intervals; VMC is the Vector Magnitude Count obtained from the accelerometer; IS is the interdaily stability and IV the intradaily variability of the VMC. Suffix wd indicates that the feature is analyzed during the working days, fd for free days and aw for all week. All the features correspond to mean values although SD (standard deviation) is specified.

The prediction error for each of the subjects and the mean

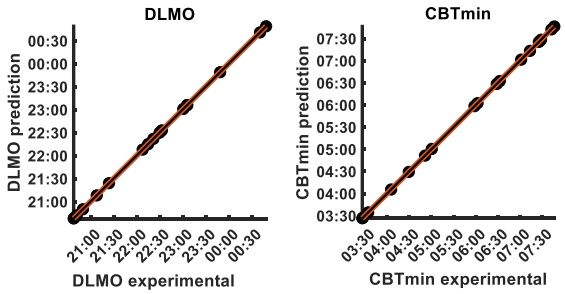

Fig. 7. DLMO (left) and CBTmin (right) prediction of the best regression model (x-axis) vs experimental data (y-axis). The black line shows the fit of a linear regression to the data, and the orange line represents a perfect prediction.

and SD are presented in Table V.

TABLE V
MINUTES OF ERROR (XEXP-XPREDICT) WITH THE REGRESSION MODELS

Subject	DLMO	CBTmin
1	-0.02	-0.05
2	-0.07	0.02
3	-0.01	-0.07
4	0.02	0.05
5	-0.05	0.03
6	0.05	0
7	0.00	0.03
8	-0.01	-0.05
9	0.01	-0.01
10	0.01	0.04
11	0.02	-0.01
12	0.04	0
13	-	-0.02
14	0.00	0.01
15	-0.01	-0.02
16	0.01	-0.02
17	-0.05	-
18	0.08	0.08
Mean	0.00	0.00
SD	0.04	0.04

The best model for predicting DLMO was an Exponential Gaussian Process regression model that considers only three features, namely, BMI, L5 of HR during working days, and M10 from VMC on free days.

The best model for predicting CBTmin was also an Exponential Gaussian process regression that uses four predictors, namely, L5 of the HR during working days, L5 of the HR during free days, standard deviation of the IS and mean of the IV of working days.

IV. DISCUSSION

The subjects recruited for this study presented a significant variability on their circadian phases assessed by their DLMOs. The age range of the participants is quite narrow, so the age was not considered a relevant predictor for the models. DLMO appeared to be significantly correlated with CBTmin as shown in other studies [20], [24]. In this study, DLMO did not present a significant correlation with the results of any of the questionnaires, which calls into question their validity. Despite its sensitivity to masking effects, CBTmin showed a strong correlation with MSFsc, DLMO and other physiological variables [22], [46].

A. DLMO cosine curve and CBT prediction(ANNs)

The best ANN to predict the DLMO cosine curve uses only features acquired with the Equivital Monitor and the light sensor. This model has 40 inputs, considering lagged measurements, which represents an important reduction with respect to other studies such as [20], which requires 115 inputs coming from an ambient light sensor and several skin sensors placed in different body positions (hands, feet, upper and lower legs, shoulders, and thorax). The selected features are mainly related to the HRV, which was expected because HRV is related to the sympathetic and parasympathetic system responses responsible for managing circadian rhythms [47], [48]. Angle position and VMC are related to the behavior of the subjects [24], and they also appear as inputs. Only 32 hours of data were used to train and validate this model, namely, the 24 hours of the melatonin collection day, plus 4 hours before and after. This ANN allows prediction of the circadian melatonin phase with less than two days of data collection and with just one piece of minimally intrusive equipment. However, it has to be noted that the DLMO cosine curve was built in silico from the DLMO values that were obtained from only 6 hours of melatonin data. This might partially explain why the fit is better for the models that directly estimate the DLMO without using the cosine curve.

For CBT prediction, skin temperature, which shows a negative but significant correlation with CBT, appears as an input in the best ANN. Its relevance could be explained by the endogenous circadian component of heat loss, and it is in agreement with other studies for CBT prediction [49]. Additionally, HRV-derived features are used in this ANN as well as in DLMO prediction. This can be explained due to the regulatory role of the SCN, which interferes with decreasing the CBT signal [50]. Angle position and VMC are essential features for predicting CBT since the activity is known to be a sensitive circadian marker [22], [50]. This ANN was generated using 24 hours of ambulatory data collection without any environmental or activity restrictions, and most of the features were acquired by only one instrument (the Equivital™ monitor).

Regarding the validation methods in ANNs, for predicting the DLMO cosine wave and CBT signal, the subset method has a lower mean error than the cross-validation method. These results could be associated with the random selection of the testing data that could lead to different results with different test data selection and tends to overestimate the model error [51], but this method of partitioning data works well with large samples as in our case [52] of approximately 30 thousand samples.

B. DLMO and CBTmin prediction (regression models)

L5 features were useful for predicting circadian phase markers. The algorithm used to obtain L5 and M10 features has been used to estimate circadian phase from activity features and wrist temperature before [24], but the new use of other variables such as HR, features from the RR intervals and CBT is novel and has shown potential for discovering valuable features to

predict circadian rhythms. Additionally, the use of machine learning methods to generate regression models with these scalar variables is a different approach compared with the time-series analysis. Regression models have been used before to predict DLMO and CBT with wake and sleep schedules [53], [54] and with a composite marker using wrist temperature, activity, and position, known as TAP [24], but all these models were linear regressions and not multivariate regression models similar to in the present work.

The best regression model for predicting DLMO needs only three predictors to achieve less than one minute of error, which is more accurate than previous models reported in the literature. BMI is known to be positively correlated with the chronotype and is among these predictors, although it did not show significant correlation with DLMO in our study. Evening chronotypes are associated with an increased BMI, due to bad dietary behavior and sleep problems [4]. Furthermore, the increase in melatonin generates a decrease in HR [55], so it is expected that individuals who have a late DLMO have a late L5 of HR too, a feature that also appears in the model and is significantly correlated with DLMO. The third predictor is related to the activity determined by the accelerometer.

Our regression models for predicting CBTmin also showed very high accuracy and dependence on HR because when melatonin increases, CBT and HR tend to decrease [55]. Several features extracted from the accelerometer were selected by the wrapper method, most likely because activity directly affects the CBT [24], and two of them, related to the interdaily stability and the intradaily variability, were selected by the final model. However, it is important to highlight that, while predictions of ambulatory CBTmin do have their value, this circadian marker is masked by sleep, activity, light, ambient temperature, meal intake and other factors, so it is not as reliable as DLMO. This is likely to account for the strong relationships observed between ambulatory CBT and other ambulatory variables measured, which are susceptible to the same masking.

Stone et al [26] found that models developed to predict melatonin rhythms in individuals on a fixed sleep schedule resulted in very large errors in night shift conditions. The present study focuses on young and healthy males on their usual sleep-wake schedules over a normal week, and the models developed here were not tested under conditions of circadian misalignment. The performance of the models was assessed using k-fold cross-validation, and therefore, they are expected to exhibit similar performance on independent data with similar characteristics. However, further studies are needed to test the validity of our models with independent datasets and with data from males and females in different age categories and under different lifestyle or work conditions, as well as diseased persons undergoing treatment.

V. Conclusion

We present here different models to predict circadian phase (DLMO and CBTmin) from ambulatory physiological data, acquired using minimally intrusive equipment, which achieve apparently better results than those from previously published models. The first approach uses ANNs, based on time-series data, as other recent works in the field. The second is a novel approach using Gaussian process regression models from BMI and novel scalar features extracted from time series. The developed models using scalar features are simpler, use fewer features, and show better accuracy than ANNs. However, they need at least one week of data collection compared to ANNs, which need less than 48 hours. The codes of the models presented here are available from the authors upon request.

The ambulatory data collection protocol allowed the integration of several possible variables that affect circadian rhythmicity throughout the week. Several models need only physiological data that can be obtained by one piece of equipment, the Equivital™ monitor, which is a minimally intrusive instrument that can be used as an ambulatory measure featuring dry electrodes that make data acquisition more comfortable than other ECG monitors, where the subjects have to replace disposable electrodes daily [20], [21]. Moreover, the selected variables with both techniques highlight the relevance of heart rate monitoring as a marker of the sympathetic/parasympathetic system for improving the precision of circadian phase prediction.

The different machine learning approaches presented here make it possible to improve circadian phase prediction using minimally intrusive physiological data that could decrease costs and uncomfortable procedures for the patients. The results of this study suggest that scalar models using one week of HR and activity data collection, together with the subjects' BMI, should be used for circadian phase prediction in chronotherapy and other real-life applications.

Acknowledgment

We acknowledge Javiera Cortés for her assistance with the melatonin assays, Tomás Egaña for the laboratory equipment, and David Necuñir for the design of Fig. 1 and Fig. 2 (necuseban@gmail.com).

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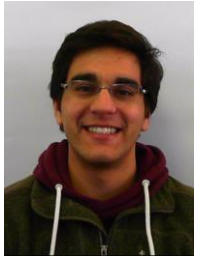

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