Ambulatory estimation of human circadian phase using models of varying complexity based on non-invasive signal modalities

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Abstract – **In this work, we introduce a number of models for human circadian phase estimation in ambulatory conditions using various sensor modalities. Machine learning techniques have been applied to ambulatory recordings of wrist actigraphy, light exposure, electrocardiograms (ECG), and distal and proximal skin temperature to develop ARMAX models capturing the main signal dependencies on circadian phase and evaluating them versus melatonin onset times. The most accurate models extracted heart rate variability features from an ECG coupled with wrist activity information to produce phase estimations with prediction errors of ~30 minutes. Replacing the ECG features with skin temperature from the upper leg led to a slight degradation, while less accurate results, in the order of 1 hour, were obtained from wrist activity and light measurements. The trade-off between highest precision and least obtrusive configuration is discussed for applications to sleep and mood disorders caused by a misalignment of the internal phase with the external solar and social times.**

I. Introduction

Human beings possess a biological clock which influences most, if not all, physiological processes and some behavioral processes. Environmental cues, known as *zeitgebers*, provide input to the circadian system enabling it to entrain to the solar cycle. The most influential of these *zeitgebers* is light [1,2]. The master circadian clock is located in the suprachiasmatic nuclei (SCN) of the brain. Because the state of the circadian clock cannot be assessed directly in humans, one must rely on indirect measures that are closely coupled to the activity of the clock itself. Core body temperature (CBT) and melatonin levels are two well-established markers of the phase of the SCN [3], each affected by different masking effects. CBT is prone to non-circadian variations caused by activity, food intake, sleep, and other environmental or behavioral influences, while melatonin concentrations are affected by exposure to bright light [4]. Given its relative resilience to masking effects, the dim light melatonin onset (DLMO) is the most practical indicator of circadian phase which can be measured from saliva samples taken, either at home or in a clinic, in the evening with a typical accuracy of 15 minutes [3]. DLMO is defined as the time at which the concentration of melatonin (released by the pineal gland) reaches a certain threshold, in this case 3pg/ml from saliva samples [5]. With at least 10% of all insomnias caused by circadian rhythm misalignments [6], determining circadian phase is a valuable tool in diagnosing and scheduling of treatment of sleep disorders, mood disorders such as seasonal affective disorder (SAD), as well as for fatigue and alertness monitoring.

Recent circadian phase estimation models have revolved around non-invasive physiological signal modalities such as heart rate and skin temperature. The types of models have ranged from simple feature-based heuristic decision to more complex mathematical algorithms. New circadian phase features, have been proposed by Ortiz-Tudela et al. and Bonmati-Carrion et al., consisting of either a combination of skin temperature, activity, and posture (TAP) [7], or derived solely from wrist skin temperature (WTiO) [8], respectively. Two mathematical models have also been recently proposed by Kolodyazhniy in 2011 and 2012, using not only six skin temperature locations but also light exposure and motion. The first model used linear regressions [9] while the second one incorporated a neural network and made no use of motion [10]. Concerning the heart rate signal, in 2013 we presented a compact autoregressive moving average with exogenous inputs (ARMAX) model which uses inter-beat intervals and light exposure to estimate circadian phase [11]. We searched for further improvements of this ARMAX model by using different heart rate derived features, skin temperature, and different model structures. In some cases we also tried expanding upon previously presented models, and applying it to different signal modalities. This has resulted in an array of possible models with varying levels of complexity and differing accuracy when compared to the gold standard of DLMO.

II. Methods

Ambulatory ECG, actigraphy, and skin temperature recordings from 16 subjects were processed and used in various models to estimate circadian phase. Subjects were healthy without pulmonary, cardiac or sleep disorders, not taking medication, non-smokers, consumed less than 3 units of alcohol per week, less than 350mg of caffeine per day, and had not taken part in shift work or travel across time zones in the three months prior to the study. Actigraphy was collected over two weeks, while ECG and skin temperature were recorded continuously over 30 hours each week. Evening saliva samples were collected in the evenings corresponding to the ECG/skin temperature recording periods. See Figure 1 for the study protocol. The accuracy of the model outputs were compared to DLMO values calculated from salivary melatonin levels.

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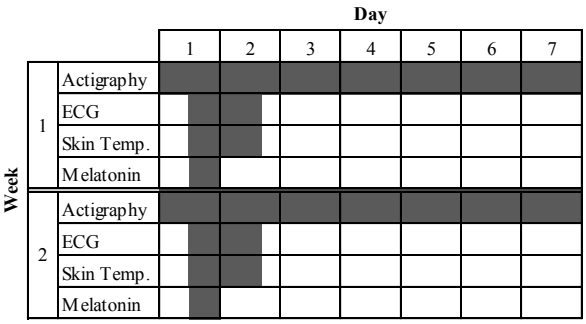

Figure 1. Study protocol. Two consecutive weeks of actigraphy, two ECG and skin temperature recordings for 30 hours each week, and salivary melatonin levels during each of those recording periods.

The ECG recordings were collected with a Nexus-10 (Mind Media BV, Herten, The Netherlands) at 256Hz using a standard 3-lead configuration. Activity levels and light exposure were measured using an Actiwatch Spectrum (Philips Respironics, Pittsburgh, USA). Skin temperature was measured at nine body locations using iButtons (Maxim Integrated, San Jose, USA) and shielded from external temperature by means of reflective isolating adhesive disks. See Figure 2 for sensor placement. Saliva was collected using Salivettes (Sarstedt AG&Co, Nuembrecht, Germany) under dim light conditions at home, assisted by blue light filtering glasses (LowBlueLights, Photonic Development LLC, Walton Hills, USA). The saliva samples were analyzed using the Buehlmann Direct Saliva Melatonin RIA (Buehlmann Laboratories AG, Schoenenbuch, Switzerland).

For training the prediction models, the inputs consisting of various signal modality combinations, have been median-filtered, and normalized. More detailed information on the processing of the signals and examples of the time series can be found in [11]. For each subject, the output signal was a cosine wave coded with the DLMO as the phase shift, as shown in equation 1.

$$y(t) = \cos(2\pi f t - \varphi_{DLMO}) \quad (1)$$

As an extension of the previously proposed ARMAX model which used RR intervals and light exposure to obtain the person's circadian phase [11], spectral and temporal heart rate variability (HRV) features calculated in 5 minute windows were used as input signals. New ARMAX models were trained and evaluated using the HRV signals as replacement signals of the RR intervals. The data was randomly split into a training subset and a validation subset.

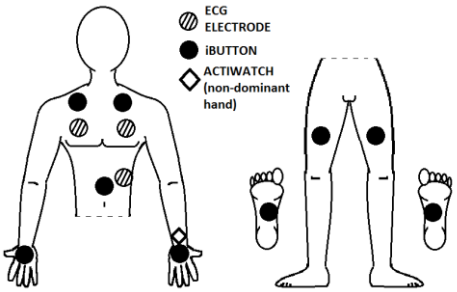

Figure 2. Sensor placement. Nine iButtons were placed as shown here by solid circles. The ECG was measured using the standard configuration shown by striped circles. Activity and light were measured at the wrist.

To obtain one model for each signal modality combination with a single set of coefficients, the best model configuration was found using the leave-one-out-cross-validation technique on the training subset. The performance of each model was then tested using the validation subset consisting of seven subjects. The ARMAX model has the following structure:

$$A(q)y(t) = B(q)\begin{bmatrix} u_1(t-n_k) \\ u_2(t-n_k) \\ \cdots \\ u_i(t-n_k) \end{bmatrix} + C(q)e(t) \quad . \quad (2)$$

Where $u(t-n_k)$ are the delayed inputs, $y(t)$ is the output, $e(t)$ is the noise model, and the A-C variables are the model coefficients as defined in equations 3-5 below.

$$A(q) = 1 + a_1 q^{-1} + a_2 q^{-2} + \cdots + a_{n_a} q^{-n_a} \quad (3)$$

$$B(q) = \begin{bmatrix} b_{11} + b_{12} q^{-1} + \cdots + b_{1n_b} q^{-n_b+1} \\ b_{21} + b_{22} q^{-1} + \cdots + b_{2n_b} q^{-n_b+1} \\ \cdots \\ b_{i1} + b_{i2} q^{-1} + \cdots + b_{in_b} q^{-n_b+1} \end{bmatrix} \quad (4)$$

$$C(q) = 1 + c_1 q^{-1} + c_2 q^{-2} + \cdots + c_{n_c} q^{-n_c} \quad (5)$$

The spectral HRV features explored were the low frequency component (LF, 0.04-0.15Hz), high frequency component (HF, 0.15-0.4Hz), and the ratio of the two (LF/HF). The temporal features of interest were the standard deviation of the normal beats (SDNN), the root mean square of successive differences (RMSSD), and the proportion of the number of pairs of successive normal beats greater than 50ms to the total number of normal beats (pNN50). In addition to the spectral and temporal HRV features, new processing schemes of the activity have been implemented that emphasize the sleep/wake schedule of the subject.

To explore alternative signal modalities which can be measured in ambulatory conditions, skin temperature from the 9 previously mentioned body locations was considered. Not only were individual skin temperature locations used, but also the distal-proximal gradient (DPG) [12]. These signals were used to train and evaluate new ARMAX models of similar structure as the model presented with RR intervals and light.

Bonmati-Carrion et al. have presented a skin temperature feature measured at the wrist called the WTiO [8]. We have adapted this feature and applied it to RR intervals. When adapting this feature to RR intervals, the 35% threshold proposed by Bonmati-Carrion et al. was modified to fit with the rise in the onset of RR intervals, which can be expected to be different than for wrist temperature. Through statistical learning, the threshold of 40% was found to be the corresponding increase onset for RR intervals. Given this threshold and the same methodology presented by Bonmati-Carrion et al., the new feature was used to predict the DLMO directly.

Furthermore, an ARMAX model was derived which used only activity levels and light exposure as measured from an Actiwatch Spectrum. Due to the design of the protocol, we

were able to estimate circadian phase daily over a period of two weeks. However, since DLMO was only collected at the beginning of each week, the accuracy of the estimates could only be assessed for the days of the saliva sampling.

Due to signal quality, only 14 of the 16 recordings could be used for extracting the temporal and spectral HRV features, as well as the skin temperature signals. The RR intervals, activity, and light signals from all 16 recordings could be used for the rest of the modeling approaches.

III. Results

Prediction errors have been defined as the difference between the expected DLMO value and the model output, and presented as the mean±standard deviation (SD) in minutes. Note that in this case, the mean is a bias or calibration factor, while the SD is the real measure of precision which can be expected from each model. A summary of all models can be found in Table I. The models are sorted in decreasing order of accuracy as defined by the standard deviation of the error.

The use of spectral and temporal HRV features in conjunction with the processed activity signal resulted in the most accurate circadian phase estimates. In the spectral domain, the high frequency (HF) feature was the most accurate with an error of 17±28 minutes (R=0.847, p=0.016), while in the temporal domain the standard deviation of normal beats (SDNN) produced the most accurate results with an error of 13±32 minutes (R=0.758, p=0.048). Using the modified activity processing and RR intervals, the accuracy of the phase estimates presented an error of 4±34 minutes (R=0.771, p<0.01).

The single skin temperature location that produced the most accurate results when paired with other modalities such as activity or light, was the temperature at the upper leg with an accuracy of 73±38 minutes (R=0.79, p=0.034). Furthermore, the DPG signal was used in the same manner and produced estimates with an error of 19±70 minutes (R=0.839, p=0.018).

Using only the activity and light inputs with the ARMAX model structure produced errors of 21±59 minutes (R=0.525, p=0.022). Lastly, the increase onset feature of RR intervals led to prediction errors of 98±72 minutes (R=0.511, p=0.072). This was the only model which made no use of the ARMAX structure, as it was directly calculated and evaluated in reference to the DLMO.

TABLE I. Summary of Results

Input Signals	Error Mean±SD (minutes)	Pearson's R	P Value
Activity+HRV_{HF}	17±28	0.847	0.016
Activity+HRV_{SDNN}	13±32	0.758	0.048
RR intervals+activity	4±34	0.771	<0.01
Upper leg+activity	73±38	0.790	0.034
RR intervals+light	2±39	0.712	<0.01
Activity+light	21±59	0.525	0.022
Activity+DPG	19±70	0.839	0.018
RR intervals onset	98±72	0.511	0.072

IV. Discussion

Taking the model with RR intervals and light as the baseline, all newly trained models were compared to it in terms of accuracy and invasiveness. All signal modalities mentioned here were used both individually and coupled with other modalities. In general, it was found that the use of a processed activity trace which emphasizes the sleep/wake cycle is a better complimentary signal than light when used in conjunction with either heart rate features or skin temperature features. The reason for this could be in the way the light data is collected. Combining the fact that the light sensor is located at the wrist and that the data was collected during the winter, the "sleeve effect" (ie. shielding of light sensor by clothing) was a common issue. The information that is found in a person's sleep/wake cycle can give a good indication of the state of the circadian clock. However, this is mostly true for healthy people that are well-entrained. It would be interesting to determine whether the combination of a signal modality such as heart rate or skin temperature, coupled with the sleep timing information, would still result in accurate phase estimates in a pathological population with circadian disruptions.

The ARMAX models making use of heart rate features as inputs have produced the most accurate estimates of circadian phase. Heart rate and HRV features, both temporal and spectral, are known to follow a circadian pattern [13]. The use of the HF feature from the HRV produced the most accurate results overall. Figure 3 shows a plot of the expected DLMO versus the predicted DLMO for the validation data subset. The HF is said to represent the parasympathetic activation of the autonomous nervous system, which is circadian modulated [14]. Furthermore, the model which uses RR intervals and activity is not only more accurate than the baseline, but also does not present the problem of sensor occlusion. Algorithmically, the model is a compact third order ARMAX model, making the implementation feasible and transparent. For this setup, the main disadvantage is the need for two separate devices: one

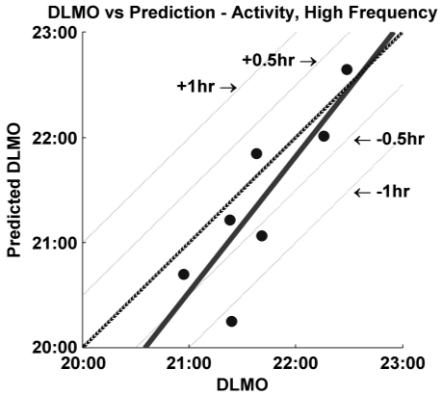

Figure 3. Linear regression of the best performing model using activity and the high frequency HRV feature with an error in minutes of 17±28 (mean±SD) and a Pearson's R value of 0.847. The heavy solid line shows the linear regression of the phase estimates, the heavy dashed line shows the ideal line, the secondary dashed lines show the 30 minute and 1 hour errors departing from the ideal line.

to measure the ECG and one for actigraphy. Having the heart rate and activity measured by a single unobtrusive device, would make this model superior to any of the models presented here in every respect.

The use of a heart rate monitor over long periods of time has not been favored due to the burden of gel electrodes and wires on the patient. Nonetheless, Holter ECG monitors have been standard protocol for numerous diagnostic and monitoring procedures, often for days or weeks at a time. The fact that only 24 hours are required makes the burden on the patient significantly low. From the various data collection studies that we have carried out, no patients have had negative experiences or complaints. Nevertheless, the monitoring of heart rate or heart rate variability features can be done in an even less invasive manner through the use of recently developed optical sensors that do not rely on gel electrodes or straps.

Another model that resulted in more accurate results used skin temperature measurements at the upper leg, together with activity and light information from an Actiwatch. Even though the nine skin temperature locations were analyzed individually with activity alone, light alone, and the combination of activity and light, it was only when considering all three signals together that the better results were achieved. In this context, this approach has the disadvantage that it requires at least two devices, an iButton and an actimeter, from which three signal modalities are used.

Perhaps the simplest approach is the model that uses only activity and light recordings from an Actiwatch device. This algorithm is able to estimate circadian phase on a daily basis from one device using a compact ARMAX model. The accuracy is one of the lowest with a standard deviation of the error of 59 minutes. Even though the accuracy was not very high, the invasiveness of actigraphy measurements is very low compared to other signal modalities. One of the problems that can be faced with this kind of measurement is the occlusion of the light sensor, typically by the person's sleeve. However, it has the advantage of only requiring a single wrist-worn device for data collection.

Unfortunately, the RR interval increase onset feature was not able to produce phase estimate within one hour. For our applications, circadian estimates with errors greater than one hour fail to serve a valuable purpose, regardless of their simplicity or practicality. A limitation of the current study is the lack of wrist temperature measurements, which, given the recent publications, could have been beneficial.

V. Conclusion

Considering the usual trade-off between simplicity and accuracy, we have presented a range of solutions for phase estimation models that can be used in different real-life scenarios. It is worth noting that all these models rely on only 24 hours of data, making them already practical alternatives to previously proposed circadian phase estimation approaches.

We define a model as "simple" when a minimum number of sensors or devices are required and when the algorithms can be implemented straightforwardly. The simplest model, which still yielded phase estimates within one hour, was the ARMAX model based on actigraphy signals. Activity and light exposure were measured using an Actiwatch Spectrum, making it non-invasive and in line with current chronobiology protocols.

We evaluated the accuracy of the models by comparing the model output to the DLMO as reference. The standard deviation of the differences gives an indication of the accuracy that can be expected when using the different models. So far, the most accurate results have been obtained from HRV_{HF} and activity levels, using two distinct signal collection devices. This increases the complexity of the current solution and motivates further work towards improved sensor technology and algorithmic performance.

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