Ambulatory assessment of human circadian phase and related sleep disorders from heart rate variability and other non-invasive physiological measurements
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CIRCADIAN PHASE ESTIMATION OF SLEEP ONSET INSOMNIA PATIENTS

Gil EA, Aubert XL, Penzel T, Beersma DGM, *Circadian phase estimation of sleep onset insomnia patients.*
7.1 ABSTRACT
Sleep on set insomnia, characterized by a difficulty falling asleep, is often caused by a delayed circadian clock. Reaching this diagnosis requires determining the circadian phase of a person, commonly done through saliva or blood samples taken during the night at a sleep clinic. Non-invasive methods based on light exposure or sleep schedules have been shown to adequately estimate circadian phase in healthy subjects. However, pathological sleep populations present challenges given that a delayed sleep interval could or could not be caused by a delayed circadian phase. One way of solving this problem is by assessing circadian phase based on physiological signals which are more closely coupled to the endogenous circadian system as opposed to exogenous behavioral effects. We have developed a model which estimates circadian phase in ambulatory conditions by using 24 hour recordings of heart rate, activity levels, and light exposure. Tested on a sample of 6 sleep onset insomnia patients, we were able to estimate the circadian phase, defined as the dim light melatonin onset, with an accuracy of 48 minutes and a Pearson’s R of 0.8934 (p = 0.016).

7.2 INTRODUCTION
Sleep onset insomnia (SOI) is a sleep disorder in which a person has difficulty initiating sleep. With the exception of a prolonged sleep onset latency, patients who suffer from sleep onset insomnia have a normal sleep architecture [1]. This is characterized by the temporal distribution of sleep stages and the percentage of time spent in each of these stages. The etiology of this condition can be multifactorial, with a delayed circadian clock being one of the most common causes [2].

The circadian clock is a timing mechanism located in the suprachiasmatic nuclei (SCN) known to influence most physiological processes, such as the sleep/wake cycle, hormone production, alertness, core body temperature, metabolism, and heart rate [3–6]. Given that the circadian system is only one of the possible causes of SOI, it is necessary to determine the circadian phase of the person in order to confirm or rule out circadian misalignment. The gold standard of circadian phase is the dim light melatonin onset (DLMO) [7,8]. The DLMO is determined by collecting blood or saliva samples during the evening or the entire night, or urine samples over the day. Using a threshold, the DLMO can be defined as the time at which the melatonin concentration reaches and stays above that threshold. The samples must be collected in constant dim light as to avoid any masking effects that arise from the exposure to bright light. This procedure can be invasive, time consuming, and inconvenient for the patients. As a result, efforts have been made to develop new ways of estimating circadian phase non-invasively and in ambulatory conditions by relying on other signal modalities which are closely coupled to the activity of the endogenous circadian pacemaker [5,9–13].
Recently, we developed a model to estimate circadian phase based on 24-hour recordings of heart rate, complemented by activity levels and/or light exposure, which was tested for healthy subjects [13]. The time series model is an autoregressive moving average with exogenous inputs (ARMAX) model of third order. The ARMAX model incorporates both stochastic and deterministic processes, making use of present and past input values. This allows for a recursive formulation that, although low in order, is able to consider long-term trends in data.

An interesting target population is sleep onset insomnia patients, since the cause of their sleep complaints may or may not be circadian in nature. The procedure to determine circadian phase is often impractical and disturbing to patient populations, therefore having a non-invasive alternative that could be used at home would greatly improve the current diagnostic practice. In this study, we aimed at assessing the accuracy of the previously developed ARMAX model on a population of diagnosed sleep onset insomnia patients to test the generalizability of the model to pathological cases.

7.3 METHODS

7.3.1 Healthy subjects
The subject characteristics and study protocol for the healthy dataset have been presented in [13]. This data consisted of 27 healthy subjects with recordings of ambulatory electrocardiograms (ECG), activity levels and light exposure, and evening salivary melatonin. The data from 11 subjects were used to train the models, while the data from 16 subjects were used to evaluate them.

7.3.2 SOI subjects
The data collection on SOI patients consisted of 20 diagnosed sleep onset insomnia patients who participated in an 8 day long study which combined ambulatory and in-clinic recordings. The patients were either referred to us by our collaborating physicians at the Charité University Hospital or were recruited from an existing patient database at the Advanced Sleep Research institute in Berlin. Patients were diagnosed with sleep onset insomnia when having a sleep onset latency (SOL) longer than 30 minutes. The patients were further examined and screened by a medical sleep specialist. Exclusion criteria included psychiatric or cardiac disorders, sleep apnea, restless legs syndrome, travel across time-zones and shift work in the previous three months, and use of sleep medication or other medication that could influence sleep. Participants meeting the inclusion criteria were explained the study protocol by the sleep physician and signed an informed consent form in accordance to the Declaration of Helsinki. The study protocol received IRB approval by the ethics committee at the Charité University Hospital.

The protocol for the SOI patients was similar to that of the healthy subjects. Ambulatory ECG recordings were performed using a different Holter ECG recorder
activity levels and light exposure were measured with a wrist-worn Actiwatch Spectrum (Philips Respironics, Pittsburgh, USA), and evening saliva samples were collected at the sleep clinic. Five saliva samples were taken using the Salivette system (Sarstedt AG & Co, Nümbrecht, Germany) and processed in the laboratory using the LDN RIA kit (Labor Diagnostika Nord GmbH & Co KG, Nordhorn, Germany). Saliva samples were taken in dim light conditions, which were verified by the light exposure measurements of the Actiwatch Spectrum during the corresponding collection time period, while patients wore special glasses to block blue light (LowBlueLights, Photonic Developments LLC, Walton Hills, USA). In addition, during the night of the saliva sampling, the patients underwent a polysomnography (PSG) recording to better assess the sleep characteristics of the SOI patients.

There were some differences between the dataset used to develop the original models. One difference was the use of a sleep clinic for the night of the saliva collection. In addition, the SOI patients underwent a polysomnography (PSG) recording to better assess sleep characteristics. Lastly, the saliva samples were processed using a different kit, namely from LDN RIA kit (Labor Diagnostika Nord GmbH & Co KG, Nordhorn, Germany).

For the salivary melatonin analysis using the LDN RIA kit, the intra-assay variance was 10.3% for the low controls and 8.0% for the high controls. Inter-assay variance was 19.8% for the low controls and 11.4% for the high controls. The functional sensitivity of the assay was 1.4pg/ml.

7.3.3 Data processing
RR intervals, defined as the time interval between consecutive R peaks in an ECG, were extracted from the ambulatory ECG recordings. The activity levels were clipped at a threshold to emphasize the sleep/wake cycle and reduce the effects of spurious activity peaks. The light exposure was transformed using a power law in order to better represent the effects of light on the human retina. Details and justifications for the signal processing are shared in Gil et al. 2013 [13].

Overall, the input signals to the model consisted of the RR intervals, clipped activity levels, and transformed light exposure. These signals were time-aligned, filtered, and standardized based on Z-scores. The output signal was based on the estimated DLMO. The DLMO was coded into a wave as a cosine with an amplitude of 1, a period of 24 hours, and a phase shift equal to the DLMO of each subject (see Equation 1).

\[ y(t) = \cos(2\pi ft - \phi_{DLMO}) \]  (1)

The approximated cosine outputted by the ARMAX model was then fitted using a cosinor approach and the maximum of this new cosine was compared to the measured DLMO value. The models were trained and selected using the leave-one-out cross validation (LOOCV) approach on half the data of healthy subjects. The
second half of the data of the healthy subjects was used to test the performance of the model. All possible input signal combinations were tested.

The models which were previously developed in the healthy population were applied to the newly collected data from sleep onset insomnia patients. They were not retrained or recalibrated in any way to the new data. The SOI data was processed in the exact same way as was the data from the healthy subjects to ensure consistency.

7.4 RESULTS
Unfortunately in the SOI dataset, 14 patients were excluded due to problems with the melatonin data. Some of the concentration values obtained by the laboratory were not reliable and showed seemingly sporadic patterns with large increases and decreases in melatonin concentration throughout the collection period. Unreliable melatonin data was excluded and this resulted in 6 SOI patients with usable data. The demographics and sleep characteristics of the patients are shown in Table 7.1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SOI/Testing (Mean±SD)</th>
<th>Healthy/Training (Mean±SD)</th>
<th>Mann-Whitney P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>5 female/1 male</td>
<td>6 female/10 male</td>
<td>0.001</td>
</tr>
<tr>
<td>Age</td>
<td>44.50 ± 10.33</td>
<td>27.10 ± 4.14</td>
<td>0.053</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.15 ± 3.11</td>
<td>21.89 ± 2.64</td>
<td>0.003</td>
</tr>
<tr>
<td>Subjective SOL (min)</td>
<td>00:30 ± 00:06</td>
<td>00:14 ± 00:09</td>
<td>0.08</td>
</tr>
<tr>
<td>MEQ</td>
<td>59.66 ± 13.63</td>
<td>49.29 ± 10.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSQI</td>
<td>10.05 ± 3.89</td>
<td>4.07 ± 1.90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MSFsc (MCTQ)</td>
<td>02:37 ± 00:19</td>
<td>04:01 ± 00:36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bed-in time</td>
<td>22:17 ± 00:32</td>
<td>00:36 ± 00:58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sleep onset time</td>
<td>22:32 ± 00:33</td>
<td>00:42 ± 00:57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sleep duration</td>
<td>07:36 ± 00:13</td>
<td>06:43 ± 01:01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Midsleep time</td>
<td>02:20 ± 00:37</td>
<td>04:04 ± 00:45</td>
<td>0.0015</td>
</tr>
<tr>
<td>Objective SOL (min)</td>
<td>00:15 ± 00:14</td>
<td>00:06 ± 00:09</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Based on all possible combinations of input signals, 4 models were applied to the SOI dataset. The models were evaluated based on the standard deviation of the errors and the Pearson’s R correlation between measured and estimated DLMO values. The error was defined as the difference between the measured DLMO and the predicted DLMO. Table 7.2 shows the accuracy of each of the models when applied to the 6 SOI patients.
Table 7.2 Accuracy of all model configurations ranked by accuracy.

<table>
<thead>
<tr>
<th>Input Signals</th>
<th>Error (mean ± SD)</th>
<th>Pearson's R</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity+RR intervals+Light</td>
<td>-1 ± 48</td>
<td>0.8934</td>
<td>0.0165</td>
</tr>
<tr>
<td>RR intervals+Light</td>
<td>11 ± 60</td>
<td>0.8531</td>
<td>0.0308</td>
</tr>
<tr>
<td>Activity+Light</td>
<td>30 ± 77</td>
<td>0.7427</td>
<td>0.0908</td>
</tr>
<tr>
<td>Activity+RR intervals</td>
<td>52 ± 97</td>
<td>0.6509</td>
<td>0.1615</td>
</tr>
</tbody>
</table>

The model based on RR intervals, activity levels, and light exposure yielded the most accurate estimates of DLMO. A plot of these results are shown in Figure 7.1 below.

![Figure 7.1 Measured ground-truth DLMO versus Estimated DLMO values of sleep onset insomnia patients using an ARMAX model based on RR intervals, activity levels, and light exposure (ARL).](image)

Circadian characteristics such as the phase angle of entrainment can have a significant impact on the model performance. Phase angle of entrainment (AE) is defined as the difference in timing between a circadian marker and an external event. The temporal organization of the input signals is naturally an important factor in the performance of the prediction model. Since the ARMAX models attributed different weights to different input signals, differences in AE between DLMO and features from each of the input signals will affect the model’s accuracy in different magnitudes. Therefore, we have evaluated different phase angles of entrainment based on features extracted from the RR intervals and the sleep timing to better understand the differences in estimation accuracy. These are shown in Table 7.3.
Table 7.3 Differences in phase angles of entrainment (hours) between healthy subjects and sleep onset insomnia patients.

<table>
<thead>
<tr>
<th>Angle of Entrainment</th>
<th>Healthy</th>
<th>SOI</th>
<th>Absolute Difference</th>
<th>Mann-Whitney P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLMO -&gt; Sleep Onset</td>
<td>2:47 ± 0:40</td>
<td>2:39 ± 1:00</td>
<td>0:08</td>
<td>0.98</td>
</tr>
<tr>
<td>DLMO -&gt; Midsleep</td>
<td>6:02 ± 0:37</td>
<td>6:27 ± 1:00</td>
<td>0:25</td>
<td>0.30</td>
</tr>
<tr>
<td>DLMO -&gt; RR interval max</td>
<td>4:35 ± 1:51</td>
<td>4:12 ± 2:31</td>
<td>0:23</td>
<td>0.59</td>
</tr>
<tr>
<td>DLMO -&gt; Lights out</td>
<td>2:41 ± 0:39</td>
<td>2:24 ± 1:02</td>
<td>0:17</td>
<td>0.71</td>
</tr>
</tbody>
</table>

7.5 DISCUSSION

Circadian phase estimation models have been previously developed on healthy subjects based on RR interval data, activity levels, and light exposure [13]. The goal of this study was to test the applicability of these models on a pathological population of sleep onset insomnia (SOI) patients.

Although a total of 20 diagnosed SOI patients were recruited, we were only able to use the data collected from 6 of the patients due to a problem with the processing of the saliva samples. Based on these 6 subjects, the circadian phase estimation model performed with an accuracy of 48 minutes (R = 0.8934, p = 0.016). In the initial development of the models, a performance of 34 minutes (R = 0.771, p < 0.01) was reported. A decrease in accuracy could be expected given the characteristics of the SOI patients compared to healthy population as discussed below.

A significant difference (p = 0.001) was found in the age of both groups. Age-related changes to the circadian system, as well as cardiovascular dynamics, have been reported [14–16]. No significant difference in BMI (p = 0.053) was found. However, BMI and weight-related sleep disorders, such as sleep apnea, were screened for and excluded during recruitment. Participants in both groups were also instructed to complete the MEQ [17], PSQI [18], and MCTQ [19] questionnaires, in order to get an assessment of chronotype and sleep quality. The results for the MEQ showed a non-significant difference (p = 0.08) between groups, as opposed to the PSQI and MCTQ which both presented highly significant differences (p < 0.001). In addition, the subjective sleep onset latency reported by the participants also showed a significant difference (p = 0.003). Given the SOI diagnosis of the patients, differences in subjective sleep quality measures from questionnaires and subjective sleep onset latency were expected and confirmed.

During the study, we obtained sleep measures based on actigraphy and polysomnography. In the healthy cohort, only sleep measures derived from actigraphy were available. These measures included bed-in time, sleep onset time, sleep duration, midsleep time, and objective sleep onset latency. With the exception of the objective sleep onset latency, significant and highly significant differences (p < 0.001) were found between both groups for all sleep measures. These differences
indicate that both groups presented different sleeping schedules and patterns. This may have an effect on the models given that activity patterns, including the schedule of rest and active periods, are used as inputs.

A highly significant difference was found between the subjective and objective sleep onset latencies of the SOI patients \( (p < 0.001) \), however only a significant difference between the two measures was found for the healthy subjects \( (p = 0.03) \). Even though these SOI patients all had undergone PSG recordings and had slept in this particular clinic in the past, the difference could be related to first-night-effect. On the other hand, the difference could be due to the unreliability of subjective self-assessments of sleep quality. The fact that the healthy subjects who slept at home also presented a significant difference in subjective and objective sleep onset latency, supports the latter. Yet, the highly significant difference found in the SOI sample could be a result of a combination of both factors. Nonetheless, the small sample of SOI patients presented on average sleep onset latencies which were below the threshold of 30 minutes used for the diagnosis. The significant differences found in the various measures of sleep timing of both groups show that two population samples had significantly different sleeping patterns. In general, the SOI patients presented significantly earlier sleep schedules.

One of the possible causes of sleep onset insomnia is an abnormal or misaligned circadian system. Assessment of the timing of the circadian clock was done through DLMO analysis and comparing various phase angles of entrainment. A phase angle of entrainment is defined as the difference in timing between a circadian marker and an external event. In this case, the circadian marker, DLMO, was compared to several sleep timing measures including sleep onset, midsleep, and lights out time. In addition, the timing of the RR intervals was also assessed by using the time of the RR interval peak during the night. From Table 3 we see that no significant differences were found for any of the aforementioned phase angles of entrainment. This indicates that the alignment in the timing of the circadian system with respect to the sleep timing was the same for both groups. As a result, we believe that the circadian misalignment was not the cause of the SOI in this cohort of SOI patients.

As circadian misalignment did not seem to be the cause of the insomnia diagnosis in these patients, the circadian phase estimation models developed for healthy subjects were not expected to be affected significantly by the SOI subject dataset. However, the models make use of not only RR intervals and activity profiles, but also light exposure. Furthermore, the interaction between signals is an important factor which is not easily compared between datasets.

### 7.6 Conclusion

As a whole, the phase estimation results obtained from this study are encouraging and warrant a follow-up investigation. Due to the small sample of SOI patients, it is not possible at this time to draw statistically reliable conclusions regarding the
performance of the phase estimation models. This study, however, serves as an initial investigation to pilot the assessment of circadian phase estimation models based on RR intervals, activity levels, and light exposure on a pathological population of sleep onset insomnia patients.

7.7 ACKNOWLEDGMENTS
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7.8 REFERENCES


