Ambulatory assessment of human circadian phase and related sleep disorders from heart rate variability and other non-invasive physiological measurements
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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8 DISCUSSION AND FUTURE RESEARCH
The aim of this thesis has been to explore the possibility of assessing the state of a person’s circadian clock, particularly the circadian phase, through the use of non-invasively collected signals. The thesis builds upon three main areas: the signal modalities, the mathematical models, and the subject populations. A large focus has been placed on the use of heart rate and heart rate-derived features. In this thesis, heart rate variability has been shown to be a signal which is rich in information coupled to the activity of the endogenous circadian system when used in conjunction with sleep timing and/or light exposure measurements. Furthermore, statistically trained time series models have been used to capture the long-term temporal dynamics of the aforementioned signals in order to provide an estimate of circadian phase. Lastly, these principles and models have been applied to both healthy and pathological subject populations, namely sleep onset insomnia patients. Differences in heart rate variability dynamics have been presented which could shed some light onto the etiology of sleep onset insomnia. These three main areas will be further discussed in detail in this chapter, based on the results presented throughout the thesis. In addition, an overview of limitations as well as insights into future research will be provided.

8.1 SIGNAL MODALITIES
Traditionally, assessing the state of the circadian clock of a person has been done based on core body temperature [1–4] or endocrinological measurements [5,6,4]. Although the mechanisms behind these processes have been thoroughly shown to be closely related to the activity of the master circadian clock, they present the limitation of being invasive. Intra-corporal sensors for core body temperature and saliva/plasma/urine samples for cortisol or melatonin, mean that monitoring of subjects or patients must be done in laboratories, clinics or under controlled conditions. This can often lead to time-consuming, expensive, and uncomfortable procedures. Motivated by these known limitations, we have explored signal modalities which can be measured non-invasively, ideally in ambulatory conditions, and can provide insights into the timing and alignment of a person’s circadian system.

8.1.1 Heart rate and heart rate variability
Heart rate is one of the core physiological signals which is monitored and analyzed in a wide range of disciplines. More importantly, the electrocardiogram provides a wealth of information regarding numerous disorders, spanning from cardiovascular conditions to psychological conditions. However, this strength is also its weakness, as it is sometimes difficult to discern between the effects on heart rate arising from different physiological processes. Isolating the effects of one particular system is a challenge which is often addressed by strictly controlling the conditions under which the signal is being collected, or through the use of signal processing and algorithmic solutions which aim at removing possible masking effects to isolate or emphasize the signal of interest.
Throughout this thesis, the use of heart rate and heart rate variability (HRV) has been a major component in our approach to circadian phase estimation. In Chapter 2 we have shown that from all the signals which were considered, the inter-beat intervals or RR intervals provided the bulk of the information needed to assess the phase of the circadian clock. From a chronobiological perspective, the effects of the endogenous circadian system on cardiovascular dynamics as measured through HRV features has been thoroughly documented [7–13]. Our research further supports these findings, yet expands the usefulness of HRV to its value in estimating circadian phase. Nevertheless, it has been made clear that RR intervals alone do not possess the entirety of the circadian information and therefore need to be complemented by signals related to sleep timing and/or light exposure.

8.1.2 Activity levels
In this thesis, activity levels have been used as the base for assessing the timing of people’s sleep intervals. In Chapters 2–4 we have shown that by using RR intervals in conjunction with processed activity profiles, the accuracy of circadian phase estimates improve significantly. Assuming proper entrainment and circadian alignment, sleep timing is closely linked to melatonin production, which in turn is the gold standard measure of circadian phase. However, being a behavioral signal as it is, departing from a regular sleep schedule is easy and, in fact, quite common. For example, the difference in sleep timing during work-days compared to free-days, called social jetlag [14], has been widely reported. Hence the limited value for circadian phase assessment using activity profiles and sleep timing alone. However, when using this information to support and guide the circadian trends extracted from the RR intervals, a clearer picture of the state of the circadian system is conceived.

Activity levels as measured by wrist actigraphy are a practical and reliable way of obtaining sleep timing information. Furthermore, accelerometers provide the flexibility of being available in a wide range of embodiments, ranging from dedicated pendants to the nearly ubiquitous smartphones. In this thesis we used two different devices. In Chapters 2–7, an Actiwatch Spectrum, which is a dedicated wrist-worn actigraph, was used to measure activity levels and light exposure. In Chapter 5, we used a Mio Alpha watch which measures activity levels and optical heart rate for fitness applications. The data obtained from both of these devices provided the necessary information to complement the RR interval data in estimating circadian phase. The approach, however, is not limited to wrist-worn devices. Since this approach has not been expanded to other embodiments, it is not certain whether the models would need to be retrained.

8.1.3 Light
Given that the timing of light exposure is the most important factor in the entrainment of the human circadian system, the inclusion of this information in any human circadian clock model is of key importance. The models presented in Chapter
2 utilized this information to improve the estimates of circadian phase from the RR intervals alone. Nevertheless, light measurements performed by a wrist-worn device do present some limitations due to the occlusion of the light sensor by clothing. Therefore, in Chapter 3 it was shown that combining both activity profiles and light exposure can lead to accurate circadian phase estimates. This is, however, dependent on the subject population and, to a certain extent, on the time of the year. In the winter months, people tend to wear long sleeve clothing which is more likely to occlude the light sensors. If this is not controlled for, then the use of activity profiles to complement the data is recommended. The behavior of the subjects is also an influential factor which can affect the reliability of light measurements. Furthermore, related to the subject behavior, the overall light exposure throughout the day can have an impact on the results. If light exposure is in general very low, then the amount of information present is diminished as the dynamics are attenuated and no clear alternation between light and dark is present. In this case, the use of activity levels can also be beneficial in compensating for the lack of circadian information. These limitations are probable explanations for the results presented in Chapters 5 and 7 where the models relied on RR intervals and both light exposure and activity profiles to accurately estimate circadian phase.

8.1.4 Skin temperature
Skin temperature was explored in Chapter 4 as an input signal to the ARMAX models first introduced in Chapter 2. The circadian rhythmicity of skin temperature, separated into proximal and distal, has been reported in literature [15]. In addition, given that it can be measured unobtrusively in ambulatory conditions, this was a candidate for our circadian phase estimation models. Furthermore, other groups had already successfully used skin temperature as an input to their models [16–19]. Nevertheless, the results presented in Chapter 4 showed that as an input to our particular models, skin temperature did not present the dynamics necessary to accurately estimate circadian phase compared to RR intervals.

There are, however, differences in the way the data was collected between our study in Chapter 4 and the results presented by Bonmati-Carrion et al. [16]. Bonmati-Carrion et al. presented results based on skin temperature measured at the wrist, which unfortunately was a location which was not included in our setup. The use of wrist skin temperature is an interesting one, especially if we refer back to the use of smartwatches and wrist-worn devices. Given that in Chapter 5 we measured optical heart rate at the wrist, the inclusion of a skin temperature sensor would be worth exploring.

8.2 Mathematical models
One of the primary goals of this thesis was to provide a non-invasive solution which can be used in ambulatory conditions, i.e. under real-life conditions. Therefore, in Chapter 2 we first presented an approach which allowed for the unrestrained
collection of data while focusing on the trends associated with the effects of the circadian system. Most masking effects are of relatively short duration. As a result, the time-series ARMAX models chosen focus on the long-term trends that are present during a given circadian cycle. By filtering the input signals and capturing the slow dynamics, we emphasize the long-term effects of a 24 hour mechanism. Inherently, the complexity of the model is also limited, as the auto-regressive model component allows for the progressive and iterative processing of the signals.

In Chapter 4 we expanded the input signals used to include heart rate variability features extracted from the RR intervals used in Chapters 2 and 3. Furthermore, skin temperature was used as an input signal, as well as the distal-proximal gradient (DPG). Both the model structure and the processing of the input signals were identical in both chapters. A novel coding of circadian phase was introduced in Chapter 2 consisting of a time shifted cosine curve where the shift was equal to the circadian phase of the subject. The accuracy of the ARMAX models presented throughout the thesis varied from 28 minutes to 48 minutes. This varied depending on the population being assessed, where the results on healthy participants were the most accurate.

The models in Chapters 2-5 and 7 possess several benefits making them suitable approaches to estimating circadian phase in research and medical applications. The following benefits have been identified:

- **Accuracy.** Although the minimum accuracy required from circadian phase estimates is debatable, the accuracy presented in the best performing models of this thesis is in line with what is expected from comparable approaches. The uncertainty that is introduced from the melatonin measurements and DLMO calculations, together with the accuracy of other non-invasive models, suggest that the limits in accuracy which can be expected are comparable to the results presented here.

- **Low complexity.** Modeling approaches are only useful if they can be implemented. The low complexity of the models in this thesis ensure that there is a low hurdle when it comes to implementing and using the models.

- **One model for all subjects.** As opposed to approaches which require models to be trained specifically for each subject resulting in different model parameters and coefficients, the models presented here are universal. Given one model with one set of parameters and coefficients, a subject can be assessed without further training or modification of the model. This is not to say that future extensions could not include a personalization step which could improve the accuracy of the estimates.

- **Short recording times.** The models presented throughout this thesis are trained to provide estimates of circadian phase given just 24 hours of data. This allows for routine circadian phase assessments, low burden to subjects
or patients, readiness of results, and even continuous tracking of circadian phase shifts.

- **Non-invasiveness in ambulatory conditions.** One of the primary goals of this work was to develop an approach for circadian phase estimation which did not require invasive measurements and that could be carried out in real-life conditions. The models presented in this thesis allow for the use of non-invasively collected signals like RR intervals, activity levels, and light exposure, without the need of controlled conditions or special instructions.

- **Sensor/signal availability.** RR intervals can be extracted from a number of sensors, yet the traditional modalities include ECG and PPG. Input signals from both of these sensor modalities have been presented in this thesis. These signals are routinely measured in hospitals and clinics, guaranteeing the availability of data in a medical setting. Furthermore, the increasing popularity and pervasiveness of optical heart rate sensors and accelerometers in smartwatches, sport watches, and other activity monitors make it easier to access the necessary data to run these models.

### 8.3 Subject Populations

Chapters 2-5 dealt with circadian phase estimates of healthy populations. Healthy subjects were defined as those who had not been diagnosed with sleep, cardiovascular, or psychological disorders. Within the healthy population, we analyzed a young cohort with an average age of 25.5 ± 3.1 years old and an older segment with an average age of 53.7 ± 7.5 years old. The younger population in Chapter 2 was a good starting point in the developing and testing of the models since one would expect proper circadian alignment and entrainment, as well as normal cardiovascular dynamics and sleeping patterns. This also resulted in the most accurate circadian phase estimates. The older subject population in Chapter 5, on the other hand, was a more challenging group due to the effects of aging on their physiology. Age is known to affect not only the autonomous nervous system which is in part responsible for HRV patterns, but also the circadian system and sleeping patterns [20–22]. Melatonin production is also reduced with age, potentially leading to an increased uncertainty in DLMO assessments. In addition, people age differently and the inter-subject characteristics could present higher variance than in a young, healthy population sample. The accuracy of the models, when applied to the older subject population, was reduced from 34 minutes to 42 minutes. The reason for the lower accuracy is not clear, however we hypothesize that the aforementioned factors negatively impacted the performance of the models.

In Chapters 6 and 7 we focused on diagnosed sleep onset insomnia (SOI) patients. These subjects were recruited from a database of previously diagnosed patients and from patients that visited the clinic and received the diagnosis of sleep onset insomnia. The diagnosis was carried out by an experienced team of sleep doctors and nurses. Although all patients had undergone polysomnography (PSG) in the
past, it seems like a first-night-effect was present during our data collection. This came through in some of the data as a sleep onset latency (SOL) lower than their subjective SOL and their previously measured SOL during diagnosis. Nevertheless, it is believed that HRV features are not affected by the first-night-effect [23] and therefore the data is of value. Classic HRV features were extract from the data, including spectral and temporal features. Chapter 6 presented a major finding where the difference in the timing of the circadian pattern of standard deviation of normal beats (SDNN) was found to peak shortly before sleep onset. Although an age- and gender-matched dataset was not available for comparison, a thorough literature search revealed the consistent pattern that the SDNN of healthy subjects peaks in the early morning shortly before wake-up time. The studies surveyed included both male and female subjects, ranged in age from 21 to 70 years old, and presented data collected in both controlled and ambulatory conditions. Against this background, the evening peak in SOI patients was a new and interesting finding. In Chapter 7, the circadian phase estimation models developed for healthy subjects were applied to the SOI patients. Unfortunately the SOI dataset was drastically reduced for this analysis due to problems with the melatonin processing. Ideally, new models would have been trained based on the data collected from SOI patients, however this was not possible due to the very low number of patients with reliable DLMO measurements. Furthermore, the generalizability of the results presented in Chapter 7 is limited also because of the low number of patients. Nevertheless, the results are very promising and warrant a follow-up study to verify the results and to train models specifically targeted to SOI patients.

8.4 **Limitations and Future Research**

As with any new model, extensive validation is needed in order to confirm or negate the initial results. The models presented in Chapters 2 and 3 were based on a total of 30 subjects, while those in Chapter 4, 5, and 7 were based on 14, 16 and 6 respectively. Follow-up studies should be carried out, particularly to expand on Chapter 7 with more sleep onset insomnia patients. An interesting extension would also be the collection of melatonin data on several consecutive days in order to test the accuracy of the models in tracking DLMO over time.

In Chapter 6, evidence was presented from literature which indicated that the healthy group, although not gender- and age-matched to our sleep onset insomnia sample population, was representative of the general healthy population. However, the findings would be strengthened given a gender- and age-matched healthy control group. Furthermore, the experimental conditions could be matched in a clinical setting, including a polysomnogram for both groups.

Moreover, the finding presented in Chapter 6 has never been reported before. As a result, the root cause(s) of the altered timing of the SDNN peak remains unclear. A follow-up study where endocrinological data is collected and psychological
assessments are carried out would help shed light onto what is causing this alteration.

A major limitation in Chapter 7 was the low number of subjects due to problems encountered in processing the saliva samples. Given a proper sample size, statistically valid conclusions could be drawn regarding the usability of the ARMAX circadian phase estimation models in a sleep onset insomnia population.

For both Chapter 6 and 7, the sleep onset insomnia patients presented sleep onset latencies (SOL) which were lower than initially expected. Although previous assessments of these patients during their diagnosis sessions showed SOLs greater than 30 minutes, this key characteristic was not present during our data collection. Including only patients which present an extended SOL during the night of our assessment would strengthen the effects of SOI on our modeling approach and would therefore test the limits of its generalizability.

Since the study presented in Chapter 5 was carried out, improvements in software and hardware have been released for the optical heart rate sensor. Therefore, the results presented are not based on the current state of the art technology. Performing a follow-up study with the new system would likely result in improved reliability of the PPG measurements, as well as eliminate the need for multiple sensors to acquire the necessary amount of data.

8.5 Conclusion
Models have been presented based on heart rate and heart rate variability features which provide accurate circadian phase estimates in both healthy and sleep onset insomnia populations. The use of heart rate for assessing the state of the circadian clock has not yet been explored in depth. Even though ECG is the most widely used biological signal, it has not found its place in circadian phase estimation. The circadian rhythmicity of the signal itself and other derived features is well documented and has been verified in numerous scenarios. The mechanism by which the circadian pacemaker influences heart rate is also understood. The heart rate based models presented here have shown to be accurate and of low complexity. Given that heart rate is used to monitor and diagnose a large number of disorders, the implementation of circadian phase monitoring into this already existing medical practice would be straightforward.

Nevertheless, drawbacks exist in regards to masking effects, comfort and in some cases, signal quality requirements. The use of long-term Holter ECG monitors or similar devices may be bulky and the need for cables may create discomfort. Recently, new sensors have been developed which allow for long term monitoring of heart rate and other HRV features based on optical measurements at the wrist via a wristwatch. An example of such a sensor was used in Chapter 5 with promising results. These heart rate monitors are becoming increasingly popular in the
consumer market thanks to smartwatches, sport watches and other forms of activity
monitors. Currently, heart rate is used to assess numerous aspects of a person’s life
including heart health, sports performance and calories burnt, among others. The
“quantified self” movement, a culture of self-tracking using wearable technology to
collect and monitor aspects of one’s life, is based on these increasingly common
sensors. Heart rate and accelerometry are the most prominent of these sensor
modalities. The use of these sensors would remove the limitations of bulkiness and
cables, while still being accurate and non-invasive.

8.6 References
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