Ambulatory assessment of human circadian phase and related sleep disorders from heart rate variability and other non-invasive physiological measurements
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12 SUMMARY

The circadian system plays a key role in our well-being and its effects can be seen in many aspects of our lives. Our master circadian clock, located deep in our brain, influences various physiological processes such as heart rate, body temperature, energy metabolism, hormones, and sleep, to name a few. Misalignments in our circadian system can lead to both short-term and long-term problems. A familiar example is the effect of jetlag on our bodies after travel over several time zones. Alignment of the circadian clock, or entrainment, occurs naturally based on the timing of our daily exposure to light by shifting the clock forwards or backwards in time. Therefore, it is also possible to willfully shift our internal clock through the use of light therapy by forcing shifts in either direction depending on the timing of the light exposure. However, in order to do this correctly and effectively, it is necessary to know the timing of the circadian clock with respect to our solar clock. This is known as the circadian phase.

The gold standard of circadian phase is based on melatonin production. The procedure involves taking hourly or half-hourly samples, typically of saliva or blood, and determining the levels of melatonin concentration over time in a laboratory. Using a threshold, the onset of melatonin production is determined. Given that melatonin production can be suppressed by exposure to bright light, it is important that people undergoing the procedure are kept in dim-light conditions. This feature is known as the dim-light melatonin onset (DLMO). The procedure is obtrusive, time consuming, inconvenient, and can be expensive. These limitations have been the motivation of this thesis to develop an approach for accurately estimating circadian phase which is non-invasive, can be done in ambulatory conditions, and yields readily available results.

We have placed a large focus on the use of heart rate variability (HRV) to estimate circadian phase. HRV is known to be influenced by the circadian system and shows a circadian pattern when measured over a day-night cycle. The use of HRV was complemented by the use of activity levels and light exposure measurements. Activity levels, when processed, can contain information regarding the person’s sleeping patterns. Moreover, given the key role that light plays in the entrainment of humans, it was intuitive to use light exposure measurements to get additional circadian information. These signals were used as inputs to a statistically trained circadian phase estimation model. The model structure was an autoregressive moving average with exogenous inputs (ARMAX) model of low order. Through the use of this model, we were able to capture long-term trends and iteratively track the progression of the input signals as a reflection of the effect of the circadian clock. We then yielded an estimate of DLMO in the form of a coded cosine curve with a phase position equal to the DLMO. This approach was applied to both healthy populations of varying ages and to a cohort of sleep onset insomnia (SOI) patients.
In addition, a novel wrist-worn optical heart rate sensor was tested as a way of collecting heart rate data in a less obtrusive way than with traditional gel electrodes. This data was then used as inputs to the ARMAX models, showing that there was no significant difference in the accuracy of the estimates regardless of the signal modality used.

Lastly, HRV features were evaluated for SOI patients in order to determine whether differences exist, compared to healthy subjects, which could impact the accuracy of our circadian phase estimation models. A new finding was presented where a well-known temporal HRV feature was shown to reach a maximum prior to sleep onset time in SOI patients, while the same peak is seen only in the early morning prior to wake-up time in healthy sleepers. This difference was highly significant and could provide insights into the etiology of sleep onset insomnia. Several hypotheses are provided along with evidence regarding their relevance for this condition. In addition, this method could potentially provide a means for diagnosing or monitoring sleep onset insomnia, based on ambulatory heart rate measurements.

In conclusion, this thesis focused on the use of statistically-trained models based on ambulatory measurements of heart rate variability as an unobtrusive approach to circadian phase estimation. We have found that it is possible to estimate circadian phase non-invasively based on 24 hours of data, driven by measurements of HRV, activity levels, and/or light exposure. The models are generalizable, within certain accuracy limits, to healthy subjects ranging from 20 to 65 years of age. Furthermore, promising initial results have been presented for their applicability to sleep onset insomnia patients. In addition, we have shown that it is feasible to use optical heart rate data measured at the wrist as an alternative to electrode-based electrocardiograms for estimating circadian phase. Lastly, a temporal difference in HRV between healthy sleepers and SOI patients has been presented, which could help in the understanding, diagnosing, and treating of sleep onset insomnia.