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A model characterizing the coupling between slow-wave activity, instantaneous heart rate and heart rate variability during sleep*

Gary Garcia-Molina, *Member, IEEE*

***Abstract*— The cyclical and progressively decreasing dynamics of electroencephalogram (EEG) based slow-wave activity (SWA) during sleep reflects the homeostatic component of sleep-wake regulation. The dynamic changes of heart rate (HR) and heart rate variability (HRV) indices during sleep also exhibit quasi-cyclic trends that appear to correlate with SWA. This article proposes a model to characterize the relationship between SWA, HR and HRV in the polar-coordinate (r-θ) domain. Polar coordinates are particularly well-suited to model cyclic shapes with simple (linear) equations in the r-θ plane. Group-level analyses and individual-level ones of the correlations between the polar-coordinate transformations of SWA and HR reveal R^2 values of 0.99 and 0.95 respectively. Given that, HR and HRV can be estimated in less obtrusive ways compared to EEG. This research offers relevant options to conveniently monitor sleep SWA.**

***Clinical Relevance*— Slow wave activity is a marker of sleep restoration that most prominently manifests in the EEG. This research suggests that an electrocardiography (ECG)-based non-linear model can approximate a polar-coordinate version of SWA. Since ECG correlates can be unobtrusively acquired during sleep, these results suggest that practical SWA monitoring can be achieved through cardiac activity measurements.**

I. Introduction

Recent research on the function of sleep has led to results identifying the central nervous system (CNS), mainly the brain, among the primary beneficiaries of sleep. The synaptic homeostasis hypothesis [1] postulates that sleep renormalizes synaptic energy to prepare the brain for subsequent wakefulness. Xie et al. [2] and Fultz et al. [3] propose that sleep, mostly deep non-rapid eye movement (NREM) sleep, drives metabolic clearance from the adult brain, and [4] elaborates on the idea that "sleep is of the brain, by the brain, and for the brain." The autonomic nervous system (ANS) also manifests specific patterns of activity depending on the sleep stage; these can be quantified by analysis of changes in heart-rate (HR) and heart rate variability (HRV) during sleep [5].

Evidence for the coupling of CNS and ANS activities during sleep is reviewed in [6]; multiple levels of CNS-ANS interaction are identified: 1) at the sleep cycle level characterized by the interaction between cyclic CNS oscillations and co-occurring changes in peripheral ANS activity, and 2) at a shorter time scale where phasic CNS events (such as K-complexes or μ-arousals) are accompanied by ANS fluctuations.

Electroencephalogram (EEG) and electrocardiogram (ECG) signals are prominent indicators of CNS and ANS activity, respectively. These signals are essential components of polysomnography (PSG), the gold-standard method for objectively studying sleep. A number of attempts have been made to jointly analyze ECG and EEG signals to elucidate the mechanisms of ANS and CNS association using PSG data. For instance, the interbeat autocorrelation coefficient was associated with changes in mean EEG frequency [7], and decreases in interbeat autocorrelation preceded increases in EEG delta power (0.5–4 Hz) [8]. Furthermore, NREM sleep promotes increases in EEG delta power and a decrease in blood pressure [9].

This article considers ECG-based HR and HRV estimated at the 30-second temporal window level (epoch) and their relationship with EEG power in the delta band (slow wave activity or SWA).

The focus on SWA is motivated by its role as a marker of sleep need and sleep restoration [10]. From the sleep need perspective, the dynamics of SWA reflect that of process "S" in the two-process model [11]. SWA accumulates during NREM sleep, declines before the onset of rapid eye movement (REM) sleep, and remains low during REM; the level of increase in successive NREM episodes gets progressively lower [12] (Figure 1). Higher SWA has been linked with higher restorative sleep. Low SWA appears to correlate with shallower sleep, and SWA naturally declines with aging [13].

The possibility of identifying ECG-based metrics that meaningfully correlate with SWA enables practical options to monitor sleep restoration, as ECG surrogates can be estimated using unobtrusive technologies including ballistocardiography [14, 15] and capacitive coupling [16].

II. Methods

Forty-five self-reported healthy sleepers (25F/20M; 41.2 ± 10.5 years old; body mass index [kg/m^2] 25.9±4.4; apnea/hypopnea index [AHI] 6.53±15.1 [events/h]) consented to participate in a single sleep lab study to assess the accuracy of sleep metrics obtained from a Sleep Number smart bed against PSG-based sleep metrics. The study was categorized as "exempt status" by the Institutional Review Board of the University of Chicago. The main results of that research are under consideration for publication in a sleep specialized journal.

In this paper we used PSG signals to model the interaction between EEG-derived SWA and ECG-derived HR and HRV.

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G. Garcia-Molina is with Sleep Number Labs, San Jose, CA 99035 USA (corresponding author email: gary.garciamolina@sleepnumber.com).

EEG and ECG signals were acquired at sampling frequencies of 200 Hz and 500 Hz, respectively.

PSG sleep stages were independently scored by three registered sleep technicians based on the AASM guidelines [17] and the sleep stage for each epoch was chosen as the stage scored by at least 2 of the 3 technicians. In the case of disagreement among the three technicians, a sleep expert (GG) made the final determination of the sleep stage. This process resulted in a consensus hypnogram per PSG recording used in this paper. The hypnogram consisted of 5 stages including wake (W), REM (R), NREM1 (N1), NREM2 (N2), and NREM3 (N3). AHI was determined from PSG signals by the sleep technician from Lakeland Sleep Center. AHI < 5 indicated an absence of apnea.

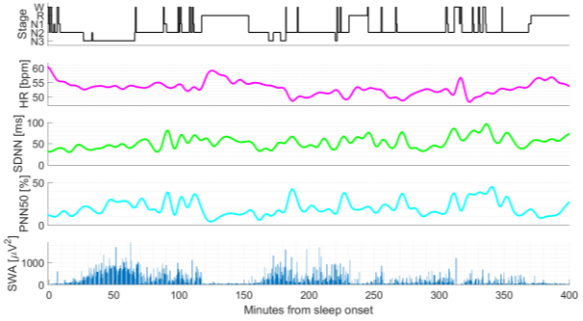

Figure 1. Consensus hypnogram (top) along with sleep stage dependent changes in HR (2nd panel), SDNN (3rd panel), PNN50 (4th panel) and SWA (bottom panel).

A. Heart rate and heart rate variability analysis

HR and temporal HRV were estimated for each PSG study using the ECG signal. R-peaks in the ECG were detected using the QRS detection algorithm in [18]. RR intervals were calculated as the time difference between the timing of consecutive R-peaks. Due to potential R-peak detection inaccuracies, RR intervals in the 1st percentile and above the 99th percentile were discarded. If applicable, RR segments shorter than 300 msec or longer than 2000 msec were also discarded. This resulted in a sequence of NN intervals ("normal" RR intervals).

HR and HRV values were calculated for each 5-minute long window as recommended [5, 19]. Let $NN_1, \ldots, NN_n$ be the sequence of NN intervals (in msec) in a given 5-minute window. Then, HR (in beats per minute) associated with that window is $60000/median(\{NN_1, \ldots, NN_n\})$. The median operator was used to reduce sensitivity against outlier NN values.

Two temporal HRV metrics were calculated, SDNN (standard deviation of NN intervals) and PNN50 (the percent of successive NN intervals that differ by more than 50 msec). The choice of time domain over frequency domain HR analyses was motivated by the fact that time domain metrics are associated with lower estimation errors [20].

To align with hypnogram- and EEG-based metrics, epoch level resolution (i.e., 30 seconds) of HR and HRV were obtained through linear up-sampling by a factor of 10 (Figure 1).

B. SWA

SWA was calculated from the frontal EEG channel F3. The choice of a single EEG signal to perform this analysis was motivated by: 1) the fact that SWA manifests more prominently on frontal EEG sites, 2) SWA trends are similar across all EEG sites [21], and 3) simplicity of analysis.

The EEG signal was first band-pass filtered in the 0.05 to 40 Hz frequency band using a second-order Butterworth filter. For each noise-free epoch that did not contain any annotated micro-arousal, the EEG power spectrum density (PSD) was estimated using the Welch method [22] using a 10-sec Hanning window and 5-sec overlap. The PSD had a 0.1 Hz resolution and SWA was calculated by integrating the PSD from 0.5 to 4 Hz (Figure 1).

C. HR and HRV versus SWA analysis

The curves in Figure 1 suggest a relationship between SWA and HR/HRV. Indeed, during NREM, HR decreases, SDNN and PNN50 increase and SWA increases. During REM, SWA decreases, HR increases and PNN50 decreases.

The (log-log) plots represented in Figure 2 show a cyclic relationship between HR/HRV and SWA. The cyclical nature of the relationship is more noticeable for HR vs SWA and SDNN vs SWA than for PNN50 vs SWA. The shape of the cycle is reminiscent of a collapsing spiral and appears to be due to the cyclic and progressively decreasing behavior of SWA, which is mirrored by HR (Figure 1).

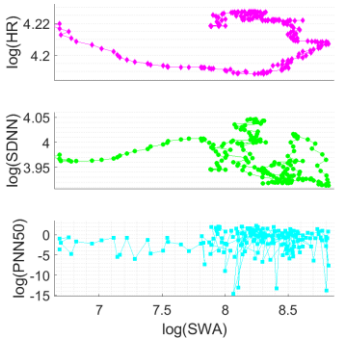

Figure 2. Log-log plots. Top: HR vs SWA. Middle: SDNN vs SWA. Bottom: PNN50 vs SWA.

Cyclic-shape curves can be conveniently modelled in polar coordinates. For instance, the equation of an Archimedean spiral is: $r = a + b \times \theta$ in the plane (r, θ). Therefore, the modelling of HR/HRV vs SWA was performed in polar coordinates using the transformation described in Equation 1.

$$r_C = \sqrt{log(SWA)^2 + log(C)^2},$$
$$\theta_C = arctan\left(\frac{log(C)}{log(SWA)}\right), \qquad \text{Equation 1}$$

where C stands for HR, SDNN, or PNN50. The subsequent step estimated the coefficients of the model $r_C = a + b\theta_C$ through linear regression along with the corresponding R^2 value.

III. RESULTS

A. Group-level results

For the group-level analysis, the 30-sec resolution temporal curves for HR, SDNN, PNN50, and SWA (Figure 1) for each PSG study were averaged in the time domain by aligning them with respect to sleep onset. This average is referred to as group-level average.

The group-level averages of HR, SDNN, and PNN50 were analyzed vs the group-level average SWA using polar coordinates (Equation 1; Figure 3). Linear regression models were then fit for each HR/HRV metric vs SWA. The results reported on Table 1 suggest that the linear models in the polar domain (i.e., spirals in the Cartesian domain) fit particularly well the relationships: (HR vs SWA; R^2=0.99) and (SDNN vs SWA; R^2=0.96). Illustration of the accuracy of the model fit, at the group-level in the SWA-HR plane is shown in

Figure 4.

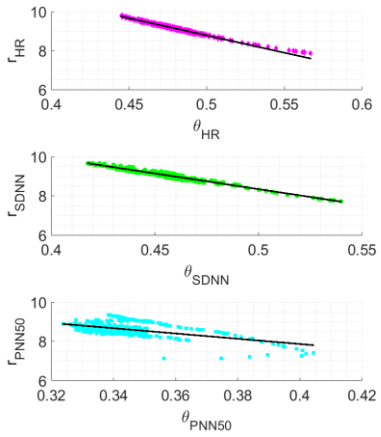

Figure 3. Group level analysis. Top: HR vs SWA. Middle: SDNN vs SWA. Bottom: PNN50 vs SWA.

B. Individual-level results

A similar modeling analysis was applied to individual-level results, i.e., using the individual SWA, HR, and HRV curves. The statistics of individual-level model parameters are reported in Table 2.

Consistent with the group-level analysis, the highest average R^2 value was obtained for the association between HR and SWA, i.e., $r_{HR}$and θ_{HR}. The lowest R^2 (=0.19) was for the PNN50-SWA association.

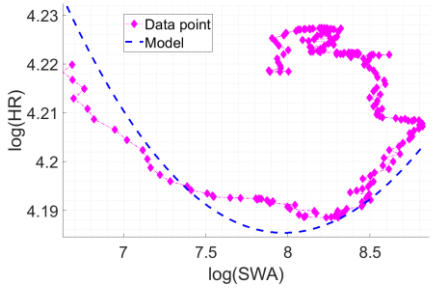

Figure 4. Group-level model fit for HR vs SWA.

IV. DISCUSSION

EEG power in the delta band (SWA) is a marker of the homeostatic sleep need of the two-process model of sleep/wake regulation. Because of the close interaction during sleep between the CNS and the ANS, it is reasonable to hypothesize that the activity of the latter can also reflect sleep need dissipation. Such insight motivated this investigation where SWA vs HR and time domain HRV (SDNN and PNN50) metrics were analyzed.

TABLE 1. GROUP-LEVEL RESULTS.

SWA versus	***Model***	***R^2***
HR	$r_{HR} = 17.63 - 17.72\theta_{HR}$	0.99
SDNN	$r_{SDNN} = 16.33 - 15.98\theta_{SDNN}$	0.96
PNN50	$r_{PNN50} = 13.22 - 13.40\theta_{PNN50}$	0.35

The polar coordinate domain appeared to be well suited to model the relationships SWA-HR, SWA-SDNN, and SWA-PNN50 at both group and individual levels. This type of transformation was inspired by the cyclic and spiral-like shapes of the curves in Figure 2, and the fact that simple, linear equations in the polar coordinate system can represent spiral-like curves.

The high R^2 of the group-level and individual-level correlations of the polar transformation of SWA and HR suggests that changes in HR are associated with changes in SWA during sleep. This is in line with recent research showing that automatic sleep staging can be accomplished using the instantaneous HR [23] or features derived thereof [24]. It is relevant to note that the parameters of the HR-SWA model in Table 2 (i.e., $a_{HR}$and b_{HR}) show a low degree of inter-individual variability. Indeed, the respective standard deviations are 6 and 12 % of the average values, respectively. This suggests that a generic, subject-independent model may exist.

TABLE 2. INDIVIDUAL-LEVEL RESULTS.

Model: $r_{HR} = a_{HR} + b_{HR}\theta_{HR}$

a_{HR}	b_{HR}	R^2
16.23 ± 0.97	-14.86 ± 1.83	0.95 ± 0.08

Model: $r_{SDNN} = a_{SDNN} + b_{SDNN}\theta_{SDNN}$

a_{SDNN}	b_{SDNN}	R^2
13.66 ± 1.72	-10.85 ± 3.08	0.66 ± 0.18

Model: $r_{PNN50} = a_{PNN50} + b_{PNN50}\theta_{PNN50}$

a_{PNN50}	b_{PNN50}	R^2
9.63 ± 3.19	-3.03 ± 6.59	0.19 ± 0.24

For SDNN, there is a substantial difference between the goodness-of-fit achieved by the group-level model (R^2 = 0.96) and that by the individual-level model (R^2 = 0.66 on average). For PNN50, neither the group-level nor the individual-level results in R^2 exceeded 0.5.

Higher noise in the estimation of SDNN and PNN50 may explain the low R^2 values of SDNN vs SWA and PNN50 vs SWA models. Indeed, the R^2 associated with the group-level analysis is higher than that of the individual-level analysis and the former, being an average, has a lower noise level compared to the latter. An alternative explanation to the low R^2 values for SDNN and PNN50 is that time-domain HRV metrics based on absolute differences of NN intervals are influenced by heart rate changes; however, the HR through sleep is certainly not stationary, as can be seen in Figure 1. A possible strategy to correct for this effect is to de-trend the NN sequence prior to the estimation of SDNN and PNN50.

V. Conclusion

This research suggests that a non-linear model resulting from a transformation in polar coordinates of the SWA-HR space fits well with the dynamics of SWA and HR during sleep. SWA reflects sleep need dissipation, and as such, constitutes a marker for sleep restoration.

By definition SWA requires analysis by EEG. Our results show that SWA may be approximated by cardiac metrics that can be estimated through unobtrusive and contact-free means (e.g., ballistocardiography or capacitive sensing).

The model presented in this paper has considered the SWA from a single EEG signal. Future research should contemplate multivariate SWA models (from several EEG channels) and multiple cardiac metrics. While frequency-domain HRV metrics are presumably associated with higher estimation errors [20], these should also be considered to more precisely investigate the sympathovagal balance. A substantially larger number of PSG recordings needs to be used to formally (within a cross-validation procedure) quantify the accuracy of the model presented in this article.

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