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Instantaneous Monitoring of Sleep Fragmentation by Point Process Heart Rate Variability and Respiratory Dynamics

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Abstract

We present a novel, automatic point-process approach that is able to provide continuous, instantaneous estimates of heart rate variability (HRV) and respiratory sinus arrhythmia (RSA) in long duration data recordings such as those during an entire night of sleep. We analyze subjects with and without sleep apnea who underwent diagnostic polysomnography. The proposed algorithm is able to quantify multi-scale high time resolution autonomic signatures of sleep fragmentation, such as arousals and stage transitions, throughout an entire night. Results demonstrate the ability of our methods to track fast dynamic transitions from sleep to wake and between REM sleep and other sleep stages, providing resolution details not available in sleep scoring summaries. An automatic threshold-based procedure is further able to detect brief arousals, with the instantaneous indices characterizing specific arousal dynamic signatures.

I. INTRODUCTION

Sleep architecture is characterized by transitions among REM and NREM sleep stages and Wake within the sleep episode. Human studies suggest that sleep fragmentation may have behavioral and physiological consequences similar to sleep deprivation [1]. Fragmentation of sleep can be manifest in various ways, including increased transition frequency within sleep, transitions to wakefulness, or brief arousals (<15 seconds) not meeting scoring criteria for wake. Given the poor relationship of subjective sleepiness with objective sleep architecture metrics (including apnea severity) [2], there is increasing interest in complementary approaches to understanding sleep architecture and fragmentation. Autonomic fluctuations, typically extracted from time series analysis of ECG signal, have yielded important insights into sleep physiology in health and disease. For example, algorithms based on ECG have been implemented for sleep staging and for detection of

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sleep apnea [3]-[7], and ECG-autonomic measures have been correlated with apnea severity [8]. Heart rate variability is the best-studied metric, with high frequency oscillations (at the respiratory frequency) representing parasympathetic activity, and low frequency oscillations being affected by both sympathetic and parasympathetic factors.

Currently, classification of an arousal requires 3-15 seconds of increased EEG frequency in NREM sleep, but questions remain regarding scoring inter-rater reliability, comparisons with automated EEG analysis, and the relationship of these arousals to clinical symptoms [9]-[11]. Another important challenge is how to study human physiology over time in the patient's natural environment, rather than in a clinical or experimental setting. ECG has the advantages of being unobtrusive and less variable than EEG, and allowing repeated recordings to capture variability that may contain clinically useful information.

We here apply a novel point-process approach to provide continuous, instantaneous estimates of heart rate variability (HRV) and respiratory sinus arrhythmia (RSA) in long duration data recordings such as those during an entire night of sleep. We analyze subjects with or without sleep apnea who underwent diagnostic polysomnography to explore, with variable time resolution, autonomic signatures of sleep fragmentation such as arousals characterized by ECG-based cardiorespiratory (CR) metrics (CR Arousals), and stage transitions throughout an entire night.

II. METHODS

A. Experimental Protocol

Polysomnogram data was obtained from the MGH sleep clinic, where subjects underwent overnight monitoring for clinical purposes. Standard recording montage included EEG (6 leads), EMG (chin and bilateral leg), ECG, respiratory effort and airflow. The ECG was a single lead placed on the left anterolateral chest, referenced to a lead placed on the right mid-upper chest. Sleep scoring was performed by experienced technicians using EEG, EMG and EOG according to the American Academy of Sleep Medicine guidelines. Signals were sampled at 200Hz, de-identified data were exported for off-line analysis. R-events were identified in the ECG by using a semi-automated procedure.

B. The Evenly-Sampled Point Process Model

A novel algorithm is applied to the R–R series to compute instantaneous estimates of HRV and RSA from ECG recordings of R-wave events. This approach is based on the point process methods already used to develop both local likelihood [12] and adaptive [13] heart rate estimation algorithms. The stochastic structure in the R–R intervals is represented by a time-varying model where the probability density of observing a beat at time τ, given the previous beat at time u_k, and the time-varying model at t, is an inverse Gaussian (IG) renewal process:

$$f(\tau, u_k, t) = \sqrt{\frac{\theta(t)}{2\pi(t-u_k)^3}}\, e^{\frac{1\theta(t)[\tau-u_k-\mu(\tau,t)]^2}{2\ \mu(\tau,t)^2(\tau-u_k)}}$$

where $\mu(\tau, t)$ is the instantaneous mean of the distribution, while $\theta(t)$ is the shape parameter of the IG distribution.

The IG probability density is derived directly from an elementary physiologically-based integrate-and-fire model [12],[13]. The model also represents the dependence of the R–R interval length on the recent history of parasympathetic and sympathetic inputs to the SA

node by modeling the mean $\mu(\tau, t)$ as a uniform time-sampled regression on the respiratory signal and on a continuous estimate of the previous R–R intervals:

$$\mu(\tau, t) = a_0(t) + \sum_{i=1}^{P} a_i(t)\,\widetilde{RR}(\tau - i\Delta, t) + \sum_{i=1}^{P} b_i(t)\,RP(\tau - i\Delta)$$

where P is the order of the model, Δ is an arbitrary sampling period, a_i and b_i are the time-varying model coefficients, RP is the observed respiratory signal, and $\widetilde{RR}$ is the continuous estimate of the previous R–R intervals. The $\widetilde{RR}(\tau, t)$ is modeled by a cubic Hermite spline estimate whose control points are the observed R-events up to time t, with tangent values evaluated as a three-point difference. An important advantage of this model is that the estimate is causal and can be updated online as new R events are observed. This choice is compatible with our ultimate goal of building an online real-time monitor of HRV and RSA.

A local maximum likelihood method [12],[14] was used to estimate the unknown time-varying parameter set $\xi = \{\{a_i\}^p, \{b_i\}^p, \theta\}$. The local log-likelihood at each time t is the weighted sum of the IG density function above, $f(u_{k+1}, u_k, t)$, evaluated at each heartbeat recorded in an observation interval $(t - l, t]$ of duration l. Even when the last RR interval was not completely observed, it was accounted for in the estimation of ξ by means of a right censoring term [12]. So, given a sequence of observed beats $\{u_k\}$, the log-likelihood of the parameter set ξ is:

$$L(\xi | u_{t-l:t}) = \sum_{k=N(t-l)+1}^{N(t)} w(t - u_k) \log\left(f(u_k, u_{k-1}, t)\right) + w\left(t - u_{N(t)}\right) \log\left(\int_t^{+\infty} f\left(\tau, u_{N(t)}, t\right) d\tau\right)$$

where $N(t)$ is a function that returns the number of events up to time t and $w(t - u_k) = 0.98^{t-u_k}$ is an exponential weighting function for the local likelihood.

This model provides two critical improvements over the approaches in [14],[15]. First, because the regressors are uniformly sampled at step Δ rather than at the heartbeats, the transformation in the frequency domain does not incur into spectral distortions due to the inherently non-uniform sampling. Second, the regression is further defined in continuous time (τ), thus overcoming discontinuities characteristic of previous discrete applications. At the same time, as the likelihood weights the probability at the beats, this model preserves the point process nature of the sequence of R events which is otherwise lost when using methods based on interpolated R-R time series.

C. Spectral indices of HRV and RSA

The set of coefficients a_i and b_i allows for estimation of the spectral power (HRV) and further decomposition into classic low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.5 Hz) spectral components as well as evaluation of the respiratory sinus arrhythmia (RSA).

We defined the RSA as the average transfer function between the respiratory input *RP* and the RR interval on the HF band (0.15-0.4 Hz) weighted by the cross-spectrum between the two:

$$RSA(t) = \frac{\int_{\omega HF-}^{\omega HF+} H_{RP\rightarrow RR}(\omega, t)\, S_{RP,RR}(\omega, t)\, d\omega}{\int_{\omega HF-}^{\omega HF+} S_{RP,RR}(\omega, t)\, d\omega}$$

The transfer function between the respiratory input *RP* and the *RR* interval $H_{RP\rightarrow RR}(\omega, t)$ could be found from the model parameters as:

$$H_{RP\rightarrow}RR(\omega, t) = \frac{\sum_{i=1}^{P} b_i(t)\, z^{-i}}{1 - \sum_{i=1}^{P} a_i(t)\, z^{-i}}\Big|_{z=j\omega\Delta}$$

The cross-spectrum $S_{RP,RR}(\omega, t)$ was evaluated as:

$$S_{RP,RR}(\omega, t) = H_{RP\rightarrow RR}(\omega, t)\, S_{RP}(\omega, t)$$

where the spectrum $S_{RP}(\omega, t)$ of the respiratory input was estimated on the same observation window using a univariate autoregressive model of order *P*.

This point process recursive algorithm is able to estimate the dynamics of the model parameters, and consequently the time-varying behavior of each spectral index, at any time resolution. This new continuous model for deriving HRV and RSA measures has been cross-validated with standard time-frequency domain approaches for HRV analysis as well as previous point process algorithms [12],[13]. The dynamic response for the point process method is found to provide a significant improvement over other methods in tracking fast dynamic changes [13]. A fixed order P=8 and a sampling period Δ=0.8s were chosen for the analysis. Indices were updated every 5 ms using the information available up to that time point. The algorithm could be virtually run in real-time and has linear complexity with recording length: processing 8-h of data took, on average, 35 min.

III. RESULTS

A. Characterization of the sleep stages

We present results from a total of 6 subjects, 3 classified as healthy, and 3 diagnosed with sleep apnea. Fig. 1 shows ~8 hours of data from one subject from each group (healthy on the left panel). The trends from the instantaneous indices follow dynamics consistent with the transitions reported by the sleep scoring, as further confirmed by the averaged results reported in Table I for NREM2 and REM sleep (the most frequently occurring stages). Statistical comparison between the two stages in both groups pointed at RSA and HF as the most discriminating indices. In distinguishing the two groups, it is worth noting the overall RSA increase in the healthy subject during the second part of the night where CR arousals are rare, which is not evident in the subject with apnea. In fact, the average RSA computed during stable NREM2 and NREM3 sleep in the second half of the night more than doubles for the healthy subject, whereas it shows a slight decrease for the apnea subject.

A. Sleep-Wake transitions

Figure 2 shows a series of transitions within a 900s time scale, from deep sleep (NREM3) to Wake at around 300s, back to NREM2 at around 420s, and from NREM2 to Wake at 720s

then back to NREM2 at 860s after a transient period in NREM1. The instantaneous indices (RSA, LF/HF and Var HR), here sampled at a 5 ms high resolution, provide clear dynamic signatures associated with changes in sleep state, often largely anticipating the sleep scoring markers, even earlier than the 30s epoch needed for the scoring procedure to provide the next scoring index. In particular, in the RSA index, a sharp drop in RSA anticipates the change in scoring at 300s by 40s, and the transition at 720s by at least 60s. Note also the clear increasing trend of RSA after the second transition, starting at around 430s until the sharp drop at 660s preceding (or indicating the more precise transition time) the second transition to wake.

B. Transitions from Non-REM to REM

Figure 3 shows a transition from NREM2 to REM sleep within a 900s time scale occurring, according to the sleep scoring index, at around 410s. Here the RSA index starts dropping sharply from values around 100s to values close to zero at around 330s, which is 90s before the indication of a transition to REM by the scoring index. Between 330s and 500s the RSA shows more complex dynamics, including a sharp variation at the time where the scoring index reports the transition. Except brief moment of sharp variations, possibly indicating arousals during REM, RSA stabilizes around lower values along the REM period, while the LF/HF index points at an increased sympathovagal modulation shifting towards a sympathetic-driven tone, characteristic of the REM state.

C. Characterization of Cardiorespiratory Arousals

For this analysis, CR arousal times are defined as the times where RSA values fall below a statistically-determined threshold for a minimum duration of 8s, and they are indicated by the red asterisks in the two recordings in Fig. 1. The algorithm is able to detect all the events triggering a sleep score transition, as well as additional shorter events due to its higher time resolution, for a total of 24 CR arousals for the healthy subject and 42 for the subject with apnea. We hypothesize (at least for the healthy individual) that CR arousals have occurred when RSA has minima. To test this hypothesis, we averaged all the detected transitions from the threshold-based procedure and used the detection as fiducial point to average all indices (as well as the raw RR series) along a 100s time scale, with the fiducial point in the center of the considered interval. One example of arousal, as well as averaged time series of all the arousals detected for the healthy subject in Fig 1, are presented in Fig. 4. The averaged series confirm previous arousal characterization [11] for the mean RR, LF/HF and the HF indices, validating our detection criterion and pointing at a novel characterization of the arousal event by our instantaneous index of RSA.

IV. DISCUSSION AND CONCLUSION

In this paper we have presented a novel, automatic point-process algorithm for the instantaneous assessment of heart rate variability (HRV) and respiratory sinus arrhythmia (RSA) and shown preliminary results obtained from one-night-long polysomnographic recordings. Our approach is able to identify fast dynamics that allow for sleep characterization at higher time resolution than traditional methods and to track fast changes in RSA that indicate brief CR arousals and transitions from deep to light sleep or wake.

In the future, we plan to further exploit the capability of this algorithm to track fast autonomic changes in order to accurately characterize different types of both ECG- and EEG-based arousal events and/or apnea episodes. A particular focus will be given to investigate if our identification can predict these transient phenomena. A potential accurate classification, together with the ability to track autonomic changes and transitions between

stages in an on-line fashion, may provide a solid base for building real-time sleep monitoring and bio-feedback devices.

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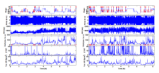

Fig. 1.

From top to bottom, the plots show the sleep stage (W=Wake, R=REM Sleep, N1-N3= different stages of NREM sleep), the respiratory input, the series of RR intervals, the RSA, the LF/HF index, and the residual variance of heart rate for one healthy subject (left) and one patient diagnosed with apnea (right),. The indices are averaged within the 30s scoring epochs to provide proper dynamics at the long time scale correspondent to the entire night The red stars mark times where the RSA value fall below a statistically determined threshold, indicating an arousal that often causes lightening of sleep.

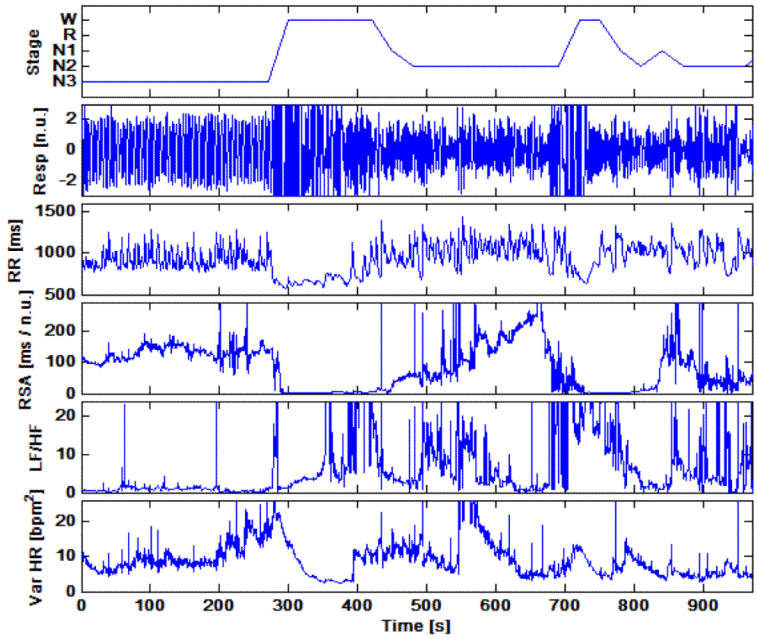

Fig. 2.

Example of transitions between sleep and wake, showing how the instantaneous indices (RSA, LF/HF and Var HR) computed at high resolution (5 ms) provide clear dynamic signatures associated to changes in sleep state during a time scale corresponding to a range of 900 s.

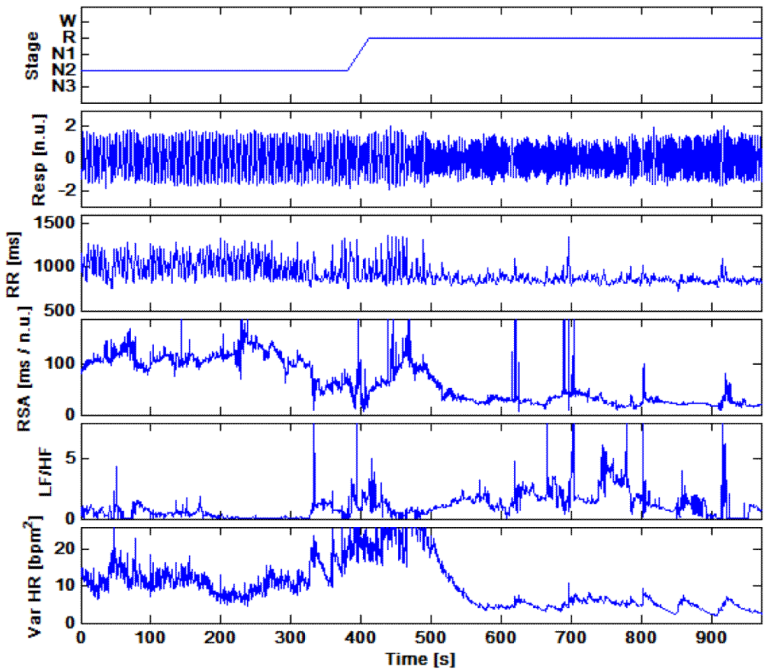

Fig. 3.
Example of a transition from NREM2 to REM.

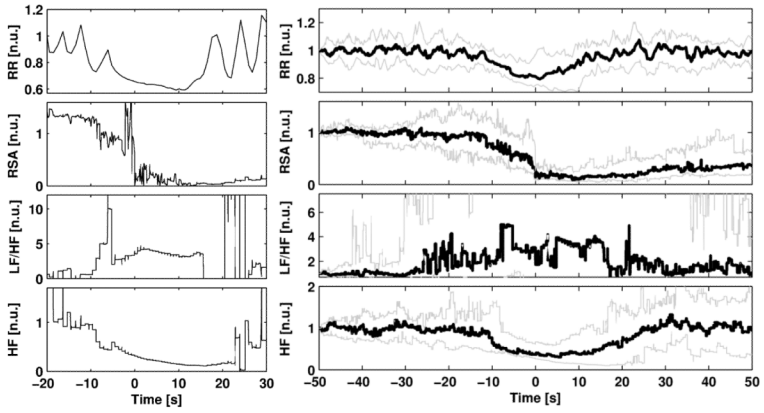

Fig. 4.

Dynamic signatures of the detected CR arousals. Time =0 is where the RSA first crosses the threshold. Left: an example of the arousals found for one healthy subject. Right, for each signal we report median (dark line) and 25th and 75th percentile (grey lines) of the distribution at each time.

TABLE I
STATISTICS OF THE RSA AND HRV MEASURES

	Healthy		OSA	
	NREM2	**REM**	**NREM2**	**REM**
RSA	20.4±16.3	6.54±4.45 **	24.8±24.5	10.3±7.2 **
LF/HF	0.54±0.55	1.87±2.19 **	0.88±1.04	1.55±1.68 *
LF	644±74	297±340 **	1165±1639	657±915 *
HF	857±794	186±151 **	1849±2324	401±463 **
LFnu	0.31±0.20	0.54±0.28 **	0.35±0.26	0.48±0.28 *
HFnu	0.69±0.20	0.46±0.28 **	0.65±0.26	0.52±0.28 *
varHR	3.39±1.72	2.89±1.42 *	2.49±1.64	2.48±1.84

Summary of the distributions of the RSA and HRV measures during 30s epochs of NREM2 and REM sleep for the two groups of subjects. For each measure, median±1.4826×MAD (1.4826 times the Median Absolute Deviation is a robust estimator of standard deviation) are reported. A Mann-Whitney test was used to assess whether the values of RSA, HF, HFnu, and varHR are higher during NREM2 w.r.t. REM and whether LF/HF, LF, and LFnu are lower. The cases marked with * are significant at $p<0.05$ while those marked with ** are significant at $p<10^{-10}$.