Investigating Phasic Activity of Time-Varying High-Order Spectra: A Heartbeat Dynamics Study During Cold-Pressor Test

Shadi Ghiasi[1], Alberto Greco[1], Mimma Nardelli[1], Vincenzo Catrambone[1], Riccardo Barbieri[2], Enzo Pasquale Scilingo[1], and Gaetano Valenza[1]

[1] Research Center “Enrico. Piaggio" & Dept. of Information Engineering, University of Pisa, Pisa, Italy; [2]Dept. of Electronics, Informatics and Bioengineering, Politecnico di Milano, Milano, Italy

Abstract

Recent modeling advances have successfully derived time-varying estimates of nonlinear heartbeat dynamics, whose quantifiers mainly rely on first-order moments (i.e., average over time). While, these metrics account for the information carried by the tonic (slow trend) nonlinear dynamics, they fail to quantify potentially meaningful information nested in the superimposed phasic (high-frequency) activity of the physiological series. In this study, we investigate new metrics from phasic activity of time-varying bispectral indexes, which are derived from nonlinear point-process modeling of heartbeat dynamics. Instantaneous phasic activity is derived using wavelet decomposition of time-varying bispectral power, and quantified using the area under the curve (AUC) and variance (VAR) metrics. Results, gathered from ECG series from 22 healthy volunteers undergoing cold-pressor test (CPT), show that phasic components of low-frequency (LL) instantaneous bispectra significantly change between resting and CPT states, as quantified by AUC and VAR. In conclusion, phasic activations of bispectral estimates carry meaningful information for the nonlinear assessment of sympatho-vagal regulation onto the heart. This study poses a foundation for a novel signal processing framework investigating time-varying estimates of nonlinear cardiovascular control.

1. Introduction

Cardiovascular dynamics are known to exhibit complex and non-stationary properties, mainly due to the nonlinear influence of the autonomic nervous system (ANS) control onto the heart [1–3]. Although specific physiological correlates of such behaviour are unknown, invasive measurements in animal studies have suggested that α-adrenoceptors, the cholinergic system, as well as adenosine 3’,5’-cyclic monophosphate are major responsible factors for the generation of complex cardiovascular oscillations [1]. In addition, multi-feedback interactions between the sympathetic and parasympathetic (vagal) branches of the ANS dynamically regulate spontaneous heart rate variability (HRV), leading to the so-called "accentuated antagonism" [1], i.e., the effect of a given vagal stimulation on heart rate strongly depends on the "background level" of sympathetic stimulation occurring at the same time.

Consequently, standard HRV time and frequency analyses, which quantify linear dynamics exclusively, are not enough to fully characterize the cardiac system, and need to be complemented by measurements from nonlinear system theory [2, 3]. Of note, many psychophysiological and pathophysiological states have been successfully assessed by nonlinear heartbeat measures [2–5]. Exemplarily, good predictors of mortality following myocardial infarct or heart failure are entropy and multifractal metrics [2, 4, 5].

In this study, we investigate dynamical properties of time-varying bispectra derived from nonlinear point-process models [6, 7]. Bispectra of heartbeat dynamics, in fact, provide estimates of sympathetic-parasympathetic interactions [6], whose abnormalities may lead to, e.g., heart failure [8]. Using an inverse-Gaussian probability density function predicting the waiting time until the next heartbeat event occurs, this framework allows to obtain instantaneous linear and nonlinear estimates along with model goodness-of-fit metrics, and with no need for preliminary interpolation procedures [6, 7]. Note that the bispectral estimation relies on a quadratic Wiener-Volterra representation of heartbeat dynamics, whose number of parametric terms is reduced by the use of orthonormal Laguerre functions [6]. In our previous endeavours, the investigation on such instantaneous nonlinear measures relied on first- [6] and second-order [9] moments, neglecting the structured phasic activity superimposed to the tonic (slow) trend.

Here we investigate the use of wavelet decomposition to disentangle the tonic and phasic bispectral series, and test the framework in an exemplary protocol inducing sympathetic activation, known as the cold-pressor test (CPT) [10–12]. Area under the curve (AUC) and variance (VAR) are used to quantify differences in ANS activity between resting and CPT states, along with standard HRV metrics

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defined in the time, spectral, and bispectral domains.

2. Materials and Methods

2.1. Acquisition set-up

The experiment was performed in a quiet dark room. Twenty-two right handed students (15 men and 7 females) of ages between 20 and 35 from the University of Pisa gave their informed consent to be enrolled in the experiment. Participants did not have any history of neurological and cardiovascular disease, and alcoholic or smoking habits. They were asked to avoid coffee, alcohol, and strenuous exercise at least 2 hours before laboratory visit. Participants were forbidden to do Valsalva maneuver and breathing holding during the experiment. Before the presence of the stressor, participants were asked to sit in a comfortable chair, while watching a black screen for a period of 3 minutes to reach a hemodynamic stabilization. For a period of 3 minutes, the subjects were asked to put their non-dominant hand up to wrist into a tank filled of ice and water with the temperature of 0-4 degrees centigrade. This choice of CPT duration is consistent with the average pain threshold of healthy subjects [10]. After the stressor, subjects removed their hand from the water and relaxed for 4 minutes. BIOPAC MP35 device with a sampling rate of 500 Hz was used to acquire the ECG signal. This study was approved by the ethical committee of University of Pisa.

2.2. Point-Process Nonlinear model at a Glance

Extensive methodological details on the point-process nonlinear model and related instantaneous bispectral estimation are reported in [6,7].

Briefly, an inverse Gaussian probability density function (PDF) defined in the following equation describes the generative mechanisms of cardiovascular dynamics from the ANS:

$$f(t|H_t,\xi(t)) = \left[\frac{\xi_0(t)}{2\pi(t-u_j)^3}\right]^{\frac{1}{2}} \exp\left\{-\frac{1}{2}\frac{\xi_0(t)[t-u_j-\mu_{RR}(t,H_t,\xi(t))]^2}{\mu_{RR}(t,H_t,\xi(t))^2(t-u_j)}\right\} \quad (1)$$

In this equation t and j are the continuous time and the index of previous R-wave event, respectively. $H_t = (u_j, RR_j, RR_{j-1}, ..., RR_{j-M+1})$ indicates the history dependence where $RR_j = u_j - u_{j-1} > 0$, and $\{u_j\}_{j=1}^{J}$ is the time of successive R-wave event. The time varying parameters are in the vector $\xi(t)$ which are estimated through the maximum likelihood procedure with Newton-Raphson algorithm [6].

The first-order moment ($\mu_{RR}(t,H_t,\xi(t))$) of the PDF is modeled following a nonlinear autoregressive Wiener-Volterra model [6]:

$$\mu_{\mathrm{RR}}(t,H_t,\xi(t)) = g_0(t) + \sum_{i=0}^{p} g_1(i,t)\, l_i(t^-) + \sum_{n=2}^{\infty}\sum_{i_1=1}^{M_1}\cdot\cdot\sum_{i_n=1}^{M_n} g_n(i_1,..,i_n,t)\prod_{j=1}^{n} l_{i_j}(t^-) \quad (2)$$

where $l_i(t^-) = \sum_{n=1}^{\widetilde{N}(t)} \phi_i(n)\mathrm{RR}_{\widetilde{\mathrm{N}}(\mathrm{t})-\mathrm{n}}$ is the output of the Laguerre filters before time t, $\widetilde{N}(t)$ is the index of the first RR interval before time t, and $\phi_i(n)$ is the i^{th}-order discrete time orthonormal Laguerre functions. Note that the use of Laguerre expansions as embedded into the model allows to reduce the number of free parameters and account for long-term history [6].

In this study we consider nonlinearities up to the quadratic terms in order to obtain instantaneous measures defined in the time domain, including for the PDF first- and second-order moments, $\mu_{RR}(t,H_t,\xi(t))$ and $\sigma_{RR}(t,H_t,\xi(t))$, respectively, as well as instantaneous measures defined in the frequency domain, including the power spectra $Q(f,t,H_t,\xi(t))$, which provide time-varying estimates in the high frequency (HF, 0.15-0.5 Hz) and low frequency (LF, 0.05-0.15 Hz) bands [6]. Moreover, the quadratic term allows for the estimation of instantaneous bispectral estimates, which effectively quantify deviations form linearity or Gaussianity [6]. Particularly, the instantaneous bispectrum $|\mathrm{Bis}(\mathrm{f}_1,\mathrm{f}_2,\mathrm{t})|$ is defined as the Fourier transform of the third order cumulant [6]. The model goodness-of-fit is assessed through Kolmogorov-Smirnov (KS) test and related KS statistics.

2.3. Tonic and phasic activations of Instantaneous Bispectral Estimates

Nonlinear sympatho-vagal interplay can be assessed by integrating $|\mathrm{Bis}(\mathrm{f}_1,\mathrm{f}_2,\mathrm{t})|$ within appropriate frequency bands [6]. Particularly, instantaneous low-low bispectral frequency interactions, $\mathrm{LL(t)}$, instantaneous low-high bispectral frequency interactions, $\mathrm{LH(t)}$, as well as instantaneous high-high bispectral frequency interactions, $\mathrm{HH(t)}$, can be derived as follows:

$$LL(t) = \int_{f_1=0^+}^{0.15}\int_{f_2=0^+}^{0.15} Bis(f_1,f_2,t)df_1df_2 \quad (3)$$

$$LH(t) = \int_{f_1=0^+}^{0.15}\int_{f_2=0.15^+}^{0.4} Bis(f_1,f_2,t)df_1df_2 \quad (4)$$

$$HH(t) = \int_{f_1=0.15^+}^{0.4}\int_{f_2=0.15^+}^{0.4} Bis(f_1,f_2,t)df_1df_2 \quad (5)$$

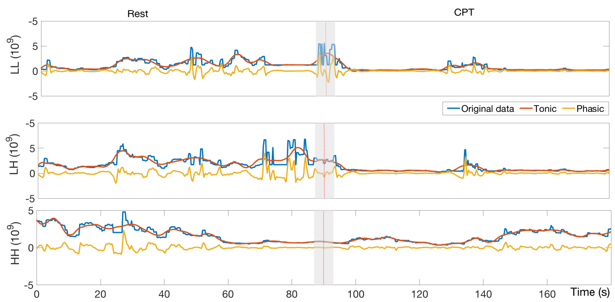

Figure 1. Instantaneous nonlinear HRV estimates along with the tonic and phasic activations for one exemplary subject. The blue, red and yellow lines indicate the original signal, low frequency and high frequency activations, respectively. The gray rectangle with 10s duration shows the transition between resting phase and CPT.

A wavelet decomposition method is applied to separate tonic and phasic components on these series. Daubechie 5 is chosen as the mother wavelet, and the signals are decomposed up to the 5th level. The first approximation and the fifth detail level coefficients are taken as the tonic and phasic components, respectively. Exemplary dynamics of time-varying bispectral estimates, along with their tonic and phasic components, from one representative subject are shown in Figure 1. On the phasic components of the bispectral series, namely LL_{ph}, LH_{ph}, and HH_{ph}, the variance and area under the curve are taken as quantifiers of the ANS activity on cardiac control.

3. Experimental Results

Experimental results related to feature dynamics are estimated over 90s time windows and reported as median and respective absolute error across subjects/recordings defined as $1.4826\mathrm{MAD(X)}/\sqrt{\mathrm{n}}$, where $\mathrm{MAD(X)} = \mathrm{Median}(|\mathrm{X}-\mathrm{Median(X)}|)$, n is the number of subjects in the dataset, X is the variable of interest which includes linear dynamics, namely μ_{RR} and σ^2_{RR}, LF, HF, LF/HF, and nonlinear dynamics, namely LL, HH, LH, as well as the result of phasic decomposition indicated as $ind(AOC)$ and $ind(var)$, where ind is the elements of the vector $[\mathrm{LL_{ph}}, \mathrm{LH_{ph}}, \mathrm{HH_{ph}}]$, and AUC and var are the area under the curve and variance of the series, respectively.

Statistics were performed at a group-wise level by comparing the last 90s of resting and first 90s CPT phases through the non-parametric Wilcoxon rank-based tests for paired data, with null hypothesis of the equality of medians between samples.

Results are shown in Table 1. Indices of linear dynamics including μ_{RR}, LF, and LF/HF ratio show a significant decrease during the CPT w.r.t. the resting phase, along with the proposed $\mathrm{LL_{ph}(AUC)}$ and $\mathrm{LL_{ph}(var)}$ phasic indices. Conversely, the trend of LL shows a significant increase during CPT w.r.t. the resting phase (Figure 3).

Table 1. Point-process heartbeat statistics between rest and CPT sessions in 22 subjects. Estimates are averaged along the last 90s of rest, and the first 90s of CPT.

	Rest(90s)	CP(90s)	P-val
μ_{RR} $[ms]$	854.93 ± 91.19	775.16 ± 114.37	**0.0001**
σ^2_{RR} $[ms^2]$	814.41 ± 668.05	651.89 ± 387.80	0.1396
LF $[ms^2]$	1600.32 ± 975.63	768.45 ± 143.54	**0.0022**
HF $[ms^2]$	663.69 ± 480.92	407.76 ± 68.95	0.178
LF/HF	2.28 ± 1.76	2.31 ± 0.44	**0.049**
LL(10^8)	6.42 ± 3.67	3.08 ± 5.89	**0.012**
HH(10^8)	7.12 ± 5.41	6.57 ± 1.87	0.76
LH (10^8)	5.39 ± 3.014	3.89 ± 1.54	0.322
$\mathrm{HH_{ph}}$ (AUC)(10^{10})	2.66 ± 2.03	1.96 ± 1.73	0.1677
$\mathrm{HH_{ph}}$ (var) (10^7)	12.42 ± 8.35	9.31 ± 8.15	0.1485
$\mathrm{LL_{ph}}$ (AUC)(10^{10})	6.04 ± 5.62	2.25 ± 1.64	**0.0262**
$\mathrm{LL_{ph}}$ (var) (10^8)	4.22 ± 4.03	1.17 ± 1.02	**0.045**
$\mathrm{LH_{ph}}$ (AUC)(10^{10})	2.16 ± 1.61	1.56 ± 1.04	0.1396
$\mathrm{LH_{ph}}$ (var) (10^7)	10.52 ± 7.93	7.58 ± 5.79	0.4077

Instantaneous tracking of linear and nonlinear indices during the resting and CPT sessions are shown in Figure 2.

4. Discussion and Conclusions

We investigated the role of phasic components of instantaneous bispectral estimates including LL, LH, and HH series in healthy subjects during prolonged sympatho-vagal changes through the so-called CPT. Instantaneous bispectra are effectively derived from nonlinear point-process models of heartbeat dynamics [6], embedding the probabilistic generative mechanisms of cardiac control through inverse-Gaussian functions and quadratic regressions employing Laguerre expansions of the Wiener-Volterra terms. In order to capture this bispectral phasic phenomena, wavelet decomposition technique was implemented in order to achieve improved results as compared to standard filtering.

Results showed significant changes between resting and CPT phases for the proposed $\mathrm{LL_{ph}(AUC)}$ and $\mathrm{LL_{ph}(var)}$ indices (see Table 1), demonstrating the effectiveness of phasic components of instantaneous bispectra as quantified through AUC and variance. The significant decrease of μ_{RR} is also in agreement with previous evidences relating CPT to a mainly sympathetic driving [13].

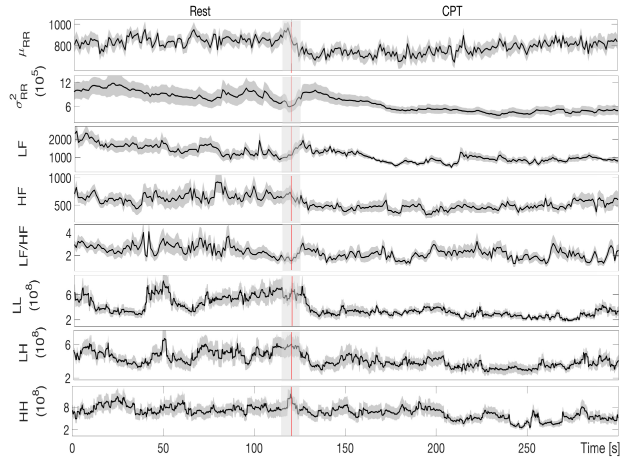

Figure 2. Instantaneous heartbeat statistics gathered from all subjects. From the top panel, the instantaneous μ_{RR}, σ^2_{RR}, LF, HF, LF/HF, as well as the nonlinear indices, LL, LH, and HH are shown. Continuous black lines indicate the median value across all subjects, whereas the superimposed grey areas indicate the MAD. The 10s grey rectangle at 120s indicates the transition between rest and CPT, which is marked with a vertical red line.

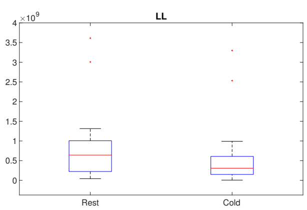

Figure 3. Boxplots of LL index during resting and CPT phases

This preliminary study complements our previous endeavours where we demonstrated the effectiveness of quantifiers from first- and second-order moments of instantaneous bispectra in health and disease [6, 9]. These quantifiers, in fact, are mainly dependent on the tonic component of the bispectral series, thus leaving unexplored its superimposed phasic activity. Future works aim to investigate the role of phasic components of instantaneous cardiac bispectra under emotional elicitations, as well as under patients with cardiovascular and/or mental disorders.

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Shadi Ghiasi. Email: shadi.ghiasi@centropiaggio.unipi.it

Computational Physiology and Biomedical Instruments group, University of Pisa, Pisa, Italy.

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