Assessment of Dynamic Autonomic Changes with Posture using Instantaneous Entropy Measures

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Abstract

Dynamic analysis provides a powerful methodological framework for characterizing physiological systems. In particular, complex heartbeat dynamics related to autonomic control mechanisms are known to change at each moment in time, and complexity measures have been proven to have prognostic value in both health and disease. Nevertheless, an instantaneous measure of complexity for cardiovascular time series (or any other series of stochastic physiological "events") is still missing. In this study we introduce a mathematical framework serving instantaneous complex estimates of heartbeat dynamics to characterize different activities, tasks, and/or pathological states. In particular we propose new definitions of inhomogeneous point-process approximate and sample entropy where the discrete events are modeled by probability density functions characterizing and predicting the time until the next event occurs as a function of past history. These definitions are built on our previous work employing Laguerre expansions of the Wiener-Volterra autoregressive terms to account for long-term memory. We demonstrate an exemplary study on heartbeat data gathered from healthy subjects undergoing postural changes such as stand-up, slow tilt, and fast tilt. Results show that instantaneous complexity is able to effectively track the complex autonomic changes as they are affected by different postural changes.

1. Introduction

Nonlinear cardiovascular dynamics arise from the complex interactions of Autonomic Nervous System (ANS) signaling on the sinus atrial node [1–5]. Accordingly, significant changes in nonlinear heartbeat dynamics have been characterized as occurring in different pathologies or different cognitive and physical states [6, 7]. These measures characterize the randomness and regularity of a time series originated by a dynamical system and, nowadays, can be computed through computational algorithms such as *approximate entropy* (*ApEn*) [8], and *sample entropy* (*SampEn*) [9] given finite experimental data [6, 10–12]. Despite the important achievements obtained studying the ANS-mediated cardiovascular control dynamics through *ApEn* and *SampEn* analysis of R-wave to R-wave (RR) interval series derived from the ECG [4, 13], these algorithms are not able to characterize the dynamic nature of the system along time. *ApEn* and *SampEn*, in fact, compute a single value given a predetermined time window, thus providing only an averaged measured of system dynamics that is instead evolving at each moment in time.

To overcome these limitations and address the nonstationary dynamics commonly associated with real biological processes, we here present two novel measures of entropy: the Inhomogeneous Point-process Approximate and Sample Entropy (*ipApEn* and *ipSampEn*, respectively). These measures are built on our previous probabilistic framework based on nonlinear inhomogeneous point processes, through which it is possible to effectively characterize the nonlinear probabilistic generative mechanism of heartbeat events, while obtaining instantaneous estimates of the underlying cardiovascular dynamics even considering short recordings under nonstationary conditions [6, 12, 14] and without using any interpolation method. Of note, this model accounts for long-term memory and high order nonlinearities using a reduced set of model parameters [6, 12] and it is used to perform instantaneous estimates of the phase-space vectors of the RR series. As detailed in the next section, the *ipApEn* and *ipSampEn* definitions are based on the distance measure between phase-space vectors as the Kolmogorov-Smirnov (KS) distance between two probability density functions (pdfs). As a result, the proposed *ipApEn* and *ipSampEn* indices, when estimated from RR interval series, are able to provide an instantaneous complexity assessment of the underlying ANS dynamics. Besides heartbeat data, we remark the general applicability of the the proposed *ipApEn* and *ipSampEn* indices in further heterogeneous stochastic series of events such as milling inserts, neural activity, geyser geologic events, and gait from short walks [6].

2. From Point-Process Nonlinear Models to Instantaneous Entropy Measures

The proposed measures of entropy are built on our previous Nonlinear AutoRegressive model with Laguerre expansion (NARL) of the Wiener-Volterra kernel, whose details are reported in [6, 12]. Briefly, assuming history dependence, the NARL point-process model addresses the pdf of the waiting time t until the next R-wave event occurs through an inverse Gaussian (IG) probability distribution [14]. Since this IG distribution is characterized at each moment in time, it is possible to obtain an instantaneous estimate of $\mu_{\mathrm{RR}}(t)$ at a very fine timescale (with an arbitrarily small bin size Δ), which requires no interpolation between the arrival times of two beats, therefore addressing the problem of dealing with unevenly sampled observations.

The IG instantaneous mean $\mu_{\mathrm{RR}}(t,\mathscr{H}_{\mathrm{t}},\xi(\mathrm{t}))$ is defined as a combination of present and past R-R intervals based on the NARL model [6, 12]:

$$\mu_{\mathrm{RR}}(t,\mathscr{H}_{\mathrm{t}},\xi(\mathrm{t})) = \mathrm{RR}_{\widetilde{\mathrm{N}}(\mathrm{t})} + \mathrm{g}_0(\mathrm{t}) + \sum_{i=0}^{p} g_1(i,t)\, l_i(t^-) + \sum_{i=0}^{q}\sum_{j=0}^{q} g_2(i,j,t)\, l_i(t^-)\, l_j(t^-) \quad (1)$$

where $\mathscr{H}_{\mathrm{t}}$ is the history given the past RR intervals, $\xi(t) = [\xi_0(t), g_0(t), g_1(0,t), ..., g_1(p,t), g_2(0,0,t), ..., g_2(i,j,t)]$ with $\xi_0(t)$ as the shape parameter of the IG distribution, and $l_i(t^-) = \sum_{n=1}^{\widetilde{N}(t)} \phi_i(n)(\mathrm{RR}_{\widetilde{\mathrm{N}}(\mathrm{t})-\mathrm{n}} - \mathrm{RR}_{\widetilde{\mathrm{N}}(\mathrm{t})-\mathrm{n}-1})$ is the output of the Laguerre filters just before time t, $\phi_i(n)$ is the i^{th} Laguerre function, $\widetilde{N}(t)$ is the left continuous sample path of the associated counting process, and g_0,$\{g_1(i)\}$, and $\{g_2(i,j)\}$ correspond to the time-varying zero-, first-, second-order NARL coefficients, respectively [6, 12, 15].

The i^{th} Laguerre function is defined as follows:

$$\phi_i(n) = \alpha^{\frac{n-i}{2}}(1-\alpha)^{\frac{1}{2}} \sum_{p=0}^{i} (-1)^p \binom{n}{p}\binom{i}{p} \alpha^{i-p}(1-\alpha)^p, \quad (2)$$

with $(n \geq 0)$, is the i^{th} Laguerre function with $0 < \alpha < 1$, which determines the rate of exponential asymptotic decline of these functions, and g_0,$\{g_1(i)\}$, and $\{g_2(i,j)\}$ correspond to the time-varying zero-, first-, second-order NARL coefficients, respectively [6, 12, 15].

Therefore, given the original RR interval series, the output of the Laguerre filters is firstly evaluated through the convolution between the derivative RR series and the Laguerre functions. Then, the parameters of eq. 1 are estimated to model the first order moment of the IG probability distribution. Moreover, eq. 1 accounts for long-term memory and reduced number of parameters needed for the linear and quadratic functions [6, 15].

We estimate the parameter vector $\xi(t)$ using the Newton-Raphson procedure to compute the local maximum-likelihood estimate [6] within a sliding time-window of $W = 90s$. Because there is significant overlap between adjacent local likelihood intervals, we start the Newton-Raphson procedure at t with the previous local maximum-likelihood estimate at time $t - \Delta$. Model goodness-of-fit is based on the KS tests and associated KS statistics [14], along with autocorrelation plots testing the independence of the model-transformed intervals [14].

Instantaneous estimates of $ipApEn$ and $ipSampEn$ measures are obtained by considering a novel definition of distance between phase-space vectors embedded within the standard ApEn and SampEn algorithms [8, 9].

In particular, let us define a distance measure $d[.]$ between two IG distributions of two heartbeat events according to the KS distance measures, i.e. maximum value of the absolute difference between two cumulative distribution functions. For each pair of phase space vectors, which are defined as $x(k) = [\mu_{\mathrm{RR}}(t_k), \mu_{\mathrm{RR}}(t_{k+1}), ..., \mu_{\mathrm{RR}}(t_{k+m-1})]$ in $\Re^m$ of the time series $\mu_{\mathrm{RR}}(t_1), \mu_{\mathrm{RR}}(t_2), ..., \mu_{\mathrm{RR}}(t_N)$ with embedding dimension $m = 2$, let us define $C_k^m(r(t),t)$ as the number of points $x(j)$ such that $d[x(k),x(j)] \leq r(t)/(N-m+1)\ \forall j$, with m and $r(t)$ as the embedding dimension and time delay of the phase-space, respectively. The time-varying quantity $r(t)$ is instantaneously expressed as $r(t) = 0.2\sigma_{\mu_{\mathrm{RR}(\mathrm{t})}}$. Then, the $ipApEn(m,r,t)$ and $ipSampEn(m,r,t)$ are instantaneously derived following the standard ApEn and SampEn algorithms [8, 9], through the calculation of the normalized term $C^m(r,t)$.

Our instantaneous complexity assessment allows for the possibility of analyzing the proposed measures also in terms of variability of their evolution along time, which we refer to as *complexity variability* . Formally, if we consider $\overline{ipApEn}(m,r,N)$ and $\overline{ipSampEn}(m,r,N)$ as the average measures of $ipApEn(m,r,N,t)$ and $ipSampEn(m,r,N,t)$ within the N^* data points time window $T = [t_1, t_2, \ldots, t_{N^*}]$, then two novel *complexity variability* measures, σ_{ipApEn} and $\sigma_{ipSampEn}$, refer to the standard deviation of the $ipApEn(m,r,N,t)$ and $ipSampEn(m,r,N,t)$ series evaluated within T.

3. Results

In this section, given a generic index variable X that can be associated to an index among $ApEn$, $SampEn$, $ipApEn$, $ipSampEn$, σ_{ipApEn}, and $\sigma_{ipSampEn}$, results are expressed in terms of inter-subject variability as $\mathrm{Median(X)} \pm \mathrm{MAD(X)}$, where $\mathrm{MAD(X)} = \mathrm{Median}(|\mathrm{X} - \mathrm{Median(X)}|)$.

We performed the instantaneous complexity analysis on RR interval time series recorded from 10 healthy subjects undergoing a stand-up/tilt-table protocol including six posture changes per recording session: 2 stand-up, 2 slow-tilt, and 2 fast-tilt. The posture change order was randomly chosen. The study, fully described in [14, 16], was conducted at the Massachusetts Institute of Technology (MIT) General Clinical Research Center (GCRC) and was approved by the MIT Institutional Review Board and the GCRC Scientific Advisory Committee.

Table 1. Results from the experimental dataset related to postural changes. Comparison between standard and novel indices.

	Stand-Up			Slow-Tilt			Fast-Tilt		
	Supine	Upright	p-value	Supine	Upright	p-value	Supine	Upright	p-value
ApEn	1.122±0.055	0.944±0.079	$< 10^{-3}$	1.167 ± 0.091	0.927 ± 0.125	$< 10^{-3}$	1.087±0.116	0.964±0.072	<0.004
ipApEn	0.283±0.069	0.256±0.062	<0.03	0.306 ± 0.042	0.254±0.035	$< 10^{-3}$	0.327±0.063	0.256±0.066	<0.005
σ_{ipApEn}	0.067±0.014	0.050±0.011	<0.05	0.071±0.014	0.072±0.011	n.s.	0.069±0.017	0.062±0.015	n.s.
SampEn	1.501±0.192	1.243±0.245	<0.025	1.495±0.173	0.900±0.247	$< 10^{-3}$	1.320±0.247	1.197±0.233	n.s.
ipSampEn	0.283±0.069	0.263±0.064	<0.05	0.306±0.048	0.251±0.054	$< 10^{-3}$	0.327±0.058	0.256±0.066	<0.01
$\sigma_{ipSampEn}$	0.084±0.017	0.065±0.017	n.s.	0.081±0.020	0.088±0.014	n.s.	0.077±0.020	0.082±0.012	n.s.

p-values from non-parametric Wilcoxon test for paired data with null hypothesis of equal medians
n.s. = not significant

The model orders $p = 4$, $q = 2$, and $\alpha = 0.2$ were chosen by preliminary KS plot goodness-of-fit analysis [6]. For each index, we evaluated the statistical differences between the two phases expressed as p-values from the Wilcoxon non-parametric test for paired data, under the null hypothesis of equal medians. Tracking results, aligned and averaged among all subjects for each of the three postural changes, are shown in Figure 1. Results averaged for each stage (2 min. supine before postural change vs. 2. min after postural change) are reported in Table 1. A significant statistical difference was found on median $ipApEn$ and $ipSampEn$ values between the supine stage and each of the three kind of postural changes (stand-up, slow and fast tilt), always showing a significant decrease in complexity once the subject is in the upright positions. These results are in agreement with previous findings [3], providing further evidence to the observed progressive decrease of complexity as a function of tilt table inclination, indicating that degree of complexity is highly correlated with sympathovagal response. Of note, standard $ApEn$ is also able to discern each of the three postural changes, whereas $SampEn$ is not able to characterize fast tilt protocols. However, it is important to notice that these traditional entropy measures are not able to follow changes in complexity.

Importantly, from our results it is possible to draw unique insights on specific dynamic signatures of complexity associated with each of the three postural changes (see Fig. 1). In particular, slow and fast tilts show a more prominent decrease in entropy, with $ipSampEn$ values oscillating around 0.1 once in the upright position. Note that slow tilt stimuli induce slower recovery increases in entropy starting one minute after complete postural change. Conversely, standing up brings to a sharp decrease in entropy comparable to the fast-tilt response, but also shows a faster recovery towards baseline entropy starting right after posture change. However, in this case the complexity variability measure σ_{ipApEn} has been found statistically different between the supine and upright positions related to the stand-up stages, demonstrating that a time-varying measure of complexity is critical for characterizing more subtle posture changes of complex heartbeat dynamics.

4. Conclusions and Discussion

We have proposed a novel definition of instantaneous approximate and sample entropy based on the inhomogeneous point-process nonlinear models using Laguerre expansion of the Wiener-Volterra autoregressive terms in the probability function mean [6, 10]). The $ipApEn$ and $ipSampEn$ definitions are able to reproduce previous findings achieved using traditional algorithms, while further ensuring continuous estimates in time without the use of any interpolation procedure, and providing effective tracking of instantaneous system dynamics. Goodness of fit measures such as KS and autocorrelation plots quantitatively allow to verify the model fit and to choose the proper model order, thus addressing another open issue of current parametric approaches. Just like other methods, our model needs a preliminary calibration phase (e.g., choice of model order, etc.) before it can be effectively used to estimate the instantaneous entropy measures.

We have shown that $ipApEn$ and $ipSampEn$ promisingly provide insightful time-varying and adaptive indices for real-time monitoring of sympathovagal dynamics, in agreement with the current literature [3]. The proposed entropy measures also allow for the study of *complexity variability*, i.e., the analysis of complex systems referring to the fluctuations in complexity instead of analysis of central tendency, which has been recently explored in disease assessment of patients with severe congestive heart failure [10]. A second application of the proposed measures of entropy is aimed at characterizing mild cognitive impairment in Parkinson's disease, and is presented in a companion paper within the same CinC proceedings. To conclude, the proposed methodology offers a promising mathematical tool for the dynamic analysis of a wide range of applications to potentially study any physical and natural stochastic discrete process (e.g. [6]).

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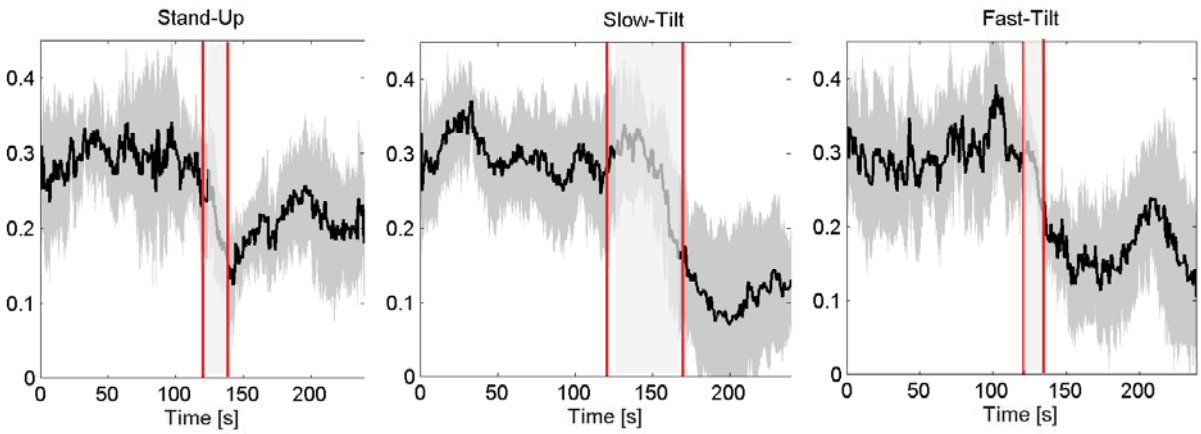

Figure 1. Averaged *ipSampEn* trends during resting and tilting phases. Considering data from all subjects, the plot shows the Median(X) $\pm$ MAD(X)).

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