Tracking Instantaneous Entropy in Heartbeat Dynamics through Inhomogeneous Point-process Nonlinear Models

Gaetano Valenza, *Member, IEEE*, Luca Citi, *Member, IEEE*, Enzo Pasquale Scilingo, *Member, IEEE*, and Riccardo Barbieri, *Senior Member, IEEE*

***Abstract*— Measures of entropy have been proved as powerful quantifiers of complex nonlinear systems, particularly when applied to stochastic series of heartbeat dynamics. Despite the remarkable achievements obtained through standard definitions of approximate and sample entropy, a time-varying definition of entropy characterizing the physiological dynamics at each moment in time is still missing. To this extent, we propose two novel measures of entropy based on the inhomogeneous point-process theory. The RR interval series is modeled through probability density functions (pdfs) which characterize and predict the time until the next event occurs as a function of the past history. Laguerre expansions of the Wiener-Volterra autoregressive terms account for the long-term nonlinear information. As the proposed measures of entropy are instantaneously defined through such probability functions, the proposed indices are able to provide instantaneous tracking of autonomic nervous system complexity. Of note, the distance between the time-varying phase-space vectors is calculated through the Kolmogorov-Smirnov distance of two pdfs.**

Experimental results, obtained from the analysis of RR interval series extracted from ten healthy subjects during stand-up tasks, suggest that the proposed entropy indices provide instantaneous tracking of the heartbeat complexity, also allowing for the definition of *complexity variability* indices.

I. Introduction

The characterization of short-term cardiovascular control by studying nonlinear and complex oscillations in Heart Rate Variability (HRV) has gained popularity and interest in the last two decades. In particular, it has been proposed that nonlinear cardiovascular fluctuations are generated by influence of the Autonomic Nervous System (ANS) [1]–[6], and that different nonlinear dynamics can be characterized in several pathologies [7], [8]. As a matter of fact, a sigmoidal static relationship was found between the vago-sympathetic balance and heart rate (HR) [9]. Accordingly, analysis methods derived from the theory of nonlinear system dynamics may open to novel interpretations of the mechanisms behind cardiovascular dynamic control.

In this study, we use the definition of entropy measures as defined by considering the phase-space behavior of the cardiac system generating the RR interval series [10]–[12]. The classic definition of entropy $H(X)$ of a mono-dimensional discrete random variable X is: $H(X) = -\sum_{x_i \in \phi} p(x_i) \log p(x_i)$, where ϕ is the set of values and $p(x_i)$ is the i-th probability function. In order to improve the entropy estimation using short-time experimental series with additive noise, entropy measures such as *approximate entropy* (ApEn) [10], sample entropy (SampEn) [11], and multiscale entropy [12] were proposed in the last decade. These algorithms compute a single value (or a set of values) given a predetermined time window, thus providing only single averaged measures of otherwise time-varying system dynamics. Accordingly, a major improvement in the assessment of complex dynamics pertaining the cardiovascular system (as well as other stochastic physiological systems) is related to the new definition of time-varying entropy measures, able to track the ANS nonlinear dynamics at each moment in time.

Inspired by our previous studies on point-process nonlinear models, in this study we propose two novel entropy measures: the Inhomogeneous Point-process Approximate and Sample Entropy (*ipApEn* and *ipSampEn*, respectively). More in detail, using the point-process theory and nonlinear autoregressive models with Laguerre expansion of Wiener-Volterra terms (NARL) [7], [13], [14], it is possible to effectively characterize the probability density function (pdf) of each heartbeat through knowledge of the past heartbeats events. Therefore, we use this inhomogeneous point-process model to perform time-varying estimates of the phase-space vectors of the RR series, while defining the distance between phase-space vectors through the Kolmogorov-Smirnov (KS) distance between two pdfs. Once the new time-varying distance between phase-space vectors is computed, the calculation of the proposed *ipApEn* and *ipSampEn* entropy measures follows the traditional ApEn and SampEn algorithms.

As a result, the *ipApEn* and *ipSampEn* indices, when estimated from RR interval series, are able to provide an instantaneous complexity assessment of the underlying ANS dynamics, even considering short recordings under nonstationary conditions commonly associated with specific physiological processes, and without using any interpolation method [7], [13]–[18]. Moreover, thanks to the Laguerre expansions, the *ipApEn* and *ipSampEn* estimates account for long-term memory and quadratic nonlinearities using a reduced set of model parameters [7], [17], [19].

II. Methods

When applied to heartbeat dynamics, the new definitions of *ipApEn* and *ipSampEn* are obtained through a parametrized nonlinear combination of the past RR samples using the discrete Wiener-Volterra series and Laguerre

G. Valenza, L. Citi, and R. Barbieri are the Neuroscience Statistics Research Laboratory, Harvard Medical School, Massachusetts General Hospital, Boston, MA 02114 USA, and also with the Massachusetts Institute of Technology, Cambridge, MA 02139 USA (e-mail: g.valenza@ieee.org; lciti@neurostat.mit.edu; barbieri@neurostat.mit.edu).

G. Valenza and E.P. Scilingo are with the Research Center E. Piaggio and the Department of Information Engineering, University of Pisa, Pisa, Italy (e-mail: e.scilingo@centropiaggio.unipi.it).

L. Citi is also with the School of Computer Science and Electronic Engineering, University of Essex, Colchester, UK.

978-1-4244-7929-0/14/$26.00 ©2014 IEEE

expansion of the autoregressive kernels. These parameters model the first moment order of a parametric pdf characterizing the next heartbeat event as dictated by point-process theory. Instantaneous estimates of the *ipApEn* and *ipSampEn* measures are obtained by considering a novel definition of distance between phase-space vectors within the standard ApEn and SampEn algorithms. Mathematical and algorithmic details follow below.

A. Point-Process Theory and Nonlinear Models of Heartbeat Dynamics

In assessing heartbeat dynamics, assuming history dependence, the point-process models address the probability distribution of the waiting time t until the next R-wave event as an inverse Gaussian (IG) probability distribution [15]:

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

where $\{u_j\}_{j=1}^{J}$ is the set of R-wave events detected from the ECG, and $\mathrm{RR}_j = u_j - u_{j-1} > 0$ denotes the j^{th} RR interval.

Here we define the IG instantaneous mean $\mu_{\mathrm{RR}}(t,\mathscr{H}_t,\xi(t))$ as a combination of present and past R-R intervals based on the NARL model [7], [19]:

$$\mu_{\mathrm{RR}}(t,\mathscr{H}_t,\xi(t)) = \mathrm{RR}_{\widetilde{N}(t)} + g_0(t) + \sum_{i=0}^{p} g_1(i,t)\, l_i(t^-) + \sum_{i=0}^{q}\sum_{j=0}^{q} g_2(i,j,t)\, l_i(t^-)\, l_j(t^-) \quad (2)$$

where $\mathscr{H}_t$ the history given the part 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 $l_i(t^-) = \sum_{n=1}^{\widetilde{N}(t)} \phi_i(n)(\mathrm{RR}_{\widetilde{N}(t)-n} - \mathrm{RR}_{\widetilde{N}(t)-n-1})$ 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 [7], [19], [20].

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

$$\phi_i(n) = \alpha^{\frac{n-i}{2}}(1-\alpha)^{\frac{1}{2}} \sum_{p=0}^{i} (-1)^p \binom{n}{p}\binom{i}{p}\alpha^{i-p}(1-\alpha)^p, \quad (3)$$

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 [7], [19], [20].

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. 2 are estimated to model the first order moment of the IG probability distribution. 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. Moreover, eq. 2 accounts for long-term memory and reduced number of parameters needed for the linear and quadratic functions [7], [21].

We effectively estimate the parameter vector $\xi(t)$ using the Newton-Raphson procedure to compute the local maximum-likelihood estimate [7] within a sliding time-window of $W = 90$. 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 [15], [22], along with autocorrelation plots testing the independence of the model-transformed intervals [15].

B. Definition of the Inhomogeneous Point-Process Entropy Measures

The *ipApEn* and *ipSampEn* mathematical definition has its foundation in correlation dimension analysis [23] and in the ApEn and SampEn computation [10], [11], respectively. Specifically, let us define a distance measure $d[.]$ between two *IG* distributions of two heartbeat 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

$$d[x(k),x(j)] \leq r(t), \forall j \quad (4)$$

and normalized by the quantity $(N-m+1)$. Parameters m and $r(t)$ are the embedding dimension and time delay of the phase-space, respectively. The time-varying quantity $r(t)$ is instantaneously expressed as $r(t) = 0.2\sigma_{\mu_{\mathrm{RR}(t)}}$, as suggested by the current literature [12].

The $ipApEn(m,r,t)$ and $ipSampEn(m,r,t)$ are instantaneously derived following the standard ApEn and SampEn algorithms [10], [11], through the calculation of the normalized term $C^m(r,t)$.

Then, from the $C_k^m(r,t)$ it is possible to define:

$$\Phi^m(r,t) = (N-m+1)^{-1} \sum_{i=1}^{N-m+1} \ln C_k^m(r,t) \quad (5)$$

and obtain:

$$ipApEn(m,r,N,t) = \Phi^m(r,t) - \Phi^{m+1}(r,t). \quad (6)$$

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.

III. Experimental Results

Given a generic entropy measure X, all results in this paper are expressed as $\text{Median}(X) \pm \text{MAD}(X)$, where $\text{MAD}(X) = \text{Median}(|X - \text{Median}(X)|)$.

In order to demonstrate that the proposed complexity assessment is able to track changes of ANS dynamics, we tested the *ipApEn* and *ipSampEn* entropy measures on RR interval time series recorded from 10 healthy subjects undergoing a protocol including several consecutive postural changes. The study, fully described in [15], [24], 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.

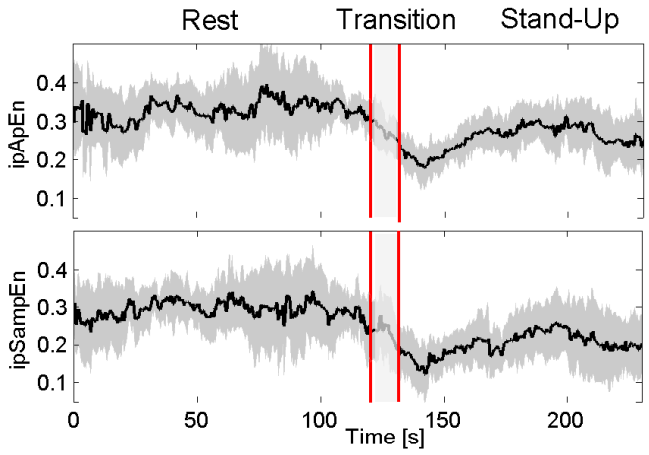

Fig. 1. Averaged *ipApEn* and *ipSampEn* trends for all rest/stand-up protocol segments among all subjects.

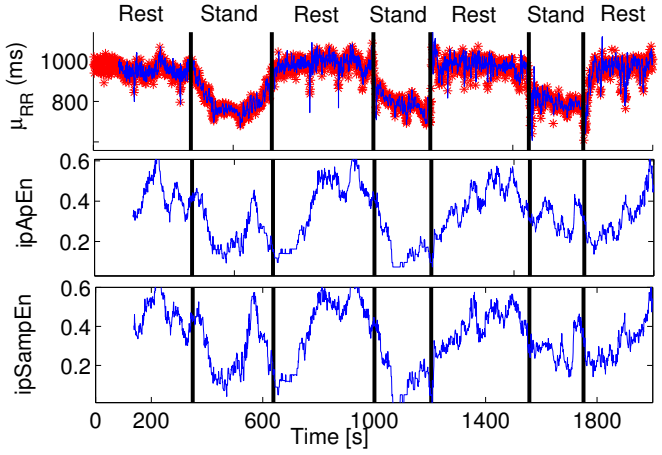

Fig. 2. Instantaneous heartbeat statistics computed from a representative subject of the postural changes protocol using a NARL point process model. In the first panel, the estimated $\mu_{RR}(t)$ is superimposed on the recorded R-R series. Below, the instantaneous ipApEn and ipSampEn complexity tracking are shown.

The model orders $p = 4$, $q = 2$, and $\alpha = 0.2$ were chosen by preliminary KS plots goodness-of-fit analysis [15]. 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. A representative tracking of the proposed entropy measures is shown in Fig. 2, whereas the averaged *ipApEn* and *ipSampEn* trends on all 10 subjects are shown in Fig. 1. These figures provide a clear portrayal of how the stand-up task, associated to sympatho-vagal changes, elicits expected changes in the dynamic signatures of complexity. On average, see Table I, a significant statistical difference was found between median *ipApEn* and *ipSampEn* values of resting and standing up phases ($p < 0.03$ and $p < 0.05$, respectively). These results are in agreement with the current literature [25], providing other evidences of decreased complexity during changes involving baroreflex. The two experimental sessions are also significantly distinguished by the complexity variability index σ_{ipApEn} with $p < 0.05$.

TABLE I Results from the experimental dataset related to the supine to stand-up changes on standard and novel entropy indices.

	Rest	Stand-Up	p-value
ApEn	1.1220 ± 0.0553	0.9443 ± 0.0789	$< 10^{-3}$
ipApEn	0.2832 ± 0.0694	0.2561 ± 0.0621	<0.03
σ_{ipApEn}	0.0672 ± 0.0145	0.0504 ± 0.0111	<0.05
SampEn	1.5008 ± 0.1921	1.2433 ± 0.2446	<0.025
ipSampEn	0.2832 ± 0.0686	0.2635 ± 0.0638	<0.05
$\sigma_{ipSampEn}$	0.0837 ± 0.0175	0.0650 ± 0.0172	n.s.

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

Of note, in this case also the traditional *ApEn* and *SampEn* measures are able to discern between rest and stand-up phases ($p < 10^{-3}$ and $p < 0.025$, respectively). However, it is important to notice that traditional measures are not able to dynamically follow changes in complexity.

IV. Conclusion and Discussion

In conclusion, we propose two novel measures of entropy, *ipApEn* and *ipSampEn*. These measures are derived by taking advantage of the standard ApEn and SampEn algorithms, and by using the powerful information and performances of inhomogeneous point processes to provide an instantaneous assessment. To our knowledge, the novel proposed measures can only be calculated within a point-process framework, because the mathematical description of *ipApEn* and *ipSampEn* is based on the KS distance between the two pdfs associated to each pair of heartbeats.

As complexity is a property that arises in nonlinear systems, we built up the mathematical bases of *ipApEn* and *ipSampEn* on our nonlinear fully autoregressive models with Laguerre expansion of the Wiener-Volterra terms. Like other parametric methods, a tuning of model parameters such as the Laguerre coefficient α, model order, time-window W size for the local-likelihood parameter estimation, and the radius $r(t)$ is required. To this extent, in the presented application we were able to obtain reproducible and reliable results by using standard values such as $\alpha = 0.2$, $r = 0.2std(X)$ (with X the RR series), a $W > 70$ seconds, as well as optimal model orders by minimizing the KS statistics. Overall, our *ipApEn* and *ipSampEn* analysis gives an accurate time-varying and adaptive characterization for real-time monitoring of HRV complexity, and also is able to summarize

results comparable to standard performances of ApEn and SampEn [25]. Remarkably, all the advantages associated to the use of point process NARL modeling [7], [13], [14], [16]–[18] (e.g. no interpolation required, model goodness of fit, effective parameter estimation as provided by the orthonormal Laguerre bases, dynamical spectra and bispectra estimates, etc.) are inherited by the *ipApEn* and *ipSampEn* definition. Moreover, the results on healthy subjects undergoing a simple stand-up task show that instantaneous entropy of heartbeat dynamics reflects a significant decrease in complex ANS dynamics when transitioning from supine to upright posture.

A more exhaustive description and further experimental results of the proposed methodology are reported in [26]. Our instantaneous complexity assessment opens to the possibility of analyzing the proposed measures also in terms of variability of the indices' evolution along time, a fascinating concept that we have recently explored in patients with severe congestive heart failure [27], and defined as *complexity variability*. Finally, 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 (see e.g. [7], [26]). Future work will be focused on characterization of the noise properties of the proposed indices, as well as performance evaluation of different datasets gathered also from pathological subjects.

ACKNOWLEDGMENT

We are grateful to R.G. Mark and T. Heldt (Harvard-MIT Division of Health Sciences and Technology) for kindly providing the tilt-table data. The research leading to these results has received partial funding from the Department of Anesthesia, Critical Care & Pain Medicine, Massachusetts General Hospital, and Harvard Medical School, Boston, MA, USA, and European Union Seventh Framework Programme FP7/2007-2013 under grant agreement n 601165 of the project "WEARHAP".

REFERENCES

[1] P. C. Ivanov, L. A. N. Amaral, A. L. Goldberger, S. Havlin, M. G. Rosenblum, Z. R. Struzik, and H. E. Stanley, "Multifractality in human heartbeat dynamics," *Nature*, vol. 399, no. 6735, pp. 461–465, 1999.

[2] A. L. Goldberger, D. R. Rigney, and B. J. West, "Science in pictures: Chaos and fractals in human physiology," *Scientific American*, vol. 262, pp. 42–49, 1990.

[3] A. Porta, G. Baselli, D. Liberati, N. Montano, C. Cogliati, T. Gnecchi-Ruscone, A. Malliani, and S. Cerutti, "Measuring regularity by means of a corrected conditional entropy in sympathetic outflow," *Biological cybernetics*, vol. 78, no. 1, pp. 71–78, 1998.

[4] H. Dabiré, D. Mestivier, J. Jarnet, M. E. Safar, and N. P. Chau, "Quantification of sympathetic and parasympathetic tones by nonlinear indexes in normotensive rats," *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 275, no. 4, pp. H1290–H1297, 1998.

[5] U. R. Acharya, K. P. Joseph, N. Kannathal, C. M. Lim, and J. S. Suri, "Heart rate variability: a review," *Medical and Biological Engineering and Computing*, vol. 44, no. 12, pp. 1031–1051, 2006.

[6] G. Valenza, P. Allegrini, A. Lanatà, and E. P. Scilingo, "Dominant lyapunov exponent and approximate entropy in heart rate variability during emotional visual elicitation," *Frontiers in neuroengineering*, vol. 5, 2012.

[7] G. Valenza, L. Citi, E. Scilingo, and R. Barbieri, "Point-process nonlinear models with laguerre and volterra expansions: Instantaneous assessment of heartbeat dynamics," *Signal Processing, IEEE Transactions On*, vol. 61, no. 11, pp. 2914–2926, 2013.

[8] A. Voss, R. Schroeder, S. Truebner, M. Goernig, H. R. Figulla, and A. Schirdewan, "Comparison of nonlinear methods symbolic dynamics, detrended fluctuation, and poincaré plot analysis in risk stratification in patients with dilated cardiomyopathy," *Chaos: An Interdisciplinary Journal of Nonlinear Science*, vol. 17, no. 1, p. 015120, 2007.

[9] K. Sunagawa, T. Kawada, and T. Nakahara, "Dynamic nonlinear vago-sympathetic interaction in regulating heart rate," *Heart and vessels*, vol. 13, no. 4, pp. 157–174, 1998.

[10] S. M. Pincus, "Approximate entropy as a measure of system complexity." *Proceedings of the National Academy of Sciences*, vol. 88, no. 6, pp. 2297–2301, 1991.

[11] J. S. Richman and J. R. Moorman, "Physiological time-series analysis using approximate entropy and sample entropy," *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 278, no. 6, pp. H2039–H2049, 2000.

[12] M. Costa, A. L. Goldberger, and C.-K. Peng, "Multiscale entropy analysis of complex physiologic time series," *Physical review letters*, vol. 89, no. 6, p. 068102, 2002.

[13] G. Valenza, L. Citi, C. Gentili, A. Lanata, E. Scilingo, and R. Barbieri, "Characterization of depressive states in bipolar patients using wearable textile technology and instantaneous heart rate variability assessment," *IEEE Journal of biomedical and health informatics*, 2014.

[14] G. Valenza, L. Citi, A. Lanatá, E. P. Scilingo, and R. Barbieri, "Revealing real-time emotional responses: a personalized assessment based on heartbeat dynamics," *Nature Scientific reports*, vol. 4, 2014.

[15] R. Barbieri, E. Matten, A. Alabi, and E. Brown, "A point-process model of human heartbeat intervals: new definitions of heart rate and heart rate variability," *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 288, no. 1, p. H424, 2005.

[16] G. Valenza, L. Citi, E. Scilingo, and R. Barbieri, "Instantaneous bispectral characterization of the autonomic nervous system through a point-process nonlinear model," in *World Congress on Medical Physics and Biomedical Engineering May 26-31, 2012, Beijing, China*. Springer, 2013, pp. 530–533.

[17] ——, "Using laguerre expansion within point-process models of heartbeat dynamics: a comparative study," in *Proceeding of IEEE-EMBC*. IEEE, 2012.

[18] G. Valenza, L. Citi, A. Lanata, E. Scilingo, and R. Barbieri, "A nonlinear heartbeat dynamics model approach for personalized emotion recognition," in *Proceeding of IEEE-EMBC*. IEEE, 2013.

[19] L. Citi, G. Valenza, and R. Barbieri, "Instantaneous estimation of high-order nonlinear heartbeat dynamics by lyapunov exponents," in *Engineering in Medicine and Biology Society (EMBC), 2012 Annual International Conference of the IEEE*. IEEE, 2012, pp. 13–16.

[20] V. Z. Marmarelis, *Nonlinear dynamic modeling of physiological systems*. Wiley-Interscience, 2004.

[21] V. Marmarelis, "Identification of nonlinear biological system using laguerre expansions of kernels," *Ann. Biomed. Eng.*, vol. 21, pp. 573–589, 1993.

[22] E. Brown, R. Barbieri, U. Eden, and L. Frank, "Likelihood methods for neural spike train data analysis," *Computational neuroscience: A comprehensive approach*, pp. 253–286, 2003.

[23] P. Grassberger and I. Procaccia, "Measuring the strangeness of strange attractors," *Physica D: Nonlinear Phenomena*, vol. 9, no. 1, pp. 189–208, 1983.

[24] T. Heldt, E. B. Shim, R. D. Kamm, and R. G. Mark, "Computational modeling of cardiovascular response to orthostatic stress," *Journal of applied physiology*, vol. 92, no. 3, pp. 1239–1254, 2002.

[25] A. Porta, T. Gnecchi-Ruscone, E. Tobaldini, S. Guzzetti, R. Furlan, and N. Montano, "Progressive decrease of heart period variability entropy-based complexity during graded head-up tilt," *Journal of applied physiology*, vol. 103, no. 4, pp. 1143–1149, 2007.

[26] G. Valenza, L. Citi, E. P. Scilingo, and R. Barbieri, "Inhomogeneous point-process entropy: An instantaneous measure of complexity in discrete systems," *Physical Review E*, vol. 89, no. 5, p. 052803, 2014.

[27] G. Valenza, L. Citi, and R. Barbieri, "Instantaneous nonlinear assessment of complex cardiovascular dynamics by laguerre-volterra point process models," in *Proceeding of IEEE-EMBC*. IEEE, 2013.