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Inhomogeneous point-process entropy: An instantaneous measure of complexity in discrete systems

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Measures of entropy have been widely used to characterize complexity, particularly in physiological dynamical systems modeled in discrete time. Current approaches associate these measures to finite single values within an observation window, thus not being able to characterize the system evolution at each moment in time. Here, we propose a new definition of approximate and sample entropy based on the inhomogeneous point-process theory. The discrete time series is modeled through probability density functions, 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 probability functions, the novel indices are able to provide instantaneous tracking of the system complexity. The new measures are tested on synthetic data, as well as on real data gathered from heartbeat dynamics of healthy subjects and patients with cardiac heart failure and gait recordings from short walks of young and elderly subjects. Results show that instantaneous complexity is able to effectively track the system dynamics and is not affected by statistical noise properties.

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I. INTRODUCTION

Measures of entropy are primarily defined to address the randomness and regularity of a dynamical system given the analysis of time series originated by the observed system [1–3]. As a primary definition, the entropy $H(X)$ of a monodimensional 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 ith probability function. Other important definitions include the Kolmogorov-Sinai entropy [4], the K_2 entropy [5], and the marginal redundancy algorithm given by Fraser [6]. To compute these theoretical entropy indices, a large number of data points are needed to achieve convergence. This is true even in the presence of low-dimensional space-state systems [7]. To this extent, Pincus proposed a family of formulas and statistics referred to as *approximate entropy* (A_E) [7], which is able to discern dynamical systems given finite, noisy data. A further modification has been recently proposed to overcome the dependency of A_E on the time series length, referred to as *sample entropy* (S_E) [8]. A measure of multiscale entropy has also been proposed [9] in order to take into account the inherent multiple-time-scale properties of dynamical systems.

All of these measures have been successfully applied to real and simulated data, with a special emphasis on physiological systems [10–12,12–18]. It has been widely accepted, in fact, that physiological systems are indeed "complex"; e.g., the quantification of complexity provides relevant information on psychophysiological and pathological states [19] being modulated by external stimuli, aging, and the presence of disease [14,16,17,19,20]. An exemplary application of these methodological approaches is given by the computational studies on cardiovascular control dynamics mediated by the autonomic nervous system (ANS). This system is very often investigated through analysis of the series obtained by computing the time intervals between two consecutive R waves detected from the Electrocardiogram, i.e., the R-R intervals, whose variability is defined as heart rate variability (HRV) [21,22].

Despite the considerable achievements obtained by studying complexity changes through A_E, S_E, and multiscale entropy, three major methodological and applicative issues have not been satisfactorily addressed.

(i) *Unevenly sampled observations:* The intrinsic discrete nature of experimental observations can lead to estimation errors, especially in studying heartbeat dynamics. R-R intervals, in fact, consist of unevenly spaced samples, thus often requiring the application of preliminary interpolation procedures that could affect complexity measures, whereas considering series as interevents does not account for their time occurrences and may miss intrinsic generative properties as reflected in complex dynamics.

(ii) *Estimation window:* Even in the case of reliable quantification of entropy and, more in general, of complexity, traditional algorithms provide a single value (or a set of values) within a predetermined time window. Therefore, given the experimental time series, these values represent averaged measures of the entire dynamics observed in that specific time window. However, a single estimation could not be sufficient to completely characterize system complexity in the face of nonstationary behavior. It is well known, in fact, that dynamical systems (particularly those associated to physiological processes) evolve and change at each moment in time.

(iii) *Noise properties:* It has been shown that measures of entropy are usually higher in the presence of uncorrelated (e.g., white noise) rather than correlated (e.g., $1/f$) underlying dynamics. This issue may lead to overestimation of complexity in systems dynamics associated with uncorrelated noise. Exemplary cases have been reported in the presence of certain pathologies such as cardiac arrhythmias and atrial fibrillation [9].

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To overcome these limitations, we propose a new definition of *approximate and sample instantaneous entropy* (A_I and S_I, respectively), as time-varying entropy measures of discrete system complexity. As suggested by the name, the A_I and S_I definitions are inspired by the already established respective algorithms. The originality of the new definitions relies in the fact that they are fully embedded in the probabilistic framework of the inhomogeneous point-process theory and introduce important differences to the mathematical formulation of the phase-space vectors and to the definition of the distance between phase-space vectors.

It has been demonstrated that, by means of a point process approach, it is possible to characterize the events' probabilistic generative mechanism and to obtain continuous estimates, even considering short recordings under nonstationary conditions. In previous studies [23,24], we demonstrated the application of these concepts to estimate instantaneous linear and nonlinear heartbeat dynamics. The unevenly spaced heartbeat intervals are represented as observations of a state-space point process model defined at each moment in time, thus allowing us to estimate instantaneous HR and HRV measures [23] without using any interpolation method. In our latest works [24,25], we focused on defining an ad-hoc framework accounting for long-term memory and high-order nonlinearities using a reduced set of model parameters. More specifically, we combined the inhomogeneous inverse Gaussian point-process framework previously defined in Ref. [23] with an effective quadratic and cubic autoregressive structure linked to input-output definitions based on Laguerre expansions of the Volterra kernels [19], namely the nonlinear autoregressive Laguerre (NARL) model.

In this study, besides testing the proposed A_I and S_I measures on synthetic data, the general applicability is further tested on heterogeneous stochastic series from three experimental datasets of heartbeat human dynamics, as well as two datasets from human gait dynamics from short walks [26].

II. MATERIALS AND METHODS

The A_I and S_I estimation is performed through a parametrized nonlinear combination of the time series using the discrete Wiener-Volterra series and Laguerre expansion of the autoregressive kernels. The nonlinear model is embedded into the point-process framework in order to allow for instantaneous estimates of the A_I and S_I measures. Mathematical and algorithmic details follow below.

A. Point-process framework and nonlinear models

As previously mentioned, the discrete time series is first modeled as a combination of present and past interevent intervals based on the Laguerre expansion of the autoregressive Wiener-Volterra terms (NARL) [24,25]. In particular, given $\widetilde{N}(t) = N(t^-) = \lim_{\tau\to t^-} N(\tau) = \max\{k : u_k < t\}$ as the left continuous sample path of the counting process associated to the event-to-event (e) series, it is possible to write the expected value of the next mean e interval as a function in continuous time:

$$\mu_e[t,\mathcal{H}_t,\xi(t)] = e_{\widetilde{N}(t)} + g_0(t) + \sum_{i=0}^{p} g_1(i,t)\, l_i(t^-) + \sum_{i=0}^{q}\sum_{j=0}^{q} g_2(i,j,t)\, l_i(t^-)\, l_j(t^-), \quad (1)$$

where $\mathcal{H}_t$ is the history given the part e intervals, $\xi(t) = [\xi_0(t), g_0(t), g_1(0,t), \ldots, g_1(p,t), g_2(0,0,t), \ldots, g_2(i,j,t)]$, with $\xi_0(t)$ as the shape parameter of the inverse Gaussian (IG) distribution, and

$$l_i(t^-) = \sum_{n=1}^{\widetilde{N}(t)} \phi_i(n)[e_{\widetilde{N}(t)-n} - e_{\widetilde{N}(t)-n-1}] \quad (2)$$

as the output of the Laguerre filters just before time t, where

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

with $(n \geqslant 0)$, is the ith 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 [19,24,25].

The nonlinear representation shown in Eq. (1) can be embedded into the point-process framework as it is used to model the first-order moment of the probability distribution of the waiting time t until the next event occurs. We have previously demonstrated that the IG probability distribution [23] provides an optimal description of the data if an integrate-and-fire model is assumed to initiate the events. Since the IG distribution is characterized at each moment in time, it is possible to obtain an instantaneous estimate of $\mu_e(t)$ 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 [*issue (i)*]. Moreover, Eq. (1) accounts for long-term memory and a reduced number of parameters needed for the linear and quadratic functions [24,27].

We propose to effectively estimate the parameter vector $\xi(t)$ using the Newton-Raphson procedure to compute the local maximum-likelihood estimate [24]. 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 Kolmogorov-Smirnov (KS) test and associated KS statistics [23,28], along with autocorrelation plots testing the independence of the model-transformed intervals [23].

B. Definition of the inhomogeneous point-process entropy measures

The A_I algorithm has its foundation in correlation dimension analysis [29] and in the A_E computation [7]. Given a distance measure $d[.]$, let us define $C_k^m[r(t),t]$ as the number of points $x(j)$, such that

$$d[x(k),x(j)] \leqslant r(t)/(N-m+1), \quad \forall j, \quad (4)$$

where $x(k)|_{k=1,2,\ldots,N-m+1}$ are vectors of the phase space defined as $x(k) = [\mu_e(t_k), \mu_e(t_{k+1}), \ldots, \mu_e(t_{k+m-1})]$ in $\mathbb{R}^m$ of the time series $\mu_e(t_1), \mu_e(t_2), \ldots, \mu_e(t_N)$. In this formulation, 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 $r(t) = 0.2\sigma_{\mu_{e(t)}}$, as suggested by the current literature [9]. According to point-process theory, it is possible to define the distance $d[x(k),x(j)]$ as the KS distance (i.e., the maximum value of the absolute difference between two cumulative distribution functions) between the IG_k and IG_j probability distributions of $\mu_e(t_{k+k_n})$ and $\mu_e(t_{j+k_n})$ for $k_n = 0,1,\ldots,m-1$. Then, from the $C_k^m(r,t)$, it is possible to define

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

and obtain

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

As the definition of the proposed entropy measure is fully embedded into the inhomogeneous point-process nonlinear framework (IGs are defined at each moment in time), it is possible to obtain instantaneous tracking of the system complexity as $A_I(m,r,N,t)$, thus overcoming the need of defining a single estimation window (*issue (ii)*).

To compute the $S_I(m,r,N,t)$ algorithm, $C_k^m[r(t),t]$ is defined as the number of j such that

$$d[x(k),x(j)] \leqslant r(t)/(N-m), \quad \forall j \neq k. \tag{7}$$

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

$$\Phi^m(r,t) = (N-m+1)^{-1} \sum_{i=1}^{N-m+1} C_k^m(r,t) \tag{8}$$

and obtain

$$S_I(m,r,N,t) = \ln \Phi^m(r,t) - \ln \Phi^{m+1}(r,t). \tag{9}$$

1. Complexity variability indices using the inhomogeneous point-process entropy measures

Our instantaneous assessment opens the possibility of analyzing the proposed measures also in terms of variability of their evolution along time, which we refer to as *complexity variability framework* . Formally, let us consider $\overline{A_I}(m,r,N)$ and $\overline{S_I}(m,r,N)$ as the average measures of $A_I(m,r,N,t)$ and $S_I(m,r,N,t)$ within the time window $T = [t_1,t_2,\ldots,t_{N^*}]$, which is sampled with N^* data points. The *complexity variability* measures, σ_{A_I} and σ_{S_I}, refer to the standard deviation of the $A_I(m,r,N,t)$ and $S_I(m,r,N,t)$ series evaluated within T as follows:

$$\sigma_{A_I} = \sqrt{\frac{\sum_{i=1}^{N^*}[A_I(m,r,N,t_i) - \overline{A_I}(m,r,N)]}{N^*-1}} \tag{10}$$

$$\sigma_{S_I} = \sqrt{\frac{\sum_{i=1}^{N^*}[S_I(m,r,N,t_i) - \overline{S_I}(m,r,N)]}{N^*-1}}. \tag{11}$$

III. EXPERIMENTAL RESULTS

In this section, results on synthetic data, as well as on two experimental heartbeat dynamics [21,22] and two gait recording datasets are reported. Given a generic index variable X that can be associated to a specific measure (i.e., A_E, S_E, A_I, S_I, σ_{A_I}, and σ_{S_I}), all results in this study are referred to intersubject analyses and expressed as median$(X) \pm$ median$(|X - \text{median}(X)|)$.

A. Synthetic data

1. Instantaneous tracking and dependence on noise

In order to validate our indices, we generated 150 realizations of synthetic e interval series by using known autoregressive coefficients of a Yule-Walker model (estimated from a series gathered from the postural changes experimental protocol described below) and by generating the new series by feeding the model with either white noise (ε_1) or $1/f$ noise (ε_2). It is important to highlight that it is not straightforward to simply add noise to an event series, as each value also represents an occurrence in time, and samples added from two separate series would not coincide in time. In fact, validation through synthetic data was performed considering either white noise or $1/f$ noise as process noise, i.e., the noise

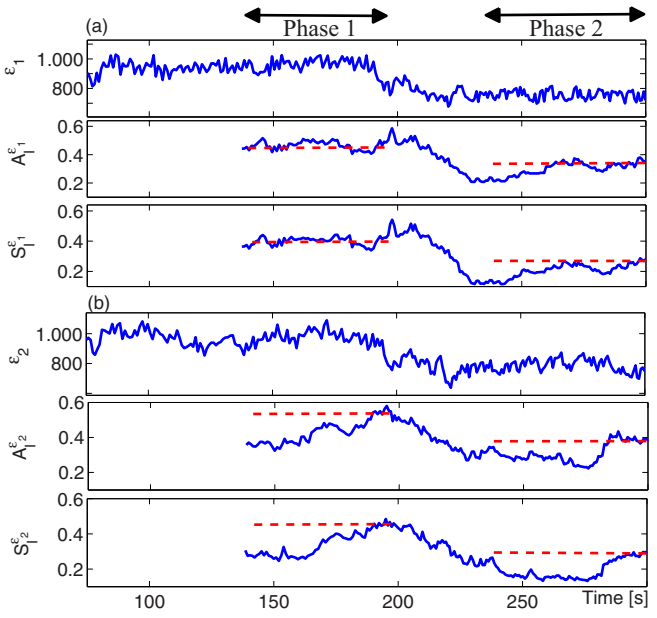

FIG. 1. (Color online) Time series of synthetic e series, estimated from known regressive coefficients, and related A_I and S_I tracking in the time domain. The coefficients are chosen so that the dynamics change to a state with lower entropy at $t = 220$ s. In panel (a), a representative realization of white process noise (ε_1) and its instantaneous $A_I^{\varepsilon_1}$ and $A_I^{\varepsilon_1}$ tracking are shown. In panel (b), a representative realization of $1/f$ process noise series (ε_2) and its instantaneous $A_I^{\varepsilon_2}$ and $S_I^{\varepsilon_1}$ tracking are shown. Dotted (red) lines indicate surrogate reference values computed considering two stationary time windows having length equal to the entire duration of phase 1 and phase 2, respectively. p values from nonparametric Mann-Whitney tests. n.s. = not significant. ε_1: white noise; ε_2: $1/f$ noise.

TABLE I. Results on synthetic data. Phase 1 for t < 220 s; Phase 2 for time >220 s. Comparison between standard approximate entropy (A_E) and our novel inhomogeneous point process approximate entropy (A_I), and sample entropy (S_E) and our novel inhomogeneous point process sample entropy (S_I).

	Phase 1	p value	Phase 2	p value
A_E	ε_1 0.885 ± 0.029 / ε_2 0.914 ± 0.031	$p < 10^{-8}$	0.948 ± 0.033 / 0.962 ± 0.032	$p < 0.03$
A_I	ε_1 0.416 ± 0.033 / ε_2 0.413 ± 0.037	n.s.	0.375 ± 0.029 / 0.368 ± 0.031	n.s.
S_E	ε_1 2.150 ± 0.143 / ε_2 2.021 ± 0.156	$p < 10^{-8}$	1.872 ± 0.110 / 1.686 ± 0.135	$p < 0.03$
S_I	ε_1 0.299 ± 0.036 / ε_2 0.310 ± 0.037	n.s.	0.279 ± 0.034 / 0.283 ± 0.037	n.s.

that enters the autoregressive state evolution equation, which is different from a simple additive observation noise. Two series and the respective A_I tracking are shown in Fig. 1. Our instantaneous entropy estimation is able to track the simulated decrease in entropy as modulated by either white or $1/f$ noise. In order to perform a fair comparison of our A_I and S_I against the standard A_E and S_E, we averaged them along the two separate segments (phase 1 and phase 2) within each realization. Results from a nonparametric Mann-Whitney test with null hypothesis of equal medians showed significant differences in standard entropy values between the two series with different noise ($A_E^{\varepsilon_1}$ versus $A_E^{\varepsilon_2}$), both in the first phase ($p < 10^{-8}$) and second phase ($p < 0.03$). Detailed values are reported in Table I. On the other hand, we found no statistically significant differences in median A_I values between series with correlated $1/f$ and uncorrelated white noise ($p > 0.05$ for both rest and tilt phases). Therefore, A_I is able to characterize specific dynamic entropy levels in systems with different underlying noise dynamics (as reported in the presence of certain pathologies [9]). Importantly, the proposed A_I and S_I indices do distinguish between events generated by integrate-and-fire models driven by white and $1/f$ noise ($p < 10^{-8}$ given by nonparametric Mann-Whitney test for 150 realization). Of note, these events have different properties than pure noise series in uniform time and, as such, they are accompanied by expectedly different values of entropy. These results suggest that our method is able to overcome the problem of value dependency on noise properties (*issue (iii)*).

2. The effect of window size

As described in Sec. II, previous samples have to be considered to perform the maximum log-likelihood estimation through the Newton-Raphson procedure in order to obtain instantaneous A_I and S_I estimates. In theory, if the model is correct, changing window length W, i.e., changing the number of past events retained for the prediction of the next event, does not affect the A_I and S_I measures because of the following reasons.

The use of the Laguerre expansion on the autoregressive Wiener-Volterra terms [see Eq. (1)] allows for the prediction of the next event as a function of all the past events, i.e., long-term memory [24]:

$$\mu_e[t,\mathcal{H}_t,\xi(t)] = e_{\tilde{N}(t)} + \gamma_0 + \sum_{i=1}^{\infty} \gamma_1(i,t)\,[e_{\tilde{N}(t)-i} - e_{\tilde{N}(t)-i-1}] + \sum_{i=1}^{\infty}\sum_{j=1}^{\infty} \gamma_2(i,j,t)\,[e_{\tilde{N}(t)-i} - e_{\tilde{N}(t)-i-1}] \times [e_{\tilde{N}(t)-j} - e_{\tilde{N}(t)-j-1}]. \quad (12)$$

As there is an infinite regression of the past events, the A_I and S_I estimates are theoretically not affected by the number of past events included within the length of the time window W. Of course, the window size is still important when estimating the kernels, and a window of sufficient length has to be considered to provide accurate results as measured by goodness-of-fit. Moreover, within this time window, we considered an exponential weighting function for the local likelihood whose constant value modulates the degree of influence of previous observations on the local likelihood and determines the trade-off between the accuracy of the estimation of the regression parameters (small constant) and the responsiveness to nonstationarities (large constant).

Figure 2 shows the effects of window size on the A_I and S_I estimates when using several lengths of W. It is possible to notice that the estimates corresponding to $W = 50$ and $W = 70$ are different, whereas estimates from larger windows tend to converge to similar signatures. This is due to the fact that $W = 70$ s is not sufficient to perform a reliable parameter estimation through the local log-likelihood procedure, as confirmed by the evaluation of the model goodness-of-fit

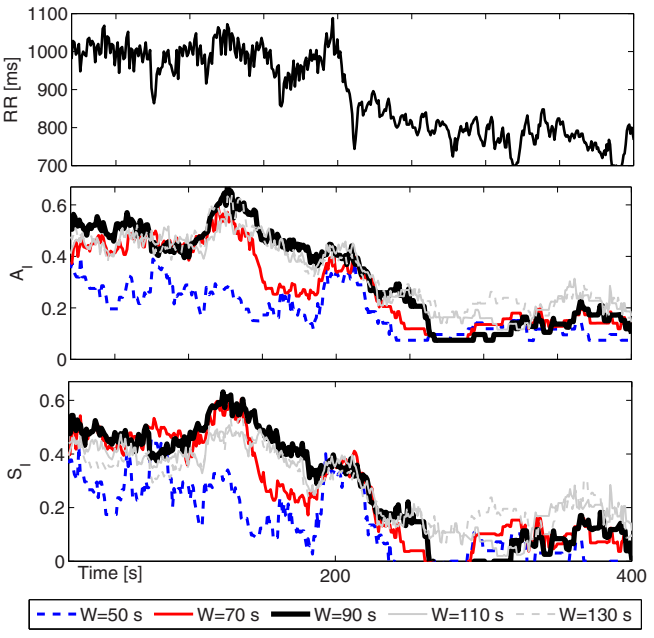

FIG. 2. (Color online) Effect of the window size on A_I and S_I. Instantaneous heartbeat statistics computed from a representative subject of the tilt-table protocol using a NARL point-process model with different size of W. From top to bottom, the recorded R-R series, the instantaneous A_I and S_I complexity tracking, and the legend related to the instantaneous measures obtained for each time window are shown.

through KS plots, according to which a window of at least $W > 90$ s is required [24].

B. Experimental data

1. Postural changes

In order to demonstrate the applicability to real cases, we performed the instantaneous analysis in a *R-R*-interval time series recorded from ten healthy subjects undergoing a tilt-table protocol, where each subject, initially lying horizontally in a supine position, is then passively tilted to the vertical position. The study, fully described in Refs. [23,30], 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.

The first-order moment $\mu_{RR}(t)$ and A_I and S_I instantaneous dynamics are shown for one representative subject in Fig. 3, whereas the averaged A_I and S_I for all ten subjects are shown in Fig. 4, providing a clear portrayal of how the postural stimulus elicits the expected changes in the dynamic signatures of complexity. On average (see Table II), a significant statistical difference was found between median A_I and S_I values of resting and tilt phases ($p < 10^{-6}$ and $p < 0.01$, respectively, given by nonparametric Wilcoxon test for paired data with null hypothesis of equal medians). In this case, also the traditional A_E and S_E measures are able to discern between rest and tilted phases ($p < 10^{-3}$ given by nonparametric Wilcoxon test for paired data with null hypothesis of equal medians). However, it is important to note that traditional measures are not able to follow changes in complexity. Remarkably, the averaged instantaneous measures provided by A_I resulted in a more discriminant statistical significance (A_I: $p < 10^{-6}$; A_E: $p < 10^{-3}$). These results are in agreement with the current literature [31,32], providing more evidences for the observed progressive decrease of complexity as a function of tilt table inclination, thus indicating that the degree of complexity is highly correlated with sympathovagal response.

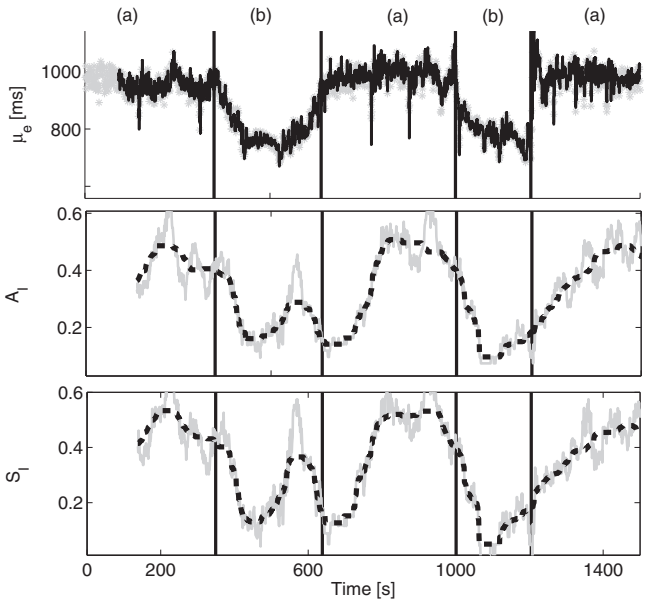

FIG. 3. Instantaneous heartbeat statistics computed from a representative subject of the tilt-table protocol using a NARL point-process model. In the first panel, the estimated $\mu_e(t)$ (top, continuous line) is superimposed on the recorded *R-R* series (gray asterisks). Below, the instantaneous A_I and S_I complexity tracking are shown in gray continuous lines along with their low-pass (two-order Butterworth FIR Filter with cutoff 0.05 Hz) derived signal (dotted line). Resting phases (a) alternate with the gravitational changes (b).

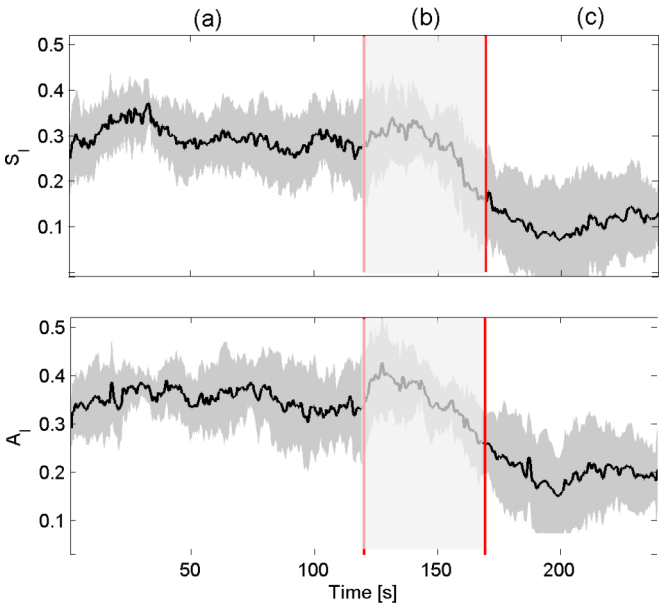

FIG. 4. (Color online) Averaged S_I and A_I trends during resting (a) and tilting (c) phases, through slow-transitioning tilt (b). Considering data from all subjects, the plot shows the median$(X) \pm$ median$[|X - \text{median}(X)|]$.

2. Cardiac heart failure

We further validated our novel indices by analyzing the averaged A_I and its variability σ_{A_I} to study the differences between healthy subjects and patients with severe congestive heart failure [33]. The dataset consists of *R-R* time series recorded from 14 CHF patients (from BIDMC-CHF Database) and 16 healthy subjects (from MIT-BIH Normal Sinus Rhythm Database). Each time series was artifact-free and lasted about 50 minutes. The first-order moment $\mu RR(t)$ and A_I and S_I

TABLE II. Results from the experimental dataset related to postural changes. Comparison between standard and novel indices. Of note, the new instantaneous formulation allows for definition of the variance of A_I (σ_{A_I}) and S_I (σ_{S_I}) as indices of *complexity variability*. p values from nonparametric Wilcoxon test for paired data with null hypothesis of equal medians. n.s. = not significant.

	Rest	Tilt	p value
A_E	1.1671 ± 0.0912	0.9274 ± 0.1255,	$p < 10^{-3}$
A_I	0.3062 ± 0.0422	0.2545 ± 0.0348	$p < 10^{-6}$
σ_{A_I}	0.0709 ± 0.0145	0.0722 ± 0.0115	n.s.
S_E	1.4949 ± 0.1731	0.8998 ± 0.2471	$p < 10^{-3}$
S_I	0.3062 ± 0.0483	0.2514 ± 0.0543	$p < 10^{-3}$
σ_{S_I}	0.081 ± 0.0196	0.0883 ± 0.0141	n.s.

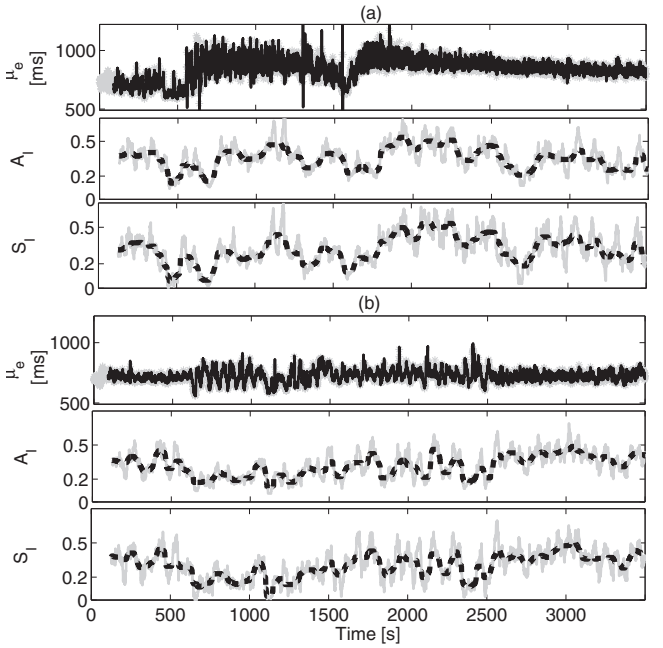

FIG. 5. Instantaneous statistics computed from a representative healthy subject (a) and a CHF patient (b), computed using a NARL model. From the top, given the heartbeat interval *R-R* (gray asterisks), the estimated $\mu_e(t)$ (continuous line) superimposed on the recorded *R-R* series. Below, the instantaneous A_I and S_I complexity tracking are shown in gray continuous lines along with their low-pass derived signal (dotted line).

instantaneous dynamics are shown for one representative healthy subject and one CHF patient in Fig. 5. Table III shows lower values of both A_I and S_I in averaging the respective indices computed from time series gathered from CHF patients rather than healthy subjects (both $p < 10^{-3}$ given by nonparametric Mann-Whitney test with null hypothesis of equal medians). This result is in agreement with the significant difference found in multiscale entropy higher scales [9].

In this case, the traditional A_E and S_E measures are not able to discern between healthy and pathological subjects ($p > 0.05$ given by nonparametric Mann-Whitney test with null hypothesis of equal medians), in agreement with the current literature [9] pointing out no complexity changes between healthy and CHF heartbeat dynamics (at least referring to traditional A_E

TABLE III. Results from the experimental healthy subjects and cardiac heart failure datasets. Comparison between standard A_E and novel A_I and standard S_E and novel S_I. p values from nonparametric Mann-Whitney tests with null hypothesis of equal medians. n.s. = not significant.

	Healthy	CHF	p value
A_E	1.2177 ± 0.1066	1.2130 ± 0.1032	n.s.
A_I	0.3476 ± 0.032	0.1674 ± 0.0483	$p < 10^{-4}$
σ_{A_I}	0.0655 ± 0.007	0.0462 ± 0.0148.	$p < 0.02$
S_E	1.4092 ± 0.1522	1.5670 ± 0.2690	n.s.
S_I	0.2876 ± 0.0353	0.1092 ± 0.0675	$p < 5 * 10^{-4}$
σ_{S_I}	0.08 ± 0.0064	0.0679 ± 0.0082.	$p < 0.05$

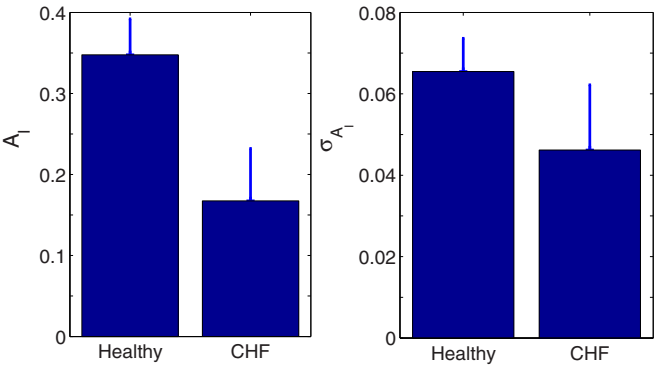

FIG. 6. (Color online) Box plots of the averaged variable A_I and σ_{A_I} showing differences between healthy subjects and CHF patients. Each plot shows the median(A_I) ± median[$|A_I$ − median(A_I)|].

which corresponds to multiscale entropy of scale 1). Also, the proposed complexity variability measures, σ_{A_I} and σ_{S_I}, are able to provide discrimination power between the two mentioned populations ($p < 0.02$ and $p < 0.05$, respectively). Summary box plots of A_I and σ_{A_I} are shown in Fig. 6.

3. *Gait dynamics from short walks*

In order to further demonstrate the potential and wide applicability of the proposed instantaneous entropy measures in a more general context, we considered stochastic series associated to gait from short walks [26]. Gait data from five young and five elderly people were gathered from the online available Physionet database and analyzed in order to perform

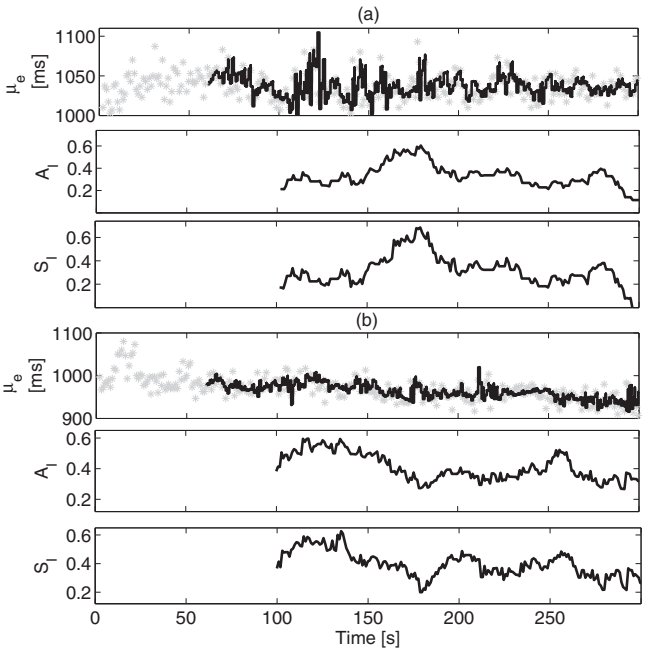

FIG. 7. Instantaneous statistics computed from a representative healthy (a) and elderly (b) subject of the gait dynamics dataset, computed using a NARL model. From the top, given the interevent interval e (gray asterisks), the estimated $\mu_e(t)$ (continuous line), superimposed on the recorded e series is shown. Below, the instantaneous A_I and S_I complexity tracking are shown.

TABLE IV. Results from the experimental young-elderly subjects datasets of gait dynamics from short walks. Comparison between standard A_E and S_E and novel A_I and S_I. p values from nonparametric Mann-Whitney tests with null hypothesis of equal medians. n.s. = not significant.

	Young	Elderly	p value
A_E	1.3722 ± 0.0165	1.4769 ± 0.0078	n.s.
A_I	0.2930 ± 0.0163	0.3745 ± 0.0472	$p < 0.05$
σ_{A_I}	0.0673 ± 0.0026	0.0632 ± 0.0025.	n.s.
S_E	1.3963 ± 0.0912	1.5921 ± 0.0271	n.s.
S_I	0.2743 ± 0.0121	0.3409 ± 0.0358	$p < 0.03$
σ_{S_I}	0.0905 ± 0.0035	0.0752 ± 0.0076.	$p < 0.02$

statistical comparison between groups. All of these series of events are suitable to be modeled using the point-process methodology whose performance can be quantified in terms of KS goodness-of-fit.

Instantaneous tracking of the gait dynamics data and estimated S_I measures on representative young and elderly subjects are shown in Fig. 7.

Experimental results on the traditional entropy measures A_E and S_E as well as the proposed instantaneous entropy measures A_I and S_I are reported in Table IV. Remarkably, the Mann-Whitney nonparametric test gave significant p values only for measures coming from the proposed methodology and nonsignificant p values otherwise ($p > 0.05$). In particular, both A_I and S_I were able to discern gait dynamics from young and elderly subjects ($p < 0.05$) as well as the variability evaluated of σ_{S_I} ($p < 0.02$). Our results suggest that gait dynamics of elderly people are characterized by a higher level of instantaneous complexity along with a reduced instantaneous complexity variability.

IV. CONCLUSION AND DISCUSSION

We have proposed a novel definition of instantaneous approximate and sample entropy based on the inhomogeneous point-process theory. The new measures are tested on synthetic data as well as on real data gathered from heartbeat dynamics of healthy subjects and patients with cardiac heart failure together with gait recordings from short walks of young and elderly subjects. Results demonstrate that instantaneous complexity is able to effectively track the system dynamics and is not affected by statistical noise properties. The proposed methodology and findings are of novel interest for the following reasons. The mathematical definition of inhomogeneous entropy completely relies on stochastic point processes, thus ensuring continuous estimates in time without the use of any interpolation procedure. In this sense, the proposed indices could provide a more meaningful quantification than traditional entropy measures. Of note, although the nonlinear model using the Laguerre expansion of the Wiener-Volterra autoregressive terms to describe the IG mean is based on our previous work in Ref. [34], the A_I and S_I definitions are not derivable from any previous achievement. Goodness-of-fit measures such as KS distance and autocorrelation plots quantitatively allow us to verify the model fit and to choose the proper model order, thus addressing another open issue of current parametric approaches.

To this extent, it is worth mentioning a pragmatic case in which traditional complexity measures do not allow a reliable assessment. Let us consider a generic experimental protocol comprising a 5-minute resting state and, then, 5 s of stimuli. Standard measures such as A_E and S_E are not able to provide reliable quantifiers distinguishing between the two conditions, as they cannot be estimated on the latter experimental session (i.e., the 5 s of stimuli). However, the proposed A_I and S_I indices can be reliably used to perform instantaneous estimates starting from the length W (of 90 s for instance) on, thus proving an instantaneous complexity assessment also during the last 5 s.

The limitations of our methodology can be related to the need of a preliminary calibration phase before it can be effectively used to estimate the instantaneous entropy measures. Moreover, concerning noise dependency, it is important to remark that the proposed A_I and S_I entropy measures do not follow the traditional and intuitive interpretation of entropy (which implies that such a measure has to vary with the underlying system noise). Nevertheless, referring to a generalization of the definition of entropy, i.e., measures addressing the randomness and regularity of a dynamical system, it is proper to say that our indices simply have different properties than traditional entropy measures. Following this philosophy, it seems reasonable to present two novel entropy measures that also show different and specific properties when applied to any system described by uneven observations (not only to study physiological systems). We demonstrated, in fact, that the proposed A_I and S_I entropy measures are able to instantaneously perform the complexity assessment of any stochastic time series of discrete events. In addition, the behavior of the A_I and S_I indices on the study of nonstationary, dynamical systems having different kinds of noise as an input reflect an important property that could be useful for characterizing physical systems. In summary, if the traditional noise-dependent complexity indices are preferred in some instances where additive noise properties are relevant, there are many other cases where the use of a complexity measure that follows only the dynamics of the autoregressive system regardless of the observation time and the input modulating noise are recommended.

We have shown that A_I and S_I promisingly provide helpful time-varying and adaptive indices for real-time monitoring of sympathovagal dynamics, which have also been proven in agreement with the current literature [31,32]. In fact, our studies on healthy subjects undergoing postural changes confirm previous results [31,32] and demonstrate that the instantaneous complexity measures appropriately reflect changes of ANS control on cardiovascular dynamics, thus improving the sympathovagal assessment in a nonstationary environment. We also found that pathological heartbeat dynamics are associated with decreased instantaneous complexity, confirming the common experimental experiences of reduced regularity, predictability, and sensitivity to initial conditions in pathological states.

We have presented further results from two additional datasets of gait recordings from short walks [26]. We have achieved significantly better performance in discerning gait dynamics gathered from young and elderly subjects by using the proposed instantaneous complexity measures. Such

positive results confirm the theoretical construction of the proposed entropy measures and enlarge the potential wide spectrum of applicability.

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 [34]. We report that A_I dynamical values are not seriously affected by the kind of noise underlying the complex system, thus ensuring truly instantaneous tracking of the dynamic system complexity. These observations suggest that absolute values of our entropy measures, significantly different from values of standard estimates, might be closer to a more objective measure of entropy. Reasonably, the independence from noise is related to the measure of distance between pairs of phase-space points A_I and S_I. In fact, they take advantage of both the Laguerre expansion and KS distance, rather than the Takens distance [7], allowing for consideration of long-term dynamical information (as achievable with multiscale entropy). Thus, the instantaneous entropy framework could open promising perspectives in understanding the actual underlying dynamical complexity changes despite intrinsic variations of physiological noise.

To conclude, the proposed methodology offers a promising mathematical tool for the dynamic analysis of a wide range of applications and to potentially study any physical and natural stochastic discrete process (e.g., Ref. [24]).

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