Entropy in the natural time domain

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A surrogate data analysis is presented, which is based on the fluctuations of the "entropy" S defined in the natural time domain [Phys. Rev. E **68**, 031106 (2003)]. This entropy is not a static one such as, for example, the Shannon entropy. The analysis is applied to three types of time series, i.e., seismic electric signals, "artificial" noises, and electrocardiograms, and it "recognizes" the non-Markovianity in all these signals. Furthermore, it differentiates the electrocardiograms of healthy humans from those of the sudden cardiac death ones. If δS and δS_{shuf} denote the standard deviation when calculating the entropy by means of a time window sweeping through the original data and the "shuffled" (randomized) data, respectively, it seems that the ratio $\delta S_{\mathrm{shuf}}/\delta S$ plays a key role. The physical meaning of δS_{shuf} is investigated.

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I. INTRODUCTION

In an electric signal consisting of N pulses, the natural time was introduced [1,2] by ascribing to the kth pulse the value $\chi_k = k/N$. The analysis is then made in terms of the couple (χ_k, Q_k), where Q_k stands for the duration of the kth pulse. The entropy S, defined [1,3] as $S \equiv \langle \chi \ln \chi \rangle - \langle \chi \rangle \ln \langle \chi \rangle$, where $\langle \chi \rangle = \Sigma_{k=1}^{N} p_k \chi_k$, $p_k = Q_k / \Sigma_{n=1}^{N} Q_n$ and $\langle \chi \ln \chi \rangle = \Sigma_{k=1}^{N} p_k \chi_k \ln \chi_k$, was found [3] to distinguish seismic electric signals (SES) activities from artificial noises (AN), where the latter terminology stands for electrical disturbances which are recorded at a measuring site due to nearby man-made electric sources. More precisely, SES activities and AN have S values smaller and larger than that (S_u) of a "uniform" (u) distribution, respectively (as the latter was defined in Refs. [1,3,4]). Furthermore, ion current fluctuations in membrane channels (ICFMC) have S very close to S_u [3].

The fact that a system contains nonlinear components does not necessarily reflect that a specific signal we measure from the system also exhibits nonlinear features. Thus, before analyzing this signal by applying nonlinear techniques, we must first clarify if the use of such techniques is justified by the data available. The method of surrogate data has been extensively used to serve such a purpose (see Ref. [5] for a review). Surrogate data refer to data that preserve certain linear statistic properties of the experimental data, but are random otherwise [6,7]. These data are prepared by various procedures; for example, Siwy *et al.* [7], in order to study the nature of dwell-time series in ICFMC, among other methods, also used surrogate data which have been obtained by three different procedures. The present paper aims, in general, at presenting a kind of surrogate data analysis using the entropy fluctuations in the natural time domain (see below) as discriminating statistics. Throughout the paper, the surrogate data are obtained by shuffling the Q_k randomly and hence their distribution is conserved. Applying such a procedure, we do the following: consider the null hypothesis that the data consist of *independent* draws from a fixed probability distribution of the dwell times; if we find significantly different serial correlations in the data and their shuffles, we can reject the hypothesis of *independence*, see paragraph 3.1 of Ref. [5]. In other words, the tested null hypothesis is that Q_k are independent and identically distributed (IID) random variables, i.e., that there are no correlations between the lengths of consecutive intervals. If the original (continuous) time series is Markovian, then the null hypothesis for the Q_k should hold, i.e., the Q_k are IID. We emphasize that the terminology "Markovian" throughout this paper always refers to the original time series.

Here, as a measure of the natural time entropy fluctuations, we consider the standard deviation δS when we calculate the value of S for a number of consecutive pulses and study how S varies when sweeping this time window through the whole time series. We use the following three data sets: Two of them are those treated in Ref. [3], i.e., SES activities and AN. As a third one, we preferred to use, instead of ICFMC, the case of electrocardiograms (ECG) for several reasons, chief among of which are (a) they are publicly accessible [8]; (b) instead of the single ICFMC example, a large variety of ECG are available (i.e., 105 individuals are employed here, 10 healthy and 95 patients); and (c) the case of ECG is similar to ICFMC, in the sense that the S value in ECG turns out to be very close to S_u as in ICFMC investigated in [3]. Note, however, that the intervals between heart beats fluctuate widely, e.g., [9].

A general agreement about whether normal heart dynamics are chaotic or not is still lacking (e.g., see Ref. [10] and references therein). The most commonly used nonlinear complexity measures are fractal dimensions of various kinds (e.g., correlation dimension, Renyi dimensions). Each of them measures different aspects of the *statistics* on the attractor. On the other hand, Liapunov exponents and the Kolmogorov-Sinai entropy (KS entropy) and entropy rates are measures of the *dynamics* on an attractor. Except for the KS entropy and entropy rates, the other categories of complexity measures assume a purely deterministic system (e.g., see Ref. [11]). Since a physiological time series may be due to a mixed process, stochastic and deterministic, the use of

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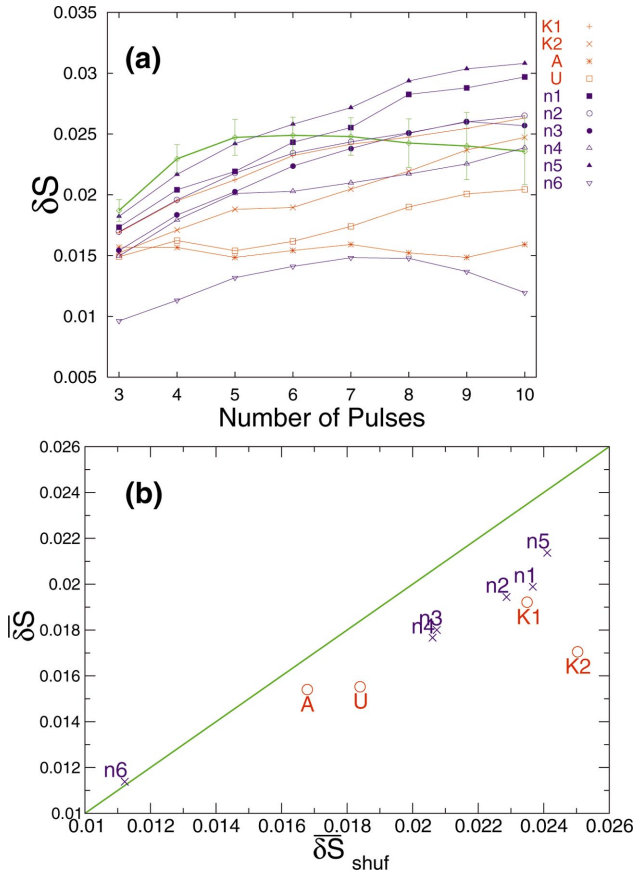

FIG. 1. (Color) (a) The δS values for each SES activity and artificial noise versus the time-window length. The corresponding values for a Markovian time series (10^2 pulses) are also plotted (green). (b) $\overline{\delta S}$ versus $\overline{\delta S}_{\text{shuf}}$ (time-window range 3–5) for all the SES activities and AN in (a). The straight line corresponds to $\overline{\delta S}_{\text{shuf}} = \overline{\delta S}$.

fractal dimensions in physiological time series has been occasionally criticized [11]. On the other hand, entropy is a concept equally applicable to deterministic as well as stochastic processes. This is why we preferred to use the entropy in natural time (more precisely its fluctuations δS) as discriminating statistics. The following point, however, should be stressed. Complexity measures based on *static* entropy (e.g., Shannon entropy) quantify *statistical* order in the time series. The underlying key property of these complexity measures is the probability distribution of the (dwell times in the) data analyzed; thus, the result of such computations should be independent of permutations performed on the (sequence of the dwell times in the) time series as in a surrogate (randomized) data set obtained by data shuffling. On the other hand, the entropy in natural time (and the relevant measures) considers, from its definition, the *sequential* order (of beats); in other words, S is a *dynamic* entropy, i.e., it captures characteristics of the dynamics in a system. Additional comments on the importance of the fluctuations of S in ECG will be made in Sec. V.

In all examples, we use a sliding window of length three to ten pulses, except otherwise stated. Concerning the symbols, we reserve δS *only* for the case when the calculation is made by a *single* time window, e.g., five pulses. The symbol

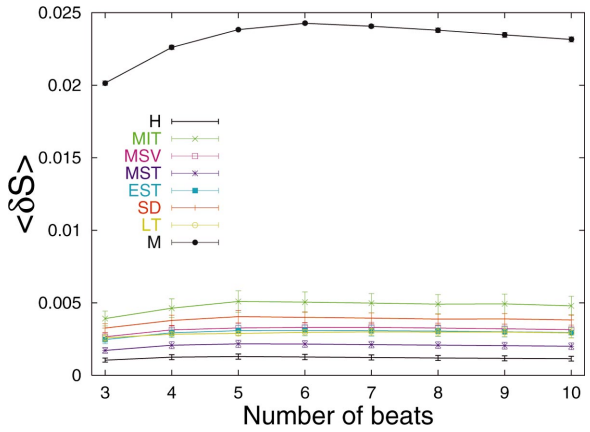

FIG. 2. (Color) The $\langle \delta S \rangle$ values for the QRS intervals (see the text) of the seven groups of humans versus the time-window length. The corresponding values for a Markovian time series (10^3 pulses, labeled *M*) are also plotted.

$\overline{\delta S}$ denotes the average of the δS values calculated for a sequence of single windows, e.g., three, four, and five pulses. Finally, $\langle \delta S \rangle$ stands for the δS values averaged over a group of individuals, e.g., the 10 healthy subjects.

The present paper is organized as follows. In Sec. II, we investigate whether a distinction between SES activities and AN can be achieved by the δS value alone. Furthermore, we examine if δS can recognize the non-Markovianity in all the signals investigated. In Sec. III, we attempt to shed light on the quantity δS_{shuf} calculated in a surrogate (randomized) data set obtained by data "shuffling." We find that δS_{shuf} in ECG is a measure of σ/μ (where μ and σ stand for the mean value and the standard deviation of the corresponding intervals; see below). Section IV shows that the δS_{shuf} value differs from δS, as expected (e.g., the entropy S is *not* static entropy, as mentioned above). The prominent role of the ratio $\delta S_{\text{shuf}}/\delta S$ in distinguishing ECG of healthy humans from those who suffered from sudden cardiac death is shown in Sec V. The conclusions are summarized in Sec. VI. Finally, an Appendix is reserved to derive an exact relationship between δS_{shuf} and σ/μ when Q_k are IID.

II. THE POSSIBILITY OF EMPLOYING δS TO "RECOGNIZE" THE NON-MARKOVIANITY

We start by examining whether the δS values alone can distinguish SES activities from AN as well as "recognize" their non-Markovianity. Recall [2,3] that SES and AN are time series of a dichotomous nature which are non-Markovian. In a *dichotomous* Markovian time series, the dwell times (Q_k) are exponentially distributed; for such a series we plot, in Fig. 1(a), the δS value versus the time-window length. (Since in the calculation of S only ratios of Q_k are involved, the result does not depend on the transition rates of the Markovian process.) The error shown in this case is on average 7%. (The calculation was made for a total number of 10^2 pulses; see below. Note that this error decreases upon increasing the number of pulses, i.e., it becomes $\approx 2\%$ for 10^3 pulses, which will be used later.) In the

same figure, we insert the δS values calculated for the four SES activities (labeled K1, K2, A, and U) and the six AN (labeled n1 to n6) depicted in Fig. 1 of Ref. [3]. An inspection of Fig. 1(a) reveals the following conclusions. First, *no* distinction between SES activities and AN (both of which have estimation errors comparable to the aforementioned error of the Markovian) is obvious. An inspection of Table I of [12] reveals that the number of pulses in three (out of the four) SES activities is around 10^2 for K2, U, and A (while for K1 it is ≈ 310) and this is why we calculated here the Markovian case for 10^2 pulses. Second, concerning the possibility of "recognizing" the non-Markovianity (as discussed and shown in Refs. [2–4] by independent procedures), this could be possibly supported *only* for the shorter time windows (i.e., three, four, and possibly five pulses) for all SES activities as well as for most AN (i.e., n6, n4, n3, n2, possibly n1, but *not* for n5); see Fig. 1(a).

We now investigate if the δS values alone can "recognize" the non-Markovianity in ECG. In a single sinus (normal) cycle of an ECG, the turning points are labeled with the letters P, Q, R, S, and T. We used here the QT database from the physiobank [8] (see also [13]), which consists of 105 15-min excerpts of Holter recordings as follows: 10 from the MIT-BIH Normal Sinus Rhythm Database (i.e., healthy subjects, hereafter labeled H), 15 from the MIT-BIH Arrhythmia Database (MIT), 13 from the MIT-BIH Supraventricular Arrhythmia Database (MSV), 6 from the MIT-BIH ST Change Database (MST), 33 from the European ST-T Database (EST), 4 from the MIT-BIH Long-Term ECG Database (LT), and 24 from sudden death patients from BIH(SD) (BIH denotes the Beth Israel Hospital). In Fig. 2, we plot, for the QRS-interval time series, the δS value averaged over each of the aforementioned seven groups versus the time-window length. Since all time series of these seven groups have $\approx 10^3$ intervals, we insert in the same figure the results calculated for a Markovian case (cf. with the procedure mentioned in the previous paragraph) of comparable length $\approx 10^3$. We see that the Markovian case exhibits δS values that are roughly one order of magnitude larger than those of the seven groups of humans, which clearly points to the non-Markovianity of *all* the signals in these groups. We emphasize that the same conclusions are drawn if we consider, instead of QRS, the series of QT intervals, or the beat-to-beat intervals (RR). In summary, the δS value alone can well recognize the non-Markovianity in ECG.

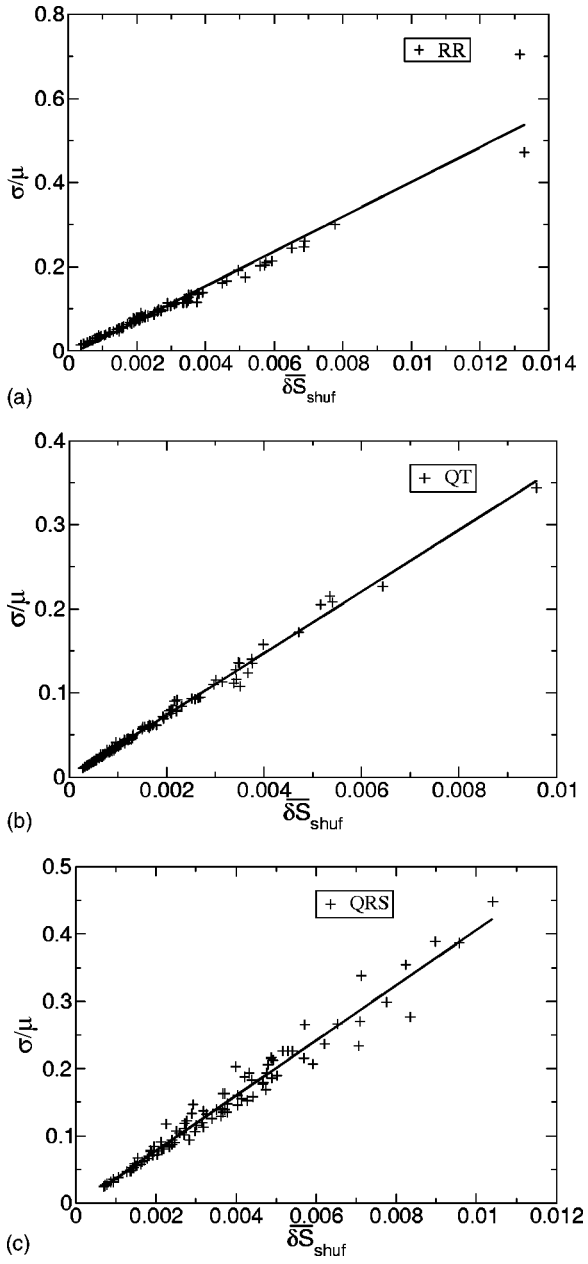

FIG. 3. The σ/μ value, for each of the 105 individuals, versus the corresponding $\overline{\delta S}_{shuf}$ value for the (a) RR, (b) QT, and (c) QRS intervals. The identity of the individual associated with each point can be found in Ref. [26].

III. THE PHYSICAL MEANING OF δS_{shuf}

In Fig. 3(a), we plot, for each of the 105 individuals, the value of σ/μ versus the corresponding value of $\overline{\delta S}_{shuf}$ (time-window range 3–10 beats) for the RR intervals. The same is repeated in Figs. 3(b) and 3(c) for the QT and QRS intervals, respectively. All three plots can be described by linear behavior, and a least-squares fitting to a straight line passing through the origin leads to the following slopes: 38.6 ± 0.6, 36.8 ± 0.2, and 40.1 ± 0.4 for the RR, QT, and QRS intervals, respectively. This points to the conclusion that δS_{shuf} provides, as intuitively expected, a measure of σ/μ. (This, however, *cannot* be supported with certainty for the SES activities and AN.) Note that, although these three slopes are more or less comparable, they differ by amounts lying outside their standard error. Furthermore, it may be worthwhile to mention that if we study *altogether* the RR, QT, and QRS intervals, for the 10 healthy humans *only* (Fig. 4), a good linearity of σ/μ versus δS_{shuf} results with a slope 37.5 ± 0.4 (e.g., if we study each of the three intervals separately, we find slopes that agree within the error margins, i.e., 37.5 ± 0.4, 37.1 ± 0.7, and 37.8 ± 0.1 for the RR, QT, and QRS intervals, respectively). The origin of this *common* behavior merits further investigation.

One could argue that Q_k may become IID upon their shuffling. In the Appendix, we show that, when Q_k are IID, δS is

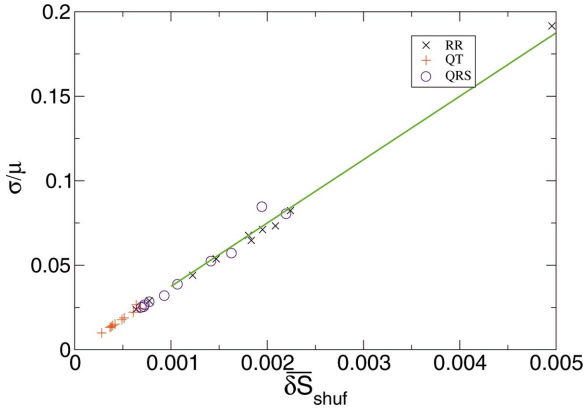

FIG. 4. (Color) The σ/μ value for RR, QT, and QRS intervals of the ten H versus the corresponding $\overline{\delta S}_{\text{shuf}}$ value (time-window range 3–10 beats). The straight line results from a least-squares fit of all 30 points. For the identity of the individual associated with each point, see Ref. [26].

actually proportional to σ/μ; the following relationship is obtained:

$$\delta S_{\text{shuf}} = \frac{\sigma}{\mu}\frac{1}{\sqrt{N-1}}\left[\sum_{k=1}^{N}\left(\frac{k}{N}\ln\frac{k}{eN\overline{\chi}}\right)^2\frac{1}{N} - \left(\sum_{k=1}^{N}\frac{k}{N^2}\ln\frac{k}{eN\overline{\chi}}\right)^2\right], \tag{1}$$

where

$$\overline{\chi} = \sum_{k=1}^{N}\frac{k}{N^2} = \frac{1}{2} + \frac{1}{2N} \tag{2}$$

and e denotes, as usual, the base of the natural logarithms. The relation (1) reveals that δS_{shuf} versus σ/μ must be a straight line with a slope ranging from 34.2 to 40.4, for a time-window length 3 to 10. This result is comparable with the slopes determined above from the analysis of the ECG data.

IV. ON THE DIFFERENCE BETWEEN δS AND δS_{shuf}

We first comment on the difference between δS and δS_{shuf} in the SES activities and AN. In Fig. 1(b), the value of δS versus the corresponding $\overline{\delta S}_{\text{shuf}}$ was plotted for each of the ten signals discussed in Fig. 1(a). The average values in Fig. 1(b) have been calculated over the three time windows of three, four, and five pulses, since we mentioned in Sec. II that the "recognition" of the non-Markovianity in all SES activities becomes possible in this time-window range. If we disregard n6, and despite the errors of around 5% (for the time-window range 3–5), we may say that there is a systematic tendency pointing to a value of $\overline{\delta S}_{\text{shuf}}/\overline{\delta S}$ larger than unity (the same conclusion is drawn if we take the averages over the time-window range 3–10). This is consistent with the non-Markovianity of all these signals, because for a Markovian case we expect $\overline{\delta S}_{\text{shuf}} = \overline{\delta S}$. (Since, by definition, δS_{shuf} corresponds to the entropy fluctuations upon *random* mixing of Q_k, see Sec. I, it is naturally expected that in a Markovian case the two quantities δS and δS_{shuf} *should* coincide.) Note that the reverse is *not* always true (thus the equality $\overline{\delta S}_{\text{shuf}} = \overline{\delta S}$ may also hold for *non*-Markovian time series), as will be demonstrated below with precise examples.

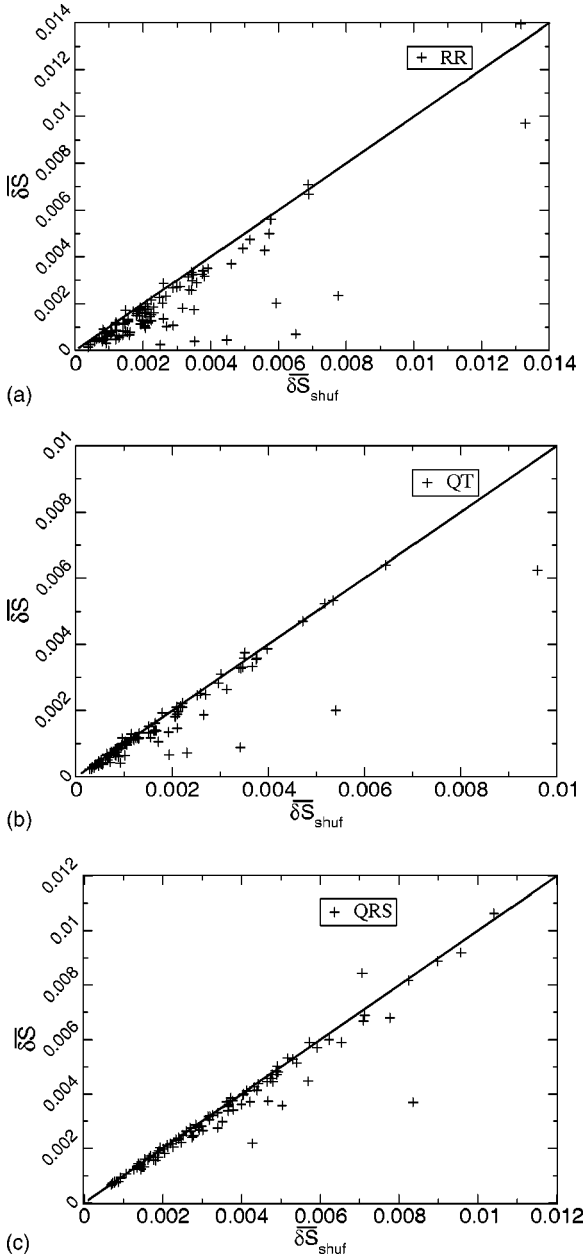

FIG. 5. The $\overline{\delta S}$ value, for each of the 105 individuals versus the corresponding $\overline{\delta S}_{\text{shuf}}$ value for (a) RR, (b) QT, and (c) QRS intervals. The straight line, drawn in each case, corresponds to $\overline{\delta S}_{\text{shuf}} = \overline{\delta S}$. For the identity of the individual associated with each point, see Ref. [26].

We now proceed to compare δS_{shuf} with δS in ECG. Figure 5(a) depicts the δS values, calculated for each of the 105 individuals, versus the corresponding $\overline{\delta S}_{\text{shuf}}$ for the RR intervals (time-window range 3–10 beats). The same is repeated in Figs. 5(b) and 5(c) for the QT and QRS intervals, respectively. In each case, we also plot the straight line $\overline{\delta S}_{\text{shuf}} = \overline{\delta S}$

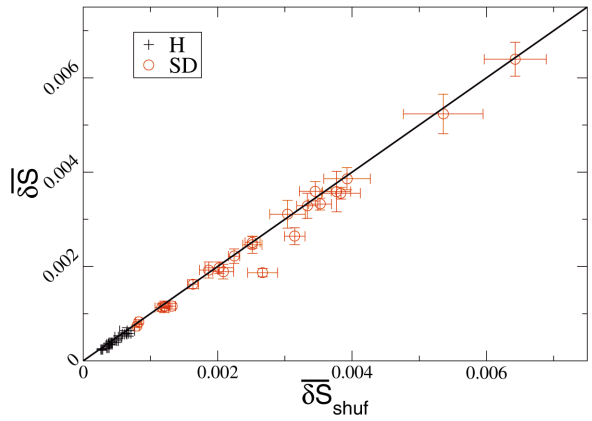

FIG. 6. (Color) The $\overline{\delta S}$ value, in each of the 10 H (black) and 24 SD (red), for the QT intervals versus $\overline{\delta S}_{shuf}$ (time-window range 3–10 beats). Note that the values of the ordinates are appreciably smaller than the δS value ($\approx 2\times 10^{-2}$) of the Markovian time series (10^3 events) depicted in Fig. 2.

to visualize that the vast majority of points fall below this line. The nonequality of $\overline{\delta S}_{shuf}$ and $\overline{\delta S}$ has also been verified by applying the Wilcoxon paired signed-rank test recommended [14] to be followed for non-Gaussian paired data. The tested null hypothesis is that the means of $\overline{\delta S}_{shuf}$ and $\overline{\delta S}$ are the same and is rejected at a level of significance well below 0.01, since the data of Figs. 5(a)–5(c) lead to normally distributed variables $z=-8.29$, -6.81 and -6.32, respectively [cf. the corresponding one-tailed asymptotic significance is given by $P(Z<z)$, i.e., the probability to obtain a normally distributed variable which is smaller than z]. Note that a least-squares fit to a straight line passing through the origin results in the following expressions: $\delta S=(0.76\pm 0.03)\delta S_{shuf}$, $\delta S=(0.85\pm 0.02)\delta S_{shuf}$, and $\delta S=(0.94\pm 0.02)\delta S_{shuf}$ for Figs. 5(a)–5(c), respectively. The sampling rate F_s in ECG is 250 Hz; thus, if we take as an example the RR intervals, the experimental error in their allocation is around $1/F_s$. The latter reflects in the calculation of δS and δS_{shuf} errors which are drastically smaller than those required to eventually justify a compatibility of the expression $\overline{\delta S}=(0.76\pm 0.03)\overline{\delta S}_{shuf}$, found from Fig. 5(a), with a straight line of slope equal to unity, i.e., $\overline{\delta S}=\overline{\delta S}_{shuf}$.

The difference between δS and δS_{shuf} in ECG could be understood in the context that the former depends on the *sequential* order (of beats), as mentioned in Sec. I, while the latter does not. Since short- (and long-) range correlations are a usual feature (see Ref. [15] and references therein) in heartbeat dynamics, which are possibly destroyed (or become weaker) upon randomizing the data, more "disorder" is intuitively expected to appear after randomization, thus reflecting $\delta S_{shuf}>\delta S$. Furthermore, note that in *all* three plots of Fig. 5 there are some drastic deviations from the straight line $\delta S=\delta S_{shuf}$. The origin of these deviations is currently being investigated in detail.

Finally, we further clarify the aforementioned point that the equality $\overline{\delta S}=\overline{\delta S}_{shuf}$ does *not* necessarily reflect Markovianity. In Fig. 6, we plot, for the QT intervals, $\overline{\delta S}_{shuf}$ versus $\overline{\delta S}$ (for a time-window range of 3–10 beats) for SD and H. We see that there are several individuals (mainly SD, see also the next section) of which their points lie practically (i.e., within the error margins) on the straight line $\overline{\delta S}=\overline{\delta S}_{shuf}$. If we plot their δS (or δS_{shuf}) values versus the time window (in a similar fashion to that in Fig. 2), we find that these values are distinctly smaller than those of the Markovian case, thus making clear that these individuals cannot be characterized as exhibiting Markovian behavior. (This non-Markovianity holds for *all* H and *all* SD.)

V. THE USE OF $\overline{\delta S}_{shuf}/\overline{\delta S}$ TO DISTINGUISH ECG OF HEALTHY HUMANS FROM SUDDEN CARDIAC DEATH ONES

Here we focus only on two groups of ECG, namely H and SD, and examine whether they can be distinguished by means of the ratio $\overline{\delta S}_{shuf}/\overline{\delta S}$. We calculate this ratio, for each type of interval, at two ranges: (i) a short (s) range of three to four beats (consider that the *smallest* number allowed for the natural time-domain analysis is three beats) and (ii) a longer (L) range of 50–70 beats. For the sake of convenience, we define $\nu\equiv\overline{\delta S}_{shuf}/\overline{\delta S}$, and hence the following ratios are investigated: $\nu_s(\tau)$ and $\nu_L(\tau)$, where τ denotes the type of interval (i.e., τ=RR, QRS, or QT) and s,L refer to the range studied (i.e., $s=3-4$ beats and $L=50-70$ beats).

The calculated values for $\nu_s(\tau)$ and $\nu_L(\tau)$ for the three types of intervals are given, for all H and SD, in Table I. The minima $\min_H[\nu_\kappa(\tau)]$ and maxima $\max_H[\nu_\kappa(\tau)]$ (where κ denotes either the short, $\kappa=s$, or the longer, $\kappa=L$, range) among the healthy subjects are also inserted in two separate rows, for each type of interval and each range studied. These minima and maxima are labeled H_{min} and H_{max}, respectively. The cases of SD which have smaller and larger values than H_{min} and H_{max} (reported in each column) are marked with superscripts "a" and "b," respectively.

A careful inspection of Table I leads to the following main conclusion: *All* SD violate one or more H limits (i.e., they have values that are smaller than H_{min} or larger than H_{max}). We intentionally emphasize that this conclusion is also drawn *even* when disregarding the results for the QT intervals. (Concerning the latter intervals: Only five SD out of 24 violate the H limits; however, in *all* SD, their δS values themselves are larger than those in H, see also Fig. 6. The usefulness of this difference will be discussed in detail elsewhere.) In other words, when focusing our investigation solely on the RR and QRS intervals, *all* SD violate one or more of the four H limits related to ν_s(RR), ν_L(RR), ν_s(QRS), and ν_L(QRS). This is important from a practical point of view, because the RR and QRS intervals can be detected more easily (and accurately) than the QT by means of an automatic threshold-based detector (e.g., see Ref. [16], which evaluated the results of a detector that has been forwarded in Refs. [17,18] to determine automatically the waveform limits in Holter ECG).

A further inspection of Table I leads to the following additional comment: When investigating the RR intervals *alone* (which can be detected automatically more easily and precisely than the other intervals), i.e., studying ν_s(RR) and ν_L(RR), the vast majority of SD (22 out of 24 cases) can be distinguished from H (only two SD, i.e., sel30 and sel47,

TABLE I. The values of the ratios $\overline{\delta S}_{\text{shuf}}/\overline{\delta S}$ in the short (s) range 3–4 (ν_s) or in the longer (L) range 50–70 beats (ν_L) in H (sel16265 to sel17453) and SD (sel30 to sel17152) for the RR, QRS, and QT intervals.

	3–4 beats (ν_s)			50–70 beats (ν_L)		
Individual	RR	QRS	QT	RR	QRS	QT
sel16265	1.82	1.00	1.24	0.48	1.02	0.76
sel16272	1.74	0.99	0.98	0.77	1.08	1.11
sel16273	2.21	1.00	1.48	0.50	0.88	0.71
sel16420	1.55	0.98	1.08	0.53	1.09	0.90
sel16483	2.25	1.02	1.14	0.52	1.16	0.92
sel16539	1.42	1.06	1.25	0.50	1.08	0.65
sel16773	1.94	1.00	0.99	0.44	1.05	0.96
sel16786	1.42	1.00	1.19	0.56	1.04	0.77
sel16795	1.18	0.98	1.08	0.73	0.96	0.99
sel17453	1.38	1.01	1.02	0.56	0.98	0.81
H_{min}	1.18	0.98	0.98	0.44	0.88	0.65
H_{max}	2.25	1.06	1.48	0.77	1.16	1.11
sel30	1.29	1.11[b]	1.09	0.65	0.72[a]	1.09
sel31	0.96[a]	1.08[b]	1.17	1.23[b]	0.94	0.62[a]
sel32	1.39	1.14[b]	1.12	1.02[b]	0.69[a]	0.90
sel33	1.05[a]	0.99	1.00	0.86[b]	0.82[a]	0.99
sel34	2.11	1.29[b]	1.11	0.42[a]	0.78[a]	0.67
sel35	1.00[a]	1.00	0.96[a]	1.01[b]	1.05	1.08
sel36	1.02[a]	1.02	1.04	0.92[b]	1.00	0.88
sel37	1.07[a]	1.18[b]	1.07	0.55	0.75[a]	0.65
sel38	0.99[a]	1.09[b]	1.13	1.37[b]	0.89	1.04
sel39	0.96[a]	1.02	1.06	2.93[b]	0.92	0.90
sel40	1.01[a]	1.00	0.93[a]	0.78[b]	0.93	1.29[b]
sel41	1.07[a]	1.04	1.02	1.07[b]	0.84[a]	0.96
sel42	1.63	1.08[b]	1.23	0.42[a]	1.06	0.67
sel43	2.71[b]	1.11[b]	1.05	0.56	0.76[a]	0.89
sel44	0.91[a]	0.95[a]	0.88[a]	2.24[b]	1.46[b]	1.32[b]
sel45	0.98[a]	1.24[b]	1.29	0.98[b]	0.86[a]	0.79
sel46	1.03[a]	1.01	1.03	1.00[b]	0.84[a]	1.01
sel47	1.56	0.97[a]	1.03	0.45	0.97	1.01
sel48	0.82[a]	1.18[b]	1.44	1.48[b]	0.68[a]	0.73
sel49	0.93[a]	1.11[b]	0.96[a]	1.22[b]	0.70[a]	1.14[b]
sel50	1.05[a]	0.98	0.98	0.93[b]	1.23[b]	1.50[b]
sel51	1.25	1.01	0.97[a]	1.05[b]	1.24[b]	0.91
sel52	1.50	1.16[b]	1.22	1.00[b]	0.73[a]	0.68
sel17152	1.64	1.01	1.04	0.90[b]	1.01	0.97

[a]These values are smaller than the minimum (H_{min}) value of $\overline{\delta S}_{\text{shuf}}/\overline{\delta S}$ in H for each range.
[b]These values are larger than the maximum (H_{max}) value of $\overline{\delta S}_{\text{shuf}}/\overline{\delta S}$ in H for each range.

obey the corresponding H limits). Specifically, concerning ν_s(RR), 15 SD have values smaller than $H_{\text{min}}=1.18$, while only one SD (i.e., sel43) has a value exceeding $H_{\text{max}}=2.25$; as for ν_L(RR), 18 SD exceed $H_{\text{max}}=0.77$, while only two SD (i.e., sel34 and sel42) have values smaller than $H_{\text{min}}=0.44$.

In what remains, we proceed to a tentative physical interpretation of the above results, the main feature of which focuses on the fact that most SD simultaneously have ν_s(RR) values smaller than H_{min}(=1.18) and ν_L(RR) values exceeding H_{max}(=0.77). The RR time series of healthy subjects are characterized by high complexity (e.g., [15,19]); this, if we recall that in a Markovian series we intuitively expect $\delta S_{\text{shuf}}/\delta S=1$ (and hence $\nu_s=1$ and $\nu_L=1$), is compatible with the fact that in *all* H *both* ν_s(RR) and ν_L(RR) distinctly differ from unity (see Table I). We now turn to SD by considering that for individuals at high risk of sudden death the fractal

physiological organization (long-range correlations) breaks down and this is often accompanied by emergence of *uncorrelated randomness* (see [15] and references therein). It is therefore naturally expected that in SD the values of $\nu_s(\mathrm{RR})$ and $\nu_L(\mathrm{RR})$ become closer to the Markovian value (i.e., unity) compared to H; thus, in SD, $\nu_s(\mathrm{RR})$ naturally becomes smaller than the value 1.18 (the corresponding $H_{\min}$ limit) and $\nu_L(\mathrm{RR})$ larger than 0.77 (the corresponding $H_{\max}$ limit).

We now focus on the following important property of H: although *both* $\nu_s(\mathrm{RR})$ and $\nu_L(\mathrm{RR})$ differ from unity, as mentioned, they systematically behave *differently*, i.e., $\nu_s(\mathrm{RR})>1$ while $\nu_L(\mathrm{RR})<1$. The exact origin of the latter difference has not yet been identified with certainty, but the following comments might be relevant: First, in the framework of the frequency-domain characteristics of heart-rate variability (e.g., [20]), we may state that $\nu_s(\mathrm{RR})$ and $\nu_L(\mathrm{RR})$ are associated with the high-frequency (HF, 0.15–0.4 Hz) and low-frequency (LF, 0.015–0.15 Hz) range in the RR tachogram ("instantaneous" heart rate, 1/RR). An important difference in the effect of the sympathetic and parasympathetic modulation of the RR intervals has been noticed (e.g., see [20] and references therein): Sympathetic tone is believed to influence the LF component, whereas *both* sympathetic and parasympathetic activity have an effect on the HF component [recall that our results show $\nu_s(\mathrm{RR})>\nu_L(\mathrm{RR})$]. Second, at short time scales (high frequencies), it has been suggested [21] that we have relatively *smooth* heartbeat oscillations associated with respiration (e.g., 15 breaths per minute corresponds to a 4-sec oscillation with a peak in the power spectrum at 0.25 Hz, see [20]); this is lost upon randomizing the consecutive intervals Q_k, thus probably leading to (larger variations—compared to the original experimental data—between the durations of consecutive intervals and hence to) δS_{shuf} values larger than δS, i.e., a $\nu_s(\mathrm{RR})$ value larger than unity (an extension of the current analysis to a surrogate sequence for a simultaneous recording of the breath rate and the instantaneous heart rate, upon considering the points discussed in paragraph 4.6 of Ref. [5], could greatly contribute to clarifying the validity of such an explanation). Such an argument, if true, cannot be applied, of course, in the longer-range 50–70 beats and hence explain why the opposite behavior, i.e., $\delta S_{\mathrm{shuf}}<\delta S$, then holds. The latter finding must be inherently connected to the nature of the long-range correlations. The existence of the latter is pointed out from the fact that (in this range also) the RR intervals result in δS values ($\sim 10^{-3}$) which significantly differ from the Markovian δS value ($\sim 10^{-2}$) (the existence of the long-range correlations in the heart-rate variability has been independently established by several applications of the detrended fluctuation analysis, e.g., see [21,15] and references therein).

A simplified interpretation of the results of Fig. 6, and in particular the reason why for the QT intervals the quantity δS is larger for the SD than for the H, could be attempted if we consider that (i) S could be thought of as a measure of the "disorder" (in the consecutive intervals), (ii) the essence of the natural time-domain analysis is built on the variation of the durations of consecutive pulses, and (iii) it has been clinically observed (e.g., see Ref. [22]) that the QT interval (which corresponds to the time in which the heart in each beat "recovers"—electrically speaking—from the previous excitation) exhibits frequent prolonged values before cardiac death. Thus, when a time window is sliding on an H-ECG, it is intuitively expected to find, more or less, the same S values (when sweeping through various parts of the ECG) and hence a small δS value is envisaged. By the same token, in an SD-ECG, we expect that, in view of the short-long-short sequences of the QT intervals, the corresponding S values will be much different (compared to H), thus leading to a larger δS value [in the same context we may also understand why the σ/μ values—and hence δS_{shuf}, see Eq. (1)—are larger in SD than those in H, as shown in Fig. 6]. The distinction between SD and H could also be understood in the context of dynamic phase transitions (critical phenomena) as follows: In SD, since the dynamic phase transition (cardiac arrest) is approached, the *fluctuations* of S are expected to become larger, thus reflecting larger δS; such intense fluctuations are not expected, of course, for H.

VI. CONCLUSIONS

The main point that emerged in the surrogate data analysis presented in this paper is the key role of the quantity $\delta S_{\mathrm{shuf}}/\delta S$. This ratio does the following:

(i) It reveals the non-Markovianity in all three types of signals analyzed here, i.e., SES activities, AN and ECG. In a Markovian case we have $\delta S_{\mathrm{shuf}}=\delta S$, but the reverse is not always valid; it may happen that $\delta S_{\mathrm{shuf}}/\delta S=1$, although δS (and δS_{shuf}) values drastically differ from that of the Markovian (this is the case of ECG).

(ii) It differentiates the ECG of healthy humans (H) from those who suffered from sudden cardiac death (SD). More precisely, in SD, the $\delta S_{\mathrm{shuf}}/\delta S$ values of the RR (i.e., beat to beat) intervals become closer to the Markovian value (i.e., unity) compared to those in H. Furthermore, in SD, *both* δS and δS_{shuf} values of the QT interval (corresponding to the time in which the heart "recovers" from its previous excitation) are larger than those in H.

As for the physical meaning of δS_{shuf} in ECG, it was shown to be a measure of σ/μ.

APPENDIX: INTERRELATION BETWEEN δS_{shuf} AND σ/μ IN THE CASE OF IID POSITIVE RANDOM VARIABLES

If we consider a time series Q_k, where $Q_k \geqslant 0, k=1,2,\ldots,N$, we obtain the quantities $p_k=Q_k/\Sigma_{l=1}^{N}Q_l$, which satisfy the necessary conditions [23] $p_k \geqslant 0, \Sigma_{k=1}^{N} p_k=1$ to be considered as point probabilities. We then define [1–3] the moments of the natural time $\chi_k=k/N$ as $\langle \chi^q \rangle=\Sigma_{k=1}^{N}(k/N)^q p_k$ and the entropy $S\equiv\langle \chi \ln \chi\rangle-\langle\chi\rangle\ln\langle\chi\rangle$, where $\langle \chi \ln \chi\rangle=\Sigma_{k=1}^{N}(k/N)\ln(k/N)p_k$. This appendix is solely focused on a uniform distribution in the natural time domain.

We now consider the case when Q_k are independent and identically distributed (IID) positive random variables. It then follows that the expectation value $\mathrm{E}(p_k)=\mathrm{E}[Q_k/\Sigma_{l=1}^{N}Q_l]$ of p_k equals $1/N$,

$$\mathrm{E}(p_k) = \frac{1}{N}. \tag{A1}$$

Equation (A1) results from the fact that, since Q_k are IID, we have $\mathrm{E}[\Sigma_{k=1}^N Q_k/\Sigma_{l=1}^N Q_l]=1=N\mathrm{E}(p_k)$. For the purpose of our calculations, the relation between the variance of p_k, $\mathrm{Var}(p_k)=\mathrm{E}[(p_k-1/N)^2]$, and the covariance of p_k and p_l, $\mathrm{Cov}(p_k,p_l)=\mathrm{E}[(p_k-1/N)(p_l-1/N)]$, is of central importance. Using the constraint $\Sigma_{k=1}^N p_k=1$, leading to $p_k-1/N=\Sigma_{l\neq k}(1/N-p_l)$, and the fact that Q_k are IID, we obtain $\mathrm{E}[(p_k-1/N)^2]=\mathrm{E}[(p_k-1/N)\Sigma_{l\neq k}(1/N-p_l)]=-(N-1)\mathrm{E}[(p_k-1/N)(p_l-1/N)]$. Thus, we get

$$\mathrm{Cov}(p_k,p_l) = -\frac{\mathrm{Var}(p_k)}{N-1}. \tag{A2}$$

The N dependence of $\mathrm{Var}(p_k)$ is obtained from

$$\mathrm{Var}(p_k) = \frac{1}{N^2}\mathrm{E}\left[\left(\frac{NQ_k}{\sum_{l=1}^N Q_l}-1\right)^2\right], \tag{A3}$$

where the quantity $\mathrm{E}[(NQ_k/\Sigma_{l=1}^N Q_l-1)^2]$ is *asymptotically* N-independent. The latter arises as follows: If $\mathrm{E}(Q_k)=\mu$ and $\mathrm{Var}(Q_k)=\sigma^2(<\infty)$, as a result of the central limit theorem [24], we have $\mathrm{E}(\Sigma_{k=1}^N Q_k/N)=\mu$ and $\mathrm{Var}(\Sigma_{k=1}^N Q_k/N)=\sigma^2/N$. The latter two equations, for large enough N, imply that $\mathrm{E}[(NQ_k/\Sigma_{l=1}^N Q_l-1)^2]\approx\mathrm{E}[(Q_k/\mu-1)^2]=\sigma^2/\mu^2$. Thus, Eq. (A3) becomes

$$\mathrm{Var}(p_k) = \frac{\sigma^2}{N^2\mu^2}. \tag{A4}$$

We now turn to the statistical properties of $\langle\chi^q\rangle$. Using Eq. (A1), we have

$$\mathrm{E}[\langle\chi^q\rangle] = \sum_{k=1}^N \left(\frac{k}{N}\right)^q \frac{1}{N}, \tag{A5}$$

which, since [25] $\Sigma_{k=1}^N k^q = N^{q+1}/(q+1)+N^q/2+o(N^q)$, reveals that $\mathrm{E}[\langle\chi^q\rangle]$ is again asymptotically N-independent because it approaches the value $1/(q+1)$ with a "small" $1/(2N)$ correction. The variance $\mathrm{Var}[\langle\chi^q\rangle][=(\delta\langle\chi^q\rangle)^2]$,

$$\mathrm{Var}[\langle\chi^q\rangle] = \mathrm{E}\left\{\left[\sum_{k=1}^N \left(\frac{k}{N}\right)^q\left(p_k-\frac{1}{N}\right)\right]^2\right\}, \tag{A6}$$

after expanding the square and using Eqs. (A2) and (A4), becomes

$$\mathrm{Var}[\langle\chi^q\rangle] = \sum_{k=1}^N \left(\frac{k}{N}\right)^{2q}\frac{\sigma^2}{N^2\mu^2} - \frac{\sigma^2}{(N-1)N^2\mu^2}\sum_{k=1}^N\left(\frac{k}{N}\right)^q \sum_{l=1,l\neq k}^N \left(\frac{l}{N}\right)^q, \tag{A7}$$

which, using Eq. (A5), finally leads to

$$\mathrm{Var}[\langle\chi^q\rangle] = \frac{\sigma^2}{(N-1)\mu^2}\{\mathrm{E}[\langle\chi^{2q}\rangle]-\mathrm{E}^2[\langle\chi^q\rangle]\}. \tag{A8}$$

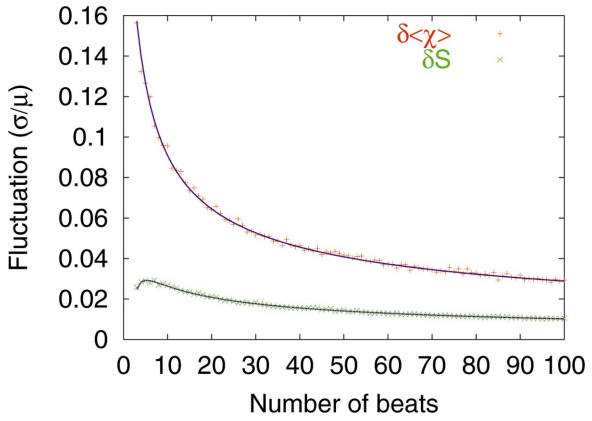

FIG. 7. (Color) Comparison of the theoretical estimations (solid lines) of $\delta\langle\chi\rangle$ and δS resulting from Eqs. (A8) and (A21), respectively, with the values obtained (plus and cross, respectively) using a Gaussian sample having values of μ, σ, and size ($\approx$1000) similar to those in ECG. Here, as well as throughout the paper, the estimator $(\delta X)^2=\Sigma(X-\overline{X})^2/N$ was used for the calculation of the sample variance of the synthetic data, and thus $N-1$ was replaced by N in Eqs. (A8) and (A21).

The proof of Eq. (A8) can be generalized for all linear functionals of p_k of the form $\langle f(\chi)\rangle=\Sigma_{k=1}^N f(k/N)p_k$ and yields

$$\mathrm{Var}[\langle f(\chi)\rangle] = \frac{\sigma^2\{\mathrm{E}[\langle f^2(\chi)\rangle]-\mathrm{E}^2[\langle f(\chi)\rangle]\}}{(N-1)\mu^2}. \tag{A9}$$

In Fig. 7, we compare the theoretical result of Eq. (A8) with synthetic (Gaussian) data which have values of μ, σ, and size ($\approx$1000) similar to those in ECG. Note that when one uses the estimator $(\delta X)^2=\Sigma(X-\overline{X})^2/N$, instead of the unbiased estimator $(\delta X)^2=\Sigma(X-\overline{X})^2/(N-1)$, in order to find the sample variance, N should replace $N-1$ in Eq. (A8).

We now proceed to the statistical properties of the entropy [1,3] $S=\langle\chi\ln\chi\rangle-\langle\chi\rangle\ln\langle\chi\rangle$. The expectation value

$$\mathrm{E}(S) = \mathrm{E}\left[\sum_{k=1}^N \frac{k}{N}\ln\left(\frac{k}{N}\right)p_k - \sum_{k=1}^N \frac{k}{N}p_k \ln\left(\sum_{l=1}^N \frac{l}{N}p_l\right)\right] \tag{A10}$$

can be evaluated as follows: we add and subtract the term $\Sigma_{k=1}^N(k/N)p_k\ln[\Sigma_{l=1}^N(l/N)1/N]$, and then expand the resulting term $\ln[1+\Sigma_{l=1}^N(l/N)[p_l-(1/N)]/\Sigma_{l=1}^N(l/N^2)]$ to first order in $[p_l-(1/N)]$; finally, using Eq. (A8), we obtain

$$\mathrm{E}(S) = \sum_{k=1}^N \frac{k}{N^2}\ln\left(\frac{k}{N}\right) - \sum_{k=1}^N \frac{k}{N^2}\ln\left(\sum_{l=1}^N \frac{l}{N^2}\right) - \frac{\sigma^2\left[\sum_{k=1}^N k^2/N^3 - \left(\sum_{k=1}^N k/N^2\right)^2\right]}{(N-1)\mu^2\sum_{l=1}^N l/N^2}. \tag{A11}$$

This equation reveals that $\mathrm{E}(S)$ depends slightly on σ/μ; upon increasing N, the last term of Eq. (A11) decays as $1/N$ (cf. the sums in the numerator and the denominator are of the form $E[\langle\chi^q\rangle]$, for $q=1$ and 2, and asymptotically lead to a

constant $1/(q+1)$, see the relevant discussion after Eq. (A5).

To simplify the calculation of the variance of the entropy $\mathrm{Var}(S)$, we define the two linear functionals

$$m[x_k] = \sum_{k=1}^{N} \frac{k}{N} x_k, \tag{A12}$$

$$L[x_k, \xi] = \sum_{k=1}^{N} \frac{k}{N} \ln\left(\frac{k}{\xi N}\right) x_k, \tag{A13}$$

and the constant time series $\mathbb{K} = \{x_k\} : x_k = 1/N, k = 1, 2, \ldots, N$. Note that for both functionals $m[x_k]$ and $L[x_k, \xi]$, in view of their linearity, we have

$$\mathrm{E}\left\{ m\left[p_k - \frac{1}{N} \right] \right\} = \mathrm{E}\left\{ L\left[p_k - \frac{1}{N}, \xi \right] \right\} = 0. \tag{A14}$$

Using Eqs. (A12) and (A13), the entropy can be written, in compact form, as follows:

$$S = L[p_k, m[p_k]], \tag{A15}$$

and its expectation value is written as

$$\mathrm{E}(S) = L[\mathbb{K}, 1] - m[\mathbb{K}] \ln m[\mathbb{K}] - \frac{\sigma^2 \kappa_{1,u}}{(N-1)\mu^2 m[\mathbb{K}]}, \tag{A16}$$

where $\kappa_{1,u} = \mathrm{E}[\langle \chi^2 \rangle] - \mathrm{E}^2[\langle \chi \rangle]$.

The variance of the entropy, $\mathrm{Var}(S) = (\delta S)^2$, can then be found by adding and subtracting the terms $m[p_k] \ln m[\mathbb{K}]$ and $m[p_k - 1/N]$ and using the expansion $m[p_k] \ln(m[p_k]/m[\mathbb{K}]) = m[p_k] m[p_k - 1/N]/m[\mathbb{K}]$; this gives

$$\begin{aligned}
\mathrm{Var}(S) &= \mathrm{E}\left\{ \left(L[p_k, 1] - m[p_k] \ln m[p_k] - L[\mathbb{K}, 1] + m[\mathbb{K}] \ln m[\mathbb{K}] + \frac{\sigma^2 \kappa_{1,u}}{(N-1)\mu^2 m[\mathbb{K}]} \right)^2 \right\}, \\
&= \mathrm{E}\left\{ \left(L\left[p_k - \frac{1}{N}, 1 \right] - m[p_k] \ln \frac{m[p_k]}{m[\mathbb{K}]} + m\left[\frac{1}{N} - p_k \right] \ln m[\mathbb{K}] + \frac{\sigma^2 \kappa_{1,u}}{(N-1)\mu^2 m[\mathbb{K}]} \right)^2 \right\}, \\
&= \mathrm{E}\left\{ \left(L\left[p_k - \frac{1}{N}, m[\mathbb{K}] \right] - \frac{m[p_k] m[p_k - (1/N)]}{m[\mathbb{K}]} + \frac{\sigma^2 \kappa_{1,u}}{(N-1)\mu^2 m[\mathbb{K}]} \right)^2 \right\}, \\
&= \mathrm{E}\left\{ \left(L\left[p_k - \frac{1}{N}, m[\mathbb{K}] \right] - m\left[p_k - \frac{1}{N} \right] - \frac{m^2[p_k - (1/N)]}{m[\mathbb{K}]} + \frac{\sigma^2 \kappa_{1,u}}{(N-1)\mu^2 m[\mathbb{K}]} \right)^2 \right\}, \\
&= \mathrm{E}\left\{ \left(L\left[p_k - \frac{1}{N}, m[\mathbb{K}] e \right] - \frac{m^2[p_k - (1/N)]}{m[\mathbb{K}]} + \frac{\sigma^2 \kappa_{1,u}}{(N-1)\mu^2 m[\mathbb{K}]} \right)^2 \right\}.
\end{aligned} \tag{A17}$$

Expanding the square in Eq. (A17), and using Eq. (A14), we find

$$\mathrm{Var}(S) = \mathrm{E}\left(L^2\left[p_k - \frac{1}{N}, m[\mathbb{K}] e \right] + 2L\left[p_k - \frac{1}{N}, m[\mathbb{K}] e \right] \frac{m^2[p_k - (1/N)]}{m[\mathbb{K}]} + \frac{m^4[p_k - (1/N)]}{m^2[\mathbb{K}]} - \frac{\sigma^4 \kappa_{1,u}^2}{(N-1)^2 \mu^4 m^2[\mathbb{K}]} \right). \tag{A18}$$

If we assume that the distribution of Q_k is *skewnessless*, i.e., $\mathrm{E}[(Q_k - \mu)^3] = 0$, the expectation value of the second term in Eq. (A18) vanishes, whereas the third and the fourth terms are of order $1/N^2$ and hence negligible with respect to the first term. Thus,

$$\mathrm{Var}(S) = \mathrm{E}\left(L^2\left[p_k - \frac{1}{N}, m[\mathbb{K}] e \right] \right), \tag{A19}$$

which can be explicitly written as follows:

$$\mathrm{Var}(S) = \mathrm{E}\left\{ \left[\sum_{k=1}^{N} \frac{k}{N} \ln\left(\frac{k}{m[\mathbb{K}] N e} \right) \left(p_k - \frac{1}{N} \right) \right]^2 \right\}. \tag{A20}$$

The right side of Eq. (A20) becomes similar to Eq. (A6), if we replace χ^q by $\chi \ln(\chi / m[\mathbb{K}] e)$; thus after expanding the square and using Eqs. (A2) and (A4), we finally obtain

$$\mathrm{Var}(S) = \frac{\sigma^2}{(N-1)\mu^2}\left[\sum_{k=1}^{N}\left(\frac{k}{N}\ln\frac{Nk}{e^{\Sigma_{k=1}^{N}k}}\right)^2\frac{1}{N} - \left(\sum_{k=1}^{N}\frac{k}{N^2}\ln\frac{Nk}{e^{\Sigma_{k=1}^{N}k}}\right)^2\right]. \tag{A21}$$

A comparison of Eqs. (A19) and (A15) reveals the following: in order to find the entropy fluctuation δS, one simply has to replace in Eq. (A15) $m[p_k]$ with $m[\mathbb{K}]e$ and then directly take its variance according to Eq. (A9). Equation (A21) is just Eq. (1) of the main text.

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