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 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 “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 $\delta S$ and $\delta S_{\text{shuf}}$ 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 $\delta S_{\text{shuf}}/\delta S$ plays a key-role. The physical meaning of $\delta S_{\text{shuf}}$ 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 $k$-th pulse the value $\chi_k = k/N$. The analysis is then made in terms of the couple $(\chi_k, Q_k)$ where $Q_k$ stands for the duration of the $k$-th pulse. The entropy $S$, defined[1, 3] as $S \equiv \langle \chi \ln \chi \rangle - \langle \chi \rangle \ln \langle \chi \rangle$, where $\langle \chi \rangle = \sum_{k=1}^{N} p_k \chi_k$, $p_k = Q_k / \sum_{n=1}^{N} Q_n$, and $\langle \chi \ln \chi \rangle = \sum_{k=1}^{N} p_k \chi_k \ln \chi_k$, 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 $\delta S$ 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). (c) The case of ECG is similar to ICFMC, in the sense that the $S$-value in ECG results 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 or not normal heart dynamics are chaotic or not chaotic is still lack-
ing (e.g., see Ref.[10] and references therein). The most commonly used non-linear 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 (K-S entropy) and entropy rates are measures of the dynamics on an attractor. Except for the K-S 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 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 $\delta S$ ) 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 forwarded in Section V.

In all examples, we use a sliding window of length three to ten pulses, except otherwise stated. Concerning the symbols: We reserve $\delta S$ only for the case when the calculation is made by a single time-window, e.g., 5 pulses. The symbol $\overline{SS}$ denotes the average of the $\delta S$-values calculated for a sequence of single windows, e.g., 3, 4 and 5 pulses. Finally, $(\delta S)$ stands for the $\delta S$-values averaged over a group of individuals, e.g., the 10 healthy subjects.

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

II. THE POSSIBILITY OF EMPLOYING $\delta S$ TO “RECOGNIZE” THE NON-MARKOVIANITY

We start by examining whether the $\delta S$-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 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 $\delta S$-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 the average 7%. (The calculation was made for a total number of $10^5$ 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 $\delta S$-values calculated for the four SES activities (labelled K1, K2, A, U) and the six AN (labelled 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, is $\approx 310$) 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., 3, 4 and possibly 5 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 $\delta S$-values alone can “recognize” the non-Markovianity in ECG. In a single sinus (normal) cycle of an ECG, the turning points are labelled with the letters P, Q, R, S and T. We used here the QT database from physiobank [8] (see also [13]), which consists of 105 fifteen-minute excerpts of Holter recordings as follows: 10 from MIT-BIH Normal Sinus Rhythm Database (i.e., healthy subjects, hereafter labelled H), 15 from MIT-BIH Arrhythmia Database (MIT), 13 from MIT-BIH Supraventricular Arrhythmia Database (MSV), 6 from MIT-BIH ST Change Database (MST), 33 from the European ST-T Database (EST), 4 from MIT-BIH Long-Term ECG Database (LT) and 24 from sudden death patients from BIH(SD). (cf. BIH denotes the Beth Israel Hospital). In Fig. 2, we plot, for the QRS-interval time-series, the $\delta S$-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...
FIG. 1: (Color) (a) The $\delta S$-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) $\delta S$ versus $\delta S_{shuf}$ (time-window range 3-5) for all the SES activities and AN in (a). The straight line corresponds to $\delta S_{shuf} = \delta S$.

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 $\delta S$-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 $\delta S$-value alone can well recognize the non-Markovianity in ECG.

III. THE PHYSICAL MEANING OF $\delta S_{shuf}$

In Fig. 3(a) we plot, for each of the 105 individuals, the value of $\sigma/\mu$ versus the corresponding value of $\delta S_{shuf}$ (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 these 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 $\pm$ 0.6, 36.8 $\pm$ 0.2 and 40.1 $\pm$ 0.4, for the RR-, QT- and QRS-intervals, respectively. This points to the conclusion that $\delta S_{shuf}$ provides, as intuitively expected, a measure of $\sigma/\mu$. (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 $\sigma/\mu$ versus $\delta S_{shuf}$ results with a slope 37.5 $\pm$ 0.4. (cf. if we study each of the three intervals separately, we find slopes that agree within the error margins, i.e., 37.5 $\pm$ 0.4, 37.1 $\pm$ 0.7 and 37.8 $\pm$ 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, $\delta S$ is actually proportional to $\sigma/\mu$; the following relationship is obtained:

$$
\delta S_{shuf} = \frac{\sigma}{\mu} \frac{1}{\sqrt{N-1}} \left\{ \sum_{k=1}^{N} \left( \frac{k}{N} \ln \frac{k}{eN\chi} \right)^2 \frac{1}{N} \right. 
- \left. \left( \sum_{k=1}^{N} \frac{k}{N^2} \ln \frac{k}{eN\chi} \right)^2 \right\} 
$$

(1)

where

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

(2)

and $e$ denotes, as usually, the base of the natural logarithms. The relation (1) reveals that $\delta S_{shuf}$ versus $\sigma/\mu$.
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 $\delta S$ AND $\delta S_{\text{shuf}}$

We first comment on the difference between $\delta S$ and $\delta S_{\text{shuf}}$ in the SES activities and AN. In Fig. 1(b), the value of $\delta S$ versus the corresponding $\delta S_{\text{shuf}}$ 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 3, 4 and 5 pulses, since we mentioned in Section II that the “recognition” of the non-Markovianity in all SES activities becomes possible in this time-window range. If we disregard $n_6$, 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 $\frac{\delta S_{\text{shuf}}}{\delta S}$ larger than unity (cf. 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 $\delta S_{\text{shuf}} = \overline{\delta S}$. (Since, by definition, $\delta S_{\text{shuf}}$ corresponds to the entropy fluctuations upon random mixing of $Q_k$, see Section I, it is naturally expected that in a Markovian case the two quantities $\delta S$ and $\delta S_{\text{shuf}}$ should coincide). Note that the reverse is not always true (thus the equality $\delta S_{\text{shuf}} = \overline{\delta S}$ may also hold for non-Markovian time series) as will be demonstrated below with precise examples.

We now proceed to compare $\delta S_{\text{shuf}}$ with $\delta S$ in ECG. Figure 5(a) depicts the $\overline{\delta S}$-values, calculated for each of the 105 individuals, versus the corresponding $\delta S_{\text{shuf}}$ 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 $\delta S_{\text{shuf}} = \overline{\delta S}$ to visualize that the vast majority of points fall below this line. The non-equality of $\delta S_{\text{shuf}}$ and $\overline{\delta S}$ has been also verified by applying the Wilcoxon paired signed-rank test recommended\[14\] to be

![FIG. 3](image1.png)

**FIG. 3:** The $\sigma/\mu$-value, for each of the 105 individuals, versus the corresponding $\delta S_{\text{shuf}}$-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].

![FIG. 4](image2.png)

**FIG. 4:** (Color) The $\sigma/\mu$-value for RR-, QT- and QRS-intervals of the ten H versus the corresponding $\delta S_{\text{shuf}}$-value (time-window range 3-10 beats). The straight line results from a least squares fit of all the thirty points. For the identity of the individual associated with each point see Ref. [26].
followed for non-Gaussian paired data. The tested null hypothesis is that the means of $\delta S_{shuf}$ and $\delta S$ are the same and is rejected at a level of significance well below 0.01, since the data of Figs. 5(a), (b) and (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

$$
\delta S = (0.76 \pm 0.03)\delta S_{shuf} \quad \delta S = (0.85 \pm 0.02)\delta S_{shuf}, \quad \delta S = (0.94 \pm 0.02)\delta S_{shuf}
$$

for the Figs. 5(a), 5(b), 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 $\delta S$ and $\delta S_{shuf}$ errors which are drastically smaller than those required to eventually justify a compatibility of the expression $\delta S = (0.76 \pm 0.03)\delta S_{shuf}$, found from Fig. 5(a), with a straight line of slope equal to unity, i.e., $\delta S = \delta S_{shuf}$.

The difference between $\delta S$ and $\delta S_{shuf}$ in ECG could be understood in the context that the former depends on the sequential order (of beats), as mentioned in Section I, while the latter does not. Since short- (and long-) range correlations is 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 the 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 investigated in detail.

Finally, we further clarify the aforementioned point that the equality $\delta S = \delta S_{shuf}$ does not necessarily reflect Markovianity. In Fig. 6, we plot, for the QT-intervals, $\delta S_{shuf}$ versus $\delta S$ (for time-window range 3-10 beats) for SD and H. We see that there are several individuals (mainly SD, see also next section) of which their points lie practically (i.e., within the error margins) on the straight line $\delta S = \delta S_{shuf}$. If we plot their $\delta S$- (or $\delta S_{shuf}$-) values versus the time-window (in a similar fashion as 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

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

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

V. THE USE OF $\frac{\delta S_{shuf}}{\delta S}$ TO DISTINGUISH ECG OF HEALTHY HUMANS FROM THE 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 $\frac{\delta S_{shuf}}{\delta S}$. We calculate this ratio, for each type of interval, at two ranges: (i) a short (s) range 3-4 beats (cf. consider that the smallest number allowed for the natural time-domain analysis is 3 beats) and (ii) a longer (L) range 50-70 beats. For the sake of convenience, we define $\nu = \frac{\delta S_{shuf}}{\delta S}$, and hence the following ratios are investigated: $\nu_s(\tau)$ and $\nu_L(\tau)$, where $\tau$ denotes the type of interval (i.e., $\tau=RR$, 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 $\min_{H}[\nu_s(\tau)]$ and maxima $\max_{H}[\nu_s(\tau)]$ (where $\kappa$ 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 5 SD out of 24 violate the H-limits; however, in all SD, their $\delta S$-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 $\nu_s(RR)$, $\nu_L(RR)$, $\nu_s(QRS)$ and $\nu_L(QRS)$. This is important from 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] and [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 $\nu_s(RR)$ and $\nu_L(RR)$, the vast majority of SD (22 out of 24 cases) can be distinguished from H (only two SD, i.e., sel30 and sel47, obey the corresponding H-limits). Specifically, concerning $\nu_s(RR)$, 15 SD have values smaller than $H_{min} = 1.18$, while only one SD (i.e., sel43) has a value exceeding $H_{max} = 2.25$; as for $\nu_L(RR)$, 18 SD exceed $H_{max} = 0.77$, while only 2 SD (i.e., sel34 and sel42) have values smaller than $H_{min} = 0.44$.

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 $\nu_s(RR)$-values smaller than $H_{min} (= 1.18)$ and $\nu_L(RR)$-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 $\delta S_{shuf}/\delta S = 1$ (and hence $\nu_s = 1$ and $\nu_L = 1$), is compatible with the fact that in all H both $\nu_s(RR)$ and $\nu_L(RR)$ 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 $\nu_s(RR)$ and $\nu_L(RR)$ become closer to the Markovian value (i.e., unity) compared to H: thus, in SD, $\nu_s(RR)$ naturally becomes smaller than the value 1.18 (the corresponding $H_{min}$-limit) and $\nu_L(RR)$ larger than 0.77 (the corresponding $H_{max}$-limit).

We now focus on the following important property of H: although both $\nu_s(RR)$ and $\nu_L(RR)$ differ from unity, as mentioned, they systematically behave differently, i.e., $\nu_s(RR) > 1$ while $\nu_L(RR) < 1$. The exact origin of the latter difference has not yet been identified with certainty, but the following comments might be relevant: First, in the frame of the frequency-domain characteristics of heart rate variability (e.g., [20]), we may state that $\nu_s(RR)$ and $\nu_L(RR)$ 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 on 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 $\nu_s(RR) > \nu_L(RR)$). 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 $\delta S_{shuf}$-values larger than $\delta S$, i.e., a $\nu_s(RR)$-value larger than unity (cf. 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 towards clarifying the valid-
be attempted if we consider that: (i) a small
quantity in particular the reason why for the QT intervals the
\( \delta S \) is larger for the SD than for the H, could
\[ \delta S_{shuf}/\delta S \] in H for each range

| Individual | 3-4 beats (\( \nu_s \)) | 50-70 beats (\( \nu_L \)) |
|------------|------------------------|------------------------|
|           | 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 | 0.82\(^a\) | 0.99 |
| sel34      | 2.13 | 1.29\(^b\) | 1.11 | 0.42\(^a\) | 0.78\(^a\) | 0.67 |
| sel35      | 1.00\(^a\) | 1.00 | 0.96\(^a\) | 1.01\(^b\) | 0.95 | 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\(^b\) | 1.02 | 1.06 | 2.93\(^b\) | 0.92 | 0.90 |
| sel40      | 1.01\(^b\) | 1.00\(^a\) | 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\(^a\) | 1.32\(^b\) |
| sel45      | 0.98\(^a\) | 1.24\(^b\) | 1.29 | 0.98 | 0.86\(^a\) | 0.79 |
| sel46      | 1.03\(^a\) | 1.03 | 1.03 | 1.00\(^b\) | 0.84\(^b\) | 1.01 |
| sel47      | 1.56 | 0.97\(^a\) | 0.96\(^a\) | 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\(^b\) | 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 \(\delta S_{shuf}/\delta S\) in H for each range
\(^b\)These values are larger than the maximum (\(H_{max}\)) value of \(\delta S_{shuf}/\delta S\) in H for each range

ity 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., \(\delta S_{shuf} < \delta S\), then holds. The latter finding must be in-
herently connected to the nature itself of the long range
correlations. The existence of the latter is pointed out
from the fact that (in this range also) the RR-intervals re-
sult in
\[ \delta S \text{-values (when sweeping through various parts of the ECG)} \]
and hence a small \(\delta S\)-value is envisaged. By the
short-long-short sequences of the QT-intervals, the
corresponding \(S\)-values will be much different (compared
\(H\)) to the same token, in an SD-ECG, we expect that, in view of
the time in which the heart in each beat “recovers” -
electrically speaking- from the previous excitation) ex-
hibits 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 \(\delta S\)-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 \(\delta S\)-value (cf. in the same
frame we may also understand why the \(\sigma/\mu\) values -and
hence \(\delta S_{shuf}\), see Eq. (1)- are larger in SD than those in
\(H\), as shown in Fig.6). The distinction between SD and
\(H\) could be also understood in the context of dy-
namic 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 $\delta S$; such intense fluctuations are not expected, of course, for H.

VI. CONCLUSIONS

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

1. 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 $\delta S_{shuf} = \delta S$, but the reverse is not always valid; it may happen that $\delta S_{shuf}/\delta S = 1$, although $\delta S$- (and $\delta S_{shuf}$-) value drastically differ from that of the Markovian (this is the case of ECG).

2. differentiates the ECG of healthy humans (H) from those suffered from sudden cardiac death (SD). More precisely, in SD, the $\delta S_{shuf}/\delta S$ 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 $\delta S$ -and $\delta S_{shuf}$- 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 $\delta S_{shuf}$ in ECG, it was shown to be a measure of $\sigma/\mu$.

APPENDIX: INTERRELATION BETWEEN $\delta S_{shuf}$ AND $\sigma/\mu$ IN THE CASE OF IID

If we consider a time-series $Q_k$, where $Q_k \geq 0, k = 1, 2, \ldots, N$, we obtain the quantities $p_k = Q_k/\sum_{i=1}^{N} Q_i$, which satisfy the necessary conditions\[23\]: $p_k \geq 0, \sum_{k=1}^{N} p_k = 1$ to be considered as point probabilities. We then define\[1-3\] the moments of the natural time $\chi_k = k/N$ as $\langle \chi^q \rangle = \sum_{k=1}^{N} (k/N)^q p_k$ and the entropy $S \equiv \langle \chi \ln \chi \rangle - (\chi) \ln(\chi)$, where $\langle \chi \ln \chi \rangle = \sum_{k=1}^{N} \langle k/N \rangle \ln(k/N)p_k$. 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 $E(p_k) = E(Q_k/\sum_{i=1}^{N} Q_i)$ of $p_k$ equals $1/N$:

$$E(p_k) = \frac{1}{N}. \quad (A.1)$$

Equation (A.1) results from the fact that, since $Q_k$ are iid, we have: $E[\sum_{k=1}^{N} Q_k/\sum_{i=1}^{N} Q_i] = 1 = NE(p_k)$. For the purpose of our calculations the relation between the variance of $p_k$, $\text{Var}(p_k) = E[(p_k - 1/N)^2]$, and the variance of $Q_k$ and $p_k$, $\text{Cov}(p_k, p_l) = E[(p_k - 1/N)(p_l - 1/N)]$, is of central importance. Using the constraint $\sum_{k=1}^{N} p_k = 1$, leading to $p_k - 1/N = \sum_{l \neq k} (1/N - p_l)$, and the fact that $Q_k$ are iid, we obtain

$$E[(p_k - 1/N)^2] = E[(p_k - 1/N)\sum_{l \neq k} (1/N - p_l)] = -(N-1)E[(p_k - 1/N)(p_l - 1/N)].$$

Thus, we get

$$\text{Cov}(p_k, p_l) = -\frac{\text{Var}(p_k)}{N-1}. \quad (A.2)$$

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

$$\text{Var}(p_k) = \frac{1}{N^2}E\left[\frac{NQ_k}{\sum_{i=1}^{N} Q_i} - 1\right]^2, \quad (A.3)$$

where the quantity $E[(NQ_k/\sum_{i=1}^{N} Q_i - 1)^2]$ is asymptotically $N$-independent. The latter arises as follows: If $E(Q_k) = \mu$ and $\text{Var}(Q_k) = \sigma^2(<\infty)$, as a result of the central limit theorem\[24\], we have $E(\sum_{k=1}^{N} Q_k/N) = \mu$ and $\text{Var}(\sum_{k=1}^{N} Q_k/N) = \sigma^2/N$. The latter two equations, for large enough $N$ imply that $E[(NQ_k/\sum_{i=1}^{N} Q_i - 1)^2] \approx E[(Q_k/\mu - 1)^2] = \sigma^2/\mu^2$. Thus, Eq.(A.3) becomes

$$\text{Var}(p_k) = \frac{\sigma^2}{N^2\mu^2}. \quad (A.4)$$

We now turn to the statistical properties of $\langle \chi^q \rangle$. Using Eq.(A.1), we have

$$E(\langle \chi^q \rangle) = \sum_{k=1}^{N} \left(\frac{k}{N}\right)^q \frac{1}{N}, \quad (A.5)$$

which, since\[25\] $\sum_{k=1}^{N} k^q = N^{q+1}/(q + 1) + N^q/2 + o(N^q)$, reveals that $E(\langle \chi^q \rangle)$ is again asymptotically $N$-independent because it approaches the value $1/(q + 1)$ with a “small” $1/(2N)$ correction. The variance $\text{Var}(\langle \chi^q \rangle) = (\delta(\langle \chi^q \rangle))^2$ after expanding the square and using Eqs.(A.2) and (A.4), becomes:

$$\text{Var}(\langle \chi^q \rangle) = \sum_{k=1}^{N} \left(\frac{k}{N}\right)^{2q} \frac{\sigma^2}{N^2\mu^2} - \frac{\sigma^2}{(N-1)N^2\mu^2} \sum_{k=1}^{N} \left(\frac{k}{N}\right)^q \sum_{l=1, l\neq k}^{N} \left(\frac{l}{N}\right)^q, \quad (A.7)$$

which, using Eq.(A.5), finally leads to:

$$\text{Var}(\langle \chi^q \rangle) = \frac{\sigma^2}{(N-1)\mu^2} E[\langle \chi^{2q} \rangle] - E^2[\langle \chi^q \rangle]. \quad (A.8)$$

The proof of Eq.(A.8) can be generalized for all linear functionals of $p_k$ of the form $\langle f(\chi) \rangle = \sum_{k=1}^{N} f(k/N)p_k$ and yields:

$$\text{Var}[\langle f(\chi) \rangle] = \frac{\sigma^2}{(N-1)\mu^2} E[\langle f(\chi)^2 \rangle] - E^2[\langle f(\chi) \rangle]. \quad (A.9)$$
In Fig. (7), we compare the theoretical result of Eq. (A.8) with synthetic (Gaussian) data which have values of \( \mu, \sigma \) and size (\( \approx 1000 \)) similar to those in ECG. Note that when one uses the estimator \((\delta X)^2 = \sum (X - \overline{X})^2 / N\), instead of the unbiased estimator \((\delta X)^2 = \sum (X - \overline{X})^2 / (N - 1)\), in order to find the sample variance, \( N \) should replace \( N - 1 \) in Eq. (A.8).

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

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

(A.10)

can be evaluated as follows: we add and subtract the term \( \sum_{k=1}^{N} \frac{k}{N} p_k \ln \left[ \sum_{l=1}^{N} \left( \frac{l}{N} \right) \right] \), and then expand the resulting term \( \ln [1 + \sum_{l=1}^{N} \left( p_l - 1/N \right) / \sum_{l=1}^{N} \left( l/N \right) ] \) to first order in \( (p_l - 1/N) \); finally, using Eq. (A.8), we obtain

\[
E(S) = \frac{N}{\sigma^2} \left[ \sum_{k=1}^{N} k^2 / N^3 - \left( \sum_{k=1}^{N} k/N^2 \right)^2 \right]
\]  

\[= \frac{\sigma^2}{(N-1)\mu^2} \sum_{l=1}^{N} l/N^2, \]  

(A.11)

This equation reveals that \( E(S) \) depends slightly on \( \sigma / \mu \); upon increasing \( N \) the last term of Eq. (A.11) decays as \( 1/N \) (cf. the sums in the numerator and the denominator are of the form \( E((\chi^q)) \), for \( q = 1 \) and \( 2 \), and asymptotically lead to a constant \( 1/(q+1) \), see the relevant discussion after Eq. (A.5)).

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

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

(A.12)

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

(A.13)

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

\[
E \left\{ m[p_k - 1/N] \right\} = E \left\{ L[p_k - 1/N, \xi] \right\} = 0. \]  

(A.14)

Using Eqs. (A.12) and (A.13) the entropy can be written, in compact form, as follows:

\[
S = L[p_k, m[p_k]], \]  

(A.15)

and its expectation value is written as

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

(A.16)

where \( \kappa_{1,u} = E((\chi^2)) - E^2((\chi)) \).

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

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

(A.16)

where \( \kappa_{1,u} = E((\chi^2)) - E^2((\chi)) \).

The variance of the entropy \( \text{Var}(S) = (\delta S)^2 \) can then be found by adding and subtracting the terms \( m[p_k] \ln m[K] \) and \( m[p_k - 1/N] \) and using the expansion \( m[p_k] \ln \frac{m[p_k]}{m[K]} = m[p_k]m[p_k - 1/N] / m[K] \); this gives:
\[ \text{Var}(S) = E \left\{ \left( L[p_k, 1] - m[p_k] \ln m[p_k] - L[K, 1] + m[K] \ln m[K] + \frac{\sigma^2_{\kappa_{1,u}}}{(N-1)\mu^2 m[K]} \right)^2 \right\}, \]

\[ = E \left\{ \left( L[p_k - \frac{1}{N}, 1] - m[p_k] \ln \frac{m[p_k]}{m[K]} + m[1] \ln m[K] + \frac{\sigma^2_{\kappa_{1,u}}}{(N-1)\mu^2 m[K]} \right)^2 \right\}, \]

\[ = E \left\{ \left( L \left[ p_k - \frac{1}{N}, m[K] \right] - m[p_k] m[p_k - \frac{1}{N}] + \frac{\sigma^2_{\kappa_{1,u}}}{(N-1)\mu^2 m[K]} \right)^2 \right\}, \]

\[ = E \left\{ \left( L \left[ p_k - \frac{1}{N}, m[K] \right] - m[p_k - \frac{1}{N}] - m^2 [p_k - \frac{1}{N}] + \frac{\sigma^2_{\kappa_{1,u}}}{(N-1)\mu^2 m[K]} \right)^2 \right\}, \]

\[ = E \left\{ \left( L \left[ p_k - \frac{1}{N}, m[K] e \right] - \frac{m^2 [p_k - \frac{1}{N}]}{m[K]} + \frac{\sigma^2_{\kappa_{1,u}}}{(N-1)\mu^2 m[K]} \right)^2 \right\}. \] (A.17)

Expanding the square in Eq.(A.17), and using Eq.(A.14), we find

\[ \text{Var}(S) = E \left( L^2 \left[ p_k - \frac{1}{N}, m[K] e \right] + 2L \left[ p_k - \frac{1}{N}, m[K] e \right] \frac{m^2 [p_k - \frac{1}{N}]}{m[K]} \right. \]

\[ \left. + \frac{m^4 [p_k - \frac{1}{N}]}{m^2 K} - \frac{\sigma^4_{\kappa_{1,u}}}{(N-1)^2 \mu^4 m^2[K]} \right). \] (A.18)

If we assume that the distribution of \( Q_k \) is skewnessless, i.e. \( E[(Q_k - \mu)^3] = 0 \), the expectation value of the second term in Eq.(A.18) vanishes, whereas the third and the fourth terms are of order \( 1/N^2 \) and hence negligible with respect to the first term. Thus,

\[ \text{Var}(S) = E \left( L^2 \left[ p_k - \frac{1}{N}, m[K] e \right] \right), \] (A.19)

which can be explicitly written as follows

\[ \text{Var}(S) = E \left\{ \left[ \sum_{k=1}^{N} \frac{k}{N} \ln \left( \frac{k}{m[K] N e} \right) \left( p_k - \frac{1}{N} \right) \right]^2 \right\}. \] (A.20)

The right side of Eq.(A.20) becomes similar to Eq.(A.6), if we replace \( \chi^4 \) by \( \chi \ln(\chi/m[K] e) \); thus after expanding the square and using Eqs.(A.2) and (A.4), we finally obtain

\[ \text{Var}(S) = \frac{\sigma^2}{(N-1)\mu^2} \left[ \sum_{k=1}^{N} \left( \frac{k}{N} \ln \frac{Nk}{e \sum_{k=1}^{N} k} \right)^2 \frac{1}{N} - \left( \sum_{k=1}^{N} \frac{k}{N^2} \ln \frac{Nk}{e \sum_{k=1}^{N} k} \right)^2 \right]. \] (A.21)

A comparison of Eqs.(A.19) and (A.15) reveals the following: in order to find the entropy fluctuation \( \delta S \), one simply has to replace in Eq. (A.15) \( m[p_k] \) with \( m[K] e \) and then directly take its variance according to Eq.(A.9). Equation (A.21) is just Eq.(1) of the main text.

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