Natural entropy fluctuations discriminate similar-looking electric signals emitted from systems of different dynamics

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Complexity measures are introduced that quantify the change of the natural entropy fluctuations at different length scales in time series emitted from systems operating far from equilibrium. They identify impending sudden cardiac death (SD) by analyzing 15 min electrocardiograms, and comparing to those of truly healthy humans (H). These measures seem to be complementary to the ones suggested recently [Phys. Rev. E **70**, 011106 (2004)] and altogether enable the classification of individuals into three categories: H, heart disease patients, and SD. All the SD individuals, who exhibit critical dynamics, result in a common behavior.

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I. INTRODUCTION

The problem of distinguishing electric signals which, although they appear to be similar, are emitted from systems of different dynamics, still attracts a strong interest. Two characteristic cases of major practical importance are as follows. First, seismic electric signals (SES) activities, which are low-frequency ($\leqslant 1$ Hz) signals of dichotomous nature that have been found in Greece [1–3] and Japan [4] to precede earthquakes, may appear to be similar to "artificial" noises (AN), which are electrical disturbances emitted from nearby man-made sources. It has been argued [1,3,5] that SES activities are emitted when the stress reaches a *critical* value in the EQ focal area. Second, sudden cardiac death (SD), which is the primary cause of mortality in the industrialized world [6], may occur even if the electrocardiogram (ECG) looks similar to that of truly healthy (H) humans. Sudden cardiac arrest may also be considered as a dynamic phase transition (critical phenomenon) [7,8].

Both cases have been treated in Ref. [8], but here we only focus on the second one. The time series will be analyzed in the natural time domain. The natural time χ is introduced [5,9] by ascribing to the mth pulse of an electric signal consisting of N pulses the value $\chi_m = m/N$, and the analysis is made in terms of the couple (χ_m, Q_m), where Q_m denotes the duration of the mth pulse. The entropy S in the natural time domain [9,10] is defined as $S = \langle \chi \ln \chi \rangle - \langle \chi \rangle \ln \langle \chi \rangle$, where $\langle \chi \ln \chi \rangle = \Sigma_{k=1}^{N} p_k \chi_k \ln \chi_k$, $\langle \chi \rangle = \Sigma_{k=1}^{N} p_k \chi_k$, and $p_k = Q_k / \Sigma_{n=1}^{N} Q_n$. It is *dynamic* entropy depending on the *sequential* order of pulses [8]. Here we calculate the value of S for a number of consecutive pulses and study how it varies within the recording (i.e., using a time window of certain length N_w sliding, each time by one pulse, through the whole time series). Thus, for a window of length N_w, when starting from the m_0th pulse, we have $S(m_0, N_w) = \langle \chi \ln \chi \rangle_w - \langle \chi \rangle_w \ln \langle \chi \rangle_w$, where $\langle \chi \ln \chi \rangle_w = \Sigma_{k=1}^{N_w} p_{k,w} \chi_{k,w} \ln \chi_{k,w}$, $\langle \chi \rangle_w = \Sigma_{k=1}^{N_w} p_{k,w} \chi_{k,w}$ with $p_{k,w} = Q_{m_0-1+k} / \Sigma_{n=1}^{N_w} Q_{m_0-1+n}$, and $\chi_{k,w} = k/N_w$. This variation is quantified by the standard deviation $\delta S (= \delta S_{N_w})$ of $\{S(m_0, N_w), m_0 = 1, 2, \ldots, N - N_w\}$. The value of δS may change to a different value δS_{shuf} when repeating the same calculation but after *shuffling* the Q_m randomly. In Ref. [8] we showed that a distinction between SD and H can be achieved when calculating both δS_{shuf} and δS at the *same* (time-window) length N_w and then studying their ratio $\delta S_{shuf} / \delta S$ (which is labeled by ν). Here we show that a similar distinction may be alternatively achieved if we introduce *appropriate* measures that quantify the δS variability upon *changing* the time-window length and, interestingly, their values approach the value of the Markovian case in SD, who exhibit critical dynamics. Furthermore, we show that the measures suggested in this paper exhibit a certain type of complementarity when compared to those discussed in [8].

In ECG, the turning points are traditionally labeled with the letters Q, R, S, T; see Fig. 1(a). [In Fig. 1(b) we show, for example, how the QT interval time-series can be read in natural time.] The RR (beat-to-beat) and QRS intervals (cf. mainly the RR) can be automatically detected [11–14] (which was followed here) more easily than the QT. In spite of this fact, we intentionally study here all these three types of intervals for the following reasons: It has been clinically observed that the QT interval usually exhibits prolonged values before cardiac death (see Ref. [15] and references therein). Interestingly, this clinical observation was found [8] to be consistent with the fact that in all SD, the δS (and δS_{shuf}) values themselves of the QT intervals exceed those of H; see Fig. 2 (the latter distinction between SD and H cannot be attributed to the allocation error of the QT interval, see Sec. VIII of Ref. [16]). Since the latter systematic behavior is not found when studying the RR or the QRS intervals [8], it is interesting to investigate here whether a systematicity occurs when employing the complexity measures suggested in this paper. Actually, we find that the latter measures seem to enable the distinction between SD and H when using the RR and QRS intervals of the original time series. Furthermore, and most interestingly, we pinpoint that, even when solely using the most easily accessible values of the RR intervals, such a distinction seems to be possible if we apply these measures to both the original time series and the one ob-

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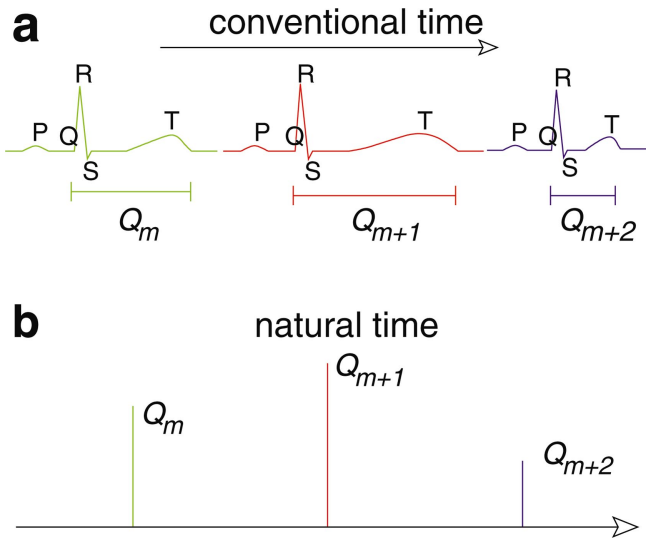

FIG. 1. (Color) (a) Schematic diagram (not in scale) of a three heartbeat excerpt of an ECG in the usual (conventional) time domain. Only the durations Q_m, Q_{m+1}, Q_{m+2} of the QT interval (marked in each single cycle of the ECG corresponding to one heartbeat) are shown. (b) The QT-interval time series of (a) read in natural time; the vertical bars are *equally* spaced, but the length of each bar denotes the duration of the corresponding QT interval marked in (a).

tained after shuffling the Q_m randomly. We use here the QT Database from physiobank [17], which includes 15 min recordings of 10 H and 24 SD (as well as recordings from four groups of heart disease patients, see below). Examples of the

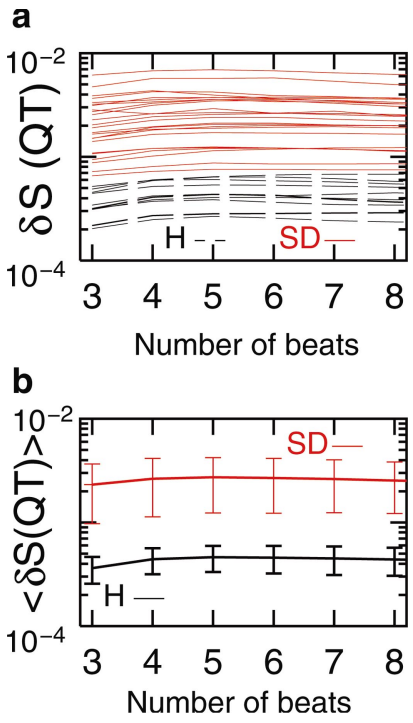

FIG. 2. (Color) (a) The δS(QT) value for each of the 24 SD and 10 H (see Table I) and (b) the average of the δS(QT) values—designated by $\langle \delta S(\mathrm{QT}) \rangle$—along with their standard error deviation for each of the two groups SD and H vs the time-window length.

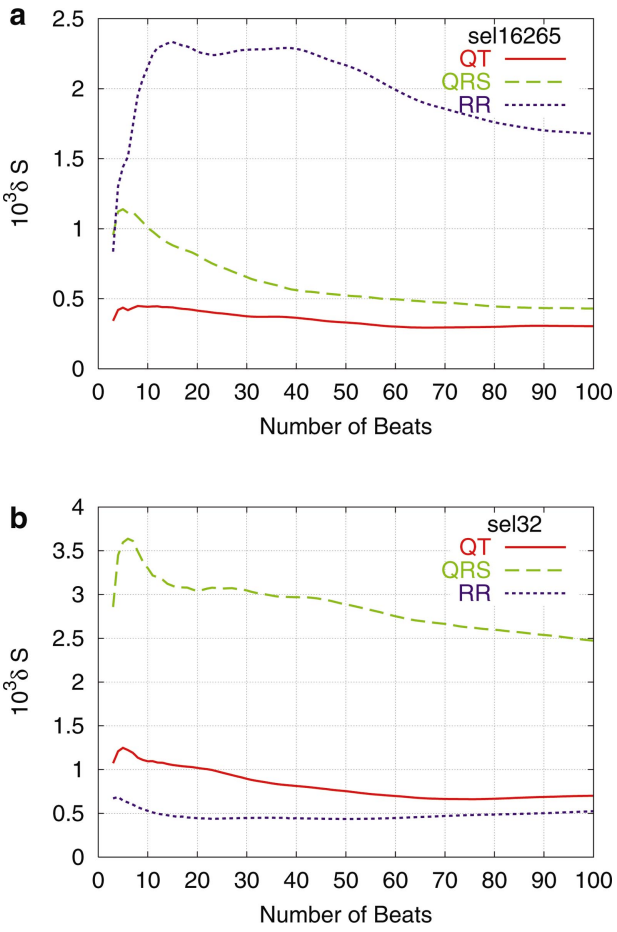

FIG. 3. (Color) The δS value vs the time-window length for one H (a) and one SD (b). Intervals: QT (solid red), QRS (broken green), and RR (dotted blue).

δS values, calculated for the RR, QRS, and QT intervals in the range 3–100 beats, are plotted in Figs. 3(a) and 3(b) for one H and one SD, respectively. As for the symbols, we use the same convention as in Ref. [8], i.e., δS is used only when the calculation is made by a single time window (e.g., five pulses), while the symbol δS stands for the average of the δS values calculated for a sequence of single windows (e.g., three and four pulses). Finally, $\langle \delta S \rangle$ denotes the δS values averaged over a group of individuals, e.g., ten healthy subjects.

Before proceeding, however, it might be useful to recapitulate the main differences of our procedure compared to several other earlier attempts by other groups. The reasons why the concept of entropy should be preferred (compared to other quantities) as discriminating statistics in physiological time series have been explained in detail in Ref. [8]. Furthermore, the advantages of using complexity measures based on *dynamic* entropy (and not on *static* entropy, e.g., Shannon entropy), as, for example, the Kolmogorov-Sinai entropy (KS entropy), have been clarified [8]. Earlier attempts in the ECG analysis have actually used measures related to dynamic entropy. For example, the so-called approximate entropy (AE) [18] or sample entropy (SE) [19] has been introduced and later used by other authors (e.g., see Ref. [20] where AE is applied beyond other measures; see also Ref.

[16]). Also, Costa *et al.* [21] introduced the multiscale entropy (MSE) approach, the algorithm of which is based on AE or SE, calculating the entropy at different scales. The S, which is also a dynamic entropy, as already mentioned, differs essentially from the other ones, because it is defined [9,10] in an entirely different time domain [see Fig. 1(b)]. Moreover, the following has been found: When studying the S values themselves, most SES activities can be clearly distinguished [10] from the majority of AN, because they have S values smaller and larger, respectively, than the value $S_u = 0.0966$ of the "uniform" distribution (as the latter was defined in Refs. [10,22]); on the other hand, when dealing with ECG they all have S values comparable, more or less, to S_u [8], see also [16], thus not allowing a clear distinction among their principal categories (the entropy values themselves have been used in earlier attempts). This is achieved, however, when we quantify the S *fluctuations* [8] and use ratios of "shuffled" and "unshuffled" S fluctuations on fixed time scales [8] or ratios on different time scales that will be introduced here in Sec. II. Thus, in order to discriminate similar-looking electric signals emitted from systems of different dynamics, the following seems to hold: signals that have S values more or less comparable to S_u (which is the case of all ECG) can be better classified by the complexity measures relevant to the fluctuations δS of the entropy; if the S values *markedly* differ from S_u (which is usually—but *not* always—the case of SES and AN), the classification of these signals should be preferably made by the use of the S values themselves.

II. THE NEW COMPLEXITY MEASURES PROPOSED. THE DISTINCTION BETWEEN SD AND H

In classical thermodynamics, the systems are studied close to equilibrium and the relevant quantities have a clear physical meaning. In nonequilibrium systems, however, the meaning of entropy and its treatment should be handled with great caution (e.g., [1]), because there is at present (e.g., see Ref. [23]) no unified statistical mechanical theory underlying these systems. [In transformations between nonequilibrium stationary states, entropy might be a not well defined concept [24]; the connection of the entropy to microscopic dynamics is still a matter of intensive research (e.g., [25] and references therein).] In complex systems operating far from equilibrium (like the case of heart dynamics [26]), long-range correlations play an important role (such correlations are, of course, of prominent importance in equilibrium systems as well, when approaching a critical point, e.g., the "critical" temperature T_c, i.e., $T \to T_c$). Thus, in the latter systems *both* correlations (i.e., short- and long-range), in general, are advisable to be studied carefully and hence appropriate complexity measures should be envisaged. This is, in simple terms, the physics underlying the present paper and stimulated the procedure that followed.

Along these lines, we introduce the ratios $\delta S_i(\mathrm{RR})/\delta S_j(\mathrm{RR})$, $\delta S_i(\mathrm{QRS})/\delta S_j(\mathrm{QRS})$, and $\delta S_i(\mathrm{QT})/\delta S_j(\mathrm{QT})$ for the RR, QRS, and QT intervals, respectively, where i, j denote the time-window length used in the calculation of δS. Assuming that $j<i$, these three ratios provide measures of the δS variability when a scale i changes to a scale j. We select as a common scale (for all RR, QRS, and QT) the *smallest* j value allowed for the natural time-domain analysis, i.e., $j=3$ beats, and for the short range (s) $i=5$, while for the longer range (L) $i=60$ beats. Thus, the following ratios are studied: $\lambda_s(\tau) \equiv \delta S_5(\tau)/\delta S_3(\tau)$ and $\lambda_L(\tau) \equiv \delta S_{60}(\tau)/\delta S_3(\tau)$, where τ denotes the type of interval, i.e., $\tau=$RR, QRS, or QT. We also define the ratios $\rho_i(\tau) = \delta S_i(\mathrm{RR})/\delta S_i(\tau)$, which provide a *relative* measure of the δS values of the RR intervals compared to either QRS or QT (for the *same* number of beats i). Here, we will use for the short range $\rho_s(\tau) \equiv \rho_3(\tau)$ and for the long range $\rho_L(\tau) \equiv \rho_{60}(\tau)$.

The calculated values for the complexity measures λ_κ, ρ_κ (where κ denotes either the short, $\kappa=s$, or the longer, $\kappa=L$, range) are given, for all H and SD, in Table I. The minima $\min_H[\lambda_\kappa(\tau)]$ and maxima $\max_H[\lambda_\kappa(\tau)]$ among the healthy individuals for the RR ($\tau=$RR) and QRS ($\tau=$QRS) intervals are also inserted in this table. We also include the corresponding minima $\min_H[\rho_\kappa(\tau)]$ and maxima $\max_H[\rho_\kappa(\tau)]$ for (the relative δS-variability measure) ρ. For the sake of simplicity, they are labeled H_{min} and H_{max}, respectively (and jointly named H *limits*). The superscripts "a" and "b" show the cases of SD which have smaller and larger values than H_{min} and H_{max}, respectively. In two individuals, i.e., sel41 and sel51, it is uncertain whether their measure λ_s(QRS) violates the value $H_{min}=1.15$.

Table I reveals that *all* SD violate one or more H limits of λ_s(RR), λ_L(RR), ρ_s(QRS), and ρ_L(QRS), and hence can be distinguished from H. In other words, the δS-variability measures of the RR intervals, together with their relative ones with respect to the QRS (i.e., four parameters in total), seem to achieve a distinction between SD and H. Note that λ_κ(RR) *alone* can classify the vast majority of SD. Furthermore, attention is drawn to the point that if we also consider the $\lambda_\kappa(\tau)$ values calculated *not* in the original but in the randomized ("shuffled") sequence of Q_m, we find that *all* SD violate one or more H *limits* of λ_κ(RR) and $\lambda_{\kappa,shuf}$(RR) (see Table VII of Ref. [16]). This allows (using again four parameters in total) the distinction of SD from H by using the RR intervals *only*.

Thus, we found that among the 10 parameters defined in the original time series extracted from each ECG (or 20 parameters, in total, if we also account for the corresponding parameters defined in the series obtained after shuffling the Q_m randomly), *only* four are required for the distinction between SD and H. We clarify that this seems to be extremely difficult to achieve by chance. In order to visualize it, if we assume (for the sake of convenience only) independent and identically distributed (iid) distributions of the parameters for one subject, we find that the probability that *all* four parameters are within the bounds (minima and maxima) set by 10 other subjects (i.e., the healthy ones) is $(1-2/11)^4 \approx 0.448$. Thus, the probability that all 24 additional subjects are classified as SD by pure chance is $(1-0.448)^{24} \approx 6.4\times10^{-7}$, i.e., extremely small. Concerning the validity of this statistical argument, we clarify that it does not remain valid if one just picks four parameters out of the original 20 ones. Only if one decides which parameters one wants to use *before* the calcu-

TABLE I. The variability measures (λ), the relative ones (ρ), and the ratios $\nu \equiv \overline{\delta S}_{shuf}/\overline{\delta S}$ in the short (s) range and in the longer (L) range in H (sel16265 to sel17453) and SD (sel30 to sel17152) along with their $\overline{\delta S}_{3-4}$(QT) values.

	RR		QRS		QT		RR over QRS		RR over QT		3–4 beats (ν_s)[c]			50–70 beats (ν_L)[c]			
Individual	λ_s(RR)	λ_L(RR)	λ_s(QRS)	λ_L(QRS)	λ_s(QT)	λ_L(QT)	ρ_s(QRS)	ρ_L(QRS)	ρ_s(QT)	ρ_L(QT)	RR	QRS	QT	RR	QRS	QT	$\overline{\delta S}_{3-4}(\mathrm{QT}) \times 10^3$
sel16265	1.72	2.38	1.19	0.52	1.27	0.88	0.88	4.01	2.44	6.62	1.87	0.98	1.29	0.48	1.02	0.75	0.38
sel16272	1.69	1.35	1.29	0.61	1.21	0.50	0.18	0.40	0.67	1.79	1.65	0.88	0.94	0.77	1.10	1.07	0.48
sel16273	1.61	2.69	1.16	0.59	1.30	1.11	1.11	5.05	3.17	7.65	2.18	0.99	1.46	0.50	0.88	0.71	0.24
sel16420	1.51	1.74	1.22	0.48	1.37	0.66	0.96	3.46	1.97	5.21	1.60	0.99	1.07	0.53	1.09	0.90	0.36
sel16483	1.43	2.37	1.23	0.49	1.31	0.68	0.25	1.22	0.96	3.37	2.27	0.99	1.17	0.52	1.15	0.92	0.35
sel16539	2.00	1.94	1.26	0.50	1.41	1.08	1.85	7.10	5.57	10.04	1.43	1.07	1.27	0.50	1.08	0.65	0.52
sel16773	1.92	2.61	1.21	0.49	1.31	0.70	0.90	4.84	1.49	5.54	1.85	1.01	0.91	0.44	1.05	0.97	0.55
sel16786	1.71	1.57	1.19	0.51	1.31	0.84	1.16	3.56	3.97	7.43	1.39	1.01	1.19	0.55	1.04	0.77	0.23
sel16795	1.77	0.99	1.24	0.55	1.16	0.56	0.77	1.37	2.87	5.08	1.10	0.98	1.05	0.74	0.95	1.00	0.56
sel17453	1.87	1.67	1.26	0.54	1.22	0.68	1.49	4.59	2.91	7.12	1.46	1.01	1.02	0.57	0.98	0.81	0.34
H_{min}	1.43	0.99	1.16	0.48	1.16	0.50	0.18	0.40	0.67	1.79	1.10	0.88	0.91	0.44	0.88	0.65	0.23
H_{max}	2.00	2.69	1.29	0.61	1.41	1.11	1.85	7.10	5.57	10.04	2.27	1.07	1.46	0.77	1.15	1.07	0.56
sel30	1.11[a]	0.89[a]	1.20	1.05[b]	1.28	0.56	0.51	0.43	1.73	2.73	1.15	1.08[b]	1.13	0.66	0.71[a]	1.10[b]	1.04[b]
sel31	0.96[a]	0.34[a]	1.39[b]	0.89[b]	1.30	0.84	1.10	0.42	0.80	0.32[a]	0.90[a]	1.06	1.15	1.23[b]	0.97	0.63[a]	3.01[b]
sel32	0.96[a]	0.67[a]	1.26	0.96[b]	1.16	0.65	0.23	0.16[a]	0.63[a]	0.64[a]	1.31	1.11[b]	1.13	1.02[b]	0.69[a]	0.90	1.14[b]
sel33	1.14[a]	0.77[a]	0.96[a]	0.52	1.21	0.53	0.79	1.17	2.41	3.50	1.07[a]	1.00	1.08	0.85[b]	0.83[a]	1.00	0.76[b]
sel34	1.87	3.04[b]	1.33[b]	1.22[b]	1.15[a]	0.85	0.40	1.00	1.16	4.12	2.13	1.11[b]	1.12	0.41[a]	0.77[a]	0.67	0.69[b]
sel35	1.12[a]	0.52[a]	1.24	0.66[b]	1.12[a]	0.44[a]	1.72	1.36	0.83	0.99[a]	1.02[a]	0.97	0.97	1.02[b]	1.05	1.07	6.45[b]
sel36	1.31[a]	0.62[a]	1.12[a]	0.51	1.26	0.60	2.35[b]	2.88	1.45	1.52[a]	1.03[a]	1.01	1.08	0.93[b]	0.99	0.89	2.08[b]
sel37	0.92[a]	0.71[a]	1.26	0.87[b]	1.11[a]	0.78	0.71	0.58	1.19	1.07[a]	1.11	1.17[b]	1.07	0.56	0.75[a]	0.64[a]	3.30[b]
sel38	0.91[a]	0.34[a]	1.27	0.65[b]	1.03[a]	0.50	0.65	0.34[a]	0.37[a]	0.25[a]	1.15	1.08	1.12	1.33[b]	0.89	1.03	2.71[b]
sel39	0.81[a]	0.11[a]	1.23	0.72[b]	1.17	0.58	0.80	0.12[a]	1.53	0.28[a]	0.97[a]	0.97	0.99	2.93[b]	0.93	0.89	2.44[b]
sel40	1.66	0.81[a]	1.14[a]	0.55	1.19	0.43[a]	0.12[a]	0.18[a]	0.20[a]	0.38[a]	1.03[a]	1.01	0.93	0.79[b]	0.94	1.30[b]	3.43[b]
sel41	1.14[a]	0.48[a]	1.18	0.70[b]	1.22	0.56	0.21	0.15[a]	0.80	0.68[a]	0.91[a]	1.04	1.06	1.05[b]	0.84[a]	0.96	1.53[b]
sel42	1.10[a]	1.81	1.16	0.51	1.31	1.01	0.95	3.40	1.62	2.89	1.63	1.09[b]	1.26	0.43[a]	1.06	0.66	0.95[b]
sel43	1.69	3.04[b]	1.24	0.77[b]	1.26	0.68	0.06[a]	0.23[a]	0.11	0.48[a]	2.79[b]	1.12[b]	1.08	0.56	0.77[a]	0.89	2.23[b]
sel44	1.18[a]	0.18[a]	1.52[b]	0.43[a]	1.02[a]	0.34[a]	0.59	0.25[a]	1.08	0.58[a]	0.91[a]	0.92	0.90[a]	2.25[b]	1.46[b]	1.33[b]	4.12[b]
sel45	0.92[a]	0.42[a]	1.16	0.73[b]	1.37	0.68	1.46	0.85	1.14	0.71[a]	0.97[a]	1.05	1.11	0.98[b]	0.88	0.79	1.71[b]

TABLE I. (*Continued.*)

	RR		QRS		QT		RR over QRS		RR over QT		3–4 beats $(\nu_s)^c$			50–70 beats $(\nu_L)^c$			
Individual	λ_s(RR)	λ_L(RR)	λ_s(QRS)	λ_L(QRS)	λ_s(QT)	λ_L(QT)	ρ_s(QRS)	ρ_L(QRS)	ρ_s(QT)	ρ_L(QT)	RR	QRS	QT	RR	QRS	QT	$\overline{\delta S}_{3-4}(\mathrm{QT})\times 10^3$
sel46	0.94[a]	0.43[a]	1.05[a]	0.71[b]	1.12[a]	0.55	1.35	0.82	1.59	1.26[a]	1.01[a]	0.99	1.01	0.99[b]	0.85[a]	1.01	3.44[b]
sel47	1.54	2.07	1.19	0.54	1.36	0.57	0.16[a]	0.63	0.14[a]	0.49[a]	1.60	0.97	0.97	0.45	0.96	1.02	2.85[b]
sel48	0.84[a]	0.30[a]	1.23	1.08[b]	1.14[a]	1.00	0.91	0.26[a]	1.36	0.41[a]	0.84[a]	1.24[b]	1.42	1.49[b]	0.68[a]	0.74	1.75[b]
sel49	0.93[a]	0.33[a]	1.17	0.83[b]	1.16	0.50	1.27	0.50	1.08	0.71[a]	0.86[a]	1.15[b]	0.96	1.21[b]	0.71[a]	1.11[b]	3.96[b]
sel50	1.32[a]	0.59[a]	1.28	0.46[a]	1.21	0.32[a]	1.78	2.31	1.21	2.26	1.07[a]	1.00	0.91	0.93[b]	1.20[b]	1.62[b]	5.21[b]
sel51	1.83	0.72[a]	1.14[a]	0.42[a]	1.24	0.66	0.16[a]	0.27[a]	0.30[a]	0.33[a]	1.30	1.04	1.00	1.05[b]	1.24[b]	0.90	1.83[b]
sel52	1.40[a]	0.73	1.32[b]	1.02[b]	1.29	1.01	0.14[a]	0.10[a]	0.42[a]	0.31[a]	1.51	1.13[b]	1.17	1.02[b]	0.73[a]	0.67	1.66[b]
sel17152	1.06[a]	0.93[a]	1.31[b]	0.58	1.13[a]	0.54	0.06[a]	0.10[a]	0.23[a]	0.40[a]	1.68	1.01	1.03	0.91[b]	1.01	0.97	1.15[b]
min	0.81	0.11	0.96	0.42	1.02	0.32	0.06	0.10	0.11	0.25	0.84	0.92	0.90	0.41	0.68	0.63	0.69
max	1.87	3.04	1.52	1.22	1.37	1.01	2.35	3.40	2.41	4.12	2.79	1.24	1.42	2.93	1.46	1.62	6.45

[a]These values are smaller than the H_{min} given in each column.
[b]These values are larger than the H_{max} given in each column.
[c]These values do not fully coincide with those given in Ref. [8] for the reasons discussed in the Appendix.

lation of the values is the argument valid (this is the reason why blind evaluation—defining all methods, parameters, and criteria studying one set of data, and *then* testing the significance using an additonal set of independent data—is considered very important in medical applications and/or publications).

We now attempt a physical interpretation of the present results, the main feature of which focuses on the fact that both ratios λ_s(RR) and λ_L(RR) become smaller, in the vast majority of SD, compared to H. Recall that the δS(RR) values themselves cannot distinguish SD from H, see Fig. 4(a), in contrast to the ratios $\delta S_i(\mathrm{RR})/\delta S_3(\mathrm{RR})$, see Fig. 4(b). Before proceeding, we mention two points. First, for individuals at high risk of sudden death, fractal organization (long-range correlations) breaks down (see Refs. [26,27] and references therein). The breakdown of fractal physiologic complexity is often accompanied by the emergence of *uncorrelated randomness* or *excessive* order (e.g., periodic oscillations appear in the heart rate recordings of "frequency" $\approx 1/\mathrm{min}$, which are associated with Cheyne-Stokes breathing) [26]. Second, if we calculate [8,10] the δS values in a (dichotomous) Markovian ($\mathcal{M}$) time series (exponentially distributed pulses), for a total number of $N=10^3$ pulses (i.e., length comparable to that of the ECG analyzed here), we find that these values (a) lead to $\lambda_s(\mathcal{M})=1.20\pm0.03$ and (b) differ drastically, see Fig. 4(a), from the δS(RR) values themselves of *both* SD and H (thus indicating that they exhibit non-Markovian behavior on the whole; this is consistent with the aspects that bodily rhythms, such as heartbeat, show complex dynamics, e.g., [26,27]). The fact that λ_s(RR) in SD becomes smaller than in H can now be understood as follows: Since H exhibit a high order of complexity, it is expected that (even) their H_{min} value (=1.43) should markedly exceed $\lambda_s(\mathcal{M})$. On the other hand, in SD this high complexity is lost, and hence their λ_s(RR) values naturally approach $\lambda_s(\mathcal{M})$, thus becoming smaller. Interestingly, the SD average value of λ_s(RR) in Table I is 1.19, i.e., it coincides with $\lambda_s(\mathcal{M})$. (Such a coincidence also occurs for the QRS intervals in *both* H and SD, which agrees with the observations [15] mentioned above that the prolonged QT intervals in SD mainly originate from enlarged ST values, while their QRS may remain the *same*.) We now proceed to the interpretation of our results related to the ratio λ_L(RR). In H, it is expected that (in view of the RR long-range correlations [26]) the corresponding values must be appreciably larger than $\lambda_L(\mathcal{M})=0.64\pm0.05$, calculated in the Markovian case [Fig. 4(b)]. We now examine the SD: If in SD "*uncorrelated randomness*" appears, this reflects that their λ_L(RR) values naturally approach $\lambda_L(\mathcal{M})$, thus becoming smaller (compared to H); this actually occurs in the vast majority of SD in Table I. *If* in SD the aforementioned periodicities appear, it is naturally expected to find *large* (see Ref. [16]) δS values when a time window of length around 60 beats or so (i.e., related to the aforementioned "frequency" $\approx 1/\mathrm{min}$) sweeps through the RR time series, thus resulting in δS values even larger than those in H (since in H *no* such periodicities appear). The latter actually occurs in the few cases marked with superscript "b" (i.e., those exceeding H_{max}) in Table I (for additional arguments on the interpretation, see [16]).

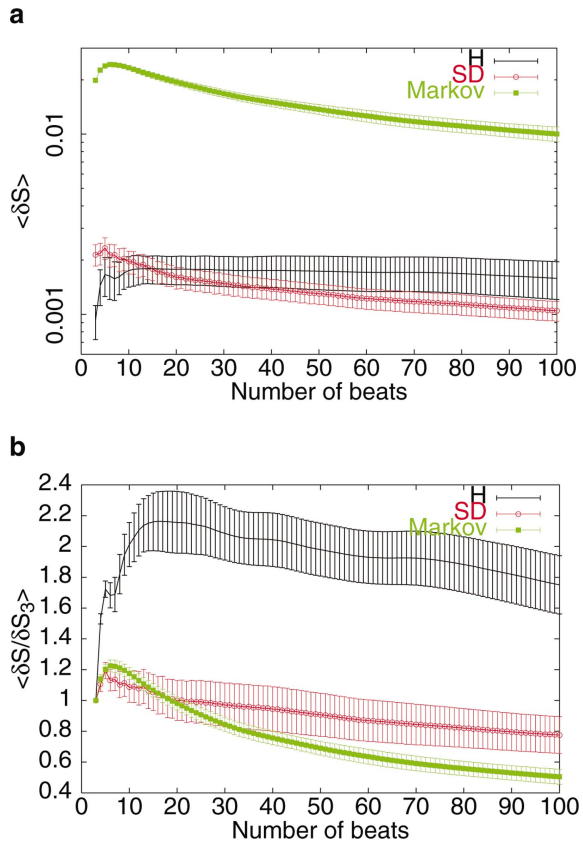

FIG. 4. (Color) The average (denoted by the brackets) values of (a): the $\delta S(\mathrm{RR})$, and (b): $\delta S(\mathrm{RR})/\delta S_3(\mathrm{RR})$ for the SD (solid black) and H (red circles) vs the time-window length; the bars correspond to the standard error of the mean. The results for a Markovian time series are also plotted (green squares), but the bars here denote the standard deviation.

The fact that the overall behavior of the complexity measures introduced in this paper (i.e., clear distinction of SD from H) is more or less similar to that of the measures discussed in Ref. [8] does not mean that the former measures are similar to the latter, because, as we shall explain below, they exhibit a certain type of complementarity in the following sense: if in the frame of the one procedure an ambiguity emerges in the distinction between SD and H, the other procedure gives a clear answer. (Recall that, as mentioned in Sec. I, in Ref. [8] we discussed entropy fluctuations—and ratios of "shuffled" and "unshuffled" entropy fluctuations—on fixed time scales, while here we study entropy fluctuations on different time scales.) This is consistent with the findings of Ashkenazy *et al.* [28] that an approach dealing with ratios on the same time scale and an approach dealing with ratios on different time scales (or corresponding scaling exponents) are somewhat complementary. We now study, as an example, the following two procedures: the one that uses $\delta S(\mathrm{QT})$ [8] and the other which combines the measures λ, ρ. The values of SD and H given in the last column of Table I are classified into two classes: the larger values correspond to SD, and the lower ones correspond to H (see also Figs. 2 and 5). Let us focus on the two lowermost SD values and the uppermost H value. The former two correspond to sel33 and sel34 $[\overline{\delta S}_{3-4}(\mathrm{QT}) = 0.000\,76$ and $0.000\,69$, respectively] and

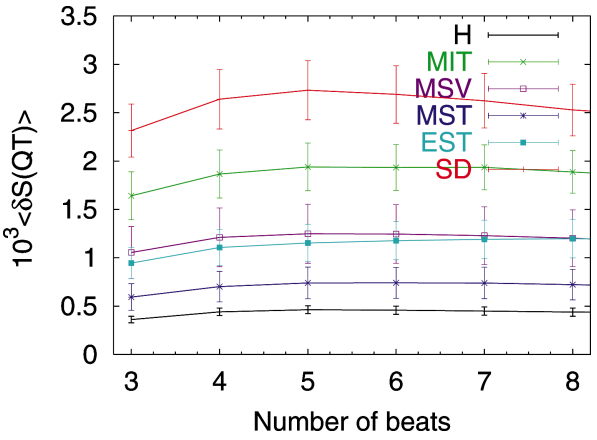

FIG. 5. (Color) The average of the $\delta S(\mathrm{QT})$ values—labeled $\langle \delta S(\mathrm{QT}) \rangle$—for each of the six groups labeled H, MIT, MSV, MST, EST, and SD (see the text) vs the time-window length. The bars denote the standard error of the mean. (The corresponding standard deviations overlap considerably and hence are not shown for the sake of clarity.) The lowermost and the uppermost curve correspond to H and SD, respectively, and hence coincide with the two curves depicted in Fig. 2(b).

the latter one to sel16795 $[\overline{\delta S}_{3-4}(\mathrm{QT}) = 0.000\,56]$. In view of their $\overline{\delta S}_{3-4}(\mathrm{QT})$ values proximity, one may wonder whether these two SD could be confused with H. This ambiguity can be dissolved in light of the other procedure (i.e., λ, ρ) as follows: Table I reveals that sel33 markedly violates both the H_{min} limit for $\lambda_s(\mathrm{QRS})$ as well as H_{min} for $\lambda_s(\mathrm{RR})$ (the latter can be visualized in Fig. 6). As for sel34, the H_{max} limit of $\lambda_L(\mathrm{QRS})$ is strongly violated. We now turn to an alternative example, i.e., sel47, which, by means of the method using the complexity measures λ, ρ (of the RR and QRS intervals), could be confused with H, because a deviation of only around 12% from the H_{min} limit of $\min_H[\rho_s(\mathrm{QRS})] = 0.18$ is

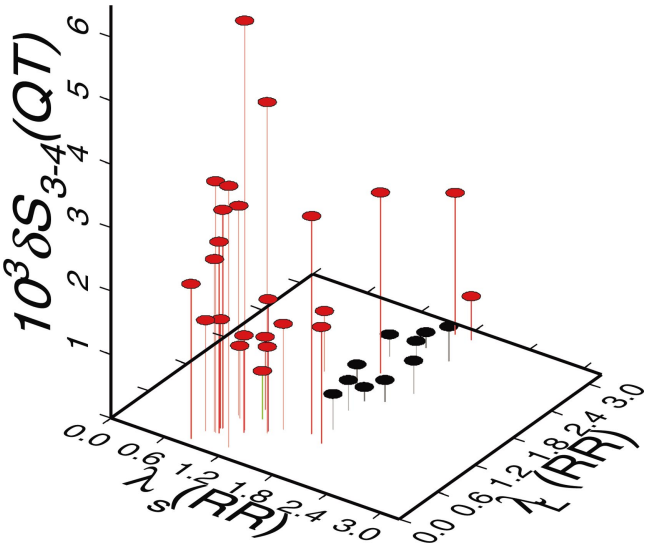

FIG. 6. (Color) The $\overline{\delta S}_{3-4}(\mathrm{QT})$ values along with those of $\lambda_s(\mathrm{RR})$—and $\lambda_L(\mathrm{RR})$—for SD (red) and H (black). The individual sel33, who is discussed as an example in the text, is marked with a green column.

TABLE II. The number of SD and patients that can be distinguished from H when using λ_κ(RR) or $\lambda_{\kappa,shuf}$(RR) alone.

Group	Total number	λ_κ(RR)	$\lambda_{\kappa,shuf}$(RR)	λ_κ(RR) and $\lambda_{\kappa,shuf}$(RR)
SD	24	23	10	24
MIT	15	14	6	14
MSV	13	13	2	13
EST	33	29	8	29
MST	6	5	0	5

noticed. This ambiguity can be dissolved by means of the procedure using δS(QT) as follows: sel47 has $\overline{\delta S}_{3-4}$(QT) $=0.0029$, which exceeds significantly, i.e., by a factor 5, the corresponding value of sel16795, which has the largest $\overline{\delta S}_{3-4}(\mathrm{QT})=0.000\,56$ value among the H.

III. THE PROCEDURE TO DISTINGUISH SD FROM PATIENTS

This section aims at distinguishing SD from patients, where the latter terminology refers to individuals suffering only from heart diseases. The QT Database of physiobank we use here includes the following four groups of patients (a fifth group that consists of four individuals only was disregarded for reasons discussed in Ref. [8]): 15 individuals from the MIT-BIH Arrhythmia Database (labeled hereafter MIT), 13 from the MIT-BIH Supraventricular Arrhythmia Database (MSV), 33 from the European ST-T Database (EST), and 6 from the MIT-BIH ST change Database (MST). The values of λ,ρ,ν, $\overline{\delta S}_{3-4}$(QT), λ_{shuf}, ρ_{shuf}, and $\overline{\delta S}_{3-4,shuf}$(QT) of all these patients are given in Ref. [16].

An inspection of the measures λ,ρ,ν shows three facts. First, all SD and all patients violate one or more *H* limits. Second, *none* of the measures λ,ρ,ν alone, nor a combination of two of them, can effectively differentiate the SD from the patients. Third, if we consider the three measures λ,ρ,ν (i.e., 16 parameters) altogether, we find that 20 SD out of 24 violate some of the limits of both patients and H, thus allowing in principle a distinction of the vast majority of SD from the other individuals. Thus, in summary, the consideration of the quantities (λ,ρ,ν) only does not lead to a distinction between *all* SD and patients. The same conclusion is drawn if we alternatively consider the quantities $(\lambda,\lambda_{shuf},\rho)$ only.

We now turn to the investigation of the δS(QT) values. In Fig. 5, the average $\langle\delta S(\mathrm{QT})\rangle$ value for each group is plotted versus the time-window length. It is intriguing that the results of the four groups (MIT,MSV,MST,EST) of patients are located between H (the lowermost curve) and SD (the uppermost curve). We emphasize, however, that if we plot the curves for each one of the 101 individuals [in a way similar to that of Fig. 2(a)], we find that there are some patients whose results overlap with either SD or H. Let us consider only the limiting cases, i.e., the lowermost and the uppermost curve, to be called hereafter $\delta S(\mathrm{QT})_{min}$ and $\delta S(\mathrm{QT})_{max}$, respectively, obtained in each groups of patients. In order to distinguish SD from patients, we must appropriately discriminate the overlap which refers to those patients that lie above the uppermost δS(QT) curve of H; the latter curve from now on will be called $\delta S(\mathrm{QT})_{max,H}$. Thus, the limits of the patients we are currently interested in do not extend from $\delta S(\mathrm{QT})_{min}$ to $\delta S(\mathrm{QT})_{max}$, since they must exceed $\delta S(\mathrm{QT})_{max,H}$, i.e.,

$$\delta S(\mathrm{QT}) > \delta S(\mathrm{QT})_{\mathrm{max},H}. \tag{1}$$

The curve which corresponds to the one of the patients that has δS(QT) lying just above the $\delta S(\mathrm{QT})_{max,H}$ corresponds to a value which will be labeled hereafter $\delta S(\mathrm{QT})_{min'}$. Thus, if we apply the condition

$$\delta S(\mathrm{QT})_{min'} \leqslant \delta S(\mathrm{QT}) \leqslant \delta S(\mathrm{QT})_{max} \tag{2}$$

to each group of patients, we are left only with those patients that actually overlap with SD.

We now recall that, as mentioned above, the measures λ,ρ,ν altogether, which are in fact ratios of δS values, enable the discrimination of the vast majority of SD from all the others (i.e., patients and H), while the δS(QT) values themselves efficiently distinguish [8] all SD from H. This motivates us to investigate whether a proper combination of these two facts can serve our purpose, which refers to the identification of all SD among the other individuals (patients and H). Thus, we now compare the quantities $\lambda,\rho,\nu,\delta S$(QT) altogether, of each SD, to the corresponding parameters of only those among the patients that happen to have δS(QT) values exceeding the corresponding values of H, i.e., obey the condition (1), or preferably the more accurate condition (2). Such a comparison reveals that some of the 17 parameters of $\lambda,\rho,\nu,\delta S$(QT), in all SD, lie outside the limits of these patients (the same happens, of course, if we compare each SD to the limits of H). These results point to the conclusion that all 24 SD are distinguished from the patients (and H). The same conclusion is drawn if we consider instead the 17 parameters $\lambda,\lambda_{shuf},\rho,\delta S$(QT). We emphasize, however, that the study of the estimation errors (see the Appendix) reveals that the confidence level for the distinction of all SD from the patients becomes appreciably larger if we combine all the measures $\lambda,\lambda_{shuf},\rho,\rho_{shuf},\nu$ (of all intervals) with the condition (2) applied to both δS(QT) and δS_{shuf}(QT) (i.e., in reality, we then consider the limits of those patients for whom *both* δS(QT) and δS_{shuf}(QT) values are larger than those in H, as shown in Fig. 6 of Ref. [8]).

We finally comment on three points. First, once the identification of SD has been completed, the distinction between patients and H can be made by identifying as patients the individuals for whom one or more of the aforementioned parameters violate the *H* limits. Second, since it is known that heart rate variability depends strongly on age, it is highly recommended that when comparing values of the aforementioned complexity measures, the corresponding limits should be taken from subjects (patients, H) of comparable age. Third, we now focus on the importance of the sequential order of Q_m on the aforementioned complexity measures. We prefer to deal with the results related to the RR intervals since it is known that the healthy heart beats irregularly and that the intervals between beats (i.e., the RR intervals) fluc-

TABLE III. The confidence levels to distinguish SD from either H or patients when considering the estimation errors ϵ_m discussed in the Appendix and given in Table VIII of Ref. [16].

Method employed				Confidence levels to distinguish SD						
				Using the limits from the data analyzed			Using broader limits[c]			
Aim	Measures	Type of intervals	No. of parameters	All SD %	All but one SD %	All but two SD[d] %	All SD %	All but one SD %	All but two SD %	All but five SD[d] %
Distinction of SD from H	λ, ρ	RR, QRS, QT	10	>99	>99	>99	88	99	>99	>99
	λ, ρ	RR, QRS	4	63	95	>99	8	43	90	>99
	λ, λ_{shuf}	RR	4	49	90	99	1	11	36	97
	ν	RR,QRS	4	32	74	96	<0.5	1	8	60
	$\delta S_{3-4}(\mathrm{QT})$	QT	1	59	93	>99	11	39	77	>99
	λ, ρ, λ_{sh}, ρ_{sh}, ν, $\delta S_{3-4}(\mathrm{QT})$, $\delta S_{sh,3-4}(\mathrm{QT})$	RR, QRS, QT	28	>99	>99	>99	>99	>99	>99	>99
Distinction of SD from patients	λ, ρ, ν, $\delta S_{3-4}(\mathrm{QT})$[a]	RR, QRS, QT	17	51	83	95	<0.1	<0.1	<0.1	1
	λ, ρ, λ_{sh}, $\delta S_{3-4}(\mathrm{QT})$[a]	RR, QRS, QT	17	62	91	98	<0.1	<0.1	<0.1	1
	λ, ρ, λ_{sh}, ρ_{sh}, ν, $\delta S_{3-4}(\mathrm{QT})$, $\delta S_{sh,3-4}(\mathrm{QT})$[b]	RR, QRS, QT	28	95	>99	>99	16	41	68	98

[a]Considering the limits of those patients that have $\delta S_{3-4}(\mathrm{QT})$ larger than those in H.
[b]Considering the limits of those patients that have *both* $\delta S_{3-4}(\mathrm{QT})$ and $\delta S_{sh,3-4}(\mathrm{QT})$ larger than those in H.
[c]By amounts ϵ_m given in Table VIII of Ref. [16].
[d]When stating, e.g., "All but one," it means when allowing, *at the most*, one SD—out of 24—to be misinterpreted as being H or patient, respectively.

tuate widely, following complicated patterns [29]. Let us investigate, for example, the possibility of using λ_κ(RR) alone to distinguish the SD as well as the four groups of patients from H, i.e., examine whether the λ_κ(RR) values of each individual violate one (at least) of the relevant *H* limits. The results show (see Table II) that the vast majority of SD and of each group of patients is well distinguished from H by means of λ_κ(RR). The situation drastically changes, however, if we use, instead of λ_κ(RR), the $\lambda_{\kappa,shuf}$ values (see the Tables V to VII in [16]): only the minority of SD and of each group of patients can be differentiated from H. Since the calculation of the λ_κ(RR) values takes into account the sequential order of Q_m, while the $\lambda_{\kappa,shuf}$(RR) values do not, this points to the following conclusion: It is the sequential order of beats that inherently contains the primary information which enables the distinction between the SD and patients, on the one hand, and the H, on the other. This might explain why procedures based on the entropy in natural time (which is dynamic entropy, affected by the sequential order [7,8], see Sec. I)—and hence they consider the complexity measures mentioned in the preceding sections—can achieve such a distinction, while a static entropy (e.g., Shannon entropy, see Ref. [8]) cannot.

IV. CONCLUSIONS

First, in SD, the δS values depend on the length scale in a way significantly different from that in H. Hence these two groups of humans can be well distinguished. Second, the SD, who exhibit critical dynamics, have λ values (being, in fact, ratios of δS values, as mentioned above) which approach those of the Markovian case. This should *not* be misinterpreted as showing that the corresponding time series are of Markovian nature, because the δS values themselves are approximately one order of magnitude smaller than those of the (dichotomous) Markovian time series [see Fig. 4(a) and Ref. [8]]. Third, the quantities λ, λ_{shuf}, ρ, ρ_{shuf}, ν, δS(QT), and δS_{shuf}(QT) *altogether* seem to enable the classification of individuals into the three categories: H, patients, and SD.

APPENDIX: THE INFLUENCE OF THE ESTIMATION ERRORS ON THE PROCEDURES FOR THE DISTINCTION OF SD

Beyond the error introduced by the use of an automatic threshold detector for the allocation of the corresponding intervals (cf. this is largest for the QT and smallest for the RR intervals), the following two sources of errors must be considered [7,8]: First, an estimation error emerges when analyzing—instead of the original time series of length $l \approx 10^3$—smaller lengths l', which, however, still significantly exceed the time-window lengths used, for example $l' \approx 2 \times 10^2$ (the errors associated with the measures in the short range, *s*, are smaller from those corresponding to the longer range, *L*, because for the latter range the l/l' values—due to the restricted length of the records available—are small, thus not allowing more reliable statistics). Second, a source of (statistical) error in the results emerges when considering the ratio(s) $\delta S_{shuf}/\delta S$ (i.e., when dealing with ν and λ_{shuf}) instead of δS itself. While δS may be considered to have a *unique* value for a (given) original Q_m time series, the value of δS_{shuf} depends on the randomly shuffled Q_m series each time selected (cf. such differences are well known [30] when dealing with randomized series of *finite* length). This is why the ν values given in Ref. [8] for SD and H do not fully coincide with those tabulated in the present paper. To account roughly for the extent of this statistical error, we averaged here the δS_{shuf} values calculated over a number (e.g., 20) of randomly shuffled Q_m series generated from the *same* original series and then the corresponding standard deviation was estimated.

The final results on the above sources could be summarized as follows: The (percentage) estimation error was found to be around 10% (cf. this is an *average* value) for the complexity measures $\lambda, \lambda_{shuf}, \rho, \rho_{shuf}, \nu$ associated with the RR and QRS intervals. Furthermore, since the error in the δS(QT) may reach 20%, the estimation error in those of the complexity measures that involve δS(QT) may be as high as $\approx$30%. Upon considering such error levels, hereafter called "plausible estimation errors" ϵ_p, a study of each of the methods for the distinction of SD was made. The study was repeated by assuming larger (percentage) estimation errors, hereafter labeled "modified estimation errors" ϵ_m, calculated from

$$\epsilon_m = \epsilon_p \left(1 + \frac{H_{max} - H_{min}}{H_{max} + H_{min}} \right) \tag{A1}$$

for each parameter (see Table VIII in Ref. [16]). Both studies led, more or less, to the same results. The calculation, in each study, was made as follows: Each parameter was assumed to be equal to its value (initially estimated from the original time series available) multiplied by a number randomly selected in the range $1 \pm \epsilon_p$ or $1 \pm \epsilon_m$, respectively, and then each of the methods for the distinction of SD was applied. This application was repeated, for each method, 10^3 times via Monte Carlo and relevant conclusions have been drawn for both studies. The extent to which these conclusions hold was also investigated in the following *extreme* case: the limits of the parameters of H (and patients), which are automatically adjusted for each "random" selection of the values described above, have been assumed to *additionally* relax by (extra) amounts equal to ϵ_p or ϵ_m. (Such a "relaxation" faces the *extreme* possibility that the populations of H and patients treated here are not considered large enough to allow a precise determination of their limits, and hence future increased populations' studies could somehow broaden these limits by *extra* amounts as large as ϵ_p or ϵ_m.)

The following conclusions were finally drawn concerning the distinction between SD and H (see also Table III): Among the four methods suggested (i.e., two in Ref. [8] and two in Sec. II), the one that uses the measures λ, ρ (associated, however, with *all* three types of intervals, i.e., 10 parameters in total) seems to be robust in the following sense: when assuming the error levels mentioned above, the use of λ, ρ still allows with a confidence level above 99% the distinction of *all* SD from H. (Then a calculation similar to that given in Sec. II concerning the probability that all 24 sub-

jects are classified, by means of 10 parameters, as SD by *pure chance*—based on the limits set by 10 other subjects—results in $[1-(1-2/11)^{10}]^{24} \approx 0.03$, i.e., too small.**)** The confidence level decreases to 63%, 49%, 32%, and 59%, respectively, when using four parameters or one parameter only as follows: First: λ_κ(RR) and ρ_κ(QRS); second: λ_κ(RR) and $\lambda_{\kappa,shuf}$(RR); third: ν_κ(RR) and ν_κ(QRS); fourth: $\overline{\delta S}_{3-4}$(QT). If we investigate the aforementioned extreme case of the additional "relaxation" of the *H limits*, the capability for the distinction of *all* SD still remains with the following results: In the case of using λ, ρ (of all intervals), the confidence level in distinguishing *all* SD is 88%, while it becomes *appreciably higher*, i.e., larger than 99%, if we use the quantities λ, ρ, λ_{shuf}, ρ_{shuf}, ν, $\overline{\delta S}_{3-4}$(QT), $\overline{\delta S}_{3-4,shuf}$(QT) *altogether*. When using, however, four parameters only in the first three combinations mentioned above, the confidence level decreases to 90%, 36%, and 8%, respectively [and to 77% when using $\overline{\delta S}_{3-4}$(QT)], even when allowing two at the most SD—out of 24—to be misinterpreted as being H. As for the corresponding conclusions related to the distinction of SD from the patients, these can be drawn on the basis of the values given in the lower part of Table III.

In summary, the study of the estimation errors reveals that (*if* the limits of the parameters will *not* be broadened by future investigations) we can satisfactorily distinguish the *totality* of SD from H as well as discriminate the totality of SD from patients, upon employing the quantities $\lambda, \lambda_{shuf}, \rho, \rho_{shuf}, \nu, \overline{\delta S}_{3-4}$(QT), $\overline{\delta S}_{3-4,shuf}$(QT) *altogether*, i.e., the sixth and the last method, respectively, in Table III. These quantities also allow the distinction of the *totality* of SD from H (as well as distinguishing the *vast majority* of SD from the patients), *even if* their limits will be eventually broadened (by ϵ_m).

The following remark should be added concerning the number of parameters required to achieve the desired distinction: In reality, only twelve *independent* quantities [i.e., the six $\delta S_\kappa(\tau)$ and the six $\delta S_{\kappa,shuf}(\tau)$, where $\kappa = \mathrm{s}, \mathrm{L}$ and $\tau = \mathrm{RR}, \mathrm{QRS}, \mathrm{QT}$] are extracted from the experimental data. Thus, for example, beyond $\overline{\delta S}_{3-4}$(QT) *or* $\overline{\delta S}_{3-4,shuf}$(QT), eleven additional parameters (out of 26) of the ratios, $\lambda, \lambda_{shuf}, \rho, \rho_{shuf}, \nu$, are in principle required to be used for the distinction. These twelve quantities, however, should *not* be fortuitously selected, but the following points must be carefully considered: (i) priority should be given to the eight parameters associated with λ values and λ_{shuf} (or ν) values of RR and QRS, (ii) using, at least, one ρ parameter [involving $\overline{\delta S}_{3-4}$(QT) or $\overline{\delta S}_{3-4,shuf}$(QT)), and (iii) examining whether the totality of the parameters used can actually reproduce the aforementioned twelve δS values determined directly from the data. However, in order to avoid the difficulty arising from the completeness (or not) of the aforementioned selection, at the present stage (i.e., until an appreciably larger number of H and patients will be analyzed to allow a better precision in the determination of the corresponding limits), the preceding paragraph recommends to use—instead of twelve—*all* the 28 parameters associated with the quantities λ, λ_{shuf}, ρ, ρ_{shuf}, ν, $\overline{\delta S}_{3-4}$(QT), and $\overline{\delta S}_{3-4,shuf}$(QT).

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