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Heart rate variability in natural time and 1/f "noise"

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Abstract – Several studies have shown that heart rate fluctuations exhibit the ubiquitous $1/f$ behavior which is altered in desease. Furthermore, the analysis of electrocardiograms in natural time reveals that important malfunctions in the complex system of the human heart can be identified. Here, we present a simple evolution model in natural time that exhibits the $1/f^a$ behavior with a close to unity. The results of this model are consistent with a progressive modification of heart rate variability in healthy children and adolescents. The model results in complexity measures that separate healthy dynamics from patients as well as from sudden cardiac death individuals.

Among the different features that characterize complex physical systems, the most ubiquitous is the presence of $1/f^a$ noise in fluctuating physical variables [1]. This means that the Fourier power spectrum $S(f)$ of fluctuations scales with frequency f as $S(f) \sim 1/f^a$. The power-law behavior often persists over several orders of magnitude with cutoffs present at both high and low frequencies. Typical values of the exponent a approximately range between 0.8 and 4 (*e.g.*, see ref. [2] and references therein), but in a loose terminology all these systems are said to exhibit $1/f$ "noise". Such a "noise" is found in a large variety of systems, *e.g.*, condensed matter systems (*e.g.*, [3]), granular flow [4], DNA sequence [5], ionic current fluctuations in membrane channels [6], the number of stocks traded daily [7], chaotic quantum systems [8–11], human cognition [12] and coordination [13], burst errors in communication systems [14], electrical measurements [15], the electric noise in carbon nanotubes [16] and in nanoparticle films [17], the occurrence of earthquakes [18], the seismic electric signals [19] (SES) activities that are series of transient low frequency ($\leqslant 1$ Hz) signals arising from cooperative orientation [20] of electric dipoles —formed due to defects [21]— *before* rupture [22,23] etc. In some of these systems, the exponent a was reported to be very close to 1, but good quality data supporting such a value exist in a few of them [3]. As an example we refer to the voltage fluctuations when current flows through a resistor [24]. As a second example we mention the case of heart rate variability to which we now turn.

Various tests of time variation have been applied to heart rate variability to show that, in healthy subjects, heart rate fluctuation displays $1/f$ noise and fractal dynamics with long-range correlation, *e.g.*, see ref. [25]. These initial studies indicated rich dynamics with differences between normal individuals and patients [26]. Heart rate variability (HRV) is a useful tool that might provide indices of autonomic modulation of the sinus mode [27] and its reduced value is a sign of autonomic imbalance. Later findings (*e.g.*, [28,29]) showed that healthy heartbeat dynamics exhibits even higher complexity, which is characterized by a broad multifractal spectrum. This high complexity breaks down in illness associated with altered cardiovascular autonomic regulation (*e.g.*, [30,31] and references therein). The decreased long-ranged fluctuations are associated with increased mortality in cardiac patients with congestive heart failure ([28,29,32], for a review see [31]).

The $1/f^a$ behavior has been well understood on the basis of dynamic scaling observed at *equilibrium* critical points where the power law correlations in time stem from the infinite-range correlations in space (see ref. [2] and references therein). Most of the observations mentioned above, however, refer to *non-equilibrium* phenomena for which —despite some challenging theoretical attempts [33,34]— possible *generic* mechanisms leading to scale invariant fluctuations have not yet been identified. In

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other words, despite its ubiquity, there is no yet universal explanation about the phenomenon of the $1/f^a$ behavior. Opinions have been expressed (*e.g.*, see ref. [8]) that it does not arise as a consequence of particular physical interactions, but it is a generic manifestation of complex systems.

It has been recently shown [22,35–42] that novel dynamic features hidden behind the time series of complex systems can emerge if we analyze them in terms of a newly introduced time domain, termed natural time χ. This time domain was shown [43] to be optimal for enhancing the signals in time-frequency space when employing the Wigner function and measuring its localization properly; in other words natural time analysis conforms to the desire to reduce uncertainty and extract signal information as much as possible [43]. In a time series comprising N events, the natural time $\chi_k = k/N$ serves as an index [22] for the occurrence of the k-th event. In an electric signal, as in the case of electrocardiograms, the evolution of the pair (χ_k, Q_k) is then studied [37,38,42], where Q_k denotes duration of the k-th pulse. Defining $p_k = Q_k / \sum_{l=1}^{N} Q_l$ and $\langle f(\chi)\rangle \equiv \sum_{k=1}^{N} f(\chi_k) p_k$, the entropy S in the natural time domain is [36] $S \equiv \langle \chi \ln \chi\rangle - \langle \chi\rangle \ln \langle \chi\rangle$, and depends on the sequential order of events [37,38]. The entropy obtained upon considering [39] the time reversal $\mathcal{T}$, *i.e.*, $\mathcal{T} p_k = p_{N-k+1}$, is labelled by S_-. It was found [39] that, in general, S_- is different from S, and hence S shows the breaking of the time reversal symmetry, thus revealing the profound importance of considering the (true) time arrow in classifying similar looking signals of different dynamics. The entropy change under time reversal $S - S_-(\equiv \Delta S)$ has been shown in ref. [42] to be able to provide the key measure that may identify an impending sudden cardiac death risk. In particular, an analysis of the time series of ΔS_i, *i.e.*, the values of ΔS obtained when a moving window of $N = i$ successive pulses is applied to the beat-to-beat (RR) or normal-to-normal (NN) intervals, revealed that the scale $i = 3$ heartbeats, identifies the sudden cardiac death risk and distinguishes the sudden cardiac death subjects from truly healthy individuals as well as from those with the life-threatening congestive heart failure (cf. the procedure to read the RR interval time series in natural time is schematically shown in fig. 1 of ref. [42]). This distinction is achieved by means of the following two complexity measures: i) $N_3 = \sigma[\Delta S_3^{shuf}]/\sigma[\Delta S_3]$, which corresponds to the ratio of the standard deviation of ΔS_3 time series obtained after shuffling the RR (NN) intervals randomly (thus destroying any information hidden in the ordering of the heartbeats) over the standard deviation of original ΔS_3 time series and ii) $\sigma[\Delta S_7]$. Furthermore, in the subjects classified as having a high sudden cardiac death risk, the measured ΔS_i at the scale $i = 13$ heartbeats provides an estimate of the occurrence time of the impending ventricular fibrillation onset. The physical origin of these complexity measures could be understood as follows if we resort to the neural influences on cardiovascular variability (see ref. [42] and references therein): physiologically, the origin of the complex dynamics of heart rate has been attributed to *antagonistic* activity of the two branches of the autonomic nervous system, *i.e.*, the parasympathetic (PNS) and the sympathetic (SNS) nervous systems (decreasing and increasing heart rate, respectively), the net result of which seems to be captured by ΔS_i (see appendix 4 in the additional information of ref. [42]). Concerning the scale i, we consider that two clear-frequency bands in heart rate and blood pressure with autonomic involvement have been established, *e.g.*, ref. [32]: i) a higher-frequency (HF) band, in the range 0.15–0.40 Hz, which is "indicative of the pressure of respiratory modulation of the heart rate" and ii) a lower-frequency (LF) band, between 0.05 and 0.15 Hz (*i.e.*, around 0.1 Hz), which corresponds to "the process of slow regulation of blood pressure and heart rate" or "it reflects modulation of sympathetic or parasympathetic activity by baroflex mechanisms". The scale $i = 3$ corresponds to the HF band while the scale $i = 13$ (as well as $i = 7$) to the LF band. Hence, the value of ΔS_i for length scales corresponding to the HF and LF bands can be thought as quantifying the extent to which the processes, modulation of vagal activity primarily by breathing and the slow regulation of blood pressure and heart rate, are "disorganized", respectively [42].

In view of the above, we propose here a simple evolutionary model which, in the frame of natural time, leads to $1/f^a$ behavior with an exponent a close to unity. The properties of this model are then compared to those of the HRV data in healthy children and adolescents versus age as well as to healthy or patient individuals.

The model proposed considers the following simple evolution picture: As the number of generations n increases by one, a new species —whose ability to survive is characterized by a number η_n— appears. The new species competes and eliminates *only* the existing species that have a smaller ability to survive. We shall show below that the number of species ϵ_n, if considered as a function of the number of generations n, exhibits an $1/f$ behavior and that it increases very slowly with n, actually logarithmically, thus very few species survive this competitive process.

The mathematical description of the model, in terms of set theory, is as follows: Let us consider the cardinality ϵ_n of the family of sets E_n of *successive extrema* obtained from a given probability distribution function (PDF); E_0 equals to the empty set. Each E_n is obtained by following the procedure described below for n times. Select a random number η_n from a given PDF (here, we use the exponential PDF, *i.e.*, $p(\eta_n) = \exp(-\eta_n)$) and compare it with all the members of E_{n-1}. In order to construct the set E_n, we *discard* from the set E_{n-1} all its members that are smaller than η_n and furthermore *include* η_n. Thus, $E_n \neq \emptyset$ for *all* $n > 0$ and E_n is a finite set of real numbers whose members are always larger or equal to η_n. Moreover, $\max[E_n] \geqslant \max[E_{n-1}]$. The increase of the cardinality $\epsilon_n \equiv |E_n|$ of these sets is at the most 1, but its decrease may be as large

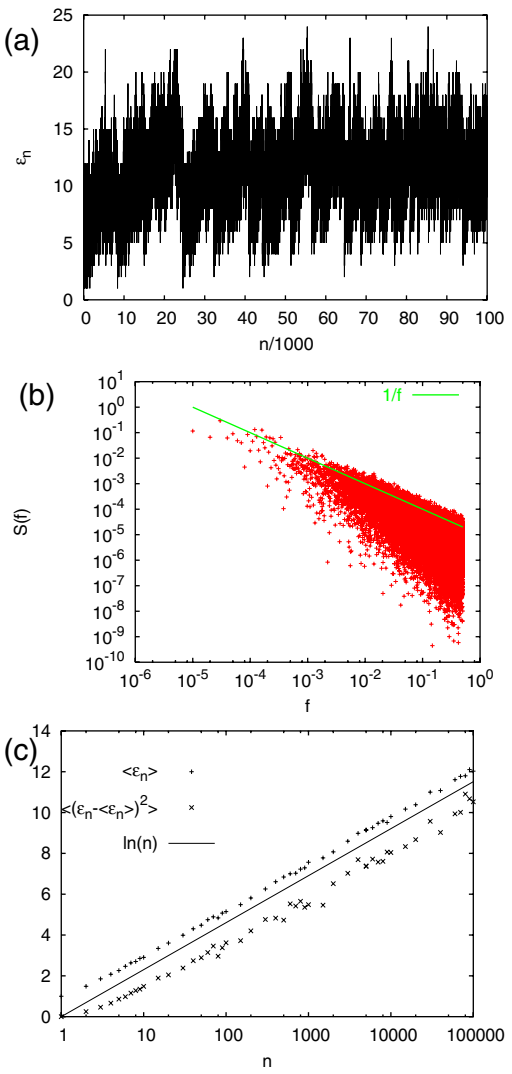

Fig. 1: (Color online) (a) Example of the evolution of ϵ_n *vs.* the number of renewals n, *i.e.*, in natural time. An exponential PDF has been considered for the selection of η_n. (b) The Fourier power spectrum of (a); the (green) solid line corresponds to $1/f$ and was drawn as a guide to the eye. (c) Properties of the distribution of ϵ_n. The average value $\langle\epsilon_n\rangle$ (plus) and the variance $\langle(\epsilon_n - \langle\epsilon_n\rangle)^2\rangle$ (crosses) as a function of n. The straight solid line depicts $\ln(n)$ and was drawn for the sake of reader's convenience.

as $\epsilon_{n-1} - 1$. This reflects an asymmetry if ϵ_n is considered as time series with respect to the *natural* number n. An example of ϵ_n *vs.* n is shown in fig. 1(a). The cardinality ϵ_n exhibits $1/f^a$ noise with a very close to unity, see fig. 1(b). The mathematical model described above, the analytical properties of which has been discussed in detail in ref. [44], corresponds to an asymptotically non-stationary process, since $\langle\epsilon_n\rangle \propto \ln n$ with a variance $\langle(\epsilon_n - \langle\epsilon_n\rangle)^2\rangle \propto \ln n$ (see fig. 1(c)). In particular, it was shown analytically that [44]:

$$\langle\epsilon_n\rangle = \sum_{k=1}^{n} \frac{1}{k}, \tag{1}$$

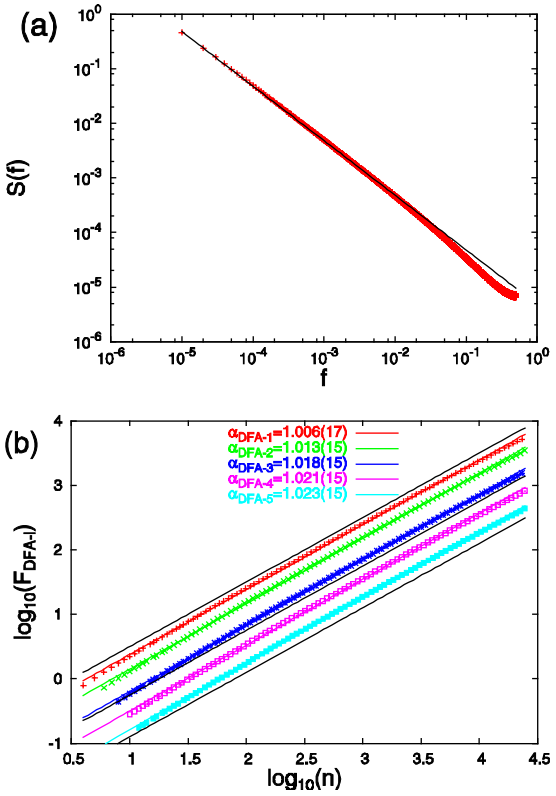

Fig. 2: (Color online) Results from 10^4 runs of the model presented in fig. 1: (a) the average power spectrum, (b) detrended fluctuation analyses of order l (DFA-l). The black solid line in (a) corresponds to $1/f$ spectrum and was drawn as a guide to the eye. For the same reason in (b), the black solid lines correspond to $\alpha_{\rm DFA} = 1$. In (b), the colored solid lines correspond to the least-square fit of the average $F_{\text{DFA-}l}$, depicted by symbols of the same color; the numbers in parentheses denote the standard deviation of $\alpha_{\text{DFA-}l}$ obtained from the 10^4 runs of the model. The various $F_{\text{DFA-}l}$ have been displaced vertically for the sake of clarity.

$$\langle(\epsilon_n - \langle\epsilon_n\rangle)^2\rangle = \sum_{k=1}^{n} \left(\frac{1}{k} - \frac{1}{k^2}\right). \tag{2}$$

Equations (1) and (2) reveal that both the average value $\mu \equiv \langle\epsilon_n\rangle$ and the variance $\sigma^2 \equiv \langle(\epsilon_n - \langle\epsilon_n\rangle)^2\rangle$ diverge logarithmically as n tends to infinity. The point probabilities $p(\epsilon_n = m)$, however, remain localized around $\mu = \langle\epsilon_n\rangle \propto \ln n$ since $\sigma/\mu \propto 1/\sqrt{\ln n}$. Thus, in simple words, the present model suggests that the cardinality ϵ_n of the family of sets E_n of successive extrema exhibits a logarithmic creep and the $1/f^a$ behavior when considered as time series with respect to the natural (time) number n. We note that a connection between $1/f^a$ noise and extreme value statistics has been established and proposed as providing a new angle at the generic aspect of the phenomena [33].

In order to check the stability of the results of fig. 1, we present in fig. 2(a) the average power spectrum obtained from 10^4 runs of the model. A sharp $1/f$ behavior is observed. Moreover, in fig. 2(b), we present the results

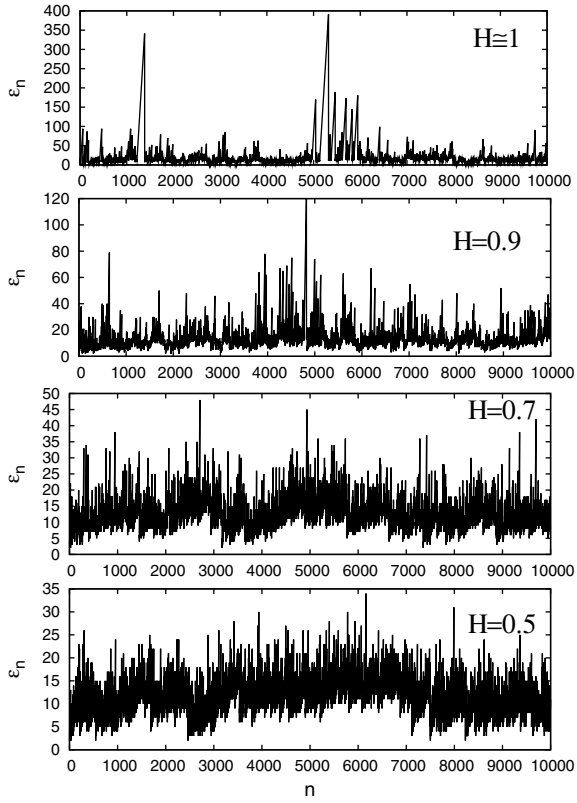

Fig. 3: Time series of ϵ_n when η_n come from fGn for various values of H (increasing from the bottom to the top).

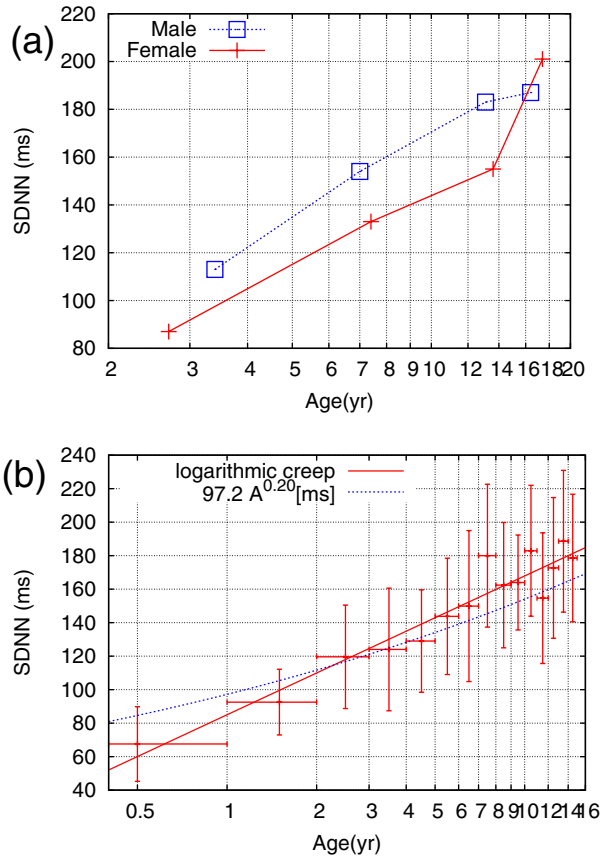

Fig. 4: (Color online) (a) The mean values of SDNN for male (blue) and female (red) subjects as a function of their age. The data come from table 1 of ref. [46]. The x-axis is in logarithmic scale. (b) Variation of SDNN with respect to age: the data come from fig. 4 of ref. [47] and are binned every year of age. The vertical error bars stand for ± one standard deviation. The dotted (blue) curve corresponds to the power law fit suggested in ref. [47] whereas the solid (red) line corresponds to a logarithmic creep.

of the corresponding average values of $F_{\text{DFA-}l}$ of the detrended fluctuation analysis [25] (DFA) obtained for various orders l (*i.e.*, when detrending with a polynomial of order l, see ref. [45]). Figure 2(b) indicates that $\alpha_{\text{DFA-}l}$ is close to unity thus being compatible with the $1/f$ power spectrum depicted in figs. 1(b) and 2(a).

We recall that in the aforementioned example of fig. 1(a) showing the evolution of ϵ_n *vs.* the number of renewals n (*i.e.*, in natural time), an exponential PDF has been considered. After investigating several different distributions of η_n, we conclude that the resulting spectral density depends only very weakly —if at all— on the PDF of η_n. We find that, in order to obtain $\alpha \approx 1$, the only essential condition to be fullfilled is that the corresponding PDF should be bounded from below. (This is a reasonable assumption if η_n is to be considered a measure of the ability to survive; a negative measure would correspond to a species that is unable to survive.) This holds, of course, under the assumption that η_n come from the *same* PDF, *i.e.*, they are independent and identitically distributed variables. Let us now investigate the case when η_n come from a stationary but long-range (time) correlated process, for example from fractional Gaussian noise (fGn). To this end, several values of the Hurst exponent (H) have been considered and indicative results are depicted in fig. 3 for $H = 0.5$, 0.7, 0.9 and ≈ 1. A noticeable difference can be visualized in this figure upon increasing H; for $H = 1$, which corresponds to the case of SES activities [22,23], the results differ greatly from those corresponding to smaller exponents, *e.g.*, $H = 0.5$–0.7, which are occasionally found in the analysis of electric signal time series emitted from man-made electrical sources [35,36].

The model proposed amounts to a sort of shot noise in a process showing logarithmic creep, a non-stationary process as mentioned above. In an effort to check whether such a non-stationarity corresponds to a case in the real-world data, we consider here the HRV data in healthy children and adolescents presented by Silvetti *et al.* [46]. In particular, the following two standard 24 h time domain measures, among others, were computed: SDNN (standard deviation of all normal sinus RR intervals over 24 h) and SDANN (standard deviation of the averaged normal sinus RR intervals for all 5 min segments). Silvetti *et al.* [46] evaluated 103 subjects (57 males and 46 females), aged 1–20 years, and found that SDNN and SDANN, overall HRV measures, increased with age and were gender-related. These data demonstrate that, in healthy children and adolescents, there is a progressive modification of HRV

that may reflect a progressive evolution of the autonomic nervous system. Using the results of Silvetti *et al.* [46], we plot in fig. 4(a) SDNN *vs.* age in a semilogarithmic plot. An inspection of this figure reveals that, for ages smaller than 14 yr, in both male (blue) and female (red) subjects an almost logarithmic creep is present, a property also exhibited by the model as already mentioned. This logarithmic creep is also present in the results of ref. [47] where the SDNN *vs.* age (A) was fitted by a power law, *i.e.*, $\mathrm{SDNN} = 97.2 \times \mathrm{A}^{0.20}$ (ms), for the period from infancy to adolescence. As can now be seen in fig. 4(b), which is drawn on the basis of the data presented in fig. 4 of ref. [47] by using averages every one year of age, a logarithmic creep seems to provide a better description for SDNN from early childhood to adolescence. This behavior could be, in principle, understood in the following context: The present model may simulate the variation of RR intervals around a mean value determined by the sinoatrial node, thus leading to the logarithmic creep of SDNN visualized in fig. 4. We note that the model intrinsically represents a competitive evolution which is also present during the period of childhood. The complexity of heart rate dynamics is high in children and illustrates [47]: "an increase of cholinergic and a decrease of adrenergic modulation of heart rate variability with age, confirming the progressive maturation of the autonomic nervous system." In other words, in order to shed light on the underlying connection between the presented model and the development of heartbeat regulation we could say the following: Physiologically, the origin of the complex dynamics of heart rate has been attributed to the *antagonistic* activity of the PNS and SNS, as already mentioned. It is this antagonistic activity which seems to be captured by the present mathematical model since the basic spirit of the latter stems from a competitive evolution process.

We now compare the results of the model in natural time with the HRV data —actually the RR time series— of patients and healthy subjects. These data come from long-time ECG recordings [48] (see also ref. [42], containing on average $N \simeq 10^5$ heartbeats for each record) of healthy (H) subjects as well as of patients with congestive heart failure (CHF) or atrial fibrillation (AF) or subjects that suffered sudden cardiac death (SCD). In order to compare with the already published results see fig. 3(b) of ref. [42] on HRV, we consider only mature models with $n \simeq 10^6$ and examine their evolution, *i.e.*, the time series ϵ_n, for the later 10^5 generations (recall that this is the order of magnitude of heartbeats in a 24 h ECG recording). The proposed model results in $N_3 = 2.52 \pm 0.19$ and $\sigma[\Delta S_7] = (2.46 \pm 0.25) \times 10^{-3}$ shown by the (black) square in fig. 5. Concerning N_3, this is close (but below) to the minimum value H_{min} computed in H and larger the N_3 values in the vast majority of SCD (where high complexity breaks down). As for the $\sigma[\Delta S_7]$ value, it lies to the right of the maximum value of $\sigma[\Delta S_7]$ observed in H as well as in the vast majority of CHF, and is located outside the shaded region which seems to separate AF

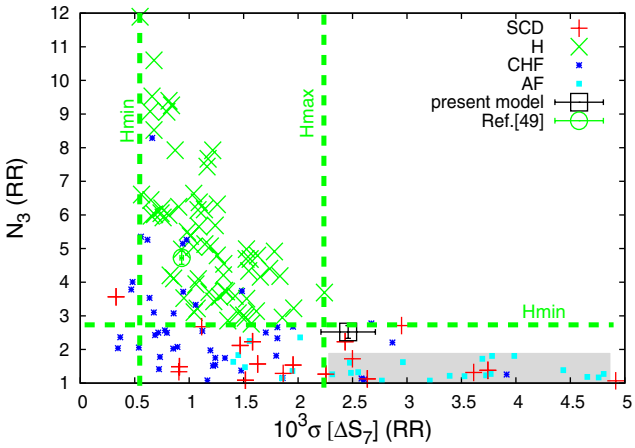

Fig. 5: (Color online) The complexity measure N_3 *vs.* $\sigma[\Delta S_7]$ for the RR time series. The green horizontal line corresponds to the minimum value of N_3, while the two vertical green lines to the minimum and maximum $\sigma[\Delta S_7]$ values, respectively, computed in H. The (black) square and the corresponding error bars depict the values of the complexity measures obtained from the model proposed here. As for the complexity measures obtained from the model suggested in ref. [49] (using the same parameters with those given in fig. 2 of ref. [49]), they correspond to the (green) circle.

from the others. This result is consistent with the fact that the (black) square corresponds to a simple $1/f$ behavior, while healthy heartbeat dynamics exhibits even higher complexity [28,29] as mentioned above. Indeed, let us consider the stochastic feedback model proposed by Ivanov *et al.* [49] which describes the *healthy* regulation of biological rhythms with a clear relation to the physiology of the heart; the effects of the sinoatrial node along with the PNS and the SNS influences were taken into account. This model leads [49] to an approximately $1/f^{1.1}$ behavior and generates complex dynamics that account for the functional form and scaling of the distribution of variations of RR. Here, we calculate the aforementioned complexity measures in natural time that correspond to this model (by using the same parameters as those mentioned in fig. 2 of ref. [49]) and the results are depicted by the (green) circle in fig. 5. Interestingly, this point lies within the H-limits, as it should.

The simple model proposed here may be useful in other disciplines as well. For example, ϵ_n may be considered as equivalent to the dimensionality of the thresholds distribution in the so-called coherent noise model (*e.g.*, see ref. [50] and references therein). Furthermore, in the frame of a formal similarity between the discrete spectrum of quantum systems and a discrete time series [9], the following striking similarity is noticed: the fact that $a \approx 1$ together with the behavior $\langle(\epsilon_n - \langle\epsilon_n\rangle)^2\rangle \propto \ln n$ of the present model, is reminiscent of the power law exponent and the $\langle\delta_n^2\rangle$ statistic in chaotic quantum systems [9,10].

In summary, using the concept of natural time, a simple competitive evolution model is proposed that exhibits $1/f^a$ behavior with a close to unity. The model amounts

to a sort of shot noise in a process showing logarithmic creep, a non-stationary process, a behavior which is similar with the fact that SDNN exhibits a logarithmic creep with age for children and adolescents. The model predicts complexity measures that separate healthy dynamics from patients as well as from SCD, as intuitively expected since it corresponds to a simple $1/f$ behavior.

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