Memory beyond memory in heart beating: an efficient way to detect pathological conditions

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We study the long-range correlations of heartbeat fluctuations with the method of diffusion entropy. We show that this method of analysis yields a scaling parameter δ that apparently conflicts with the direct evaluation of the distribution of times of sojourn in states with a given heartbeat frequency. The strength of the memory responsible for this discrepancy is given by a parameter ϵ^2, which is derived from real data. The distribution of patients in the (δ, ϵ^2)-plane yields a neat separation of the healthy from the congestive heart failure subjects.

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The analysis of time series of physiological significance is currently done using the paradigm of anomalous scaling [1]. This letter, resting on this paradigm, aims at showing that the entropy of a diffusion process generated by a physiological time series according to the prescriptions of Refs. [2,3] yields a scaling exponent that depends only on genuine events, namely, events whose occurrence time is unpredictable. We call this method of analysis Diffusion Entropy (DE) method and, by means of simple dynamic models, we prove it to be insensitive to pseudo events, namely, to events whose occurrence times are correlated to those of earlier events.

Let us consider first a dynamic model that generates events (really random events). This is given by

$$\dot{x} = \Phi(x) > 0, \tag{1}$$

where x denotes the coordinate of a particle, moving within the interval $I \equiv [0, 1]$, from the left to the right, with times of arrival at $x = 1$ determined by Eq.(1) and by the initial condition. When the particle reaches the right border of I, it is injected back to a new initial condition selected with uniform probability on I. Consequently, the times of arrival at $x = 1$, $t_1, .., t_i..$, are a fair example of real events. It is straightforward to prove that the choice $\Phi(x) = \kappa x^z$, with $z > 1$ and $k > 0$, yields for the waiting times $\tau_i \equiv t_i - t_{i-1}$ the following distribution density

$$\psi(\tau) = (\mu - 1)\frac{T^{\mu-1}}{(T + \tau)^{\mu}}, \tag{2}$$

with $\mu = z/(z - 1)$ and $T = (\mu - 1)/\kappa$. Note that the mean waiting time $\langle\tau\rangle$ is determined by T through $\langle\tau\rangle = T/(\mu - 2)$. Let us convert now the time series $\{\tau_i\}$ into a random walk. We select the rule [3] that makes the random walker move, always in the same direction and by a step of constant intensity, only when an event occurs. This means that the sequence $\{\tau_i\}$ is converted into a sequence of 0's and 1's as follows. We create a sequence of patches, one patch for each τ_i, with a width given by the integer part of τ_i; we fill the sites of each patch with 0's and we signal the border between two nearest-neighbor patches with 1's. Then, the resulting sequence is converted into many trajectories of a given length l with the method of the moving window. A window of size l moves along the sequence and for any window position, the portion of the whole sequence spanned by the window is regarded as a single trajectory of length l. All these trajectories are assumed to start from the origin, and are used to create a diffusion distribution, at time l. If there is scaling, with scaling parameter δ, the entropy $S(l)$ takes the form [2,3]

$$S(l) = A + \delta \ln(l). \tag{3}$$

Consequently, the rate of entropy increase in logarithmic time scale is the value of the scaling parameter we are looking for. The DE method has been widely discussed in earlier papers [3,4] and it has been pointed out that, without using any form of detrending, it yields the correct scaling parameter δ. In some cases [4] this method detects the Lévy scaling that would imply an infinite variance and, consequently, would be incompatible with the adoption of methods based on variance. In the specific case of the model of Eq.(1) the adoption of this method of analysis yields a scaling parameter δ that, in the case where $2 < \mu < 3$, fits the theoretical prediction

$$\delta = \frac{1}{\mu - 1}, \tag{4}$$

while for $\mu > 3$ one gets $\delta = 0.5$. This is a proof that the direct evaluation of the power law index μ is equivalent to detecting the scaling δ by means of the DE method. It is well known [5] that a Markov master equation, namely a

stochastic process without memory, is characterized by a waiting time distribution $\psi(\tau)$ with an exponential form, thereby implying that a marked deviation from the exponential condition is a signature of the presence of memory. This is the kind of memory that is usually associated with the detection of an anomalous scaling parameter, namely $\delta \neq 0.5$. We refer ourselves to this memory as memory of the first type. To prepare the ground for the kind of memory that is the focus of this paper, we have to discuss a dynamic model generating both events and pseudo events. For this purpose let us consider a two-variables model. The first equation, referring to the first variable, is given by Eq.(1), and the second equation, concerning the new variable y, is given by

$$\dot{y} = \chi(y) > 0. \tag{5}$$

The variables x and y are the coordinates of two particles, both moving in the interval I, always from the left to the right. The initial conditions of the variable y are always chosen randomly. The initial conditions of x, on the contrary, are not always chosen randomly, but they are only when the variable y reaches the border at least once, during the sojourn of x within the interval. Let us consider the sojourn time interval $[t_i, t_{i+1}]$. If in this time interval the variable y remains within the interval, without touching the right border, then we set $x(t_{i+1}) = x(t_i)$. This is a pseudo event. Thus, the sequence $\{t_i\}$ is a mixture of events and pseudo events. Let us consider the case where $\chi(y) = k' y^{z'}$ with $z' > 1$ and $k' > 0$, so as to produce the power index $\mu' = z'/(z'-1)$, with $\mu' > 2$, a property of real events. Let us set the condition $\langle\tau\rangle_x \ll \langle\tau\rangle_y$. In this case it is straightforward to show that the waiting time distribution of x is still given by Eq.(2). However, the power index μ is not more a reflection of real events. Fig.1 reveals a very attractive property: the DE now yields $\delta = 1/(\mu' - 1)$, which is very different from the theoretical prediction of Eq.(4) that makes $\mu > 3$ yield $\delta = 0.5$. Note that in the case of Fig.1 $\mu = 5$ and $\mu' = 2.41$. The breakdown of Eq.(4) is referred to by us as *memory beyond memory* effect. In fact, the existence of pseudo events implies correlation among different times of the series $\{\tau_i\}$, and thus a memory of earlier events. This memory is annihilated by shuffling the order of these times, as we do with a bunch of cards. In fact, as shown by the inset of Fig.1, we see that shuffling has the effect of yielding $\delta = 0.5$, in accordance with the theoretical prescription of Eq.(4). It is impressive that the scaling detected by the DE method does not depend on the pseudo events, but only on the hidden events that would be invisible to an analysis based on the direct evaluation of $\psi(\tau)$.

Let us apply this model to the real data taken from [6]. We apply our technique to 33 long-time ECG records (about 20 hours each), 18 healthy and 15 showing pathological behavior related to Congestive Heart Failure (c.h.f.). Following Ref. [6], we refer to all the ECG records of the *MIT-BIH Normal Sinus Rhythm Database* and of the *BIDMC Congestive Heart Failure Database*, for the healthy and the c.h.f. patients, respectively.

The data under study are time series of the kind of that illustrated in Fig. 2, where the length of the vertical lines expresses $T(i) = t_i - t_{i-1}$ as a function of the integer number i. The integer number i denotes the i-th heart beating of an electrocardiogram, and t_i is the time at which the R wave of this heart beat occurs.

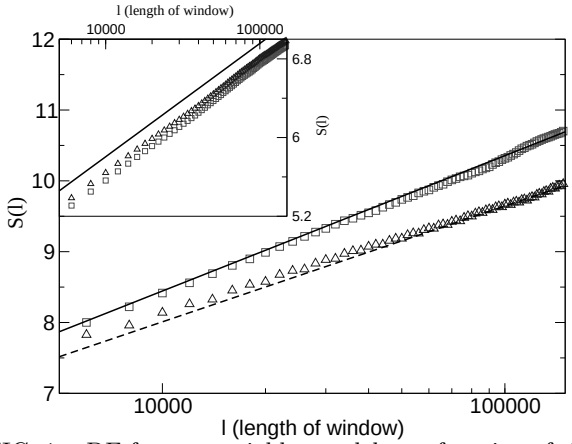

FIG. 1. DE for two-variables model as a function of time. The squares correspond to k'=0.018, z'=1.83 while the diamonds to k'=0.011, z'=1.71. For both curves k=0.4, z=1.25. In the inset: the same curves after shuffling, the straight line slope is 0.5.

We make these data suitable for the illustration of the *memory beyond memory* effect as follows. We adopt a procedure illustrated with the help of Fig.2. The vertical axis, concerning the variable $T(i)$, is divided into many cells of a given size ΔT. Thus the $(T(i), i)$-plane is divided into many horizontal strips with a constant width equal to ΔT. This coarse-graining prescription yields the thick line of Fig.2. The curve corresponds to many horizontal intervals separated by vertical up and down jumps. The widths of these horizontal intervals define a sequence of numbers τ_i that is the object of our statistical analysis. To make this analysis as efficient as possible we have to make a proper choice of the value of ΔT, since an excessively small value would produce too many pseudo events and an excessively large would yield poor statistics. The results of our statistical analysis were proven to be insensitive to changing ΔT over a wide range of values. We therefore assign to ΔT the mean value of this range, which turns out to be $\Delta T = 1/30$ sec.

The events under study refer to the jumps from one to another strip. To assess whether they are events or pseudo events, we have to compare the waiting time distribution $\psi(\tau)$ to the scaling detected by means of the DE method. For the sake of statistical accuracy we decided to evaluate the probability of finding waiting times

larger than a given value τ. This is the function $\Psi(\tau)$ defined by $\Psi(\tau) \equiv \int_t^\infty d\tau\psi(\tau)$. The results illustrated in the inset of Fig.2 imply the Brownian scaling $\delta = 0.5$. In fact, the function $\Psi(\tau)$ of the heart failure subject is a stretched exponential and the healthy subject yields $\mu = 3.9$. The same Brownian condition applies to all the subjects. On the contrary, the DE method yields for the healthy subjects the mean value $\delta = 0.82 \pm 0.04$ and for the heart failure subject $\delta = 0.71 \pm 0.06$. It is interesting to notice that Fig.3 refers to the same subjects as those of the inset of Fig.2, and yields for the healthy $\mu' = 2.17$ and for the heart failure subject $\mu' = 2.4$. If we shuffle the numbers of the sequence τ_i we recover $\delta = 0.5$, a fact proving that the *memory beyond memory* effect is a genuine property of heartbeat.

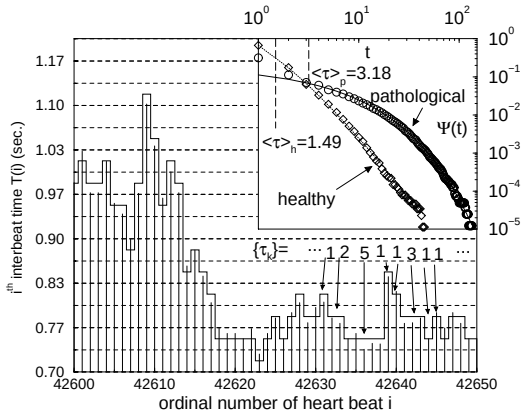

FIG. 2. The inter-beat time $T(i)$ as a function of the number of beats, i. The thick line denotes the trajectory corresponding to the coarse graining given by $\Delta T = 1/30$ sec. The vertical lines denote the height of the original data. The arrows and the integer labels illustrates how the sequence of τ_k's is generated. Inset: Survival probabilities. The circles denote the c.h.f. patients and the corresponding fitting function is $\Psi(t) = 0.19\exp[-(t/3.1)^{0.6}]$. The diamonds denote the healthy patient and the corresponding fitting function is $\Psi(t) = 5.71/(0.93+t)^{3.25}$.

The additional memory is confirmed by the numerical evaluation of the normalized correlation function of the variable $\tau_i - \langle\tau_i\rangle$, denoted by $C_{exp}(t)$, where the symbol t is the continuous approximation of the discrete patch label i. The two-variables model that we are using to explain the *memory beyond memory* effect would yield

$$C(t) \propto 1/t^\beta. \tag{6}$$

The index β in that case would be a complicated function of the four parameters involved by the two-variable model. This means that the DE is a memory detector more efficient and much less ambiguous than the correlation function. The DE selects from the distribution of times described by the arbitrary $\psi(\tau)$ the really random events yielding a non arbitrary distribution with a unique μ'. The correlation function $C(t)$, on the contrary, depends on the details of the model, but does not afford an easy way to define them. For the main purpose of this letter it is enough to point out that the form of the correlation function $C_{exp}(t)$ is

$$C_{exp}(t) = (1-\epsilon^2)W(t) + \epsilon^2 C(t). \tag{7}$$

Here $W(t)$ denotes a function dropping from 1 to 0 in one time step, while the function $C(t)$, with the asymptotic form of Eq.(6), is continuous for for $t \to 0$.

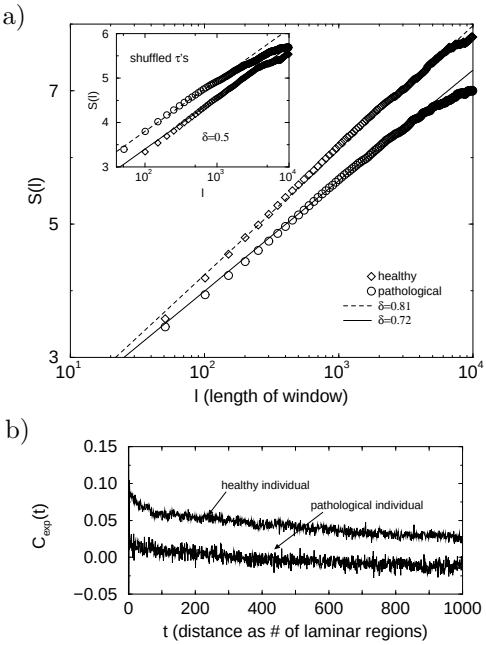

FIG. 3. a) The DE as a function of l. The inset illustrates the effect of shuffling, the two lines correspond to $\delta = 0.5$. b) The correlation function $C_{exp}(t)$ as a function of t on a healthy and on a c.h.f. individual.

We account for the structure of Eq.(7) as follows. The sequence $\{\tau_i\}$ is generated by the joint use of two models. The first is the model of Eq.(1) with no additional variables and no *memory beyond memory* property, the second is the model with two variables. These two models generate two independent sequences $\{\tau_i\}$. To any index i we assign, with probability ϵ, the value provided by the model with additional memory, and, with probability $1-\epsilon$, the value provided by the model with only one variable. This model is reminiscent of one adopted to account for the statistical properties of DNA sequences [7]. The function $C_{exp}(t)$ in one step drops from the value $C_{exp}(0) = 1$ to the value $C_{exp}(1) = \epsilon^2 C(1) \simeq \epsilon^2$, thereby allowing us to derive ϵ from the experimental correlation function at $t = 1$.

In conclusion, the meaning of the parameter ϵ is as follows. The value $\epsilon = 1$ would imply that the heart beating is described only by a model with two variables, x and y. In other words, the larger ϵ the larger the weight of the

memory beyond memory effect. The parameter δ is connected to the time distance between two nearest-neighbor real events. If this time distribution is exponential, there is no memory of conventional type, as earlier observed. If μ' becomes closer and closer to $\mu' = 2$, this conventional memory becomes stronger and stronger. Thus, to establish a more intuitive understanding of what happens to memory, regardless of whether it is of the conventional or of the new type, let us adopt the following perspective. The condition of highest memory corresponds to $\epsilon = 1$ and $\delta = 1$. This would mean that the heart beating depends only on the *memory beyond memory* model, and, that, at the same time, $\mu' = 2$. The opposite case, of complete absence of memory, implies $\epsilon = 0$ and $\mu' \to \infty$. This would mean that the heart beating is very well modeled by the one-variable model of Eq.(1), with an exponential distribution of waiting times, in other words, without any memory of whatsoever form. This leads us to express the distribution of patients in the (δ, ϵ^2)-plan of Fig.4. We note the surprising result that all the healthy subjects and all the heart failure subjects are contained in the top-right region and in the bottom-left one, respectively. We also notice that all the healthy subjects, but two of them, are localized within a small portion of the top-right region of the graph, not far from the border with the heart failure region. We have the impression that this reflects the fact that the healthy function of the heart beating system depends on a proper balance of memory and randomness that the analysis of this letter makes ostensible. The distribution of the heart failure subjects within the bottom-left region is much broader. It would be desirable to have at our disposal the patient survival probability as, for example, in Ref. [8], to assess whether a physiological reaction to the c.h.f. pathology, responsible for the bottom-left broadened distribution, plays a negative or a positive role. The advocates of the second possibility might argue that higher randomness and broader distribution reflect an effort of the perturbed heart beating system to explore all possible states to recover the lost function.

It is difficult to establish a connection with the earlier research work in this field since, to the best of our knowledge, the *memory beyond memory* effect was never observed, and we did not find any explicit mention to it in the field of heart beating. Is there a correspondence between the *memory beyond memory* effect and the multifractal properties observed in Ref. [9]? We are inclined to believe that there is, due to the similarity between Fig.4 and Fig.4b of [9].

As to the memory property expressed by δ, and by the corresponding μ', as well, we would like to mention Ashkenazy *et al.* [10] whose results show for the healthy patients a deviation from ordinary scaling higher than that of c.h.f patients. If we identify the scaling detected by these authors in the case of magnitude fluctuations and in the large-time regime, with the scaling parameter δ determined by the DE method, we see that our $\delta = 0.82 \pm 0.04$ for the healthy subjects corresponds to their $\delta = 0.82$, and that our $\delta = 0.71 \pm 0.06$ for the heart failure subjects corresponds to their $\delta = 0.71$. Thus, we conclude that our findings do not conflict, or do not necessarily do, with the earlier findings.

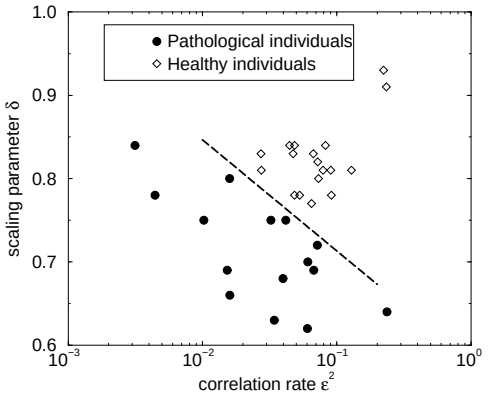

FIG. 4. Values of the scaling parameter δ and of ϵ^2 for the healthy and c.h.f. individuals of this analysis.

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