Real event detection and the treatment of congestive heart failure: an efficient technique to help cardiologists to make crucial decisions

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Abstract

Using a method of entropic analysis of time series we establish the correlation between heartbeat long-range memory and mortality risk in patients with
congestive heart failure.

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This paper deals with an advanced aspect of statistical mechanics whose recent demonstration [1] is proven here to afford an efficient criterion to deal with the mortality risk of patients with Congestive Heart Failure (CHF). We define the condition corresponding to the mean position of healthy subjects in a plane, called, as we shall see, physiological plane. We show that the distance of a CHF patient from this optimal condition correlates with mortality, and that the CHF patients very close to it survived. The importance of this criterion does not need to be defended. We think that the demonstration of this important property is of interest for both researchers at the frontier of statistical mechanics and cardiologists. The first step of our approach is based on observing a sequence of numbers \( \{T_i\} \), denoting the distance between two nearest neighbor pulses of a given electrocardiogram (ECG). One way to denote the time between two pulses is to measure the time elapsed between two adjacent R waves in the recorded electrical signal. This time is referred to as the RR interval, and the resulting sequence is consequently denoted as RR sequence.

We considered for this study 13 male CHF patients, from a study base of 320 subjects, who experienced cardiac death during a follow-up of 26 months (average 19 months, median 22 months). Inclusion criteria were absence of pulmonary or neurological disease, absence of acute myocardial infarction or cardiac surgery within the previous 6 months, absence of any other disease limiting survival, stable therapy for at least 2 weeks and good quality 24-hour Holter recordings, with an ectopy rate less than 5%. A comparable number of control subjects (16 patients), matching for age, sex, NYHA class (a functional and therapeutic classification for prescription of physical activity for cardiac patients) and etiology, was then selected. These latter patients did not experience cardiac death after follow-up. All patients had a 24-hour Holter recording at baseline, together with standard functional evaluation including measurement of left ventricular ejection fraction (LVEF), peak VO2 and Sodium (Na). Finally, RR series for 10 healthy subjects were taken from the NOnLinear TIime Series AnaLysIS (NOLTISALIS) archive. This latter data set is the result of the collaboration of several interdisciplinary Italian research centers. Experienced analysts edited these Holter recordings, manually correcting interbeat times due to ectopic beats. This editing work
yielded the RR sequence, from which we generated the time series \( \{T_i\} \).

The meaning of a given value \( T_i \), as earlier stated, is the time distance between the \( i - th \) and the \( (i + 1) - th \) pulse. The sequence \( \{T_i\} \) can be studied as a new time-series, with \( i \) playing the role of “time”. Moreover, the value \( T_i \), expressed as a function of \( i \) with \( i \gg 1 \), can be thought of as a function \( T(t) \), namely, as a function of a continuous time variable \( t \).

The real curve \( T(t) \) looks erratic and disordered. However, our method of analysis shows that it is quite different from a random process. For the reader to get an intuitive understanding of this attractive but perplexing conclusion, let us describe first an ideal model, with extended memory (EM), for the time evolution of \( T(t) \). First of all, we assume that for a given time \( \tau_{em} \), the curve \( T(t) \) keeps a given slope \( \alpha \), then it abruptly gets a new slope, \( \alpha' \), for an interval of time \( \tau'_{em} \), after which a new abrupt transition to a new slope \( \alpha'' \) takes place, for a time \( \tau''_{em} \), and so on. It is evident that the resulting \( T(t) \) has the form of a zig-zag curve. We shall refer to the individual straight line intervals of this curve as laminar regions. Any laminar region is associated with its own \( \tau_{em} \). Then we introduce the extended memory property. This is done by assuming for the waiting time distribution \( \psi(\tau_{em}) \) the following inverse power law form

\[
\psi(\tau_{em}) = (\nu - 1) \frac{\langle \tau_{em} \rangle^{\nu - 1}}{\langle \tau_{em} \rangle^{\nu - 1} + \tau_{em}} \langle \tau_{em} \rangle^{\nu - 1},
\]

with \( 2 < \nu < 3 \), where \( \langle \tau_{em} \rangle \) is the average waiting time. This means that if the EM model is directly observable, we can derive from \( T(t) \) the sequence \( \{\tau_{em}(j)\} \), where the discrete index \( j \) denotes the time order of a given laminar region.

It is interesting to notice that this dynamic process is essentially equivalent to the strong anomalous diffusion model recently proposed by the authors of Refs. [2,3] to explain the effects of a ballistic mechanism in the Rayleigh-Bénard convection. This model, in turn, is nothing but a generalization of the dynamic approach to Lévy statistics proposed years ago by the authors of Ref. [5]. In fact, the model of Ref. [5] is recovered from the model we are adopting here, by assuming that the slope \( \alpha \) has only two values, of equal intensity and opposite sign [6]. With this equivalence in mind, we adopt the specific walking prescription

\[
\psi(\tau_{em}) = (\nu - 1) \frac{\langle \tau_{em} \rangle^{\nu - 1}}{\langle \tau_{em} \rangle^{\nu - 1} + \tau_{em}} \langle \tau_{em} \rangle^{\nu - 1},
\]
proposed by Ref. [4]. We consider a given time \( t \) and we evaluate the number of laminar regions that have been completed within this time. Let us call this number \( n \). Then the trajectory is

\[
y(t) = nW.
\]  

(2)

This means that the random walker makes a jump ahead, by the same quantity \( W \), at the end of any laminar region. The quantity \( W \) is arbitrary and in the following we assume \( W = 1 \). Then, according again to the prescriptions of Ref. [4], we create the trajectories

\[
x(l) = y(t + l) - y(t).
\]  

(3)

It is evident that we can move the index \( t \) from \( t = 0 \) to \( L - l \), where \( L \) is the total time length of the sequence under study. This makes it possible for us to evaluate the probability distribution \( p(x, l) \), which at \( l = 0 \) is a delta of Dirac located at \( x = 0 \), broadening upon time increase. Note that an important step of our approach rests on the determination of the Shannon entropy of this distribution, namely

\[
S(l) = - \int_{-\infty}^{\infty} dx p(x, l) \log p(x, l).
\]  

(4)

This is the reason why this technique of analysis has been termed Diffusion Entropy (DE) method [7]. According to the theory of Ref. [4] we immediately reach the conclusion that \( p(x, l) \) fulfils the scaling property

\[
p(x, l) = (1/l^\delta)F(x/l^\delta),
\]  

(5)

with \( \delta \) being the scaling parameter, which is related to \( \nu \) by

\[
\delta = 1/(\nu - 1).
\]  

(6)

In this specific case, it is straightforward to prove, by plugging \( p(x, l) \) of Eq. (5) into Eq.(4), that

\[
S(l) = A + \delta \log(l).
\]  

(7)
This means that the DE should yield for $S(t)$, expressed in a linear-log plot, a straight line, whose slope is the searched value of the scaling parameter $\delta$.

This way of proceeding is impossible in practice, because the real $T(t)$ curve significantly departs from the zig-zag form of the EM model. We make the conjecture that the departure from this ideal condition is caused by the fact that the actual signal $T(t)$ is the superposition of the EM model signal and a much stronger, but totally random component. This makes it impossible for us to directly evaluate $\psi(\tau_{em})$. We proceed as follows. Let us represent the $T(t)$ time evolution in a $(T,t)$ plane, with the ordinate referring to $T$ and the abscissa to $t$. The ordinate axis is divided into cells of equal size, called $s$. This means that we divide the $(T,t)$ plane into strips of size $s$, and that in the ideal case of constant frequency the trajectory $T(t)$ would move forever remaining within the same strip. Actually, transitions from one strip to the other occur frequently. We call these transitions markers. These markers might have quite different origins. The majority of the markers are determined by the short-time noise. Many other markers correspond to the hidden laminar regions of the underlying EM model; we call these markers “pseudoevents”. As in Ref. [1], we indicate with the term pseudoevent a marker that does not correspond to an unpredictable transition, but it is a consequence of the division of the $(T,t)$ planes into strips. Only a very small number of markers coincide with the turning points of the EM signal, or are sufficiently close to them. We call these markers real events.

Now we have to explain why the DE is sensitive only to the real events. The time distance between the $j$-th and the $(j+1)$-th marker, defines the time $\tau_{exp}(i)$ of the experimental sequence $\{\tau_{exp}(i)\}$. It is evident that even in the case where $T(t)$ were an exact realization of the EM model, the waiting time distribution $\psi(\tau)$ might turn out to be totally different from $\psi(\tau_{em})$. In fact, if $s$ is very small the same laminar region is divided into many smaller time intervals, with the same length. These are pseudoevents. It is evident that these pseudoevents do not contribute to the spreading of the distribution $p(x,l)$, and consequently do not contribute to the entropy increase. This means that the DE method is insensitive to pseudoevents.
What about the short-time random events? They, in principle, contribute the entropy increase, and consequently could affect the determination of the crucial parameter $\delta$. We can show that they do not. Notice that in the presence of the short-time random component the actual signal $\tau_{\text{exp}}(t)$ is given by

$$
\tau_{\text{exp}}(t) = a\tau_{\text{st}}(t) + bR(t),
$$

with $a \ll 1$ and $b$ close to 1. The first contribution corresponds to the EM model, and the second is generated by short-time random fluctuations. The correlation function of this signal is

$$
C_{\text{exp}}(t) = pC_{\text{st}}(t) + (1-p)C_{\text{random}}(t),
$$

where $C_{\text{st}}(t)$ is an inverse power law relaxation and $C_{\text{random}}(t)$ a relaxation function decaying to zero in one time step. If we take, without loss of generality $\langle \tau_{\text{st}}^2 \rangle = \langle R^2 \rangle = \langle \tau_{\text{exp}}^2 \rangle$, implying $a^2 + b^2 = 1$, then we have $p = a^2$ and $(1-p) = b^2$. How should parameter $p$ be evaluated? This is easily done monitoring the experimental correlation function at the first time step. According to the fact that $C_{\text{random}}(t)$ decays to zero in one step, while $C_{\text{st}}(t)$ is much slower, we immediately obtain $p = C_{\text{exp}}(1)$. Its evaluation is not independent of that of the other parameter, $s$. This is so because the experimental evaluation of $\tau_{\text{exp}}(t)$ is dependent on $s$.

However, while $p$ is $s$-dependent, the parameter $\delta$ is not. The DE method has the surprising capability of yielding a value for $\delta$ that is independent of $s$, even in the case when a strong short-time random component is present, and not only when the ideal EM model applies. How can it be so? This is so because the EM model component yields superdiffusion, while the random component generates ordinary diffusion. In the asymptotic limit of very large values of $l$, the superdiffusion component, which is faster than the ordinary diffusion, becomes predominant, and the DE method detects again the correct scaling $\delta$ even in the case where $p \ll 1$.

The parameter $p$ is very important, since it defines the statistical weight of the EM component present in the experimental signal $T(t)$. However, its dependence on $s$ makes its
use questionable. However, we see that all curves $p(s)$ share the same properties of getting small values for both small and large values of $s$, with a clearly defined maximum in between, which is referred to by us as $\pi$. This maximum is a property independent of $s$. Infact, we note that almost all the healthy patients get their maximum at 30 ms, while most of the CHF patients get theirs at 20 ms. The typical dependence of $p$ on $s$ is illustrated in Fig. 1, where we can see both the case of 5 healthy subjects with $\pi$ located at 30 ms, and 5 CHF patients, with $\pi$ located at 20 ms. We think that the parameter $\pi$ is a reliable measure of the EM component. Consequently, we decided to represent the physiological conditions of all patients, healthy and CHF alike, in the $(\delta, \pi)$ that we call physiological plane. The criteria adopted to define the physiological plane make the resulting “phase-space” diagram independent of the coarse-graining parameter $s$, and the location of any patient in the physiological plane is an objective property independent of the coarse graining parameter $s$. A mere visual inspection shows that the healthy and CHF patients do not mix but in relatively small region. The overlap region is so small as to make it possible for us to claim that healthy and CHF patients belong to two distinct regions of the physiological plane [8].

The division of the CHF patients into two groups, dead and alive, make the result of our analysis still more remarkable. To show this important property we proceed as follows. First of all, we define the center of gravity of the healthy patient, denoted with a white square in Fig. 2. We call this point optimal condition. Then, for any CHF patient we measure the Euclidean distance from the optimal condition, thereby making it possible for us to rank the CHF patients in order, according to this distance. In other words, the first CHF patient is the one with minimum distance from the optimal condition. Then we observe the remaining patients, and we rank as second the one with minimum distance from the optimal condition, and so on. We find that the first 7 patients are alive. The eighth patient is dead, and from now on the patients are either alive or dead. This suggests that the closer the patient to the optimal condition the higher the survival probability.

To support in a more rigorous way this important property, we apply the Mann-Whitney method [9]. This is a non-parametric test, namely it does not rest on Gaussian distributions
for the data. Let us count the number of patients dead, \( N_{\text{dead}} \), and the number of patients alive, \( N_{\text{alive}} \). The data of Fig. 2 refer to a case where \( N_{\text{dead}} = 13 \) and \( N_{\text{alive}} = 16 \). Let us consider the group with the smaller number of individuals. This means the group of dead patients. Then, let us evaluate the sum of the ranks of this group and let us call it \( \mu_{\text{exp}} \). We note that \( \mu_{\text{exp}} = 246 \). Under the hypothesis of no correlation between our parameters and the death probability, this resulting sum has a probability distribution that, for more than 8 elements is expected [9] to be approximately a Gaussian with mean \( \mu_T \) and standard deviation \( \sigma \) given by

\[
\mu_{\text{dead}} = N_{\text{dead}} \frac{N + 1}{2} \quad \sigma = \left( N_{\text{dead}} N_{\text{alive}} \frac{N + 1}{12} \right)^{1/2}.
\]

From the data of Fig. 2 we obtain \( \mu_{\text{dead}} = 195 \) and \( \sigma = 22.8 \), while, as earlier noticed, \( \mu_{\text{exp}} = 246 \). This means that the distance of \( \mu_{\text{dead}} \) from \( \mu_{\text{exp}} \) is 2.37\( \sigma \). In practice, we are allowed to rule out the hypothesis of no correlation between the death of CHF patients and their distance from the optimal condition: the probability for the distribution of dead and alive patients of Fig. 2 to be fortuitous, is less than 3%.

Moreover, it is important to remark that the alive patients corresponding to points in the physiological plane far from the optimal conditions, either had a serious pathology, being classified as NYHA class III (severe physical limitations, they are comfortable only at rest) and therefore required a heart transplant anyway, or had a very short follow-up time (less than 6 months). Only six alive patients did not belong to either of the above conditions, but it is remarkable that all six of them occupy positions which overlap with the zone of the healthy subjects. Unfortunately, the small number of sequences available to us at this time does not allow us to calculate the survival curves, or attempt any further conclusion.

It is convenient to compare the result of this paper to the literature in the field of nonlinear or fractal analysis of chardiological data. The most recent examples are those of Refs. [1,10,11]. Although based on different perspectives, multifractality [10,11] and memory beyond memory [1] as a sign of healthy physiological condition, neither of these two groups could address the ambitious step of granting physicians a reliable criterion to make crucial
decisions about the CHF patients. These findings, however suggest that $\delta$ and $\pi$ indexes, and especially the distance from the optimum condition in the physiological plane, should be considered for inclusion in the candidate predictors’ list of future large-scale prospective studies for risk stratification of CHF patients.

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FIG. 1. $p$ as a function of $s$ for: a) a group of healthy subjects; b) a group of CHF patients.

For clarity, we have plotted only 5 subjects for each group.
FIG. 2. Positions of healthy (circles) and CHF (diamonds) subjects in the physiological plane. The white diamonds correspond to patients alive after the end of the experiment, while the black ones to patients who were either dead or urgently transplanted. The white square (optimal condition, see text) represents the average position of healthy subjects in the plot.