Multifractality and heart rate variability

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Additional information on Chaos

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In this paper, we participate to the discussion set forth by the editor of Chaos for the controversy, "Is the normal heart rate chaotic?" Our objective was to debate the question, "Is there some more appropriate term to characterize the heart rate variability (HRV) fluctuations?" We focused on the ≈ 24 h RR series prepared for this topic and tried to verify with two different techniques, generalized structure functions and wavelet transform modulus maxima, if they might be described as being multifractal. For normal and congestive heart failure subjects, the h_q exponents showed to be decreasing for increasing q with both methods, as it should be for multifractal signals. We then built 40 surrogate series to further verify such hypothesis. For most of the series ($\approx 75\%$–80% of cases) multifractality stood the test of the surrogate data employed. On the other hand, series coming from patients in atrial fibrillation showed a small, if any, degree of multifractality. The population analyzed is too small for definite conclusions, but the study supports the use of multifractal series to model HRV. Also it suggests that the regulatory action of autonomous nervous system might play a role in the observed multifractality. © *2009 American Institute of Physics.*
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Is there an appropriate term to characterize the heart rate variability (HRV) fluctuations? Starting from this question set forth by the editors of Chaos, we analyzed the 15 series prepared by Physionet as common reference. Given the fact that the debate around the chaotic nature of HRV is still wide open, we focused on characteristics of the signal itself. Our goal is to contribute to the discussion with a fair report on the possibility of observing multifractality on such series. Apart from being a fundamental issue, "multifractal" parameters derived from HRV might furnish new diagnostic tools given the fact that they describe the series on long time scales. Findings were tested through a comparison with surrogate data. As HRV is strongly influenced by the autonomic nervous system, the tests we performed suggested that multifractals might model HRV series. The observations, while drawn from a small population, are in line with previous studies. On the other hand, they do not enable any speculation on the chaotic nature of HRV.

I. INTRODUCTION

Since the early 60s, when the first long-term Holter electrocardiogram (ECG) recorders appeared, researchers inspected them far beyond the simple search for anomalous patterns. Such long series permitted to push further the knowledge on HRV and its links with pathological conditions. The first attempts were made through a rather simple statistical description of the interbeat series and postacute myocardial infarction was the condition of choice (which appears sensible as myocardial infarction is one of the pri-

mary causes of death in World Health Organization regions and that postevent screening already took place). The indexes that proved valuable were mainly the standard deviation of the normal-to-normal intervals[1] and the HRV triangular index.[2]

It was also soon noticed that the interbeat (RR) series displayed a power law power spectral density (PSD) for time scales ranging from a few minutes to hours.[3] Mathematically, stationary stochastic processes displaying a PSD of the form $1/f^\alpha$ are called "scaling"[4] or "self-affine." Taking the integral of a scaling leads to a nonstationary process for which it is generally possible to define some generalized correlation function and PSD that displays a correspondent $1/f^{\alpha+2}$ scaling.[5] Both scalings and their integrated counterpart have (generalized) correlation functions which decay very slowly (hyperbolically) implying that the decorrelation time is not well defined: the values of the series are affected by its long-term history. For this reason in the literature such processes are referred to as having "long-memory" or "long-range dependence." Self-affine processes are fractal by definition: when rescaled both in time and amplitude they conserve the same statistical properties.

The RR series display characteristics which for certain scales are approximately similar to those of self-affine processes. But as long as the fractal dimension of a long-memory process is linked to α by the linear relation $D=(5-\alpha)/2$,[6] it was soon speculated that different levels of "fractality" might have been connected to distinct health status.[7] Also the outcomes were suggesting quite a change in perspective: physiological studies were showing that the HRV of an healthy individual usually displayed a larger fractal dimension and irregularity was the mark of health and not a deviation from the classical homeostasis principle.

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But a strange attractor is generally a fractal set: So was the scaling at low frequencies suggesting the presence of an underlying attractor where the trajectories of a low dimensional dynamical system were confined? The possibility of reconstructing the state space dynamics from the time series with Takens' time-delay theorem was tempting. The mathematical tool was widely employed in the quest of an underlying low dimension dynamical system displaying deterministic chaos.[8,9] Contradictory results followed[10,11] and made clear an issue which was initially overlooked: these methods were themselves based on the assumption that the time series under analysis was indeed generated by a chaotic system.

A quest to prove the chaotic nature of the cardiovascular system from HRV started. Coming from other sorts of problems, physicists were already on their way on this path: starting from the work of Osborne and Provenzale,[12] a clear concept emerged in literature that nonlinear time series methods should be trusted only when applied to controlled natural or laboratory systems for which reasonable models were known. Otherwise, proper statistical tests, such as surrogate data,[13] were only necessary conditions which had to be met on the series under analysis for any further claim. Many methods were proposed over the years, but up to date, none established a sufficient condition for a system to be chaotic, especially in experimental biological time series which are necessarily corrupted by noises (of endogenous or exogenous origins). Among the most promising and robust, noise titration[14] evoked that such sufficient condition was finally met, but recent studies[15,16] showed that unfortunately it is not the case.

As of today, we are not aware of any mathematical proof of a sufficient condition to confirm the presence of deterministic chaos in a time series. We surely acknowledge that the cardiovascular system is a complex mechanism, where several nonlinearities are accounted for; but the fact that a given system includes nonlinear components does not necessarily imply that the nonlinearities are also contained in a specific signal measured from it. For these reasons, we think that no definite conclusion might be drawn on the nature of HRV. Fortunately, the wealth of method developed over the years is nevertheless valuable at distinguishing populations of patients[17] and might serve as useful statistical indices in the diagnosis process.

In the following, we will address the second question set forth by the editor of Chaos: "If the normal heart rate is not chaotic, is there some more appropriate term to characterize the fluctuations?" We will do so verifying on the data made available if the hypothesis that the HRV series are fractal or multifractal stands the test of surrogate data.

The study of multifractals is tightly connected with the theory of deterministic chaos.[18] For example, many strange attractors are multifractal objects (when one takes as observable the density of points distributed according to the natural measure), or maps close to a tangent bifurcation might undergo on-off (temporal) intermittency displaying a multifractal series of on-off states.[19] But, as much as fractal objects, multifractal ones might as well be generated by geometric or stochastic processes. Therefore, the claim that a given set is

multifractal does not necessarily imply that the related system is chaotic.

II. METHOD

Multifractals are broadly speaking entity composed of a set of interwoven subfractals. Typically one defines a measure supported by the set: if such measure has different fractal dimension on different parts of the support, then it is named *multifractal*.[20] When the entity under analysis is a time series, the measure typically employed is the local singularity index evaluated at a given point with a Lipschitz (Hölder) exponent.[21] But finite sampling and numerical resolution makes difficult a direct measure. In particular, direct box-counting assessment might lead to the detection of spurious multifractality on series.[22]

Two more robust approaches are generally applied. The first employs the computation of *generalized* structure functions (GSFs) so avoiding completely the introduction of a measure. Works on this subject were pioneered in the context of fully developed turbulence.[23] For a random process X_n, for a time lag Δ, and order q, GSFs are defined as

$$\text{GSF}(\Delta, q) \equiv \langle |X_{n+\Delta} - X_n|^q \rangle.$$

If the series has fractal nature, it does exist a scaling region where $\text{GSF}(\Delta, q) \sim \Delta^{qh_q}$. When h_q is constant with q ($h_q = h_2 = H, \forall q$), the signal is monofractal (or self-affine), exactly like in the case of standard Brownian motion and white noise for which $\text{GSF}(\Delta, q) \sim \Delta^{q/2}$ and $\text{GSF}(\Delta, q) \sim \Delta^0$, respectively. In a true multifractal signal the scaling exponents decrease for increasing q ($h_q < h_p$ for $q > p$). Finally one might compute the generalized fractal dimension spectrum D_k via the Legendre transform $D_k = \min_q[qk - qh_q + 1]$.[24] The spectrum D_k can be associated with the presence of nonlinear correlations in the signal.

The second technique builds on the ability of wavelets to remove polynomial trends (up to a certain order) that could cause the failure of box-counting techniques in quantifying the local scaling exponents. In the first approximation, the wavelet-transform modulus-maxima (WTMM) method[24] first computes the wavelet transform $T_\psi[X_i](b, a)$ of the series X_i and the local maxima u_p of $|T_\psi[X_i](b, a)|$ at each scale a then defines the partition function

$$Z(a, q) = \sum_p |T_\psi[X_i](u_p, a)|^q,$$

where the sum is computed only across all the local maxima u_p. The partition function should scale as $Z(a, q) \sim a^{\tau(q)}$, where a nonlinear function $\tau(q)$ characterizes multifractal series (fractal ones have a linear $\tau(q)$). Also in this case the generalized fractal dimensions can be computed by mean of a Legendre transform $D_k = \min_q[qk - \tau(q)]$. Loosely speaking, the scaling exponents of the two methods, $\tau(q)$ and h_q, are linked by the relation $\tau(q) = qh_q - 1$.
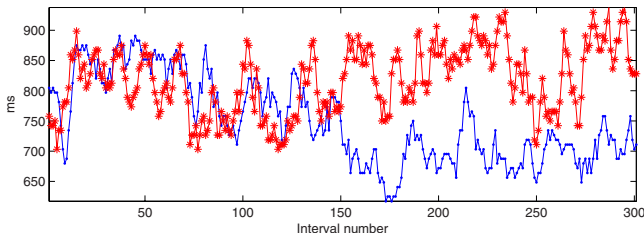
FIG. 1. (Color online) About 4 min of RR series for subject $n5$ is displayed in the picture (dots). Also included is a surrogate series obtained with the IAAFT method (five iterations, stars).

III. RESULTS

We applied both the generalized structure function and WTMM method on data provided by PhysioNet for the discussion of this "controversial topic." In particular, we considered five series obtained from normal subjects: $(21.8 \pm 1.8$ h; ECG sample frequency: 128 Hz; $91\,262 \pm 8884$ points) five series from congestive heart failure patients $(20.0 \pm 0.1$ h; ECG sample frequency: 250 Hz; $88\,701 \pm 16\,085$ points), and five series obtained while the patients were undergoing atrial fibrillation (AF) $(23.4 \pm 1.9$ h; ECG sample frequency: 250 Hz; $116\,677 \pm 24\,041$ points). We did not apply any extra correction and simply used the filtered series as provided (nn files). A few minute sample of HRV signal for one healthy subject is reported in Fig. 1.

Generalized structure functions were computed for each RR series with $q = 1, \ldots, 10$ and $\Delta < N/2$. GSFs for subject $n5$ are displayed in Fig. 2. Three different regions can be recognized: (i) a steep growth for the smallest time lags $(\approx \leq 10)$ where the HRV modulating system is not strong enough to prevent the RR series from randomly walking and GSF scale as $\Delta^{1/2}$, (ii) a good linear scaling region at intermediate scales $(\Delta \in [100; 5000])$ where we estimated the exponent h_q by linear fitting, and (iii) a third region at large scales where the stationarity hypothesis breaks down and the behavior gets unpredictable $(\Delta > 5000)$.

Panel (a) of Fig. 3 illustrates the h_q exponents computed on the GSFs of Fig. 2. In this case, the linear scaling holds for up to $q = 7$. The h_q exponents show a clear decreasing trend supporting the hypothesis of multifractality in this series. To verify a step further this hypothesis, we prepared for each sequence a set of 40 iterated amplitude-adjusted Fourier-transform (IAAFT) surrogate data with an iterative technique[25] (five iterations). As Ref. 22 points out, the technique is able to correctly identify the spurious origin of multifractality in most cases. The hypothesis we would like to nullify is, "The signal is generated by a linear stochastic process distorted by a nonlinear filter expressed by monotonically increasing function." Generalized structure functions and the corresponding scaling exponent h_q^* were computed on each surrogate sequence. The h_q^* values obtained for subject $n5$ are included in Fig. 3(a); they remain constant for increasing q or decrease only slightly. Although having the same power spectrum of the original RR series, they lack phase correlations and are only colored noise.
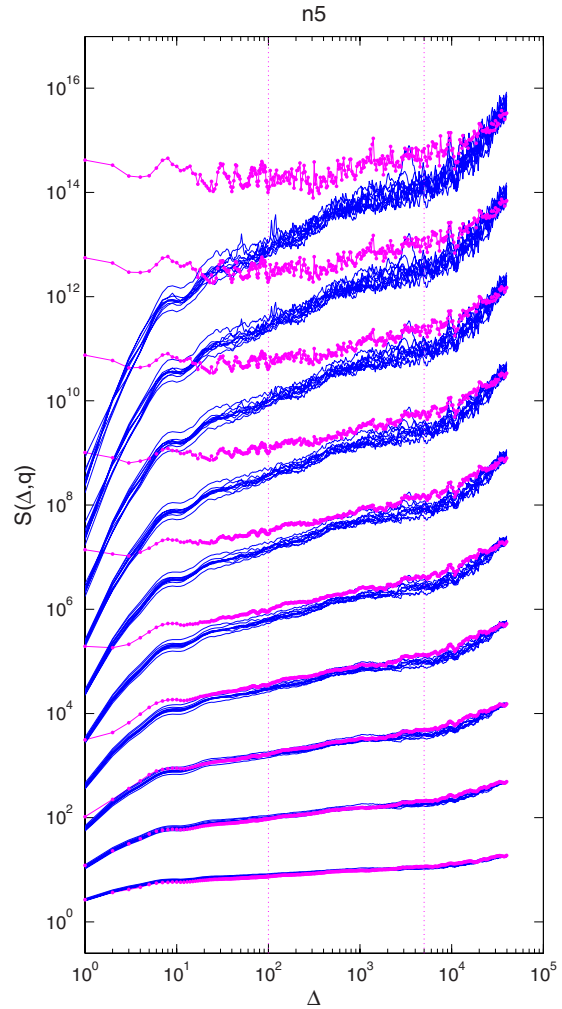

FIG. 2. (Color online) Generalized structured functions for subject $n5$ (dotted line). GSFs for ten (out of 40) IAAFT surrogate series are included for comparison. The dotted lines include the scales where the scaling exponents were estimated.
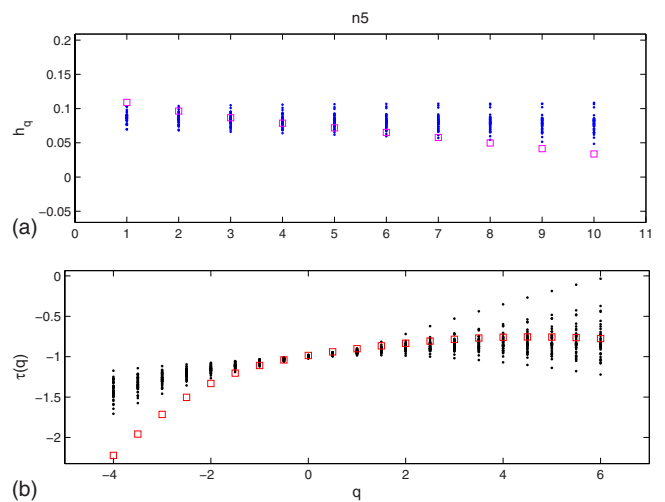

FIG. 3. (Color online) Panel (a): GSFs h_q scaling exponents estimated on the RR series for subject $n5$ (square). Panel (b): Scaling exponents $\tau(q)$ computed with the WTMM technique for subject $n5$ (square). In both panels, the corresponding exponents as obtained on ten IAAFT surrogate series are also reported for comparison (dots).

TABLE I. Scaling exponents were computed on ten RR series. For each sequence the columns contain (i) GSF(Δ, q) l.s.: higher value of q for which a good linear scaling of the corresponding generalized structure function holds in the range [100; 5000]. The value was evaluated by visual inspection; (ii) $\tau(q) \cap \nearrow$: higher value of q for which WTMM scaling $\tau(q)$ is a convex and increasing function; (iii) GSF $p < 5\%$?: a ✓ symbolizes that the h_q value obtained from the RR series was outside the 95% tolerance interval (95% population coverage) estimated from surrogate data; (iv) WTMM $p < 5\%$?: as for column 3 but for WTMM h_q^w.

No.	GSF(Δ, q) l.s.	$\tau(q) \cap \nearrow$	GSF $p < 5\%$?	WTMM $p < 5\%$?
$n1$	$q \leq 8$	$q \leq 0.5$	✓	No
$n2$	$q \leq 10$	$q \leq 2$	✓	✓
$n3$	$q \leq 10$	$q \leq 6$	No	✓
$n4$	$q \leq 2$	$q \leq 5$	…	✓
$n5$	$q \leq 8$	$q \leq 4$	✓	✓
$c1$	$q \leq 2$	$q \leq 3.5$	…	✓
$c2$	$q \leq 7$	$q \leq 6$	✓	No
$c3$	$q \leq 4$	$q \leq 3$	✓	✓
$c4$	$q \leq 4$	$q \leq 3$	✓	✓
$c5$	$q \leq 3$	$q \leq 2$	✓	✓
$a1$	$q \leq 8$	$q \leq 3.5$	No	No
$a2$	$q \leq 7$	$q \leq 6$	No	No
$a3$	$q \leq 7$	$q \leq 6$	No	No
$a4$	$q \leq 8$	$q \leq 6$	No	No
$a5$	$q \leq 7$	$q \leq 3.5$	✓	No

Detailed considerations on the computation of the scaling exponents are included in Table I. In general, for each recording in the database, a good linear scaling region was present in the range [100; 5000] for certain values of q. The h_q spectrum was decreasing in each series of the healthy and congestive heart failure (CHF) group, thus supporting the hypothesis of multifractality. For AF series, h_q values were nearly constant or slightly decreasing.

A similar approach was undertaken using the WTMM method. The implementation is critical as the method requires to follow the maxima at the different scales. Therefore, we employed LASTWAVE, a code provided by E. Bacry.[24] As analyzing wavelet, we selected the fourth derivatives of the Gaussian function and the partition function $Z(a, q)$ was computed in the interval $q \in [-4, 6]$. By visual inspection we verified that the ten normal and CHF series led to fractal dimension spectra D_k which were convex functions [self-similar signal necessarily shows convex D_k (Ref. 21)]. For these cases, the linear scaling of the partition function $Z(a, q)$ was generally good in the interval [32; 2048]. We also verified which was the largest value q^* for which $\tau(q)$ was a convex and increasing function of q.[21] Further details are given in Table I. The values of $\tau(q)$ for subject $n5$ are reported in Fig. 3(b) as long as the exponents are computed on 40 surrogate series. The exponents $h_q^w = [\tau(q) + 1]/q$ for $q \neq 0$ were decreasing as they are expected for multifractal series. AF series need a separate mention: the span of the dimension spectra pointed to a possible fractal nature as opposed to multifractal (h spans were 0.55 ± 0.16 and 0.56 ± 0.22 for N and CHF subjects, respectively, while only 0.2 ± 0.064 for AF series).

Finally, starting from the values h_q^* and $\tau^*(q)$ obtained from surrogate series, we built the 95% tolerance intervals (population coverage: 95%; $K_\alpha = 2.445$) and verified if the corresponding h_q and $\tau(q)$ were outside them. That is, we verified if the results obtained for the scaling exponents on real RR series were statistically different ($p = 5\%$) from those obtained from surrogate series. For GSFs, comparisons were established at the largest q listed in Table I and discarding the cases for which $q < 3$. Among normal and CHF subjects, in seven out of 8 cases, surrogate data provided different results with GSFs exponents (series $n4$ and $c1$ were not included in the test as the corresponding GSFs showed linear scaling only for $q \leq 2$). With WTMM, given the availability of negative moments, comparisons were established at the largest q listed in Table I and at $q = -2$. In eight out of ten cases (normal and CHF), h_q^w exponents were significantly different than surrogate data in either of the two comparisons. Tests generally failed for series recorded during AF both with GSFs as well as WTMM. See Table I for further technical details.

IV. DISCUSSION

Throughout this paper we discussed about the possibility that RR series might be characterized as being multifractal. We employed two different methods to evaluate the scaling exponents h_q. For healthy and CHF patients, both methods agreed that such exponents were decreasing with increasing q, thus supporting the multifractal nature of the series. Such results are coherent with previous similar studies.[26] On the contrary recordings collected during AF showed a small, if any, degree of multifractality. Surrogate data tests generally corroborated the findings, even if the scenario appeared less definite.

The small differences between the two methods might be reasonably charged to nonstationarity present in the signal (to which WTMM is less sensitive). Knowing more information about the sleeping period, it might have helped in analyzing more stationary series.

So, is multifractal an appropriate term to characterize HRV fluctuations? Surely the number of cases is too small to lead to definite conclusions, but a few considerations might be drawn. First, we recall that the method of surrogate data can only nullify the hypothesis set forth, thus it provides a necessary condition only. As stated in the Introduction, no sufficient test does exist. Therefore, the results obtained herein reasonably support the possibility of modeling HRV on long time scales with a multifractal time series (without this implying any chaotic nature of the signal). Second, the scaling of the series did capture characteristics of the populations which might prove useful in the diagnostic process. We verified that normal and CHF series were distinguishable with respect to the GSFs scaling exponents once considered only as statistical indices: h_1, h_2, and h_3 had different means across healthy and CHF subjects (t test; $p < 1\%$). (This consideration also contributes to the discussion on the third question set forth by Chaos editors.) Third, the fact that series obtained during AF were better described as simply fractals hints that the multifractality of HRV could be generated, through the regulatory interaction of the autonomous nervous system. In fact, during AF, ventricular contractions are triggered by the first fibrillation wave which reaches the atrio-

ventricular node after the end of the refractory period. Thus, the time between two consecutive heart contractions is largely independent from the autonomous nervous system and its regulation mechanisms.

In conclusion, this work supported the idea of using multifractals to model HRV. The scaling parameters h_i extracted from GSFs showed to be statistically different among health and CHF patients and suggested (in line with previous studies) that further work on this topic might lead to new prognostic indices. Finally, the differences between healthy and AF series reasonably indicated that multifractality is significantly an effect of the way in which vagal and sympathetic nervous systems interact (see also Ref. 27).

We hope that this study might contribute to evaluate the importance of new nonlinear parameters for a better physiological investigation and for finding new clinical correlates. Actually, only fractal properties (i.e., the α coefficient in long-term ECG recordings) have been recognized as relevant nonlinear parameters in HRV studies: multifractality might provide a new observational window into the complexity mechanisms of heart rate control.

ACKNOWLEDGMENTS

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