



Statistical physics and physiology: Monofractal and multifractal approaches

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Abstract

Even under healthy, basal conditions, physiologic systems show erratic fluctuations resembling those found in dynamical systems driven away from a single equilibrium state. Do such “nonequilibrium” fluctuations simply reflect the fact that physiologic systems are being constantly perturbed by external and intrinsic noise? Or, do these fluctuations actually contain useful, “hidden” information about the underlying nonequilibrium control mechanisms? We report some recent attempts to understand the dynamics of complex physiologic fluctuations by adapting and extending concepts and methods developed very recently in statistical physics. Specifically, we focus on interbeat interval variability as an important quantity to help elucidate possibly non-homeostatic physiologic variability because (i) the heart rate is under direct neuroautonomic control, (ii) interbeat interval variability is readily measured by noninvasive means, and (iii) analysis of these heart rate dynamics may provide important practical diagnostic and prognostic information not obtainable with current approaches. The analytic tools we discuss may be used on a wider range of physiologic signals. We first review recent progress using two analysis methods – detrended fluctuation analysis and wavelets – sufficient for quantifying *monofractal* structures. We then describe very recent work that quantifies *multifractal* features of interbeat interval series, and the discovery that the multifractal structure of healthy subjects is different than that of diseased subjects. © 1999 Published by Elsevier Science B.V. All rights reserved.

1. Introduction

A central task of statistical physics is to deal with macroscopic phenomena that result from microscopic interactions among many individual components [1]. This problem,

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which is at the root of many of the contributions to this conference, is a problem on which much progress has been made in the last third of this century. In particular, physiologic systems under neuroautonomic regulation [2,3], such as heart rate regulation, are good candidates for such an approach, since (i) the systems often include multiple components, thus leading to many degrees of freedom, and (ii) the systems usually are driven by competing forces, e.g., parasympathetic versus sympathetic stimuli. Therefore, it seems reasonable to consider the possibility that dynamical systems under neuroautonomic regulation may exhibit temporal structures that are similar, under certain conditions, to those found in physical systems. Indeed, new conceptual frameworks and corresponding methodologies are being developed in order to deal with three particularly vexing features of physiologic time series.

(i) *Nonstationarity*. Traditional methods of statistical analysis assume that the statistical properties of a signal are the same throughout the signal [4]. This is not true for many signals of interest in physiology – e.g., the statistical properties of the heart rate change when a subject rises to a standing position. Such nonstationarity problems arise in other contexts in the discipline of statistical physics, and novel techniques such as *detrended fluctuation analysis* (DFA) [5] and *wavelets* [6–8] have been successfully developed to study nonstationary signals. Hence we are exploring the degree to which the solutions found in statistical physics can be usefully applied to physiologic signals.

(ii) *Nonlinearity*. Traditional methods of analysis also assume that to a large degree the system can be viewed as linear, so that departures from linearity can be treated perturbatively. This is not true for most physiologic systems, which are intrinsically nonlinear. A salient feature of nonlinear systems is that their components interact with each other, and therefore their outputs are not proportional to the strength of the inputs. The field of statistical physics has in the past 10 yr focused on nonlinear systems, and has developed a conceptual framework within which a wide range of nonlinear phenomena can be usefully treated. Hence we are seeking to uncover which of these methodologies can be usefully applied and carefully adapted to data. In particular, *multifractal* methods [9,10] offer a new and potentially promising avenue for quantifying features of a range of physiological signals that differ in health and disease.

(iii) *Nonequilibrium phenomena*. From the time of Bernard [11] and Cannon [12], it has been assumed that physiologic systems possess feedback and control mechanisms that serve to restore an equilibrium-like state when a system is perturbed away from some set point. Recent research, however, has shown that physiologic systems are inherently out-of-equilibrium systems [13]. Nonequilibrium statistical mechanics has made advances in recent years that have yet to be applied in the physiologic domain.

The statistical methods we are developing are particularly attractive for the analysis of heart rate time series because they can be reliably applied to complex signals from stochastic, deterministic, or mixed systems. Further, these techniques are specifically designed to cope with the output of highly nonstationary processes. As such, these

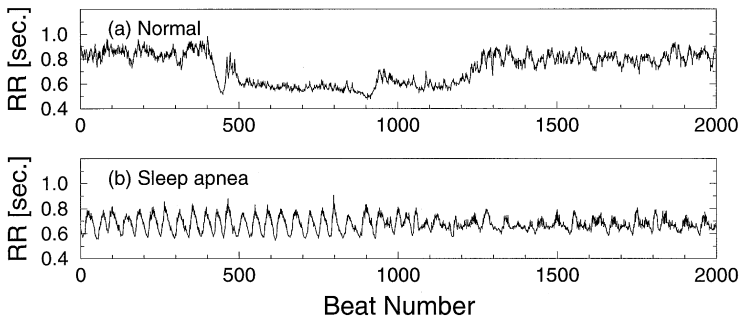


Fig. 1. Representative complex physiologic fluctuations. Cardiac interbeat interval (normal sinus rhythm) time series of 2000 beats from (a) a healthy subject and (b) a subject with obstructive sleep apnea. Note the nonstationarity of these time series, which limits the applicability of traditional methods of analysis and modeling. This figure is courtesy of J. Mietus.

methods complement approaches derived from the analysis of deterministic systems which may be less appropriate for nonstationary data [14–16].

2. Information in nonstationarity physiologic signals

A major problem in contemporary physiology (and cardiology in particular) is the presence of nonstationarity in time series. The signals obtained under constantly varying conditions raise serious challenges to both technical and theoretical aspects of time series analyses.

Representative examples of complex dynamical behavior under physiologic and pathologic conditions are shown in Fig. 1. Fig. 1a shows a cardiac interbeat time series – the output of a spatially and temporally integrated neuroautonomic control system. The time series shows erratic fluctuations and “patchiness”. These fluctuations are usually ignored in conventional medical studies that focus on averaged quantities. In fact, these fluctuations are often labeled as “noise” to distinguish them from the true “signal” of interest. Generally, in the conventional approach it is assumed that there is no meaningful structure in apparent noise and, therefore, one does not expect to gain any understanding about the underlying system through the study of these nonequilibrium fluctuations. However, by adapting and extending methods developed in modern statistical physics and nonlinear mathematics, we have recently found that the physiologic fluctuations shown in Fig. 1a exhibit unexpected hidden scaling structure. Furthermore, these patterns change with pathological perturbations (shown in Fig. 1b). These findings raise the possibility that understanding the origin of such temporal structures and their alterations may (i) elucidate certain basic features of heart rate control mechanisms, and (ii) have practical value in clinical monitoring.

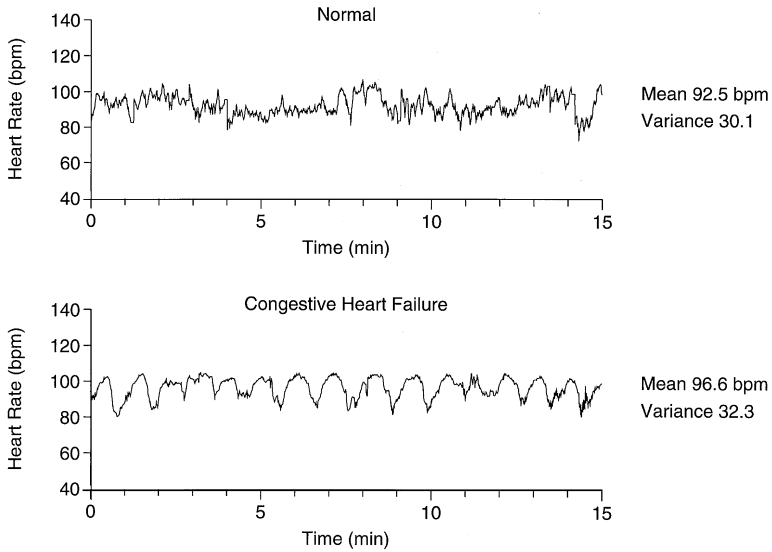


Fig. 2. Two heart rates time series with identical values of their means and standard deviations. However, dramatic differences in their dynamics can be easily visualized. Note that the healthy subject shows a complex type of variability while the subject with heart failure shows a more periodic pattern with an apparent loss of complexity. This figure is courtesy of J. Mietus.

3. Limitations of traditional techniques

3.1. Averages, standard deviations and distribution functions

A technique widely used to analyze time series is the study of the moments of the distribution of measured values. Fig. 2 shows two sequences of interbeat intervals, one for a normal individual and one for a subject with congestive heart failure. Visual inspection makes clear the existence of differences in the dynamics generating the two signals. However, the signals have the same averages and standard deviations. Hence additional methods are required if these two signals are to be distinguished.

3.2. The power spectrum of nonstationary signals

A quantity widely used to measure correlations in a time series is the power spectrum, which measures the relative frequency content of a signal. A power spectrum calculation assumes that the signal studied is stationary, and when applied to nonstationary time series can lead to misleading results. To illustrate this point, we analyze two artificial signals: one (Fig. 3a) is stationary – two different frequencies are present at all times. The other (Fig. 3b) is nonstationary – one frequency is present in the first half of the signal and another frequency in the other half. The calculation of the power spectrum for these signals leads to almost *identical* results! Similarly, the

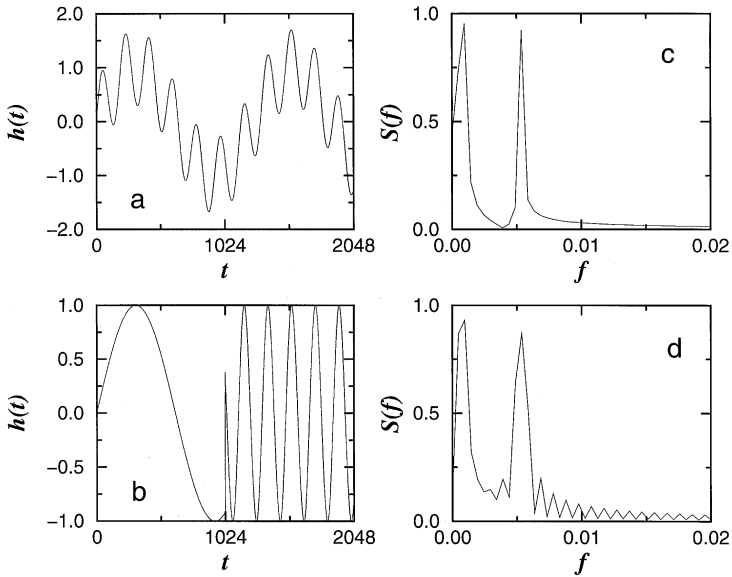


Fig. 3. (a) *Stationary* signal resulting from the sum of two sine waves with frequencies $1/(200\pi)$ and $1/(60\pi)$. (b) *Nonstationary* signal with a first regime comprised of a sine wave with frequency $1/(200\pi)$, and a second regime comprised of a sine wave with frequency $1/(60\pi)$. (c) and (d) Note how the power spectra of the two signals are almost identical. (They would be identical except for the small high frequency fluctuations due to the spurious singularity at $x = 1024$.) Thus, a power spectrum analysis cannot distinguish these signals, despite their obvious differences. This figure is courtesy of L.A.N. Amaral.

presence of linear or higher-order polynomial trends can mask the frequency content of a signal. Since the power spectrum is incapable of distinguishing between these types of behavior, it must not be used as the *only* form of analysis for nonstationary signals.

4. Monofractal analysis: detecting and quantifying long-range correlations

To quantitatively describe noisy cardiac signals is not an easy task. Techniques for analysis must be selected carefully in order to extract robust features hidden in these complex fluctuations. We have developed several complementary algorithms in the last few years for this purpose. We will first discuss some interesting results obtained by applying these new methods.

4.1. Measurement of long-range correlations in physiologic interbeat interval dynamics

An important question is whether the “heterogeneous” structure of physiologic time series arises trivially from external and intrinsic perturbations which push the system

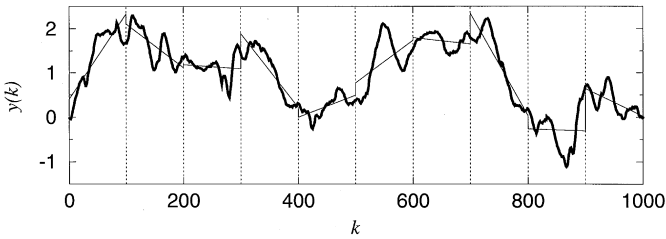


Fig. 4. The integrated time series: $y(k) = \sum_{i=1}^k [RR(i) - RR_{ave}]$, where $RR(i)$ is the interbeat interval shown in Fig. 1a. The vertical dotted lines indicate box of size $n = 100$, the solid straight line segments are the estimated “trend” in each box by least-squares fit. This figure is courtesy of C.-K. Peng.

away from a homeostatic set point. An important alternative hypothesis is that the fluctuations are, at least in part, due to the underlying dynamics of the system. The key problem is how to decompose subtle fluctuations (due to intrinsic physiologic control) from other nonstationary trends associated with external stimuli.

To this end, our multidisciplinary team recently introduced the *detrended fluctuation analysis* (DFA) method [5]. The advantages of DFA over conventional methods are that it permits the detection of long-range correlations embedded in a seemingly nonstationary time series and also avoids the spurious detection of apparent long-range correlations that are an artifact of nonstationarity. The DFA method (Fig. 4) has been tested on control time series that consist of long-range correlations with superposition of a nonstationary external trend. It has also been successfully applied to detect long-range correlations in highly heterogeneous DNA sequences [5,17–19]. Of note is a recent independent review of fractal fluctuation analysis methods which determined that DFA was one of the most robust methods [20].

The computational details of DFA are described elsewhere [5,17]. Briefly, a moving window of size n is used to study how the fluctuation $F(n)$ grows with n for the interbeat interval time series. The slope of the line relating $\log F(n)$ to $\log n$ determines the scaling exponent (self-similarity parameter) α (Fig. 5).

4.2. Alteration of correlation properties in pathologic states

Assessing correlations under pathologic conditions is likely to be particularly informative for patients with congestive heart failure due to severe left ventricular dysfunction since these individuals have abnormalities in both the sympathetic and parasympathetic control mechanisms [21] that regulate beat-to-beat variability. Previous studies have demonstrated marked changes in short-range heart rate dynamics in heart failure compared to healthy function, including the emergence of intermittent relatively low-frequency (~ 1 cycle/min) heart rate oscillations associated with the well-recognized syndrome of periodic (Cheyne–Stokes) respiration, an abnormal breathing pattern often associated with low cardiac output [21]. Of note is the fact that patients with congestive heart failure are at very high risk for sudden cardiac death.

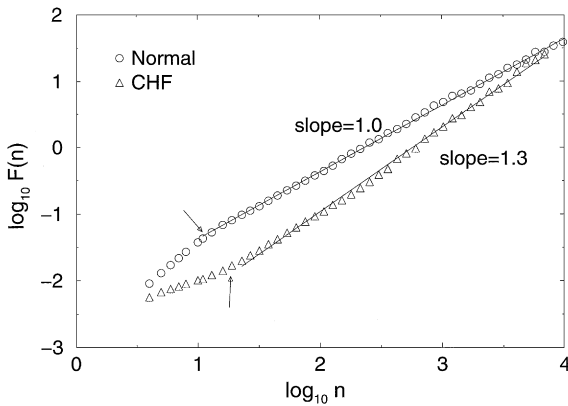


Fig. 5. Plot of $\log F(n)$ vs. $\log n$ for two long interbeat interval time series (~ 24 h). The circles are for a representative healthy subject while the triangles are from a subject with congestive heart failure. Arrows indicate “crossover” points in scaling. Note altered scaling with heart failure, suggesting apparent perturbations of both short and long-range correlation mechanisms. This figure is courtesy of C.-K. Peng (see [26]).

Fig. 5 compares the DFA analysis of representative 24 h interbeat interval time series of a healthy subject (\circ) and a patient with congestive heart failure (\triangle). Notice that for large time scales (asymptotic behavior), the healthy subject shows almost perfect power-law scaling over more than two decades ($20 \leq n \leq 10\,000$) with $\alpha = 1$ (i.e., $1/f$ noise) while for the pathologic data set $\alpha \approx 1.3$ (closer to Brownian noise). This result is consistent with our previous finding [22,23] that there is a significant difference in the long-range scaling behavior between healthy and diseased states.

To study the alteration of long-range correlations with pathology, we analyzed cardiac interbeat data from three different groups of subjects: (i) 29 adults (17 male and 12 female) without clinical evidence of heart disease (age range: 20–64 yr, mean 41), (ii) 10 subjects with fatal or near-fatal sudden cardiac death syndrome (age range: 35–82 yr) and (iii) 15 adults with severe heart failure (age range: 22–71 yr; mean 56). Data from each subject contains approximately 24 h of ECG recording encompassing $\sim 10^5$ heartbeats.

For the normal control group, we observed $\alpha = 1.00 \pm 0.10$ (mean value \pm S.D.). These results indicate that healthy heart rate fluctuations exhibit long-range power-law (fractal) correlation behavior over three decades, similar to that observed in many dynamical systems far from equilibrium [24,25]. Furthermore, both pathologic groups show significant deviation of the long-range correlations exponent α from the normal value, $\alpha = 1$. For the group of heart failure subjects, we find that $\alpha = 1.24 \pm 0.22$, while for the group of sudden cardiac death syndrome subjects, we find that $\alpha = 1.22 \pm 0.25$. Of particular note, we obtained similar results when we divided the time series into three consecutive subsets (of ~ 8 h each) and repeated the above analysis [26]. Therefore, our findings are not simply attributable to different levels of daily activities. Our results have been independently verified by Turcott and Teich at Columbia University [27].

4.3. Clinical utility

Recently, fractal scaling analysis has been applied to three retrospective clinical studies [28–30]. Results from all three studies indicate that additional information can be extracted from heart rate time series with the method we developed. Furthermore, these information can be used for prognostic purpose. We have also shown [31] that the scale-free parameters we introduce have a greater potential for more accurate diagnosis than recently suggested scale-specific measures [32].

4.3.1. Forecasting clinical outcomes: Framingham Heart Study

A major question regarding this new fractal long-range measurement is the following: *Does DFA have clinically predictive value, independent of conventional time- and frequency-domain indices?* To answer this question, the predictive power of the DFA exponent in comparison with 10 other conventional indices has been studied. Ho et al. analyzed 2 h ambulatory ECG recordings of 69 participants (mean age 71.7 ± 8 yr) in the Framingham Heart Study – a prospective, population-based study [28]. Importantly, they found that this fractal measurement carries prognostic information about mortality not extractable from traditional methods of heart rate variability analysis.

4.3.2. Heart rate dynamics in patients at high risk of sudden death after myocardial infarction

Mäkikallio and co-workers compared short-term (< 11 beats) and long-term (> 11 beats) correlation properties of RR interval data in three groups: (i) 45 postinfarction patients with a recent history of ventricular tachyarrhythmia and inducible ventricular tachyarrhythmia by programmed electrical stimulation, (ii) 45 postinfarction patients without clinical ventricular tachyarrhythmia events or inducible ventricular tachyarrhythmia, and (iii) 45 healthy control subjects. The short-term scaling exponent (α_1) was significantly lower in the ventricular tachyarrhythmia group than in postinfarction control group ($p < 0.001$) or healthy controls ($p < 0.001$) [29]. In stepwise multiple regression analysis, the short-term exponent was the strongest independent predictor of vulnerability to ventricular tachyarrhythmia. The data suggest that short-term correlation properties of RR interval dynamics are altered in postinfarction patients with vulnerability to ventricular tachyarrhythmia, and that abnormal beat-to-beat heart rate dynamics may be related to vulnerability to ventricular tachyarrhythmia in postinfarction patients.

4.3.3. Heart rate dynamics in patients with stable angina pectoris

Recently, Mäkikallio [30] also compared conventional measures of heart rate variability with short term (≤ 11 beats, α_1) and long-term (> 11 beats, α_2) fractal correlation properties and with approximate entropy of RR interval data in 38 patients with stable angina pectoris without previous myocardial infarction or cardiac medication at the time of the study and 38 age-matched healthy controls. The short- and long-term fractal

scaling exponents (α_1, α_2) were significantly higher in the coronary patients than in the healthy controls (1.34 ± 0.15 vs. 1.11 ± 0.12 [$p < 0.001$] and 1.10 ± 0.08 vs. 1.04 ± 0.06 [$p < 0.01$], respectively), and they also had lower approximate entropy ($p < 0.05$), standard deviation of all RR intervals ($p < 0.01$), and high-frequency spectral component of heart rate variability ($p < 0.05$). The short-term fractal scaling exponent performed better than other heart rate variability parameters in differentiating patients with coronary artery disease from healthy subjects, but it was not related to the clinical or angiographic severity of coronary artery disease or any single nonspectral or spectral measure of heart rate variability in this retrospective study.

5. Multifractal analysis: application to physiologic signals

The DFA method can measure only one exponent characterizing a given signal. This fact implies that the method is more appropriate for the study of monofractal signals. Monofractals are homogeneous in the sense that they have the same scaling properties, characterized by a single singularity exponent h_0 , throughout the entire signal [33–38]. On the other hand, multifractal signals or objects require an infinite number of indices to characterize their scaling properties. Multifractals can be decomposed into many – possibly infinitely many – sub-sets characterized by different exponents h . The singularity spectrum, $D(h)$, quantifies the *fractal dimension* of the sub-set characterized by the exponent h . Thus, multifractal signals are intrinsically more complex, and inhomogeneous, than monofractals (Fig. 6).

Multifractal structures have been uncovered in a number of classical physical problems such as voltage drops across a random resistor network [39], spatial distribution of the dissipation field of fully developed turbulence [40,41], viscous fingering [42,43], and diffusion-limited aggregation [44,10]. However, in physics and other applied sciences, fractals appear not only as singular objects (measures) but also as singular functions generated by dynamical systems. There have been only a few attempts to extend the concept of multifractality to singular functions: for velocity in turbulence [45] and for rough surfaces [46].

Physiologic signals are generated by complex self-regulating systems that process inputs with a broad range of characteristics. Monofractal signals are homogeneous and have “linear” properties. Many physiologic time series – such as interbeat interval sequences – are in fact inhomogeneous, suggesting that different parts of the signal have different scaling properties. In addition, there is evidence that heartbeat dynamics exhibits nonlinear properties [47–49]. Up to now, robust demonstration of multifractality for nonstationary time series has been hampered by problems related to a drastic bias in the estimate of the singularity spectrum due to diverging negative moments. Moreover, the classical approaches based on the box-counting technique and structure function formalism fail when a fractal function is composed of a multifractal singular part embedded in regular polynomial behavior.

Change of local Hurst exponent h :

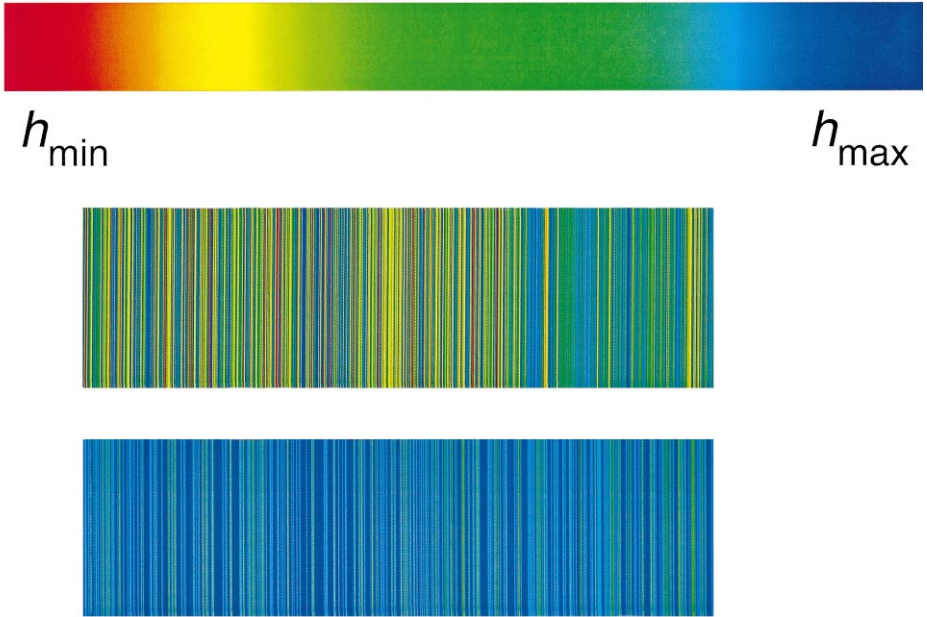


Fig. 6. Hurst introduced an exponent, now called the Hurst exponent h , to describe the fluctuations in rise and fall of the Nile River as a function of the time scale over which these fluctuations are analyzed. Here we show the Hurst exponent for two representative subjects, one of whom is healthy (top) and one of whom is diseased (bottom). Remarkably, we see that for the healthy subject, a single Hurst exponent is not found. Rather, h varies over a factor of almost two. How can we quantify this change? One way is to divide the continuum rainbow spectrum into, say, 10 discrete bins, where $i = 1, 2, \dots, 10$ indexes the bins. Then imagine that we examine this rainbow successively – through 10 different pieces of colored film, each of which allows only wavelengths near a characteristic value λ_i to pass. For each piece of color film i , we will see a “fractal dust” corresponding to the sparse set of colors that passes through film i . We then calculate the 10 fractal dimensions $D(h)$ corresponding to each of the ten different fractal dusts. Fig. 9 plots the function $D(h)$, and we see that $D(h)$ varies more as h increases from its minimum value h_{\min} to its maximum value h_{\max} for the health subjects than for the diseased. This figure is courtesy of Z. Struzik.

The calculation of the multifractal spectrum involves the following steps:

- (i) The wavelet transform is found for this signal (for each scale a).
- (ii) The maxima of the absolute values of the wavelet transform are found.
- (iii) The moduli of these local maxima raised to power q are all summed to form a partition function $Z_q(a)$.
- (iv) $Z_q(a)$ is plotted on a double log scale against a .
- (v) The slopes of these plots for different values of the moment q are the exponents $\tau(q)$ which are related to the multifractal spectrum of the signal (Figs. 7 and 8).

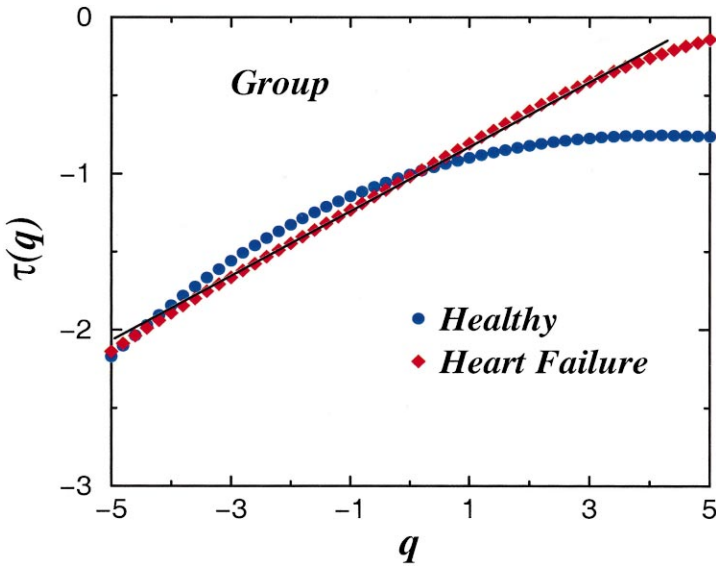


Fig. 7. Multifractal spectrum $\tau(q)$ of the group averages for daytime and nighttime records for 18 healthy subjects and for 12 patients with congestive heart failure. Each record extends for about 6 hs and has close to 30,000 beats. The results show multifractal behavior for the healthy group and distinct change in this behavior for the heart failure group. However, the multifractal formalism is a general framework, not only able to confirm the DFA results but also to provide us with information about different types of singularity. This figure is courtesy of P. Ivanov.

By not summing over the entire set of wavelet transform values along the time series at given scale a but only over the wavelet transform modulus maxima, we directly incorporate the multiplicative structure of the singularity distribution into the calculation of the partition function $Z_q(a)$ [50]. Thus by studying the scaling behavior of $Z_q(a) \sim a^{\tau(q)}$ in the limit $a \rightarrow 0$ we can obtain information about the self-similarity (fractal) properties of the signal. This approach is known as the wavelet transform modulus maxima method [50].

We recently adopted this new methodology to human heartbeat interval series obtained from electrocardiogram records [51]. Our initial findings (Fig. 9) include several encouraging results:

- (i) The diurnal heart rate of healthy humans is a multifractal with nonzero fractal dimension for sub-sets characterized by singularity exponents in the interval -0.1 to 0.5 .
- (ii) Records for patients with a nearly terminal pathology, congestive heart failure, show a significant loss of multifractal complexity displaying a smaller range of values of h .

From a physiologic perspective, the detection of robust multifractal scaling in heart rate dynamics is of interest for a number of reasons. First, previous analyses have focused

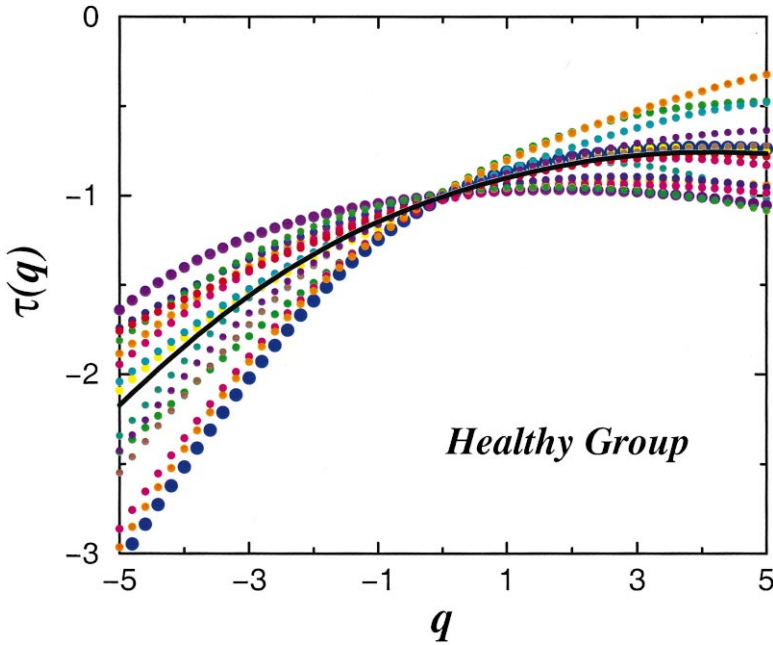


Fig. 8. Demonstration that all 18 patients from the healthy group display multifractality, as evidenced by the fact that $\tau(q)$ is not linear. This figure is courtesy of P.Ch. Ivanov (see also [51]).

only on the quantification of a single scaling exponent (monofractal) behavior to account for the apparently $1/f$ spectrum of healthy interbeat intervals over a wide range of time scales. We show for the first time that the healthy heartbeat is even more complex than previously suspected, requiring multifractal scaling with multiple exponents for its characterization. Second, our analysis indicates that the observed multifractality is related to nonlinear features of the healthy heartbeat dynamics, which are encoded in the Fourier phases [47,51] able to detect subtle diurnal differences in this multifractal scaling. Third, we find a loss of multifractal complexity in a major pathologic condition – namely congestive heart failure, suggesting possible bedside applications. Fourth, our results are notable because they pose a challenge to ongoing efforts to develop realistic models of heart rate control and other processes under neuroautonomic regulation. There is currently no precedent in physiology to account for such complex behavior which in physical systems has been connected with turbulence and related multiscale phenomena. Our findings raise the intriguing possibility that the control mechanisms regulating the heartbeat interact as part of a coupled cascade of feedback loops in a system operating far from equilibrium.

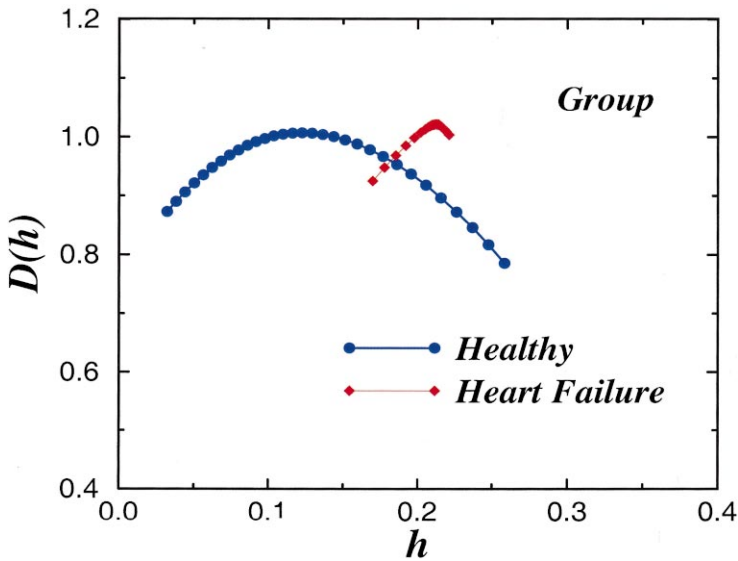


Fig. 9. Fractal dimensions $D(h)$ obtained through a Legendre transform from the group averaged $\tau(q)$ spectra of Fig. 7. The shape of $D(h)$ for the individual records and for the group average is broad, indicating multifractal behavior. On the other hand, $D(h)$ for the heart failure group is very narrow, indicating monofractality. Specifically, we can see the broad range of values of h for the healthy group, from h close to zero which implies strong anti-correlations, to $h \approx 0.5$. A monofractal signal would appear as a spike for some particular value of h . Note the smaller range of values for h for the congestive heart failure group and the lower values of the $D(h)$ for identical values of the h exponent, indicating a clear loss of complexity with disease. These results are in agreement with those reported for the detrended fluctuation analysis (DFA): The peak of the multifractal spectrum $D(h)$ for the congestive heart failure group is shifted closer to a random walk behavior $h=0.5$ compared to the healthy group. Specifically, we can see the broad range of values of h for the healthy group, from h close to zero which implies strong anti-correlations, to $h \approx 0.5$. A monofractal signal would appear as a spike for some particular value of h . Note the smaller range of values for h for the congestive heart failure group and the lower values of the $D(h)$ for identical values of the h exponent indicating a clear loss of complexity with disease. These results are in agreement with those reported for the detrended fluctuation analysis (DFA): The peak of the multifractal spectrum $D(h)$ for the congestive heart failure group is shifted closer to a random walk behavior $h=0.5$ compared to the healthy group. The different form of $D(h)$ for the heart failure group may reflect perturbation of the cardiac neuroautonomic control mechanisms associated with this pathology. This figure is courtesy of L.A.N. Amaral.

6. Discussion and summary

Our preliminary results applying methods of modern statistical physics to questions of interest in the discipline of physiology suggest the following findings:

- Heart rate dynamics under normal conditions display nonequilibrium fluctuations that cannot be detected or analyzed with traditional methods, but which reveal a remarkable physiologic structure when analyzed using methods adapted from statistical physics.

- This healthy nonequilibrium behavior is altered under three major pathological syndromes where neuroautonomic function is known to be perturbed, congestive heart failure, sudden cardiac death, and obstructive sleep apnea.
- By applying the new technique detrended fluctuation analysis (DFA) – developed recently by our group – we were able to analyze nonstationary heartbeat time series and found the presence of long-range power-law correlations in the fluctuations of the heart beat intervals over multiple time scales. Furthermore, we observed significant alterations and sometimes even a complete breakdown these long-range correlation properties with congestive heart failure. These results have been independently tested and confirmed by other research groups [27].
- We demonstrated the ability of DFA to help predict mortality in a population-based study of heart failure subjects and controls in the Framingham Heart Study.
- The observation of nonlinear multifractal behavior shows even greater complexity of the cardiac dynamics than previously thought, and indicates that a broad range of scaling exponents are needed to describe this complexity. The multifractal approach shows also a potential to discriminate healthy from sick hearts even when the correlations described by the DFA are *identical*. These multifractal features are *not* accounted for by traditional physiologic mechanisms and motivates new modeling strategies to understand nonequilibrium control systems under healthy and pathologic conditions.

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