Fractal Response of Physiological Signals to Stress Conditions, Environmental Changes, and Neurodegenerative Diseases

In the past two decades the biomedical community has witnessed several applications of nonlinear system theory to the analysis of biomedical time series and the development of nonlinear dynamic models. The development of this area of medicine can best be described as nonlinear and fractal physiology. These studies have been intended to develop more reliable methodologies for understanding how biological systems respond to peculiar altered conditions induced by internal stress, environment stress, and/or disease. Herein, we summarize the theory and some of our results showing the fractal dependency on different conditions of physiological signals such as inter-breath intervals, heart inter-beat intervals, and human stride intervals. © 2007 Wiley Periodicals, Inc. Complexity 12: 12–17, 2007

NICOLA SCAFETTA, RICHARD E. MOON, AND BRUCE J. WEST

Nicola Scafetta is with the Department of Physics, the FG Hall Environmental Laboratory, and the Free Electron Laser Laboratory, Duke University, Durham, NC 27708. Richard E. Moon is with the Departments of Anesthesiology and Medicine and the FG Hall Environmental Laboratory, Duke University, Durham, NC 27708. Bruce J. West is with the Department of Physics, Duke University, Durham, NC 27708 and the Mathematics Division of the US Army Research Office, Research Triangle Park, NC 27709.

Nonlinear dynamics, chaos theory and fractal analysis have suggested strategies where the focus has shifted from the traditional study of averages, histograms and simple power spectra of a physiological variable to the study of the patterns in the fluctuations of the variable [1–4]. In fact, it has been known for a long time that biophysical time series are stochastic, but it is only more recently that these time series have been identified as fractals and as being generated by scaling phenomena. This novel approach is justified by the fact that physiological time series fluctuate in an irregular and complex manner as a response to the dynamics of the entire biological system under study. These fluctuations are indeed found to exhibit complex autocorrelation patterns and fractal properties suggesting that the dynamics and the structure of the underlying biology are indeed nonlinear, chaotic and/or fractal, either in space, time, or both.

An example of such physiological time series consists of the beat-to-beat intervals of the human heart, called the heart rate variability (HRV) time series. Peng et al. [5] were the first to show that the scaling of the central moments of HRV time series yield the fractal dimension of the cardiovascular control system. It was shown in a number of subsequent studies [6] that the HRV time series, rather than being monofractal, are in fact multifractal. Walking is another phenomenon that is described by scaling time series when looked at properly. Hausdorff et al. [7] were the

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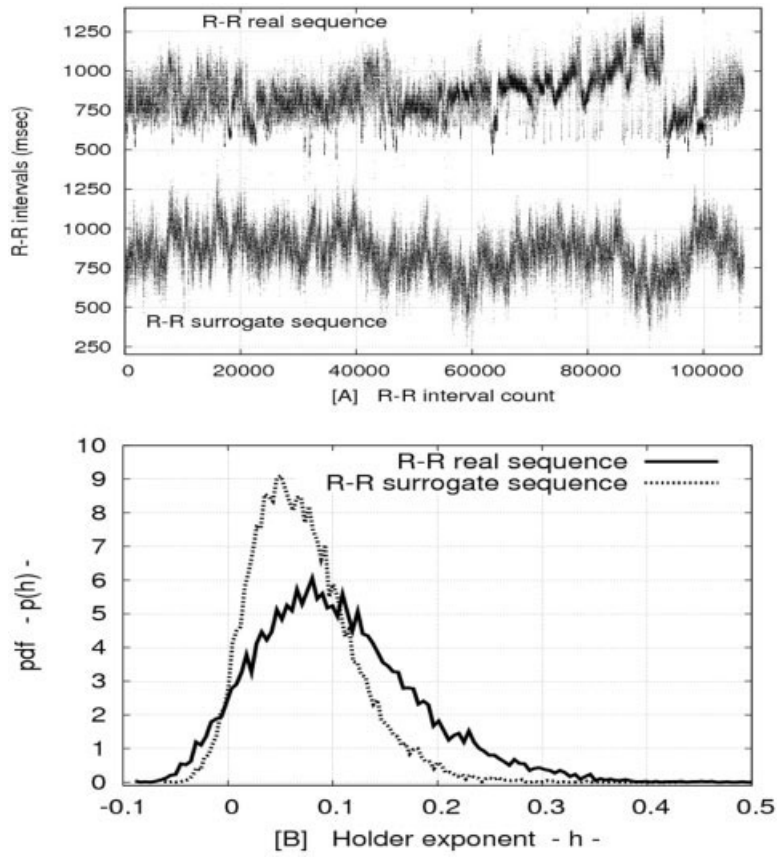
first to show that the stride-to-stride interval time series, called stride rate variability (SRV), manifest scaling in a way similar to the HRV time series and that SRV memory patterns might depend on aging or disease [8]. The SRV time series were subsequently shown to also be multifractal rather than monofractal [9].

Thus, an important class of physiological phenomena has been proven to be characterized by fractal and/or multifractal properties. Historically, fractal or long-range correlated processes [10, 11] have been classified as 1/f-phenomena, because their time series have power spectra that exhibit an inverse power law with respect to frequency, $P(f) \sim 1/f^{\beta}$. In addition to the power spectrum exponent β, the degree of long-range correlation of a time series can be equivalently assessed from the Hurst exponent $H = (\beta + 1)/2$ and from the fractal dimension $D = 2 - H$ [10, 11]. The algorithms used to estimate directly the Hurst exponent are usually quite simple and stable [12]. One of these algorithms is based on the estimation of the standard deviation of the diffusion process $D(\tau)$ generated by integrating the data of the time series. This function of the diffusion time τ, in the case of long-range correlations, yields a curve of the type $D(\tau) = c\tau^{H}$, where c is a constant and H is the Hurst exponent [12]. Another common algorithm used to evaluate the Hurst exponent H is the detrended fluctuation analysis [13].

The interpretation of the Hurst exponent is as follows. The value $H = 0.5$ characterizes random sequences that are known as white noise because their power spectrum is flat, $\beta = 0$. A value $0 < \beta < 1$ or $0.5 < H < 1$ characterizes persistent or long-range correlated sequences, where an event is correlated positively with the previous ones. Thus, persistent sequences are characterized by a stochastically up-up or down-down pattern. A value $\beta = 1$ or $H = 1$ characterizes pure 1/f-phenomena known in the literature as pink noise. In a generalized sense it is possible to have values $\beta > 1$ or $H > 1$. Sequences characterized by these values would not properly be characterized as *noises* but processes that are more properly referred to as *walks,* that is, integrals of noises. The simplest example of a walk is the *random walk,* which is the integral of random noise, that has $\beta = 2$ or $H = 1.5$. Finally a value $\beta < 0$ or $0 < H < 0.5$ characterizes antipersistent sequences where each event is correlated negatively with the previous one. Antipersistent sequences are characterized by a rapid stochastically alternating up-down pattern.

FIGURE 1



(A) Comparison between a typical R-R interval sequence and a monofractal computer generated sequence having the same average, variance and Hurst exponent. (B) Hölder exponent histograms for the two sequences. The real R-R sequence is multifractal as indicated by the wider width of its Hölder exponent histogram.

It has been found that physiological sequences are persistent noises and/or walks, that is, they are characterized by a value of the Hurst exponent ranging from $H = 0.5$ to $H = 1.5$. This finding suggests that biological systems, far from being random processes, are indeed processes that are regulated by complex dynamics that incorporate memory of past events. The strength of this memory, which is measured by the Hurst exponent, is expected to be altered under internal stress, environment stress, and/or disease because the dynamics of a biological system are likely modified by altered physiological conditions.

In addition, modern scientific literature distinguishes monofractal time se-

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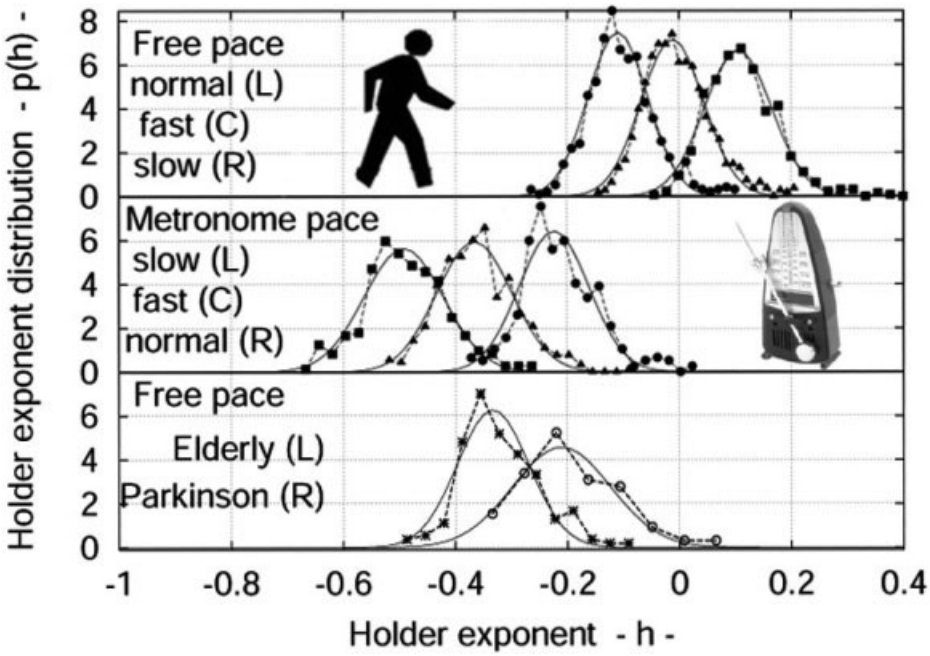
FIGURE 2



Typical Hölder exponent histograms for the stride interval sequences during free walking and metronome-paced conditions for normal, slow and fast paces and for a normal elderly person and a subject with Parkinson's disease. The histograms are fitted with Gaussian functions. (L, Left; C, Center; R, Right). Data from http://www.physionet.org.

ries, where a single scaling exponent characterizes the sequence, from multifractal time series that are characterized by an infinite hierarchy of sets, each with its own fractal dimension [11, 14]. There is also a wide class of phenomena in which the fractal dimension changes from point to point in the time series. These local scaling exponents are commonly referred to as local Hölder exponents [15]. So, rather than the fractal dimension having a single value, it may take on many values and the time series may be considered multifractal. The full range of the scaling properties of multifractal phenomena is more properly described by a singularity spectrum or a probability distribution of local Hölder exponents. These curves are characterized by at least three independent parameters: the position of the maximum, the width and the asymmetry of the singularity spectrum or probability distribution curve. These multifractal parameters are likely to be altered under internal or environment stress and/or disease.

Data processing techniques based on wavelet transforms are generally used to determine singularity spectra and local Hölder exponent distributions [9, 14, 15]. There exists also a method called multifractal detrended fluctuation analysis [16]. The average Hölder exponent, h_0, is approximately related to the Hurst exponent as $h_0 = H - 1$ [9]. Figure 1 shows an example that explains the importance of the multifractal analysis. Figure 1(A) shows two long sequences: an actual inter-beat (R-R) sequence and a surrogate sequence. The surrogate sequence was obtained by means of a computer algorithm such that the two sequences have the same average, the same standard deviation, and the same Hurst exponent, which has a value slightly larger than $H = 1$, corresponding to the average Hölder exponent $h_0 = H - 1 = 0$. Thus, they would be considered equivalent by adopting traditional measures and also a monofractal measure of the data, such as the Hurst analysis. However, Figure 1(B) shows the Hölder exponent distributions of the two sequences, and although the two distributions are approximately centered on the same values of the Hölder exponents, a clear difference in the widths of the two distributions emerges. In fact, the surrogate sequence is a monofractal sequence, whereas the real R-R sequence presents multifractal properties, as indicated by a wider Hölder exponent distribution. Note that according to the adopted algorithm, the Hölder exponent distribution of a monofractal sequence of a limited length will be characterized with a certain width that might depend on the signal length, but the distribution width for an equally long sequence increases for a multifractal sequence, indicating a higher level of variability and complexity [9].

Examples of fractal dependency of physiological time series such as interbreath intervals, inter-beat (R-R) intervals, and human stride intervals on environmental stress and physiological pathologies deriving from acute hypobaric hypoxia, progressive central hypovolemia, and neurodegenerative diseases, as well as from different kinds of physical exercises, are shown in the following.

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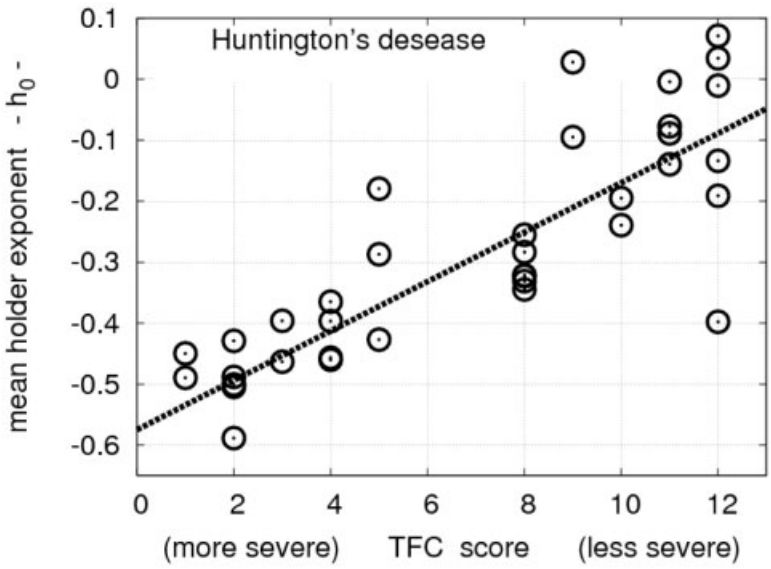
FIGURE 3



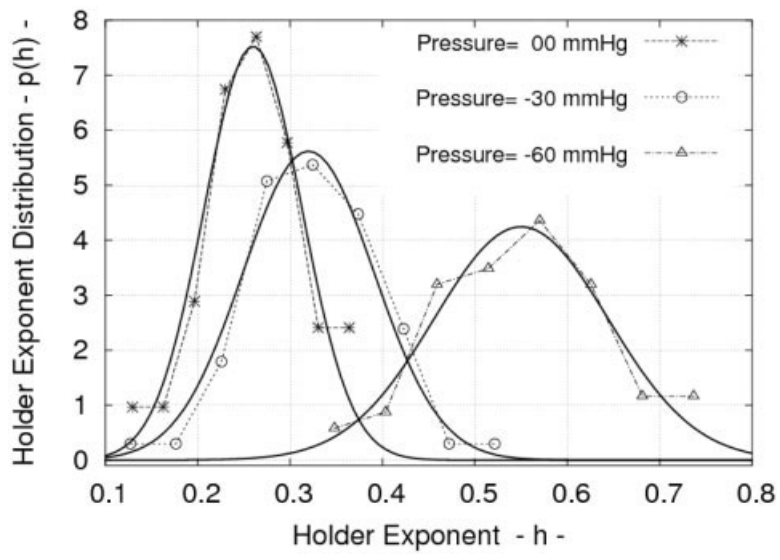
Mean Hölder exponent vs. TFC score for stride interval sequences for a group of patients. Disease severity is measured by using total functional capacity (TFC) score of Unified Huntington's disease rating scale (0 = most impairment; 13 = no impairment). The mean Hölder exponent decreases (that is, the sequences become more random) as the disease severity increases. The two measures are highly correlated ($r^2 = 0.64$, $P < 0.005$). Data from http://www.physionet.org.

An interesting first example regards human stride interval sequences under different conditions. Figure 2 shows typical Hölder exponent distributions obtained from these sequences. The fractal and multifractal nature of the stride interval fluctuations becomes slightly more pronounced under faster or slower paced frequencies relative to the normal paced frequency of a subject [9, 17]. This is indicated by the shift toward the right, that is, toward higher values of the Hölder exponent distribution and by the increased width of the distributions. In fact, the meaning of this finding might be that under this type of stress a subject has to focus on the task and as a consequence the correlation of the physiological system increases. On the contrary, the randomness of the fluctuations increases (the Hölder exponent distributions shift toward the left) if subjects are asked to synchronize their gait with the frequency of a metronome. The rationale might be that the psychological synchronization acts continuously and disrupts the natural physiological temporal correlations of walking.

In Figure 3 we have analyzed stride interval sequences of a group of patients with Huntingdon's disease. We have measured their mean Hölder exponent, h_0, and found that it is strongly correlated with the total functional capacity (TFC) score that measures the severity of impairment: the more severe the impairment the more random the sequence. These findings can be modeled by means of a super central pattern generator [17]. As a result of neuronal deterioration, a network of neurons controlling human locomotion could be expected to become less correlated than a healthy neuronal network, and the leftward shift of the Hölder exponent distribution is expected to increase with the severity of the neurodegenerative disease, as Figure 3 shows. Thus, fractal analysis is found to be a powerful tool to investigate physiological control mechanisms during exercise and in health, for example, in neurological diseases.

In another study we determined the dependency of the fractal properties of R-R interval time series during progressive central hypovolemia with lower body negative pressure [18]. We found that by increasing the lower body negative pressure these time series became more persistent and the distributions of Hölder exponents became wider as shown in Figure 4. Because physiological responses to lower body negative

FIGURE 4



Typical Hölder exponent histograms for R-R interval time series for a patient subjected to progressive central hypovolemia using lower body negative pressure [18]. Results regarding sequences for three different values of the pressure are shown. The histograms are fitted with Gaussian functions (solid curves).

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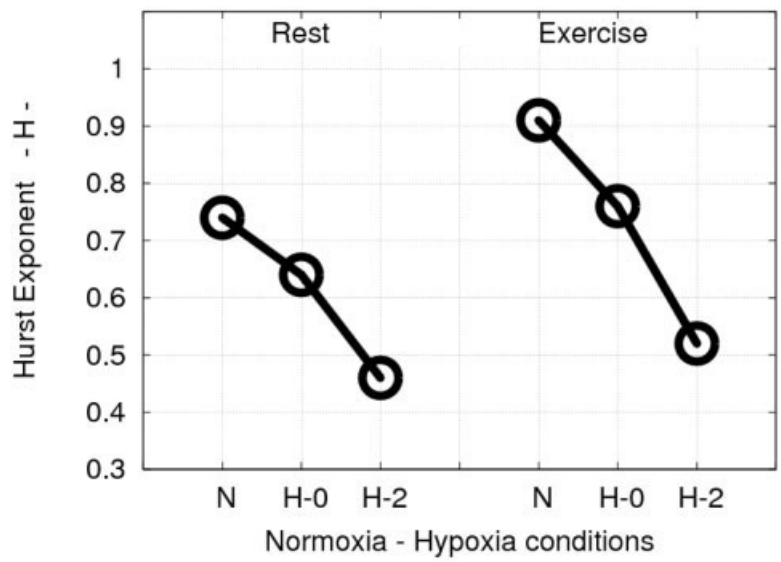
FIGURE 5



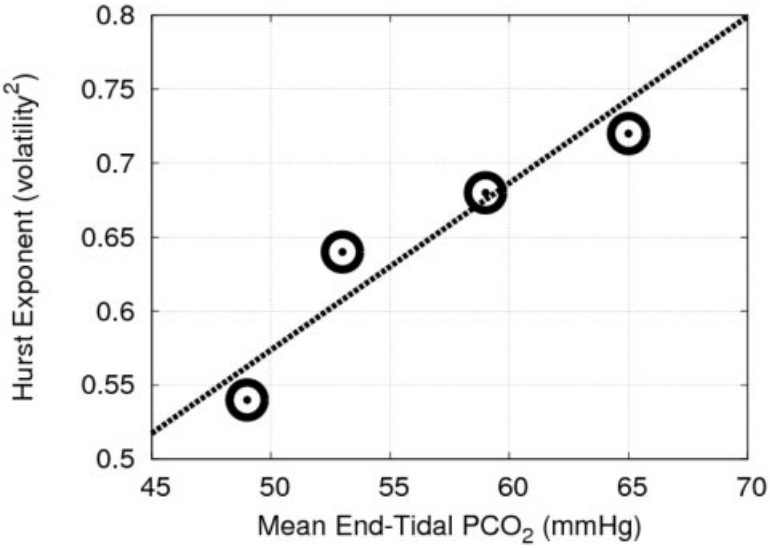
Typical Hurst exponents of inter-breath interval sequences for a subject during normoxia (N) and hypoxia in a hypobaric chamber at a simulated altitude of 15,000 feet. H-0 is a measurement at the beginning of the hypoxic exposure; H-2 is after 2 h of continuous hypoxia. The analysis is done for a subject at rest and during exercise.

pressure are similar to those experienced during hemorrhage shock, multifractal analysis may be a powerful tool to predict incipient shock.

In a preliminary study we analyzed inter-breath interval sequences of a resting normal human volunteer during normoxia and during a 2-h period of acute hypoxia. Figure 5 shows that these time series exhibit persistence, although after 2 h of hypoxia inter-breath interval time series tended to become more random, or less correlated, as indicated by a decrease in the value of the Hurst exponent. This finding suggests that respiratory rhythm generation is disrupted by sudden acute hypoxia. The same individual was also asked to exercise for approximately 10 min during each condition and, although these time series also became more random during acute hypoxia, we observed that for each condition under exercise the sequences were more persistent (higher values of the Hurst exponent) than at rest. The latter finding is equivalent to what we have observed for the stride interval sequences (Figure 2), which become more persistent during exercise. This suggests that, in general, forced exercise induces an increase of the dynamical correlation of a physiological system. Thus, we can hypothesize that fractal analysis might be a useful tool with which to probe mechanisms involved in control of breathing under different environmental conditions. In this particular case it might be argued that the physiology of a subject might slowly adapt to a hypoxic environment and the breathing might become more regular. The fractal analysis of the inter-breath intervals might indicate when this physiological adaptation occurs.

In another preliminary study we analyzed postoperative inter-breath interval sequences of a group of patients. The purpose of the study was to determine whether the Hurst exponent of these data could be correlated with respiratory depression, as indicated by a high end-tidal P_{CO_2}. This study is important because the continuous monitoring of arterial blood P_{CO_2} is impractical, and measurement of end-tidal P_{CO_2} inaccurate. Moreover, although respiratory depression is conventionally associated with a low respiratory rate, we have found that a simple diagnosis based on respiratory rate can be severely misleading. On the contrary, we have found that a significant correlation seems to exist between mean end-tidal P_{CO_2} pressure and Hurst exponent value of the square of the volatility of the inter-breath interval sequences (see Fig-

FIGURE 6



Mean Hurst exponent for the square of the volatility index of the inter-breath interval sequence for the first 36 h after upper abdominal surgery in four patients. The Hurst exponent is highly correlated with mean end-tidal P_{CO_2} ($r^2 = 0.93$, $P = 0.008$).

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ure 6). Volatility has been defined as the difference between two consecutive inter-breath intervals. Thus, the development of a novel diagnostic strategy based on the simple study of a relatively inexpensive and noninvasive continuous monitoring of inter-breath interval might be of great utility.

The above physiological phenomena and their response to stress or environmental changes can be modeled by a simple stochastic central pattern generator that ideally reproduces the control system, which then drives respiratory neurons, causing contraction of respiratory muscles, producing a cyclical output [17]. The central nervous system is capable of firing at time intervals whose sequences present persistent correlation patterns. However, the intensity of the autocorrelation of the actual neural firing time intervals is expected to be influenced by both a change of internal neural correlation among the nervous firing centers and/or a change in peripheral feedback. Thus, such simple models can reproduce observed data in humans obtained under a variety of circumstances.

In conclusion, we have shown a few examples where fractal and multifractal analysis of physiological signals have been of great utility for better characterized complex biological systems under different conditions and, as a direct consequence, we believe these novel techniques could help develop novel clinical strategies for diagnosing pathology and detecting adverse events.

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