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Physica A 249 (1998) 491–500

PHYSICA A

Multiple-time scales analysis of physiological time series under neural control

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Abstract

We discuss multiple-time scale properties of neurophysiological control mechanisms, using heart rate and gait regulation as model systems. We find that scaling exponents can be used as prognostic indicators. Furthermore, detection of more subtle degradation of scaling properties may provide a novel early warning system in subjects with a variety of pathologies including those at high risk of sudden death.

1. Introduction

Scale-invariant properties in biological systems have received much attention recently [1,2]. The absence of characteristic temporal (or spatial) scales may confer important biological advantages, related to adaptability of response [2,3]. In this paper, we present some recent progress in applying scale-invariant (fractal) analysis to physiological time series. We will concentrate on the output of two model physiological systems: (1) human heartbeat time series under neuroautonomic control; and (2) human gait time series under the control of central nervous system.

2. Human heartbeat dynamics

Clinicians often describe the normal activity of the heart as "regular sinus rhythm". But, in fact, cardiac interbeat intervals normally fluctuate in a complex, apparently

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0378-4371/98/$19.00
PII S0378-4371(97)00508-6

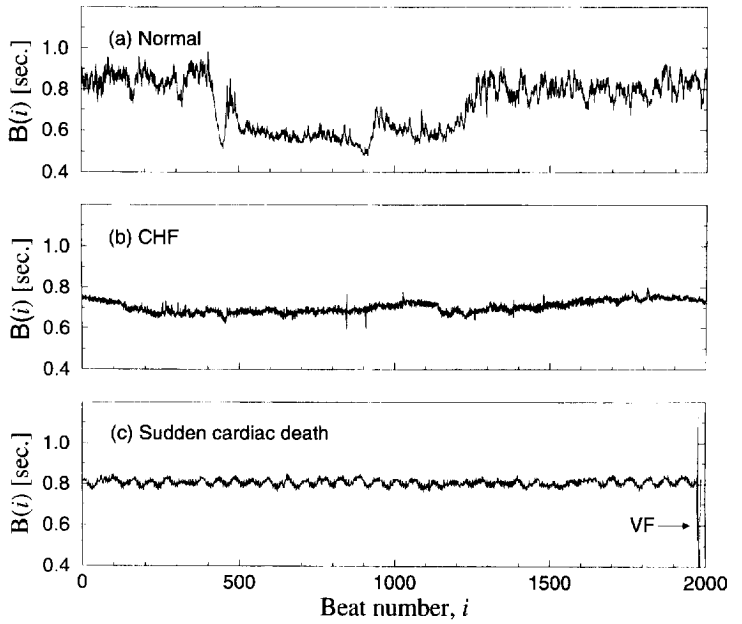

Fig. 1. Representative complex physiological fluctuations. Cardiac interbeat interval time series of 2000 beats from (a) a healthy subject, (b) a subject with congestive heart failure (CHF) and (c) a sudden cardiac death subject with ventricular fibrillation (VF).

erratic manner [2,4] (Fig. 1). This highly irregular behavior has recently motivated researchers [5,6] to apply time-series analyses that derive from statistical physics, especially methods for the study of critical phenomena where fluctuations at all length (time) scales occur. These studies show that under healthy conditions, interbeat interval time series exhibit long-range power-law correlations reminiscent of physical systems near a critical point [7,8]. Furthermore, certain disease states may be accompanied by alterations in this scale-invariant (fractal) correlation property. Here we explore the potential utility of such scaling alterations in the detection of pathological states.

Our analyses are based on the beat-to-beat heart-rate fluctuations of digitized electrocardiograms recorded with an ambulatory (Holter) monitor. The time series obtained by plotting the sequential intervals between beat i and beat $i + 1$, denoted by $B(i)$, typically reveals a complex type of variability (Fig. 1). The mechanism underlying such fluctuations appears to be related primarily to countervailing neuroautonomic inputs. Parasympathetic stimulation decreases the firing rate of pacemaker cells in the heart's sinus node. Sympathetic stimulation has the opposite effect. The nonlinear interaction (competition) between the two branches of the autonomic nervous system is the postulated mechanism for the type of erratic heart-rate variability recorded in healthy subjects [4,9].

2.1. Detrended fluctuation analysis (DFA)

Difficulties of quantitatively analyzing physiological time series arise mainly from their nonstationarity and sometimes short data length. We have developed a scaling analysis, called *detrended fluctuation analysis* (DFA) [10,11], which takes these factors into account. DFA is a modified root-mean-square analysis of a random walk based on the following concept: a stationary time series with long-range correlations can be integrated, i.e., form an accumulated sum, to form a self-similar process. Therefore, measurement of the self-similarity scaling exponent of the integrated series can tell us the long-range correlation properties of the original time series. In short, we integrate the original time series once; then we determine the fluctuations $F(n)$ of the integrated signal around the best linear fit in a time window of size n. The slope of the line relating $\log F(n)$ to $\log n$ determines the scaling exponent (self-similarity parameter) α. The DFA method has been validated on control time series that consist of long-range correlations with the superposition of a non-stationary external trend [10]. It has also been successfully applied to detect long-range correlations in highly heterogeneous DNA sequences [10,12,13], and other complex physiological signals [11,14,15].

Fig. 2 compares the DFA analysis of representative 24 h interbeat interval time series of a healthy subject and a patient with congestive heart failure (CHF). Notice that for large time scales (asymptotic behavior), the healthy subject interbeat interval time series shows almost perfect power-law scaling over two decades ($20 \leqslant n \leqslant 10\,000$) with $\alpha = 1$ (i.e., $1/f$ noise) while $\alpha \approx 1.3$ (closer to Brownian noise) for the CHF patient.

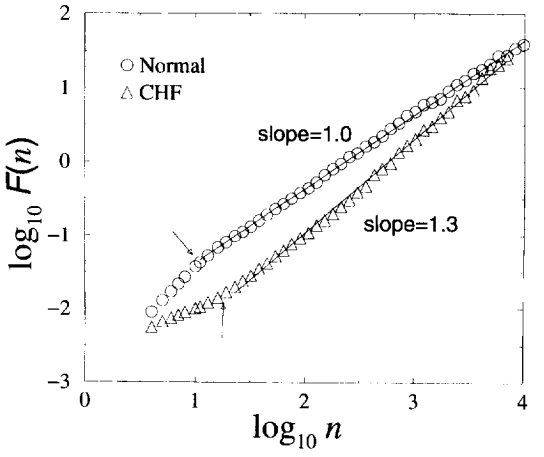

Fig. 2. Plot of $\log F(n)$ versus $\log n$ for two 24 h interbeat interval time series. The circles are from a healthy subject while the triangles are from a subject with congestive heart failure. Arrows indicate "crossover" points in scaling, from Ref. [11].

2.2. Short- and long-time scaling properties

We note that for short time scales, there is an apparent *crossover* exhibited for the scaling behavior of some data sets (arrows in Fig. 2). For the healthy subject, the α exponent estimated from very small n (< 10 beats) is larger than that calculated from large n (> 10 beats). This is probably due to the fact that on very short time scales (a few beats to ten beats), the physiologic interbeat interval fluctuation is dominated by the relatively smooth heartbeat oscillation associated with respiration, thus giving rise to a large α value. For longer scales, the interbeat fluctuation, reflecting the intrinsic dynamics of a complex system, approaches that of $1/f$ behavior as previously noted [5,16]. *In contrast, the CHF data set shows a very different crossover pattern* (Fig. 2). For very short time scales, the fluctuation is quite random (close to white noise, $\alpha \approx 0.5$). As the time scale becomes larger, the fluctuation becomes smoother (asymptotically approaching Brownian noise, $\alpha \approx 1.5$).

2.3. Practical utilities

Several recent studies have demonstrated that scaling exponents (both short- and long-time scales) might be useful clinical indicators for detecting pathological dynamics. In particular, these studies revealed:

(1) For a group of 12 healthy adults without clinical evidence of heart disease and a group of 15 adults with severe heart failure, the long-range exponents (for time scales $10^2 \sim 10^4$ beats) are significantly different. For the group of healthy cardiac interbeat interval time series (mean value $\pm$ S.D.): $\alpha = 1.00 \pm 0.11$. This result is consistent with previous reports of $1/f$ fluctuations in healthy heart rate (by spectral analysis) [3,16]. The pathologic group shows a significant ($p < 0.01$ by Student's t-test) deviation of the long-range correlation exponent, $\alpha = 1.24 \pm 0.22$, from normal. Of interest, some of the heart failure subjects show an α exponent very close to 1.5 (Brownian noise), indicating random walk-like fluctuations. The group-averaged exponent α is less than 1.5 for the heart failure patients, suggesting that pathologic dynamics may only transiently operate in the random-walk regime or may only approach this extreme state as a limiting case.

(2) The above observation of a differential crossover pattern for healthy versus pathologic data motivated us to extract two parameters from each data set by fitting the scaling exponent α over two different time scales: one short, the other long. To be more precise, for each data set we calculated an exponent α_1 by making a least-squares fit of $\log F(n)$ versus $\log n$ for $4 \leqslant n \leqslant 16$. Similarly, an exponent α_2 was obtained from $16 \leqslant n \leqslant 64$. Since these two exponents are not extracted from the asymptotic region, relatively short data sets are sufficient, thereby making this technique applicable to "real-world" clinical data.

We applied this quantitative fluctuation analysis to the two different groups of subjects mentioned above to measure the two scaling exponents α_1 and α_2 [11]. All data set records were divided into multiple sub-sets (each with 8192 beats $\sim$ 2 h) and

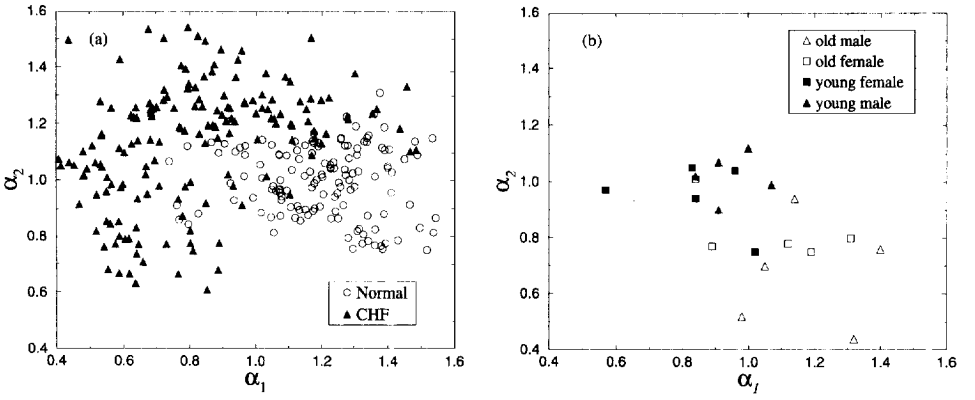

Fig. 3. Scatter plot of scaling exponents α_1 versus α_2 for (a) the healthy subjects and subjects with congestive heart failure, (b) young and elderly healthy subjects. Note good separation between healthy and heart disease subjects in (a), with clustering of points in two distinct "clouds." Similarly, there is good separation between young and elderly subjects in (b).

the two exponents were calculated for each subset. For healthy subjects, we find that $\alpha_1 = 1.20 \pm 0.18$ (mean $\pm$ S.D.) and $\alpha_2 = 1.00 \pm 0.12$. For the group of congestive heart failure subjects, we find that $\alpha_1 = 0.80 \pm 0.26$ and $\alpha_2 = 1.13 \pm 0.22$, both significantly ($p < 0.0001$ for both α_1 and α_2) different from normal. Furthermore, we show in Fig. 3a that fairly good discrimination between these two groups can be achieved by using these two scaling exponents. [1]

(3) Based on the hypothesis that there is a region of scaling behavior (in Fig. 3a) over which the normal (healthy) cardiac control operates, we have recently found another promising application of DFA in analyzing data sets from Framingham heart study – a prospective, population-based study [17]. The primary group of interest was individuals with congestive heart failure (CHF); 28 CHF cases and 41 sex- and age-matched healthy control cases were analyzed by our scaling analysis. Briefly, using Holter monitor data (approximately 2 h) from each subject of the Framingham study, we assigned an index (range from 0 to 1) to each individual by estimating the probability that this particular heartbeat time series was operating in the appropriate region in Fig. 3a (normal versus pathologic). Does this measure add independent information to conventional measures? In comparison with other 10 time and frequency measures, we found that the DFA index may carry prognostic information about mortality not extractable from these traditional methods of heart rate variability analysis [17].

(4) Similar analysis was applied to study the effect of physiologic aging. Ten young (21–34 yr) and ten elderly (68–81 yr) healthy subjects underwent 2 h of continuous supine resting ECG recording. In healthy young subjects, no obvious crossover behaviour was observed ($\alpha_1 \simeq \alpha_2$), scaling exponent α is close to a value of 1.0. In the group of healthy elderly subjects, the interbeat interval time series also had two scaling

[1] Not all subjects in our preliminary study show an obvious crossover in their scaling behavior.

regions. Over the short range, interbeat interval fluctuations resembled a random walk process (Brownian noise, $\alpha = 1.5$), whereas over the longer range they resembled white noise ($\alpha = 0.5$). Short- (α_1) and long-range (α_2) exponents were significantly different in the elderly subjects compared with the young (see Fig. 3b) [18].

3. The dynamics of human walking

Human gait is a complex process. The locomotor system incorporates input from the cerebellum, the motor cortex and the basal ganglia, as well as feedback from visual, vestibular and proprioceptive sensors [19,20]. Under healthy conditions, this multi-level control system produces a remarkably stable walking pattern; the kinetics, kinematics and muscular activity of gait appear to remain relatively constant from one step to the next even during unconstrained walking [21]. However, closer examination reveals fluctuations in the gait pattern, even under stationary conditions [21,22]. The origin and the implications of these fluctuations are unknown. In this section, we analyze the step-to-step fluctuations in gait in order to gain insight into locomotor function and its control mechanisms. To this end, we use the same DFA method we developed for studying the dynamics of heartbeat time series. Ultimately, these insights should increase the understanding of neurophysiological control of normal and pathological walking and might also prove useful clinically in the diagnosis and prognosis of gait disorders.

A representative stride interval time series is shown in Fig. 4a. First, note the stability of the stride interval; during a 9 min walk the coefficient of variation was only 4%. Thus, a good first approximation of the dynamics of the stride interval would be a constant. However, fluctuations occur about the mean. The stride interval varies irregularly with some underlying complex "structure". This structure changes after random shuffling, as seen in Fig. 4b, demonstrating that the original structure is a result of the sequential ordering of the stride interval and not a result of the stride interval distribution. Fig. 4c shows the DFA plot with $\alpha = 0.83$ for the original time series and 0.50 after random shuffling.

3.1. Changes in gait dynamics with aging and Huntington's disease

To gain further insight into the basis for this long-term, fractal dependence in walking rhythm, we investigated the effects of advanced age and Huntington's disease, a neurodegenerative disorder of the central nervous system, on stride interval correlations [23]. Using DFA, we compared the stride interval time series (i) of 10 healthy elderly subjects and 22 healthy young adults, and (ii) of 17 subjects with Huntington's disease and 10 healthy controls.

We found that α was closer to 0.5 (uncorrelated, white noise) for the group of elderly subjects. This indicates that the stride-interval fluctuations are more random and less

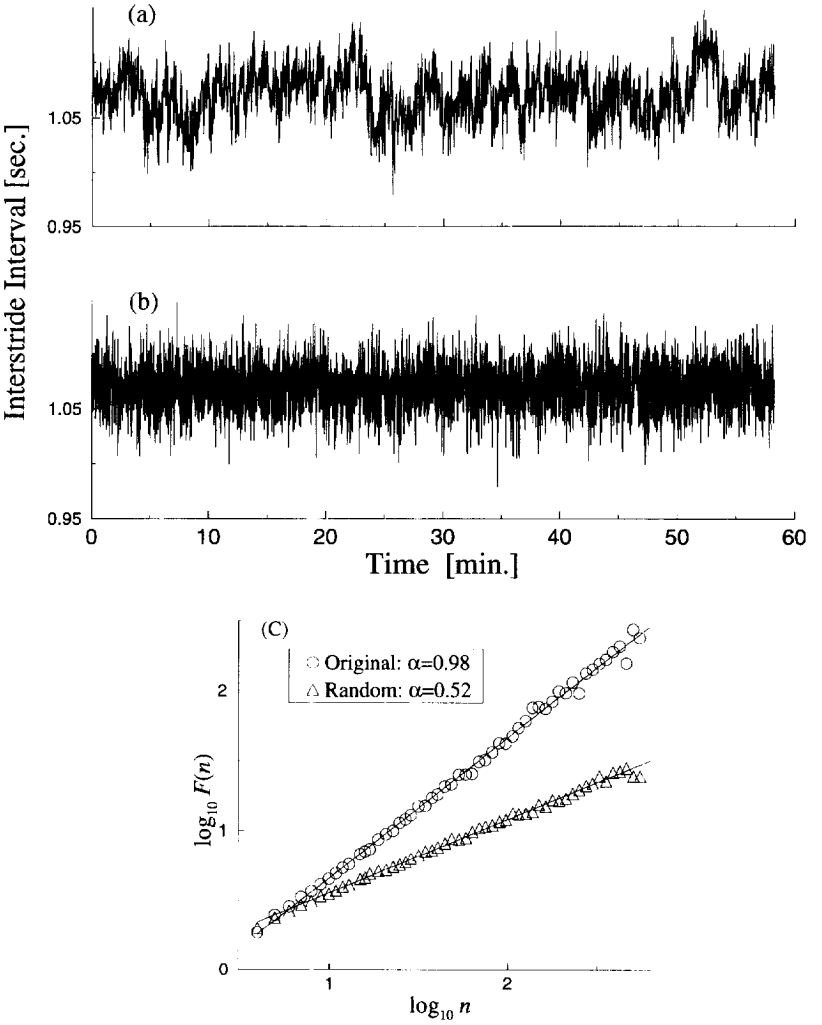

Fig. 4. Representative stride interval time series (a) before and (b) after shuffling and (c) the DFA analysis.

correlated for elderly subjects than for the young subjects. α was 0.68 ± 0.14 for the elderly group versus 0.87 ± 0.15 for the young group ($p < 0.003$).

Interestingly, the elderly and young subject groups had comparable similar average stride intervals (elderly: 1.05 ± 0.10 s; young: 1.05 ± 0.07 s) and required almost identical amounts of time to perform a standardized functional test of gait and balance. The magnitude of stride-to-stride variability (i.e., stride-interval coefficient of variation) was also very similar in the two groups (elderly: $2.0 \pm 0.7\%$; young: $1.9 \pm 0.4\%$). These results show that while α was different in the two age groups, the gross measures of gait and mobility function of these elderly subjects were not significantly affected by age. Average gait speed of elderly subjects was slightly less than that of the young

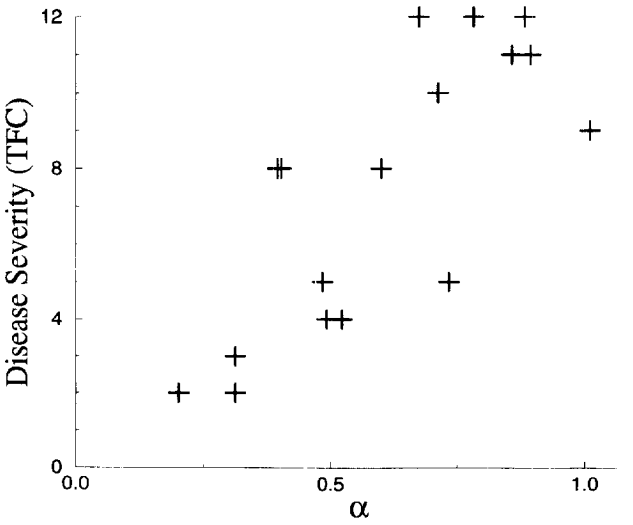

Fig. 5. Relationship between disease severity and degree of stride interval correlations (α) among subjects with Huntington's disease. Disease severity is measured using the total functional capacity (TFC) score of the Unified Huntington's Disease Rating Scale (0=most impairment; 13=no impairment). This clinical measure of function has been shown to correlate with positron emission tomography (PET) scan indices of caudate metabolism.

subjects; however, α was not associated with gait speed ($r = -0.07$; $p > 0.7$). Furthermore, multiple regression analysis demonstrated that even after adjusting for any potential confounders (e.g., speed), age still remained independently associated with α ($p < 0.0005$).

The scaling exponent α was also reduced in the subjects with Huntington's disease compared to disease-free controls (Huntington's disease: 0.60 ± 0.24; controls: 0.88 ± 0.17; $p < 0.005$). Moreover, among the subjects with Huntington's disease, α was related to degree of functional impairment ($r = 0.78$, $p < 0.0005$; see Fig. 5).

4. Conclusions

Our finding of nontrivial long-range correlations (or power-law scaling) in healthy heart rate and gait dynamics is consistent with the observation of long-range correlations in other biological systems that do not have a characteristic scale of time or length [2]. Such behavior may be adaptive for at least two reasons. (i) The long-range correlations serve as an organizing principle for highly complex, nonlinear processes that generate fluctuations on a wide range of time scales. (ii) The lack of a characteristic scale helps prevent excessive *mode locking* that would restrict the functional responsiveness of the organism. Support for these related conjectures is provided by observations from severe diseased states such as heart failure where the breakdown of long-range correlations is

often accompanied by the emergence of a dominant frequency mode (e.g., the Cheyne–Stokes frequency). Analogous transitions to highly periodic regimes have been observed in a wide range of other disease states including certain malignancies, sudden cardiac death, epilepsy and fetal distress syndromes [3].

It is known that biological systems contain a wide range of time scales. The scaling exponents discussed here can be thought of as a quantitative measure of how "balance" are these time scales. At least, for the purpose of first-order approximation to the dynamics of these system. Therefore, subtle or intermittent degradation of scaling properties may provide an early warning of incipient pathology [17]. Finally, we note that to fully describe the dynamics of these physiological systems, more sophisticated methods are needed to probe the nonlinear interaction (coupling) between those different time scales in the system.

In summary, we apply a new fluctuation analysis (modified from classical random-walk analysis) to the nonstationary heartbeat time series from healthy subjects and those with severe heart disease (congestive heart failure) as well as to normal stride interval time series. We show that this method can detect the presence of long-range correlations in physiological time series. Furthermore, this method is capable of identifying crossover behavior due to differences in scaling over short versus long time scales. These findings are of interest from a physiologic viewpoint since it motivates new modeling approaches to account for the control mechanisms regulating cardiac and neuromuscular dynamics on different time scales. From a practical point of view, quantification of these scaling exponents may have potential applications for bedside and ambulatory monitoring [3].

Acknowledgements

We are grateful to K.K.L. Ho, Z. Ladin, L.A. Lipsitz, G.B. Moody, P. Purdon and J.Y. Wei for valuable discussions. Partial support was provided to CKP and JMH by NIMH (MH54081), to JMH by NIA (AG 14100), to HES and SH by NSF and to ALG by the G. Harold and Leila Y. Mathers Charitable Foundation and NASA.

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