BREAKDOWN OF SCALING PROPERTIES IN ABNORMAL HEART RATE VARIABILITY

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ABSTRACT

The heart rate variability (HRV) of subjects with normal sinus rhythm (NSR) and subjects with congestive heart failure (CHF) is compared by using a structure function borrowed from turbulence studies. Firstly, it is shown that the HRV of subjects with NSR displays a power law scaling property, which indicates the presence of structured heartbeat control mechanisms. Secondly, it is found that such a scaling property is partially lost for subjects with CHF. The absence of scaling properties is associated to the presence of uncorrelated (i.e., noise-like) heart rate variations. In order to gain insights on the source of the scaling property, the HRV is analyzed from a systemic (i.e., feedback control) viewpoint in the frequency domain. It is found that the HRV of subjects with NSR is governed by a stable adaptive control mechanism presumably located in the autonomic nervous system. In the case of subjects with CHF, the results show that this regulation mechanism is partially or totally absent, which is interpreted as the cause of the breakdown of the scaling law property.

KEYWORDS. Heart Rate Variability; Scaling Properties, Breakdown; Frequency Response.

1 INTRODUCTION

A significant relationship between the neurocontrol systems (including the autonomic nervous system, ANS in short) and cardiovascular mortality, including sudden cardiac death, has been recognized in the last 25 years (see, for instance, [1] and references therein). Existing experimental evidence showing the association between propensity for lethal arrythmia and signs of neurocontrol malfunctioning have moti- vated studies for the development of measures of the autonomic activity. In this way, it is now accepted that heart rate variability (HRV) plays an important role in the determination of neurocontrol, includ- ing the ANS as an important case, and non-neurocontrol systems. Additionally, the easy derivation of this measure by means of many commercial devices has popularized its use into the medical commu- nity. However, the human cardiovascular system is characterized by a high degree of complex variability, such that many standard measures obtained from HRV can lead to incorrect conclusions and dangerous extrapolations [2]. As a consequence, the recent two decades have witnessed the developments of system- atic procedures to characterize, both qualitatively and quantitatively, the HRV of healthy and unhealthy subjects.

Classical statistical analysis in time and frequency domains have widely explored, and include the computation of means, standard deviations, histograms, power spectra distribution, etc. [2,3]. Of particular interest is the use of spectral analysis based on autoregressive models, which shows dominant activities at low (around 0.1 Hz) and high (around 0.25 Hz) frequencies. In turn, these dominant dynamics have been related to the activity of the

neurocontrol systems via, e.g., sympathetic and parasympathetic mechanisms [1,4,2]. Classical statistical analysis is based on the assumptions of linearity, stationary and equilibrium nature of HRV signals. If one conceptualizes the cardiovascular system as a control mechanism responding to wide variety of, e.g., physiological requirements, including oxygen and nutrient transportations, then one is tempted to suspect that nonlinear phenomena are involved in the genesis of HRV. In fact, they are determined by complex interactions of hemodynamic, electrophysiological, and humoral variables as well as by the autonomic and central nervous regulations [5]. It has been speculated that methods borrowed from nonlinear analysis might provide important insights for physiological interpretation of HRV and for the assessment of the risk of sudden death. Nonlinear dynamics and fluctuation analysis include the computation of Lyapunov exponents, Poincare sections, fractal Hurst exponent [6,3], and detrended fluc- tuation analysis (DFA) [7]. In particular, DFA has been shown that there is a difference in the long-range scaling between heart beats in healthy and unhealthy subjects [8] and between sleep and wake periods [6]. Multifractality features of HRV time series have been also explored [9]. Ashkenazy et al. [10] also used DFA to study magnitude and sign correlations in HRV. They found that the magnitude series relates to the nonlinear properties of the original time series, while the sign series relates to the linear properties. Lin and Hughson [11] proposed a turbulence analogy for the long-term HRV of healthy humans. Based on such an analogy, the equivalence of an inertial range was found and a stochastic cascade model was proposed. Robustness of the cascade model was subsequently studied [12] showing that a rigid structure for the multiple time scales is not essential for the multifractal scaling in healthy HRV.

Recent Physica A's papers have used methods borrowed from statistical physics to study certain stilized features of heartbeat dynamics. Dudkowska and Makowiec [13] presented a visual method for qualifying a heart rate signal. The method converts a time series into a dot plot, which offers to the human aye an extra possibility to uncover similarities and differences between heart rate patterns of healthy and ill persons. Sakki *et al.* [14] showed that low-variability periods follows a scaling power law. It has been conjectured that the values of the scaling exponents are personal characteristics and depend on the daily habits of the subject. Imponente [15] used DFA to provide further evidences of scaling properties in the heartbeat dynamics. These results show that methods borrowed from statistical physics represent potential tools for HRV assessment. However, further exploration of fluctuation analysis methods is required in order to establish standards and assess the full scope of these methods.

In this paper, a further exploration of fluctuation analysis for the HRV of persons with normal sinus rhythm (NSR) and persons with congestive heart failure (CHF) is studied. Specifically, our aim is twofold:

i) To detect scaling differences between NSR and CHF cases based on the original (*i.e.*, nondetrended and nonsmoothed) RR time series. To this end, a structure function approach, analogous to that used for developed turbulence is used [11,16]. Contrary to most fluctuation analysis reported so far, no detrending of the HRV is made in order to retain both high- and low-frequency characteristics of the heartbeat dynamics.

ii) To interpret the scaling behavior of RR time series from a feedback control framework [17,18] in order to gain insights on the dominating control mechanisms that regulate the RR dynamics [19].

Our results shows that the HRV of subjects with NSR displays a power law scaling property, which indicates the presence of well organized heart rate control mechanisms. In contrast, it is found that such a scaling properties are totally or partially lost for subjects with CHF. The absence of scaling properties is associated to the presence of non structured (i.e., noise-like) heart rate variations. Going beyond existing fluctuation analysis results, and to gain insights on the source of the scaling property, a frequency domain is used to give a system theory explanation of the HRV. It is found that the HRV of subjects with NSR is governed by a stable adaptive control mechanism, which is presumably located in the autonomic nervous system. In the case of subjects with CHF, the results show that this regulation mechanism is partially or totally absent, which is interpreted as the cause of the breakdown of the scaling law property.

Our contribution with respect to previously reported results on scaling power laws for HRV [6- 8,10,14,15] can be summed-up as follows:

- It is shown that a fluctuation analysis based on the original (*i.e.*, non detrended) HRV signal has the potential of detecting differences between healthy and unhealthy subjects. It should be emphasized that, although the scaling properties of RR time series with no detrending was studied by Lin and Hughson [11], the authors focused mainly on theoretical aspects aimed to propose a cascade model to describe the main stochastic features of HRV. In this way, studies on the discrimination of healthy and unhealthy subjects based on the original (*i.e.*, non detrended) RR time series have been not explored previously. Our results show that such a discrimination is possible when used the so-called structure function [16].

- The power law scaling property is related to the presence of a stable adaptive control mechanism [20], whose functioning has been deteriorated in unhealthy subjects. To the best of our knowledge, a relationship between scaling properties of RR time series and feedback control mechanisms has not been reported previously. Indeed, a complete understanding of the underlying feedback con- trol mechanisms involved in the cardiorespiratory system functioning is required for assessing its response capability in the face of environmental disturbances [19].

In this way, together with existing results, our results can help to asses the potentiality of fluctuation analysis for detecting and measuring stylized features of HRV.

2 HRV DATA

In our analysis, the HRV data were taken from the public-domain MIT-BIH database www.physionet.org.

The data correspond to beat-at-beat time intervals, so that the HRV data can be seen as signals sampled from ECG records, with non-constant sampling period. The original analog recordings were made using ambulatory ECG recorders with a typical recording bandwidth of the order of 0.1 – 40 Hz. Annotation files were prepared following the procedure described in [6,13]. The selection of the data sets was made under the following guidelines:

a) Each data set corresponds to ECG records over a 24 hours period. A nocturnal database fraction from midnight to 05:00 and a diurnal fraction from 12:00 to 17:00 were used for analysis.

b) As made in Figure 2 of Dudkowska and Makowiec [13], 12 recordings were chosen for analysis: 6 from subjects with NSR and 6 from subjects with CHF. Subjects included both men and women, aged 30 to 71. NSR records are nsr06, nsr08, nsr09, nsr10, nsr12 and nsr13. On the other hand, CHF records are chf01, chf02, chf04, chf07, chf08 and chf12. It should be emphasized that, although we have used such a limited number of HRV records, our conclusions will be of general nature in the sense that they still hold for the HRV recordings non reported in this paper.

c) Only the intervals between normal beats were determined from annotation files and intervals containing non-normal beats were eliminated. The moving-window averaging procedure proposed by Dudkowska and Makowiec [13] was applied to eliminate outliers due to missed beat detections. In this way, for NSR data, an average of 0.01% of the intervals were eliminated, and for the CHF data, an average of 0.12% of the intervals were eliminated. No interpolation was done for the eliminated intervals.

Figure 1 shows a fraction of the RR intervals, denoted by ri, for a NSR subject (nsr06) and a CHF (chf01) subject. Notice that the HRV is composed by high frequency fluctuations evolving on a baseline and a trending. In the following section, a fluctuation function will be introduced aimed to extracting hidden information from the complex cardiac series.

Since the RR interval is a signal sampled with a nonconstant sampling period, one must introduce a suitable time measure. This is done by taking the beat number i as a time scale. In fact, there is a one-to-one strictly increasing function between the discrete time index i, and the physical time t, namely, $t_i = \sum_{k=1}^{i} r_k$. Hence, in the sequel we will use the beat number i as the time-scale for the RR interval dynamics. In this way, time-scale will be used as a synonymous of beat-scale, and vice versa.

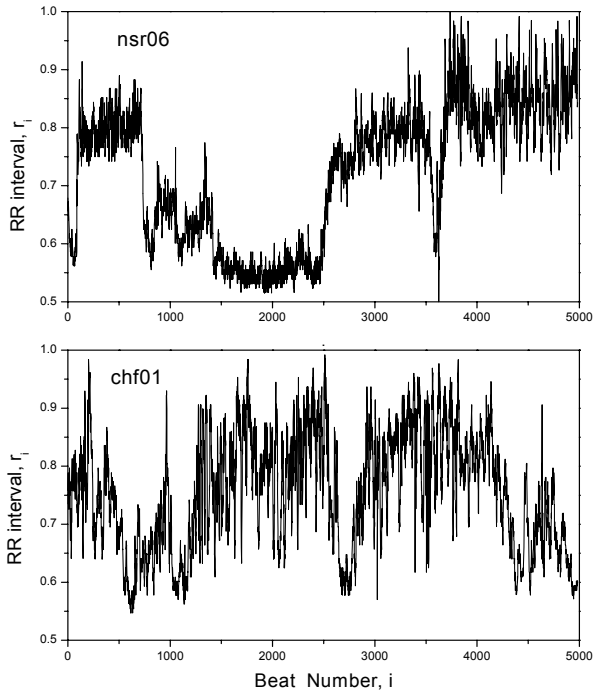

Figure 1. RR interval dynamics for (a) a NSR case and (b) a CHF case.

3 Structure Function

Figure 1 shows that the RR interval dynamics is composed of both high- and low-frequency fluctuations. High-frequency fluctuations seem to evolve on a low-frequency trending. In principle, RR interval fluctuations reflect the heart response to baroreflex-feedback regulation commands introduced by different control centers [19]. For instance, a decrement in the RR interval can be responding to a larger blood flowrate requirement in a body section. In turn, such a requirement can be induced by a given (routine or non-routine) physical and / or mental activity. In this way, a sustained activity may result in a trending change. If the HRV is the response to high-and low-frequency feedback control commands generated by e.g., the ANS, it seems to be reasonable to study how such RR interval fluctuations change over different time-scales. In order to capturer the main stylized features of these dynamics, one should analyze the original HRV time series without executing detrending and smoothing (e.g., low-pa s filtering, integration, etc.) procedures. As a first approach to address this analysis, in this work we will consider the turbulence analogy proposed by Lin and Hughson [11]. To this end, let $f_{ij} = r_i - r_{i-j}$ be the instantaneous RR interval fluctuation over the beat-scale j. For the beat series $\{r_i\}_{i=1}^{N}$, consider the *structure function* [16,21,22,11]:

$$F_q(j) = \left[\frac{1}{N} \sum_{i=1}^{N} \left| f_{ij} \right|^q \right]^{1/q} \tag{1}$$

The function $F_q(j)$ is also called as the qth-order fluctuation function and can be seen as the q-norm of the signal $\{r_i\}_{i=1}^{N}$. It is expected that if the beat series $\{r_i\}_{i=1}^{N}$ is scaling, then a power law behavior is displayed as follows:

$$F_q(j) \propto j^{H_q} \tag{2}$$

where H_q is called as the generalized qth order Hurst exponent [21,22].

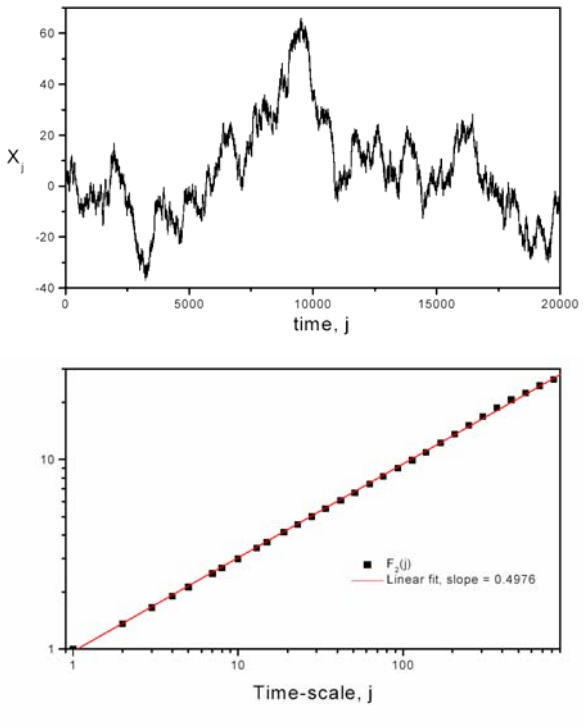

Figure 2. Scaling properties of a Brownian motion. Notice that $H_2 = 0.5$.

Some comments regarding the Hurst exponents H_q are in order [16,21,22]:

• If H_4 varies with q, a nontrivial multiaffinity spectrum is obtained. Basically, multifractal analysis allow us to analyze the mixing state of fractal dimensions as displayed in the complex nature of the time series $\{r_i\}_{i=1}^{N}$. According to [16,21], multiaffinity arises from the kinetic surface roughening with power-law-distributed amplitudes of uncorrelated noise.

• For $q = 2$, one obtain that $-(2H2 + 1)$ is the slope of the Fourier power spectrum $S(f)$ of $\{r_i\}_{i=1}^{N}$

Thus, $S(f)$ contains information about the exponent H_2. However, $F_2(\tau)$ is superior in estimating H_2 [16] because $F_2(\tau)$ is a smoother function than $S(f)$. In fact, $S(f)$ can fluctuate significantly and as a result scaling regions are often masked. The relation between the fractal dimension D_f and the Hurst exponent H_2 can be expressed as $D_f = 2 - H_2$. So, by finding H_2, we can estimate the fractal dimension of the time series.

• It has been shown [16] that the correlation function $C(\tau)$ of future values with past values, is given by $C(\tau) \propto 2(2^{2H_q - 1} - 1)$. A value of $H_q = 0$ corresponds to a zero-mean, stationary process withindependent increments (*e.g.*, Gaussian noise). A value of $H_q = 5$ results from uncorrelated time series and corresponds to a purely random walk or Brownian motion (BM) (see Figure 2). In this case, $\{r_i\}_{i=1}^{N}$ is characterized by "integrated" white noise, which means that future predictions of the time series is impossible. But for $H_q \neq 0.5$, one has

that $C(\tau) \neq 0$ independent of the time horizon τ. This indicates infinitely long correlations and leads to scale-invariance associated with positive long-range correlations (*persistence*) for $H_q > 0.5$ (*i.e.*, in increasing trend in the past implies an increasing trend in the future) and to a scale-invariance associated with negative long-range correlations (antipersistence) for $H_q < 0.5$ (*i.e.*, an increasing trend in the past implies a decreasing trend in the future). Random walks with $H_q \neq 0.5$ are referred to as fractional Brownian motions (*f*BM). It is important to note that persistent stochastic processes have little noise whereas anti-persistent processes show presence of high-frequency noise.

One can interpret the q-norm $F_q(j)$ as the statistical response of the cardiovascular system to (internal and external) disturbances and control commands from different control centers acting in the beat-scale j. For the sake of illustration, Figure 3 shows the RR interval fluctuation time series for $j = 1$ and $j = 100$ for a NSR data (nsr06). Notice that the variation of the time series $f_{i,100}$ is larger than the variation of the time series $f_{i,1}$, implying that $F_2(100) > F_2(1)$. In this way, the dynamics of the RR interval data nsr06 (corresponding to a NSR person) are less forecastable for larger beat-scale horizons. Alternatively, this can indicate that the nsr06 case is more sensitive to high than to low beat-scale disturbances. In the sequel, to focus on the very basic scaling properties of the HRV, *only the case* $q = 2$ will be considered in this work.

4 SCALING PROPERTIES OF HRV

The scaling properties of the HRV are studied in this section for both the NSR and the CHF cases. In the sequel, the reported scaling results are the average of the computations from nocturnal and diurnal data.

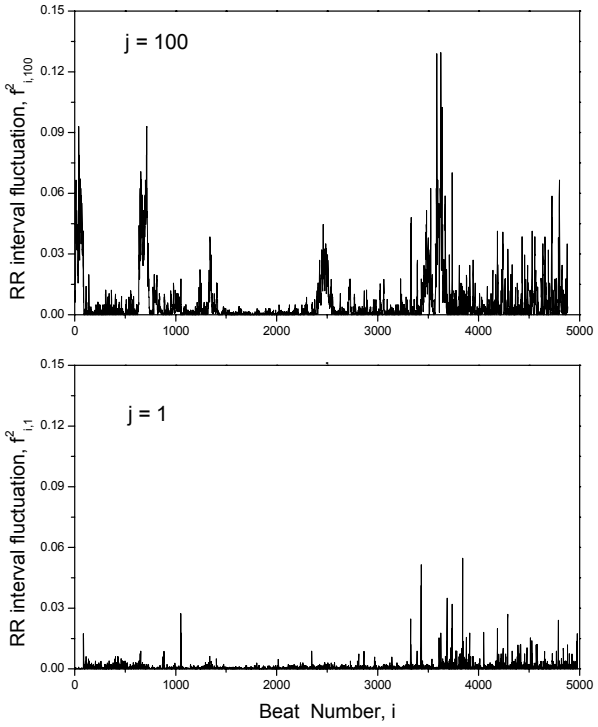

Figure 3. RR interval fluctuation time series for j = 1 and j = 100 for a NSR data (nsr06).

4.1 Regularities in the scaling of NSR

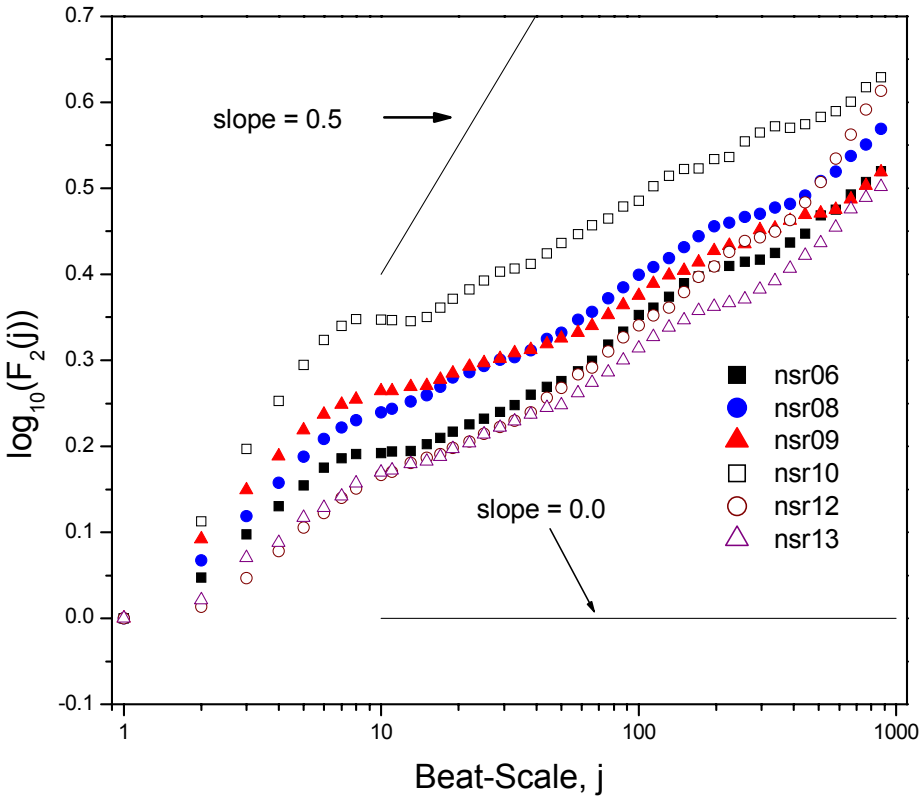

Figure 4. Log-log plot of the fluctuation function $F_2(j)$ *as a function of the beat-scale* $j \in [1,1000]$*, for the NSR data.*

Figure 4 shows a log-log plot of the fluctuation function $F_2(j)$ as a function of the beat-scale $j \in [1,1000]$, for the NSR data described in Section 2. For the sake of presentation, the fluctuation function $F_2(j)$ has been normalized by $F_2(1)$, so that all graphs start in the unity. As has been observed previously by Echeverria *et al.* [23], the HRV does not follows a unique scaling power law. In fact, the fluctuation function $F_2(j)$ can be well-described as a piecewise power law function as follows:

a) A first crossover is located at $j_{cr,1} = 10$ beats. Below $j_{cr,1}$, the slope is about 0.5, which means that the dynamics of heartbeat fluctuations below 10 beats behaves as a random walk. It is interesting to note that this behavior was reported recently by Echeverria *et al.* [2003] by means of DFA approach.

b) A second crossover is located at around $j_{cr,2} = 42$. Below $j_{cr,2}$, H_2 is of the order of 0.1 – 0.15, showing that the dynamics in this beat scales are antipersistent. This noise-like effect can be attributed to a short-range competition between the different neurocontrol systems (*e.g.*, sympathetic and the parasympathetic) [24]. In fact, it is known that the sympathetic control system reduces the RR interval while the parasympathetic one increases it. The result is a highly-oscillating RR interval dynamics around a certain "nominal" beat frequency [24].

c) A third crossover is observed at around $j_{cr,3} = 250$. In the domain $j \in [j_{cr,2}, j_{cr,3}]$ one finds that H_2 is of the order of 0.25 – 0.35, showing that antipersistent behavior is still the dominating phenomena in this beat scale. Similar to the range $j < j_{cr,2}$, This antipersistent effect can be attributed to a short-range competition between the sympathetic and the parasympathetic control centers However, a more dominating effect of the parasympathetic

control centers, which reduces the high variability induced by the sympathetic control centers, seems to be present.

d) A transition plateau located at about P = [250, 350] is observed. In this case, H_2 is around zero, which indicates that the dynamics of the HRV behaves very likely as a zero-mean, uncorrelated noise.

e) Beyond the plateau P, the scaling exponent H_2 is around 0.45 – 0.5, indicating that the large-range dynamics behaves as a random walk. Large-range dynamical behavior is associated to the trending, which are introduced by changes in the nominal operating point of the cardiovascular system. That is, a change in physiological processes (induced maybe by physical and/or mental activities) requires a change in the cardiovascular system operation. For instance, the transition between the different sleep stages can involve a change in the muscular stress [25], which implies a change in the oxygen and nutrient demands. Such a change is reflected in the cardiorespiratory frequency, which is modulated by the control systems to satisfy the physiological requirements. In this way, a value of H_2 slightly below 0.5 indicates that the nominal operating point dynamics behaves closely to an uncorrelated process.

The impressive regularity of the fluctuation function $F_2(j)$ for the NSR cases, which is in agreement with the results displayed in Figure 2 of Dudkowska and Makowiec [13], seems to indicate that the scaling properties discussed above are likely to be distinctive of persons with a healthy cardiovascular system.

4.2. Discussion

Since the pioneering work by Peng *et al.* [7], a large set of results has been reported on the different aspects of HRV scaling properties. In the introduction, we have made a brief description of these scaling results. In this subsection, the scaling properties described above are discussed in comparison to the main existing results in the open literature.

a) Peng *et al.* [7] also used the structure function approach to study the heartbeat dynamics finding that the RR interval follows an antipersistent (*i.e.*, anticorrelation) behavior, which is in agreement with our results. Unfortunately, Peng *et al.'s* conclusions are based on only one case study, which makes not easy a fair comparison with our results where several (public domain) cases were considered. Lin and Hughson [11] reported the 3rd-order fluctuation function $F_3(j)$ for a "typical" subject from the physionet databank, showing the result in their Figure 2.a (database2 as tagged by the authors). Unfortunately, the figure lacks details, so that, as in the Peng et al.'s case, a fair comparison is difficult. However, Lin and Hughson's result shows a nontrivial behavior of the structure function $F_3(j)$, presumably a log-periodic behavior. In particular, crossovers can be observed at about 10 and 250 beats, which are in agreement with the results displayed in our Figure 4.

b) Most studies on scaling properties of HRV have followed a conventional DFA approach. The motivation relies on the fact that spurious detection of correlations are reduced. In fact, classical techniques like the autocorrelation function and the power spectrum are not suited for non-stationary time series. Basically, DFA shows that the RR dynamics of healthy individuals are correlated with $\alpha \approx 1.4$ and at long scales it is less correlated with $\alpha \approx 1.0$. On the other hand, the opposite behavior was observed for unhealthy subjects [6,7,10]. In this way, two main differences are found between the results obtained with DFA and structure function approaches: i) DFA predicts less correlation at large scales while structure function predicts more correlation at the same beat scales, and ii) DFA gives persistent behavior while structure function leads to antipersistent behavior. The for- mer difference can be explained from the fact that correlation function approach is based on the nondetrended heartbeat time series, so that large scale correlations related to stable changes in the cardiovascular respiratory system, are retained. Conversely, DFA approach eliminates this long-range behavior, such that the observed decrement in correlation is a consequence of the reduction of forecastibility associated to a detrended time series. The second difference is a more subtle one that can be attributed to the fact that, while the structure function approach uses the original (i.e., non smoothed) time series r_i, the DFA bases its computations on the *integrated* time series $z_j = \sum_{i=1}^{j} r_i$.

It is known that integration behaves as a low-pass filter [18], which smoothes the dynamics, with a consequent increment in the predictability, of the time series. In turn, such a predictability incre- ment implies also a correlation increment. To illustrate this, Figure 5 shows the results of DFA, with a first-order detrending, based on the original r_j and the integrated z_j heartbeat dynamics for the nsr012 case. For the integrated time series, the scaling exponent is about 1.32, which is in the magnitude order reported previously [6]. Notice that the data can be well-fitted along the domain [10, 1000] with a sole straight line. In the case of the original time-series, the scaling exponent is around 0.279, which is in the magnitude order of the scaling exponents estimated with the structure function approach. Notice that the difference between the scaling exponent of the integrated and the original time series is about 1.0. This seems to be reasonable since, for power functions, integration increases the exponent by 1.0. It is also noticed that, contrary to the original time series case, the log-log plot displays local structure with at least one crossover at about $j_{cr} = 50$, which is in agreement with the results displayed in Figure4. Despite the fact that conventional DFA based on the original time series r_j can lead to results similar to that found with the structure function approach, the latter has two main advantages; namely, i) more details on the local scaling behavior can be obtained, and ii) it allows us to obtain a feedback control interpretation as will be shown in Section 5 .

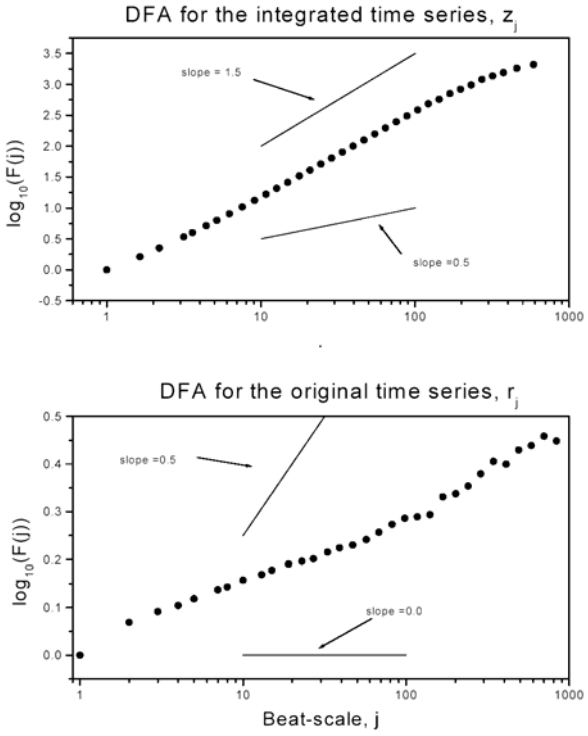

Figure 5. DFA, with a first-order detrending, based on the original r_j and the integrated z_j heartbeat dynamics.

4.3 Breakdown of Scaling Properties in CHF Data

Similar to Figure 4, Figure 6 shows a log-log plot of the fluctuation function $F_2(j)$ as a function of the beat-scale $j \in [1,1000]$, for the CHF data described in Section 2. For a better visualization of scaling breakdown effects, the cases are presented as two plots. Contrary to the behavior shown in Figure 4 for NSR data, no common scaling behavior is observed. The behavior of the fluctuation function $F_2(j)$ for the six cases studied is briefly described as follows:

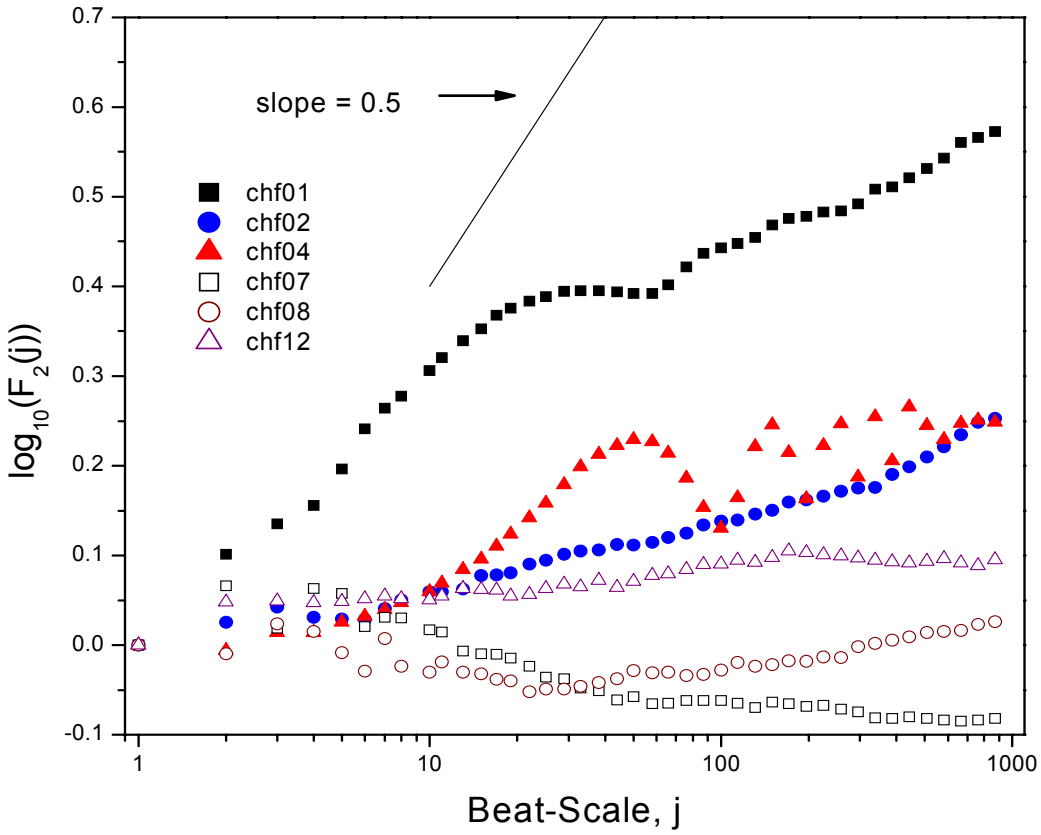

Figure 6. Log-log plot of the fluctuation function $F_2(j)$ as a function of the beat-scale $j \in [1,1000]$, for the NSR data.

a) chf01. A plateau is observed in the range (20, 70). In this case, the crossover for NSR is expanded to cover a wide range of beat-scales.

b) chf02. The fluctuation function $F_2(j)$ meets a single power law scaling property in the whole range [5, 500]. In this case, the crossover j_c is lost, which might indicate that the control mechanism acting at high beat-scales has no effect in the HRV.

c) chf04. The fluctuation function $F_2(j)$ has not a clear scaling property because of certain oscillatory phenomena with period of about 80 beat-scales. However, $F_2(j)$ can be described as an oscillatory scaling power law of the form $\sin^2(\pi w j) j^{H_2}$. Notice that such a periodic behavior is also observed in the AIP diagram shown in Figure 2 of Dudkowska and Makowiec [13].

d) chf07. Interestingly, the fluctuation function $F_2(j)$ meets an anomalous scaling power law with *negative* exponent of the form $F_2(j) \alpha\ j^{-H_2}, H_2 > 0$. That is, fluctuations at larger beat-scales are less volatile than fluctuations at smaller beat-scales. This a contraintuitive situation since, in this cases, fluctuations at larger beat-scales are more predictable than fluctuations at smaller beat-scales.

e) chf08 and chf12. In these cases, the fluctuation function $F_2(j)$ satisfies a scaling power law with a scaling exponent H_2 very close to zero. That is, the beat-series $\{f_{i,j}\}_{i=1}^{N}$ presents weak scaling properties, resembling the

behavior of a Gaussian noise dynamics.

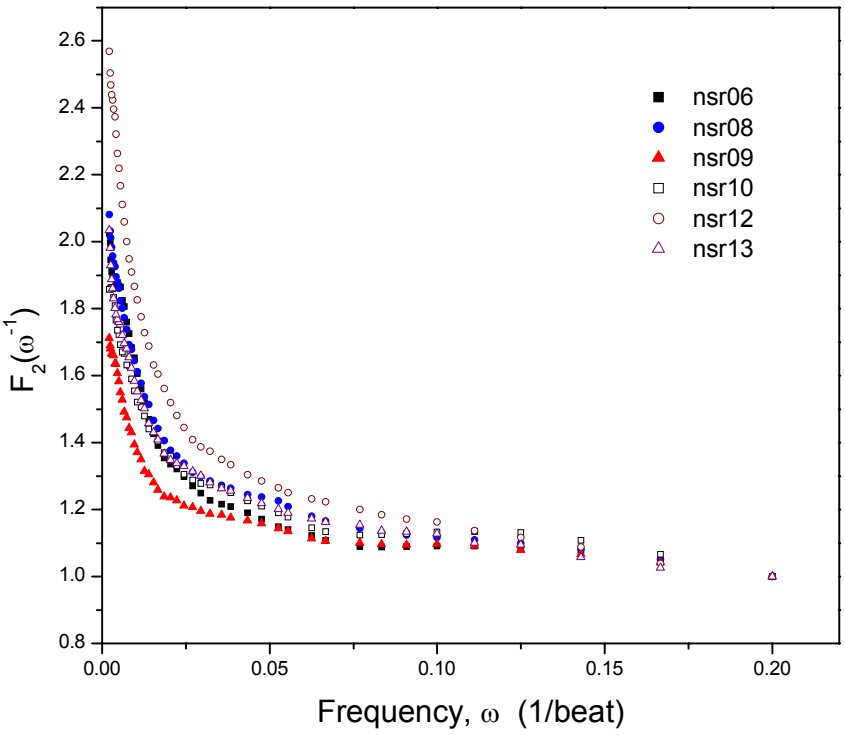

Figure 7. Linear plot of $F_2(w^{-1})$ *versus* w *for the NSR cases.*

Summarizing, the above results indicates the potential of the fluctuation function $F_2(j)$ to distinguish between normal and abnormal HRV patterns. Specifically, while NSR data display a well-defined $F_2(j)$ scaling behavior with a several crossovers, these characteristics are lost in the case of data corresponding to CHF illness. In the latter cases, no unique pattern of scaling properties lost is observed, showing that congestive heart failure is an illness where the failure of the cardiovascular control mechanisms can be due to a wide variety of situations. It is observed that the chf01 case behaves similarly to the nsr cases. This observation suggests that by performing a more detailed analysis of the scaling behavior, as opposed to the conventional linear characterization, it would be possible to recover information about the degree of severity of the CHF condition [23].

5. A SYSTEMIC INTERPRETATION OF HRV BEHAVIOR

So far, we have used time domain to look at scaling properties of the fluctuation function $F_2(j)$. However, as discussed in [1], complementary information on the HRV can be obtained in the frequency domain. Traditionally, this frequency domain interpretation of the HRV has been addressed with spectral analysis of RR interval variability based on either fast Fourier transformation or autoregressive models [2,3]. The resulting PSD from autoregressive models shows dominant dynamics at low - (around 0.1 Hz) and high- frequency (around 0.25 Hz) which has been related to the activity of neurocontrol systems. For instance, the efferent vagal activity is a major contributor to the high-frequency components, as seen in clinical and experimental observations of autonomic maneuvers [26]. More controversial is the interpretation of the low-frequency components, which is considered by some [26,27] as a marker of the sympathetic modulation. The underlying idea behind the interpretation of the frequency domain results is that the heart rate and rhythm are largely under the control of the ANS [4]. In this way, one can see the heart as an actuator that responds to control commands generated by the ANS. Such control commands are intended to modulate the heart rhythm in order to met certain physiological specifications (*e.g.*, to increase the blood circulation flowrate to fulfill nutrient and oxygen requirements during physical activity) [19]. Then, under this view, a

healthy cardiovascular system must provide a stable and robust (*e.g.*, resilient to disturbances) response to control commands within a certain operating frequency range. According to the most standard concepts of feedback control theory [17,18], if the heart is the final actuator of a stable control system, its dynamics should contain at least two components; namely; i) An adaptive scheme to reject exogenous disturbances (*e.g.*, loads), and ii) Low sensitivity at relatively high-frequencies to avoid unstable behavior due to high-frequency dynamics. Issue i) can be met if the controller is equipped with an integral compensator [20], which becomes the regulatory component of the controller. In fact, integral feedback control is a basic engineering strategy for ensuring that the output of a system robustly tracks its desired value independent of noise or variations in system parameters. On the other hand, issue ii) can be obtained if the dynamics of the controller are dominated by low-pass filtering components at high-frequencies. In turn, this dynamics are induced by stabilizing feedback control actions commanded from, *e.g.*, the ANS.

Let us assume that the RR interval dynamics can be modeled as a continuous-time linear system as follows:

$$y(s) = G(s)c(s)$$

where $y(s) = r(s) - \bar{r}$ is a RR interval deviation from a basal (*i.e.*, nominal) RR interval $\bar{r}$, $c(s)$ is a vector of control commands from neurocontrol systems, and $G(s)$ is a causal transfer function with s being the differential (or difference) operator. We have seen that the RR interval response $y(s)$ is a complex signal (see, for instance, Fig.1) with components of different frequency and magnitude values. Since (3), this implies that the control command signal $c(s)$ should be also display complex time-varying dynamics. From a statistical standpoint, we can consider the control command as a signal with a mean magnitude *m*. That is,

$$\langle c(s) \rangle \approx m\sigma(s)$$

where $\sigma(s)$ is a signal with unitary magnitude (*i.e.*, $|\sigma(wi)| = 1$, for all frequency w, where $i = \sqrt{-1}$).

The resulting RR interval response corresponds to the statistical averaged signal

$$\langle y(s) \rangle = G(s)\langle c(s) \rangle \approx mG(s)\sigma(s)$$

One can move to the frequency domain by the identification $s \to wi$, such that $\langle y(wi) \rangle \approx mG(wi)\sigma(wi)$.

Hence, the following relationship is obtained:

$$|\langle y(wi) \rangle| \approx m|G(wi)||\sigma(wi)| = m|G(wi)|$$

In principle, a statistical estimate of the frequency characteristics, represented by $|G(wi)|$, of the control transfer function $G(s)$ can be obtained if the RR interval response $|\langle y(wi) \rangle|$ and the control command mean *m* are known. Since we have not access to the control command signals $c(s)$, the mean value *m* is not available. However, if *m* is assumed to be statistically stationary, the shape of $|G(wi)|$ can be estimated modulo the scaling coefficient m^{-1} (*i.e.*, $|G(wi)| = m^{-1}|\langle y(wi) \rangle|$). In this way, we can take the frequency response $|\langle y(wi) \rangle|$ as a measure of the frequency characteristics of the control transfer function $G(s)$.

One knows that $\left|\langle y(wi)\rangle\right|$ corresponds to the magnitude of the RR interval fluctuations as a function of the exciting frequency w. That is, $\left|\langle y(wi)\rangle\right|$ is proportional to the magnitude of the RR interval fluctuation when the heart control system is stimulated by a signal of frequency w. In this way, in order to estimate $\left|\langle y(wi)\rangle\right|$ one should compute the fluctuations $\langle y(wi)\rangle$ at different frequencies. It is noted that the fluctuation function $F_2(j)$ (see Eq. (2)) provides a measure of the RR interval fluctuations for the time-scale j. Hence, it seems to be natural to define the "beat fluctuation frequency" as $w = j^{-1}$, so that the following identification is considered:

$$\left|\langle y(wi)\rangle\right| \equiv F_2(w^{-1})\alpha\left|G(wi)\right|$$

In this form, one has that the frequency characteristics of the control transfer function $G(s)$ can be statistically represented by $F_2(w^{-1})$.

For the NSR cases, Figure 7 presents a linear plot of $F_2(w^{-1})$ versus w obtained from Figure 4. It is interesting to note that the frequency responses display the basic characteristics around a stable robust controller; namely, i) integral feedback compensation represented by high sensitivity for very low frequencies, and ii) low sensitivity for relatively large frequencies. In this way, one can say that a normal RR interval dynamics reflects the action of a stable and robust ANS-heart system. We conclude that the scaling power law of the RR interval dynamics is not merely an esoteric feature; rather, it reflects the presence of control mechanisms (maybe dominated by the autonomous nervous system [28,29]) with regulatory and stabilizing capabilities which yield fine tune of heart-to-heart intervals. On the other hand, Figure 8 presents the corresponding plot for the studied CHF cases where the following can be observed:

a) In all cases, the low-frequency sensitivity is significantly reduced. This would imply that a neurocontrol-cardiorespiratory system with CHF has lost its regulation capabilities (*i.e.*, the integral feedback compensation scheme is totally or partially lost). In turn, this means that, *e.g.*, the heart is unable to fulfill the blood flowrate and pressure required by the command control, or that the control command is not correct because a malfunctioning of the neurocontrol mechanisms.

b) No unique behavior is displayed. In fact, while the NSR cases display a similar behavior, the CHF cases present different shapes: a) chf01 retains certain low-frequency regulatory capabilities but displays a resonant peak at about $w_{rf} = 0.35 beat^{-1}$, which can lead to unacceptable sensitivity of the RR interval for disturbances with frequencies around w_{rf}, b) chf02 and chf012 present a plateau for most frequencies, which would imply that the cardiovascular system acts as an amplifier with constant gain. Similar to a noise-like behavior, this situation may indicate a lack of learn-ing/adaptive mechanisms that endow the control system with desirable robustness properties [20],

c) chf04 displays oscillations, which can be due to the presence of delayed control actions [17] due maybe to by-pass flowing, d) chf07 and chf08 behaves as a high-pass filter, showing a heart exces-sively sensitive to high-frequency disturbance (*e.g.*, noise). In this case, the neurocontrol systems ANS seem to be unable to regulate the RR interval dynamics around stable beat conditions.

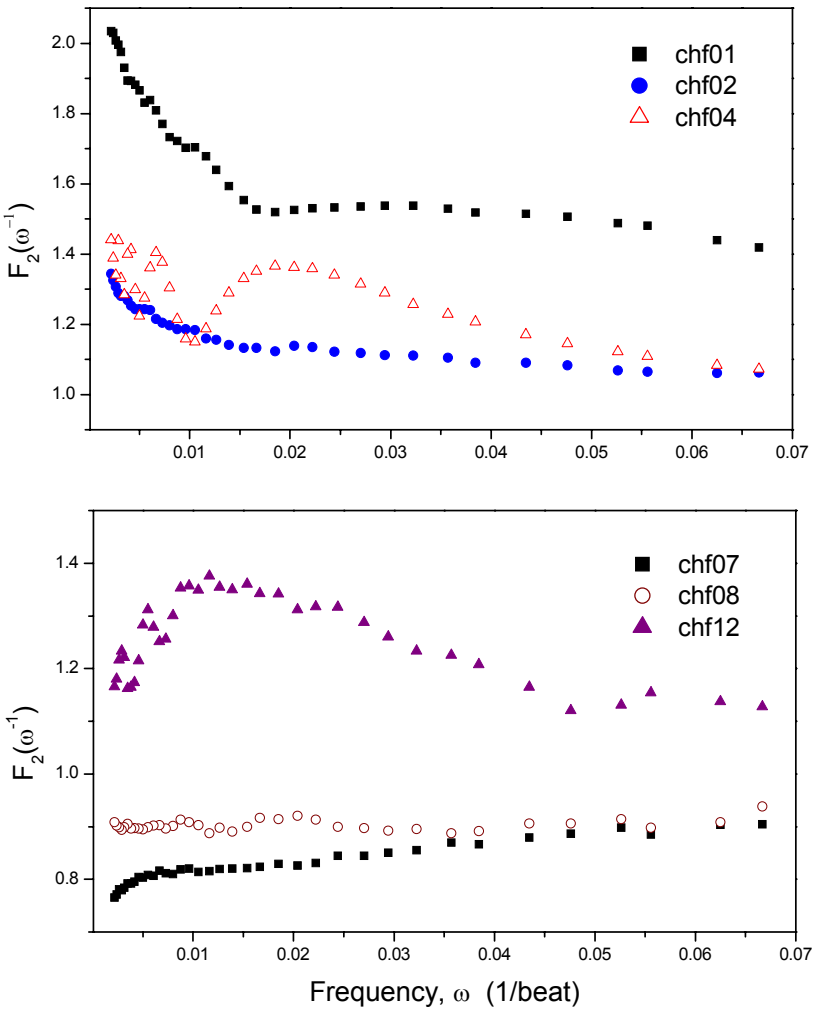

Figure 8. Linear plot of $F_2(w^{-1})$ versus w for the CHF cases.

The above preliminary results show the potential of alternative (linear and nonlinear) techniques to extract hidden useful information from HRV.

6. CONCLUSIONS

Our results have shown that a suitable combination of nonlinear statistical and system theory (*e.g.*,feedback control) tools can provide important insights on the stylized features of RR interval dynamics. Of particular interest is the fact that the existence of a scaling power law can be related to the action of stable control mechanism associated to the autonomic nervous system. In this way, CHF cases are characterized by a lost of the regulation capabilities of the control mechanisms, which can lead to excessive sensitivity of the heart beat dynamics to relatively high-frequency disturbances. In turn, such a loosing of the regulatory capabilities could lead to lethal arrhythmias and signs of ANS malfunctioning [1]. Further work should be directed towards a more detailed classification of CHR cases according to the frequency characteristics of the RR interval fluctuations. Additionally, a physical interpretation of the crossovers for healthy subjects in relation to the vagal and sympathetic neurocontrol mechanisms is an interesting issue that deserve further analysis.

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