Hierarchical structure in healthy and diseased human heart rate variability

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It is shown that the healthy and diseased human heart rate variability (HRV) possesses a hierarchical structure of the She-Leveque (SL) form. This structure, first found in measurements in turbulent fluid flows, implies further details in the HRV multifractal scaling. The potential of diagnosis is also discussed based on the characteristics derived from the SL hierarchy.

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The heart beat interval in humans is known to exhibit fluctuation which is referred to as heart rate variability (HRV). Power spectrum analysis of the fluctuation revealed a $1/f$-like scaling [1]. Recent studies indicated that healthy human HRV exhibits even higher complexity which can be characterized by multifractal scaling [2,3,5]. In contrast, HRV in the pathological state such as congestive heart failure (CHF) exhibits more monofractal-like scaling [2]. The change in the $1/f$ law of CHF HRV is consistent with this result [4]. Such a multifractal-monofractal transition was also reported in parasympathetic nervous system blockade experiment [3]. Hence the manifestation of multifractal HRV is indicative of the proper autonomic regulation of the heart rate. Further studies revealed that the multifractal HRV has properties analogous to those found in fluid turbulence [5]. However, there is little understanding beyond the phenomenological description of multifractal HRV.

In this paper, we exploit further the analogy of HRV to fluid turbulence and show the existence of a hierarchical structure in healthy and diseased HRV. This structure allows us to model the multifractality of HRV and make conjecture to the heart beat dynamics responsible for the multifractal scaling. The hierarchy, first proposed by She and Leveque (SL) to understand the statistical properties of turbulent fluid flows, provides a successful framework to discuss and characterize the deviation from Kolmogorov monofractal scaling of the velocity fluctuations in fluid turbulence [6]. When applied to the study of HRV, the SL hierarchy provides a model structure which possesses two advantages: (a) it simplifies the functional description of the multiscaling by using a maximum of only three parameters, and (b) it indicates predictive power for HRV scaling in a pathological physiological state such as congestive heart failure. One immediate suggestion is the potential use of this notion in applications such as diagnosis.

The results presented in this work are based on an analysis of the beat-to-beat (RR) interval recordings. The RR interval (RRi) measures the time span of successive ventricular contractions. The contraction results from the almost synchronous depolarization of the cardiac cells, which reverses the potential across the cell membrane. This event is picked up in the electrocardiaogram (ECG) recording and RRi is extracted from the time interval of successive peaks in the ECG signal. Let the RRi be $r(t)$, where t is the discrete beat number, and its increment be $\Delta r(\tau)=r(t+\tau)-r(t)$. The SL hierarchy implies, for a range of τ,

$$\left[\frac{S_{p+2}(\tau)}{S_{p+1}(\tau)}\right]=A_p\left[\frac{S_{p+1}(\tau)}{S_p(\tau)}\right]^{\beta}[S^{\infty}(\tau)]^{1-\beta}. \tag{1}$$

Here $0<\beta<1$ is a parameter of the hierarchy, A_p a function of p, $S_p(\tau)=\langle|\Delta r(\tau)|^p\rangle$ the pth order moment of $|\Delta r(\tau)|$ denoted as the pth order RRi structure function, $S^{\infty}(\tau)\equiv\lim_{p\to\infty}S_{p+1}(\tau)/S_p(\tau)$ and $\langle\cdot\rangle$ denotes the statistical average. Since $S^{\infty}(\tau)$ is dominated by the statistics of large $\Delta r(\tau)$, it characterizes the largest amplitude fluctuations in HRV. Moreover, given the empirical law $S_p(\tau)\sim\tau^{\zeta(p)}$ in HRV [5], the hierarchy (1) implies the scaling model [6]

$$\zeta(p)=h_0p+C(1-\beta^p), \tag{2}$$

where h_0 and C are two other parameters of the hierarchy. It follows from Eqs. (1) and (2) that $S^{\infty}(\tau)\sim\tau^{h_0}$. A nonlinear functional dependence of $\zeta(p)$ on p indicates multifractal scaling. Thus, the parameter β measures the degree of multifractality. In particular, $\beta\to1$ leads to monofractal scaling. In the multifractal description of fluid turbulence, the parameter C can be shown to be the codimension of the set of the largest amplitude fluctuation of the flow [6]. Here we adopt these ideas in fluid turbulence to interpret the meaning of the parameter C in HRV: a smaller (larger) C generally implies a larger (smaller) probability of the occurrence of large amplitude fluctuations.

We follow the procedure developed in Ref. [7] to check whether the RRi data possess a hierarchical structure of the SL form. This approach is based on a scaling property implied by the hierarchy which describes a power-law relationship between the normalized structure functions:

$$\frac{S_p(\tau)}{[S_n(\tau)]^{p/n}}\sim\left\{\frac{S_q(\tau)}{[S_n(\tau)]^{q/n}}\right\}^{\rho_n(p,q)}. \tag{3}$$

Such a scaling property is known as generalized extended self-similarity in fluid turbulence [8,9]. In the case of SL hierarchy, the exponents $\rho_n(p,q)$ depend only on the model parameter β:

$$\rho_n(p,q)=\frac{n(1-\beta^p)-p(1-\beta^n)}{n(1-\beta^q)-q(1-\beta^n)}. \tag{4}$$

It follows that

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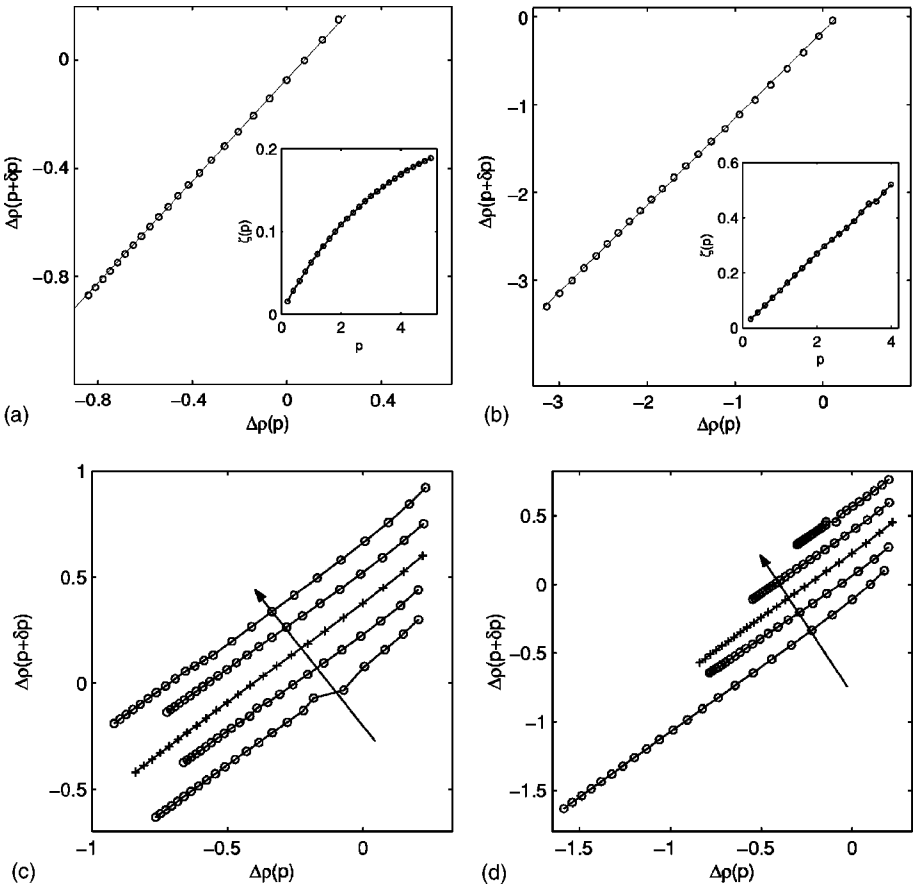

FIG. 1. Typical $\Delta\rho_n(p+\delta p,q)$ vs $\Delta\rho_n(p,q)$ plots for (a) healthy HRV and (b) CHF HRV with $\delta p=0.2$. We used $q=1$ and $n=2$ for healthy HRV and $q=0.8$ and $n=1.2$ for CHF HRV. The solid lines are least-square fits and the estimated values of β are 0.74 and 0.95, respectively, for healthy and CHF HRV. The insets show the corresponding $\zeta(p)$. The curve in (a) is also calculated using different choices of n and q: (c) $n=2$ and $q=0.6,0.8,1.2,1,4$ and (d) $q=1$ and $n=1.6,1.8,2,2.2,2.4$ (parameter increasing in the direction of the arrow). A rather insensitive dependence of the slopes on the choices of n and q is evident.

$$\Delta\rho_n(p+\delta p,q)=\beta^{\delta p}\Delta\rho_n(p,q)-\frac{\delta p(1-\beta^n)(1-\beta^{\delta p})}{n(1-\beta^q)-q(1-\beta^n)}, \tag{5}$$

where $\Delta\rho_n(p,q)\equiv\rho_n(p+\delta p,q)-\rho_n(p,q)$. One can then plot $\Delta\rho_n(p+\delta p,q)$ vs $\Delta\rho_n(p,q)$ to check (5) and hence the validity of the SL hierarchy.

We use several databases to perform the calculations (3) and (5) to study the validity of the hierarchy in HRV. The first database (DB1) contains ten sets of daytime ambulatory RRi recordings taken from healthy young adults [5]. The second database (DB2) contains 18 sets of daytime normal sinus rhythm RRi data downloaded from public domain [10]. The third database (DBCHF) contains 45 sets of data from congestive heart failure patients downloaded from the same public domain [10]. In our analysis, certain abnormal beat patterns due to missed beat, improper triggering on ventricular repolarization (T wave) as well as depolarization (QRS complex) are removed or modified. For example, two short RRi's due to triggering on the T wave are replaced by their sum and a small number of alternate RRi's lying significantly outside the local data trend are interpolated. Those cases showing excessive abnormal beat patterns caused mainly by ectopic beats are discarded from the analysis to avoid complication in the estimation of $S_p(\tau)$. The resulting number of data sets used in the analysis is 54, with 24 from healthy objects and 30 from CHF patients [11].

Equation (3) is found to hold in both healthy and CHF HRV. The exponent $\rho_n(p,q)$ is then estimated from (3) and used in (5) to calculate $\Delta\rho_n(p,q)$. Typical $\Delta\rho_n(p+\delta p,q)$ vs $\Delta\rho_n(p,q)$ plots are shown in Figs. 1(a) and 1(b). The observed linear trend is consistent with Eq. (5). Hence, SL hierarchy is compatible with the multifractal scaling in HRV. From such plots, we estimate the value of β from the slope of the fitted straight line and verify that the intercept obtained by substituting the estimated β into Eq. (5) agrees with the fitted value. We further check that the values of β obtained have no sensitive dependence on the choices of q and n [see Figs. 1(c) and 1(d)]. The results for β are shown in Fig. 2(a). The values of β from healthy HRV (DB1,DB2) cluster in the range [0.6,0.9] while the values of β from DBCHF are generally larger due to more monofractal-like scaling. Those $\zeta(p)$ showing less curvature are being characterized by larger β values as seen in Figs. 1(a) and 1(b).

To gain insight of the hierarchy, She and Waymire (SW) arrived at the hierarchy (1) using multiplicative random cascade [12]. Their cascade consists of two dynamic components. One is the basic component that generates the singular dynamics over a continuum of scales. It can be shown that this dynamical component gives rise to the scaling term h_0p in Eq. (2). The SW cascade contains an extra component, which modulates the singular structure through the multiplication of β in discrete steps [12]. It can be shown that this modulating component contributes to the nonlinear term $C(1-\beta^p)$ in Eq. (2). Since RRi $r(t)$ does not exist for t in between heart beats from the ECG recording, continuous scale invariance cannot be defined in HRV. This suggests a dominant modulating component in the generation of the multifractal scaling of HRV and a scaling model with h_0

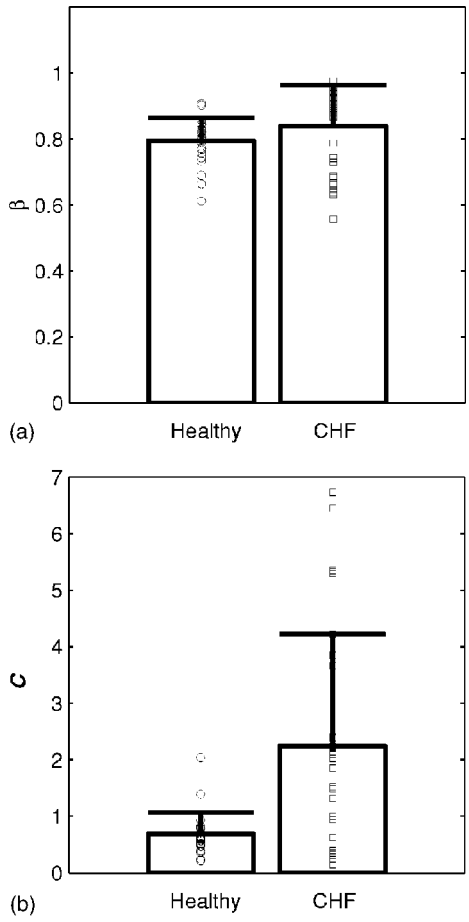

FIG. 2. Estimated values for model parameters (a) β and (b) C. Estimates from DB1 and DB2 for 24 healthy subjects are given in circles and those from DBCHF for 30 congestive heart failure subjects are given in squares. The upper end of the bars indicates the value of the mean and the horizontal line above the bars shows the value corresponding to the mean plus one standard deviation.

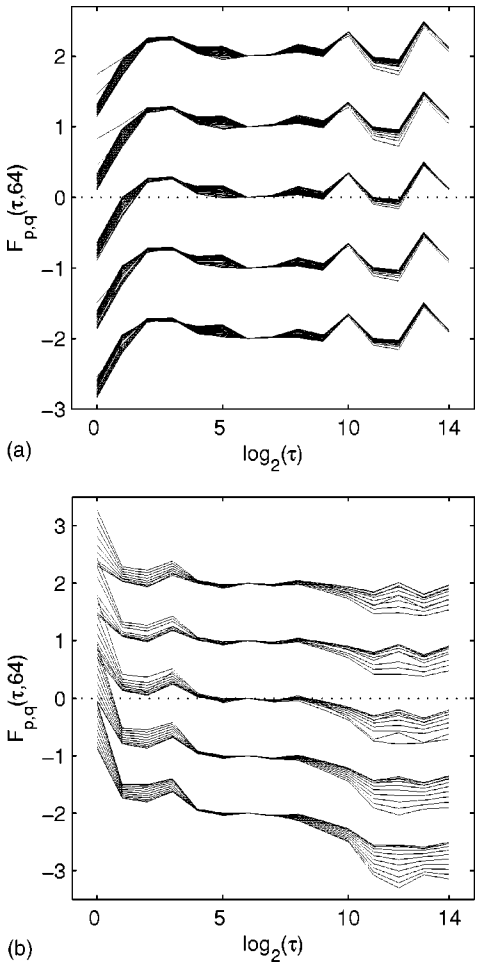

FIG. 3. Evidence of τ-independent $S^{\infty}(\tau)$. $F_{p,q}(\tau,64)$ vs $\log_2(\tau)$, for various values of p (superimposed) and $q=1.2,1.6,2,2.4,2.8$ (from top to bottom, curves shifted for clarity). (a) A healthy subject ($p=0.2-5$) and (b) a CHF patient ($p=0.4-2.6$). The β needed in the calculation of $\mu(p,q)$ [see Eq. (7)] is obtained from that estimated by Eq. (5).

~ 0. Equivalently, this implies a hierarchy with a τ-independent S^{∞}. Since S^{∞} cannot be directly calculated, to verify such a model we first rewrite Eq. (1) as

$$S_p(\tau) \sim [S^{\infty}(\tau)]^p \left\{ \frac{S_q(\tau)}{S^{\infty}(\tau)^q} \right\}^{\mu(p,q)}, \tag{6}$$

where $\mu(p,q) \equiv (1-\beta^p)/(1-\beta^q)$ [7]. We then form the quotient of Eq. (6) at distinct values of τ and τ_0, which, after some algebra, yields

$$\log_2\left[\frac{S^{\infty}(\tau)}{S^{\infty}(\tau_0)}\right] = \frac{\log_2[S_p(\tau)/S_p(\tau_0)] - \mu(p,q)\log_2[S_q(\tau)/S_q(\tau_0)]}{p - q\mu(p,q)} \equiv F_{p,q}(\tau,\tau_0). \tag{7}$$

Hence, $F_{p,q}(\tau,\tau_0)$ is independent of p and q, and a τ-independent $S^{\infty}(\tau)$ implies a "constant" $F_{p,q}(\tau,\tau_0)$ over a range of τ and τ_0 values. Figure 3 shows $F_{p,q}(\tau,\tau_0)$ for healthy and CHF HRV for various values of p at certain choices of q. The convergence of $F_{p,q}$ for different p and q values is verified. Moreover, $F_{p,q}$ is consistent with zero for a range of τ showing that the condition $h_0 \sim 0$ can be statistically ascertained and that $\zeta(p) \sim C(1-\beta^p)$. Given this, C is obtained by averaging $\zeta(p)/(1-\beta^p)$ over a range of p and its result has been shown in Fig. 2(b). As shown in Fig. 4, C, as a function of β, shows an increasing trend as $\beta \to 1$. This functional relationship is consistent with the observations $h_0 \sim 0$ and that $\zeta(p)$ becomes almost proportional to p as $\beta \to 1$. It can also be inferred from the earlier experimental studies, as we now explain.

Recall that the fractal dimension $D(h)$ of the set with a local scaling exponent h is related to $\zeta(p)$ through a Legendre transform

$$D(h) = \min_p[ph + d - \zeta(p)], \tag{8}$$

where d is the dimension of the embedding space. From Eq. (2) and with $h_0 \approx 0$, $D(h)$ can be explicitly obtained as

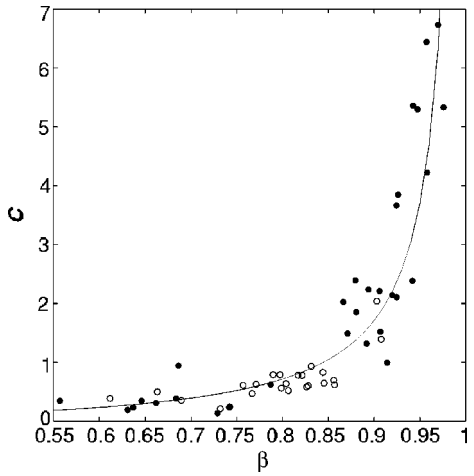

FIG. 4. C vs β empirical law for healthy subjects (open circles) and congestive heart failure patients (solid circles). The solid line is the fit $C=0.2\beta/\ln(1/\beta)$.

$$D(h) = d - C + \left[\frac{1 + \ln C + \ln(\ln 1/\beta)}{\ln(1/\beta)}\right]h - \frac{h \ln h}{\ln(1/\beta)}. \quad (9)$$

Let h^* be the scaling exponent of the singular set with largest dimension, i.e., $D(h^*)$ is the maximum. For HRV, h^* was found to increase its value from the multifractal-like scaling in a healthy state to the monofractal-like scaling in the diseased and pathological states [2,3]. Using Eq. (9), h^* is derived explicitly as

$$h^* = C \ln(1/\beta). \quad (10)$$

If C is constant, h^* decreases as monofractal scaling is approached $(\beta \to 1)$, which contradicts what was observed [2,3]. In order for h^* to increase with β in the limit of $\beta \to 1$ as observed, $C(\beta)$ must diverge as $1/\ln(1/\beta)$. Indeed, we find that the dependence of C on β can be well described by $0.2\beta/\ln(1/\beta)$ (Fig. 4). Thus we have the result $h^* \sim 0.2\beta$ with h^* increasing with β in accord with the experimental observations [2,3]. Finally, the diverging behavior of C as $\beta \to 1$ presents a more favorable condition for diagnosis as explained below. The CHF HRV generally shows more monofractal-like scaling with β value closer to 1. As a result, the corresponding C value will be larger than those for the healthy subjects [see also Fig. 2(b)]. Thus a large value of C would provide a good characteristic for a diagnosis of potential CHF. Indeed, as seen in Fig. 4, C values larger than 3 are all from CHF patients. We discussed earlier that a larger value of C generally implies a smaller probability of the occurrence of large amplitude fluctuations. In this sense, our work also indicates that the CHF HRV has simpler dynamics than the healthy HRV.

In summary, we show that a hierarchical structure of the SL form exists in the healthy and diseased human HRV. This property allows us to model the multifractal HRV in terms of only two parameters, C and β. Interestingly, C and β are related by an empirical law captured in Fig. 4. This finding is important for two reasons. First, the empirical law appears to be universal and is capable of describing both healthy and congestive heart failure data. Second, the divergence of C as $\beta \to 1$ implies potential in diagnosis of congestive heart failure using the hierarchical structure.

To find a model that is compatible with the current finding, we adopted the SW cascade which leads to further implications beyond the phenomenological description of multifractal HRV scaling. It is known that biological regulation relies on feedback control which in principle operates additively. The modulating component of the SW cascade has the effect of reducing the fluctuation of turbulent flow (since $\beta < 1$) which is similar to the effect of feedback control on stabilizing a physiological state in biological systems. Hence the SW model might provide an example of how feedback can be integrated into an entirely multiplicative cascade [5] in HRV modeling. Further experiments will be needed to test and quantify these possibilities in more detailed physiological terms.

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