INVITED PAPER

Multiscale Analysis of Intensive Longitudinal Biomedical Signals and Its Clinical Applications

Recent advances in wearable and/or biomedical sensing technologies have made it possible to record continuous biomedical signals over long periods of time. This paper reviews multiscale approaches for their analysis.

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ABSTRACT | Recent advances in wearable and/or biomedical sensing technologies have made it possible to record very long-term, continuous biomedical signals, referred to as biomedical intensive longitudinal data (ILD). To link ILD to clinical applications, such as personalized healthcare and disease prevention, the development of robust and reliable data analysis techniques is considered important. In this review, we introduce multiscale analysis methods for and the applications to two types of intensive longitudinal biomedical signals, heart rate variability (HRV) and spontaneous physical activity (SPA) time series. It has been shown that these ILD have robust characteristics unique to various multiscale complex systems, and some parameters characterizing the multiscale complexity are in fact altered in pathological states, showing potential usability as a new type of ambient diagnostic and/or prognostic tools. For example, parameters characterizing increased intermittency of HRV are found to be potentially useful in detecting abnormality in the state of the autonomic nervous system, in particular the sympathetic hyperactivity, and intermittency parameters of SPA might also be useful in evaluating symptoms of psychiatric patients with depressive as well as manic episodes, all in the daily settings. Therefore, multiscale analysis might be a useful tool to extract information on clinical events occurring at multiple time scales during daily life and the underlying physiological control mechanisms from biomedical ILD.

KEYWORDS | Autonomic nervous system; complex biosignals; dynamical disease; heart failure; heart rate variability; multiscale fluctuations; psychiatric disorder; spontaneous physical activity

I. INTRODUCTION

Ambulatory assessments have recently started to become rapidly pervasive on a global scale. The development of such technologies allows us to obtain large-scale data by longitudinal recording of biomedical signals, such as heart rate and physical activity time series. For instance, in the last few years, a number of wearable devices and cloud services using them for healthcare management have been released at low cost [5]–[7]. However, methods to analyze this kind of data collected continuously in daily life, or so-called intensive longitudinal data (ILD) [9], have not yet been fully established. To gain useful information for better healthcare uses, it is important to characterize signal features related to underlying

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physiological control mechanisms and clinical events occurring on multiple time scales.

In this review, we introduce studies on statistical and dynamical characterizations of signals called heart rate variability (HRV) [13], a sequence of heart inter-beat intervals measured by ambulatory electrocardiography, and spontaneous physical activity (SPA), or sometimes called locomotor activity, measured by acceleration sensors built, for instance, into a wrist band/watch [14], [15]. Because the data collection for these signals is one of the easiest modes of ambulatory monitoring, these data are indeed two typical examples of ILD [9] that can be obtained from time scales of seconds, minutes, hours, and even days (or months in the case of SPA). These types of data contain signal components due to changes in physiological states and/or behavioral episodes (exercise, sleep, eating, etc.) in daily life. In addition to these limited number of within-day states and/or episodes, they also contain an even greater amount of fluctuations around changes in local means, known to show characteristics unique to various multiscale complex systems. These characteristics include long-range correlation [16], [17], fractality [18]–[21], multifractality [22], non-Gaussian [17], [23] and/or non-Poissonian [1], [2] behavior, and intermittency [3], [4], [11], [23]–[25].

From a biomedical perspective, the massive existence of signal components exhibiting such multiscale complexity is considered important for two reasons. First, as it is difficult for an individual to control her/his physiological states and behavioral episodes over a number of multiple time scales at the same time for a long period of recording during daily life, these components are most likely to be generated unconsciously without being affected much by the specific life-styles of patients. Thus, they are considered to provide robust measures reflecting intrinsic characteristics of underlying physiological control mechanisms [26]. Notwithstanding this, these measures for multiscale complexity have been shown to be altered in pathological states: e.g., myocardial infarction [27], [28] and heart failure [11], [23]–[25], [29] for HRV, and major depressive disorder [1], [2], [30] and schizophrenia [31] for SPA. Second, and more intriguingly, it may be possible that statistical as well as dynamical features of these components (fluctuations) could provide information about early signs of abrupt changes in the state of the system [32], and in this case health and medical status.

The importance of studying statistical and dynamical features of fluctuations can be understood by using a schematic view of the dynamics of physiological regulations and the transition to a "dynamical disease" [33], [34] state [Fig. 1]. Traditionally, physiological regulations have been explained using the concept of *homeostasis* (i.e., stability through constancy), maintaining constancy of a vital variable by sensing its deviation from a set point and providing feedback to correct the error. Short-range

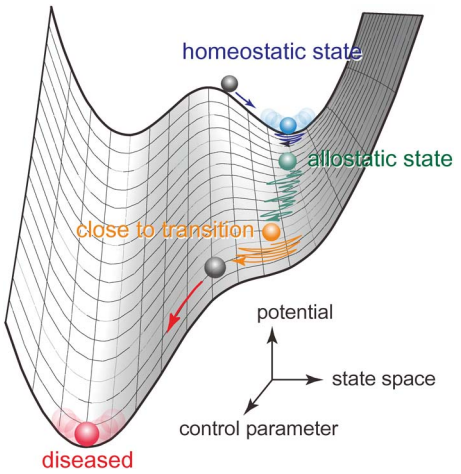

Fig. 1. ***A current schematic view on the onset of (transition to) dynamical disease and multiscale fluctuations in state space.***

negative correlations of state variables are expected in such a case. In 1988, Sterling and Eyer [35] extended this concept to that of *allostasis* (i.e., stability through change) to account for the ability to adapt successfully to the challenges of "daily life" by the brain's mechanisms to maintain viability, emphasizing the extremely demanding and complex biological imperative that "an organism must vary all the parameters of its internal milieu and match them appropriately to environmental demands." In this allostatic state, the spatiotemporal complexity of the brain's control systems may give rise to multiscale complexity in the state variables, and it has indeed been shown that both HRV [24] and SPA [1], [2], [31] exhibit long-range correlation and intermittent dynamics only in the daily life condition (not, e.g., during non-Rapid Eye Movement sleep). While allostasis is necessary to make physiological regulations during daily life, further activation of this state may bring a system to the critical transition point where the emergence of longer period oscillation (e.g., critical slowing down [32]) and/or larger deviations could be early signs of disease onset and/or exacerbation. In this review, we will show some examples for such a scenario including that increased intermittency and appearance of larger non-Gaussian deviation of HRV, due most likely to the sympathetic over-excitation, were associated with increased mortality in severe heart failure patients [25].

The above concept of dynamical disease [i.e., the qualitative transition (bifurcation) to a diseased state through changes in control parameters] is not new and was indeed proposed almost a couple of decades ago [33], [34]. While it is intuitively useful in disease forecasting, prevention and control, verification has been difficult because it requires large amount of data for the state variables to gain quantitative insights into the dynamical state of the system; now it may be possible, by

using biomedical ILD, to quantitatively study the dynamical disease. Therefore, the purpose of this review is to provide an overview of multiscale fluctuation analysis of emerging biomedical ILD and its clinical applications. Specifically, in Sections II and III, respectively for HRV and SPA, we will introduce: 1) the physiological background, a brief history of research and unsolved problems; 2) characterizations of multiscale dynamics mainly focusing on intermittent and non-Gaussian behaviors in signals; and 3) examples of clinical applications and implications provided through the analysis of multiscale fluctuations. This will be followed by Section IV, which summarizes the findings and discusses future directions. Numerous multiscale analysis tools have so far been developed, mostly in the fields of statistical physics and biosignal processing (cf., e.g., [36]–[40]). The present contribution concentrates specifically on tools that focus on a joint analysis of the intermittent and non-Gaussian nature of data. Interested readers are referred to, e.g., [41] for a comprehensive review of multiscale analysis tools and their clinical applications for HRV.

II. HEART RATE VARIABILITY

A. What is HRV and Why is it Important?

Normal heart contraction is initiated by electrical impulses from the sinoatrial (SA) node acting as the natural pacemaker of the heart. On an electrocardiogram, normal beating (called normal sinus rhythm) generates a seemingly periodic and well-defined pattern [Fig. 2(a)]. However, closer examination reveals that the heartbeat intervals fluctuate in a complex and irregular manner even for a healthy individual at rest [Fig. 2(b)]. This fluctuation is caused by that of the pacing rate of the SA node modulated primarily as well as continuously by the activity of sympathetic and/or parasympathetic (vagal) nervous fibers via the autonomic nervous system (ANS) [42]. Sympathetic stimulation exerts facilitatory effects on the heart and increases heart rate, whereas parasympathetic stimulation exerts inhibitory effects and decreases heart rate. In addition, the ANS has a broader range of cardiovascular effects (e.g., on blood pressure), generating much more dynamical and complex behaviors in heart rate. Therefore, through the analysis of heart rate fluctuations, called heart rate variability (HRV), it is possible to evaluate various aspects of ANS function [13], [43].

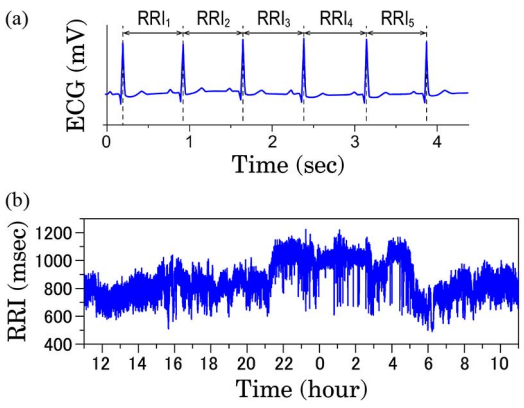

Fig. 2. ***Definition of R-R interval (RRI) and 24 hour heart rate variability (HRV). In general HRV analysis, the R-peak in normal sinus rhythm is assumed. (a) The R wave can be detected as a sharp positive peak in the standard electrocardiogram (ECG), and the RRI is defined as the duration between successive R-waves. (b) 24 hour HRV (normal-to-normal R-R intervals) in a 31-yr-old male subject.***

Clinically, an ambulatory electrocardiography device called the Holter monitor, used for the diagnosis of arrhythmias, is used to continuously monitor HRV usually for 24 hours [44], and it has been reported that reduced and/or abnormal HRV in cardiac patients is associated with higher mortality during follow-up periods [45]–[47]. Hence, HRV characteristics are expected to serve as prognostic as well as diagnostic markers of various cardiovascular disorders. Heart rate in healthy subjects is well controlled by parasympathetic function; higher parasympathetic activity is known to result in slower heart rate and increases in parasympathetic markers (see Section II-B) of HRV. On the other hand, decreased parasympathetic activity evaluated by higher heart rate and reduced HRV is associated with increased risk of mortality in cardiac patients, such as those after acute myocardial infarction (AMI) [47].

More importantly, available epidemiological and clinical data have shown that increased activity of the sympathetic nervous system leads to an increase in cardiovascular morbidity and mortality [48]. Accumulating evidence has suggested that sympathetic hyperactivity is a potential cause of fatal cardiovascular events, and presumably the major contributor to arrhythmic events [48]. Therefore, the noninvasive assessment of sympathetic activity to the heart is of great importance. However, as shown in Section II-B, currently most HRV markers are considered to reflect primarily parasympathetic functions, and there is no widely accepted and well tested HRV index used as a marker of sympathetic nervous system activity [49].

Fourier power spectral density estimation has been a main tool in conventional HRV analysis [13]. The power spectral density provides a full characterization of stochastic processes only when they are stationarity and linear [50]. Notably, power spectral density does not account for any departure of data from Gaussianity. However, many real-world signals including HRV time series cannot be fully characterized based on the assumption of stationary Gaussian linear processes, and display much more complex behavior. To quantify such nonlinear features, concepts and analysis methods developed in

statistical physics and nonlinear dynamics have been applied to HRV analysis [51]. The nonlinear indices which have been proposed include scaling exponents characterizing fractal and long-range correlation characteristics [16], [52], multifractal properties [22], Poincaré plot-based indices [53], entropy measures [54]–[57], symbolic pattern statistics [55], [58] and non-Gaussian properties [23]. Some of these nonlinear indices are expected to provide complementary information on HRV characteristics contributing to better diagnosis and prognosis than conventional time and frequency domain indices.

With regards to a dynamical disease perspective [Fig. 1], the following aspects of the HRV dynamics should be considered as important: (1) common dynamical properties of HRV have been observed in healthy subjects even in daily life, when the measurements are performed, [23], [26], although these properties can depend on age [59], [60]; (2) these properties arise from endogenous HRV dynamics, not from behavioral and environmental factors [23], [26]; and (3) an alteration of such properties are associated with morbidity and mortality in cardiac patients [25], [28], [61], [62]. These properties have been observed in long-range correlation [26], multifractality [22] and scale invariant non-Gaussianity [23]. These characteristics are evaluated based on multiscale (or multiresolution) analysis, and have been examined as mortality risk markers for cardiac patients. Moreover, some markers are suggested to be associated with overall sympathetic hyperactivity during daily life. Thus, multiscale analysis approaches could provide new insight into HRV dynamics.

In this section, we discuss multiscale characteristics of HRV and the key issues for evaluation of ANS functions, especially sympathetic activity thought to play an important role in the transition of the allostatic state.

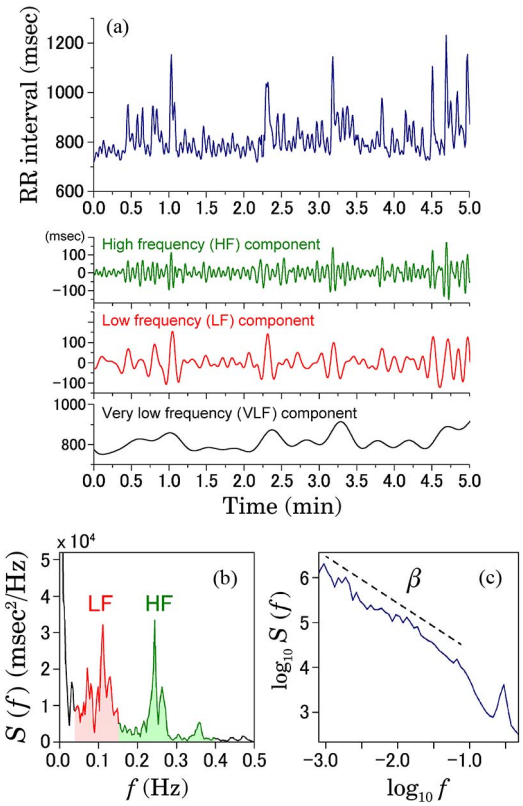

Fig. 3. ***Frequency domain HRV analysis. (a) Time series of R-R intervals in a 31-yr-old male subject (top) and its frequency band components (3 bottom rows). The time series was resampled at evenly spaced intervals (2 Hz). The R-R time series was decomposed into high frequency (HF: 0.15 to 0.40 Hz), low frequency (LF: 0.04 to 0.15 Hz) and very low frequency (0 to 0.04 Hz) components. These components were obtained using the inverse Fourier transform of corresponding frequency components. (b) Power spectral density of the R-R time series (a). (c) Assessment of the scaling exponent β of 24-h HRV. The power spectrum was estimated from the resampled time series at 2 Hz.***

B. Frequency Domain HRV Markers and the Limitations

Frequency domain analysis based on Fourier power spectral density estimation is a widely used tool for the investigation of HRV [13]. HRV power spectral density serves to detect a number of physiological processes working at different and multiple time scales. In healthy subjects under controlled conditions, a typical power spectrum of HRV is comprised of two oscillating components in high-frequency (HF; 0.15 to 0.4 Hz) and low-frequency (LF; 0.04 to 0.15 Hz) bands [Fig. 3(b)], and a $1/f$ noise-like component in very-low-frequency (VLF; below 0.04 Hz) band. The HF component reflects effects of respiration on heart rate, referred to as respiratory sinus arrhythmia (RSA) while the LF component, associated with so-called Mayer waves (approximately 0.1 Hz), represents oscillations related to regulation of blood pressure and vasomotor tone. The origin of the VLF component remains an open issue: it is however commonly thought to relate to hemodynamic functions [13], [43], [63], [64], such as thermoregulation and kidney function. For the noninvasive assessment of ANS functions, power of the HF component is taken as a marker for cardiac parasympathetic activity; the LF component is a marker for cardiac sympathetic activity, or both the sympathetic and parasympathetic influences, and the ratio of LF to HF power (LF/HF ratio) indicates sympathovagal balance, which is usually interpreted as reflecting the relative sympathetic predominance [13], [65]. In this view, an increase in LF power is assumed to indicate an increase in sympathetic activity, and a higher value of LF/HF ratio indicates a shift of sympathovagal balance toward sympathetic predominance.

It is generally accepted that HF power reflects RSA mediated by the parasympathetic activity [66]. However, the origin and clinical significance of LF power have aroused considerable controversy. In short-term HRV recordings ($\sim$ minutes) under experimental conditions affecting

autonomic response, the relative power contribution of LF component is considered as a marker for sympathetic modulation [65], [67]. However, many studies using pharmacological, physiological and psychological manipulations affecting sympathetic activity on HRV have challenged the association of cardiac sympathetic activity with LF power [68], [69]. The available data have suggested that over a wide frequency range including HF and LF bands, the HRV power spectrum is mainly determined by the parasympathetic system [70]. It has also been suggested that the LF power constitutes an index of baroreceptor reflex gain (or sensitivity) in mediating oscillations in blood pressure and vasomotor activity [71], [72].

More controversial was the interpretation of LF power and LF/HF ratio obtained from 24-hour ambulatory HRV recordings in patients with a marked reduction in ventricular function. While in these patients, sympathetic activity was reported to be markedly elevated [48], a decrease in LF power and LF/HF ratio is more commonly observed, and associated with increased risk of mortality [18], [73]. Therefore, clinical significance of association of cardiac sympathetic activity with LF power-related indices is questionable.

In addition to scale-specific behavior of HRV observed in HF and LF bands, it has also been proposed that HRV fluctuations show fractal, or scaling properties in the VLF band (< 0.04 Hz), related to long-range correlations [16], [17], [20], [59], [74], [75]. A time series is said to exhibit long-range correlations when the data points across widely separated times are correlated and the autocorrelation function of the time series or its increments shows a power-law decay: $C(\tau) \sim \tau^{-\gamma}$, where τ is the time lag [76]. Although the general mathematical mechanism for generating long-range correlations is not clear, in some numerical studies of complex systems, long-range correlations emerge as a result of the collective behavior of multiple interacting components, each with its own, specific and different characteristic time scales [77].

The conventional way to quantify long-range correlations is to use power spectral analysis. Although long-range correlated processes with $S(f) \sim f^{-\beta}$ power spectra have no characteristic time scale, such processes can be characterized by a scaling exponent β [Fig. 3(c)]. The $1/f^{\beta}$ power spectrum over large time scales is related to the power-law autocorrelation $(\sim \tau^{-\gamma})$ by $\beta = 1 - \gamma$ when $0 < \gamma < 1$ [78]. By estimating the slope in a log-log plot of the $1/f^{\beta}$-type power spectrum, the scaling exponent β can be obtained. A representative stochastic process exhibiting monofractal behavior is fractional Brownian motion (fBm) as a generalization of Brownian motion [79]. This process is a Gaussian process $B_H(t)$ and self-similar in terms of statistical properties: $B_H(at) \stackrel{\Delta}{=} |a|^H B_H(t)$, where "$\stackrel{\Delta}{=}$" denotes equality of the probability distribution, $0 < H < 1$ is a scaling exponent, called the Hurst exponent, and related to β by $\beta = 2H + 1$. In addition, the increment process of fBm exhibits long-range correlation and is referred to as fractional Gaussian noise (fGn), with $\beta = 2H - 1$.

In HRV analysis of healthy individuals, the value of β is close to one in young adults, and gradually increases with aging [59]. Moreover, an abnormal increase of β (> 1.5) has been reported to be associated with an increased risk of mortality in cardiac patients [61], [62]. To consider this phenomenon, it is important to note that the long-range correlated nature over the range of several tens of seconds to a few hours arises from endogenous HRV dynamics, not from exogenous effects such as behavioral and environmental factors [26]. To explain the mechanism of the long-range correlated HRV, analogies with critical phenomena have been proposed [23], [24]. The characteristic features at the critical point of a phase transition are the divergence of relaxation time with strongly correlated fluctuations and the scale invariance in statistical properties. A healthy human heart rate has been confirmed robustly to show the $1/f^{\beta}$-type power spectrum. In addition, it is also reported that HRV in healthy individuals undergoes a phase-transition-like behavior [24]. That is, highly correlated fluctuations are observed only during daily activity, and a breakdown of these characteristics occurs during prolonged, strenuous exercise and in the nocturnal sleep period.

In the scaling analysis of HRV, it is important to note that power spectrum analysis may provide spurious detection of scaling properties caused by nonstationarity of the time series [76]. The nonstationarity, such as a smooth baseline trend and heterogeneous statistical property, is known to introduce spurious scaling. To avoid such artifacts and to provide more accurate estimates of scaling exponents, alternative analysis methods have been developed, such as detrended fluctuation analysis (DFA) [16] and multiresolution time-frequency analysis based on wavelet transform [80], [81]. In clinically oriented studies, the DFA has been frequently used, and some studies demonstrated its clinical significance (see [41] for a comprehensive review). On the other hand, multiresolution time-frequency analysis based on wavelet transform has also been recognized as a tool to study non-stationary signals [80], [81]. In this analysis, a time series is decomposed into different time-scale components. An advantage of wavelet analysis is that it can have a salutary effect called vanishing moments which eliminates smooth trends in the observed time series. Wavelet analysis can provide more detailed information about the time-varying properties of HRV. Therefore, it may be a useful tool to detect and predict fatal events. The ability of wavelet analysis to model and describe the scale-free properties of HRV temporal dynamics has been well documented in [23], [82]–[85].

C. Intermittent Fluctuations of HRV

In addition to $1/f^{\beta}$ scaling as observed in fBm and fGn, multiscaling (multifractal) properties of HRV have

been studied mainly in the field of statistical physics [22], [82], [86]–[88]. Ivanov *et al.* reported, for the first time, multifractality of HRV in normal subjects and reduced multifractality in patients with congestive heart failure (CHF) [22]. Further, it has been suggested that multifractal HRV is associated with ANS functions and mainly with parasympathetic modulation [89], [90]. Recent methodological developments in multifractal analysis are expected to expand its potential applications to HRV analysis [83]–[85], [91], [92].

Multifractal analysis was initially introduced to study the so-called intermittency phenomenon of the fluid velocity field in fully developed turbulence [93]. The multifractality of the intermittent turbulent behavior is closely related to a multiplicative cascade process where the local energy on a given scale is linked to local energy on a larger scale via a random multiplier [94], [95]. The observed multifractality of HRV implies the intermittent nature of HRV fluctuations and is analogous to the multiplicative cascade process [96].

A one-dimensional discrete time series based on the idea of the multiplicative cascade can be constructed as follows [97]: one starts with a discrete time series of Gaussian noise $\{X_t\}$ of length 2^m where m is the total number of cascade steps, and split the interval into two equal subintervals. On each subinterval, the local standard deviation (SD) is multiplied by random weights e^Y, where Y are independent Gaussian random variables with variance λ^2/m and $\lambda \geq 0$ is a shape parameter controlling the strength of non-Gaussianity. Each of the two subintervals is again cut in two equal subintervals and the process is repeated. After m cascade steps, the time series $\{b_t\}$ is given by

$$b_t = X_t \exp \sum_{j=1}^{m} Y^{(j)}_{\left\lfloor \frac{(t-1)}{2^{m-j}} \right\rfloor} \tag{1}$$

where $\lfloor \cdot \rfloor$ is the floor function. As shown in Fig. 4(a), this process exhibits intermittent bursts due to the multiplication of multiple random variables. One of the main tools to characterize these intermittent fluctuations has been multifractal analysis [e.g., Fig. 4(c)]. On the other hand, a remarkable property of the intermittent fluctuations is heterogeneity of variance, which results in non-Gaussian probability density functions (PDF's) [Fig. 4(b)]. Thus, characterization of intermittent fluctuations is possible through the analysis of the deformation process of

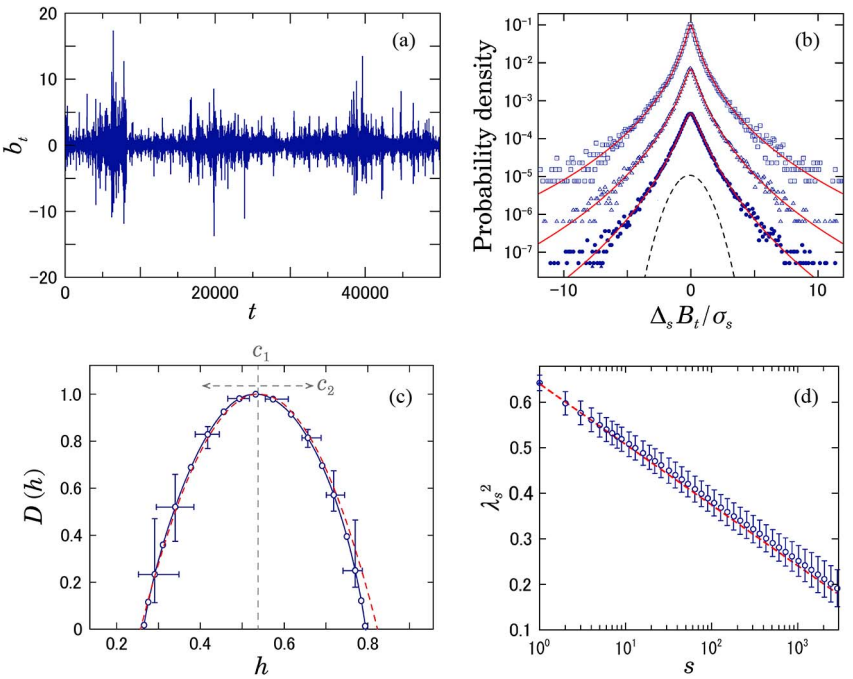

Fig. 4. ***Characterization of intermittent fluctuations. (a) An example of an intermittent time series*** $\{b_t\}$ ***generated by a multiplicative cascade model (Eq. (1) with*** $\lambda^2 = 0.8^2$, $m = 16$***). (b) Deformation of PDF's of*** $\{\Delta_s B(t)\}$***, where*** $B(t) = \sum_{k=1}^{t} b(k)$ ***and*** $\Delta_s B(t) = B(t+s) - B(t)$***. Standardized PDF's for different scales are shown for (from top to bottom)*** $s = 1,\ 4,\ 16$***. In the solid lines, we superimposed the PDF's approximated by a multiplicative log-normal model [Eq. (3) with a Gaussian kernel*** G***]. For comparison, the dashed lines denote a Gaussian distribution. (c) The singularity spectrum*** $D(h)$ ***of the integrated series*** $\{B(t)\}$***.*** $D(h)$ ***was estimated from 64 samples using*** p***-exponent and*** p***-leader based multifractal analysis with*** $p = 1$ ***(see [8] for details). (d) Scale dependence of*** λ^2 ***of*** $\{\Delta_s B(t)\}$***. Dashed lines indicate theoretical predictions:*** $\lambda_s^2 = \lambda^2(1 - \log_2 s/m)$ ***[10]. Error bars indicate standard deviations.***

the non-Gaussian PDF's across scales [Fig. 4(d)] [10], [97], [98]. Recently, the non-Gaussianity of HRV has been suggested as a marker potentially related to sympathetic cardiac overdrive [11], [25], [28]. Therefore, perhaps even more so than conventional HRV markers associated mainly with parasympathetic activity, this approach may be useful to evaluate another important physiological function. In addition, long-range correlation, multifractality, and large non-Gaussian deviations are commonly observed near dynamical transition points [99], [100] [Fig. 1]. Therefore, such properties may be useful for finding early warning signals for fatal and catastrophic events.

1) Multifractal Analysis—HRV as Multiplicative Cascades: Multifractal analysis is able to characterize the fluctuations over time of the (ir-)regularity or *singularity* of a signal $X(t)$, measured by a pointwise regularity (Hölder) exponent $h(t)$, by means of the so-called singularity spectrum, defined as the fractal (Hausdorff) dimension of the set of time instances with the same regularity [101]:

$$D(h) = \dim_H \{t_i | h(t_i) = h\}. \tag{2}$$

The practical counterpart enabling the estimation of $D(h)$ from data termed multifractal formalism relies on the characterization of scaling behavior of higher order statistics.

Many methods have been proposed to estimate the singularity spectrum $D(h)$ from observed time series (cf. [84] for a review). As for the multifractality of HRV, wavelet transform modulus maxima (WTMM) methods [38] and multifractal detrended fluctuation analysis (MFDFA) [39], [40] have been mainly employed [22], [82], [86], [87], [89], [90].

Most recently, a framework has been proposed that extends the wavelet based analysis of self-similar processes and the estimation of the Hurst parameter H to the analysis of multifractal scaling and to the estimation of the multifractal spectrum $D(h)$ [8]. It is referred to as p-exponent and p-leader based multifractal analysis, and it permits, beyond the limitation of the Hölder exponent ($\geq$0), accounting for negative regularity, widely observed in the real-world time series and notably in HRV. Thus, this approach could provide a new and powerful tool to examine the multifractality of HRV, as shown in Fig. 6(d).

Matlab code implementing the wavelet analysis of self-similarity and multifractality is available at http://www.irit.fr/~Herwig.Wendt/software.html#wlbmf.

2) Non-Gaussian Properties of HRV: In studies of developed turbulence and non-equilibrium systems exhibiting intermittent fluctuations, it has been demonstrated that the observed non-Gaussian probability distributions with fat tails are often described effectively by a superposition of Gaussian distributions with fluctuating variances [102]. Based on this framework, the observed distribution can be approximated by

$$P(x) = \int_0^\infty \frac{1}{\sigma} P_L\left(\frac{x}{\sigma}\right) G(\ln \sigma) d(\ln \sigma) \tag{3}$$

where P_L is the standard Gaussian distribution and G is a distribution describing the fluctuation of the standard deviations. In the analysis of intermittent fluctuations, we focus mainly on the estimation of the variance of G and its scale dependence [102].

Based on this framework, Kiyono *et al.* proposed a multiscale probability density function (PDF) analysis including a detrending procedure [23], [98]. The procedure of this analysis is as follows: (1) Time series of R-R intervals are interpolated and resampled at 4 Hz, yielding interpolated time series $\{b_t\}$. After subtracting the mean from the interpolated time series, integrated time series $\{B(t)\}$ are obtained by integrating $\{b(t)\}$ over the entire series length. (2) The integrated time series $\{B(t)\}$ are divided into overlapping segments of length $2s$ with 50% overlap, where s is the scale of coarse graining ($s = 25$ sec in Fig. 5). In each segment, the local trend is eliminated by third-order polynomial fit. (3) Coarse grained variation $\Delta_s B(t)$ is measured as the increment with a time lag s of integrated and detrended time series. (4) $\{\Delta_s B(t)\}$ is standardized by its standard deviation to quantify the PDF. Then, the non-Gaussianity index λ_s is estimated based on the qth-order moment of $\{\Delta_s B(t)\}$ as

$$\lambda_s^2(q) = \frac{2}{q(q-2)} \left[\ln \left(\frac{\sqrt{\pi} E\left(|\Delta_s B(t)|^q\right)}{2^{\frac{q}{2}} \Gamma\left(\frac{q+1}{2}\right)} \right) \right] \tag{4}$$

where $E(X)$ is the expectation value of X and Γ is the Gamma function [97]. In previous studies [25], [28], λ_s is estimated based on the 0.25th-order moment ($q = 0.25$) to emphasize the center part of PDF. In this analysis, the observed non-Gaussian shape [Fig. 4(b)] at each scale is quantified by the non-Gaussianity index λ_s defined as the standard deviation of $\ln \sigma$ in (3), where G is assumed to be a Gaussian. The greater the λ_s, the greater the proportion of large deviation than what is expected from the Gaussian distribution.

Using this method, Kiyono *et al.* reported robust scale-invariant properties in non-Gaussian distributions observed in healthy human HRV spanning the range of

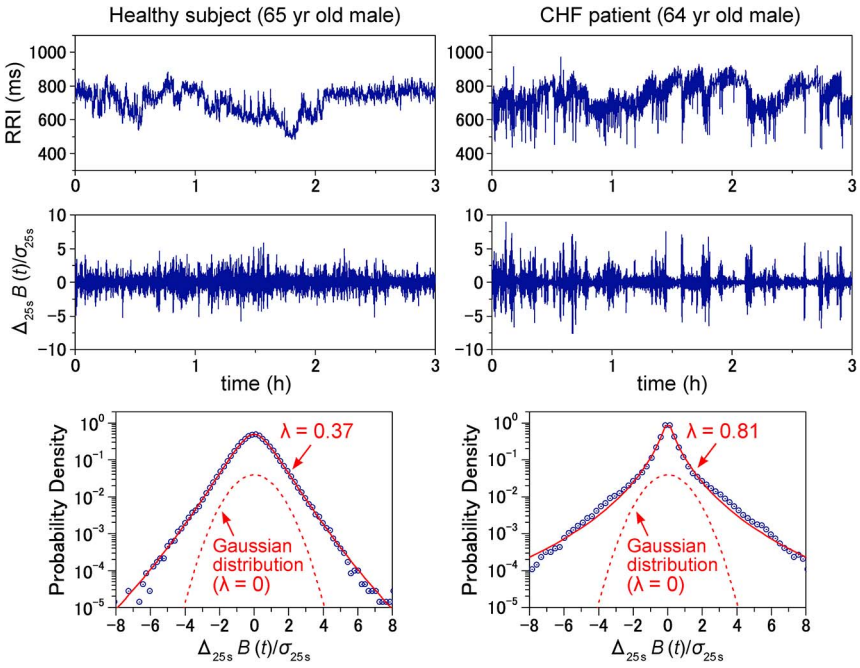

Fig. 5. ***Representative examples of non-Gaussian heart rate fluctuations during the daytime in a healthy subject and a congestive heart failure patient. Time series of normal-to-normal R-R intervals (top row), standardized time series of coarse grained heart rate variations*** $\{\Delta_{25\ \mathrm{sec}}B(t)\}$ ***(middle row), and standardized PDFs of*** $\Delta_{25\ \mathrm{sec}}B(t)$ ***(bottom row). Estimated values of the non-Gaussianity index*** $\lambda_{25\ \mathrm{sec}}$ ***are shown in each panel in the bottom row. The solid lines represent the PDF approximated by a multiplicative log-normal model [(3) with a Gaussian kernel*** G***].***

about 20–2000 beats, which were preserved not only in a quiescent condition, but also in a dynamic state where the mean level of the heart rate was dramatically changing [23]. In addition, in patients with CHF, increased non-Gaussianity at scale of 40 beats of 24-hour ambulatory HRV predicts increased mortality risk, while none of the conventional HRV indices, including those reflecting vagal heart rate control, were predictive of death [25]. Moreover, Hayano *et al.* reported that, in patients after AMI, an increased non-Gaussianity index $\lambda_{25\ \mathrm{sec}}$ at a scale of 25 sec is associated with increased cardiac mortality risk, and its predictive power is independent of clinical risk factors and of other HRV predictors [28].

The aspects characterized by $\lambda_{25\ \mathrm{sec}}$ are related to amplitude modulation properties of LF component as shown in Fig. 3(a). The detrending procedure in multiscale PDF

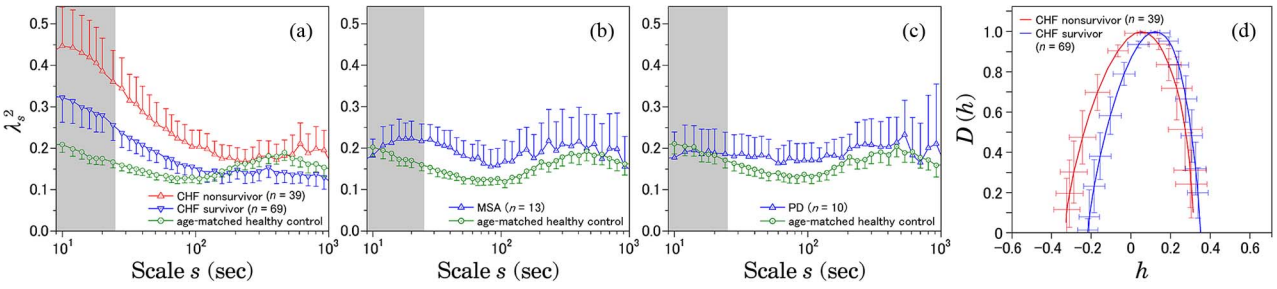

Fig. 6. ***Scale dependence of the non-Gaussianity index*** λ_s^2 ***and Multifractal spectrum*** $D(h)$ ***of daytime HRV (12:00-18:00). The result for: (a) congestive heart failure (CHF) patients, both for survivors*** $(n = 69)$ ***and non-survivors*** $(n = 39)$ ***within the follow-up period of*** 33 ± 7 ***months; (b) multiple system atrophy (MSA); and (c) Parkinson disease (PD) patients. Age-matched controls were selected from a database of healthy subjects. Error bars indicate 95%-confidence intervals of the group means. The gray shaded range corresponds to low-frequency band*** $(s<25\ \mathrm{sec})$***. Marked increases in*** λ_s^2 ***in the gray shaded scales are observed only in CHF patients, particularly non-survivors (a).*** $D(h)$ ***are estimated in the range of 10–200 sec using*** p***-exponent and*** p***-leader based multifractal analysis with*** $p = 1$ ***(see [8] for details). These figures are modified versions from [11].***

analysis acts as a high-pass filter that removes low frequency components below a given time scale, and the calculation of partial sums (or increments of integrated series) acts as a low-pass filter. In the estimation of $\lambda_{25\ \mathrm{sec}}$, the combination of these procedures acts as a band-pass filter that allows mainly the LF component to pass. The increased $\lambda_{25\ \mathrm{sec}}$ indicates an increase in amplitude heterogeneity of LF oscillation as seen in Fig. 5 (middle rows). Note that the $\lambda_{25\ \mathrm{sec}}$ can change independently of the value of LF power. Thus, the $\lambda_{25\ \mathrm{sec}}$ can provide complementary information beyond conventional frequency domain indices.

As for the association of $\lambda_{25\ \mathrm{sec}}$ with the ANS functions, the following facts should be considered: (1) The HRV in the scales corresponding to HF and LF bands are mediated almost exclusively by neural autonomic mechanisms [13], [103]. (2) The $\lambda_{25\ \mathrm{sec}}$ showed no substantial correlation with the HRV indices reflecting vagal heart rate regulation [25], [28]. (3) $\lambda_{25\ \mathrm{sec}}$ was decreased in post-AMI patients taking beta-blockers suppressing the sympathetic influence [28]. Based on these facts, Hayano *et al.* suggested that $\lambda_{25\ \mathrm{sec}}$ captures heart rate fluctuation at least partly mediated by intermittent activations of cardiac sympathetic activity [28].

In addition, in the study of daytime HRV in patients with multiple system atrophy (MSA) and with Parkinson disease (PD), it is reported that a marked increase in non-Gaussianity on a relatively short time scale observed in CHF patients was not observed in these patients with sympathetic dysfunction [11]. Both MSA and PD are progressive neurodegenerative disorders, although autonomic lesions in MSA are caused by preganglionic sympathetic failure [104], and those of PD are ganglionic and postganglionic [105], [106]. As shown in Fig. 6, compared with an age-matched healthy control group, mean values of λ_s in CHF patients, especially nonsurvivors in comparison to survivors during the follow-up period, display marked increases in relatively small scales covering the LF band. On the other hand, as shown in Fig. 6(b) and (c), such marked increases were not observed in MSA and PD patients. This result also supports the view that an increase of $\lambda_{25\ \mathrm{sec}}$ could be a hallmark of overall cardiac sympathetic overdrive detectable with ambulatory HRV monitoring.

The fact that heart rate dynamics of CHF patients with elevated sympathetic activity exhibit a marked increase in non-Gaussianity and its decays with scales within LF and VLF ranges suggests a sympathetic origin for HRV intermittency. In these scales (< 200 sec), heart rate dynamics reflect cardiovascular regulation by neural, humoral, and thermal influences [107]. These subsystems are considered to be compensatory; therefore, it is likely that only simultaneous failure of all these subsystems operating on multiple time scales, compatible with the reciprocal of cascade steps "j" in (1) could result in sympathetic overdrive, leading to intermittent heart rate fluctuations with large deviations. We propose that such a multiplicative picture would provide a deeper physiological understanding of the nature of sympathetic function [11]. As shown in Fig. 6(d), intermittent nature of HRV in CHF patients may also be characterized by multifractal analysis. Also, the fact that HRV of non-surviving CHF patients exhibit stronger LF intermittency than that of surviving patients [Fig. 6(a)] would indicate a relationship between appearance of the HRV intermittency (due to sympathetic overdrive as a control parameter) and a pathological transition [Fig. 1]. The same scenario also applies to AMI patients in [28].

D. Remarks and Other Methods

Sympathetic nervous system activity is thought to be an important factor in many health problems, not only in cardiovascular diseases but also in the development of a wide variety of chronic illnesses [108]. Therefore, multiscale analysis characterizing the intermittent nature of HRV may have widespread applications in various fields of health management. Among HRV indices that have been suggested as markers of sympathetic activity, an increased non-Gaussianity of HRV may reflect hazardous effects of elevated cardiac sympathetic activity in cardiac patients. In addition, some other nonlinear markers not mentioned in this paper, such as approximate and sample entropies, have been suggested to be associated with sympathetic activation [109], [110]. Moreover, multiscale entropy analysis [36], [37] and other multiscale tools, such as empirical mode decomposition [111] may have potential clinical applications. However, to establish associations between sympathetic activity and the clinical significance of these approaches, systematic validation and further studies on a large scale data are yet required.

III. SPONTANEOUS PHYSICAL ACTIVITY

A. Alterations of SPA in Psychiatric Diseases

In the fields of psychiatry and mental healthcare, prevention and early intervention are crucially important and widely accepted as effective strategies to reduce the number of patients with serious psychiatric disorders and ultimately medical/healthcare related costs [112]–[114]. In order to develop a reliable and effective strategy based on clinical evidence, the identification of an objective biomarker for psychiatric disorders is essential because it could contribute to the early detection of warning signs for pathogenic and/or pathological changes resulting in the development of these illnesses [115]. However, such an objective measure has not been fully developed.

The recent development of information and communication technologies, such as wearable/mobile devices, provides massive longitudinal, non-medical data from our daily lives (e.g., physical activity, heart rate, GPS,

etc.), which are thought to include useful information on our physiological and/or pathological conditions. While the extraction of pathological information available for clinical use is still challenging, many researchers have recently studied and reported promising outcomes [116]–[118]. In this section, we introduce examples of objective evaluation of psychiatric disorders based on physical activity easily assessed by using a wearable device.

1) Behavioral Abnormalities in Psychiatric Disorders: Physical activity can be continuously monitored in a quantitative and noninvasive way, e.g., through the use of a wrist watch- type or band-type acceleration sensor, a method referred to as *actigraphy*. This type of device has the capability of detecting small changes in bodily/wrist acceleration so that even slight movements by the subjects are registered. Therefore, the data recorded include information on both conscious and unconscious behaviors in daily life. In this review, we call this type of longitudinal behavioral data spontaneous physical activity (SPA).

Behavioral alteration is one of the cardinal signs of psychiatric disorders, and many psychiatric disorders, including depression, indeed have diagnostic criteria which require an assessment of altered physical activity [15]. For instance, one of the known disease signs of depression is psychomotor retardation, involving a recognizable alteration in physical activity such as slowing down of movement [119]. Therefore, behavioral dynamics is considered to contain rich information on pathological symptoms of psychiatric disorders and is thought to be useful for objective diagnosis of disorders.

In order to characterize behavioral abnormalities, including chronobiological disturbances, basic statistics (e.g., mean and variance) and periodicities (by, e.g., cosinor method or Fourier analysis) of SPA have been traditionally evaluated. For example, reduced daily activity levels have been reported in patients with major depressive disorder (MDD) [14], [15] and schizophrenia [120], [121]. On the other hand, increased activity levels were shown in patients with attention-deficit hyperactivity disorder [122], [123] and patients with bipolar disorder (BD) during manic phases [124]. In addition, significant associations of these statistics with clinical variables have also been confirmed [125]–[127]. From the viewpoint of dynamical properties of SPA, Hauge *et al.* examined an entropy measure to show the increase in complexity of SPA in schizophrenia [120]. Indic *et al.* examined the scaling behavior of amplitudes of SPA on multiple time scales and reported altered scaling behavior in BD as well as associations with clinical states, indicating the utility of monitoring SPA for objective evaluation of pathological states of BD [128].

The direct connection between alterations in these traditional measures and the underlying pathophysiology is unknown, but several studies using neuroimaging approaches have recently suggested the existence of associations of SPA with brain structures or functions in the motor control systems [129]–[132]. For example, altered associations of SPA with structures and functions of motor regions of brain, including anterior cingulate cortex, supplementary motor area, and thalamus, have been reported in schizophrenia patients [129], [131], [133]. In addition, a relationship between dysfunction of cortico-basal ganglia pathways in white matter and the pathophysiology of hypokinesia in schizophrenia has been reported, suggesting that structural disconnectivity could lead to disturbed motor behavior in schizophrenia [132]. Studies about MDD have also demonstrated the link between psychomotor retardation and white matter integrity of the motor system [134], [135]. These reports manifest the existence of underlying neurological bases for SPA.

B. On-off Intermittency and Scale-Invariance in SPA

As detailed in this subsection, Nakamura *et al.* recently studied the dynamical properties of SPA and discovered robust statistical laws of behavioral organization, specifically how resting and active periods derived from physical activity data are interwoven into daily life [1], [2], [31]. Furthermore, they reported alterations in the resting period statistical law in patients with MDD [1] and schizophrenia [31] reflecting increased intermittent bursts in activity counts characterized by reduced activity levels associated with occasional bursts of physical activity. These studies manifest that the quantitative and objective evaluation of intermittency of physical activity could provide appropriate behavioral measures capable of probing alterations in pathological states in psychiatric disorders.

1) Intermittent Nature of SPA and its Alterations: Fig. 7 shows typical fluctuations of SPA in a healthy subject and in a patient with MDD. In the healthy subject [Fig. 7(a)], a clear circadian rest-activity cycle is observed, while in the MDD patient [Fig. 7(b)], this rhythmic pattern is notably disrupted, reflecting the reported chronobiological abnormality in depression [14]. During the daytime, physical activity of the healthy subject is characterized by consistently higher activity levels, whereas the MDD patient exhibits intermittent bursts in activity counts with more episodes of slowing down or cessation of movements [1], [31]. As mentioned below, the intermittent burst is a significant dynamical feature of physical activity and its alteration is a robust and effective indicator for behavioral abnormalities observed in psychiatric disorders.

2) Statistical Laws of Behavioral Organization: In order to characterize the intermittent patterns in physical activity, Nakamura *et al.* evaluated the cumulative probability distribution $P_C(x \geq a)$ of durations a of both resting periods, where the activity counts were successively lower

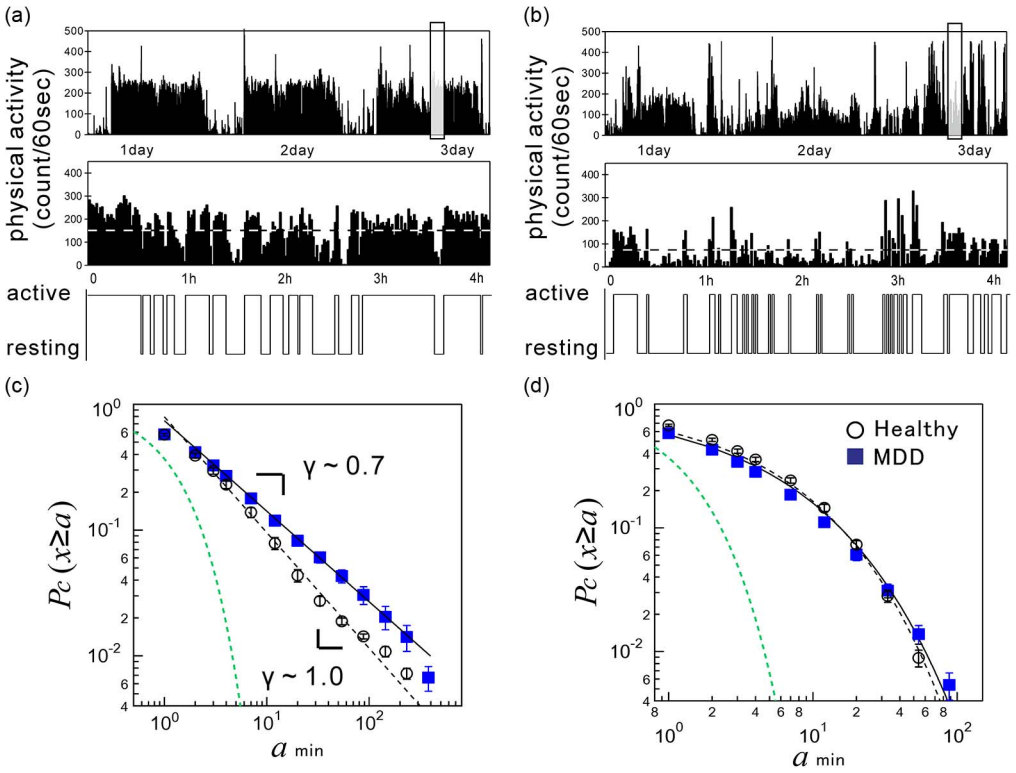

Fig. 7. ***Fluctuations in spontaneous physical activity and their statistical laws of behavioral organization (modified from [1], [2]). Illustrative examples of physical activity data for a healthy adult (a), and a patient with major depressive disorder (MDD) (b) over three consecutive days (top panels). These data were measured by a watch-type device (Ambulatory Monitors Inc., Ardsley, NY, USA) worn on the wrist of their non-dominant hand. The zero-crossing mode, which measures counts of events in which an acceleration signal crosses a zero level within a predefined time (e.g., 1 min), is used. The middle panels are magnifications of the top panels with 4 h periods during the third day. The overall average of non-zero activity counts was used as the threshold (horizontal dotted line), and the period during which the activity counts were successively below or above the threshold is defined as a resting or active period, respectively (bottom panels). (c) Cumulative distributions*** $P_C(x \geq a)$ ***of resting period durations*** a ***for healthy adults (open circles) and MDD patients (blue filled squares). Straight lines are eye guides with the overall mean values; the power law distribution with*** $\gamma \sim 1.0$ ***for healthy adults and*** $\gamma \sim 0.7$ ***for MDD patients, respectively. The green curve indicates a random case (i.e., an exponential functional form). (d) The same as (c) but for active period durations. The stretched exponential functions were nicely fitted to the active distributions. Error bars indicate standard error of the mean.***

than a certain predefined threshold value (e.g., an overall average of non-zero activity counts), and of active periods, where the counts were successively higher than the threshold values [1], [2] [the bottom panels in Fig. 7(a) and (b)]. The robust statistical laws they found in healthy subjects [1], [2], against factors such as difference in study populations and choice of different thresholds, were the power-law distribution $P_C(x \geq a) \sim a^{-\gamma}$ with the scaling exponent $\gamma \sim 1.0$ for the distributions of resting period durations [Fig. 7(c)] and the stretched exponential functional form $P_C(x \geq a) = \exp(-\alpha a^{\beta})$ with the stretching parameter $\beta \sim 0.5$ for the distribution of active period durations [Fig. 7(d)]. In addition, they reported that these statistical laws found in healthy humans were shared by wild-type mice (i.e., no significant difference in values of the scaling exponent γ and the stretching parameter β), suggestive of the presence of an underlying principle governing behavioral organization, or behavioral switching, across species [2]. Furthermore, a significant decrease in γ of resting period distributions among humans with MDD or schizophrenia [1], [31] and mice with deficiency in a circadian clock gene (Period 2) [2] has also been reported. These findings indicate that alterations in intermittency of behavioral dynamics characterized by γ are useful for describing abnormalities in SPA observed in psychiatric disorders. Another important point to be emphasized is the possibility that the cross-species translation provided by the statisitcal law of behavioral organization may play a crucial role in bridging the gap between specific genetic substrates and behavioral endophenotypes in psychiatric disorders [136], [137].

3) A Model for on-off Intermittency in Behavioral Organization: In order to elucidate the underlying mechanisms of the alteration in resting period distributions, a mathematical model based on queuing theory [12], [124], which models a decision-making strategy for selection of

a biological "cue" to response [4], was considered. This model is based on the following assumptions; spontaneous movements in animals would be triggered by continuously presented internal or external demands and/or stimuli (e.g., appetite, emotion, etc.); on the basis of their biological importance, one demand/stimuli is probabilistically chosen either consciously or unconsciously. This decision-making process can be modeled well by a stochastic priority queuing model. In [4], we demonstrated that a strategy where each demand/stimuli is probabilistically chosen every time in proportion to its biological importance can explain the unique statistical law of resting periods with $\gamma \sim 1.0$. Mathematically, with the probability of response to a demand/stimuli with priority x given by $\prod(x) \sim x$ [black line in Fig. 8(a)], the cumulative distribution of durations of resting periods is analytically derived to follow the power-law functional form [12] with the exponent $\gamma = 1$ [Fig. 8(b)]. In contrast, the decrease of γ observed in MDD, schizophrenia, and BD during the depression phase [Fig. 8(c); see III-C below] can be reproduced by assuming $\prod(x) \sim x^{\lambda}$ with λ greater than unity (e.g., $\lambda = 1.4$) [blue curve in Fig. 8(a)]. This assumption implies that a demand/stimuli with higher priority is preferentially selected, giving rise to a fatter distribution tail and frequent episodes of longer resting periods, generating a more intermittent sequence of onset of activity bursts [Fig. 8(c)]. Also, the increase of γ, observed in a patient with BD during a manic episode, can be modeled by assuming λ smaller than unity (e.g., $\lambda = 0.8$) [red curve in Fig. 8(a) and (d)]. Based on the findings for mice with deficiency in Period 2 also showing decreased γ [138], [139], we discussed [4] that these strategic changes in decision-making —preferential selectivity to demands and/or stimuli with higher priority—may be related to reinforcement of rewarding neural networks induced by dysfunction of the dopamine and/or glutamatergic systems.

C. Towards Monitoring and Early Detection of Psychiatric Disorders

1) ILD of SPA in Bipolar Disorder: Bipolar disorder is a major psychiatric disorder demonstrating recurrent and alternating periods of manic (or hypomanic), depressive, and mixed episodes, with varying intervals [119], [140], [141]. Mania, a period of elevated or irritable mood, as well as increased energy (overactivity) and a decreased need for sleep, is the defining feature of BD. On the other hand, like MDD, depressive episodes are characterized by lack of interest, loss of energy, insomnia, fatigability, and suicidal thoughts. The most prominent feature

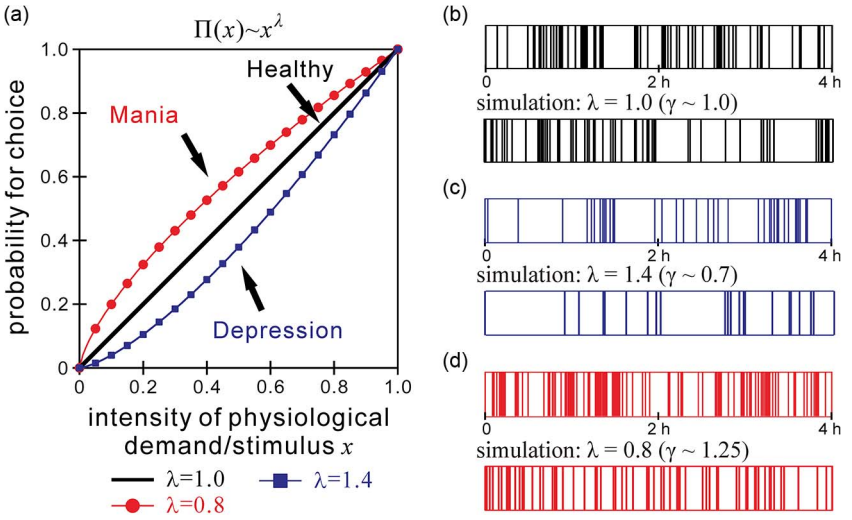

Fig. 8. ***Sequences of resting period durations and their model (modified from [4]). (a) Probability density function*** $\prod(x) \sim x^{\lambda}$ ***for choosing a demand/stimulus with physiological priority*** x***. The sequence of onset of activity bursts (resting durations) derived from physical activity of a (b) healthy adult*** $(\gamma \sim 1.0)$***, (c) a bipoloar disorder (BD) patient in the depressive phase*** $(\gamma \sim 0.7)$***, and (d) in the hypomanic phase. The sequence of waiting times simulated from the priority stochastic queuing model with (b)*** $\lambda = 1.0$ ***(i.e.,*** $\gamma = 1.0$***), (c)*** $\lambda = 1.4$ ***(i.e.,*** $\gamma \sim 0.7$***), and (d)*** $\lambda = 0.8$ ***(i.e.,*** $\gamma \sim 1.25$***) are also shown. The simulated sequences of waiting time were generated on the base of the stochastic priority queuing model [12] with a priority list comprising*** $L = 10$ ***demands, where a priority parameter*** x_i $(i = 1, \ldots, L)$ ***chosen from a uniform distribution*** $\rho(x) = U(0,1)$ ***is assigned to each demand. At each time step, one demand is selected from the list (in the brain) according to*** $\prod(x) \sim x^{\lambda}$ ***for execution (or act), and then removed from the list. At that moment, a new demand is added to the list with a priority randomly selected from*** $\rho(x)$***. The probability that a demand with priority*** x ***is executed at time*** t ***is given by*** $f(x,t) = (1 - \prod(x))^{t-1} \prod(x)$***, and the average waiting time of a demand with priority*** x ***is obtained by averaging over*** t ***weighted with*** $f(x,t)$***, giving rise to*** $\tau(x) = \sum_{t=1}^{\infty} t f(t,x) = 1/\Pi(x) \approx 1/x^{\lambda}$***. Analytically, with the conservation law of probability*** $(\rho(x)dx = P(\tau)d\tau)$***, the waiting time distribution of the demands is given by*** $P(\tau) \approx \rho(\tau^{-1/\lambda})/\tau^{1+1/\lambda}$***. Note that each vertical line separates the successive waiting time of demands chosen according to their priority.***

of BD is the switching dynamics between depressive and manic phases. Elucidating the underlying mechanism of these sudden changes in pathological states is important as it would contribute to the precise and reliable prediction of the timing of these transitions. This in turn would lead to the development of timely and efficient clinical interventions, and novel treatments aimed at the prevention of suicide and decreasing the risk of issues with social relationships, loss of job and financial problems. However, little attention has been given to these sorts of dynamical features (*clinical phase transitions*) of pathological states in BD.

A longitudinal study design allows us to investigate dynamical aspects in pathological states during the period of clinical phase transitions in BD, along with interrelationships between psychological and behavioral variables. Indeed, studies examining BD using longitudinal designs have demonstrated dynamical changes related with phase transitions in subjective mood [142], [143], physical activity (including sleep and circadian rhythm) [144], [145], and biochemical variables [146].

Nakamura *et al.* recently measured ILD of SPA and self-reported symptoms in bipolar patients (type-II) to capture clinical phases transitions [3]. Fig. 9(a) and (b) represent an example of physical activity data and subjective mood scores continuously monitored over almost one year, respectively, including a period of well-identified clinical phase transition. The activity levels during around 110–140 days were consistently low with worsening of mood, indicative of a depressive episode. After this period, the mood scores gradually increased and then reached at the maximum score (the patient rated the best) on day 165. In parallel with this rapid mood change, the activity levels increased, manifesting the transition from the depressive phase to manic phase. The physical activity [labeled "A" in Fig. 9(a)] during the depressive phase showed frequent intermittent bursts in the activity counts during the daytime [Fig. 9(d)], while the data [labeled "B" in Fig. 9(a)] in the manic phase was characterized by more sustained higher activity levels [Fig. 9(e)] [3].

In this subsection, we demonstrate the possibility to objectively monitor changes in pathological states based on alterations of behavioral dynamics (i.e., intermittency) and further discuss the detection of early signs for clinical phase transition.

2) Objective and Continuous Monitoring of Pathological States: Application of the method for behavioral organization (see Fig. 7) during the clinical phase transition revealed that the resting period distributions in both depressive and hypomanic phases took a power-law form $P_C(x \geq a) \sim a^{-\gamma}$ over almost two decades (from 2 min to 100 min), with considerable difference in their scaling exponent [$\gamma = 0.85$ for the data during depressive phase shown in Fig. 9(d) and $\gamma = 1.22$ for the data during hypomanic phase shown in Fig. 9(e)]. The increase in longer resting periods in the depressive phase, like MDD, suggests more episodes of slowing down or cessation of movement in depressive phase than in hypomanic phase.

The continuous nature of physical activity data allows us to evaluate daily changes in values of γ in a continuous fashion [Fig. 9(c)]. The objective behavioral index γ can distinguish the differences in pathological states in BD; the values of γ were lower in depressive phase than those in hypomanic phase. In addition, the low-frequency fluctuations (> 7 days) in the value of γ demonstrated the significant concurrent association with self-reported mood scores and the values of γ [3]. This indicates the possibility of quantitatively and continuously capturing manic-depressive phase transitions from physical activity monitored using a wearable device.

3) Detection of Early Signs for Pathological Transitions From the Viewpoint of Dynamical Systems: Investigation into a theory for aperiodic alterations between depressive and manic episodes, by developing a dynamical model, may help elucidate the underlying mathematical mechanisms of the pathological phase transitions in BD and develop novel prediction methods, leading to timely and effective interventions.

The most prominent dynamical feature of BD is the coexistence of two extreme mood states (depression and mania) and oscillating/switching dynamics between them with unequal durations of each episode [143]. In addition, clinical observations suggest that this aperiodicity in transition periods is determined by the interaction between the biological mechanisms generating periodicity and environmental and psychological stresses in daily life [144], [147]. These complex and nonlinear dynamical phenomena are reminiscent of *bistability*. Although other dynamical models could be considered to describe the alternating phenomena between manic and depressive states [143], we start from hypothesizing a bistable system as a simple model to explain the switching mechanism. Indeed, by proposing a mathematical model with bistability, Goldberter successfully simulated the recurrent and alternating switching dynamics between depression and mania, together with the antidepressant effects clinically observed [148] (e.g., a transition to mania or rapid cycling triggered by antidepressants [149]).

Bifurcation of the bistable system reproduced the phenomena clinically observed in patient with BD well. If the same mechanism exists in actual pathological transitions, there is a possibility to detect a tipping point of pathological transitions by evaluating the dynamical features of fluctuations in physiological parameters (e.g., mood and/or physical activity) because the system displays complex and unique fluctuations around a bifurcation point [32]. Fig. 10(a)–(c) shows potential landscapes illustrating a bifurcation phenomenon of a bistable system as a model for pathological cycling in BD. Under the condition where a control parameter governing the dynamics of the system is sufficiently close to a bifurcation point, the steady states (potential wells) become unstable,

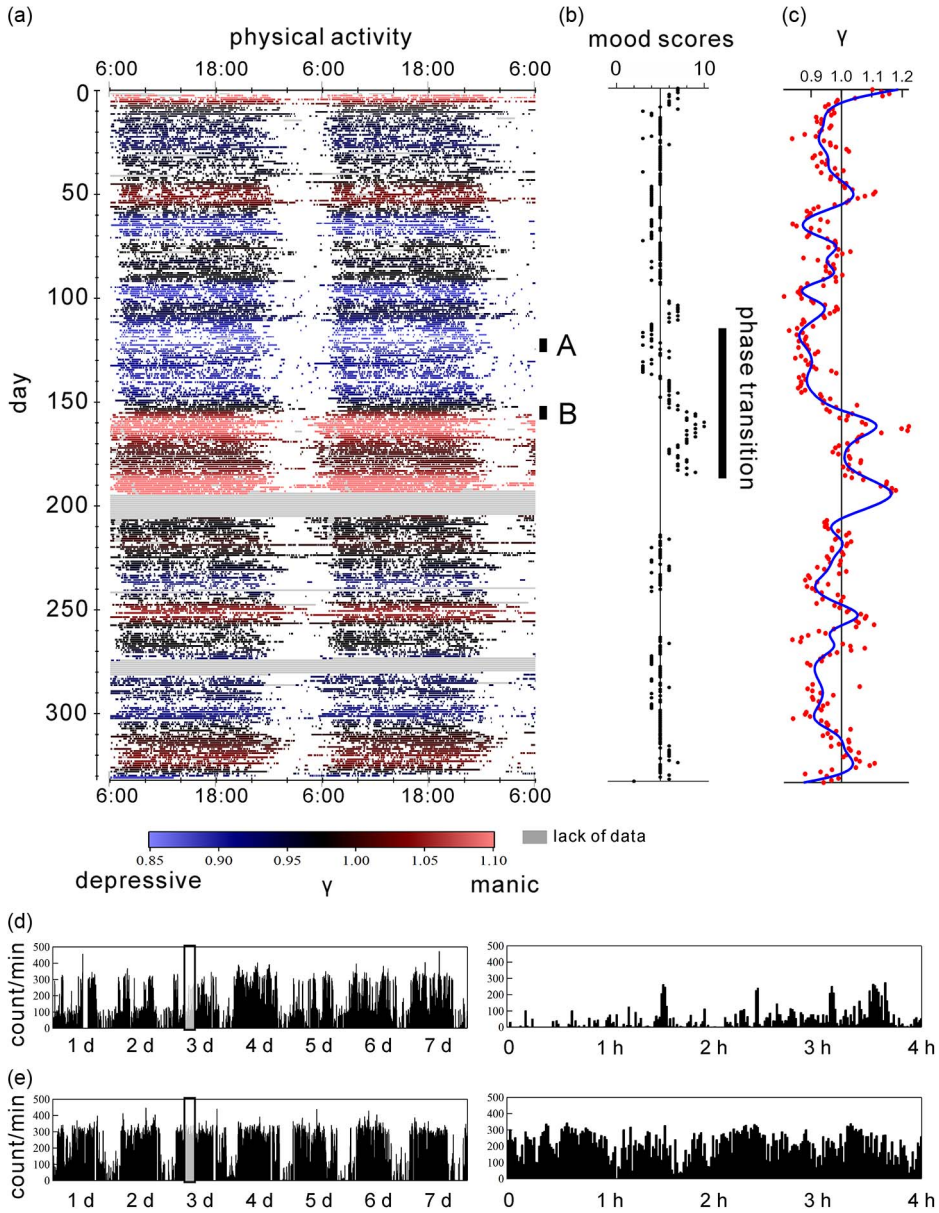

Fig. 9. ***Dynamics of spontaneous physical activity and subjective mood during clinical phase transitions in bipolar disorder (BD) (modified from [3]). (a) A double-plot actogram of physical activity data of a patient with BD over 333 days. For presentation purposes, the activity data were converted into resting and active periods and then color coded according to the corresponding value of γ [see (c)]. (b) Fluctuations in subjective mood scores reported by the patient every night, ranging from the 0 (the worst) to 10 (the best). The clinical phase transition*** **from a depressive phase to a hypomanic phase occurred during the period between days 140–150. (c) The continuous evaluation of the scaling exponent γ of resting period distributions. Here, the value of γ was continuously estimated by using a sliding window of 7-day width by shifting 1 day [red filled circles in (c)]. The trend of γ [blue curve in (c)] significantly traced pathological changes of depressive-manic cycles rated by subjective mood [3]. The physical activity data during depressive phase (d) and manic phase (e), labeled "A" and "B" in the panel (a), respectively, are shown in (d) and (e). Their magnification with 4 h periods during the third day is also shown. The value of γ was 0.85 and 1.22, respectively.**

and the system can no longer remain at these states, starting to fluctuate in a unique manner [Fig. 10(b)]. Therefore, the evaluation of dynamical features of fluctuations in state variables allows us to detect a tipping point of pathological transitions, like the dynamical disease scenario in Fig. 1. For example, *critical slowing down* is known as a characteristic dynamical phenomenon emerging in the vicinity of a phase transition or a critical point [32], indicating the occurrence of bifurcation in the underlying systems. These early warning signs are commonly observed in a variety of fields from economics to climate systems [32], [150]–[153]. Systems showing

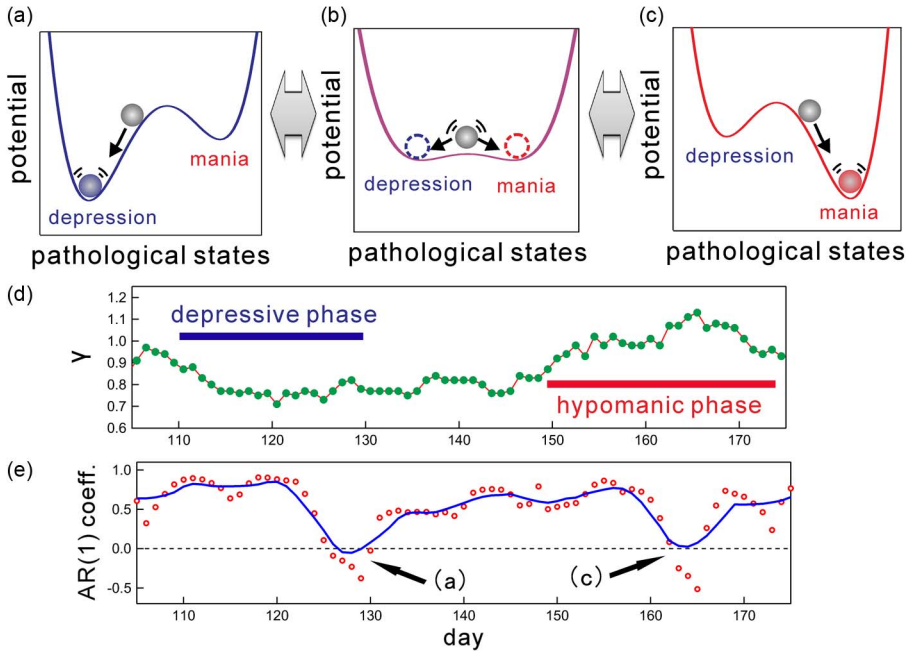

Fig. 10. *A bifurcation phenomenon of a bistable system and early warning signs for clinical phase transitions in bipolar disorder (BD). (a) and (c): the potential landscapes for a depressive phase (a) and a manic phase (c). (b) is an illustration of a potential function at the bifurcation point (e.g. saddle node bifurcation). When the control parameter of the system is sufficiently close to the bifurcation point, the steady states become unstable and the most unstable direction in phase space dominates the behavior of the system. This direction is determined by the eigenvector of the Jacovian corresponding to the eigenvalue for which the eigenvalue becomes zero real valued. Around this point, fluctuations with unique dynamical properties (e.g., critical slowing down) can be observed. (d) The fluctuations in γ around the period of the phase transition from depression to mania. (e) The alteration in autocorrelation coefficients obtained by fitting an autoregressive model of order 1 [AR(1) model] to the data of γ within a sliding window of size 10-days. The locations where the values of autocorrelation coefficient approach to zero may correspond to the "stable" depressive and manic phase [labeled "(a)" and "(b)"] as illustrated in panel (a) and (b), respectively.*

critical slowing down are theoretically characterized by a decreasing rate of recovery from small perturbations (slowness), which results in the accumulation and persistence of perturbations over time, leading to increases in local variance and autocorrelation around critical points [32]. Fig. 10(e) as applied to the BD transition shows the changes in autocorrelation coefficients obtained by fitting an autoregressive model of order 1 [i.e., AR(1) model] to the data of γ [shown in Fig. 10(d)] within a sliding window of size 10 days. During the transition period from depressive to manic phase (from 130–150 days), the autocorrelation coefficients of daily fluctuations of γ gradually increase, possibly giving rise to an early warning sign for the phase transition. On the other hand, during clinically "stable" states in depressive and manic phases, the decrease of correlation coefficients to around zero value can be observed. This implies that the state of the system randomly fluctuates around a stable well [Fig. 10(a) or (c)]. This example suggests the possibility of detecting early warning signs for pathological transitions by evaluating the dynamical features of SPA, and also the viability of utilizing biomedical ILD to empirically study disease dynamics, i.e., dynamical disease.

IV. SUMMARY AND FUTURE DIRECTIONS

In this paper, we have shown the application of multiscale analysis to two types of intensive longitudinal biomedical signals, i.e., HRV and SPA time series. Recent advances in wearable and/or biomedical sensing technologies [5]–[7] are enabling us to collect these data with large temporal scales up to days and months during daily life. Thus, it is now timely to start thinking about the rigorous "use" of this type of data. In particular, it is considered important to begin investigation into how to robustly characterize their statistical and dynamical properties and how to practically utilize the analytical results in medicine and healthcare.

It was shown that these ILD indeed have robust characteristics unique to various multiscale complex systems, and that some parameters for multiscale complexity are in fact altered in pathological states, indicating potential usability as new types of ambient diagnostic and/or prognostic tools. For example, parameters characterizing increased intermittency (like λ_s; Section II) of HRV are found to be potentially useful in detecting abnormalities in the state of the autonomic nervous system, in

particular overall sympathetic hyperactivity, and the intermittency of SPA (characterized by γ; Section III) might also be useful in evaluating symptoms in psychiatric patients with depressive as well as manic episodes, all in daily settings. Furthermore, increased deviations and low frequency correlation appeared to be observed around transition points of disease states, with a potential application to disease forecasting, prevention, and control under the concept of dynamical disease [33], [34].

In conclusion, multiscale analysis might be a useful tool to extract information on clinical events occurring on multiple time scales during daily life, and on the underlying physiological control mechanisms from biomedical ILD. In the following, we put forward some promising directions for future research:

1) *Multiscale analysis of physiological signals*: While the multiscale analysis performed off-line on high quality data have shown the ability to assess the physiological status of subjects, the developments of a variety of wearable devices as well as their massive use yield further changes for analysis tools. First, low price devices may have limited performance, with high rates of missing data or strong quantizations. It is thus important to develop robust methodology against such crucial issues. Second, the explosion of data size would eventually make *a posteriori* off-line processing impossible. Thus, further development of multicale analysis algorithms with low memory and computational costs, and on-the-fly architecture. Such an on-line architecture would also play important roles for disease prevention and control involving forecasting.
2) *Validation and reliability tests of multiscale analysis in clinical applications*: HRV has been used to study various pathological conditions, such as heart failure, coronary artery disease, arterial hypertension, diabetes, stroke, etc. [64]. Despite the widespread use and expected applications of HRV, studies related to its application in clinical medicine are still very limited. To establish the physiological and clinical significance of HRV, especially that based on multiscale analysis of ILD for early prediction, diagnosis, and risk assessment, extensive validations are needed. The same also applies to SPA time series. To do this, a close collaboration between clinicians, biomedical physicists and engineers is an important factor [154].
3) *Intensive longitudinal data and data mining*: While HRV and SPA are currently typical ILD, the development of wearable and/or biomedical sensing technologies, the prevalence of high-speed Internet access and low-cost data storage have now made it possible to collect various types of massive biomedical ILD. The application of the multiscale analysis introduced here to a variety of this "bio-big data" including, e.g., blood pressure, glucose, and symptom diaries, will also be important for health-related applications. Also, feature selection and machine learning approaches [155], which provide different information compared to assessment by multiscale and conventional analysis, might be promising [156]. The optimal choice of these approaches would contribute to extract important bio-markers for early prediction, diagnosis and risk assessment of diseases.
4) *Multiscale mechanisms of dynamical disease*: Massive biomedical ILD and extracted disease specific bio-markers can be used to gain insights into the dynamical systems underlying pathological transitions and/or pathogenesis of diseases, enabling elucidation of their mathematical models based on concepts of nonlinear dynamics such as multi-stability and bifurcation of attractors. These approaches would lead to the methodological developments for early detection of disease onset and exacerbation based on analysis of biomedical ILD measured in daily life. The early detection or prediction of pathological transitions enables control of the risk of disease and significantly contributes to effective healthcare management and disease prevention. ■

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