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Entropy-based complexity measures for gait data of patients with Parkinson's disease

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Shannon, Kullback-Leibler, and Klimontovich's renormalized entropies are applied as three different complexity measures on gait data of patients with Parkinson's disease (PD) and healthy control group. We show that the renormalized entropy of variability of total reaction force of gait is a very efficient tool to compare patients with respect to disease severity. Moreover, it is a good risk predictor such that the sensitivity, i.e., the percentage of patients with PD who are correctly identified as having PD, increases from 25% to 67% while the Hoehn-Yahr stage increases from 2.5 to 3.0 (this stage goes from 0 to 5 as the disease severity increases). The renormalized entropy method for stride time variability of gait is found to correctly identify patients with a sensitivity of 80%, while the Shannon entropy and the Kullback-Leibler relative entropy can do this with a sensitivity of only 26.7% and 13.3%, respectively. © *2016 AIP Publishing LLC*.
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There are various natural phenomena which exhibit spatially ordered patterns as a result of increasing order within synthetic or real physical systems. This process of increasing order within the system until forming a stationary state is called self-organization and cannot be analyzed through ordinary means of closed systems. As an alternative, we consider the renormalized entropy as a complexity measure to detect healthy and patient states and show advantages of it with respect to the Shannon and the Kullback-Leibler entropies using Stride Time Variability (STV) and Total Reaction Force (TRF) for gait data of the patients with Parkinson's disease and the healthy controls. Our analysis shows, for the first time, its advantage in terms of risk predictor and applicability of the renormalized entropy on the STV like that of the Heart Rate Variability (HRV).

I. INTRODUCTION

Parkinson's disease (PD) is a neuro-degenerative disease which affects gait and mobility related to the motor functions. This disease causes functional disorder and death of vital nerve cells producing dopamine being a chemical messenger that sends messages to the part of the brain that controls movement and coordination.[1] Decreasing the amount of dopamine in brain primarily affects mobility of a person and motor control of gait.

The stride-to-stride fluctuations as a gait variability implies changes of the stride interval (or time) from one stride to the next. Fluctuation dynamics of a gait comes from the variability of the stride in time when a person is walking. Also, other quantities like walking velocity, total reaction force, and swing interval for patients with PD or healthy control may exhibit fluctuations with large or small magnitudes in time. It was reported that fluctuation dynamics in STV for healthy adults shows self-similarity within fractal structures[2,3] and stride lengths (times) are correlated variables possessing some memory effect and hidden temporal structure.[4–6] For a patient with PD, these self-similar structures disappear and fluctuations with short magnitude about the mean in STV become completely random (i.e., statistically independent).[7] Hausdorff and co-workers originally showed for many physiological data, including also the data sets discussed in this work, using detrended fluctuation analysis (DFA) that physiological data from healthy subjects generally possess fractal scaling indices of around 0.8–1.0, while the DFA scaling exponent becomes close to 0.5 for gait rhythm of a patient with PD. Any value between 0.8 and 1.0 represents long-range correlations, whereas values close to 0.5 will be representative of uncorrelated, random occurrences.[4,7–11]

From the viewpoint of non-equilibrium open systems, one can state that the beat-to-beat fluctuations of the cardiovascular system for healthy adults are similar to the fluctuations of chaotic dynamical systems driven away from an equilibrium state.[12,13] Moreover, it was demonstrated that fluctuations of STV for healthy adults can be described using a fractional Langevin equation.[14–16] For systems which are described by ordinary differential equations or discrete maps, the comparison of the degree of order of different regimes (healthy/patient, periodic/chaotic, etc.) or transition between them may be characterized by the Lyapunov exponent or different entropy measures, such as Shannon,[17] K-entropy,[18] or Kullback-Leibler relative entropy.[19,20] The Lyapunov exponent which measures the rates at which nearby orbits diverge and the K-entropy that is a

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diffeomorphic invariant of dynamical systems are of special importance for measuring dynamical complexity. However, it is noted that, as the Lyapunov exponent cannot separate differences between unstable points and quasi-periodic regions,[21] the K-entropy is not sensitive to different regimes of regular oscillations. It is also known that the concept of classic entropy does not include an appropriate description for some open systems, since the invariant measures of the regimes of such a system, and so their entropies, do not only depend on the structures of these regimes, but also on their energies.[22]

To compare the regimes with different energies, Klimontovich suggested the *S*-theorem (the letter *S* here stands for self-organization), which renormalizes the entropy of a regime so as to make the mean energies of two regimes equal.[23–27] This theorem allows to compare relatively the entropies of two closed systems in equilibrium state and also the entropies of open systems driven to a non-equilibrium stationary state from an equilibrium one. It is also known that this "renormalized entropy" enables to identify transition points of different regimes (periodic, quasi-periodic, chaotic) with great ability,[21,22] and only through combining renormalization and the Kullback-Leibler measure, one can obtain the renormalized entropy.[28,29] The renormalized entropy as a complexity measure was applied to paradigmatic model systems, such as the logistic map,[22] the standard sine-circle map,[21] as well as to outdoor data as electroencephalograms of epilepsy patients[28] and HRV of cardiovascular system.[30–32] It was shown that it can detect anomalous behavior at transition regions of different regimes,[28] and separate healthy and patient adults with a high sensitivity (72.2%) and uncover patients with high-risk.[33] In this contribution, we will apply different entropy measures to gait data of patients with PD and healthy controls in order to analyse possible advantages of the renormalized entropy compared to the Shannon and Kulback-Leblier entropies.

Our paper is organized as follows: In Section II, we present two different data sets which we use in our analysis and explain the preprocessing of these data sets. We also demonstrate the estimation of the spectral distribution required in the calculation of entropies and introduce the method of renormalized entropy. Next, we apply this method to (i) reaction force records to classify patients with PD with respect to their disease severity (i.e., Hoehn and Yahr Stage[34]) and (ii) STV to separate healthy and patient groups from gait data and determine the sensitivity. Moreover, for comparison, we also calculate the Shannon and Kullback-Leibler entropies for the same data sets. Finally, we discuss the obtained results.

II. DATA AND PRE-PROCESSING

A. Data sets

We analyze two different data sets that were collected by the Hausdorff's group.[35] They have developed a footswitch system including gait variables of patients with PD and healthy controls and their data sets are available in Ref. 36.

(i) The first data set includes vertical ground reaction force records of subjects when they walk normally (no tasking conditions) on a self-selected pace for approximately 120 s on the ground level. Underneath each foot there are 8 sensors that measure force (in Newtons) as a function of time. The output of each of these 16 sensors has been digitized and recorded with $\Delta t = 0.01$ (s). These records also include two signals that reflect the sum of the 8 sensor outputs for each foot.[37] For the first analysis, we use here the data of total reaction forces recorded from these 16 sensors to calculate the entropies. In the analysis, we use 18 healthy probands (for whom disease severity can be taken as 0) and 14 patients with PD that have disease severity with 2.5 and 3.0. It should be noted that the increase in disease severity (Hoehn and Yahr Stage) indicates a more advanced disease.

(ii) For the second data set, subjects are instructed to walk at their normal pace along a 77 -m-long hallway for 300 s. Stride-to-stride measures of footfall contact times are derived from the signal taken by using force-sensitive resistors. The data including stride interval (in seconds) in the range of approximately (20 s, 300 s) are recorded.[38] We use the left stride interval and calculate the Shannon entropy, Kullback-Leibler relative entropy, and renormalized entropy to separate the healthy group (n = 16 probands) from patients (n = 15).

B. Data pre-processing

To get uniformly sampled data in the second data set, we use the well-known cubic-spline interpolation with $\Delta t = 0.04$ (s) for non-uniform data in the range of (20 s, 300 s) leading to a uniform data set with a length of 7001. Due to uniformity of the first data set, this preprocessing is not necessary for it.

III. DEFINITION OF THE ENTROPY MEASURES

A. Shannon entropy

Let us consider two time series $X(t, c_1)$ and $X(t, c_2)$ from two adults where t is time and c_i are the control parameters which symbolize every adult. The normalized probability distributions related to these time series are $f(X, c_1) = f_0(X)$ and $f(X, c_2) = f_1(X)$, respectively. The corresponding Shannon entropies read

$$S(f_\nu(X)) = -\int f_\nu(X) \ln f_\nu(X) dX \quad , \tag{1}$$

where $\nu = 0$ or 1.

B. Renormalized entropy

Let us now assume that the system with index 0 is in an equilibrium or near-equilibrium with minimum energy. Then, setting the equilibrium inverse temperature $\beta_{eq} = 1$, the normalized Boltzmann-Gibbs distribution reads

$$f_0(X) = \exp\left[-H_{eff}(X)\right] \tag{2}$$

with the following effective energy:

$$H_{eff} = -\ln f_0(X)\,. \tag{3}$$

It is clearly seen from this setting that the inverse temperature β determines whether a system is in equilibrium or near-equilibrium with minimum energy and maximum disorder. Klimontovich's S-theorem states that the mean effective energies of these two states denoted by the indices 0 and 1 must be equal in order to apply Boltzmann's H-theorem to open systems.[23–27] This implies that the transfer of entropy across the boundaries of the system in the second law formulation of Prigogine is equal to zero.[39] The distribution $f_0(X)$ is transformed to $\tilde{f}_0(X)$ in order to apply the H-theorem and to compensate for mean energy differences, i.e., turning an open system into a closed one. The probability distribution of the renormalized state is defined by

$$\tilde{f}_0(X) = C\left[f_0(X)\right]^{\beta_{eff}} = C\,\exp\left[\frac{-H_{eff}(X)}{T_{eff}}\right], \tag{4}$$

where C is the normalization constant. β_{eff} is calculated from equality of both mean energies

$$\int \tilde{f}_0(X)\ln\tilde{f}_0(X)dX = \int f_1(X)\ln\tilde{f}_0(X)dX\,. \tag{5}$$

Then, the renormalized entropy $\Delta\tilde{S}$ is calculated by an interchanging algorithm:

(i) If $\beta_{eff} < \beta_{eq}$, then the initial assumption that the state denoted by index 0 is the most disordered one will be true. Therefore, f_0 is really the reference state and

$$\Delta\tilde{S} = S(f_1(X)) - S(\tilde{f}_0(X)). \tag{6}$$

(ii) If $\beta_{eff} > \beta_{eq}$, then the initial assumption that the state denoted by index 0 is the most disordered one will not be true. Therefore, f_1 is the reference state. All calculations are repeated by an interchanging algorithm and

$$\Delta\tilde{S} = S(f_0(X)) - S(\tilde{f}_1(X)). \tag{7}$$

C. Kullback-Leibler entropy

The Kullback-Leibler (KL) entropy between $f_1(X)$ and $f_0(X)$ is defined as[29]

$$KL\left(f_1(X)|f_0(X)\right) = \int f_1(X)\ln\frac{f_1(X)}{f_0(X)}dX. \tag{8}$$

In order to relate KL entropy to the renormalized entropy, one can rewrite the same equation as

$$KL\left(f_1(X)|f_0(X)\right) = \int\left[f_1(X)\ln\frac{f_1(X)}{f_0(X)}dX + f_0(X)\ln f_0(X) - f_0(X)\ln f_0(X)\right] \tag{9}$$

and using the Klimontovich's mean energy equality given in Eq. (5), it can be easily found that

$$\Delta\tilde{S} = -KL(f_1(X)|\tilde{f}_0(X))\,. \tag{10}$$

It must be noted that $KL(f_1(X)|\tilde{f}_0(X)) \neq KL(f_1(X)|f_0(X))$ and this equality is only valid for special cases $\tilde{f}_0(X) = f_0(X)$ or $f_1(X) = \tilde{f}_0(X)$.

D. Estimation of the entropy measures

Calculation of renormalized entropy and the other entropies (namely, Shannon and Kullback-Leibler) requires the estimation of distributions. In order to achieve this, we use the autoregressive spectral distributions in our calculations. In the case of this process, the spectrum is estimated using an autoregressive (AR) model

$$X(t) = a_1X(t-1) + a_2X(t-2) + \cdots + a_MX(t-M) + \epsilon(t)\,, \tag{11}$$

where M is the maximum order of the AR model, a_p are the AR parameters which are estimated from the data, and ϵ is the white noise driving signal.[33,40] This model assumes that the value of $X(t)$ in step t can be described by a linear aggregate of its previous values and the value of an ϵ white noise in step t.[41] Estimation of the AR parameters a_p, which are called Yule-Walker estimates, can be done by the Levinson-Durbin algorithm.[41–43] Once the parameters are computed, the autoregressive spectral distribution is given by[40]

$$P_{AR}(w) := \frac{2\sigma^2}{\left|1 - \sum_{p=1}^{M} a_p\,\exp(-2\,\pi\,i\,w\,p)\right|^2}\,, \tag{12}$$

where σ^2 is the variance of the white noise driving signal. The order of the model M can be chosen by the variance or FPE (final prediction error) criteria which was defined as

$$\mathrm{FPE}(p) := \frac{N+p+1}{N-p-1}\sigma(p)^2\,, \tag{13}$$

where N is the number of data samples, p is the trial model order and $\sigma(p)^2$ is the variance corresponding to order p. As p is increasing successively up to L, the order of the model M is given by the minimum of FPE(p) with $p = 1,2,\ldots, M,., L$. Moreover, the variance σ^2 will not significantly change after this appropriate M value.[40,41,44,45] We estimate the AR parameters up to order $L = 100$ and the order of the model is chosen by variance criterion as $M = 30$.

It must be noted that the time interval Δt is 0.01 and 0.04 for the first and second data sets, respectively. After obtaining the normalized spectral distributions which was given by

$$f_\nu(w) = \frac{P_{AR}(w)}{\sum_w P_{AR}(w)} \tag{14}$$

in the frequency (w) range of [0, 1/2Δt], these distributions are used instead of $f_\nu(X)$ in the calculation processes of the

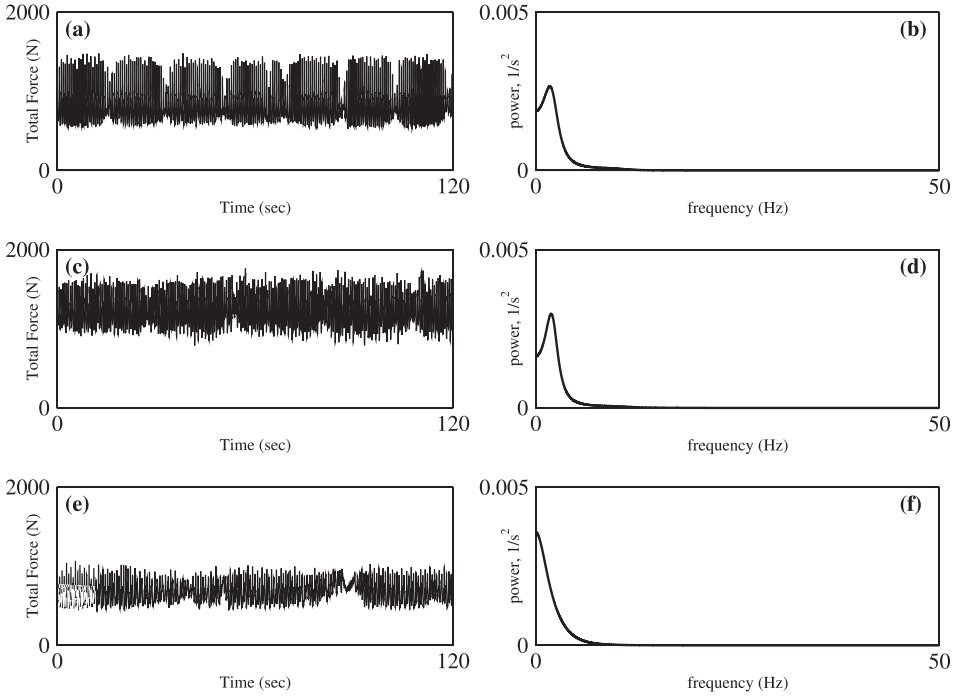

FIG. 1. (a) and (b) Time series of total reaction force, autoregressive spectral estimations for reference healthy state possessing disease severity (Hoehn-Yahr Stage) with 0, respectively. (c) and (d) Time series of total reaction force, autoregressive spectral estimations for patient state possessing disease severity with 2.5, respectively. (e) and (f) Time series of total reaction force, autoregressive spectral estimations for patient state possessing disease severity with 3.0, respectively.

all entropy measures, Shannon in Eq. (1), Kullback-Leibler in Eq. (8) and renormalized entropy in Eq. (7).

As examples of preprocessing and process of spectrum estimation, in Fig. 1, we plot the original time series as total reaction forces recording from 16 sensors underneath two feet of (a) healthy adult with disease severity 0, (c) patient adult with disease severity 2.5, and (e) patient adult with disease severity 3.0. Corresponding autoregressive spectral densities are plotted in the right column as (b), (d), and (f), respectively. Moreover, in Fig. 2, (a) stride time variability, (b) cubic-spline interpolated stride time variability, (c) autoregressive spectral density for a healthy adult and (d) stride time variability, (e) cubic-spline interpolated stride time variability, (f) autoregressive spectral density for an adult patient are shown.

IV. RESULTS

For the first data set of total reaction forces, the values of renormalized entropy $\Delta\tilde{S}$ (all of which have negative values) are calculated for healthy group with 18 adults after the estimation of autoregressive spectral distributions and choosing the distribution with minimum energy as the reference state (adult 4). Then, the renormalized entropy is calculated for patient groups with disease severity 2.5 and 3.0. The results of $\Delta\tilde{S}$ are shown in Fig. 3. It is clearly shown that the

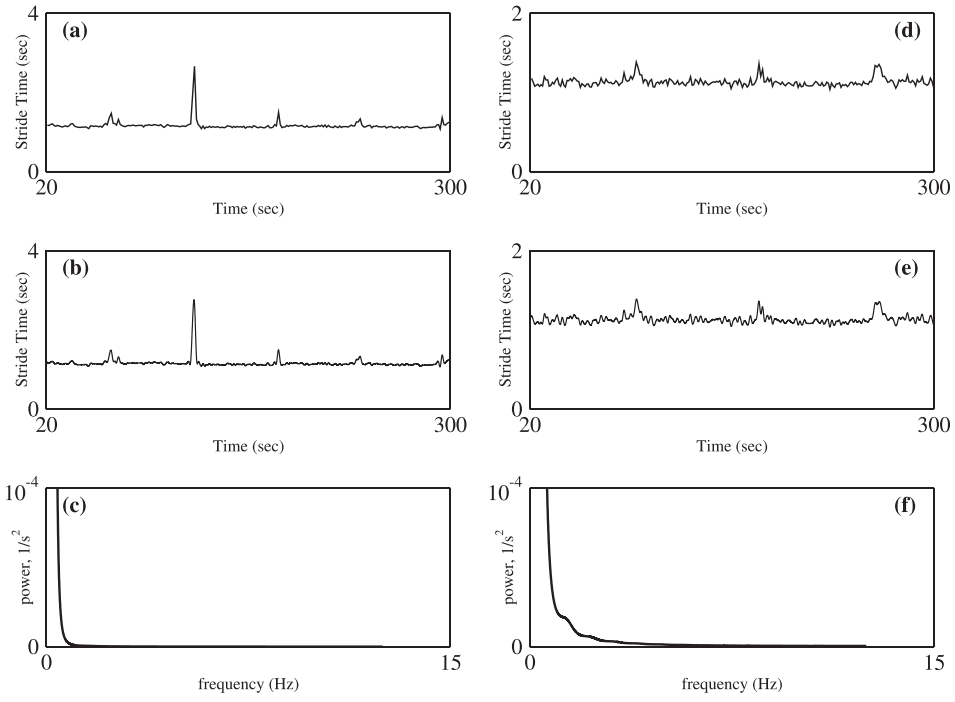

FIG. 2. (a) Original time series of STV, (b) time series of cubic spline interpolated STV, and (c) autoregressive spectral estimations for reference healthy state. (d) Original time series of STV, (e) time series of cubic spline interpolated STV, and (f) autoregressive spectral estimations for patient state.

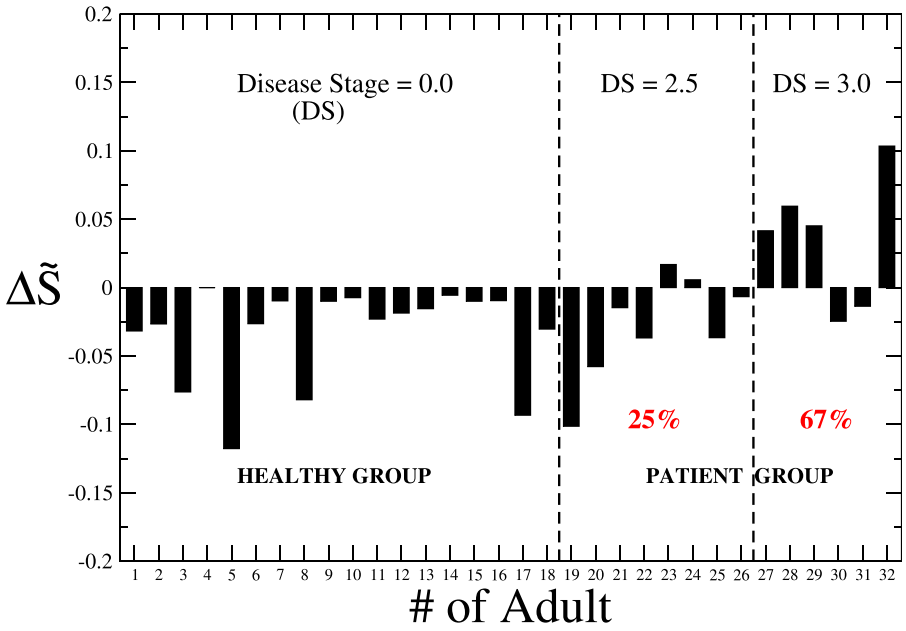

FIG. 3. The results of renormalized entropy for total force records. Adult 4 of healthy group shows the most disordered distribution with minimum energy and is chosen as reference state. 67% of patient group with disease stage 3.0 has values greater than zero; 25% of patient group with disease stage 2.5 has values greater than zero.

sensitivity increases from 25% to 67%, when the renormalized entropy analysis for separation of healthy and patient subjects and identification of the sensitivity are used, while their disease severity (Hoehn-Yahr stage) increases from 2.5 to 3.0. Here, it should be noted again that the Hoehn-Yahr stage goes from 0 to 5 as the disease severity increases.

For the second data set of STV, the values of renormalized entropy (all of which have negative values) are calculated for the healthy group with 16 adults after the estimation of autoregressive spectral distributions and choosing the distribution with minimum energy as the reference state (adult 2). The results of (a) Shannon, (b) Kullback-Leibler, and (c) renormalized entropy in order to compare their advantages/disadvantages with respect to each other are calculated and plotted in Fig. 4. As Shannon and KL entropies can detect only 4 (26.7% sensitivity) and 2 (13.3% sensitivity) of 15 patients, respectively, whereas renormalised entropy $\Delta\tilde{S}$ correctly classifies 12 (80% sensitivity) of 15 patients.

V. DISCUSSION

The advantage of renormalized entropy as a complexity measure, when it is compared to the Shannon and Kullback-Leibler entropies, is to compare regimes with different mean energies of the dynamical systems in hand. The renormalized entropy takes into account the degree of order/disorder of the

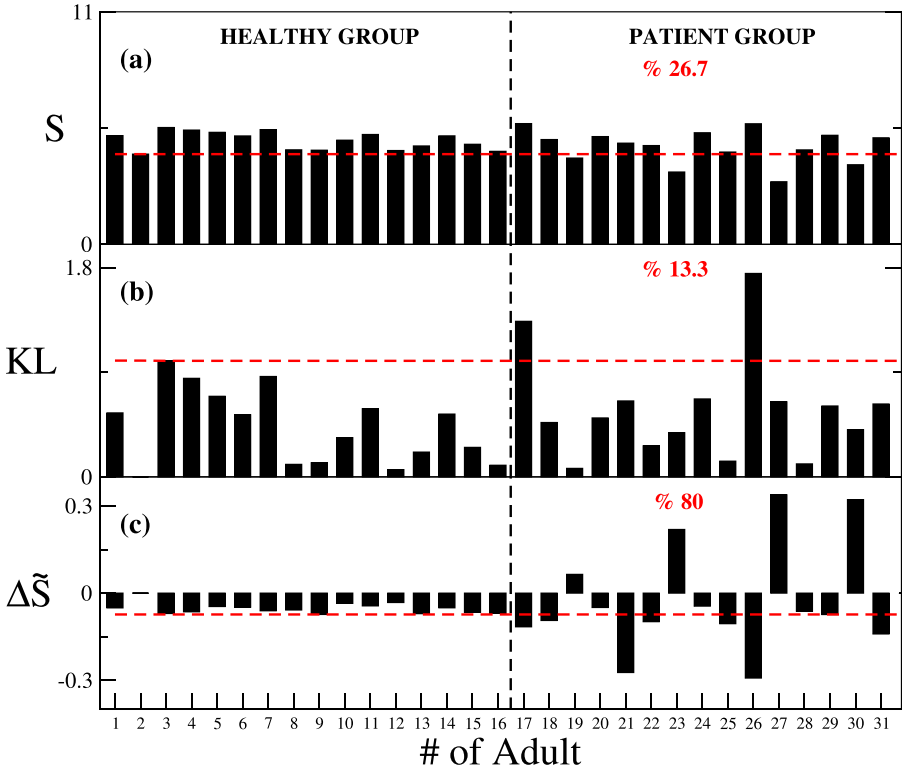

FIG. 4. The results of (a) Shannon, (b) Kullback-Leibler, and (c) renormalised entropies for stride length (time) records are given. Adult 2 of healthy group showing the most disordered distribution (in the sense of renormalised entropy) with minimum energy is chosen as the reference state. For the Shannon entropy, obtained entropy values of four distributions of the patient group are less than the border of entropy with minimum value from the healthy adult (denoted by the red dashed line). For the KL entropy, obtained entropy values of two distributions of the patient group are greater than the border of the KL entropy with maximum value from the healthy adult. For the renormalized entropy, obtained entropy values of four distributions of the patient group are the most disordered cases than the reference distribution and have values greater than zero. Moreover, obtained entropy values of eight distributions of patients are less than the minimum value of the renormalized entropy from the healthy adults.

system with regard to energy differences of regimes due to its formal structure. This method has been applied to two different time series, total reaction force and STV, from gait variability of patients with PD and the control group.

The analysis of the renormalized entropy of reaction force of gait shows that it is useful to compare patients with respect to disease stages and the success rate of separation of disease severity is strongly related to the Hoehn-Yahr stage.

The data used in this study were originally analyzed in the context of DFA which makes one to conclude that the fluctuations in the STV for patients with Parkinson's disease are random. A fundamental problem with DFA is that it is extremely sensitive to presence of low frequency trends in the data.[46] In fact it is easy to replicate the findings of DFA by adding noise to a low frequency sinusoid. The power in the fluctuations in the low frequency range in Figs. 2(c) and 2(f) shows us that entropy measurements could also be sensitive to low frequency trends. One source of low frequency trends is phenomenon related to "turns" in the stride length fluctuations for patients with Parkinson's disease. It seems from the data in Fig. 2 that there are 5 turns for healthy subject and 3 turns for patient subject. In the light of this discussion, it is evident that it might be useful to repeat the calculation of DFA in this system so that one could directly compare these results to those obtained from entropy measures on the same data sets using the same data preprocessing in this work. Moreover, the recurrence quantification analysis (RQA)[47] that is a very useful tool to distinguish different regimes in short time series could be also useful to analyze the time series between two "turns."

The STV of a gait is similar to the HRV due to some properties of its dynamics. In order to do a separation between healthy and patient adults, the method of renormalized entropy has been applied to the dynamics of beat-to-beat fluctuations of heart for many years. It is known that the success rate of the method closely depends on preprocessing of the analysis. Up to now, in the HRV literature, the best success rate obtained in this separation was 72% for a preprocessing including an autoregressive spectral application of filtered and interpolated tachograms.[33] In this work, using a simpler preprocessing for STV, it is shown that the method of renormalized entropy as a risk predictor can identify patients with a sensitivity of 80%, while the Shannon entropy and the Kullback-Leibler relative entropy can identify patients with a sensitivity of 26.7% and 13.3%, respectively. All these results show that a risk stratification might be performed in the future between HRV and STV.

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