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ORIGINAL ARTICLE

Assessing the complexity of short-term heartbeat interval series by distribution entropy

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Abstract Complexity of heartbeat interval series is typically measured by entropy. Recent studies have found that sample entropy (SampEn) or fuzzy entropy (FuzzyEn) quantifies essentially the randomness, which may not be uniformly identical to complexity. Additionally, these entropy measures are heavily dependent on the predetermined parameters and confined to data length. Aiming at improving the robustness of complexity assessment for short-term RR interval series, this study developed a novel measure—distribution entropy (DistEn). The DistEn took full advantage of the inherent information underlying the vector-to-vector distances in the state space by probability density estimation. Performances of DistEn were examined by theoretical data and experimental short-term RR interval series. Results showed that DistEn correctly ranked the complexity of simulated chaotic series and Gaussian noise series. The DistEn had relatively lower sensitivity to the predetermined parameters and showed stability even for quantifying the complexity of extremely short series. Analysis further showed that the DistEn indicated the loss of complexity in both healthy aging and heart failure patients (both $p < 0.01$), whereas neither the SampEn nor the FuzzyEn achieved comparable results (all $p \geq 0.05$). This study suggested that the DistEn would be a promising measure for prompt clinical examination of cardiovascular function.

Keywords Short-term RR interval series · Complexity · Sample entropy (SampEn) · Fuzzy entropy (FuzzyEn) · Distribution entropy (DistEn)

1 Introduction

Complexity of time series has served as an essential property for understanding the mechanism governing the dynamics of the system. It opens new avenues, by applying methods from chaos theory, to real-world physiological problems. One such problem encountered frequently in cardiology is to extract physiological or pathological information from an episode of heart rate data, which is believed to be capable of revealing the autonomic nervous control [38].

Multiple methods, including fractal dimension, correlation dimension, and Lyapunov exponents, etc., have long been developed for quantifying complexity. Their calculations are also not as time-consuming as they usually were, since various fast algorithms have been developed [3]. However, a sufficient large data set is required in the calculation to reconstruct the attractor and its trajectories. Thus, they may not be acceptable in clinical examination of cardiovascular function within a short screening time (e.g., 5 min) [37], which actually draws great attention nowadays with the emergence of personal health care and point-of-care diagnosis [7, 23].

A family of entropy measures, e.g., approximate entropy (ApEn) [25, 26], sample entropy (SampEn) [30], etc., has proved potential for such applications. However,

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discussions on their statistical performances have never stopped [4, 6, 14–16, 19, 21, 29, 40]. It has been suggested that they are still highly unstable in short series [40] and lack consistency due to their great sensitivity to the predetermined parameters, especially to the threshold value r (similarity criterion) [16, 19]. These limitations discount the clinical value of entropy measures.

To attenuate the influence of r, Xie et al. [39] and Chen et al. [5] introduced fuzzy logic in the classification procedure in ApEn and SampEn algorithm and defined thereby the fuzzy entropy (FuzzyEn) measure. But one study suggested that the results of FuzzyEn would also switch when different values for r were assigned [15]. Its performance in short-term data sets thus requires further examination. Lake and Moorman developed the COSEn measure by SampEn with log ($2r$) and heart rate correction [14]. It could effectively differentiate atrial fibrillation (AF) from normal sinus rhythm in even 12 RR intervals. Thus, it was a very promising AF diagnosis index, but would be relatively difficult to be generalized to a complexity measure.

In addition, Costa et al. [8, 9] have addressed another issue of ApEn and SampEn that they quantify the irregularity of a series per se. Irregularity increases with the degree of randomness; hence, the increase in entropy may not be necessarily indicative of an increase in complexity. However, certain diseased systems in such as AF patients may be characterized by RR series with highly erratic fluctuations that resemble white noise [8]. Such algorithms may assign them a higher value of entropy, whereas they are presumed to have less complexity than those derived from healthy subjects [10, 13, 18, 27, 38]. This paradox also exist in many other entropy measures such as FuzzyEn [5, 39], permutation entropy [2], and conditional entropy [29], which always achieve maximum in a complete random process.

One reason for the problem may be the fact that these measures do not take into account the multiple temporal scales inherently in complex dynamics [8, 9]. Through a multiscale analysis framework, Costa et al. [8, 9] have developed a multiscale entropy measure, which evaluates the irregularity of series at multiple scales. However, fairly large data sets seem to be the prerequisite of robust multiscale analysis [8, 9, 24]. Although there have been a couple of refined multiscale procedures [1, 12, 36], their significance over short-term application is still undetermined.

We here in this study adopt the idea of Costa et al. [8, 9] that a relevant measure of complexity under the above biomedical explanation should be maximized in inherently complex series. We will argue that one possible reason for the limitations of SampEn in stability and consistency would arise from the incomplete use of vector-to-vector distances information in the state space. In this study, this information is accepted as an interpretation of the spatial structures (which are different from the temporal structures applied in the multiscale entropy), and it is presumed to be maximized in complex series. We will introduce a new measure named distribution entropy (DistEn) based on novel complete quantification of this information in the next section. Then, stability and consistency of the DistEn will be examined by simulation tests, and its capability on assessing the complexity of physiological series will finally be examined over short-term RR interval data.

2 Methods

2.1 DistEn algorithm

We summarize the DistEn algorithm for a series $\{u(i),\ 1 \le i \le N\}$ of N points as follows. For specification, we will explain the idea on DistEn in the Sect. 4

1. State-space reconstruction: Form $(N-m)$ vectors $\mathbf{X}(i)$ by $\mathbf{X}(i) = \{u(i), u(i+1), \ldots, u(i+m-1)\}$, $1 \le i \le N-m$. Here m indicates the embedding dimension.
2. Distance matrix construction: Define the distance matrix $\mathbf{D} = \{d_{i,j}\}$ among vectors $\mathbf{X}(i)$ and $\mathbf{X}(j)$ for all $1 \le i, j \le N-m$, wherein $d_{i,j} = \max\{|u(i+k) - u(j+k)|, 0 \le k \le m-1\}$ is the Chebyshev distance between $\mathbf{X}(i)$ and $\mathbf{X}(j)$.
3. Probability density estimation: The distribution characteristics of all $d_{i,j}$ for $1 \le i, j \le N-m$ should be complete quantification of the information underlying the distance matrix $\mathbf{D}$. We here apply the histogram approach to estimate the empirical probability density function (ePDF) of $\mathbf{D}$. If the histogram has M bins, we use p_t, $t = 1, 2, \ldots, M$ to denote the probability (frequency) of each bin. To reduce bias, elements with $i = j$ are excluded when estimating the ePDF.
4. Calculation: Define the DistEn of $u(i)$ by the classical formula of Shannon entropy, that is

$$\overline{\text{DistEn}}(m, M) = -\sum_{t=1}^{M} p_t \log_2 (p_t). \tag{1}$$

Note that we mark a '–' in (1) to differentiate this form from the following one. DistEn is thus expressed in bits. But it can certainly be also expressed in nats if we utilized the natural logarithm function. In this work, we used the base-2 logarithm so that we could choose a value of M as the integer power of 2. It should be noted that the selection of M is not as critical as the selection of r in ApEn or SampEn because a relatively large value of M should properly unfold the distribution of $\mathbf{D}$. The total amount of elements in matrix $\mathbf{D}$ except its main diagonal is $(N - m)(N - m - 1)$, and this should then be the maximum value that M can be assigned. The spatial structures will be over-unfolded if $M > (N - m)(N - m - 1)$, and consequently the information underlying $\mathbf{D}$ cannot be properly quantified. Additionally, we note that $d_{i,j} = d_{j,i}$. Thus, $\mathbf{D}$ itself is symmetrical. Only the upper or lower triangular matrix will actually be adequate for the estimation of the ePDF. This attribute can be used to facilitate its fast calculation.

The theoretical lower and upper limits of DistEn are 0 and $\log_2(M)$, corresponding to one-peak and fully flat ePDF, respectively. To consolidate the DistEn results calculated with different M, we again defined the normalized DistEn of $u(i)$ as

$$\text{DistEn}(m) = -\frac{1}{\log_2(M)} \sum_{t=1}^{M} p_\text{t} \log_2(p_\text{t}). \tag{2}$$

Thus, the range of DistEn should be within [0, 1]. Note that $p_t \log_2(p_t) = 0$ when $p_t = 0$ in both (1) and (2).

2.2 Simulation tests

2.2.1 *Theoretical data*

It was essential to observe first the performances of DistEn in series with known complexity levels. We thus applied simulated chaotic series, Gaussian noise, MIX(p) processes, and periodic signals generated by customized MATLAB (Ver. R2013a, Mathworks Inc, MA, USA) codes. The Logistic attractor $x(n + 1) = \omega \times x(n) \times (1 - x(n))$ was considered with $\omega = 4.0$ for chaotic series and $\omega = 3.5$ for periodic signals (period 4), respectively. The MIX(p) process is in nature sinusoid signal of length N, where $N \times p$ randomly chosen points are replaced with independent identically distributed random noise [25]. We applied $p = 0.1$ and 0.2, respectively, to generate two MIX(p) processes with different complexity levels. The Gaussian noise was generated by the random number function (randn) in MATLAB.

Twenty realizations of each model were performed to eliminate random factors (20 randomly chosen initials were adopted for Logistic attractors to generate 20 realizations of chaotic and periodic series, whereas 20 independent realizations were directly performed for MIX(p) process and Gaussian noise). Besides, we always allowed a transient (200 data points) before sampling a data set to ensure the dynamics had settled down on its attractor.

2.2.2 *Assessing complexity of chaotic series and stochastic processes*

As mentioned above, the chaotic series should have the maximum complexity; its DistEn should be maximized in consequence. Additionally, Gaussian noise and MIX(p) process were both stochastic in nature. Their complexity levels should be in accordance with their irregularity levels (for the same type of series). Therefore, DistEn should reduce from Gaussian noise to MIX(0.2), and further to MIX(0.1) gradually. The periodic series should have the minimum DistEn unquestionably.

We would here testify the above assumption by the theoretical data. In this test, the series were all generated in length of 400 points as this was nearly the average data length for 5-min short-term RR interval series. We chose $m = 2$ and $M = 512$ (2^9) in the calculation of DistEn. For comparison, we also calculated the SampEn [30] and FuzzyEn [5] results with parameters $m = 2$ and $r = 0.2\sigma$, wherein σ was the standard deviation of each realization. We applied $r = 0.2\sigma$ here since it had been recommended that r could be selected from the interval $[0.1\sigma, 0.25\sigma]$ [25, 30], and greater r value could, to some extent, avoid the appearance of invalid ln(0). We did not perform ApEn because the weight of self-matches in ApEn would be very important in such small data sets [28]. It would introduce considerable bias in ApEn results.

We then employed surrogate data analysis to better understand the results. Twenty surrogates were performed for each realization of the Logistic chaotic series. Surrogate data analysis should contaminate the complex structures in the Logistic chaos, and consequently, the results could resemble a random process. Increased SampEn and FuzzyEn results of surrogates would be obtained, whereas reduced DistEn results should be expected. The Fourier transform algorithm was applied here to generate the surrogate data [34]. Besides, traditional SampEn and FuzzyEn are variance-independent measures. To understand the variance effect on DistEn, we here rescaled the amplitude of the logistic chaotic series by different factors so as to monitor DistEn as a function of variance.

2.2.3 *Length effects*

To assess the algorithms' sensitivity to data length, we evaluated DistEn in the aforementioned five series as a function of data length N, which was set at ten different values from 50 to 2,000 logarithmically to stress its short-term application. We chose $m = 2$ and $M = 512$ in all calculations of DistEn. Similarly, we also calculated the SampEn and FuzzyEn results with parameters $m = 2$ and $r = 0.2\sigma$ for comparison purposes.

2.2.4 *Sensitivity to input parameters*

The DistEn is a function of m and M. Actually, M serves as an intermediate parameter just as what r plays in SampEn-based measures. We have mentioned that traditional

Table 1 Subjects characteristics

Variables	Healthy controls	HF patients	p
No.	30	21	–
Men	17	11	0.23
Age (years)	56.5 ± 7.9	59.5 ± 10.1	0.24
BMI (kg/m^2)	22.8 ± 3.3	23.4 ± 5.1	0.61
SBP (mmHg)	115 ± 13	120 ± 10	0.14
DBP (mmHg)	71 ± 8	73 ± 7	0.36
LVEF (%)	66 ± 4	38 ± 6	<0.01

Data are expressed as number or mean ± standard deviation

No. number, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *LVEF* left ventricular ejection fraction

SampEn-based measures lacked consistency because they were all extremely sensitive to r. Then, we should here first show the dependence of DistEn on M. We set M at 40 different values chosen from 128 (2^7) to 1,024 (2^{10}) with equal steps. For comparison purposes, we calculated the SampEn and FuzzyEn results with 20 r values chosen from 0.025 to 0.5 with a step of 0.025.

We should then show the dependence of DistEn on m. Here m was set at 10 different values chosen from 1 to 10 at a step of 1. Larger values for m were not tested, since it was commonly set at 2, 3, or 4 and other values had rarely been selected [40]. Again for comparison purposes, we calculated SampEn and FuzzyEn results at each value of m. Parameter r was set at 0.2σ in the SampEn and FuzzyEn calculation and M at 512 in the DistEn. All series were generated in length of 400 points.

2.3 Experiments

2.3.1 *Aging effects on complexity of short-term RR interval data*

We applied the DistEn algorithm to the Fantasia database, which is publicly accessible from the PhysioNet website [11]. It contains 20 young (21–34 years old) and 20 elderly (68–85 years old) rigorously screened healthy subjects with their ECG collecting for 120 min in supine position at a sampling frequency of 250 Hz. In this study, only the first or the second 5-min (in 9 recordings, the corresponding second 5-min episode was used instead because of poor signal quality in the first one) episode was applied in each recording so as to construct the short-term RR series.

R peaks in each episode were detected first through a template matching procedure (the detection results had showed high coincidence with the annotations encapsulated in the database). Ectopic R peaks were marked afterward by also a template matching-based algorithm [17]. RR interval series were constructed by the intervals of consecutive normal R peaks. Anomalous intervals were again filtered out by impulse rejection filtering [20]. DistEn with $m = 2$ and $M = 512$ was calculated, and for comparison, SampEn and FuzzyEn with $m = 2$ and $r = 0.2\sigma$ were performed. The standard deviation of normal-to-normal intervals (sdNN) and normalized high-frequency band power (Phfn), and their corresponding Pearson correlations with DistEn were also calculated to show the variance effects on DistEn. Detrend and resampling processes were performed prior to the frequency-domain analysis [33].

2.3.2 *Changes in complexity of short-term RR interval data in heart failure (HF) patients*

Twenty-one HF patients and 30 healthy volunteers were recruited and provided informed consents for this study. Their characteristics are presented in Table 1. The HF patients were in New York Heart Association (NYHA) class II–III with functional classification confirmed by the ultrasonic cardiogram. The left ventricular ejection fractions (LVEF) from three cardiac cycles were measured by one cardiologist, and their average value was used as the reference LVEF for the specific subject. Measurements were undertaken in a quiet, temperature-controlled clinical measurement room (25 ± 3 °C) at Qilu Hospital of Shandong University, by a cardiovascular function detection device (CV FD-I) produced by Huiyironggong Technology Co., Ltd, Jinan, China. ECG data in standard limb II configuration were recorded in supine position for 5 min at a sampling frequency of 1 kHz after a 10-min rest. All study procedures were approved by the Clinical Ethics Committee of the Qilu Hospital of Shandong University and conformed with the principles in the Declaration of Helsinki.

RR interval series were constructed automatically by the same procedure described above. Then SampEn, FuzzyEn, and DistEn were calculated with $m = 2$, $r = 0.2\sigma$ (for SampEn and FuzzyEn), and $M = 512$ (for DistEn). Again the sdNN, Phfn, and their corresponding Pearson correlation coefficients with DistEn were finally performed.

2.4 Statistical analysis

Since the Kolmogorov–Smirnov test suggested that all the entropy indices followed a non-normal distribution, the Mann–Whitney U test was applied to determine their differences between healthy aging and healthy young, as well as between HF patients and healthy volunteers. Student's t test was performed to show the differences of sdNN and Phfn between groups. Statistical significance was accepted at $p < 0.05$. All the above statistical analysis was performed using the SPSS software (Ver. 20.0, IBM, NY, USA).

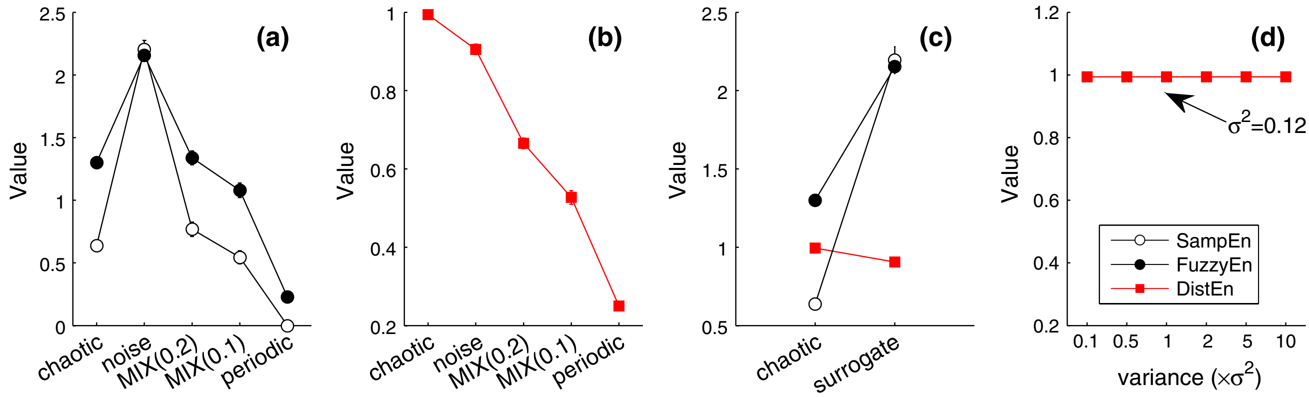

Fig. 1 Complexity results of the chaotic series, Gaussian noise, MIX(0.2), MIX(0.1), and periodic series. **a** SampEn (*open circles*) and FuzzyEn (*closed circles*). **b** DistEn. **c** surrogate data test results of SampEn (*open circles*), FuzzyEn (*closed circles*) and DistEn (*closed diamonds*). **d** DistEn shown as a function of variance. *Error bar* indicates the standard deviation of 20 realizations of each series (color figure online)

3 Results

3.1 Simulation results

3.1.1 Complexity levels between chaotic series and stochastic processes

Complexity levels of the five series evaluated by SampEn, FuzzyEn, and DistEn are shown in Fig. 1a and b. The Gaussian noise series has higher SampEn and FuzzyEn values than the other series. SampEn reduces gradually from chaotic series to MIX(0.2), and then to MIX(0.1). And finally, it is 0 in periodic series. FuzzyEn reaches also around 0 in periodic series. It increases with the proportion of random noise in the MIX(p) process. But it cannot make a distinction between the chaotic series and MIX(0.2). By contrast, DistEn reaches the highest value for the chaotic series, and its values for the Gaussian noise, MIX(0.2), MIX(0.1), and the periodic series decrease gradually. The DistEn of periodic series is not zero, which is different from the SampEn and FuzzyEn. Figure 1c incorporates the surrogate data test results. The structures among the original Logistic chaos are destroyed as indicated by increased SampEn and FuzzyEn results in surrogates. Declined DistEn of surrogates is shown as expected, since the surrogates resemble a random process, in comparison with that of the original Logistic chaos. Thus, all entropy measures are capable of differentiating original nonlinear chaotic dynamics from its linear surrogates. Figure 1d shows DistEn as a function of variance. The amplitude of the original logistic chaotic series was rescaled by certain factors so that the variances of the rescaled series were adjusted to 0.1, 0.5, 2, 5, and 10 times the variance of the original series (0.12 specifically). DistEn remains unchanged as expected, indicating the DistEn a variance-independent measure.

3.1.2 Stability

Figure 2 shows SampEn, FuzzyEn, and DistEn as functions of data length. SampEn and FuzzyEn of the Gaussian noise and two MIX(p) processes in small data sets all lack stability as shown by large error bars. Also, they can hardly tell the difference between the chaotic series and the MIX(0.2) process because the results switch (SampEn) or overlap (FuzzyEn) with increased data length. SampEn of the Gaussian noise with very small data sets (~50 points) even has invalid results (ln0). By contrast, DistEn is much more stable. It can classify the five series even as the length decreased to 50 points.

3.1.3 Consistency

Figure 3 shows the dependence of SampEn and FuzzyEn on r, and DistEn on M. Both SampEn and FuzzyEn vary significantly with the change of r for especially the Gaussian noise. Besides, both SampEn and FuzzyEn switch with the variation of r for MIX(0.2) and the chaotic time series, which makes it difficult to tell the differences in their complexity levels. Also the switching occurs although r has already been in the recommended range. By contrast, only slight variation of DistEn is showed with the changes of M. It is very stable for almost all values of M in a large range of [512, 1,024].

Figure 4 shows the dependence of all three measures on m. It again appears invalid SampEn results for the Gaussian noise when $m > 3$. SampEn results of MIX(0.1) and MIX(0.2) fall sharply from $m = 1$ to $m = 3$ and maintain a low level when $m > 3$. The average SampEn results of the Logistic chaos appear to change slightly, but the standard deviations increase obviously. FuzzyEn results of all simulated series but the Gaussian noise fall sharply with

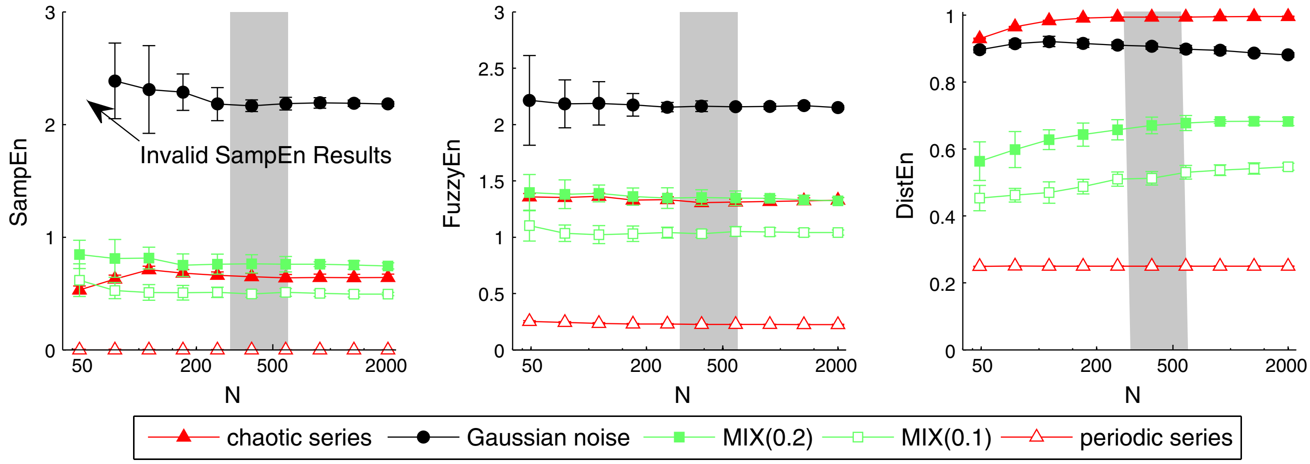

Fig. 2 SampEn, FuzzyEn, and DistEn of 5 series are shown as functions of data length. *Error bar* indicates the standard deviation of 20 realizations. *Filled area* indicates the most likely range in short-term RR interval analysis, which is around [300, 600]. The abscissa is shown in logarithmic scale. Note that the *error bar* of DistEn is very trivial (color figure online)

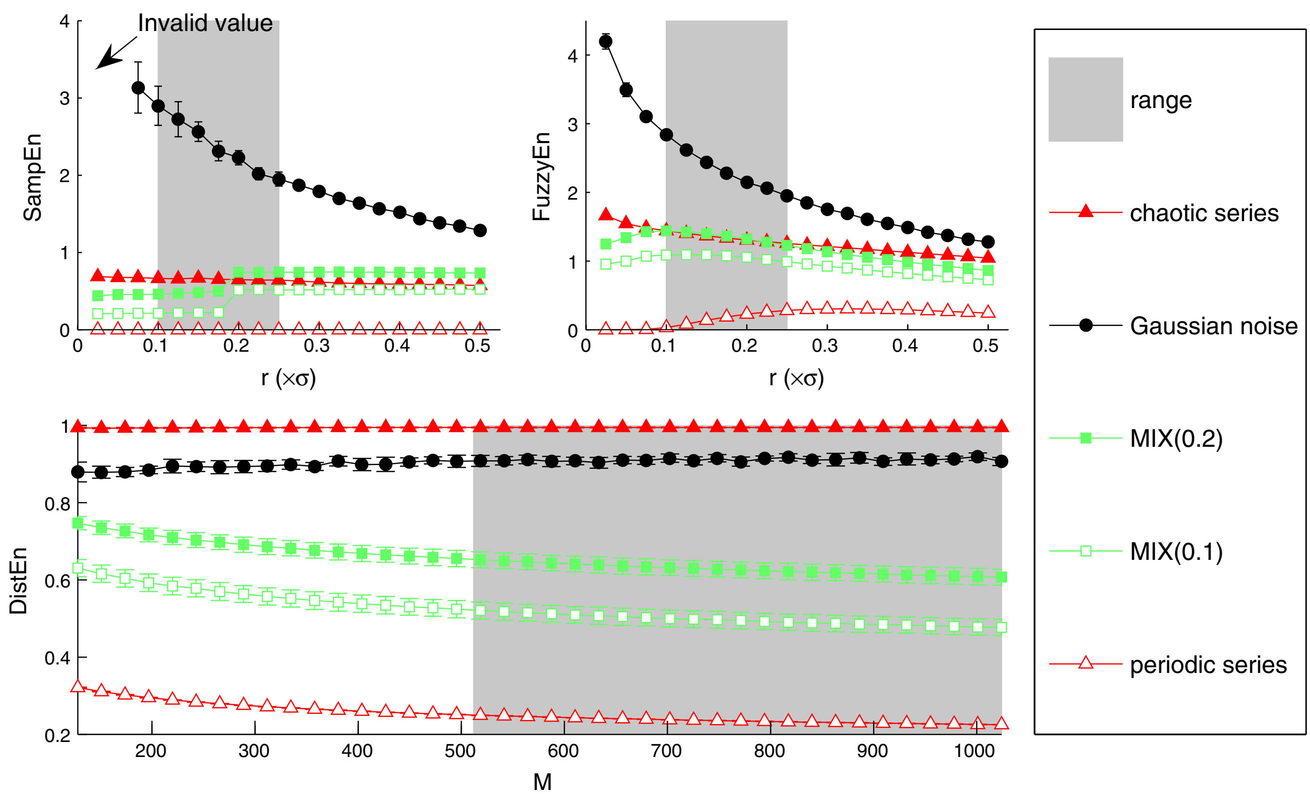

Fig. 3 SampEn, FuzzyEn of 5 series are shown as functions of r and DistEn as a function of M. *Error bar* indicates the standard deviation of 20 realizations and filled area the recommended ranges for the selection of r and M, which are $[0.1, 0.25]\sigma$ and [512, 1,024], respectively (color figure online)

the increase in m and then stabilize at a low average level. No invalid FuzzyEn result appears in the Gaussian noise with the increase in m, but it starts to fluctuate widely. By contrast, DistEn results are very stable in both the average levels and the standard deviations. Note that DistEn of the Logistic chaos declines gradually when $m > 2$, and it even falls below the level of the Gaussian noise when $m > 6$. This decrease in DistEn may be partly due to the low dimension of Logistic map, which does not require a state-space reconstruction at a high dimension.

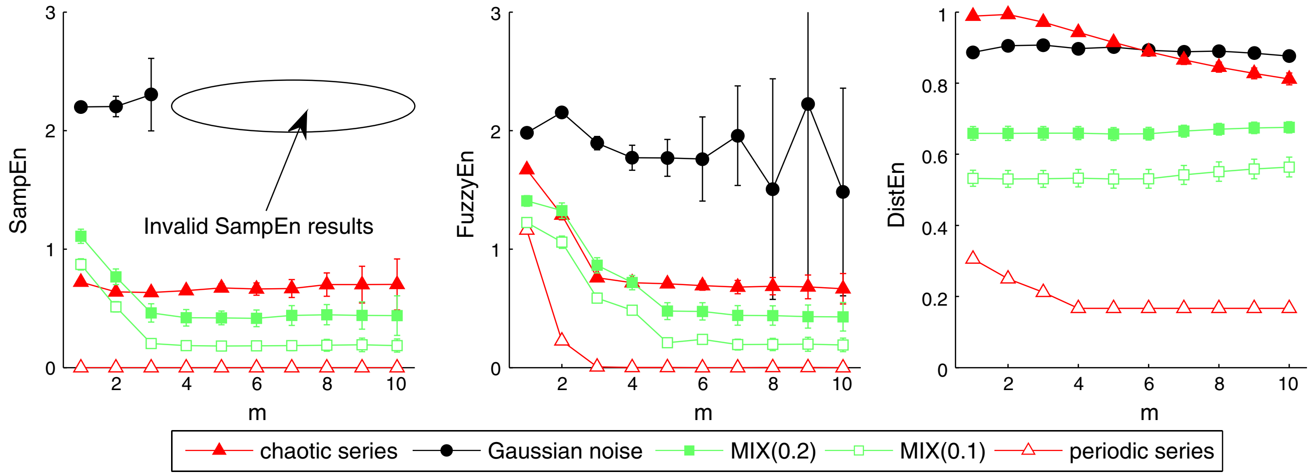

Fig. 4 SampEn, FuzzyEn, and DistEn are shown as functions of *m*. *Error bar* indicates the standard deviation of 20 realizations (color figure online)

Table 2 Experimental results

	Healthy aging group	Healthy young group	*p*	HF patients	Healthy controls	*p*
sdNN (ms)	31.75 ± 28.69	57.31 ± 44.30	0.04	15.15 ± 16.89	30.90 ± 28.60	0.03
Phfn (n.U.)	0.29 ± 0.17	0.40 ± 0.19	0.07	0.22 ± 0.15	0.31 ± 0.18	0.06
SampEn	1.73 ± 0.32	1.90 ± 0.28	0.08	1.96 ± 0.64	1.88 ± 0.28	0.71
FuzzyEn	1.35 ± 0.28	1.49 ± 0.22	0.05	1.31 ± 0.45	1.45 ± 0.22	0.32
DistEn	0.80 ± 0.06	0.88 ± 0.03	<0.01	0.61 ± 0.11	0.79 ± 0.07	<0.01

Data are expressed as mean ± standard deviation

sdNN standard deviation of normal-to-normal intervals, *Phfn* normalized high-frequency band power, *SampEn* sample entropy, *FuzzyEn* fuzzy entropy, *DistEn* distribution entropy

3.2 Experimental results

The effects of healthy aging and HF on the complexity of short-term RR interval data are shown in Table 2. Mann–Whitney *U* test shows that there is a weak reduction of both SampEn and FuzzyEn in the healthy aging group. But the difference is not or less statistically significant ($p = 0.08$ and 0.05, respectively). Besides, no significant difference between HF patients and healthy controls is shown by both SampEn and FuzzyEn ($p = 0.71$ and 0.32, respectively). However, Mann–Whitney *U* test shows a significant loss of DistEn in both healthy aging and HF patients (both $p < 0.01$). Besides, the standard deviation of DistEn in each group is distinctly smaller than that of SampEn and FuzzyEn.

The average level of the two linear indices—sdNN and Phfn—decreased in both healthy aging and HF patients groups (Table 2). But the decreases are not as significant as the reduction in DistEn. In addition, our Pearson correlation analyses show that DistEn is weakly correlated with the two indices in all four groups (all $0.01 < p < 0.05$).

4 Discussion

4.1 Complexity versus irregularity

A novel DistEn measure was established in this study based on the ePDF of distances among vectors in the state space. It consistently yielded higher values for the Logistic chaos compared with the Gaussian noise (Fig. 1), which is in common with the idea of Costa et al. [8, 9]. It reduced gradually with the proportion of random noise for the three stochastic processes (Gaussian noise and 2 MIX(p) processes), indicating also good sensitivity to the randomness. The nonzero DistEn values in analysis of the simulated periodic series (period 4) suggest a certain level of complexity. It is highly possible that DistEn would be further lowered in less complex series (e.g., periodic series with period 2), whereas SampEn and FuzzyEn would remain at 0, suggesting an improved performance using DistEn in discrimination of periodic series with different periods. Our surrogate data test rejected the null hypothesis that the Logistic chaotic series came from a linear Gaussian process. It is true for the Logistic chaos;

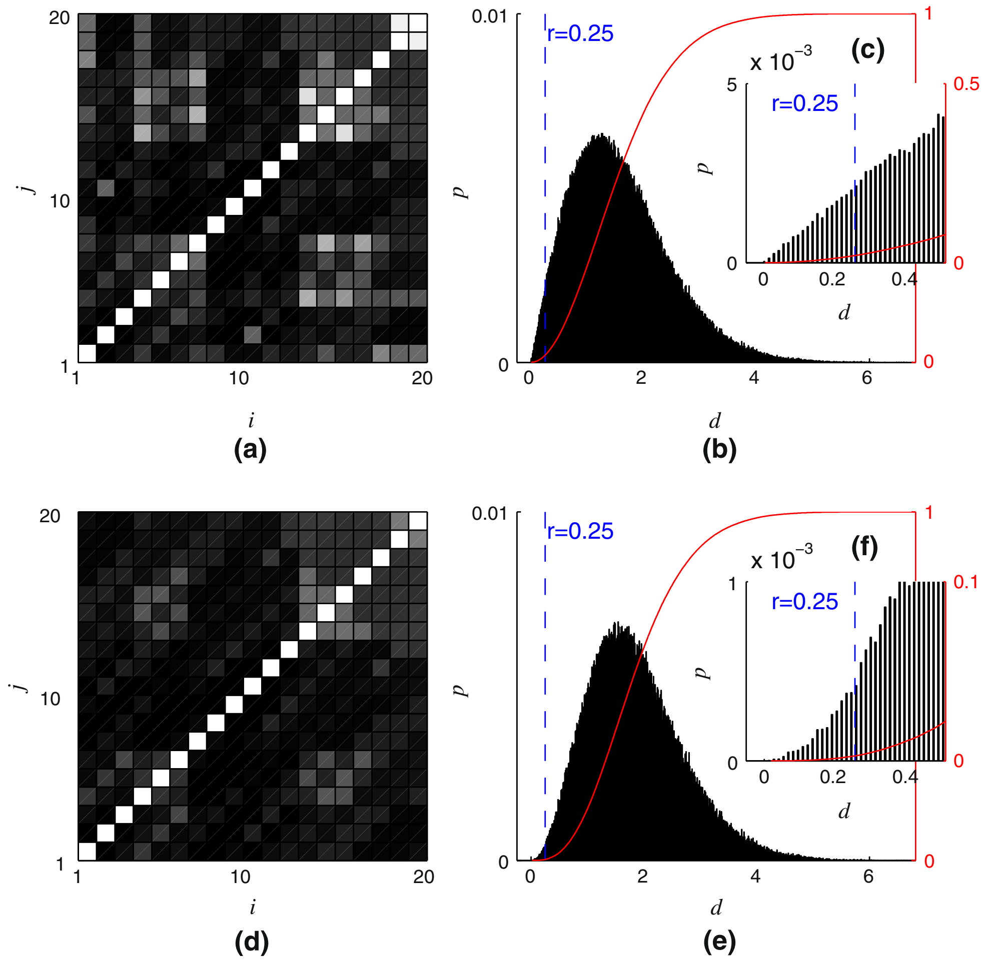

Fig. 5 Main calculation procedures of SampEn and DistEn. **a**, **d** Distance matrices with $m = 2$ and 3, respectively. But only $1 \le i \le 20$ and $1 \le j \le 20$ are showed for illustrating details. *Dark-colored area* indicates larger distances and vice versa. **b**, **e** The corresponding ePDF (*histogram*) and the cumulative distribution curves (*solid line*) of the distance matrices in **(a)** and **(d)**, respectively. **c**, **f** The corresponding enlarged parts of **(b)** and **(e)**. The *dashed line* in **(b)**, **(c)**, **(e)**, and **(f)** indicates the threshold value *r*, which is set at 0.25. Note that the series applied here is normalized by its standard deviation first; thus, it is not necessary for *r* to multiply the standard deviation (color figure online)

hence, DistEn indeed can be used to capture the nonlinear properties in time series. In addition, DistEn is inherently derived from the global distribution characteristics of distances among vectors. These characteristics will not be altered by variance rescaling since we concerned here was the probability density estimated by a fix bin number. What is altered by variance rescaling is the range of distances not the probability of each bin. Thus, DistEn should be variance independent. It was also proved by our simulation tests that DistEn results did not change after the amplitude-rescaling.

The novel DistEn took account of the global characteristics of distances among vectors in the state space, which were quite different from SampEn-based measures. For specification, we would like here to use Fig. 5 to anatomize the main differences between SampEn and DistEn.

Distance matrices (**D** in the DistEn algorithm) with $m = 2$ and 3 of one simulated Gaussian noise series in above simulations are showed in the left panel of Fig. 5 (but only the elements with $1 \le i \le 20$ and $1 \le j \le 20$ were depicted for clarity). Features applied in both SampEn and DistEn are showed in the right panel (for all values of i, j except elements with $i = j$, which are the self-matching distances, also the main diagonal of the distance plots in the left panel). SampEn divides those elements in **D** into the similar and dissimilar ones. Only the probability of similar ones (bars on the left of the dashed line in the right panel of Fig. 5, the probability can be easily calculated by their cumulative distribution, which is depicted here by solid line) is considered in SampEn calculations. Note that $r = 0.25\sigma$ ($\sigma = 1$ here because the series is normalized first by its original standard deviation) was depicted by the dashed line in Fig. 5 because it is usually the maximum value in application and even in such relative large *r*, the features used in SampEn are still very trivial. Thus, SampEn does not completely quantify the distance information, whereas DistEn takes the full characteristics into account.

Different to studies of Costa et al. [8, 9], this study did not discuss the temporal structures at varied time scales; the ePDF is most likely a reflection of the spatial structures. There are certainly other ways to capture such structures, e.g., the permutation patterns of the amplitudes in permutation entropy [2]. But structures estimated in

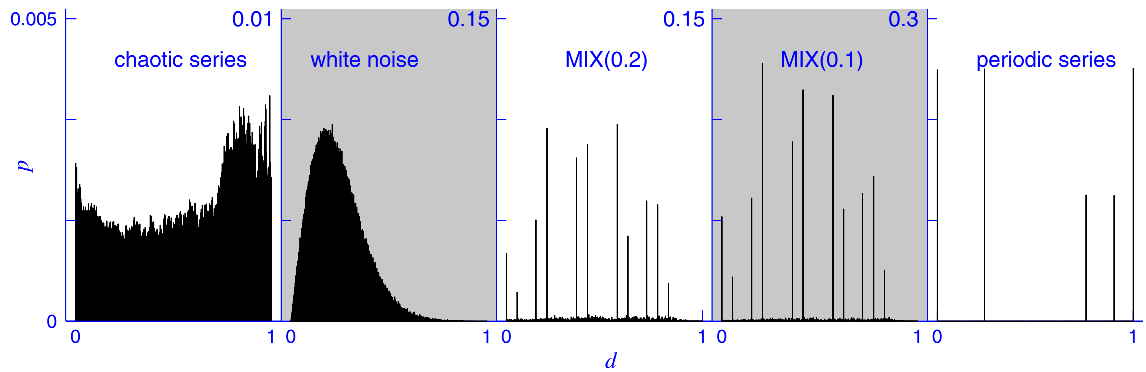

Fig. 6 The ePDF of 5 series estimated by histograms with 512 bins. Note that the series are normalized first by the corresponding maximum distance; thus, the ranges of all abscissas are within [0, 1] (color figure online)

permutation entropy should also be associated with the irregularity since it is maximized in totally random processes. Figure 6 shows the corresponding ePDFs of the simulated five series. They are quite distinct from each other, which thus indicate that the global quantification of vector-to-vector distances by ePDF is very likely a reasonable good way to reveal the inherent structures in series.

4.2 Statistical abilities of DistEn

Simulation results indicated that DistEn had improved performances in terms of stability and consistency. It worked very well in series formed by 300–600 points (showed in filled area in Fig. 2), which are the typical data lengths of short-term RR interval series. Even as the data length decreased to only 50 points, the DistEn still showed acceptable results. In addition, DistEn showed a lower sensitivity to input parameters than SampEn and FuzzyEn did.

The remarkable improvements in both the stability and the consistency should be also mainly due to the global quantification based on probability density estimation. Since SampEn and FuzzyEn only consider the similar vectors in the state space, the features adopted should be very trivial when the data sets are relatively small. However, they are still quite considerable for DistEn. For example, for a Gaussian noise series of 100 points, there are totally ~10,000 (100 × 100 approximately) distances that will be evaluated in DistEn. But within those distances, there are probably not more than 300 values, which are less than r (the probability is smaller than 0.03 in most of our simulations when $r = 0.2\sigma$) in calculations of SampEn and FuzzyEn. In addition, this little information adopted in SampEn and FuzzyEn is immensely easy to vary with r, which makes them very sensitive to input parameters.

4.3 Application to short-term RR interval data analysis

An age-related loss of fractal organization, thus complexity, of RR interval data was previously observed by detrended fluctuation analysis (DFA) in a subset (10 young and 10 elderly) of the Fantasia database [13]. However, another most recent study used all but five subjects, which contained many episodes of typical sleep apnea patterns in the same database (19 young and 16 elderly) and reported that these properties did not decline with advanced age by also the DFA approach [31]. It was totally controversial. But since all subjects were recorded while watching the relaxing movie Fantasia, there was a possibility that some of them might fall asleep (at least the physiological conditions under the Fantasia protocol more closely resembled sleep), which affected much on the fractal properties [32].

We only used the first or the second 5-min episode in each recording to construct the short-term RR interval series. Under this protocol, we could assure the awake condition of all subjects, and thus, it seemed to be more acceptable than the long-term DFA procedure in both of the mentioned studies [13, 31]. Our results showed that there was a significant reduction of DistEn in healthy aging group (Table 2), which supports the previous finding that the complexity of RR interval series decreases with healthy aging by means of short-term analysis.

Results also showed that both SampEn and FuzzyEn failed to differentiate between the two groups (Table 2). One reason may be the instability of SampEn and FuzzyEn in this short-term analysis and the other one the selection of r. We note that r was only set at 0.2σ arbitrarily in our analysis. It has the possibility that SampEn or FuzzyEn can tell them apart for a more seriously selected r. But the central issue is which value should physician select for a new subject. The DistEn parries effectively this thorny problem through the developed global quantification approach based on probability density estimation.

In addition, a significantly reduced DistEn in HF patients was shown in our clinical tests (Table 2), indicating great potential of DistEn in short-term examination of clinical data. Similarly, no significant difference in SampEn and FuzzyEn between the HF patients and healthy control groups has been found, which may be due to their relatively instability and inconsistency in such short-term analysis.

Our experiments also supported previous results that the sdNN and Phfn are reduced in healthy aging and HF patients. However, the large intra-group standard deviations made the reduction not that significant, which may be partly because that the RR interval data are non-stationary in nature and short-term linear indices cannot thus well capture their inherent features. The Pearson correlation analyses between DistEn and the two linear indices also supported the simulation results that DistEn is independent of variance.

Since mainly the parasympathetic activities attenuate with healthy aging while HF mostly injures the sympathetic tones, our results show that DistEn is sensitive to the information related to both activities, and thus, it should also have great potentials in revealing possible pathological conditions in subjects with other cardiovascular diseases. More rigorous tests should thus be scheduled for further validation.

The distinctly reduced standard deviations (Figs. 2, 3, 4; Table 2) in DistEn results indicate that our approach has also reasonable robustness against additive noise (since different realizations of the Gaussian noise and MIX(p) processes exhibit different distributions of noise). Regarding RR interval data, the main interference originates from the false detection of R and the ectopic beats, which manifest themselves in spikes other than additive noise [22]. They can be filtered out effectively by established algorithms [17, 20]. Thus, we can apply DistEn in the analysis of RR interval data without much consideration on the noise effects. To fully automate the complexity analysis, we will illustrate the influence of spikes on DistEn in our future studies.

Besides, the sampling frequency should be another potential influencing factor on DistEn (it certainly has important effects on SampEn-based measures [35]). Theoretically, when a series is over-sampled, there should be plenty of 'redundant' information in the distance matrix mainly because it is not properly reconstructed in the state space with relatively small m, but fairly large sampling frequency. These redundant information should contaminate the spatial structures considered in DistEn because they may provide additional probabilities in distances that are assumed to have zero probability. However, there seems to be no over-sampling problems in RR interval data. Thus, similarly we can apply DistEn directly without much consideration. To fully understand its ability, we will, however, discuss in detail the influence of sampling frequency in our future works.

5 Conclusions

This study has established a novel measure—DistEn—for the complexity analysis of short-term heartbeat interval series. DistEn takes full advantage of the information hidden in the state space by the estimation of the probability density of distances among vectors. The DistEn algorithm has been validated on both simulation data and on real-world short-term heartbeat interval data. Improved performances of DistEn suggest it a very promising measure in prompt clinical examination of cardiovascular function.

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References

1. Amoud H, Snoussi H, Hewson D, Doussot M, Duchene J (2007) Intrinsic mode entropy for nonlinear discriminant analysis. IEEE Signal Process Lett 14(5):297–300
2. Bandt C, Pompe B (2002) Permutation entropy: a natural complexity measure for time series. Phys Rev Lett 88(17):174102
3. Bolea J, Laguna P, Remartínez JM, Rovira E, Navarro A, Bailón R (2014) Methodological framework for estimating the correlation dimension in HRV signals. Comput Math Methods Med 2014:1–11
4. Castiglioni P, Di Rienzo M (2008) How the threshold *r* influences approximate entropy analysis of heart-rate variability. In: Computers in Cardiology, Bologna, Italy, pp 561–564
5. Chen W, Zhuang J, Yu W, Wang Z (2009) Measuring complexity using FuzzyEn, ApEn, and SampEn. Med Eng Phys 31(1):61–68
6. Chon K, Scully CG, Lu S (2009) Approximate entropy for all signals. IEEE Eng Med Biol Mag 28(6):18–23
7. Clifford GD, Moody GB (2012) Signal quality in cardiorespiratory monitoring. Physiol Meas 33(9):E01
8. Costa M, Goldberger AL, Peng CK (2002) Multiscale entropy analysis of complex physiologic time series. Phys Rev Lett 89(6):068102
9. Costa M, Goldberger AL, Peng CK (2005) Multiscale entropy analysis of biological signals. Phys Rev E 71(2):021906
10. Goldberger AL (1996) Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at the bedside. Lancet 347(9011):1312–1314
11. Goldberger AL, Amaral LAN, Glass L, Hausdorff JM, Ivanov PC, Mark RG, Mietus JE, Moody GB, Peng C-K, Stanley HE (2000) PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals. Circulation 101(23):e215–e220
12. Hu M, Liang H (2012) Adaptive multiscale entropy analysis of multivariate neural data. IEEE Trans Biomed Eng 59(1):12–15
13. Iyengar N, Peng CK, Morin R, Goldberger AL, Lipsitz LA (1996) Age-related alterations in the fractal scaling of cardiac interbeat interval dynamics. Am J Physiol 271(4):R1078–R1084
14. Lake DE, Moorman JR (2011) Accurate estimation of entropy in very short physiological time series: the problem of atrial fibrillation detection in implanted ventricular devices. Am J Physiol Heart Circ Physiol 300(1):H319–H325

15. Li P, Liu C, Wang X, Li B, Che W, Liu C (2012) Cross-sample entropy and cross-fuzzy entropy for testing pattern synchrony: how results vary with different threshold value *r*. In: World Congress on Medical Physics and Biomedical Engineering, Beijing, China, pp 485–488
16. Li P, Liu C, Wang X, Li L, Yang L, Chen Y, Liu C (2013) Testing pattern synchronization in coupled systems through different entropy-based measures. Med Biol Eng Comput 51(5):581–591
17. Li P, Liu C, Wang X, Zheng D, Li Y, Liu C (2014) A low-complexity data-adaptive approach for premature ventricular contraction recognition. Signal Image Video Process 8(1):111–120
18. Lipsitz La GAL (1992) Loss of complexity and aging: potential applications of fractals and chaos theory to senescence. JAMA 267(13):1806–1809
19. Liu C, Liu C, Shao P, Li L, Sun X, Wang X, Liu F (2011) Comparison of different threshold values *r* for approximate entropy: application to investigate the heart rate variability between heart failure and healthy control groups. Physiol Meas 32(2):167–180
20. Liu C, Li L, Zhao L, Zheng D, Li P, Liu C (2012) A combination method of improved impulse rejection filter and template matching for identification of anomalous intervals in RR sequences. J Med Biol Eng 32(4):245–249
21. Lu S, Chen X, Kanters JK, Solomon IC, Chon KH (2008) Automatic selection of the threshold value *r* for approximate entropy. IEEE Trans Biomed Eng 55(8):1966–1972
22. Molina-Pico A, Cuesta-Frau D, Aboy M, Crespo C, Miro-Martinez P, Oltra-Crespo S (2011) Comparative study of approximate entropy and sample entropy robustness to spikes. Artif Intell Med 53(2):97–106
23. Nikita KS, Lin JC, Fotiadis DI, Arredondo MT (2012) Editorial: special issue on mobile and wireless technologies for healthcare delivery. IEEE Trans Biomed Eng 59(11):3083–3089
24. Nikulin VV, Brismar T (2004) Comment on 'multiscale entropy analysis of complex physiologic time series'. Phys Rev Lett 92(8):089803
25. Pincus SM (1991) Approximate entropy as a measure of system complexity. Proc Natl Acad Sci USA 88(6):2297–2301
26. Pincus S, Singer BH (1996) Randomness and degrees of irregularity. Proc Natl Acad Sci USA 93(5):2083–2088
27. Poon CS, Merrill CK (1997) Decrease of cardiac chaos in congestive heart failure. Nature 389(6650):492–495
28. Porta A, Gnecchi-Ruscone T, Tobaldini E, Guzzetti S, Furlan R, Montano N (2007) Progressive decrease of heart period variability entropy-based complexity during graded head-up tilt. J App Physiol 103(4):1143–1149
29. Porta A, Castiglioni P, Bari V, Bassani T, Marchi A, Cividjian A, Quintin L, Rienzo MD (2013) K-nearest-neighbor conditional entropy approach for the assessment of the short-term complexity of cardiovascular control. Physiol Meas 34(1):17
30. Richman JS, Moorman JR (2000) Physiological time-series analysis using approximate entropy and sample entropy. Am J Physiol Heart Circ Physiol 278(6):H2039–H2049
31. Schmitt DT, Ivanov P (2007) Fractal scale-invariant and nonlinear properties of cardiac dynamics remain stable with advanced age: a new mechanistic picture of cardiac control in healthy elderly. Am J Physiol Regul Integr Comp Physiol 293(5):R1923–R1937
32. Schmitt DT, Stein PK, Ivanov P (2009) Stratification pattern of static and scale-invariant dynamic measures of heartbeat fluctuations across sleep stages in young and elderly. IEEE Trans Biomed Eng 56(5):1564–1573
33. Tarvainen MP, Ranta-Aho PO, Karjalainen PA (2002) An advanced detrending method with application to HRV analysis. IEEE Trans Biomed Eng 49(2):172–175
34. Theiler J, Eubank S, Longtin A, Galdrikian B, Doyne Farmer J (1992) Testing for nonlinearity in time series: the method of surrogate data. Physica D 58(1):77–94
35. Thuraisingham RA, Gottwald GA (2006) On multiscale entropy analysis for physiological data. Phys A 366:323–332
36. Valencia JF, Porta A, Vallverdu M, Claria F, Baranowski R, Orlowska-Baranowska E, Caminal P (2009) Refined multiscale entropy: application to 24-h Holter recordings of heart period variability in healthy and aortic stenosis subjects. IEEE Trans Biomed Eng 56(9):2202–2213
37. Voss A, Heitmann A, Schroeder R, Peters A, Perz S (2012) Short-term heart rate variability–age dependence in healthy subjects. Physiol Meas 33(8):1289–1311
38. Wagner CD, Persson PB (1998) Chaos in the cardiovascular system: an update. Cardiovasc Res 40(2):257–264
39. Xie H-B, He W-X, Liu H (2008) Measuring time series regularity using nonlinear similarity-based sample entropy. Phys Lett A 372(48):7140–7146
40. Yentes J, Hunt N, Schmid K, Kaipust J, McGrath D, Stergiou N (2013) The appropriate use of approximate entropy and sample entropy with short data sets. Ann Biomed Eng 41(2):349–365