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Analysis of heart rate variability using fuzzy measure entropy

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ABSTRACT

This paper proposed a new entropy measure, Fuzzy Measure Entropy (FuzzyMEn), for the analysis of heart rate variability (HRV) signals. FuzzyMEn was calculated based on the fuzzy set theory and improved the poor statistical stability in the approximate entropy (ApEn) and sample entropy (SampEn). The simulation results also demonstrated that the FuzzyMEn had better algorithm discrimination ability when compared with the recently published fuzzy entropy (FuzzyEn), The validity of FuzzyMEn was tested for clinical HRV analysis on 120 subjects (60 heart failure and 60 healthy control subjects). It is concluded that FuzzyMEn could be considered as a valid and reliable method for a clinical HRV application.

1. Introduction

The approximate entropy (ApEn) has been introduced as a quantification of regularity in a time series. It was initially motivated by being applied to the relatively short and noisy time series [1]. More frequently, it was used in the analysis of heart rate variability (HRV) signals. It is derived from the computation of the correlation integral. By maximizing the irregularity, the ApEn provided a formulation for analyzing the complexity of a finite time series [2]. Because the calculation of ApEn is relatively easy, it has been widely applied to clinical cardiovascular studies [1,3–10]. However, the ApEn produces biased estimation for the complexity of physiological signals with self-matching . To relieve this bias, Richman et al. proposed another statistic, the sample entropy (SampEn) [11].

Either ApEn or SampEn has recently been proven that they both have the poor statistical stability [12–15]. To explore the reasons for the poor statistical stability of the traditional entropy measures (ApEn and SampEn), researchers initially paid much attention to the selection criterion of the threshold r, which was set to a constant of 0.2 times the standard deviation (SD) of the series. However, a constant $r=0.2$ was recently found to be problematic in the similarity judgment, particularly for the fast dynamic series [12,13]. Selection methods for the dynamic threshold have been proposed to replace the constant r. For example, the threshold r maximizing ApEn (r_{max}) was selected from 0.01 to 1.0 times the SD of the series. Irrespective of using the constant $r=0.2$ or the r_{max}, the poor statistical stability in the ApEn and SampEn has not been solved. The inherent reason for their poor statistical stability is that the two entropy measures are based on the Heaviside function of the classical sets, which is basically a two-state classifier that judges two vectors as either "similar" or "dissimilar", with no intermediate states. This hypothesis has been proven in the study by [14]. Similar conclusions were also found in our recent study [15].

To overcome the poor statistical stability in the ApEn and SampEn, Chen et al. [12,16] proposed a statistic named fuzzy entropy (FuzzyEn), in which the Heaviside function was replaced by the Zadeh fuzzy sets. Compared to the two-state classifier, the Zadeh fuzzy sets provided a graduated similarity classifier and thus achieved a better statistical stability than the ApEn and SampEn. One limitation of the FuzzyEn is that it focuses only on the local characteristics of the sequence. However, the global fluctuation in the large scales has been widely found in the sequence. Therefore, it is important to test the effect of the global fluctuation on the FuzzyEn.

This study aimed to develop an improvement method, the fuzzy measure entropy (FuzzyMEn) for HRV analysis. The results were compared with the traditional ApEn, SampEn and the recent FuzzyEn, and its validity was tested on both simulation database and clinical subjects.

2. Methods

2.1. Subjects

120 subjects aged between 18 and 75 participated in this study. The clinical characteristics of the subjects are shown in

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Table 1. No subjects had taken medications or smoked cigarettes before the test. The subjects generally fell into two groups – the heart failure group and the healthy control group. Each group contained 60 subjects. Prior to the test, each subject was given a detailed description of the study objectives and the requirements of the experiment. Informed consent was then read and signed. Nobody had participated in any other "clinical trials" within the previous three months. The subjects in the healthy control group had normal performances in the ultrasonic cardiogram (UCG), blood lipid and glucose checks and electrocardiogram (ECG). The subjects in the heart failure group were consistent with Classes II–III of the New York Heart Association (NYHA) Functional Classification and everyone had a left ventricular ejection fraction (LVEF) value less than 50% in the UCG detection. Those with severe organ damage or psychiatric disorders were excluded. The study obtained the full ethical approval from the Clinical Ethics Committee of the Qilu Hospitals of Shandong University.

Table 1
Statistics of the investigated subjects.

Statistics	Heart failure (N=60)	Healthy control (N=60)	Total (N=120)
Sex (female/male)[a]	28/32	33/27	61/59
Age (year)[a]	57.4 ± 9.7	54.9 ± 14.6	55.8 ± 16.3
Height (cm)[a]	164.6 ± 5.9	167.1 ± 9.3	165.5 ± 11.2
Mass (Kg)[a]	63.4 ± 8.4	68.8 ± 11.7	65.9 ± 13.9
BMI (Kg/m^2)[a]	25.3 ± 3.3	23.5 ± 3.1	24.6 ± 4.5
HR (beat/minute)[a]	66.1 ± 9.8	65.2 ± 7.3	65.6 ± 12.5
LVEF (%)[b]	42 ± 8	67 ± 13	53 ± 17
SBP (mmHg)[a]	107.0 ± 13.2	112.9 ± 12.9	109.3 ± 15.9
DBP (mmHg)[a]	75.5 ± 9.4	73.7 ± 8.8	74.8 ± 11.0

Note: Data are expressed as number (male/female) or mean ± standard deviation. Abbreviations: BMI: body mass index; HR: heart rate; LVEF: left ventricular ejection fraction; SBP: systolic blood pressure; DBP: diastolic blood pressure.

[a] There is no significant difference between heart failure and healthy control groups.

[b] There is significant difference between heart failure and healthy control groups.

2.2. Data acquisition

The subjects were asked to lie down on a bed and maintain the supine position during the test. Standard limb II–lead ECG data were recorded for 10 min for each subject using the Cardiovascular System Function Detecting Instrument (HUIYIRONGGONG, China). ECG data were sampled at 1000 Hz and filtered through a band-pass filter with a 0.05–125 Hz bandwidth. The *R*-wave peaks of the ECG were detected using the Wavelet Transform Modulus Maxima (WTMM) method described in [17,18]. The adjacent *R*-wave peaks were used to calculate the RR interval and then form the original RR sequence.

Each original RR sequence included several hundred RR intervals and usually contained some anomalies caused by detector errors or ectopic beats [19]. For detector-error caused anomalies, a false beat caused by a low amplitude *R*-wave was defined as a false negative (FN), and a false beat caused by noise masking was a false positive (FP). The anomalies caused by ectopic beats were classified into supra-ventricular ectopic beats (sVEB) and ventricular ectopic beats (VEB), depending on the localization of the ectopic focus. Fig. 1 shows the four types of anomalies mentioned above, (a) an FN anomaly (b) an FP anomaly (c) a sVEB anomaly and, (d) a VEB anomaly. Each upper panel in Fig. 1 shows a segment of the ECG data for 8 s and the positions of the *R*-wave peaks automatically detected by the WTMM method. Because the anomalies exhibit a sharp transient in the original RR sequence (see the lower panel in Fig. 1), they contaminated the real RR sequence. Thus, it is necessary to correct the original RR sequence prior to the HRV analysis. In this study, the anomalies were identified using our recently-developed method [20], which combined the advantages of the impulse rejection filter (IRF) and the template-matching methods. The identified anomaly was replaced with the mean values of the adjacent normal RR

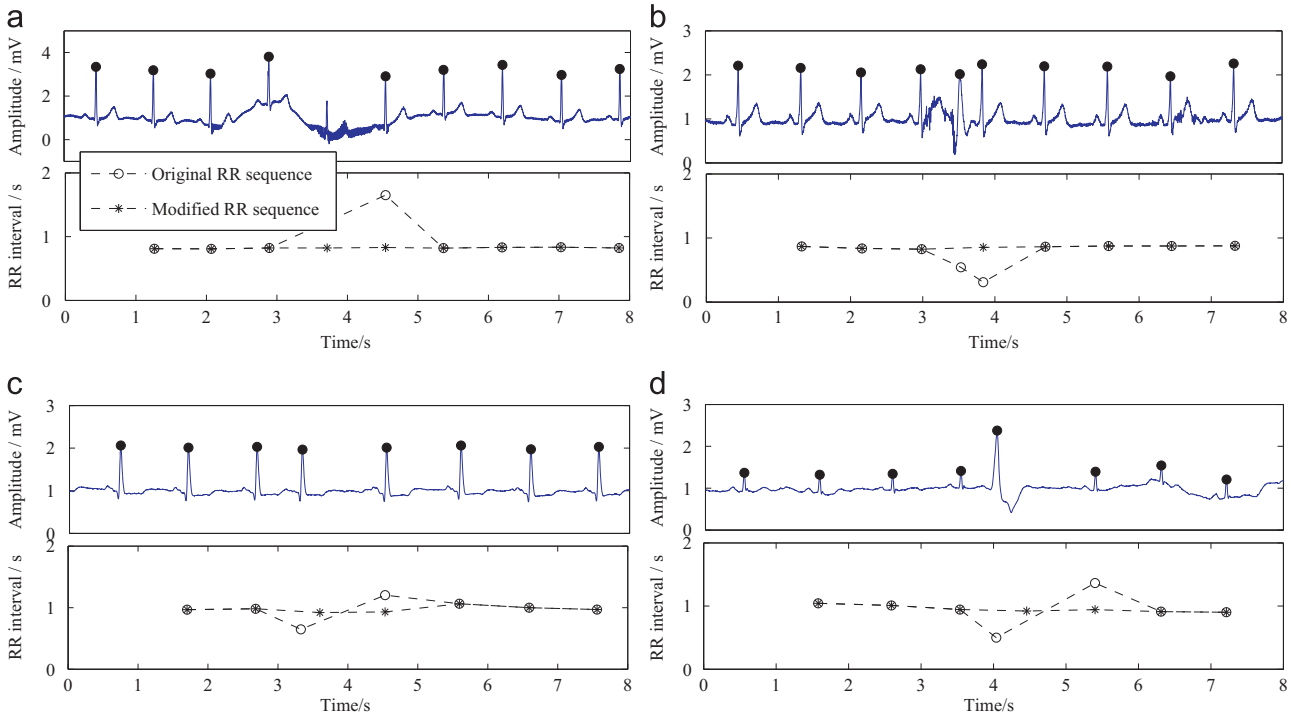

Fig. 1. Four types of anomalies in the ECG, (a) FN anomaly, (b) FP anomaly, (c) sVEB anomaly, and (d) VEB anomaly.

intervals. Each lower panel in Fig. 1 shows the original and modified RR sequence.

2.3. Construction of the simulation database

The simulation database was composed of identically-distributed random sequences, periodical sinusoidal sequences and non-linear logistic sequences. All sequences had the length $N=1000$. The random sequences were generated by the normally-distributed random number with the standard deviation (SD) of 1. The sinusoidal sequences were low-frequency sine waves sharing the same amplitudes with SD=1, but with different oscillation periods. The oscillation periods were 100, 50 and 20 points per cycle respectively. Given the sampling rate of 1000 Hz, the oscillation frequencies corresponded to $f1=10$ Hz, $f2=20$ Hz and $f3=50$ Hz. These sinusoidal sequences were simply named S_1, S_2 and S_3 and were shown in Fig. 2.

The logistic sequence was considered an approved non-linear chaotic sequence and generated by the following iteration function:

$$x(n+1)=\omega\times x(n)\times(1-x(n)), \tag{1}$$

where the initial value, $x(0)$, is in the range from 0.1 to 0.9 and ω is a constant parameter that determines the complexity of the sequence. As ω increased, the complexity of the sequence increased. Here, ω used the values of 3.6, 3.8 and 3.9, respectively, and the corresponding logistic sequences were recorded as L_1, L_2 and L_3.

2.4. Comparison of ApEn, SampEn, FuzzyEn and FuzzyMEn

In this study, four types of entropy measures were compared, ApEn [2,21], SampEn [11], FuzzyEn [16,22] and FuzzyMEn. The detailed calculation process of the FuzzyMEn is given in the Appendix A. Their relationships and differences were investigated through an in-depth theoretical analysis following a simulation test.

ApEn and SampEn usually exhibit a poor statistical stability, because the absolute two-state classifier of the Heaviside function is used and the selection of the threshold r is experience-based [16,22]. The similarity of a sequence segment $X(i)$ to another $X(j)$ is decided as follows:

$$\theta(d_{ij},r)=\begin{cases}1 & d_{ij}\le r\times\sigma_X\\ 0 & d_{ij}>r\times\sigma_X\end{cases}, \tag{2}$$

where d_{ij} denotes the distance between the two sequence segments $X(i)$ and $X(j)$. The Heaviside function is essentially a two-state classifier, as shown in Fig. 3. Only the sequence segments within the boundary ($d_{ij}\le r\times\sigma_X$) are treated equally, while those outside the boundary ($d_{ij}>r\times\sigma_X$) are neglected. This rigid two-state classifier property leads to instability in the similarity judgments of the sequence segments and poor statistical stability of the ApEn and SampEn.

The above limitation could be improved using Zadeh's concept of fuzzy sets theory [23], which provides a new measurement according to the "membership degree" that could be a gauge of the classifier. Using the fuzzy function μ_X, the conventional two-state classifier was replaced with a continuous membership degree between 0 and 1. The nearer the value of μ_X to 1, the higher is the membership degree of the sequence segment to the given class. This new evaluation protocol for the two sequence segments $X(i)$ and $X(j)$ can be symbolized as:

$$X(i),X(j)\xrightarrow{\mu_X(X(i),X(j))}[0,1] \tag{3}$$

In the FuzzyEn and FuzzyMEn, the above fuzzy sets theory was used to measure the similarity degree. Similar to [16], an exponential function $\exp(-(d_{ij}/r)^n)$ was used as the fuzzy function in this study. As shown in Fig. 3, the exponential function offers the smoothness and continuity for different values of r and there is no rigid boundary.

By setting the embedding dimension $m=2$ and the threshold $r=0.19$, 0.20 and 0.21, both the Heaviside and exponential functions were used to calculate the similarity degree of the sequence segments $X(m)$ and $X(n)$ to $X(i)$ (see Fig. 4). The similarity degrees after using the Heaviside function are as follows: if r was 0.19, they were between 0 and 0; with $r=0.20$ and 0.21, they changed to 0 and 1, 1 and 1, respectively. A sharp change was observed with increased r. However, the similarity degree with the exponential function changed relatively slowly

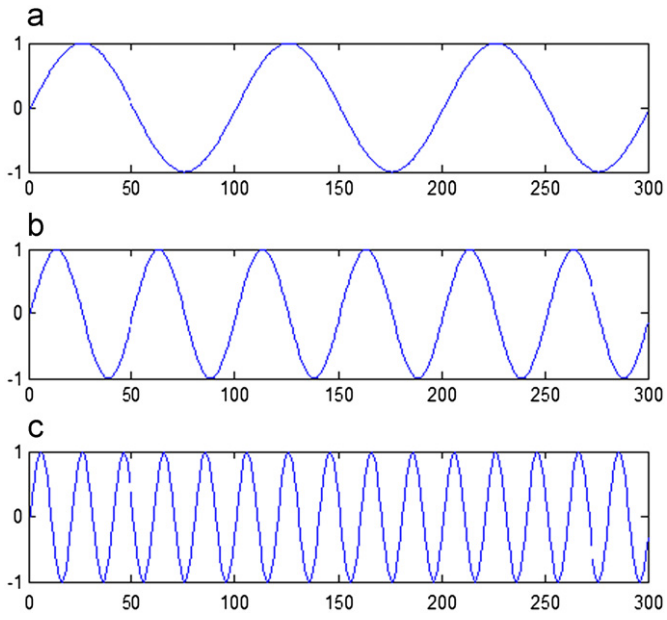

Fig. 2. Three sinusoidal sequences with the same oscillation amplitude and different oscillation frequency, (a) S_1 (10 Hz), (b) S_2 (20 Hz), and (c) S_3 (50 Hz).

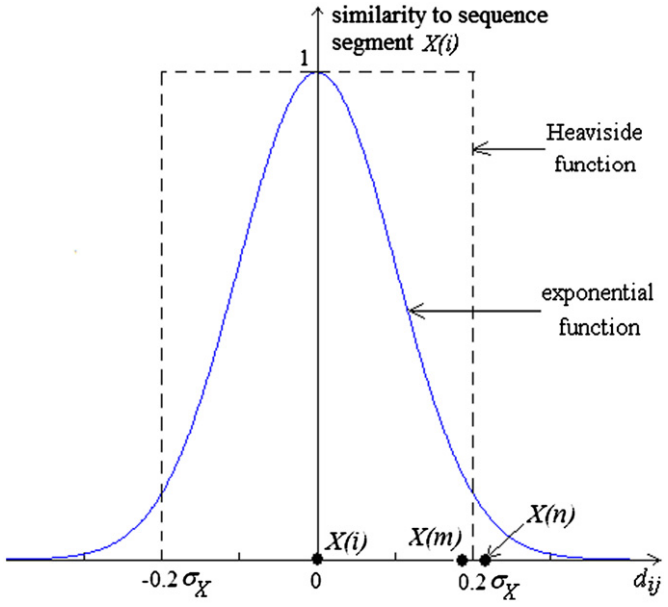

Fig. 3. The functions of similarity judgment for different sequence segments: the Heaviside function (broken line) and exponential function (real line). If the threshold r changes slightly around the edge of the Heaviside function, the results will be opposite. But the exponential function can avoid this problem.

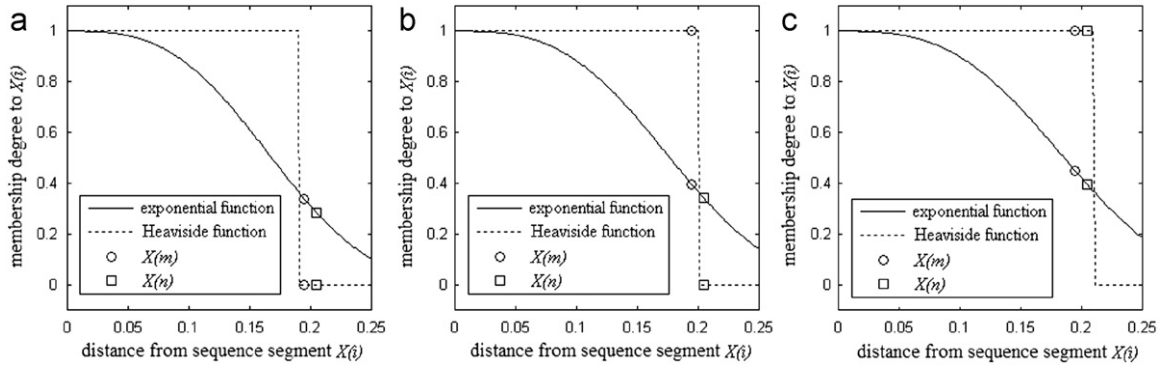

Fig. 4. The comparison of similarity degrees of sequence segments $X(m)$ and $X(n)$ to the given $X(i)$ when the r changes, (a) $r=0.19$, (b) $r=0.20$, and (c) $r=0.21$.

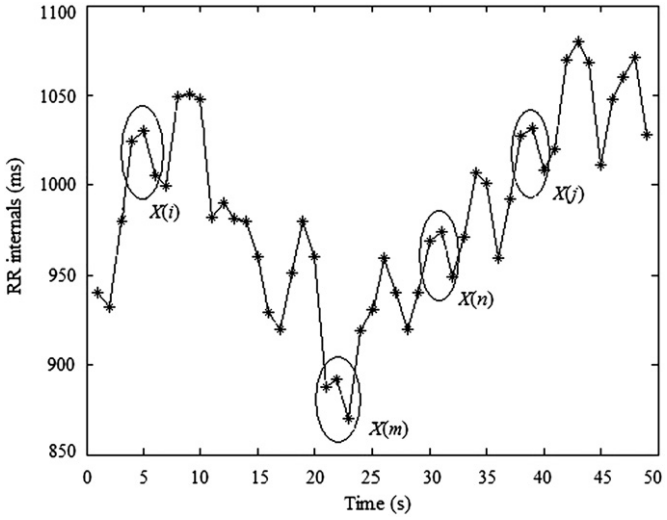

Fig. 5. The similarity of sequence segments both in local and global characteristics of a HRV sequence. The sequence segment $X(j)$ is similar to the given $X(i)$ both in local and global characteristics, while the sequence segment $X(m)$ and $X(n)$ present obvious distinctions in global characteristic.

with increased r. They were between 0.34 and 0.28 ($r=0.19$), 0.40 and 0.34 ($r=0.20$), 0.45 and 0.40 ($r=0.21$). Therefore, the FuzzyEn and FuzzyMEn could perform continuous results with an exponential function.

Despite the same theoretical foundation, the distinctions between the FuzzyEn and FuzzyMEn still exist. The FuzzyEn focuses only on the local characteristics of the sequence, without considering any global characteristics of the sequence. From the four example sequence segments $X(i)$, $X(m)$, $X(n)$ and $X(j)$ given in Fig. 5, a high-level similarity could be obtained using the FuzzyEn. However, the global fluctuations in the large scales have not been considered, such as the fluctuation between $X(i)$ and $X(m)$, and between $X(i)$ and $X(n)$. If both the local and global characteristics are considered, $X(j)$ is more similar to $X(i)$ than the other two segments. Our novel FuzzyMEn integrated both local and global characteristics and could reflect the entire complexity in a time series.

2.5. Consistency analysis of ApEn, SampEn, FuzzyEn and FuzzyMEn

Let a denote a parameter of the given entropy measure algorithm. Given two time series, X and Y, then the algorithm consistency is defined as follows: if there is an $a_0 \in a$, inducing the complexity of X is higher than Y, that is, $Algorithm_X(a_0) > Algorithm_Y(a_0)$, then for all $a_k \in a$, $Algorithm_X(a_k) > Algorithm_Y(a_k)$ will be true. This shows that the algorithm has a fine consistency. This can be generalized in the following equation:

$$\ni\ a_0 \in a \quad \text{if } Algorithm_X(a_0) > Algorithm_Y(a_0)$$
$$\Rightarrow \quad \forall a_k \in a\ Algorithm_X(a_k) > Algorithm_Y(a_k) \tag{4}$$

Sinusoidal sequences S_1, S_2 and S_3 were used for the test of consistency in this study.

2.6. Discrimination ability analysis of the FuzzyEn and FuzzyMEn

Let a denote a parameter of the given entropy measure algorithm. Given n sequences X_1, X_2, …, X_n, whose complexities increase orderly, if Eq. (5) will be true for all $a_k \in a$, this demonstrates that the algorithm has a fine discrimination ability.

$$Algorithm_{a_k}(X_1) < Algorithm_{a_k}(X_2) < \cdots < Algorithm_{a_k}(X_n) \tag{5}$$

Logistic sequences L_1, L_2 and L_3 were used for the test of discrimination ability in this study. Significant differences in the complexity of the logistic sequences L_1, L_2 and L_3 have been generally accepted. To construct a more exquisite sequence with a slightly different complexity, we add each L_1, L_2 and L_3 with the random sequence (denoted as R) and sinusoidal sequence S_1. R and S_1 have the same amplitude. The logistic sequences were extended as follows:

$$L_{ij} = L_i + A_j \times (S_1 + R) \tag{6}$$

where L_i ($i=1, 2, 3$) denotes the original logistic sequences; A_j ($j=1, 2, 3$) denotes the amplitude ratio between the sinusoidal and logistic sequence. In this study, A_j was set to be 0, 0.05 and 0.1, respectively. Fig. 6 shows the nine sequences L_{11}, L_{12}, L_{13}, L_{21}, L_{22}, L_{23}, L_{31}, L_{32} and L_{33} generated from Eq. (6). These nine sequences fell into three groups according to the original sequence L_i. The complexities of the extended sequences satisfy the following conditions, $L_{11} < L_{12} < L_{13}$, $L_{21} < L_{22} < L_{23}$, and $L_{31} < L_{32} < L_{33}$.

2.7. Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (V16, SPSS Inc., Chicago, IL, USA). Normal distribution and variance homogeneity tests were used for the assessment of different entropy measures between normal and heart failure groups. If the entropy measures passed the tests, the Independent Sample t-test was performed. If not, the Wilcoxon rank sum test was used. A box plot was then used to summarize the data in graphic form. All statistical results were considered as statistically significant for p-values of less than 0.05.

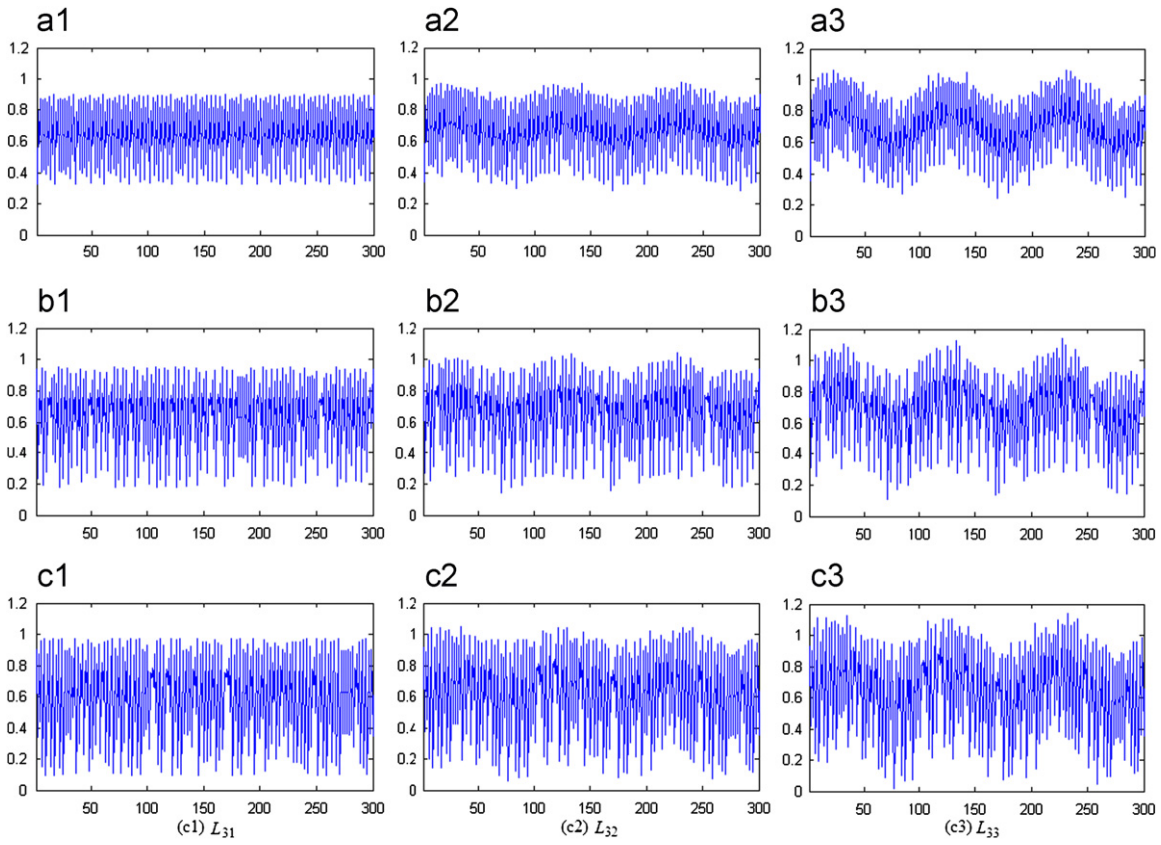

Fig. 6. Examples of nine sequences obtained from Eq. (6). Figures are listed as, (a1) L_{11}, (a2) L_{12}, (a3) L_{13}, (b1) L_{21}, (b2) L_{22}, (b3) L_{23}, (c1) L_{31}, (c2) L_{32}, and (c3) L_{33}.

3. Results

3.1. Consistency of the ApEn, SampEn, FuzzyEn and FuzzyMEn

The three sinusoidal sequences S_1, S_2 and S_3 used to test the consistency of the four entropy measures are given in Fig. 2. From S_1 to S_3, the oscillation frequency became large; the complexities of these three sequences were therefore different. The trends of the different entropy measures with r increasing from 0 to 1 are shown in Fig. 7. It can be clearly seen that the FuzzyEn and FuzzyMEn exhibited a better consistency compared to the ApEn and SampEn. If r was large enough, the ApEn and SampEn could exhibit the differences in the three sinusoidal sequences, but not when r fell below a certain value. The ApEn and SampEn could change abruptly with a small change of r, thus they had a poor consistency. However, no similar effects were found when using the FuzzyEn and FuzzyMEn. Therefore, the FuzzyEn and FuzzyMEn performed better in terms of smoothness and continuity with an increasing r.

3.2. Discrimination ability of the FuzzyEn and FuzzyMEn

The trends of the FuzzyEn and FuzzyMEn with r increasing from 0 to 0.4 are shown in Fig. 8. Each group of extended sequences showed an increased complexity, but the trend lines are blind in the groups analyzed using the FuzzyEn. In contrast, the trend lines in the FuzzyMEn groups was discerned separately. Therefore, in comparison with the FuzzyEn, FuzzyMEn performs better in the discrimination ability in the complexity differences.

3.3. HRV analysis using the ApEn, SampEn, FuzzyEn and FuzzyMEn

After applying the ApEn, SampEn, FuzzyEn and FuzzyMEn to the RR sequences of the heart failure and healthy control groups, the results of entropy measures are shown in Table 2. The two groups did not exhibit significant differences using the ApEn ($p=0.394$), SampEn ($p=0.288$) and FuzzyEn ($p=0.053$), but a significant difference was found when the FuzzyMEn ($p=0.032$) was used . The fuzzy-based entropy measures, particularly the FuzzyMEn, performed better in the classification between the heart failure and the healthy control subjects.

The box plots of four entropy measures are shown in Fig. 9. The difference in the two groups in the FuzzyMEn was relative larger than those in the other three entropies. It was noted that the distribution ranges of the different entropy measures in the heart failure group are larger than those in the healthy control group. One reason may be that the course of the heart failure is often accompanied by fatal arrhythmias, such as supraventricular ectopic beats, ventricular ectopic beats and even, ventricular fibrillation or atrial fibrillation. This can cause the acute fluctuations in the RR sequences. In addition, the RR sequence of the heart failure subject without arrhythmia had a regular change caused by the weakening of the regulatory functions of the autonomic nervous system. A more definite explanation will require physiological research in future to investigate the actual mechanisms.

4. Discussion and conclusion

In this study, a new entropy measure, named the FuzzyMEn, has been proposed for HRV analysis. It has been confirmed that

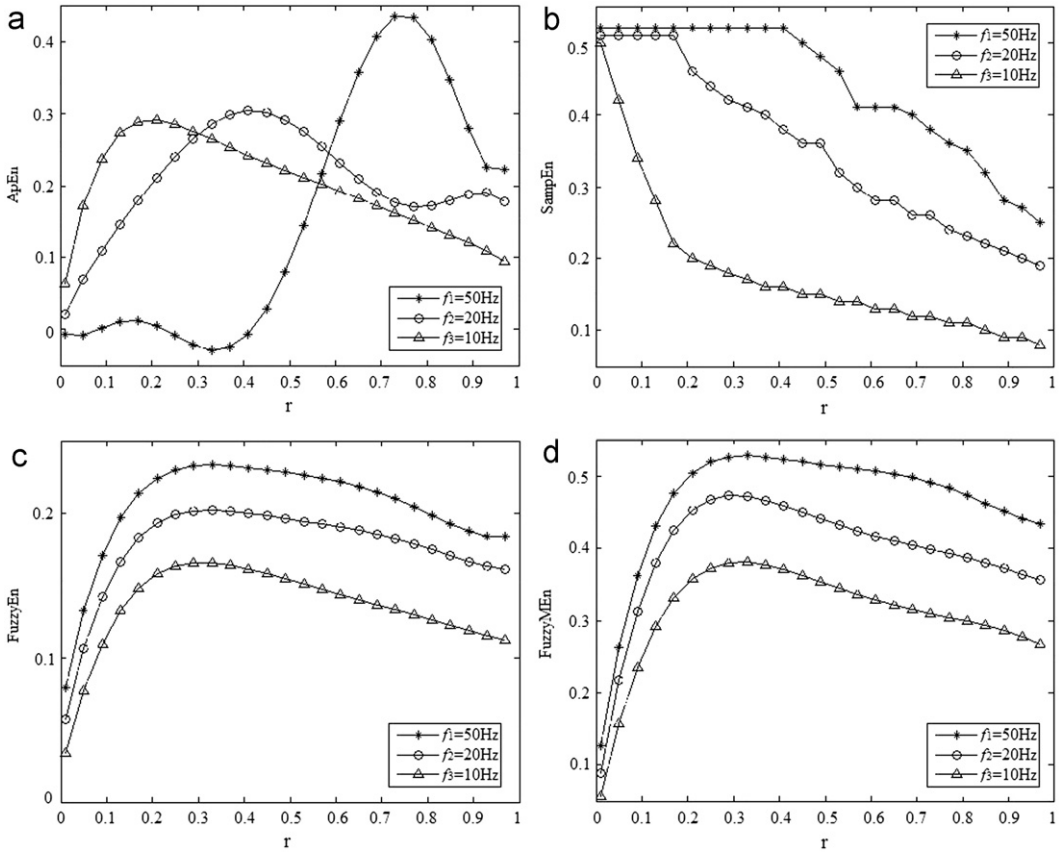

Fig. 7. Consistency of four entropy measures showing the trends with r increases from 0 to 1, (a) ApEn, (b) SampEn, (c) FuzzyEn, and (d) FuzzyMEn.

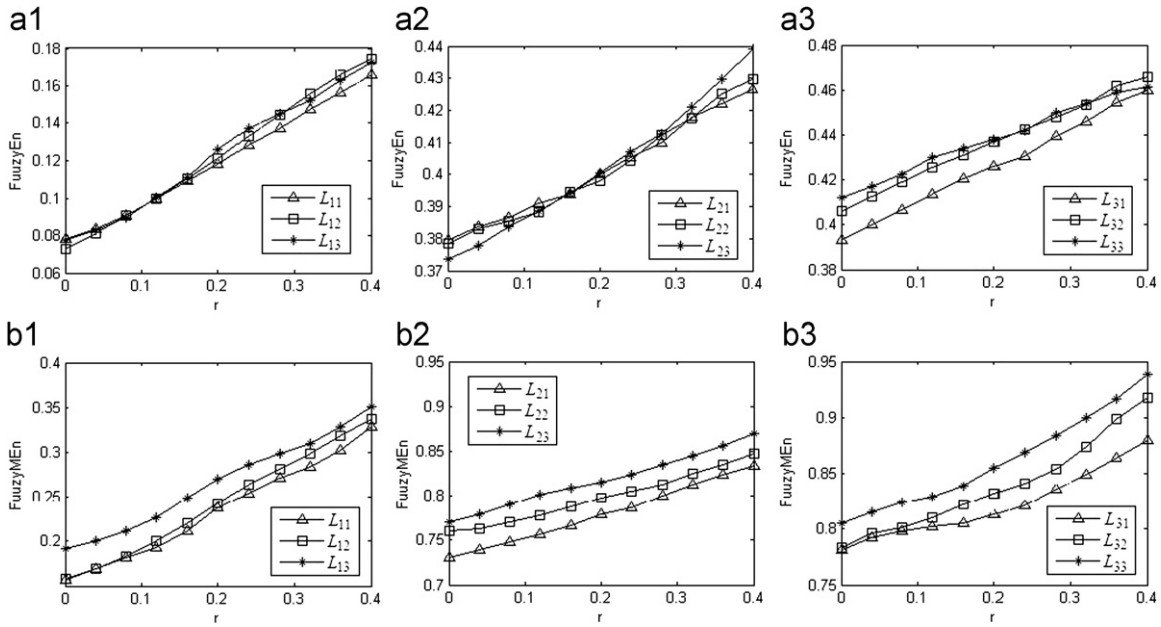

Fig. 8. Discrimination ability of FuzzyEn and FuzzyMEn showing the trends with r increases from 0 to 0.4. The results of FuzzyEn were showed in (a1)–(a3) while the results of FuzzyMEn were showed in (b1)–(b3).

Table 2
The results of ApEn, SampEn, FuzzyEn and FuzzyMEn between the heart failure and healthy control groups.

Entropy measures	Heart failure group				Healthy control group				*p*-values
	Mean	Maximum	Minimum	SD	Mean	Maximum	Minimum	SD	
ApEn	1.043	1.247	0.218	0.241	1.107	1.305	0.689	0.202	0.394
SampEn	0.869	1.026	0.459	0.216	0.797	0.936	0.433	0.188	0.288
FuzzyEn	0.976	1.173	0.687	0.187	1.052	1.218	0.775	0.190	0.053
FuzzyMEn	1.941	2.103	1.552	0.170	2.038	2.329	1.851	0.158	0.032

SD: Standard Deviations.

the HRV analysis is important in the early detection and quantitative evaluation of cardiovascular diseases [6,8]. The ApEn and SampEm are two popular entropy measures for the HRV because of the ease of their calculations and the small data requirements [11]. However, recent studies have found that these two entropy measures have a poor statistical stability, particularly in the analysis of the rapid physiological signals [12,13]. In this study, we investigated the inherent reasons and found that the two-state classifier property of the Heaviside function is the main reason for the poor statistical stability in the traditional entropy measures. Therefore, we applied the concept of the fuzzy theory and used the membership degree of the fuzzy function to describe the similarity of a given segment to a given class. This judgment standard exhibited the gentle boundary effect, and overcame the traditional rigid 0–1 judgment standard [22].

Subsequently, we compared the FuzzyMEn with the FuzzyEn algorithm. The FuzzyMEn employed both the fuzzy local measure entropy and the fuzzy global measure entropy to reflect the local and global characteristics. The entire simulation test confirmed that, in comparison with the ApEn and SampEn, the FuzzyEn and FuzzyMEn had a better consistency, and compared with the FuzzyEn, the FuzzyMEn had better discrimination ability. The detailed differences between the ApEn, SampEn, FuzzyEn and FuzzyMEn are summarized in Table 3. The result achieved in this study ensured confidence in researching the theoretical reason for the poor statistical stability and, hence, leads to new ways for exploring the inherent physiological mechanisms when using the entropy measure.

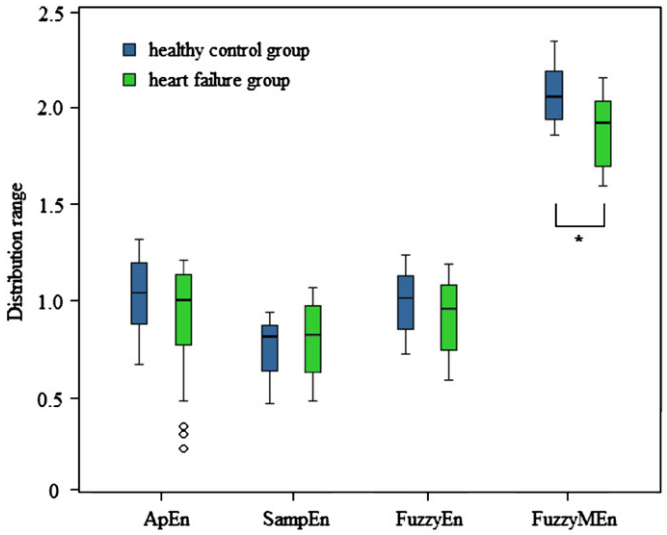

Fig. 9. The distribution ranges of ApEn, SampEn, FuzzyEn and FuzzyMEn between heart failure and healthy control groups. The symbol "*" means there is a significant difference between heart failure and healthy control groups.

Finally, the four entropy measures were compared by applying them to the clinical HRV signals. The distribution ranges of the different entropy measure in the heart failure group were also larger than those in the healthy control group. This could mainly be caused by fatal arrhythmias in the heart failure subjects [15]. The results also showed that the differences between the heart failure and the healthy control groups were relative larger from the FuzzyMEn than from the ApEn, SampEn or the FuzzyEn, confirming that the FuzzyMEn had a better performance in distinguishing the heart failure subjects from the healthy control ones. This indicated that the FuzzyMEn could be an effective method for the clinical HRV application.

5. Summary

It has been confirmed that heart rate variability (HRV) analysis is important in the early detection and quantitative evaluation of heart diseases and the entropy measures are important methods for the HRV analysis. However, either the traditional measures, such as Approximate Entropy (ApEn) and Sample Entropy (SampEn) or the recent fuzzy entropy (FuzzyEn) must be considered as validated before the clinical application. This paper aimed to investigate the limitations of the entropy measures mentioned above and proposed a new entropy measure, named the Fuzzy Measure Entropy (FuzzyMEn) for the clinical HRV analysis.

Because the FuzzyMEn was constructed with the membership degree of a fuzzy function instead of using the '0–1' judgment of the Heaviside function that is typically used in the ApEn and SampEn, it improved the poor statistical stability of the ApEn and SampEn. In addition, our novel FuzzyMEn employed both the fuzzy local measure entropy and the fuzzy global measure entropy to reflect the entire complexity in the time series. The simulation results showed that, in comparison with the ApEn and SampEn, the FuzzyEn and FuzzyMEn had a better consistency and, compared with the FuzzyEn, the FuzzyMEn had better discrimination ability.

To test the clinical validity of the novel FuzzyMEn, 120 subjects were enrolled (60 heart failure patients and 60 normal subjects). The statistical differences in the four different entropy measures (ApEn, SampEn, FuzzyEn and FuzzyMEn) between the heart failure and healthy control groups were analyzed. The Independent Sample *t*-test results showed that the ApEn ($p=0.394$) and the SampEn ($p=0.288$) had no statistical differences between the two groups, with the FuzzyEn ($p=0.053$) having a borderline result; while the FuzzyMEn ($p=0.032$) had a significant difference. This result showed that, compared to the ApEn, SampEn and even FuzzyEn, the FuzzyMEn had a better performance in distinguishing the heart failure subjects from the healthy control subjects. This indicated that the FuzzyMEn could be an effective method for the clinical HRV application.

Table 3
The detailed differences of ApEn, SampEn, FuzzyEn and FuzzyMEn.

Difference aspects	ApEn	SampEn	FuzzyEn	FuzzyMEn
Sets theory	classical	classical	fuzzy	fuzzy
Judgment a sequence segment to a given class	0–1 judgment	0–1 judgment	membership degree	membership degree
Judgment function	Heaviside function	Heaviside function	fuzzy function	fuzzy function
Is self-matching calculated?	yes	no	no	no
Is a bias estimation?	yes	no	no	no
Description characteristic	global	global	local	local and global
Algorithm consistency	relative poor	relative poor	relative fine	relative fine
Algorithm discrimination ability	relative poor	relative poor	relative moderate	relative fine

Conflict of interest statement

None declared.

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Appendix A. The calculation process of the fuzzy measure entropy (FuzzyMEn)

The algorithm of the FuzzyMEn was inspired by the study of Chen et al., in which the fuzzy sets were introduced to improve the statistical stability. The detailed description for the FuzzyMEn is shown as follows:

(1) Given a sequence $X=\{x_1, x_2, \ldots, x_N\}$, the embedding dimension m is set to be a constant 2.0. In the following description, the sequence X is assumed as the RR sequence. Thus, the element x_i ($i=1,2,\ldots,N$) of sequence X is the RR interval, with the unit of a millisecond (ms). Then, from the first element of X, choose m consecutive x values to form a sequence segment $X_m(i)=[x_i, x_{i+1}, \ldots, x_{i+m-1}]$, where the i is from 1 to $N-m+1$. The total number of the sequence segments is $N-m+1$. The calculation process of the FuzzyMEn excludes self-matches and considers only the first $N-m$ sequence segments. Let x_{0i} denotes the mean value of the sequence segment $X_m(i)$.

(2) The local sequence segment $XL_m(i)$ is defined by removing the mean of the sequence segment $X_m(i)$ from the $X_m(i)$, i.e. $XL_m(i)=[x_i-x_{0i}, x_{i+1}-x_{0i}, \ldots, x_{i+m-1}-x_{0i}]$. The global sequence segment $XF_m(i)$ is defined by removing the mean of the entire sequence X from the $X_m(i)$, that is, $XF_m(i)=[x_i-x_{mean}, x_{i+1}-x_{mean}, \ldots, x_{i+m-1}-x_{mean}]$, where the x_{mean} denotes the mean value of the sequence X. Then, the distance of the local sequence segments between $XL_m(i)$ and $XL_m(j)$ can be denoted as $dL_m(i,j)$; at the same time, the distance of the global sequence segments between $XF_m(i)$ and $XF_m(j)$ can be denoted as $dF_m(i,j)$. The $dL_m(i,j)$ and $dF_m(i,j)$, also with the unit in ms, are calculated as follows:

$$\begin{cases} dL_m(i,j)=d[XL_m(i),XL_m(j)]=\max\left|(x_{i+k}-x_{0i})-(x_{j+k}-x_{0j})\right| & 0\le k\le m-1 \\ dF_m(i,j)=d[XF_m(i),XF_m(j)]=\max\left|(x_{i+k}-x_{mean})-(x_{j+k}-x_{mean})\right| & 0\le k\le m-1 \end{cases}. \quad (A1)$$

(3) Then, the local fuzzy function $\mu_L(dL_m(i,j),n_L,r_L)$ and global fuzzy function $\mu_F(dF_m(i,j),n_F,r_F)$ can be calculated as

$$\begin{cases} \mu_L(dL_m(i,j),n_L,r_L)=\exp(-(dL_m(i,j)/r_L)^{n_L}) \\ \mu_F(dF_m(i,j),n_F,r_F)=\exp\left(-(dF_m(i,j)/r_F)^{n_F}\right), \end{cases} \quad (A2)$$

where, a typical exponential function is used for both the local and global fuzzy functions. This is because that exponential function can provide smoothness and continuity for different thresholds. The r_L and r_F denote their thresholds, respectively. In this study, the r_L and r_F were set to be 0.2 times the SD of the sequences. The n_L and n_F are their weights of sequence segments' similarity. If n_L or n_F is higher than 1, the similarity of the close sequence segments will be weighted, but that of the far sequence segments will be unweighted; if n_L or n_F is lower than 1, an inverse effect performs. If n_L or n_F were large enough or close to infinity, the exponential function in equation A3 will be reduced to the Heaviside function. In this study, the n_L and n_F were set to be 3 and 2. The local similarity degree $DL_m(i,j)$ between $XL_m(i)$ and $XL_m(j)$ and the global similarity degree $DF_m(i,j)$ between $XF_m(i)$ and $XF_m(j)$ can be calculated as follows:

$$\begin{cases} DL_m(i,j)=\mu_L(dL_m(i,j),n_L,r_L)=\exp(-(dL_m(i,j)/r_L)^{n_L}) \\ DF_m(i,j)=\mu_F(dF_m(i,j),n_F,r_F)=\exp\left(-(dF_m(i,j)/r_F)^{n_F}\right). \end{cases} \quad (A3)$$

For all $1\le i,j\le N-m$, the mean values of $DL_m(i,j)$ and $DF_m(i,j)$ are described as $\varphi L_m(n_L,r_L)$ and $\varphi F_m(n_F,r_F)$ and can be calculated as follows:

$$\begin{cases} \phi L_m(n_L,r_L)=\frac{1}{N-m}\sum_{i=1}^{N-m}\left(\frac{1}{N-m-1}\sum_{j=1,j\ne i}^{N-m}DL_m(i,j)\right) \\ \phi F_m(n_F,r_F)=\frac{1}{N-m}\sum_{i=1}^{N-m}\left(\frac{1}{N-m-1}\sum_{j=1,j\ne i}^{N-m}DF_m(i,j)\right) \end{cases}. \quad (A4)$$

(4) Then $XL_{m+1}(i)$ and $XF_{m+1}(i)$ are constructed with a length to $m+1$. The steps from (1) to (3) should be repeated for the calculation of $\phi L_{m+1}(n_L,r_L)$ and $\phi F_{m+1}(n_F,r_F)$.

(5) Then fuzzy local measure entropy *FuzzyLMEn* and the fuzzy global measure entropy *FuzzyFMEn* are defined as follows:

$$\begin{cases} FuzzyLMEn(m,n_L,r_L,N)=\ln\phi L_m(n_L,r_L)-\ln\phi L_{m+1}(n_L,r_L) \\ FuzzyFMEn(m,n_F,r_F,N)=\ln\phi F_m(n_F,r_F)-\ln\phi F_{m+1}(n_F,r_F) \end{cases}. \quad (A5)$$

Finally, the FuzzyMEn of the sequence X is calculated as follows:

$$FuzzyMEn(m,n_L,r_L,n_F,r_F,N)=FuzzyLMEn(m,n_L,r_L,N)+FuzzyFMEn(m,n_F,r_F,N) \quad (A6)$$

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