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Measuring synchronization in coupled simulation and coupled cardiovascular time series: A comparison of different cross entropy measures

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ABSTRACT

Synchronization provides an insight into underlying the interaction mechanisms among the bivariate time series and has recently become an increasing focus of interest. In this study, we proposed a new cross entropy measure, named cross fuzzy measure entropy (C-FuzzyMEn), to detect the synchronization of the bivariate time series. The performances of C-FuzzyMEn, as well as two existing cross entropy measures, i.e., cross sample entropy (C-SampEn) and cross fuzzy entropy (C-FuzzyEn), were first tested and compared using three coupled simulation models (i.e., coupled Gaussian noise, coupled MIX(p) and coupled Henon model) by changing the time series length, the threshold value for entropy and the coupling degree. The results from the simulation models showed that compared with C-SampEn, C-FuzzyEn and C-FuzzyMEn had better statistical stability and compared with C-FuzzyEn, C-FuzzyMEn had better discrimination ability. These three measures were then applied to a cardiovascular coupling problem, synchronization analysis for RR and pulse transit time (PTT) series in both the normal subjects and heart failure patients. The results showed that the heart failure group had lower cross entropy values than the normal group for all three cross entropy measures, indicating that the synchronization between RR and PTT time series increases in the heart failure group. Further analysis showed that there was no significant difference between the normal and heart failure groups for C-SampEn (normal 2.13 ± 0.37 vs. heart failure 2.07 ± 0.16, $P = 0.36$). However, C-FuzzyEn had significant difference between two groups (normal 1.42 ± 0.25 vs. heart failure 1.31 ± 0.12, $P < 0.05$). The statistical difference was larger for two groups when performing C-FuzzyMEn analysis (normal 2.40 ± 0.26 vs. heart failure 2.15 ± 0.13, $P < 0.01$).

1. Introduction

Measuring the coupling relationship between two cardiovascular time series, as well as named synchronization measurement, has been an increasing focus of interest in clinical research [1–3]. It is a prerequisite for the understanding of the complexity of underlying signal generating mechanisms and thus for the detection of cardiovascular disorders and ongoing perturbations to the circulation system [4]. Traditionally, the cross-correlation in the time domain as well as the cross-spectrum or coherency in the frequency domain has been used for synchronization measurement [5]. These techniques are able to give the linear relationship between two systems. However, they are not suitable for characterizing the real cardiovascular signals, which are non-stationary and inherently nonlinear [6].

In recent years, entropy-based measures, such as the typical approximate entropy (ApEn) and sample entropy (SampEn), have been widely used for the physiological time series analysis to explore their inherent complexity. And their generalized forms, cross-approximate entropy (C-ApEn) [7] and cross-sample entropy (C-SampEn) [8], were used for the synchronization test [9–12]. For fixed bivariate time series $x(i)$ and $y(i) (1 \le i \le N)$, C-ApEn measures the conditional regularity or frequency of y-patterns similar to a

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given x-pattern of embedding dimension m within the threshold value r. When coupling in two time series is tight, patterns in one time series cause predictable patterns in the other one, inducing the low C-ApEn value [8,10]. In the calculating process of C-ApEn, each vector must match at least one vector when embedding dimension comes from m to $m+1$ [6,13]. However, there is no self-matching in C-ApEn, and thus there is no assurance that the probability will be defined. Moreover, C-ApEn is not direction independent, i.e., C-ApEn(m, r, N)($y|x$) does not equal to C-ApEn(m, r, N)($x|y$), which brings difficulties to the practical application. In order to handle these potential difficulties, Richman and Moorman [14] proposed the SampEn method instead of counting the self-matching of the vectors and generalized it to C-SampEn for bivariate time series. Compared with the fact that C-ApEn was a biased evaluation and was sensitive to noisy, C-SampEn could reduce the bias and showed better relative consistency than C-ApEn. Meanwhile, C-SampEn is direction independent, i.e., C-SampEn(m, r, N)($y|x$) equals to C-SampEn(m, r, N)($x|y$). Thus it has been used as an alternative nonlinear statistic to analyze physiological time series [8,10].

Similar to ApEn and SampEn, in both C-ApEn and C-SampEn, the similarity of two vectors is judged using the Heaviside function, i.e., binary classification, which makes the boundary very rigid. Only the vectors within the threshold r are treated equally, whereas the vectors outside of this threshold r are ignored. This rigid boundary may induce to the abrupt changes of entropy values when the threshold r changes slightly, and it may even fail to define the entropy if no vector-matching could be found for this very small threshold r [14]. To enhance the statistical stability, a new entropy measure, named fuzzy entropy (FuzzyEn), has been proposed for univariate time series analysis by emerging the notion of entropy with the fuzzy theory [15,16]. FuzzyEn employed a fuzzy function to replace the Heaviside function to make a gradually varied entropy value when the threshold r monotonously changes. Its generalized form, cross fuzzy entropy (C-FuzzyEn), has also been developed for the bivariate time series analysis [6,10].

However, no matter for FuzzyEn or C-FuzzyEn, the local vector similarity is overemphasized. Thus both of them might give inaccurate results for some slow signals since they both neglected the signal global characteristics. In our previous work, we developed a novel fuzzy measure entropy (i.e., FuzzyMEn) that combined both the local and global similarity, and FuzzyMEn has shown better algorithm discrimination ability than FuzzyEn [17,18]. In this study, we generalized the FuzzyMEn method for the bivariate time series analysis and compared its performance with C-SampEn and C-FuzzyEn for quantifying the synchronization in both coupled simulation and coupled cardiovascular time series. We defined this new synchronization measure as cross fuzzy measure entropy (i.e., C-FuzzyMEn).

The rest of the paper is organized as follows: Section 2 gives the definition of C-SampEn, C-FuzzyEn and C-FuzzyMEn to allow the detailed comparison and inspection of these three cross entropy measures to be observed. Section 3 discusses the experimental design where three coupled simulation models (i.e., coupled Gaussian noise, coupled MIX(p) and coupled Henon signals) and two cardiovascular time series (RR interval and pulse transit time (PTT) time series) from both the normal and heart failure subjects were constructed for the cross entropy analysis. In Section 4, the results of cross entropy measures from both coupled simulation and coupled cardiovascular time series are provided. Finally, Section 5 draws the discussions and identifies the future work.

2. Cross entropy measures

In this section, we first give a brief introduction for C-SampEn and C-FuzzyEn, and then describe the definition of C-FuzzyMEn.

2.1. Cross sample entropy (C-SampEn)

The calculation process of C-SampEn was summarized as follows [8,14]:

The time series $x(i)$ and $y(i)(1 \le i \le N)$ were first normalized to have a mean value of 0 and standard deviation of 1. Then given the input parameters m and r, the vector sequences X_i^m and Y_j^m were formed as follows:

$$\begin{aligned} X_i^m &= \left\{x(i), x(i+1), \ldots, x(i+m-1)\right\} \\ Y_j^m &= \left\{y(j), y(j+1), \ldots, y(j+m-1)\right\} \end{aligned} \quad 1 \le i, \quad j \le N-m \tag{1}$$

These vectors represent m consecutive x and y values, respectively. Then the distance between X_i^m and Y_j^m based on the maximum absolute difference is defined as:

$$d_{i,j}^m = d\left[X_i^m, Y_j^m\right] = \max_{k=0}^{m-1} \left|x(i+k) - y(j+k)\right| \tag{2}$$

For each X_i^m, denote $B_i^m(r)$ as $(N-m)^{-1}$ times the number of Y_j^m $(1 \le j \le N-m)$ that meets $d_{i,j}^m \le r$. Similarly, set $A_i^m(r)$ is $(N-m)^{-1}$ times the number of Y_j^{m+1} that meets $d_{i,j}^{m+1} \le r$ for all $1 \le j \le N-m$.

Finally C-SampEn is defined as

$$C - SampEn(m, r, N) = -\ln\left(\frac{\sum_{i=1}^{N-m} A_i^m(r)}{\sum_{i=1}^{N-m} B_i^m(r)}\right) \tag{3}$$

2.2. Cross fuzzy entropy (C-FuzzyEn)

In both C-ApEn and C-SampEn, the decision rule for vector similarity is very rigid because X_i^m and Y_j^m are considered as similar vectors only when $\max_{k=0}^{m-1} \left|x(i+k) - y(j+k)\right| \le r$. In the definition of C-FuzzyEn, the vectors X_i^m and Y_j^m are formed as follows:

$$\begin{aligned} X_i^m &= \left\{x(i), x(i+1), \ldots, x(i+m-1)\right\} - \bar{x}(i) \\ Y_j^m &= \left\{y(j), y(j+1), \ldots, y(j+m-1)\right\} - \bar{y}(j) \end{aligned} \quad 1 \le i, \quad j \le N-m \tag{4}$$

These vectors X_i^m and Y_j^m also represent m consecutive x and y values respectively but removing the local baseline $\bar{x}(i)$ and $\bar{y}(j)$, which are defined as:

$$\begin{aligned} \bar{x}(i) &= \frac{1}{m}\sum_{k=0}^{m-1} x(i+k) \\ \bar{y}(j) &= \frac{1}{m}\sum_{k=0}^{m-1} y(j+k) \end{aligned} \quad 1 \le i, \quad j \le N-m \tag{5}$$

Calculate the distance between X_i^m and Y_j^m also using the maximum absolute difference:

$$d_{i,j}^m = d\left[X_i^m, Y_j^m\right] = \max_{k=0}^{m-1} \left|(x(i+k) - \bar{x}(i)) - (y(j+k) - \bar{y}(j))\right| \tag{6}$$

Given vector similarity weight n and threshold r, calculate the similarity degree $D_{i,j}^m(n, r)$ between X_i^m and Y_j^m by a fuzzy function $\mu(d_{i,j}^m, n, r)$:

$$D_{i,j}^m(n, r) = \mu(d_{i,j}^m, n, r) = \exp\left(-\frac{(d_{i,j}^m)^n}{r}\right) \tag{7}$$

Define the function $\phi^m(n,r)$ as:

$$\phi^m(n,r)=\frac{1}{N-m}\sum_{i=1}^{N-m}\left(\frac{1}{N-m}\sum_{j=1}^{N-m}D_{i,j}^m(n,r)\right) \tag{8}$$

Similarly, define the function $\phi^{m+1}(n,r)$ for $m+1$ vectors X_i^{m+1} and Y_j^{m+1} $(1\le i,j\le N-m)$:

$$\phi^{m+1}(n,r)=\frac{1}{N-m}\sum_{i=1}^{N-m}\left(\frac{1}{N-m}\sum_{j=1}^{N-m}D_{i,j}^{m+1}(n,r)\right) \tag{9}$$

Then C-FuzzyEn is finally defined by:

$$\text{C-FuzzyEn}(m,n,r,N)=-\ln\left(\phi^{m+1}(n,r)/\phi^m(n,r)\right) \tag{10}$$

2.3. Cross fuzzy measure entropy (C-FuzzyMEn)

In our previous work [17,18], we reported that the FuzzyEn only focuses on the local waveform characteristics of the time series by removing the local baseline $\bar{x}(i)$ and $\bar{y}(j)$, without considering any global signal characteristics. So we proposed the FuzzyMEn method to integrate both the local and global signal characteristics. Herein, we generalized the FuzzyMEn to C-FuzzyMEn for the bivariate time series analysis.

For two normalized time series $x(i)$ and $y(i)(1\le i\le N)$, given the input parameters m and r, first form the local vector sequences XL_i^m and YL_j^m and the global vector sequences XG_i^m and YG_j^m:

$$\begin{aligned}
XL_i^m&=\{x(i),x(i+1),\ldots,x(i+m-1)\}-\bar{x}(i)\\
YL_j^m&=\{y(j),y(j+1),\ldots,y(j+m-1)\}-\bar{y}(j)\\
XG_i^m&=\{x(i),x(i+1),\ldots,x(i+m-1)\}-\bar{x}\\
YG_j^m&=\{y(j),y(j+1),\ldots,y(j+m-1)\}-\bar{y}
\end{aligned}\quad 1\le i,\quad j\le N-m \tag{11}$$

where $\bar{x}(i)$ and $\bar{y}(j)$ are the local baseline with the same definition as illustrated in Formula (5) and $\bar{x}$ and $\bar{y}$ are the global mean values of time series $x(i)$ and $y(i)$: $\bar{x}=1/N\sum_{i=1}^{N}x(i)$ and $\bar{y}=1/N\sum_{i=1}^{N}y(i)$.

Then the distance between the local vector sequences XL_i^m and YL_j^m and the distance between the global vector sequences XG_i^m and YG_j^m are defined respectively as follows:

$$\begin{aligned}
dL_{i,j}^m&=d\left[XL_i^m,YL_j^m\right]=\max_{k=0}^{m-1}\left|(x(i+k)-\bar{x}(i))-(y(j+k)-\bar{y}(j))\right|\\
dG_{i,j}^m&=d\left[XG_i^m,YG_j^m\right]=\max_{k=0}^{m-1}\left|(x(i+k)-\bar{x})-(y(j+k)-\bar{y})\right|
\end{aligned} \tag{12}$$

Given the local vector similarity weight n_L and the local threshold r_L, as well as the global vector similarity weight n_G and the global threshold r_G, calculate the similarity degree $DL_{i,j}^m(n_L,r_L)$ between the local vectors XL_i^m and YL_j^m by the fuzzy function $\mu L\left(dL_{i,j}^m,n_L,r_L\right)$, as well as calculate the similarity degree $DG_{i,j}^m(n_G,r_G)$ between the global vectors XG_i^m and YG_j^m by the fuzzy function $\mu G\left(dG_{i,j}^m,n_G,r_G\right)$:

$$\begin{aligned}
DL_{i,j}^m(n_L,r_L)&=\mu L(dL_{i,j}^m,n_L,r_L)=\exp\left(-\frac{(dL_{i,j}^m)^{n_L}}{r_L}\right)\\
DG_{i,j}^m(n_G,r_G)&=\mu G(dG_{i,j}^m,n_G,r_G)=\exp\left(-\frac{(dG_{i,j}^m)^{n_G}}{r_G}\right)
\end{aligned} \tag{13}$$

Define the function $\phi L^m(n_L,r_L)$ and $\phi G^m(n_G,r_G)$ as:

$$\begin{aligned}
\phi L^m(n_L,r_L)&=\frac{1}{N-m}\sum_{i=1}^{N-m}\left(\frac{1}{N-m}\sum_{j=1}^{N-m}DL_{i,j}^m(n_L,r_L)\right)\\
\phi G^m(n_G,r_G)&=\frac{1}{N-m}\sum_{i=1}^{N-m}\left(\frac{1}{N-m}\sum_{j=1}^{N-m}DG_{i,j}^m(n_G,r_G)\right)
\end{aligned} \tag{14}$$

Similarly, define the function $\phi L^{m+1}(n_L,r_L)$ for $m+1$ vectors XL_i^{m+1} and YL_j^{m+1} and the function $\phi G^{m+1}(n_G,r_G)$ for $m+1$ vectors XG_i^{m+1} and YG_j^{m+1}:

$$\begin{aligned}
\phi L^{m+1}(n_L,r_L)&=\frac{1}{N-m}\sum_{i=1}^{N-m}\left(\frac{1}{N-m}\sum_{j=1}^{N-m}DL_{i,j}^{m+1}(n_L,r_L)\right)\\
\phi G^{m+1}(n_L,r_L)&=\frac{1}{N-m}\sum_{i=1}^{N-m}\left(\frac{1}{N-m}\sum_{j=1}^{N-m}DG_{i,j}^{m+1}(n_G,r_G)\right)
\end{aligned} \tag{15}$$

Then the cross fuzzy local measure entropy (C-FuzzyLMEn) and the cross fuzzy global measure entropy (C-FuzzyGMEn) are defined by:

$$\begin{aligned}
\text{C-FuzzyLMEn}(m,n_L,r_L,N)&=-\ln\left(\frac{\phi L^{m+1}(n_L,r_L)}{\phi L^m(n_L,r_L)}\right)\\
\text{C-FuzzyGMEn}(m,n_G,r_G,N)&=-\ln\left(\frac{\phi G^{m+1}(n_G,r_G)}{\phi G^m(n_G,r_G)}\right)
\end{aligned} \tag{16}$$

Finally, the C-FuzzyMEn of the time series $x(i)$ and $y(i)$ is calculated as follows:

$$\begin{aligned}
\text{C-FuzzyMEn}(m,n_L,r_L,n_G,r_G,N)=&\ \text{C-FuzzyLMEn}(m,n_L,r_L,N)\\
&+\text{C-FuzzyGMEn}(m,n_G,r_G,N)
\end{aligned} \tag{17}$$

3. Experiment design

3.1. Coupled simulation signals

Coupled Gaussian noise, coupled MIX(p) and coupled Henon models are used as the simulation signals for testing the performances of the three cross entropy measures. The coupled Gaussian noise model could produce the pure white noise. The coupled MIX(p) model is regarded as a composite signal composing of noise and certain signals. The coupled Henon model could generate the typical nonlinear signals [19].

3.1.1. Coupled Gaussian noise model

The coupled Gaussian noise signals, x and y, were generated by mixing the common Gaussian noise n_1 with two independent white noises n_2 and n_3 [1],

$$\begin{aligned}
x&=cn_1+(1-c)n_2\\
y&=cn_1+(1-c)n_3
\end{aligned} \tag{18}$$

where c is the coupling degree.

3.1.2. Coupled MIX(p) model

The MIX(p) model is a sinusoid signal of N points, where $N\times p$ (p is the probability parameter whose value is between 0 and 1) random chosen points are replaced with the random noise. The detail description for MIX(p) model is summarized in [20]. The coupled MIX(p) signals, x and y, were generated by mixing one MIX(p) process with the other two so as to simulate the real world systems which contain a large proportion of low-frequency trend defined as:

$$x = c\text{MIX}(p_1) + (1-c)\,\text{MIX}(p_2)$$
$$y = c\text{MIX}(p_1) + (1-c)\,\text{MIX}(p_3) \tag{19}$$

where c is the coupling degree, p_1, p_2 and p_3 are probability parameters with a value of 0.3, 0.5 and 0.7, respectively.

3.1.3. Coupled Henon model

Mathematically, the coupled Henon signals, x and y, can be generated by the following iterations [19]:

$$\begin{aligned} \text{For}\quad x \quad & \begin{cases} x_{n+1} = 1.4 - x_n^2 + b_x u_n \\ u_{n+1} = x_n \end{cases} \\ \text{For}\quad y \quad & \begin{cases} y_{n+1} = 1.4 - \left(c x_n y_n + (1-c) y_n^2\right) + b_y v_n \\ v_{n+1} = y_n \end{cases} \end{aligned} \tag{20}$$

where c is the coupling degree, b_x and b_y are both set as 0.3 to yield the identical systems.

For the above three coupled simulation signals, the time series length N and coupling degree c were used as the control parameters to test the performances of the three measures. In addition, previous research has shown that the threshold value r for entropy calculation could have a great impact on entropy values [9,13]. So the threshold value r was also selected as a control parameter.

We used the time series length N as the first control parameter to test what extent the different cross entropy measures are influenced by this parameter and then to select a suitable length for the following analysis. Entropy methods are suitable to analyze the short-term time series and are usually applied to several hundreds of sequences [7,13,14,20]. Herein, the time series length N was set from 50 to 800 with a step of 50. The threshold value r was set as the second control parameter to investigate whether the results of different cross entropy measures have consistency for distinguishing the different coupled signals under the setting of different threshold r values. For the normalized time series, the recommended r value is usually between 0.1 and 0.25 [13,14,16,20]. Herein, the threshold r was set from 0.05 to 0.8 with a step of 0.05. It is worth to note that for C-FuzzyMEn, the values of the local threshold r_L and the global threshold r_G are always set equal to the r. In addition, the most common choice for the embedding dimension parameter is $m=2$, as it was recommended by Pincus and Goldberger for ApEn [21], by Yentes et al. for SampEn [22], and confirmed by [23]. Recently, Aktaruzzaman and Sassi suggested that $m=1$ could also get the good performance for very short series ($N=75$) when employing the autoregressive parametric estimation method for SampEn [24]. We also perform the comparison between $m=1$ and $m=2$ to explore the effect of the threshold parameter r on different cross entropies. Finally, the coupling degree c was set as the third parameter to test what extent the different cross entropy measures are able to distinguish different degrees of coupling. This is essential in most of synchronization tests since rarely is the absolute value of synchronization of interest, but rather the change of synchronization between different states. It is believed that the synchronization of the two coupled systems increases with the increase of the coupling degree c. Simultaneously, similar patterns are prone to occur and the cross-predictability also increases; hence the three cross entropy measures are expected to monotonously decrease [2,9,10]. Herein, the coupling degree c was set from 0 to 1 with a step of 0.05. Two time series are totally independent when $c=0$ and become identical when $c=1$. Fig. 1 gives the examples of the coupled model maps for the three coupled signals with different coupling degree values c. It clearly shows that with the increase of the coupled degree, two time series x and y become more and more synchronous. Fig. 2 shows the typical examples of the time series for the three coupled signals when setting coupling degree $c=0.4$.

To eliminate the influences of random factors on the coupled Gaussian noise and MIX(p) signals, for each control parameter of N, r or c, 20 realizations were generated and the mean values were used as the final cross entropy results. For coupled Henon signals, for each control parameter of N, r or c, totally 60,000 points were first generated and 20 pairs of episodes (i.e., 20 realizations) were selected with no overlap from the last 50,000 points for the analysis. The mean entropy values of the 20 realizations were also used as the final cross entropy results.

For calculating the three cross entropy measures, other fixed parameters are set as: the embedding dimension $m=2$ for testing the effects of time series length N and coupling degree c, $m=1$ and 2 for testing the effect of threshold value r, the vector similarity weight $n=2$ for C-FuzzyEn, the local vector similarity weight $n_L=3$ and the global vector similarity weight $n_G=2$ for C-FuzzyMEn.

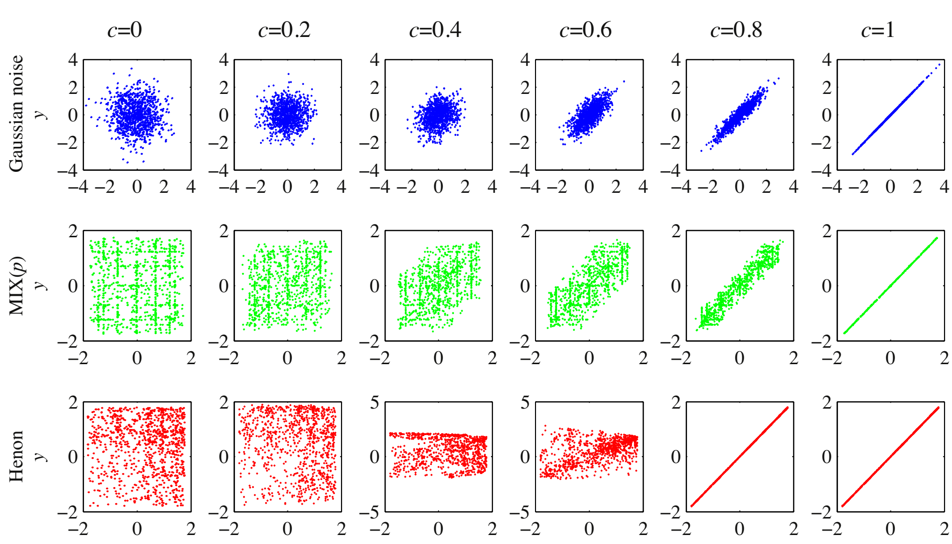

Fig. 1. Examples of the coupled model maps for the three coupled signals with different coupling degree values for c (0, 0.2, 0.4, 0.6, 0.8 and 1). In each sub panel, the time series x is plotted versus the time series y.

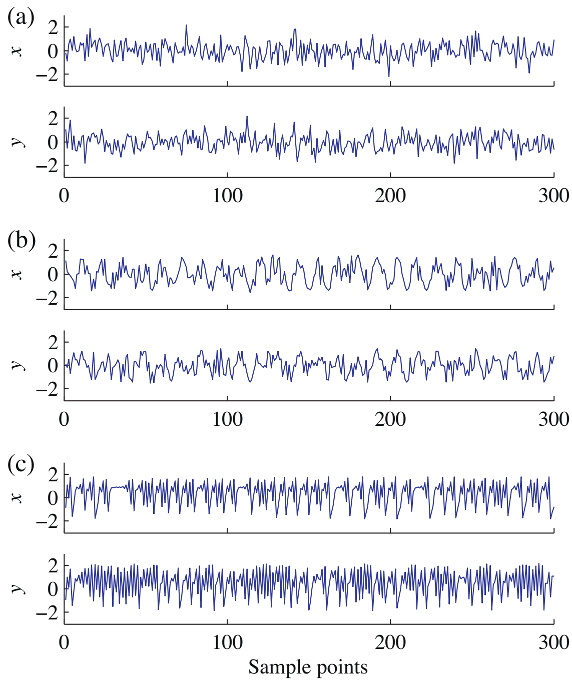

Fig. 2. Examples of the time series for the three coupled signals when setting coupling degree $c = 0.4$. (a) Coupled Gaussian noise, (b) coupled MIX(p) and (c) coupled Henon time series.

3.2. Coupled cardiovascular signals

To test the practical applications for the three cross entropy measures, we compared the performances of them on the coupled cardiovascular signals: RR interval and PTT time series. Thirty normal subjects and 30 heart failure patients were enrolled in this study. All subjects gave their written informed consent to participate in the study, and confirmed that they had not participated in any other 'clinical trial' within the previous three months. The study obtained a full approval from the Clinical Ethics Committee of the Qilu Hospitals of Shandong University and all clinical investigation was conducted according to the principles of expressed in the Declaration of Helsinki. The demographic information is given in Table 1. Two groups were matched by age, gender, height, weight, heart rate and blood pressure. The heart failure subjects were in

Table 1
Demographic data for the subjects studied.

Variables	Normal	Heart failure	*P*-values
Age (year)	56 ± 9	59 ± 8	0.1
Male/female	16/14	21/9	0.2
Height (cm)	166 ± 8	168 ± 10	0.5
Weight (kg)	65 ± 7	67 ± 8	0.4
HR (beats/min)	67 ± 9	71 ± 11	0.1
SBP (mmHg)	120 ± 12	123 ± 10	0.5
DBP (mmHg)	69 ± 10	70 ± 8	0.8
LVEF (%)	68 ± 5	39 ± 7	<0.001

Data are expressed as number or mean ± standard deviation (SD). HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, LVEF: left ventricular ejection fraction.

classes II–III of the New York Heart Association with functional classification confirmed by an ultrasonic cardiogram and has a left ventricular ejection fraction (LVEF) less than 50%. The normal subjects had a LVEF between 58 and 81%.

Each subject was asked to lay supine on a measurement bed for a 5 min rest period to allow cardiovascular system stabilization before the signal recording. Subjects were told to breathe regularly and gently during the measurements. For each subject, electrocardiograms (ECG) and radial pulses were simultaneously recorded for more than 5 min with a sample rate of 1 kHz. The R-wave peaks of the ECG were detected using the wavelet transform modulus maxima method [25]. Ectopic beats and false detection beats were identified [26] and excluded with the visual comfirmation. After the location of R-wave peaks, their corresponding pulse feet (starts of pulse) were identified [27]. RR time series were obtained from the adjacent R-wave peaks and PTT time series were obtained from the R wave peaks to the corresponding pulse feet. The time resolutions of RR and PTT time series were 1 ms. Fig. 3 shows the examples of RR and PTT time series from a normal subject and a heart failure subject and their corresponding coupled maps.

For both RR and PTT time series, the initial 300 points were used for the cross entropy calculation. We named the length of 300 as short time series due to the recommendation from The Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology [28]—"a duration of 5 min ECG recording for short time recordings, which would result in 300 data points at an average heart rate of 60 beats per second." Threshold value r was set as 0.2 and embedding dimension m was set as 2 for all three cross entropy measures. Vector similarity weight n was set

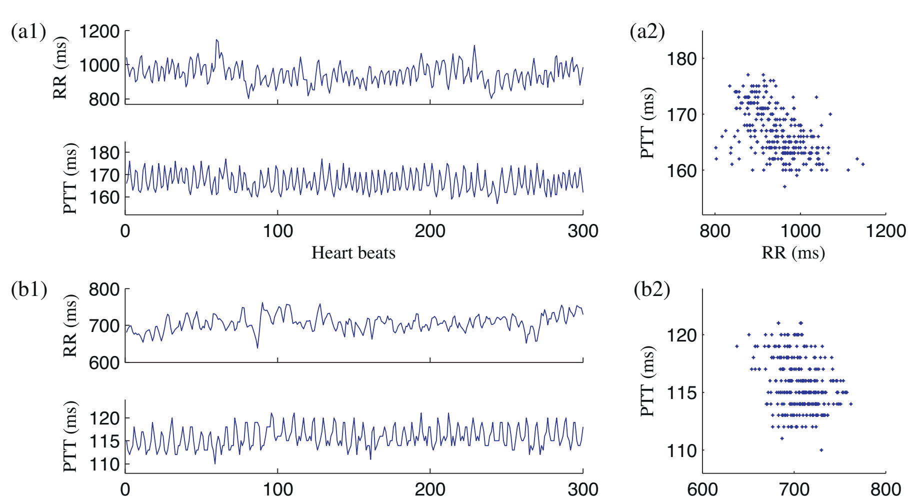

Fig. 3. Examples of RR and PTT time series from a normal subject (a1) and a heart failure subject (b1). (a2) and (b2) Show their corresponding coupled maps (RR versus PTT time series). The values of C-SampEn, C-FuzzyEn and C-FuzzyMEn for (a1) are 2.05, 1.46 and 2.34, respectively, and for (a2) are 2.03, 1.29 and 2.04, respectively.

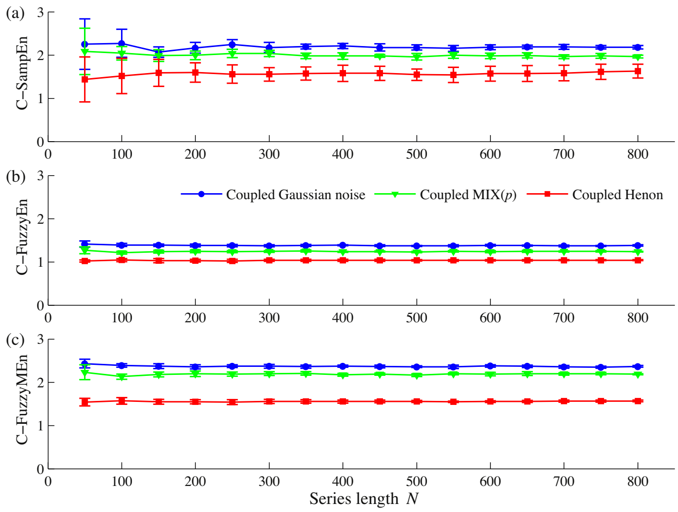

Fig. 4. Dependence of the three cross entropy measures on the time series length N when applied to the coupled Gaussian noise, coupled MIX(p) and coupled Henon signals respectively with (a) for C-SampEn, (b) for C-FuzzyEn and (c) for C-FuzzyMEn.

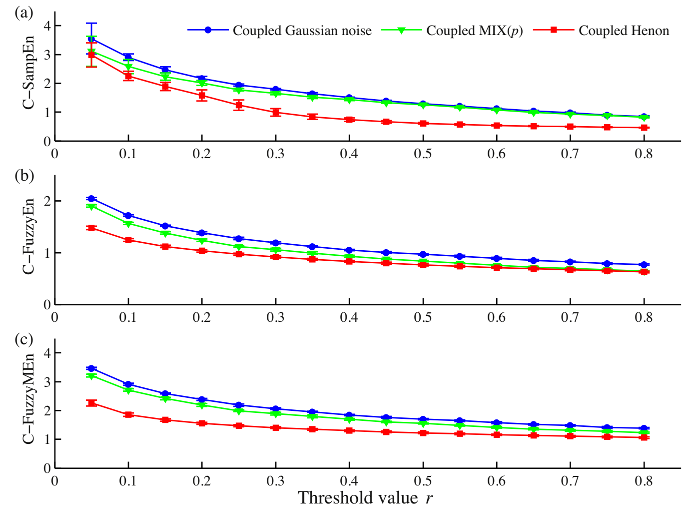

Fig. 5. Dependence of the three cross entropy measures on the threshold value r at the constant setting of $m = 2$ when applied to coupled Gaussian noise, coupled MIX(p) and coupled Henon signals respectively with (a) for C-SampEn, (b) for C-FuzzyEn and (c) for C-FuzzyMEn.

as 2 for C-FuzzyEn while local vector similarity weight n_L was set as 3 with global vector similarity weight n_G set as 2 for C-FuzzyMEn.

3.3. Statistical analysis

Mean ± standard deviation (SD) of the three cross entropy measures were obtained across all subjects (30 normal and 30 heart failure subjects). All cross entropy measures were first test for normal distribution by the Kolmogorov–Smirnov test. Then they were tested using the Student *t*-test to compare the statistical differences between normal and heart failure groups if they met the normal distribution or were tested using the non-parametric tests if they did not meet the normal distribution. Statistical significance was set a priori at $P < 0.05$.

4. Results

4.1. Effect of the time series length

In this section, the first control parameter, i.e., the time series length N, changed from 50 to 800 with a step of 50, was tested for all three cross entropy measures. The other two control parameters are set as constant values: threshold value $r = 0.2$ and coupling degree $c = 0.5$. Fig. 4 shows the mean ± SD results from the 20 repeats of the three cross entropy measures when N increases. First, for each coupled signal, the mean values for each of the three cross entropy measures keep permanent when series length N is more than 300. So in the following Sections 4.2–4.4, the N is set as a constant of 300. Second, for each of three coupled signals, compared with C-FuzzyEn and C-FuzzyMEn, C-SampEn usually presents the larger SD values. In addition, C-FuzzyMEn could distinguish three coupled signals more clearly than C-FuzzyEn.

4.2. Effect of the threshold value

In this section, the second control parameter, i.e., the threshold value r, changed from 0.05 to 0.8 with a step of 0.05, was tested for all three cross entropy measures. The other two control parameters are set as constant values: time series length $N = 300$ and coupling degree $c = 0.5$. Fig. 5 shows the mean ± SD results from the 20 repeats of the three cross entropy measures at the constant setting of $m = 2$ when r increases. For each coupled signal, the mean values for each of the three cross entropy measures monotonously decrease with the increase of r. In addition, for larger r values, there are obvious overlaps between coupled Gaussian noise and coupled MIX(p) signals in C-SampEn, and there are also obvious overlaps between coupled MIX(p) and coupled Henon signals in C-FuzzyEn. However, there are not obvious overlaps among the three coupled signals for the whole range of r in C-FuzzyMEn.

As comparison, Fig. 6 shows the mean ± SD results from the 20 repeats for the three cross entropy measures at the constant setting of $m = 1$ when r increases. Compared with $m = 2$, there are obvious reversal of C-FuzzyEn values for coupled Henon time series, which could induce the confusing conclusion for the real application. C-SampEn shows similar results with $m = 2$ but the SD values at the low r range decreased when $m = 1$. The discrimination ability of C-FuzzyMEn for the three coupled signals also decreased when $m = 1$.

4.3. Effect of the coupling degree

In this section, the third control parameter, i.e., the coupling degree c, changed from 0 to 1 with a step of 0.05, was tested for

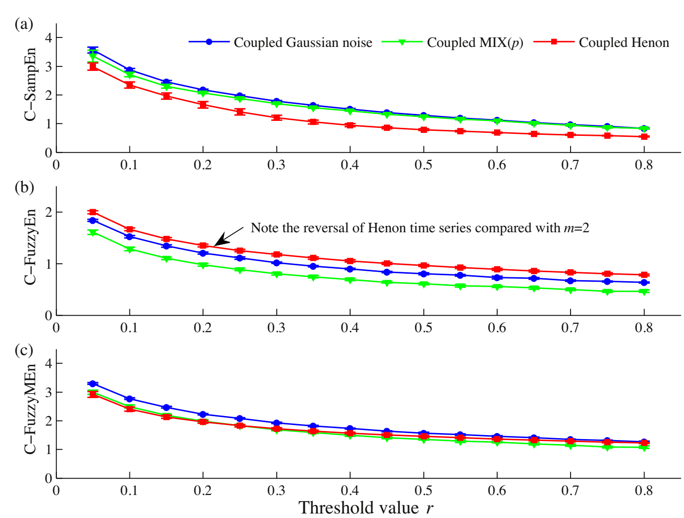

Fig. 6. Dependence of the three cross entropy measures on the threshold value r at the constant setting of $m = 1$ when applied to coupled Gaussian noise, coupled MIX(p) and coupled Henon signals respectively with (a) for C-SampEn, (b) for C-FuzzyEn and (c) for C-FuzzyMEn.

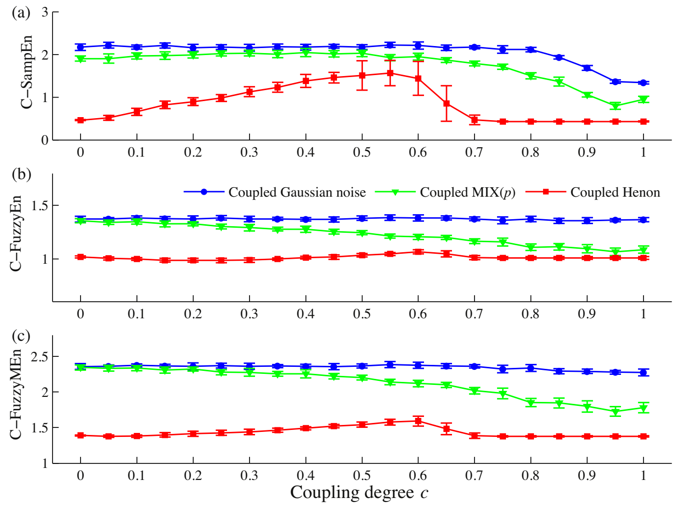

Fig. 7. Dependence of the three cross entropy measures on the coupling degree c when applied to coupled Gaussian noise, coupled MIX(p) and coupled Henon signals respectively with (a) for C-SampEn, (b) for C-FuzzyEn and (c) for C-FuzzyMEn.

all three cross entropy measures. The other two control parameters are set as constant values: time series length $N = 300$ and threshold value $r = 0.2$. Fig. 7 shows the mean ± SD results from the 20 repeats of the three cross entropy measures when coupling degree c increases. For both coupled Gaussian noise and coupled MIX(p) signals, the three cross entropy measures show monotonously decrease trends with the increase of c. Moreover, these monotonously decrease trends are more obvious for coupled MIX(p) signal than for coupled Gaussian noise signal. However, for coupled Henon signal, all three cross entropy measures have ceiling effect, i.e., the unexpected increase of entropy values with c increasing from 0 to 0.6.

4.4. Comparison between the normal and heart failure groups

Fig. 8 shows the mean ± SD of the three cross entropy measures for both normal and heart failure subjects. For all three cross entropy measures, the normal group has higher entropy values than the heart failure group. The differences between the two groups showed no statistical significance in C-SampEn (normal 2.13 ± 0.37 vs. heart failure 2.07 ± 0.16, $P = 0.36$), but had statistical significance in both C-FuzzyEn (normal 1.42 ± 0.25 vs. heart failure 1.31 ± 0.12, $P < 0.05$) and C-FuzzyMEn (normal 2.40 ± 0.26 vs. heart failure 2.15 ± 0.13, $P < 0.01$). The level of statistical significance in C-FuzzyMEn is higher than that in C-FuzzyEn.

5. Discussions

This study proposed a new synchronization measure, named cross fuzzy measure entropy (C-FuzzyMEn), for measuring the coupling relationships between the bivariate time series. Meanwhile, this study aimed to perform a comparison of different cross entropy measures on both coupled simulation and coupled cardiovascular time series to decide which measure may be most suitable for the practical application.

For the three cross entropy measures that we focus on in this study, i.e., C-SampEn, C-FuzzyEn and C-FuzzyMEn, they are all the negative natural logarithm of the conditional probability that two sequences of length N, having similar patterns for m points within a boundary r, will also repeat for $m + 1$ points. Meanwhile, they all have the direction-independent property that C-ApEn lacks. The smaller values in the cross entropy measures correspond to more common characteristics in the time series structure while larger values indicate larger characteristic difference in their time series structure. In this study, coupled Gaussian noise has largest cross entropy values in almost all experiments, followed by coupled MIX(p) signal, and coupled Henon signal has lowest cross entropy values, which indicates that entropy measure maximizes the bivariate time series with more random feature rather than series with more nonlinear complicated feature. Therefore, entropy measure seems to be able to better denote the unpredictability (opposite of regularity) of time series rather than the complexity. This viewpoint has also been discussed in [29]. In addition, because most of physiological data are of limited length, whether cross entropy measure is suitable for the analysis of a relatively small amount of time series is crucial. Although C-SampEn has been reported in [6] that it is not independent of series length, when using more repeats (20 repeats) in this study, all three cross entropy measures show fine independences of series length as if series length $N \geqq 300$. Thus they are proved to be applicable for short-term data analysis.

Unlike C-SampEn, where the decision rule for vector similarity is based on Heaviside function, both C-FuzzyEn and C-FuzzyMEn use fuzzy function (herein the exponential function) to redefine the decision rule for vector similarity. The differences between Heaviside and fuzzy functions are shown in Formula (21) and Fig. 9. The rigid membership degree determination in Heaviside function could induce the poor statistical stability in C-SampEn, which means that the entropy value may have a sudden change when the threshold value r changes slightly. This phenomenon has been reported in recent research studies [6,10–12,17,18]. In this study, for the three employed coupled simulation signals, no matter the series length, the threshold value, or the coupling degree changes, C-SampEn has prominently larger SD values than C-FuzzyEn and C-FuzzyMEn, which also prove the poor statistical stability of C-SampEn. Both C-FuzzyEn and C-FuzzyMEn employ fuzzy function to determine the similarity of two vectors. This

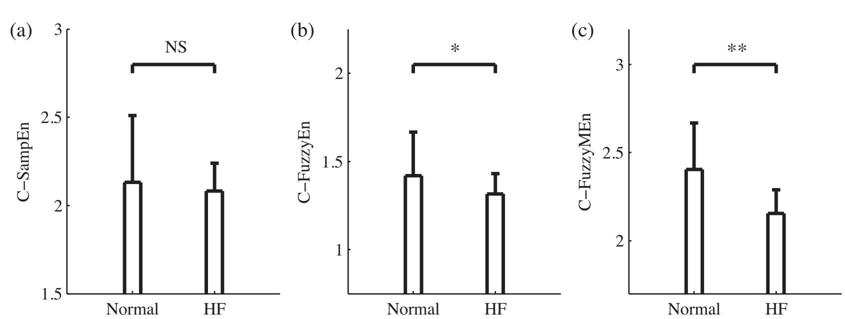

Fig. 8. Mean ± SD of the three cross entropy measures for both normal and heart failure subjects: (a) C-SampEn, (b) C-FuzzyEn and (c) C-FuzzyMEn. 'HF': heart failure, 'NS': statistical significance $P \geqq 0.05$, '*': statistical significance $P < 0.05$, '**': statistical significance $P < 0.01$.

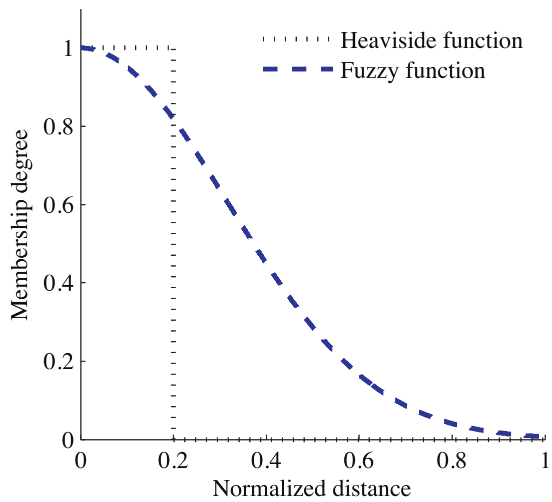

Fig. 9. The changing curve of the membership degree with the increase of normalized distance between two vectors. Black dotted line shows the determination criterion of the Heaviside function and blue dash line shows the determination criterion of the fuzzy function. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

determination criterion exhibits the gentle boundary effect, while the traditional 0–1 judgment criterion is rigid in the boundary of the threshold r. This is the reason why C-FuzzyEn and C-FuzzyMEn have better relative consistency than C-SampEn, evidenced by the relative small SD values in Figs. 4–7.

$$\begin{aligned} &\text{For Heaviside function}: \ \text{Membership\_degree}(d_{i,j}, r) = \begin{cases} 1 & d_{i,j} \le r \\ 0 & d_{i,j} > r \end{cases} \\ &\text{For Fuzzy function}: \ \text{Membership\_degree}(d_{i,j}, r) = \exp\left(-\frac{(d_{i,j})^n}{r}\right) \end{aligned} \tag{21}$$

where $d_{i,j}$ means the distance of two vectors X_i and Y_j, r is the threshold value and n is the vector similarity weight.

However, unlike C-FuzzyEn, where only the local vector sequences are generated by removing the local baseline using Formula (4), C-FuzzyMEn generates both the local and global vector sequences by removing both the local baseline and global mean value using Formula (11). Because C-FuzzyEn only focuses on the local shape characteristic but ignoring the global value difference of two vectors, it lacks the fine discrimination ability [17,18]. Comparing the sub-figures (b) and (c) in Fig. 5, especially for the relative large range of threshold r, there are obvious overlaps between coupled MIX(p) and coupled Henon signals in C-FuzzyEn but not in C-FuzzyMEn, which means the latter is able to distinguish the three signals better than the former and also agrees with the result that FuzzyMEn has better algorithm sensitivity than FuzzyEn in [17]. In addition, when employing the embedding dimension $m = 1$, the discrimination ability of C-FuzzyMEn for the three coupled signals decreased (see Fig. 6), indicating that $m = 1$ is not enough for fully represent the inherent structure characteristics for the time series length $N = 300$.

It should be noted that when employing the coupling degree as a control parameter to test what extent the different cross entropy measures are able to distinguish different degrees of coupling, there is caveat in this evaluation since this approach is built on a fundamental assumption, which is that an increase of the coupling degree necessarily leads to an increase of synchronization [2]. However, the different coupled models investigated in this study exhibit very different behavior in their transition to synchronization with increasing coupling degree. In Fig. 1, the different coupled model maps of the three coupled signals with the same coupling degree $c = 0.8$ show this phenomenon: coupled Henon signal becomes totally synchronous but coupled Gaussian noise and coupled MIX(p) do not. So the relation of increased coupling degree leading to increased synchronization may be not hold for all types of coupled models. It has been reported that with the increased coupling degree, increased synchronization does not occur in some constructed coupled signals [30–32]. In such cases measures designed to detect different types of synchronization (pattern, phase or generalized synchronization) are expected to behave differently. Although existing works reported that cross entropy measures have been accepted as a good pattern synchronization measures [9,10], more intensive and explicit research should be done for what types of synchronization the cross entropy measure could or could not reveal, as well as what types of coupled models the cross entropy measure could or could not accurately measure. The latter also is very important because for coupled Gaussian noise and coupled MIX(p) signals, all the three cross entropy measures in this study have approximately monotonous decrease with the increase of coupling degree, whereas for coupled Henon signal, all the three cross entropy measures first increase to a peak and then monotonously decrease. This unexpected peak effect was named as ceiling effect and also was found in the other two nonlinear dynamic coupled models: Lorenz and Rossler coupled models [10,30]. So the behavior measurement based on cross entropy approaches for nonlinear dynamic coupled models should be further investigated.

As an application, the new proposed C-FuzzyMEn, as well as C-SampEn and C-FuzzyEn, have been used for the coupling analysis of cardiovascular time series to detect their discrimination ability between the normal and heart failure groups. Short-term, beat-to-beat cardiovascular variability reflects the dynamic interplay between ongoing perturbations to the circulation and the compensatory response of neurally mediated regulatory mechanisms. While the univariate time series analysis may be employed to quantify the variability itself, the bivariate or multivariate time series analysis permits the quantification for the dynamic characterization of the cardiovascular regulatory mechanisms. Compared with the univariate time series, the bivariate or multivariate time series analysis may be even more illuminating, as it can provide a quantitative characterization of the cardiovascular regulatory mechanisms responsible for coupling the beat-to-beat variability between signals rather than merely the variability that is elicited [33]. Aberrant cardiovascular regulatory function may result from disease and environmental changes. Heart failure is a prevalent disease affecting short-term cardiovascular regulation [34]. An increased synchronization, consequently a decreased C-SampEn, for RR and PTT time series in heart failure patients, has been reported in our previous research [11]. Reduced short-term variability has also been found for heart failure patients [35]. In this study, a relative large group with heart failure patients has lower cross entropy values than the normal group with the same size in C-SampEn, C-FuzzyEn and newly proposed C-FuzzyMEn, proving that the synchronization between RR and PTT time series increases in heart failure patients. Although C-SampEn has lower mean value in heart failure group than that in normal group, it could not significantly distinguish the two groups ($P = 0.36$). However, C-FuzzyEn and C-FuzzyMEn could ($P < 0.05$). When using C-FuzzyMEn, the discrimination ability becomes even better ($P < 0.01$), which indicates that the newly proposed C-FuzzyMEn approach could better characterize the synchronization for cardiovascular time series, providing a potential solution to understand the different cardiovascular coupling between the normal subjects and heart failure patients.

It was also worth to note that the respiratory induced modulations of RR and PTT time series may be a potential influence factor for the statistical difference measurement between the normal and heart failure groups when using the three cross entropy measures. We did not discuss this respiratory induced modulation in the present study. However, during the signal recording, we told the subject to breathe regularly and gently during the measurements to minimize the impact of the respiratory induced modulation.

In summary, this study demonstrated that compared with C-SampEn, C-FuzzyEn and C-FuzzyMEn have better statistical stability and compared with C-FuzzyEn, C-FuzzyMEn has better discrimination ability for both coupled simulation and coupled cardiovascular signals. In future experiments, we expect that the newly proposed cross entropy measure will be useful in the practical clinical applications for not only cardiovascular coupled signals but also other physiological coupled signals analysis.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

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