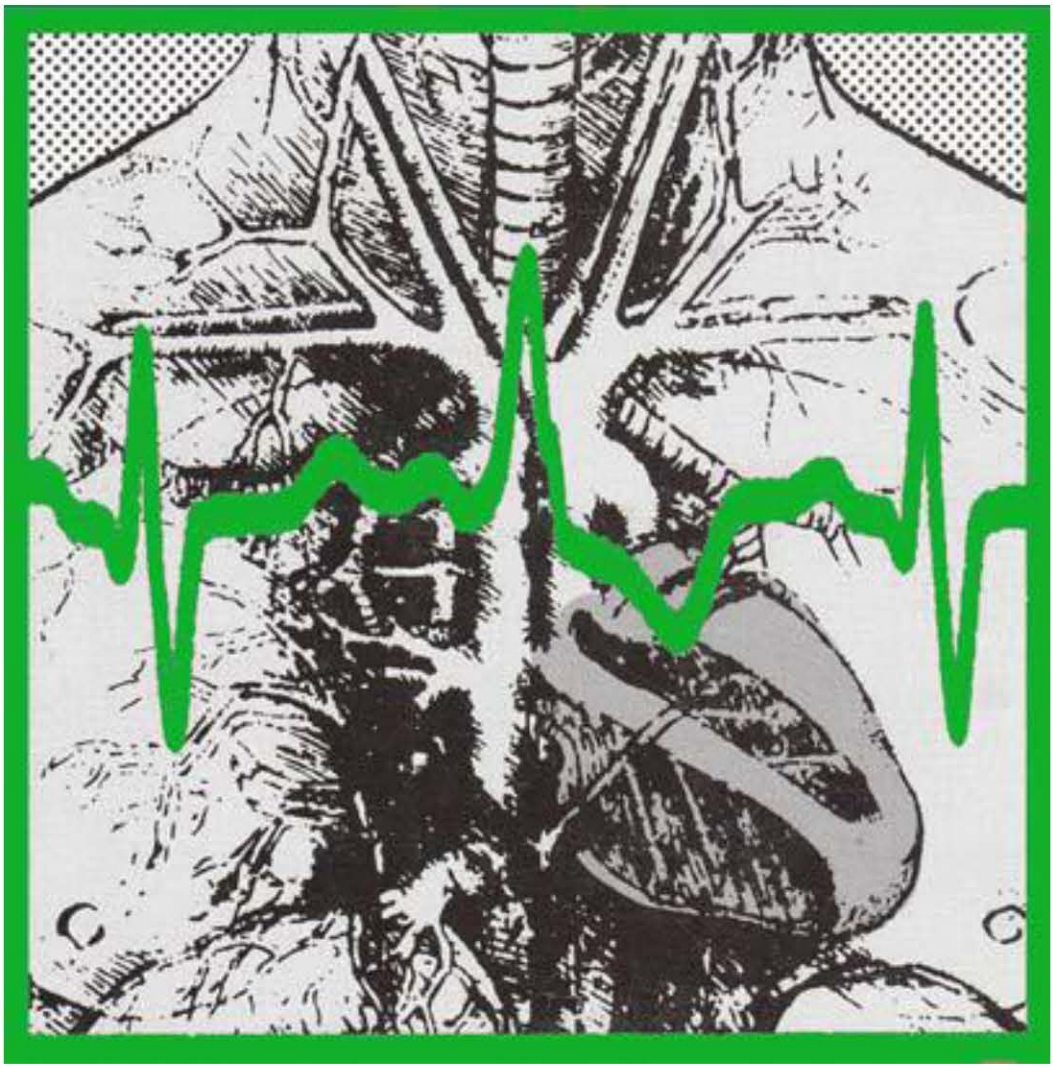
COMPUTING IN CARDIOLOGY 2013

Volume 40



COMPUTING IN CARDIOLOGY 2013

Volume 40

September 22-25, 2013
Zaragoza, Spain

Is Cross-sample Entropy a Valid Measure of Synchronization between Sequences of RR Interval and Pulse Transit Time?

Chengyu Liu[1,2], Dingchang Zheng[1], Peng Li[2], Lina Zhao[2], Changchun Liu[2], Alan Murray[1]

[1]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK
[2]School of Control Science and Engineering, Shandong University, China

Abstract

Synchronization provides an insight into mechanisms underlying the interaction among bivariate physiological signals where their coupling is not known a priori. Cross-sample entropy (C-SampEn) has been used to quantify their synchronization. However, traditional C-SampEn has a poor statistical stability because a rigid decision rule is applied to define the similarity between two vectors. In this study, a fuzzy membership function was implemented to redefine the decision rule in C-SampEn with its performance evaluated using simulated and real cardiovascular coupling signals (RR interval and pulse transit time sequences from 10 normal subjects and 10 heart failure patients).

Simulation results verified the decrease of both C-SampEn with increasing coupling degree. The analysis of cardiovascular coupling signals demonstrated a significant difference between normal and heart failure patients (normal 1.17 ± 0.09 vs. heart failure 1.02 ± 0.10, P<0.01) with the improved C-SampEn, but not the traditional C-SampEn. Our improved C-SampEn provides a better understanding of the different cardiovascular coupling between normal subjects and heart failure patients.

1. Introduction

Measuring synchronization between two physiological systems has attracted great interest [1-3]. Traditionally, the cross-correlation in the time domain as well as the cross-spectrum or coherency in the frequency domain have been used to test their synchronization [4]. However, they are not suitable for characterizing real physiological signals that are non-stationary and inherently nonlinear. Recently, entropy-based measures, such as the typical approximate entropy and sample entropy, have been widely used for the analysis of physiological time series to explore their inherent complexity [5]. And their generalized forms, cross-approximate entropy (C-ApEn) and cross-sample entropy (C-SampEn) [6], have been used to test synchronization for physiological time series. In comparison with C-ApEn, C-SampEn could reduce bias and show better relative consistency than C-ApEn [6].

However, both C-ApEn and C-SampEn have poor statistical stability due to the use of binary classification based on the Heaviside function. Cross-fuzzy entropy (C-FuzzyEn), as the variation of C-SampEn [7], is based on the concept of Zadeh's fuzzy set theory, and requires fewer parameters and shorter data lengths, and thus provides relatively robust results. However, removing the local baseline during the algorithm implementation may produce inaccurate results for some slow signals because it neglects the global trend. To solve this issue, we recently reported a fuzzy measure entropy that combined both the local similarity and the global similarity [8, 9].

The aim of this study was to improve the C-SampEn by redefining the decision rules between vector similarities. The performance of our improved C-SampEn was evaluated using simulated and real cardiovascular coupling signals.

2. Methods

2.1. Cross-sample entropy

The calculation process of C-SampEn is summarized as follows [6; 10]:

For two normalized sequences $u(i)$ and $v(i)$, $1 \le i \le N$, the vector sequences are:

$$X_i^m = \{u(i), u(i+1), \mathrm{L}\ , u(i+m-1)\}$$
$$Y_j^m = \{v(j), v(j+1), \mathrm{L}\ , v(j+m-1)\} \quad 1 \le i, j \le N-m+1 .$$

The distance between two vectors is then defined as:

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

Denote $B_i^m(r)$ the average number of j that $d_{i,j}^m \le r$ and $A_i^m(r)$ that $d_{i,j}^{m+1} \le r$ for $1 \le j \le N-m$.

The C-SampEn is then defined as:

$$\text{Cross-SampEn}(m,r) = -\ln\left(\sum_{i=1}^{N-m} A_i^m(r) \Big/ \sum_{i=1}^{N-m} B_i^m(r)\right) \quad (1)$$

2.2. Improved cross-sample entropy

Traditional C-SampEn has a rigid decision rule for the vector similarity because it is decided from the Heaviside function that is described as follows:

$$\theta(d_{i,j}, r) = \begin{cases} 1 & d_{i,j} \le r \\ 0 & d_{i,j} > r \end{cases} \quad (2)$$

With this decision rule, only the vectors within the boundary are treated as similar vectors, while those outside the boundary are neglected. This two-state classifier can lead to instability of C-SampEn .

The fuzzy membership function has been reported to replace the Heaviside function [7; 8]. It is described as:

$$\mu(d_{i,j}, r) = \exp(-(d_{i,j})^2 / r)$$

However, this membership degree of two vectors has an immediate decline if their distance is more than 0, which is too sensitive to the noise.

In this study, we redefined the published fuzzy membership function to:

$$\mu(d_{i,j}, r, \lambda) = \begin{cases} 1, & 0 \le d_{i,j} \le \lambda \\ \exp(-(d_{i,j} - \lambda)^2 / r), & x > \lambda \end{cases} \quad (3)$$

where r is the threshold parameter and λ denotes the range that regards the vectors as absolutely similar.

Compared with the reported fuzzy membership function, the decision rule for vector similarity from our modified function has more robust ability and could be immune to slight noise. Figure 1 shows the comparison between the above three decision rules.

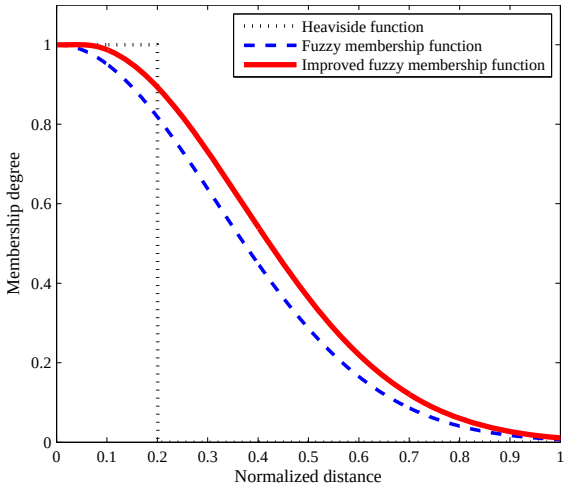


Figure 1. Three decision rules for vector similarity: black dotted line is the Heaviside function, blue dash line is the fuzzy membership function and red solid line is the improved fuzzy membership function.

2.3. Evaluation experiments

The performance of the traditional and improved C-SampEn was evaluated on cardiovascular coupling signals and their simulated data. Cardiovascular coupling signals were the sequences of the RR interval and corresponding pulse transit time (PTT, from the R wave peak of the ECG to the foot of the corresponding pulse). They came from 10 normal subjects (58±7 years) and 10 heart failure patients (60±6 years). The subjects in two groups were matched by age. Electrocardiograms (ECG) and radial pulses were simultaneously recorded for more than 5 min to obtain the sequences of RR interval and PTT. The initial 300 beats were used for the analysis. Figure 2 shows an example of the two sequences from a normal subject. To reveal and compare different coupling relationships between RR interval and PTT sequences, simulated cardiovascular coupled data were also produced.

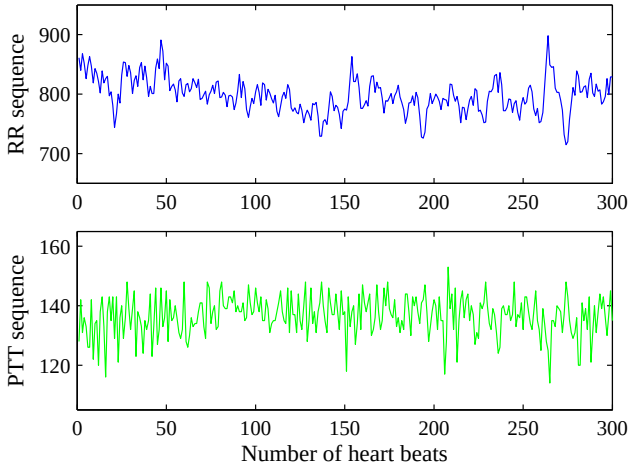


Figure 2. Example of the acquired RR interval and PTT sequences (Unit: ms).

1) Simulated cardiovascular coupled data 1 from one normal subject

Coupling signal 1 was set as a real RR sequence (A in Figure 3) and coupling signal 2 was set as different types of PTT sequences (B1-B5 in Figure 3).

B1: Real PTT; a real PTT sequence.

B2: Constant PTT; a constant sequence, denoting a constant time delay of pulse from heart to peripheral artery.

B3: Constant PTT plus RR; a repeat of the coupled RR sequence, denoting perfect coupling .

B4: Constant PTT plus noise;the Gaussian noise denotes the most irregular coupling.

B5: Constant PTT plus nonlinear noise signal; a Logistic sequence iterated by $x(n+1) = w \times x(n) \times (1 - x(n))$, where the initial value $x(0)$ is between 0 and 0.9 and w is 3.8 [8]. This sequence denotes the most complex coupling.

2) Simulated cardiovascular coupled data 2

Coupling signal 1 was set as a real RR sequence and coupling signal 2 was set as the same RR sequence after normalization and subtraction of mean, but with a percentage of elements randomly replaced by Gaussian

noise (B4 in Figure 3) or nonlinear signals (B5 in Figure 3). The replaced proportions were set as 20%, 40%, 60% and 80% respectively. For each proportion, 20 realizations were generated and used as the final entropy values: mean±standard deviation (SD).

3) Real cardiovascular coupled data

Coupling signal 1 and 2 were the real RR and PTT sequences from all 20 subjects. For each subject, both traditional and improved C-SampEn measurements were applied to the two sequences with the mean±SD calculated across all subjects. Student's *t*-test was used to compare the statistical differences between normal subjects and heart failure patients. Statistical significance was set a priori at $P<0.05$.

3. Results and discussion

Figure 3 shows the results from one subject for traditional and improved C-SampEn for the RR and different types of PTT sequences. For both cross entropies, the type of constant PTT plus nonlinear noise signal gives the maximum value (2.10 and 1.34 respectively). Constant PTT plus noise also gives relative high entropy values (1.95 and 1.21). Constant PTT gives the minimum value for improved C-SampEn whereas constant PTT plus RR gives the minimum value for the traditional one. The two entropy values (2.00 and 1.14) from the real cardiovascular coupled data are lower than that with nonlinear signals but higher than those exhibiting unchanged (1.56 and 0.64) and perfect coupling (1.16 and 0.87) signals.

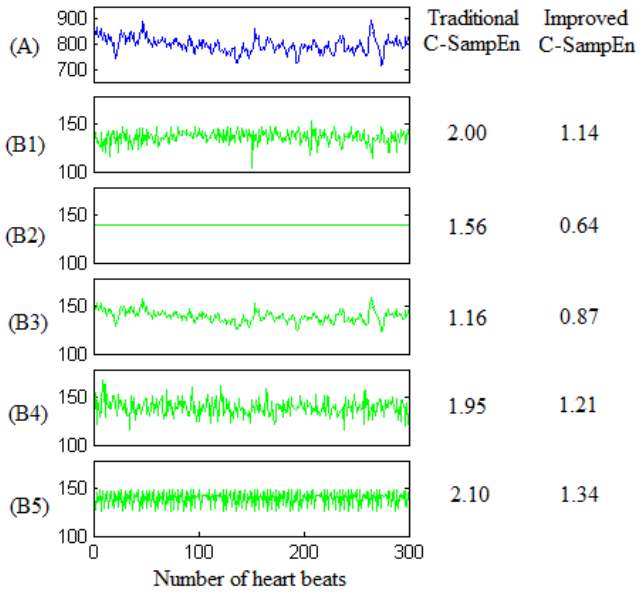


Figure 3. The results from simulated cardiovascular coupled data 1 (Vertical axes is in ms).

The left two panels in Figure 4 show the traditional C-SampEn results for the simulated cardiovascular coupled data 2, in which a percentage of elements of one coupled RR sequence were randomly replaced by Gaussian noise (A1) or nonlinear signals (A2). The right panels show the corresponding results for the improved C-SampEn: (B1) for Gaussian noise and (B2) for nonlinear signal. The synchronization of the two coupled sequences decreased with the increase of the proportions of Gaussian noise or nonlinear signals. The results from the traditional and improved C-SampEn changed as expected.

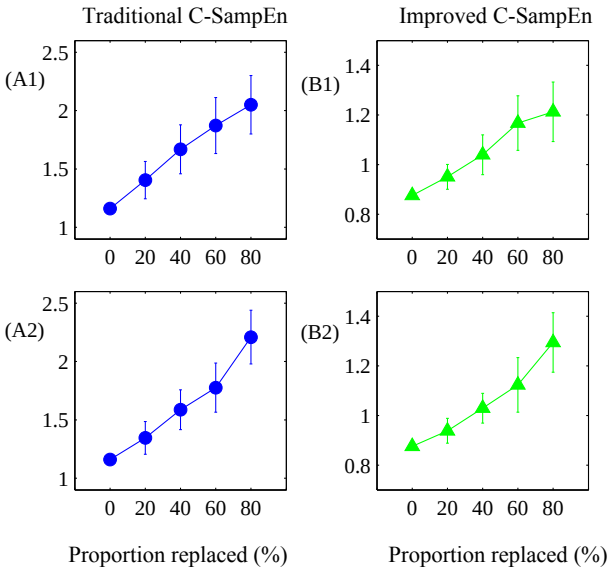


Figure 4. The results from simulated cardiovascular coupled data 2.

Figure 5 shows the results from both the traditional and improved C-SampEn for normal and heart failure subjects. For both C-SampEn, with the parameters set as: embedding dimension $m=2$, threshold value $r=0.2$ and sequence length $N=300$. For improved C-SampEn, parameter λ was 0.05. Using the traditional C-SampEn measurement on RR and PTT sequences, there was no significant difference between the two groups (normal 2.03±0.10 vs. heart failure 1.97±0.08, $P=0.13$). However, with the improved C-SampEn, they were significantly different (normal 1.17 ± 0.09 vs. heart failure 1.02 ± 0.10, $P< 0.01$).

4. Conclusion

This study developed a modified C-SampEn to improve the poor statistical stability of traditional C-SampEn. Similarly to the traditional C-SampEn, improved C-SampEn is 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. However, unlike the traditional C-SampEn, where the decision rule for vector similarity is based on the Heaviside function, the

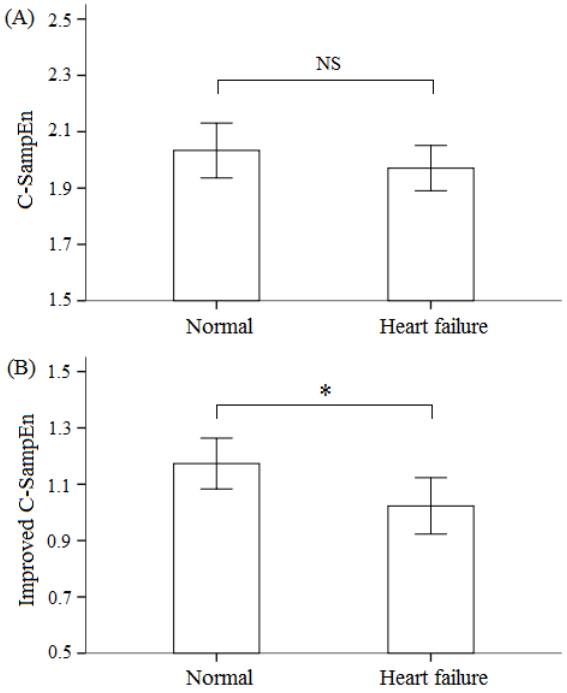


Figure 5. Results (mean±SD) of the traditional C-SampEn (A) and improved C-SampEn (B) for normal and heart failure groups.
'NS': no significant difference; '*': $P<0.01$.

improved C-SampEn uses a piecewise function to redefine the decision rule.

Although the results from simulated cardiovascular coupled data 2 showed that both C-SampEn decreased monotonically with increasing coupling degree c, the analysis of cardiovascular coupling signals demonstrated significant difference between normal and heart failure patients were found by the improved C-SampEn, but not the traditional C-SampEn. Our improved C-SampEn provides a potential solution to understand different cardiovascular coupling between normal subjects and heart failure patients.

The improved C-SampEn could also be applied to quantify the synchronization of other bivariate physiological sequences with short data lengths.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (61201049), the China Postdoctoral Science Foundation (2013M530323) and the China Postdoctoral International Academic Exchange Program.

References

[1] Ansari-Asl K, Senhadji L, Bellanger JJ, Wendling F. Quantitative evaluation of linear and nonlinear methods characterizing interdependencies between brain signals. Phys Rev E 2006; 74: 031916.

[2] Kreuz T, Mormann F, Andrzejak RG, Kraskov A, Lehnertz K, Grassberger P. Measuring synchronization in coupled model systems: A comparison of different approaches. Physica D 2007; 225: 29-42.

[3] Bartsch RP, Schumann AY, Kantelhardt JW, Penzel T, Ivanov PC. Phase transitions in physiologic coupling. Proc Natl Acad Sci USA 2012; 109: 10181-6.

[4] Nunez PL, Srinivasan R, Westdorp AF, Wijesinghe RS, Tucker DM, Silberstein RB, Cadusch PJ. EEG coherency. I: Statistics, reference electrode, volume conduction, laplacians, cortical imaging, and interpretation at multiple scales. Electroencephalogr Clin Neurophysiol 1997; 103: 499-515.

[5] Li P, Liu CY, Wang XP, Li LP, Yang L, Chen YA, Liu CC. Testing pattern synchronization in coupled systems through different entropy-based measures. Med Biol Eng Comput 2013; 51: 581-91.

[6] Zhang T, Yang, Z, Coote JH. Cross-sample entropy statistic as a measure of complexity and regularity of renal sympathetic nerve activity in the rat. Exp Physiol 2007; 92: 659-69.

[7] Xie HB, Zheng YP, Guo JY, Chen X. Cross-fuzzy entropy: A new method to test pattern synchrony of bivariate time series. Inform Sciences 2010; 180: 1715-24.

[8] Liu CY, Li K, Zhao LN, Liu F, Zheng DC, Liu CC, Liu ST. Analysis of heart rate variability using fuzzy measure entropy. Comput Biol Med 2013; 43: 100-8.

[9] Liu CY, Zhao LN. Using fuzzy measure entropy to improve the stability of traditional entropy measures. Computing in Cardiology 2011; 38: 681-4.

[10] Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. Am J Physiol Heart Circ Physiol 2000; 278: H2039-49.

Address for correspondence.

Chengyu Liu
Medical Physics Department
Newcastle University
Royal Victoria Infirmary
Newcastle Upon Tyne
NE1 4LP, UK
Tel: +44-7455592002
E-mail: chengyu.liu@ncl.ac.uk