Assessing Skin Blood Flow Dynamics in Older Adults Using a Modified Sample Entropy Approach

Fuyuan Liao and Yih-Kuen Jan

Abstract—The aging process may result in attenuated microvascular reactivity in response to environmental stimuli, which can be evaluated by analyzing skin blood flow (SBF) signals. Among various methods for analyzing physiological signals, sample entropy (S_E) is commonly used to quantify the degree of regularity of time series. However, we found that for temporally correlated data, S_E value depends on the sampling rate. When data are oversampled, S_E may give misleading results. To address this problem, we propose to modify the definition of S_E by using time-lagged vectors in the calculation of the conditional probability that any two vectors of successive data points are within a tolerance r for m points remain within the tolerance at the next point. The lag could be chosen as the first minimum of the auto mutual information function. We tested the performance of modified S_E using simulated signals and SBF data. The results showed that modified S_E is able to quantify the degree of regularity of the signals regardless of sampling rate. Using this approach, we observed a more regular behavior of blood flow oscillations (BFO) during local heating-induced maximal vasodilation period compared to the baseline in young and older adults and a more regular behavior of BFO in older adults compared to young adults. These results suggest that modified S_E may be useful in the study of SBF dynamics.

Key words— Skin blood flow dynamics, older adults, modified sample entropy.α(t)

I. Introduction

The aging process causes structural and functional changes in the cardiovascular system [1]. These changes may attenuate microvascular reactivity in response to environmental stimuli [2]. A variety of test protocols have been used to assess microvascular reactivity [3], among which local heating-induced skin blood flow (SBF) response is commonly used to assess microvascular endothelial function [4, 5]. When the skin is rapidly heated to 42°C, SBF shows a biphasic response: an initial peak followed by a nadir, and then a slow increase to a plateau (the second peak) [4, 5]. The initial phase relies predominantly on local sensory nerves and is mediated by an axon reflex; the second peak is mediated largely by nitric oxide [4, 5]. Hence, ratio of the first peak to baseline flow and ratio of the second peak to baseline flow are used to evaluate vasodilatory impairments [6]. Furthermore, wavelet-based spectral analysis has been utilized to explore the underlying mechanisms of the response [6] and nonlinear analysis has been utilized to study its dynamics [7]. Wavelet analysis of blood flow oscillations (BFO) in human skin has revealed five characteristic frequencies between 0.0095 and 2.0 Hz [8]. They are originated from or associated with heart beats (~ 1 Hz), respiration (~0.3 Hz), the myogenic activity of vascular smooth muscle (~0.1 Hz), the neurogenic activity of the vessel wall (~0.04 Hz), and the metabolic activity of endothelium (~0.01 Hz), respectively. Previous studies by our group have shown that decreased vasodilation with age during local heating is associated with diminished metabolic, neurogenic, and myogenic activities [6] and that altered SBF dynamics in advanced age could be characterized by a loss of complexity [7].

Various nonlinear measures have been introduced to probe different aspects of complexity of physiological time series, among which sample entropy (S_E) [9] is commonly used to quantify the degree of regularity of time series. S_E is defined as the negative natural logarithm of the conditional probability that any two vectors of successive data points are within a tolerance r for m points remain within the tolerance at the next point. Although S_E has been demonstrated to have important advantages over approximate entropy [9], we found that for temporally correlated data, $S_E$value depends on the relationship between the frequency of the studied dynamics and the sampling rate. As a consequence, when data are oversampled, S_E may give misleading results.

A possible approach for resolving the above problem is to include a lag between successive data points of the vectors to be compared. This idea has been proposed by Richman et al. [10] and Govindan et al. [11] but, to our knowledge, has not been applied to real data. Additionally, no study has been conducted to address the choice of the lag for SBF data. We found that for simulated deterministic signals and SBF data, the first minimum of the automutual information (MI) function is a good choice of the lag.

In this study, we propose to modify the definition of S_E by including a lag between successive data points of the vectors to be compared with the lag being the first minimum of the auto MI function. We tested the performance of modified S_E using simulated signalsand SBF data. Then, we applied the modified S_E approach to sacral SBF response to local heating in young and older adults. We hypothesized that modified S_E would be able to characterize alterations in SBF dynamics in older adults.

II. Methods

A. Subjects

Seventeen healthy young subjects and 13 older subjects were recruited into this study. The young group included 8 males and 9 females, age 25±5.6 yrs (mean ± SD), and body

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mass index 23.6±2.8 kg/m^2; the older group included 6 males and 7 females, age 72.3±5.8 yrs, and body mass index 25.1±2.4 kg/m^2. The exclusion criteria included any diagnosed cardiopulmonary diseases, smoking history, or use of any medication that may affect cardiopulmonary function. This study was approved by a university institutional review board for human subject research.

B. Data Acquisition

Room temperature was maintained at 24±2°C. Each subject was asked to stay in the laboratory for at least 30 min to acclimate to the room temperature. When the subject was in a prone position, a combined probe of heating and laser Doppler flowmetry (LDF) (Probe 415-242 & PF5010, Perimed AB) was used to heat the sacral skin to 42°C in 2 min and to maintain that temperature level. Skin blood flow was recorded by LDF at a sampling rate f_s=32 Hz. The protocol included a 10-min baseline, a 50-min heating period, and a 10-min recovery period. Fig. 1 shows typical SBF responses in a young subject and an older subject.

C. Sample Entropy S_E

For a time series of length N, $\{x(i),\ i = 1, \dots,\ N\}$, the S_E algorithm is as follows [9].

Consider vectors of length m: $\mathbf{x}_m(i) = \{x(i+k), 0 \le k \le m-1\}$, $1 \le i \le N-m$. The distance between two such vectors is defined as $d[\mathbf{x}_m(i), \mathbf{x}_m(j)] = max\{|x(i+k) - x(j+k)|, 0 \le k \le m-1\}$. For a given vector $\mathbf{x}_m(i)$, let $n_i^m(r)$ be the number of vectors $\mathbf{x}_m(j)$ that satisfy the condition $d[\mathbf{x}_m(i), \mathbf{x}_m(j)] \le r$, where $j \ne i$. Thus $C^m(r) = [\sum_{i=1}^{N-m} n_i^m(r)]/(N-m)$ represents the probability that any vector $\mathbf{x}_m(j)$ is within r of the vector $\mathbf{x}_m(i)$. Likewise, $C^{m+1}(r)$ represents the probability that any two vectors $\mathbf{x}_{m+1}(i)$ and $\mathbf{x}_{m+1}(j)$ are within r of each other, where $j \ne i$. S_E is defined as

$$S_E(m,r) = lim_{N\to\infty} -ln\frac{C^{m+1}(r)}{C^m(r)}, \quad (1)$$

which is estimated by the statistic

$$S_E(m,r,N) = -ln\frac{C^{m+1}(r)}{C^m(r)}. \quad (2)$$

The tolerance r is usually set to be r×SD, where SD is the standard deviation of normalized time series (SD=1).

A problem with S_E is that for temporally correlated data, S_E is dependent on the relationship between the frequency of the studied dynamics and the sampling rate. To demonstrate this point, we calculated S_E for the sine wave $sin(2\pi \cdot 0.1t)$ and the variable x_1 of Rössler attractor

$$\begin{aligned} dx_1/dt &= -x_2 - x_3, \\ dx_2/dt &= x_1 + 0.2x_2, \\ dx_3/dt &= 0.2 + x_3(x_1 - 5.7). \end{aligned} \quad (3)$$

As shown in Fig. 2, for the sine wave and Rössler attractor, S_E of the series sampled at δ_t=0.125 is greater than that of the series sampled at δ_t=0.0625 for m=2, 3. With increasing m values, the difference in S_E due to different sampling intervals becomes smaller. For the SBF signal shown in Fig. 1 during 1-10 min (young subject), S_E of the series sampled at f_s=8 Hz is distinctively different from that of the series sampled at f_s=16 Hz for m from 2 to 5.

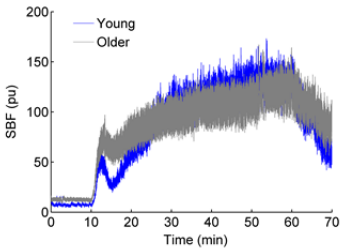

Fig. 1. Sacral skin blood flow (SBF) in response to rapid local heating to 42°C in a young subject and an older subject. pu, perfusion unit.

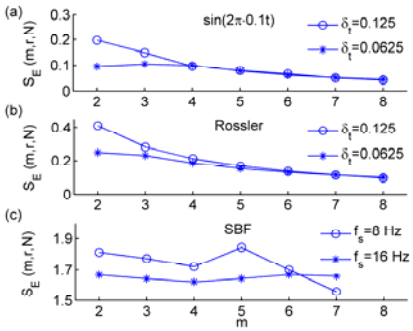

Fig. 2. Values of sample entropy, $S_E(m,r,N)$, for numerically simulated signals and SBF data, where r=0.2 and N=4800. (a) $S_E(m,r,N)$ for $sin(2\pi \cdot 0.1t)$ sampled at δ_t=0.125 and 0.0625, respectively. (b) $S_E(m,r,N)$ for the variable x_1 of Rössler attractor sampled at δ_t=0.125 and 0.0625, respectively. (c) $S_E(m,r,N)$ for the SBF signal shown in Fig. 1 during 1-10 min (young subject) sampled at f_s=8 and 16 Hz, respectively.

The dependence of S_E on sampling rate is mainly attributed to the correlation in time series. When data are sampled at a higher sampling rate, values of successive data points are more close to each other and hence two vectors within r for m points likely remain within r at the next point. In this case, a larger value of $C^{m+1}(r)/C^m(r)$ will be obtained, which leads to a smaller value of S_E. In contrast, a lower sampling rate leads to a lager value of S_E. This means that different sampling rates can lead to different interpretations of the same process in terms of "regularity". Later we will show that if SBF data are oversampled, S_E may not be able to reflect changes in BFO in the frequency interval 0.0095-2 Hz.

D. Modified S_E

The influence of sampling rate on S_E estimation may be eliminated by including a lag between the successive data points of the vectors to be compared. We make two alterations to the original S_E algorithm. First, we use time-lagged vectors, which have the following form

$$\begin{aligned} &\mathbf{x}_m^\tau(i) = \{x(i+k\tau), 0 \le k \le m-1\}, \\ &1 \le i \le N - m\tau, \end{aligned} \quad (4)$$

where τ is the lag. The condition $1 \le i \le N - m\tau$ ensures that $\mathbf{x}_{m+1}^\tau(i)$ will be defined when $i = N - m\tau$. Second, when counting the number of $\mathbf{x}_m^\tau(j)$ that are within r of $\mathbf{x}_m^\tau(i)$, we consider only the vectors $\mathbf{x}_m^\tau(j)$ that satisfy $|j-i| > \tau$; likewise, for each vector $\mathbf{x}_{m+1}^\tau(i)$, we consider only the vectors $\mathbf{x}_{m+1}^\tau(i)$ that satisfy $|j-i| > \tau$. This constraint condition is aimed to minimize the influence of the correlation on entropy estimation. The modified S_E is denoted as $S_E(m,r,\tau,N)$.

To calculate $S_E(m,r,\tau,N)$, it is critical to choose an appropriate lag τ. In previous studies on this topic, the lag has been chosen as the first zero crossing of the autocorrelation function [12], the time point where the autocorrelation function drops to $1/e$ or $1-1/e$ of its initial value [13, 14], or the first minimum of the auto MI function [15]. Abarbanel [16] suggested that the first minimum of the auto MI function is a more appropriate choice of the lag because MI function can be viewed as a nonlinear analog of the autocorrelation function. In our case, because SBF data exhibit long-range correlations, the autocorrelation function descends very slowly with increasing lag. The lag where the autocorrelation function drops to $1/e$ or $1-1/e$ of its initial value would be too large for reconstructing vectors. Alternatively, we found that the first minimum of the auto MI function is a good choice of the lag.

E. Validation of Modified S_E

We first examined whether $S_E(m,r,\tau,N)$ depends on sampling rate. As shown in Fig. 3, for the sine wave and Rössler attractor, $S_E(m,r,\tau,N)$ is independent of sampling rate for m from 2 to 8. For the SBF signal shown in Fig. 1 during 1-10 min (young subject), $S_E(m,r,\tau,N)$ is independent of sampling rate for m from 2 to 5 (Fig. 3c).

We next tested whether $S_E(m,r,\tau,N)$ and $S_E(m,r,N)$ are able to reflect changes in BFO in response to local heating. As mentioned earlier, it has been found that SBF signals in human skin contain five characteristic frequency components in the frequency interval 0.0095-2 Hz [8], each of which corresponds to a specific underlying mechanism. We performed the following experiment. For the SBF signal shown in Fig. 1 (young subject), we calculated $S_E(m,r,\tau,N)$ and $S_E(m,r,N)$ for the 1-10 min and 51-60 min segments before and after removing the components with frequencies higher than 2 Hz. The parameters m=2, 3, 4, 5 and r=0.2 were used. Fig. 4 shows the results for the SBF signal sampled at 32 Hz. For the original signal, $S_E(m,r,N)$ of the 51-60 min segment is much lower than that of the 1-10 min segment, whereas for the filtered signal, $S_E(m,r,N)$ values of the two segments are almost identical. This implies that when SBF signals are sampled at 32 Hz, $S_E(m,r,N)$ does not reflect changes of BFO below 2 Hz. In contrast, $S_E(m,r,\tau,N)$ shows distinct differences between two segments for both the original and filtered signals, suggesting that $S_E(m,r,\tau,N)$ is able to reflect changes of BFO below 2 Hz.

F. Application of Modified S_E to SBF Data

Because the second peak of local heating-induced SBF response reflects microvascular endothelial function [4, 5], we calculated $S_E(m,r,\tau,N)$ and $S_E(m,r,N)$ for SBF signals during the baseline (1-10 min) and second peak (51-60 min). The parameters m=2, 3, 4, 5 and r=0.2 were used. For each data series, the lag τ was chosen as the first minimum of the auto MI function. To further validate the proposed method, we also calculated $S_E(m,r,\tau,N)$ and $S_E(m,r,N)$ for the SBF signals resampled at 8 Hz. Wilcoxon signed rank test was used to examine the difference between the baseline and second peak; Wilcoxon rank sum test was used to examine the difference between two groups. All statistical tests were performed using SPSS 16 (SPSS, Chicago, IL) and the significant level was set at 0.05.

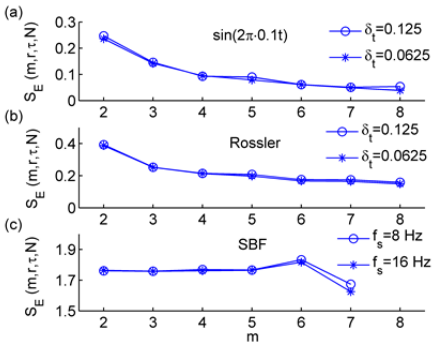

Fig. 3. The modified sample entropy, $S_E(m,r,\tau,N)$, for numerically simulated signals and SBF data, where r=0.2 and N=4800. The lag τ was determined separately for each time series. (a) $S_E(m,r,\tau,N)$ of $sin(2\pi\cdot 0.1t)$ sampled at δ_t=0.125 and 0.0625, respectively. (b) $S_E(m,r,\tau,N)$ of the variable x_1 of Rössler attractor sampled at δ_t=0.125 and 0.0625, respectively. (c) $S_E(m,r,\tau,N)$ of the SBF signal shown in Fig. 1 during 1-10 min (young subject) sampled at f_s=8 and 16 Hz, respectively.

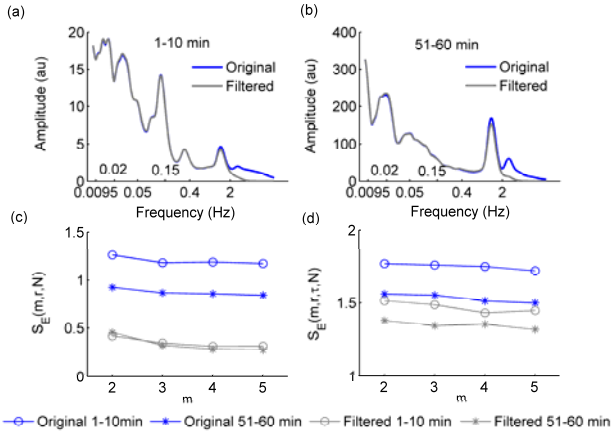

Fig. 4. $S_E(m,r,\tau,N)$ and $S_E(m,r,N)$ of the SBF signal shown in Fig. 1 (young subject) during 1-10 min and 51-60 min before and after removing the components with frequencies higher than 2 Hz. The data series were sampled at 32 Hz. The parameter r=0.2 and N=4800 were used. (a) (b) Wavelet amplitude spectra of the original and filtered signals during 1-10 min and 51-60 min. Here, wavelet amplitudes were averaged absolute values of the wavelet transform over time. The Morlet wavelet was used to implement continuous wavelet transforms. (c) For the original signal, $S_E(m,r,N)$ shows distinct difference between the 1-10 min segment and 51-60 min segment, whereas for the filtered signal, $S_E(m,r,N)$ yields almost identical values for the two segments. (d) $S_E(m,r,\tau,N)$ shows distinct difference between the two segments for both the original and filtered signals.

III. RESULTS

Fig. 5 shows the results of $S_E(m,r,\tau,N)$ and $S_E(m,r,N)$ of the SBF data. The values of lag τ did not show significant difference either between the baseline and second peak or between two groups (Fig. 5a). Since the values of $S_E(m,r,\tau,N)$ for f_s=32 Hz were almost identical to those for f_s=8 Hz, only the results for f_s=32 Hz are presented (Fig. 5b). However, the results of $S_E(m,r,N)$ for f_s=32 are different from those for f_s=8 Hz (Fig. 5c, 5d).

The results showed that in both groups, $S_E(m,r,\tau,N)$ of BFO during the second peak is significantly lower than that during the baseline ($p<10^{-3}$) (Fig. 5b). Although $S_E(m,r,\tau,N)$ of BFO during the baseline does not show significant difference between two groups ($p>0.05$), during the second

peak it shows significantly lower values in older adults compared to young adults ($p<10^{-3}$).

IV. Discussions and Conclusions

In this paper, we propose a modified S_E approach for the assessment of SBF dynamics. The new measure reflects the degree of regularity of time series regardless of sampling rate. Using the new approach, we observed a more regular behavior of BFO during the maximal vasodilation period compared to the baseline in young and older adults and a more regular behavior of BFO in older adults compared to young adults.

The algorithm of S_E is based on the assumption that the vectors to be compared are independent of each other [9]. However, there might be many pairs of matched vectors that are dependent because of the correlation of the data and overlapping pairs of matches with points in common. In the modified S_E algorithm, any two successive data points of the vectors are separated by a lag τ. Abarbanel [16] suggested that when the lag τ is chosen as the first minimum of the auto MI function, the measurements are somewhat independent, but not statistically independent. Because the lag in time is a constant, the first minimum of the MI function is usually proportional to the sampling rate. This feature ensures a constant degree of dependence between successive data points of the vectors to be compared when different sampling rates are used.

A great difficulty of analyzing BFO is the extremely low frequencies of the oscillatory components associated with the local control mechanisms of SBF. The characteristic frequency of the cardiac component (~1 Hz) is about 100 times the characteristic frequency of the endothelia-related metabolic activity (~0.01 Hz). Thus, any sampling rate that is appropriate for the cardiac component may be too high for the metabolic component. As we demonstrated earlier, when using a sampling rate of 32 Hz, S_E does not to reflect changes of BFO with frequencies below 2 Hz (Fig. 4c), whereas when using a sampling rate of 8 Hz, changes of BFO below 2 Hz indeed result in changes in S_E (Fig. 5d). Therefore, when applying S_E to SBF data considerations need to be given as to what sampling rate should be used and cautions should be taken in interpreting the results. Our results show that modified S_E can yield consistent results regardless of sampling rate (Fig. 4d).

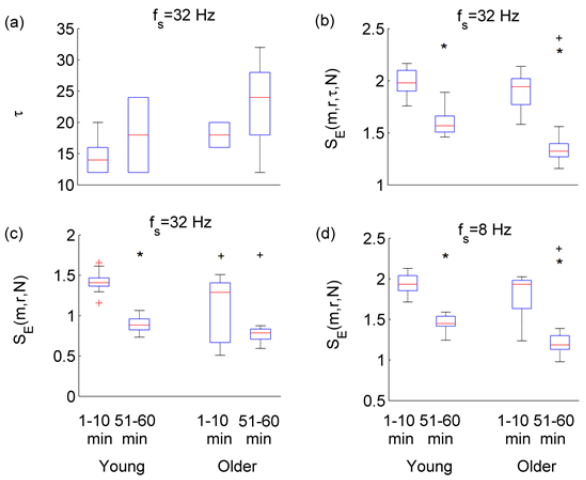

Fig. 5. Results of $S_E(m,r,\tau,N)$ and $S_E(m,r,N)$ for SBF data during the baseline (1-10 min) and second peak (51-60 min) period in young and older adults. The parameters m=2, 3, 4, 5 and r=0.2 were used. Only the results for m=3 are shown. The stars indicate a significant difference between 1-10 min and 51-60 min period ($p<10^{-3}$); the pluses indicate a significant difference between two groups ($p<10^{-3}$). (a) Box plots of τ for f_s=32 Hz. (b) Box plots of $S_E(m,r,\tau,N)$ for f_s=32 Hz. (c) Box plots of $S_E(m,r,N)$ for f_s=32 Hz. (d) Box plots of $S_E(m,r,N)$ for f_s=8 Hz.

Our results indicate that during the second peak (51-60 min) BFO were more regular compared to the baseline in both groups, especially for older adults, and that BFO were more regular in older adults compared to young adults (Fig. 5b). However, to fully understand the mechanism associated with impaired vasodilation in older adults, further studies may be required to identify the reasons responsible for more regular behavior of BFO in older adults during the second peak.

In summary, our results suggest that the modified S_E is able to reflect the degree of regularity of BFO regardless of sampling rate. This approach may be useful in the study of SBF dynamics.

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