Multiscale Analysis of Microvascular Blood Flow and Oxygenation

Marjola Thanaj, Andrew J. Chipperfield, and Geraldine F. Clough

Abstract

The purpose of this study is to investigate the feasibility of nonlinear methods for differentiating between haemodynamic steady states as a potential method of identifying microvascular dysfunction. As conventional nonlinear measures do not take into account the multiple time scales of the processes modulating microvascular function, here we evaluate the efficacy of multiscale analysis as a better discriminator of changes in microvascular health. We describe the basis and the implementation of the multiscale analysis of the microvascular blood flux (BF) and tissue oxygenation (OXY: oxyHb) signals recorded from the skin of 15 healthy male volunteers, age 29.2 ± 8.1y (mean ± SD), in two haemodynamic steady states at 33 °C and during warming at 43 °C to generate a local thermal hyperaemia (LTH). To investigate the influence of varying process time scales, multiscale analysis is employed on Sample entropy (MSE), to quantify signal regularity and Lempel and Ziv (MSLZ) and effort to compress (METC) complexity, to measure the randomness of the time series. Our findings show that there was a good discrimination in the multiscale indexes of both the BF ($p = 0.001$) and oxyHb (MSE, $p = 0.002$; METC and MSLZ, $p < 0.001$) signals between the two haemodynamic steady states, having the highest classification accuracy in oxyHb signals (MSE: 86.67%, MSLZ: 90.00% and METC: 93.33%). This study shows that "multiscale-based" analysis of blood flow and tissue oxygenation signals can identify different microvascular functional states and thus has potential for the clinical assessment and diagnosis of pathophysiological conditions.

Keywords

Blood flow • Tissue oxygenation • Skin microcirculation
Sample entropy • Lempel and Ziv complexity
Effort to compress complexity • Multiscale analysis

1 Introduction

Blood flow in microvascular networks has been investigated in a range of physiological and pathophysiological states [1]. Recent studies have shown that in many disease states, such as metabolic disease and ageing, appears to be a reduction in the adaptive capabilities of the microvascular network and a consequent loss of physiological information content [2, 3].

Previously [4], we have investigated the time-dependent behaviour of microvascular blood flux and tissue oxygenation using time series analysis, power spectral density and complexity. We found differences in the spectral composition of the signals that were influenced by local skin warming such that differences in complexity were observable in the two haemodynamic steady states.

Nonlinear methods such as entropy and complexity techniques have been used widely to quantify the regularity and the randomness, respectively, of physiological signals and are well suited for the analysis of short length signals [5–8]. We and others have applied these approaches to BF signals derived from the skin in humans [4] and in animal models [7, 9], demonstrating clear differences in Lempel and Ziv (LZ) complexity between haemodynamic states. These studies demonstrate a diagnostic potential for complexity analysis of microvascular BF signals.

However, traditional algorithms for measuring entropy and complexity have the drawback that they can only study the behaviour at one scale. To address this, Costa et al. [2] introduced an improved multiscale entropy algorithm to

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L. Lhotska et al. (eds.), *World Congress on Medical Physics and Biomedical Engineering 2018*,
IFMBE Proceedings 68/2, https://doi.org/10.1007/978-981-10-9038-7_36

estimate the entropy over multiple scales. Such multiscale analyses have been shown to be effective in quantifying the complexity of physiological signals in multiple spatial and temporal scales [2, 6, 10]. Similar studies [11], applied the multiscale entropy in the cardiac inter-beat interval to measure the regularity of the cardiac signal of young, elderly and subjects with heart failure in both waking and sleeping periods. They found good discrimination between these periods for all groups and reported that the multiscale entropy analysis was a valid method for quantifying the complexity of the cardiac signal across multiple scales.

In this study, we aim to investigate the feasibility of nonlinear methods for differentiating between signals derived from the microvasculature during two haemodynamic steady states. We explore the changes in entropy and complexity of the microcirculatory dynamics using multiscale analysis of sample entropy (SampEn), LZ and effort to compress (ETC) complexity methods in order to understand the effect of scale on these nonlinear metrics and their efficacy in classifying these haemodynamic steady states.

2 Methodology

2.1 Subjects

Microvascular blood flux (BF) and oxygenation (OXY: oxyHb) signals were recorded from the skin of 15 healthy male volunteers, age 29.2 ± 8.1y (mean ± SD). BF and OXY recordings were obtained at the skin of the forearm using a combined laser Doppler flowmetry (LDF) and white light reflectance (WLS) probe mounted in a heating block (Moor Instruments Ltd, Axminster UK) in two haemodynamic steady states, with the heating block clamped at 33 °C and during warming to 43 °C to generate a local thermal hyperaemia (LTH).

2.2 Study Procedure

All recordings were captured at a sampling rate of 40 Hz using the manufacturer's software. Figure 1 illustrates the BF, oxyHb and the temperature outputs and the selection of the 10 min artefact free segments marked as grey at 33 °C and at 43 °C, respectively. The truncated data could then be analysed and calculations made for the multiscale analysis. We elected to focus on the oxyHb output as the prime OXY signal for the nonlinear analysis as suggested by our previous studies [4].

2.3 Signal Analysis

Encoding

Nonlinear methods such as complexity measures are based on the complex information content of a finite time series to calculate the regularity of a binary time series representation. From previous studies [12, 13], it was reported that the binary conversion is sufficient to estimate the complexity in biomedical signals. As suggested by Yang et al. [14] a straightforward way to maintain the important characteristics of the dynamics contained in the original physiological signal is by using the increase and decrease encoding method whereby a zero is recorded if a value is less than the previous value in the time series or a one otherwise. Here this method will be referred to as delta encoding.

Nonlinear Analysis

The nonlinear methods employed here are estimated as follows:

Sample entropy: Sample entropy (SampEn) [15] was used to quantify signal regularity a time series. SampEn provides an applicable finite sequence formulation that discriminates the data sets by a measure of regularity, from totally regular to completely random. This method measures the logarithmic likelihood that runs of samples that are close for m continuous observations that remain close (within the same tolerance window r) on subsequent incremental comparisons.

$$SampEn(m, r, N) = \ln \frac{\Phi^m(r)}{\Phi^{m+1}(r)}$$

As suggested in the literature [15, 16], the parameter values to calculate SampEn can be chosen as $m = 2$ and $r = 0.15$ times the standard deviation of the binary time series.

Lempel and Ziv complexity: Lempel and Ziv (LZ) [17] complexity is a method for quantifying the randomness present in a sequence by estimating the number of production processes contained in a binary sequence, S. The production process called production history, $H(S)$, is denoted as:

$$H(S) = S(1, h_1)S(h_1 + 1, h_2)\ldots S(h_{m-1} + 1, h_m),$$

where m are the "words" of the history, h. The sequence is parsed from left to right and the complexity increases by one unit when a new sub-sequence of continuous symbols is encountered.

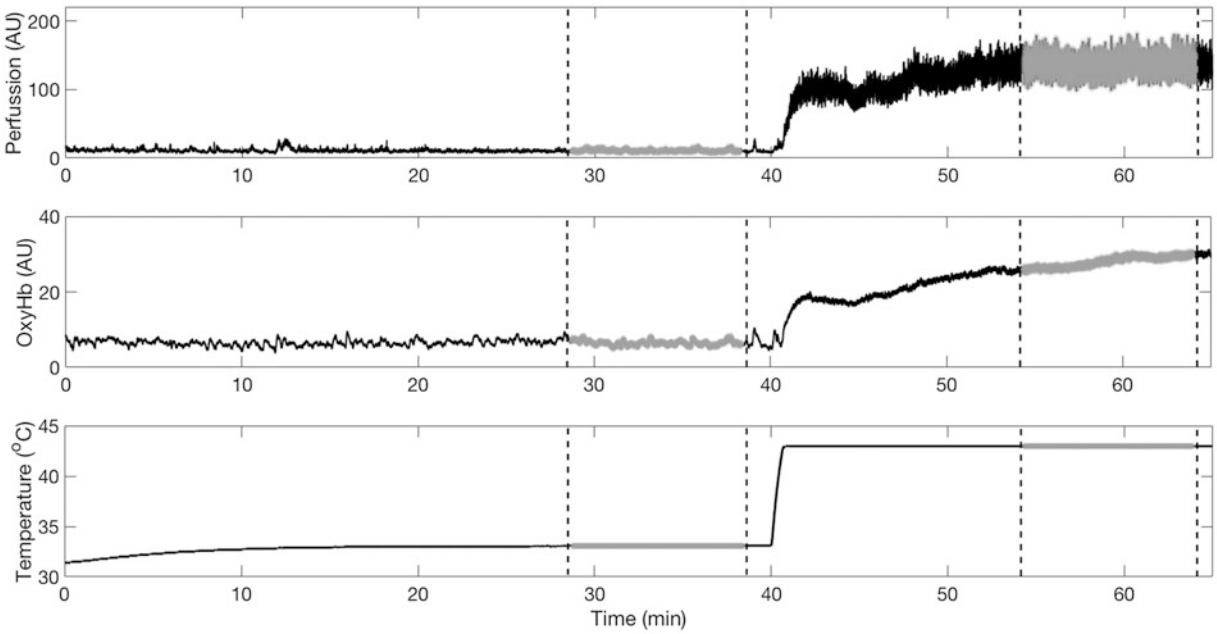

Fig. 1 Selection of the 10 min segments (grey area) for the data analysis at 33 and 43 °C. Blood flow in arbitrary perfusion units (PU), oxygenated haemoglobin (oxyHb) and temperature (°C) plots were obtained from one individual (Color figure online)

In order to define the complexity $c(S)$ of a sequence S, let denote $c_H(S)$ the least number of the components generated form the history $H(S)$ so,

$$c(S) = \min\{c_H(S)\}$$

To obtain a complexity measure independent of the length of the sequence, $c(S)$ should be normalized as:

$$C(S) = \frac{c(S)}{\frac{n}{log_2(n)}}$$

Effort to compress complexity: Effort to compress (ETC) complexity [18] is a similar complexity method based on the lossless compression algorithm known as Non-sequential Recrusive Pair Substitution (NSRPS) [19]. ETC complexity is defined by the pair of symbols with the maximum occurrence and replaces all its non-overlapping occurrences with a new symbol at each iteration.

$$N \rightarrow \textit{Number of iterations of NSPRS algorithm for entropy} \rightarrow \textit{zero}$$

Therefore, N is the number of iterations, of NSPRS algorithm, required for the given sequence to be transformed to a constant sequence with zero entropy. Here the ETC complexity is normalized as: $\frac{N}{L-1}, 0 \leq N-1 \leq 1$, with L = length of the sequence.

Multiscale Analysis

These nonlinear measures are used to analyse signals on a single scale, however, when applying these methods in physiological complex systems, it is essential to take into account the multiple time scales in that system. Costa et al. [2], proposed the Multiscale Entropy (MSE) technique for analysing biological signals using the coarse-graining method that resamples the original signal by reducing the scale factor, τ, of the time series and then determining the sample entropy for each scale. So, for a time series $\{x_1, \ldots, x_N\}$, the coarse-grained time series, y^τ, will be:

$$y_i^\tau = \frac{1}{\tau} \sum_{i=(i-1)\tau+1}^{i\tau} x_j, 1 \leq i \leq \mathrm{N}/\tau. \quad (1)$$

Here, the coarse graining method was applied in entropy and complexity methods and we call these procedure multiscale entropy (MSE), multiscale Lempel and Ziv complexity (MSLZ) and multiscale effort to compress complexity (METC).

Statistical Analysis

A Student t-test statistical test was performed to evaluate the differences between of the multiscale analysis of the two haemodynamic steady states for both BF and oxyHb signals. p-values less than 0.05 were taken to indicate statistical significance. Discriminant analysis with leave-one-out

cross-validation (LOO) was applied on multiscale methods of both BF and oxyHb signals, to find the classification accuracy in of all methods between the two haemodynamic steady states.

3 Results and Discussion

We set out to investigate whether the information content in the BF and oxyHb signals could be used to discriminate between two microvascular haemodynamic states in a cohort of healthy volunteers. The results showed a decrease in MSE during LTH in both BF ($p = 0.001$) and oxyHb signals ($p < 0.001$). MSLZ and METC also showed a significant reduction in the complexity in BF signals ($p = 0.001$, for both) and oxyHb signals ($p < 0.001$, for both). The decline in randomness of the skin BF signal that we observe in healthy human skin during LTH is consistent with that reported by Tigno et al. [8] in the skin of primates during skin warming. Recent studies [1, 20] have suggested that the greater variability of the blood flux signal may indicate a more effective microvascular perfusion, whereas a lower variability in microvascular activity may correspond to a loss of the system's ability to adapt to pathophysiological conditions [21].

As shown in Fig. 2 the estimates for entropy and complexity of both BF and oxyHb signals showed a lower variability during LTH compared with the signals at 33 °C.

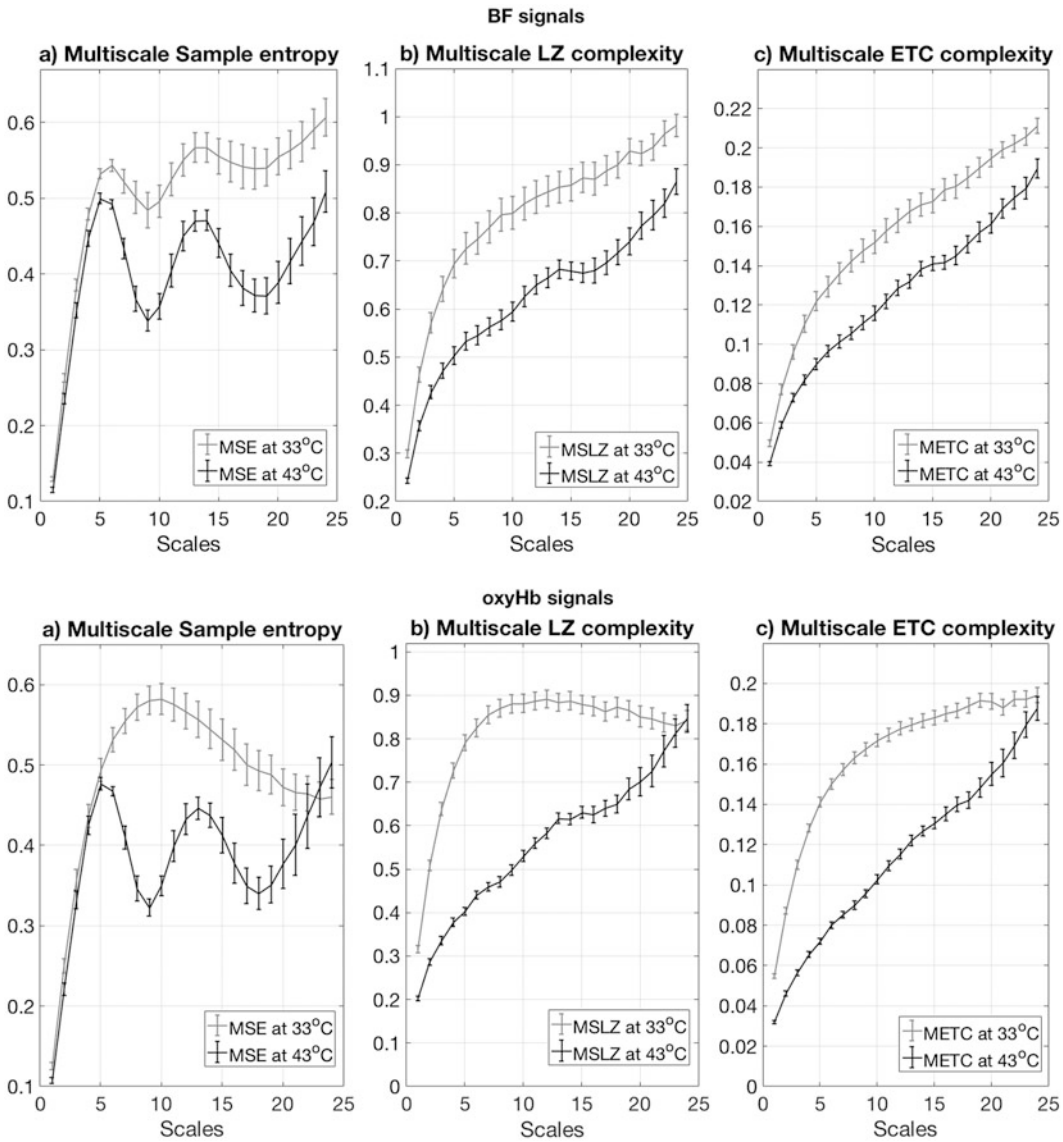

Fig. 2 The average multiscale analysis for BF (upper plots) and oxyHb (lower plots) signals at 33 °C (grey) and at 43 °C (black). **a** MSE, **b** MSLZ, **c** METC. Values are presented as means ± mean standard errors, (n = 15) (Color figure online)

Table 1 Statistical analysis and classification accuracy for all multiscale methods of both BF and oxyHb signals between the two haemodynamic steady states

Methods	BF		oxyHb	
	p-value	Classification accuracy (%)	p-value	Classification accuracy (%)
MSE	0.001	70.00	0.002	86.67
MSLZ	0.001	73.33	<0.001	90.00
METC	0.001	73.33	<0.001	93.33

We also observe that the separation between the haemodynamic states is greater in the oxyHb signal than in the BF signal. It is also worth noting that at the largest scales, the oxyHb signals during local heating become more complex than the ones at 33 °C when using the MSE method and approaches the signals at 33 °C when using both MSLZ and METC complexity measures. This increase of the complexity on larger scales may be a useful new index of increased adaptive capacity in larger time scales.

From Table 1 it is interesting to note that all three multiscale measures relating to the oxyHb signal indicate a good classification accuracy of the two haemodynamic steady states. The highest classification accuracy rates of 90.00% and 93.33% were reached with the MSLZ and METC complexity, respectively. By this test we showed that the characteristics of the multiscale analysis can be used in classification algorithms to separate two different data sets. High accuracy was achieved using the multiscale complexity analysis (MSLZ, METC), which indicates a classification effectiveness of the two haemodynamic steady states using the multiscale complexity measures and therefore, this may be valuable in clinical applications. Kalev et al. [22], using multiscale LZ complexity to examine the EEG signals for objective measures of depression, were able to demonstrate an 86% classification accuracy by accounting for the different frequencies of information content in the EEG. These authors also showed more statistically significant results using the multiscale LZ complexity than using the traditional LZ complexity.

We found that all the multiscale analysis methods we used were able to distinguish between the two haemodynamic steady states. However, we noticed that MSLZ and METC showed a more significant separation than MSE. These findings were consistent with those of Costa et al. [11], who found a good discrimination between wake and sleep periods. We note that the microvascular oxyHb signals showed better separation between the two haemodynamic steady states than the BF signals. This suggests that these measures may be valuable in clinical assessment of conditions of tissue under-perfusion [23].

Recent studies in an animal model have shown that the loss of adaptability throughout the microvascular network may be a major indicator of cardio-metabolic disease risk [21]. They further suggested that the spatial distribution and temporal behaviour of flow in a microvascular network may be more suitable measures with which to understand the impact of disease risk on the microcirculation. More experiments need to be conducted in pathological groups to examine changes in complexity arising from external perturbation for evaluating the microvascular dysfunction.

4 Conclusions and Future Work

In this work, we estimated the regularity and the complexity of microvascular blood flow signals in multiple scales, to inform how a change in system flexibility may allow a microvascular network to adapt to an imposed stressor. All multiscale methods showed a good discrimination between the two imposed haemodynamic steady states. They particularly showed a good discrimination between the oxyHb signals at low and high flows which make these methods a promising tool for further analysis of the microvascular function. For a better understanding of the nonlinear indexes of the microvascular function these methods need now to be extended to disease state.

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