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Attractor Reconstruction Analysis for Blood Flow Signals

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

*Abstract*— Attractor reconstruction analysis has been previously used to determine changes in the shape and variability of fairly periodic signals such as arterial blood pressure signals and electroencephalogram signals, providing a two-dimensional attractor with features like density and symmetry. Since BF signals are fairly periodic and quasi-stationary, we set out to investigate whether attractor reconstruction method could be applied in signals derived from the microvascular perfusion. We describe the basis and the implementation of attractor reconstruction analysis of the microvascular blood flux (BF) signals recorded from the skin of 15 healthy male volunteers, age 29.2 ± 8.1y (mean ± SD). The efficacy of attractor reconstruction analysis (ARA) as a potential method of identifying changes in the microvascular function is evaluated in two haemodynamic steady states, at 33°C, and during warming at 43°C to generate a local thermal hyperaemia (LTH). Our findings show a significant drop of the maximal density derived from the ARA, during increased flow and that there was good discrimination of the blood flow signals between the two haemodynamic steady states, having good classification accuracy (80%). This study shows that ARA of BF signals can identify different microvascular functional states and thus has a potential for the clinical assessment and diagnosis of pathophysiological condition.

*Keywords*— Microvascular blood flow, attractor reconstruction analysis.

# INTRODUCTION

Microvascular perfusion has been investigated in a range of physiological and pathophysiological states [1]. Recent studies have shown that in many cardio-metabolic disease states and in ageing there 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, 5], we have investigated the time-dependent behaviour of microvascular blood flux and tissue oxygenation using time series, power spectral density and complexity (Lempel and Ziv complexity) analysis. We found differences in the spectral composition of the signals that were influenced by local skin warming such that differences in the nonlinearity were observable in the two haemodynamic steady states.

Recently, a new approach, attractor reconstruction analysis (ARA), which quantifies the changes in the morphology and variability of a quasi-periodic signal without affecting the signal information. Aston et al. [6] have applied ARA to arterial blood pressure (ABP) signals, photoplethysmogram (PPG) signals and electrocardiogram (ECG) signals captured from animals and humans with and without pharmacological treatment and shown it to identify changes in the cardiovascular function [3, 6-9]. González et al. [10], investigating the attractors of rheoencephalographic signals in human volunteers, found that nonlinear features derived from the attractors, were able to detect the changes in the cerebral blood flow during apnoea.

In this study, we aim to investigate the feasibility of attractor reconstruction method in order to enable the characterisation of the flexibility of the microvascular network. We explore the changes of the microcirculatory dynamics using attractor reconstruction analysis to understand the applicability of this mathematical approach and its efficacy in classifying two haemodynamic steady states.

# Methodology

## A. Subjects

Microvascular blood flux (BF) signals were recorded from the skin of 15 healthy male volunteers, age 29.2 ± 8.1y (mean ±SD). The 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) under two haemodynamic steady states, (i) with the heating block clamped at 33 and (ii) during warming to 43 to generate a local thermal hyperaemia (LTH). All recordings were captured at a sampling rate of 40 Hz using the manufacturer’s software. Data were exported to Matlab (R2018a, Mathworks, UK) for analysis. The study was approved by the Research Ethics Committee of University of Southampton and Southampton General Hospital (REC Number: SOMSEC091.10; RHMMED0992). The study was performed in accordance with standards set by the Declaration of Helsinki.



## B. Signal Analysis

BF signals are fairly periodic and quasi-stationary signals to which we can apply the attractor reconstruction analysis method. However, before performing this analysis, the data were filtered with a finite impulse response (FIR) filter using a Hamming window to design a 20th order low pass filter with 2 Hz cut-off frequency to attenuate high frequencies beyond the known range of microvascular oscillation, 0.0095 - 1.6Hz [11]. The data where then resampled to increase the sampling rate up to 160Hz and therefore increase the number of data points for analysis. A stationarity test was applied in the processed time series to examine whether our data had a consistent variance over time.

## C. Attractor Reconstruction Analysis (ARA)

Attractor reconstruction analysis was introduced by Aston et al. [6], to determine the changes in the variability of heart rate in arterial blood pressure and ECG signals. The main aim of this analysis is to perform and assess the variability of a quasi-periodic signal as a form of an attractor. The steps of the ARA are summarized below as [7, 8]:

* First, the signals are reconstructed in three-dimensional space with a time delay, τ, computed using the mutual information analysis where the average mutual information between two instances and reaches its first relative minimum [12, 13]. So, for a time series , the two additional variables will be: and . The reconstructed phase space can be now plotted as .
* Then, the variation of the time series of the attractor is removed by projecting the attractor in two-dimensional space, referred as plane (v, w) perpendicular to the vector forming two new variables: and . The two-dimensional plane (v, w) will be defined as periodic, with period when a symmetric triangular shape is observed.
* To better understand the morphology of the attractor referring to the shape and variability of the time series, the density, is generated providing information based on the thickness or thinness of the attractor indicating the most frequent or infrequent overlap of the region. The density, , is obtained from the square grid with time delay, . Then the data are rotated in and to achieve and , respectively. The average density function will then be: . Here, it is also noted that consists of the average of the three sides of the density and therefore, if the attractor is symmetric then, .
* Then the rotational symmetry of the attractor is calculated as: and plotted over time delay, τ and the optimised time delay, is observed when the symmetry measure is minimized.
* Then the signals period can be calculated as . Blood flow signals consist of multiple frequency components [11, 14]. Therefore, if the signal is dominated by the high frequency heart rate component (~60bpm) then the optimised time delay will be , seconds.
* After achieving the optimized time delay, the two-dimensional density , is constructed and the maximum value of the density defines a thinner attractor and a much more concentrated density.
* The rotational symmetry function of the first and the second optimized time delay, and , respectively are also computed and the ratio of the symmetry measures is estimated as .
* The polar angles of the attractor over a radius of the circle from the centre were also calculated and was defined as the mean of these angles. Then, the mean difference between these angles was defined as angular spread, , where a value close to 0 indicate that the attractor is close to being symmetric.

## D. Analysis Procedure

In this study, the blood flow signals were divided into windows of 20 seconds each to provide sufficient cycle per window and sufficient data points. The density was calculated using a probability density estimate depended on a normal kernel smoothing function at 160 points [15]. Then, the density was generated on square grid boxes with size 160×160 and the volume of the density is normalised to one. Firstly, the ARA method was applied on a 65-minutes blood flow signal of one individual at resting skin temperature (20 minutes), then the heating block clamped at 33 (20 minutes), during transition from 33 to 43 (~50 seconds) and at 43 (~25 minutes). Secondly, to better interpret the two haemodynamic steady states, the BF signals recorded from entire dataset (n=15) where cut into 10-minutes artefact-free segment at both 33 and 43 and ARA was applied in each 20-second window of the signals. The choice of the segments were described elsewhere [4, 5].

## E. Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 25 (IBM United Kingdom Limited, UK). Data were tested for normal distribution using D'Agostino & Pearson omnibus normality test and presented as either mean ± standard deviation (SD) for normally distributed data or median with interquartile range (IQR) for non-normally distributed data.

## F. Classification Analysis

Linear discriminant analysis (LDA) with leave-one-out (LOO) cross-validation [16] was applied on the measures of the ARA, to determine the classification accuracy between two haemodynamic states at 33 and at 43. The features of the ARA for BF signals where determined as: the maximum density, the rotational symmetry and the angular spread. The LDA method was applied to transform the features from a higher dimensional space into a space with lower dimensions, which in this way the ratio of the distance between the means of the classes in the projected space and the scatter within each class is maximized and thereby the classes are maximally separated [16, 17].The accuracy is assessed using the LOO cross-validation in which here 30 runs took place, and in each run the classifier trained the set apart from one sample which was presented as the test set. From the confusion matrix of the LDA analysis the sensitivity and specificity, were also calculated, referred as the true positive rate of the ARA features derived from signals identified as the features at 33 and as the true negative rate of the ARA features derived from signals being identified being as the features at 43, respectively.

# Results

1. a) Windows of 20 seconds each derived from the blood flow signal at 33, during transition time and at 43 oC. b) A blood flow signal of one healthy volunteer at baseline temperature, at 33oC, during transition time from 33 to 43 and during local warming at 43. Lines indicate the end of each window. c) The reconstructed attractors for each of these windows.

Fig. 1 shows how the BF signal variability recorded from one individual changes in different haemodynamic states. The windows of the blood flow signals in Fig. 1(a) illustrate the segments from the signal in Fig. 1(b) corresponding to the attractors in Fig. 1(c). The window of the BF signal at 33 is shown to be dense with many overlaps. The window at the transition time illustrates the BF signal during the last 20 seconds of the transition, showing the increase of the signal amplitude and therefore the attractor becomes wider and less dense. Similarly, the window at 43 shows the BF signal at 43 corresponding to larger attractor as the amplitude of the signals is increased. Additionally, the attractor here was blurred indicating a lower density.

Table I illustrates the statistical analysis for all features of ARA and the classification accuracy of the LDA classifier to classify the blood flow signals from the overall dataset (n=15) between the two haemodynamic states using all the features of ARA. The optimized time delay appeared to be approximately a third of a heart rate cycle in both haemodynamic states. It

1. Statistical Analysis and Classifcation Accuracy for Blood Flow Signals between the two Haemodynamic Steady State

| **ARA measures** | Median(IQR) | LDA classification measures |
| --- | --- | --- |
|  | 0.227(0.036) - 33 oC 0.264(0.080) - 43 oC | Accuracy: 80%  Sensitivity: 93.3%  Specificity: 66.7% |
|  | 0.283(0.457) - 33 oC 0.001(0.002) - 43 oC |
|  | 0.006(0.018) - 33 oC 0.001 (0.001) - 43 oC |
|  | 1.004(0.185) - 33 oC 1.093(0.144) - 43 oC |
|  | 0.080 (0.027) - 33 oC 0.073 (0.021) - 43 oC |

also showed slightly higher values for signals at 43 than at 33. The maximum density measure showed a significant decrease for signals at 43 (0.283(0.457) at 33 and 0.001(0.002) at 43, median (IQR)). Similarly, the rotational symmetry showed values that were closer to 0 for both signals indicating a good symmetry. The ratio of the symmetry measures showed values closer to 1 at both temperatures and the angular spread values for both signal where close to 0 indicating a symmetric attractor at both temperatures. The LDA classifier was able to classify 12 out of 15 subjects giving 80% classification accuracy between the states with a high sensitivity (93.3%) although, the specificity was 66.7% indicating that there was a small percentage (33.3%) of the ARA features derived from the BF signals at 43 being identified as not having the features from the signals at 43.

# Discussion

In this study we have explored the application of the attractor reconstruction analysis of blood flow signals derived from the skin microcirculation. The main purpose of this study was to demonstrate the feasibility of the ARA in identifying changes in the morphology and variability of physiological data under differing haemodynamic conditions. Firstly, we generated the attractors from the entire signal obtained from one individual, under thermoneutral conditions, during the transition and at higher skin temperature. We observed that the attractors generated from the blood flow signal at 33 and during transition time appeared more defined with more overlaps. The attractor during the dynamic changing state showed a larger attractor than the attractor of the BF signal at 33 as it represents the amplitude of the signal. This finding is consistent with the recent study by [3, 7], using attractor reconstruction analysis in arterial blood pressure signals, suggesting that the size of the attractor corresponds to a high amplitude signal.

Attractor reconstruction analysis was then applied in the 15 volunteers at the two haemodynamic steady states at 33 and at 43, showing significant changes in the ARA measures. The time delay from the signals was approximately one third of a heart rate cycle and therefore the attractors was able to quantify the high-frequency component of the blood flow signals. The rotational symmetry measures appeared to be close to 0 for both temperatures indicating a good symmetry of the attractors. Similarly, the ratio of the symmetry measures appeared to be close to 1 indicating a high periodicity of the signals. Moreover, the angular spread for both groups appeared close to 0, indicating that in both haemodynamic states the atractors were symmetric. Recent studies [8], investigating ABP and PPG signals from human volunteers, suggest that the angular spread appeared to identify the performance and reliability of the attractor reconstruction method.

Our findings also demonstrate that the maximal density derived from the signals at 43 decreases during LTH. Here, we show that as the amplitude of the signals increases during vasodilation due to increased local heating, considering that the volume is normalised, the attractor becomes wider and therefore the maximal density is more probable to decrease. Finally, we found that the ARA measures were able to distinguish between the two haemodynamic steady states giving 80% seperability, achieving a higher classification accuracy than the nonlinear methods (73.33%) we used previously in the same dataset [4]. More experiments need to be conducted in pathological groups to investigate changes in ARA measures and evaluating microvascular dysfunction.

# Conclusion

In this work we applied the attractor reconstruction analysis and estimated the measures derived from the attractors, to better evaluate the changes of the microvascular network under an imposed stimulus. The measures showed a substantial decrease in maximal density of the attractors during vasodilation induced through local heating and were able to differentiate between the two haemodynamic steady states. These findings makes the method a promising tool for further analysis of the microvascular function and it suggests that ARA could be used to identify changes in the microvascular system.

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   M. Thanaj is with the Bioengineering Science Group, Faculty of Engineering and Physical Sciences, University of Southampton, Highfield, Southampton, SO17 1BJ England (e-mail: [m.thanaj@soton.ac.uk](mailto:m.thanaj@soton.ac.uk) ).

   A. J. Chipperfield is with the Bioengineering Science Group, Faculty of Engineering and Physical Sciences, University of Southampton, Highfield, Southampton, SO17 1BJ England (e-mail: [a.j.chipperfield@soton.ac.uk](mailto:a.j.chipperfield@soton.ac.uk) ).

   G. F. Clough is with Human Development and Health, Faculty of Medicine, University of Southampton, Southampton General Hospital, SO16 6YD, England (e-mail: [g.f.clough@soton.ac.uk](mailto:g.f.clough@soton.ac.uk)). [↑](#footnote-ref-1)