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ORIGINAL RESEARCH

Convergent cross mapping: a promising technique for cerebral autoregulation estimation

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Abstract

Background: Cerebral autoregulation (CA) is the physiological mechanism that keeps the cerebral blood flow velocity (CBFV) relatively constant despite changes in arterial blood pressure (ABP). Currently, transfer function analysis (TFA) is widely used to assess CA non-invasively. TFA is based on the assumption that CA is a linear process, however, in reality CA is a non-linear process. This study explores the usability of convergent cross mapping (CCM) as a non-linear analysis technique to assess CA.

Methods: CCM determines causality between variables by investigating if historical values of a time-series X(t) can be used to predict the states of a time-series Y(t). The Pearson correlation is determined between the measured Y(t) and the predicted Y(t) and increases with increasing time-series length to converge to a plateau value. When used for CA, normal and impaired CA should be distinguishable by a different plateau value. With impaired CA, ABP will have a stronger influence on CBFV, and therefore the CBFV signal will contain more information on ABP. As a result, the correlation converges to a higher plateau value compared to normal CA. The CCM method was validated by comparing normal CA (normocapnia: breathing 0-2% CO_2) with a model of impaired CA (hypercapnia: breathing 6-7% CO_2).

Results: CCM correlation was higher (p=0.01) during hypercapnia (0.65 ± 0.16) compared to normocapnia (0.51 ± 0.18).

Conclusion: CCM is a promising technique for non-linear cerebral autoregulation estimation.

Keywords: Cerebral autoregulation, Convergent cross mapping, Non-linear analysis.

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Introduction

The high metabolic demand of the brain requires an adequate cerebral blood flow (CBF). However, changes in arterial blood pressure (ABP) or intracranial pressure may influence CBF. To keep CBF relatively constant and to return CBF to baseline after a fast change in ABP, adaption of the cerebrovascular resistance (CVR) occurs. This process is called cerebral autoregulation (CA) [1]. When CA is disturbed, the brain may become excessively sensitive to fluctuations in ABP, causing hypo- and/or hyperperfusion. Hypo- and hyperperfusion can lead to ischemia or haemorrhages, respectively [2]. CA failure has been associated with increased morbidity and mortality [3]. Therefore, the ability of accurately quantifying the quality of CA may be of great importance in clinical practice.

CA can be determined as static CA or dynamic CA. With static CA, the response of the CBF to changes in ABP is studied in a semi-steady state, i.e. a measurement of CBF is obtained first at a constant baseline ABP and constant CBF, followed by another measurement that is taken after the autoregulatory response to a manipulation of ABP has been completed [4]. However, static CA represents the overall effect of the autoregulatory action, but does not address the time in which this is achieved.

The use of Transcranial Doppler (TCD) ultrasound combined with servo-controlled finger photoplethysmography makes it possible to measure the process of CA itself, the dynamic CA [2, 5]. Ideally, clinical monitoring of CA should be non-invasive, continuous, bedside, and precise. Because static CA measurement only provides steady-state point measurements and therefore is not a continuous measurement, the dynamic approach is preferable.

Despite the importance of measuring dynamic CA, there is no consensus about the best way to analyze dynamic CA [6]. Currently, the most frequently described method in the literature is transfer function analysis (TFA) [6]. However, this method is based on the assumption that the relation between ABP and CBF is linear, while physiologically CA exhibits nonlinear dynamics [7]. In our study, a new non-linear analysis method, convergent cross mapping (CCM) is applied to asses dynamic CA. Originally CCM was proposed to detect causality in complex ecosystems. According to its definition, CA can be quantified as the causal influence of ABP on CBF and this causal influence can be determined with CCM. Therefore the goal of this study is to explore the use of CCM in assessing dynamic CA.

Methods

Experimental procedure

The CCM model was validated by comparing normocapnic data with hypercapnic data. Hypercapnia causes vasodilation of the cerebral vasculature and can therefore be used as a model for impaired CA [8]. This study included 19 healthy adults, male and female, with an age of 69 ± 4 (mean ± SD). ABP was measured non-invasively in the middle finger of the right hand using photoplethysmography (Finapres Medical Systems, Amsterdam, the Netherlands). The hand and arm were supported securely and comfortably with a sling, providing a stable position of the hand and arm at the heart level. It has been shown that ABP measured indirectly using the Finapres is a reliable technique to track changes in ABP that correlate well with auscultatory ABP measurements in the upper arm [9]. TCD is used to measure CBF velocity (CBFV) in the middle cerebral artery (MCA) by insonating the left and right MCA using a 2 MHz TCD probe (Multi-Dop, Compumedics DWI, Germany) [10]. It is assumed that changes in CBFV represent changes in CBF, because the diameter of the vessel remains constant [8, 11]. End tidal CO_2 ($etCO_2$) was monitored with a nasal cannula using capnography (Biopax Systems, Goleta, Ca, USA). ABP, CBFV and $etCO_2$ were recorded with a 200 Hz sampling frequency.

Subjects were asked to inhale a gas mixture mimicking room air, containing 0% CO_2, 21% O_2, and 79% N_2 through a tightly fitting mouthpiece until a stable plateau of CBFV had been reached. Next, the percentage of CO_2 was increased every 30 seconds, until a CO_2 concentration of 7% was obtained. The first 90 seconds with a 0-2% CO_2 concentration and the last 90 seconds with 6-7% CO_2 were selected as normocapnia and hypercapnia, respectively. Beat-to-beat data of the ABP and CBFV were obtained using a low pass fourth-order Butterworth filter with a cut-off frequency of 0.5 Hz. Thereafter, CBFV and ABP were downsampled to a sampling frequency of 10 Hz.

Data analysis

Mathematical background of convergent cross mapping

Sugihara et al. [12, 13] presented CCM as a new non-linear analysis method to determine causality between variables in a dynamical system. CCM is described in detail by Sugihara et al [12, 13]. In short, a dynamical system can be represented by a so called attractor manifold (M). **Figure 1A** depicts as example the manifold of the Lorentz attractor consisting of three variables, represented by the time-series X(t), Y(t) and Z(t). Interestingly, the dynamics of a system can also be represented using only one of the time-series, for example Y(t). Lagged coordinates of this time-series, for example Y(t-τ) and Y(t-2τ) can be used to reconstruct a shadow manifold My. (**Figure 1B**). Tau (τ) is defined as a number of samples. My reproduces the two-lobed butterfly of M, i.e. My represents the dynamics of M. Similarly, shadow manifolds Mx and Mz can be reconstructed using X(t) and Z(t), respectively. CCM consists of two main steps that use these shadow manifolds to determine causality between variables: cross mapping and convergence.

Cross mapping

In a dynamical system, consisting of two variables (X(t) and Y(t)), cross mapping investigates if it is possible to

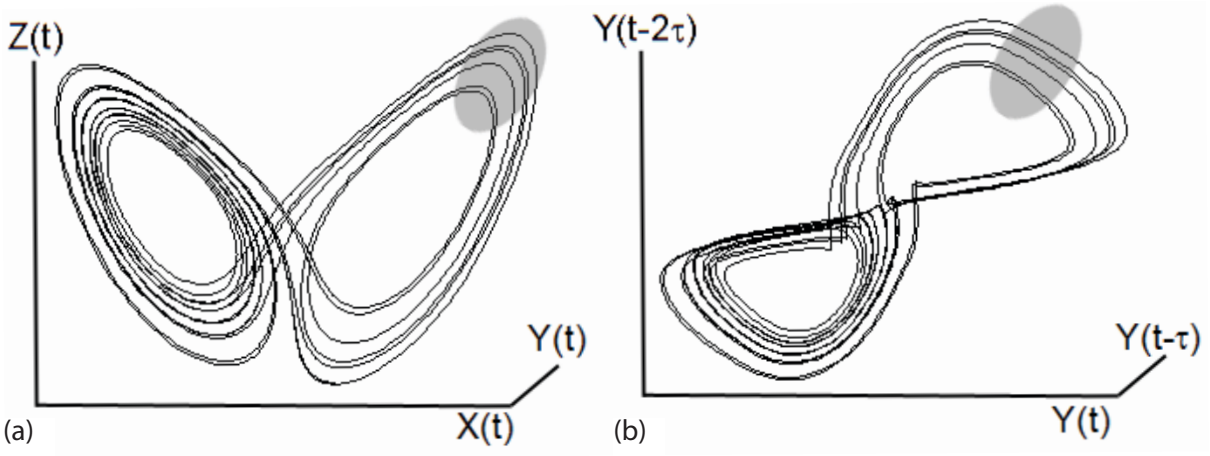

Figure 1. (a) Attractor Manifold (M) of the Lorenz attractor. A point of M is defined by X(t), Y(t) and Z(t). **(b)** Shadow manifold My with E=3 dimensions and τ = 1.4 seconds. Each point on the manifold is defined by Y(t), Y(t-τ) and Y(t-2τ). The grey area in A corresponds to the grey area in B. E = dimensions of the shadow manifold, τ = time-lag. Adapted from Sugihara et al. [12].

predict a point on My from Mx using the nearest neighbor principle.

This nearest neighbor principle is depicted in **Figure 2**. Point A is a random point on Mx and A' is the in time corresponding point of A on My. The basic principle is that if nearest neighbors of A on Mx can accurately predict A' on My, it can be stated that historical values of X(t) can be used to estimate states of Y(t). This is only possible if X(t) contains information on Y(t), in other words as Y(t) causally influences X(t).

Cross mapping is applied to each point on Mx resulting in a prediction of Y(t): $Y_{Pred}(t)$. To estimate the accuracy of the $Y_{Pred}(t)$, the correlation between the $Y_{Pred}(t)$ and Y(t) is determined.

Convergence

Convergence is based on the fact that the longer the time-series length of X(t) and Y(t), the smaller the distance between the trajectories on the manifold. As a result, the estimation error decreases. Therefore, if Y(t) causally influences X(t), the correlation should increase to a plateau value with increasing time-series length, which is defined as convergence. The faster the convergence the stronger the coupling between the two variables.

Figure 3 illustrates the convergence principle [13]. The cases that Y(t) does, and Y(t) does not causally influence X(t) are represented by the solid and dashed line, respectively.

Validation of CCM

CCM is applied to determine CA quality during normocapnia (0-2% CO_2) and hypercapnia (6-7% CO_2). As CA quality can be quantified as the causative effect of ABP on CBFV, the shadow manifold of CBFV was used to predict ABP. Generically, the shadow manifold maps 1:1 to the original manifold M. If a 1:1 mapping occurs then the shadow manifold is defined as an embedding [14]. Optimal embedding parameters, embedding dimension E and lag τ, were determined with the method of Gautama et al. [15], which is based on differential entropy. The determined optimal embedding parameters were E is 3 dimensions and τ is 1 sample. In this study, the correlation corresponding to the plateau value was used instead of the rate of convergence. A window of 890 samples was used to calculate the plateau value. Shifting the window of 890 samples through the entire dataset results in 10 correlations of which the mean is determined. The complete algorithm of CCM is described in more detail in the Supplementary materials of Sugihara et al. [13].

Statistical analysis

Results are presented as means ± standard deviation. Statistical significance was tested using a paired t-test. Significance was set at $p < 0.05$.

Results

Figure 4 depicts the correlation results for normocapnia and hypercapnia. The correlation differed between normocapnia (0.51 ± 0.18) and hypercapnia (0.65 ± 0.16), p = 0.01.

Discussion

Our study showed that the non-linear method of CCM is able to distinguish normal dynamic CA from impaired dynamic CA. In clinical practice, the ability to measure CA may be of great importance, as impaired CA can result in hypo- or hyperperfusion of the brain. Impaired CA is also associated with increased morbidity and mortality [3].

Several methods have been developed to measure CA, however no gold standard exists. In literature, TFA is currently the most applied method to quantify CA. However,

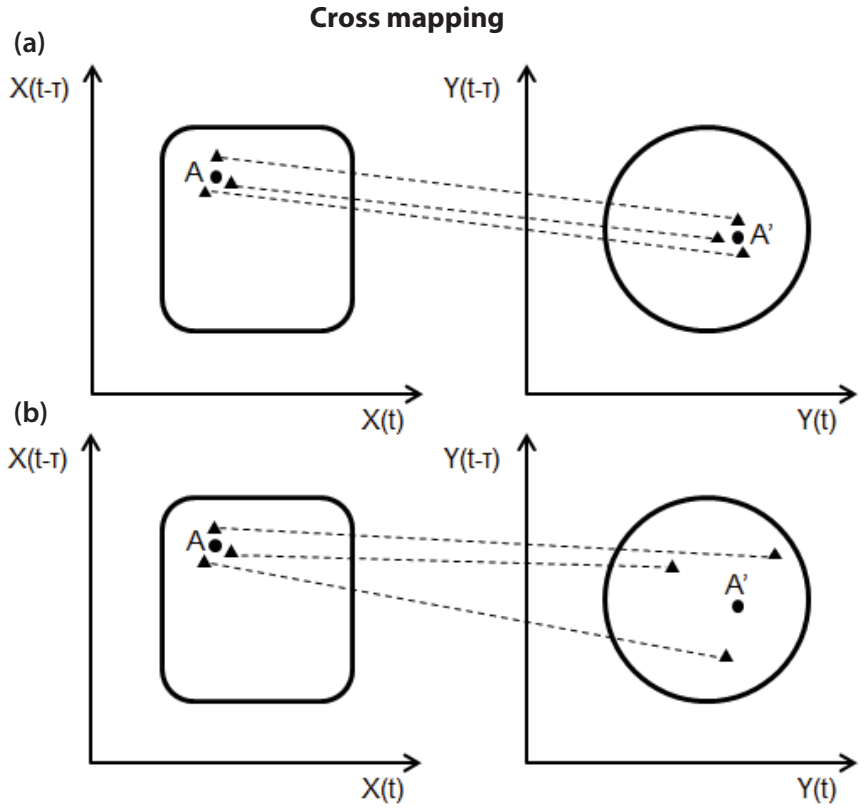

Figure 2. The nearest neighbor principle. **(a)** Nearest neighbors (triangles) of point A (dot) on Mx are also nearest neighbors of the in time corresponding point A' on My. Therefore Mx can be used to estimate the states of Y(t), i.e. Y(t) causally influences X(t). **(b)** Nearest neighbors (triangles) of point A (dot) on Mx are not nearest neighbors of point A' on My. Therefore Mx cannot be used to estimate the states of Y(t). Mx: shadow manifold of M with time-lagged coordinates of X(t) (E=2). My: shadow manifold of M with time-lagged coordinates of Y(t) (E = 2). E = dimension of the shadow manifold. Adapted from Sugihara et al. [13].

this technique assumes that CA is a linear process, while in fact CA exhibits non-linear dynamics. Zhang et al. [16] pointed out that a coherence <0.5 in the low frequency range using TFA is an indicator of non-linear behavior of CA. In addition, Mitsis et al. [7] showed that with the use of a non-linear model (Laguerre-Voltera network) a 20% reduction of the normalized mean square error was seen compared to a linear model when predicting CBFV based on the input ABP.

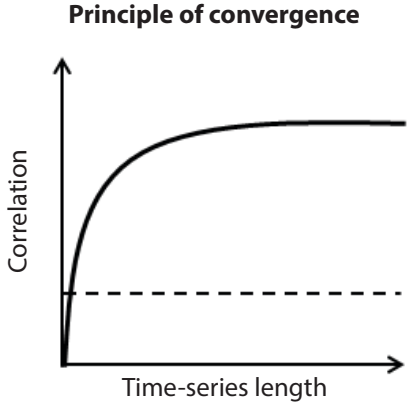

Figure 3. Principle of convergence. **Solid line:** Y causally influences X. **Dashed line:** Y does not causally influence X. The solid line shows convergence with increasing time-series length while the dashed line does not. Adapted from Sugihara et al. [13].

CCM is a non-linear analysis technique, which was originally proposed by Sugihara et al. [12] to detect causality in complex ecosystems. They applied CCM on a classic predator-prey dynamic system. In a classic predator-prey dynamic system, there is bidirectional causality between the predator and the prey, i.e. they both causally influence each other. The correlation converged when predicting the state of the prey using the predator data and also when predicting the state of the predator using the prey data. This indicates indeed that both factors causally influence each other. CCM was also applied on a dynamical system of sardines, anchovies and sea surface temperature. CCM showed that anchovies and sardines do not causally influence each other, but are both causally influenced by the sea surface temperature.

As CCM takes non-linear dynamics into account, this technique might also be more accurate for the quantification of CA. A well-functioning CA attenuates the effect of changes in ABP on changes in CBF, i.e. ABP has as only a small causal influence on CBF. During impaired CA the effect of changes in ABP on changes in CBF are less attenuated, i.e. ABP has a larger causal influence on CBF. There-

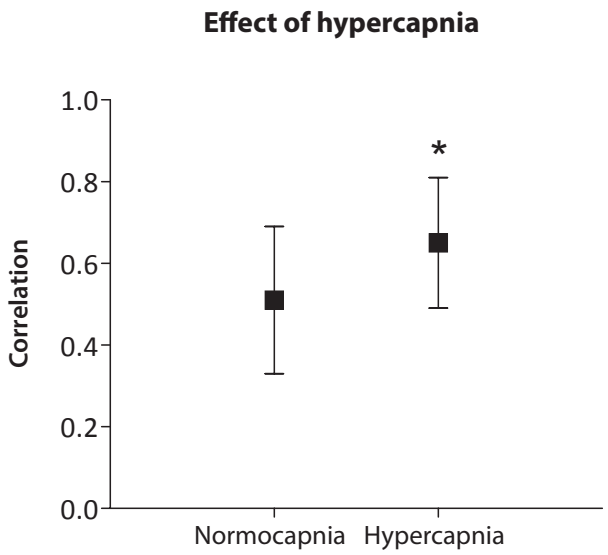

Figure 4. Correlation between real ABP and predicted ABP during normocapnia and hypercapnia circumstances (n=19). Correlation is significantly increased during hypercapnia (breathing 6-7% CO_2) compared to normocapnia (breathing 0-2% CO_2).
* p<0.05. ABP = arterial blood pressure.

fore the causal influence of ABP on CBF is a measure of impairment of CA and CCM can be applied to assess the functioning of CA.

In this study, the ability of CCM to quantify CA was explored using a hypercapnia model. Hypercapnia is a well-known model to simulate impaired CA [17]. Hypercapnia causes vasodilation, reducing the ability of the cerebral vessels to respond to changes in ABP, leading to impaired CA. In our study a significantly higher CCM correlation value was found during hypercapnia which indicates a less efficiently functioning CA. This underlines the potential of CCM to quantify CA.

However, still a large spread is seen in the outcome of CCM. The standard deviation was 0.2 and 0.16 for normo- and hypercapnia, respectively. Therefore, optimization of this technique is necessary before it can be easily applied in clinical practice.

There are several explanations for the large spread in CCM outcomes. First, the degree of impaired CA of each subject during hypercapnia is unknown and might differ between subjects. As a results, the spread in CCM outcome is large. However, breathing 7% CO_2 is the physiological limit. Therefore it is likely that all subjects did reach their plateau of impaired CA.

Second, besides the possible difference in effect of the CO_2 on CA in subjects during hypercapnia, also the breath-to-breath $etCO_2$ fluctuations in normo- and hypercapnia circumstances between subjects might influence the correlation. Mitsis et al. [18] showed that $etCO_2$ fluctuations have a considerable effect in the lower frequencies, i.e. below 0.04 Hz. Incorporating the breath-to-breath $etCO_2$ fluctuations might therefore reduce the spread in CCM outcome.

Third, the respiratory frequency is below 0.5 Hz and because the respiratory frequency is below the cut-off frequency of 0.5 Hz, it is still present in the ABP and CBFV signal. If the respiratory frequency is very constant, prediction of ABP using CBFV might be easier because the fluctuations caused by respiration are then very predictable. This might result in a high CCM outcome value. On the other hand, if the respiratory frequency is less constant, prediction of ABP using CBFV is harder, because the fluctuations caused by the respiration are less predictable. This results in a lower CCM outcome value. Therefore, differences in variability of the respiratory frequency between subjects might be responsible for the large spread in CCM outcome. Using a low-pass filter with a cut-off frequency of 0.15 Hz might reduce the large spread in CCM outcome, because the breathing frequency is above 0.15 Hz. Because CA is most prominent in frequencies below 0.15 Hz, it can be justified to use a cut-off frequency of 0.15 Hz.

Besides the large spread in CCM outcome values, it should also be noted that in this study the plateau value was used to quantify the causal influence of ABP on CBFV instead of the rate of convergence as suggested by Sugihara et al. [12]. The choice for the plateau value was based on a pilot study in which the validity of the model was investigated using the autoregulatory index of Tiecks et al. [4]. In this pilot study, the plateau value could discriminate the autoregulatory indexes. However, a situation might be possible in which the correlation does not converge, but remains horizontal (dashed line in **Figure 3**). In this case, using only the plateau value, might give inaccurate results. If this correlation is high, the plateau value falsely represents a high influence of the ABP on CBFV while actually there is no influence at all. Using the rate of convergence overcomes this problem. In our study, convergence was seen in all subjects during normo- and hypercapnia. Therefore, using the plateau value was seen as a valid choice in this study. Furthermore, calculating the rate of convergence is more time-consuming than calculating the plateau value. This plateau value is therefore more promising for bedside CA monitoring.

Furthermore it should be noted that the used embedding parameters were E=3 dimensions and τ=1 sample. These embedding parameters were determined using the differential entropy technique [15]. A τ of 1 sample is a delay of 0.1 seconds, which is within one heartbeat. It is difficult to interpret this τ physiologically, because a τ of at least one heartbeat (± 8-10 samples) is expected.

Conclusions

The ideal clinical monitoring device of CA should be non-invasive, continuous, bedside and precise. CCM is indeed a non-invasive measurement which uses spontaneous fluctuations of the ABP and CBFV to assess CA. The use of spontaneous fluctuations has the additional advantage that

no interventions have to be performed, making continuously measuring CA possible.

Furthermore, CCM can quantify CA using small datasets and the outcome of CCM is a single value, which is very important and practical for bedside monitoring. When the spread in CCM outcome can be reduced, perhaps with the aforementioned optimizations, CCM could be a very promising technique for future bedside monitoring of CA.

Abbreviations

ABP: Arterial blood pressure; CA: Cerebral autoregulation; CBF: Cerebral blood flow; CBFV: Cerebral blood flow velocity; CCM: Convergent cross mapping; CVR: Cerebrovascular resistance; $etCO_2$: End tidal CO_2; MCA: Middle cerebral artery; TCD: Transcranial Doppler; TFA: Transfer function analysis

Competing interests

The authors declare no conflict of interest.

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