OPTIMIZING THE ASSESSMENT OF CEREBRAL AUTOREGULATION FROM LINEAR AND NONLINEAR MODELS

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Abstract: Autoregulation mechanisms maintain blood flow approximately stable despite changes in arterial blood pressure. Mathematical models that characterize this system have been used in the quantitative assessment of function/impairment of autoregulation as well as in furthering the understanding of cerebral hemodynamics. Using spontaneous fluctuations in arterial blood pressure (ABP) as input and cerebral blood flow velocity (CBFV) as output, the autoregulatory mechanism has been modeled using linear and nonlinear approaches. From these models, a small number of measures have been extracted to provide an overall assessment of autoregulation. Previous studies have considered a single – or at most- a couple of measures, making it difficult to compare the performance of different autoregulatory parameters (and the different modeling approaches) under similar conditions. We therefore compare the performance of established autoregulatory parameters in addition to novel features extracted from the models' response to a band-pass filtered impulse. We investigate if some of the poor performance previously reported can be overcome by a better choice of autoregulation parameter to extract from the model. Twenty-six recordings of ABP and CBFV from normocapnia and hypercapnia in 13 healthy adults were analyzed. In the absence of a 'gold' standard for the study of dynamic cerebral autoregulation, lower inter and intra subject variability of the parameters and better separation between normo- and hyper-capnia states were considered as criteria for identifying improved measures of autoregulation. We found that inter- and intra- subject variability in the assessment of autoregulation can be significantly improved by a careful choice of autoregulation measure extracted from either linear or non-linear models.

1 INTRODUCTION

The active control of the diameter of small blood vessels in the brain, usually referred to as cerebral autoregulation (CA), protects the brain against injury due to insufficient or excessive blood flow resulting from a temporary drop or surge in arterial blood pressure (ABP). Autoregulation is of great clinical interest as it can be impaired or lost in a number of conditions, such as stroke and subarachnoid haemorrhage (Panerai, 1998, Panerai, 2007). In much of the published literature, blood flow is recorded by the safe and non-invasive Doppler ultrasound method in response to transient changes in ABP. Sudden deflation of a thigh cuff, large sinusoidal variations in lower-body negative pressure, periodic breathing or squatting, and the Valsalva maneuver have been used to provoke larger changes in ABP (Panerai, 1998). However the most desirable experimental protocol for assessing autoregulation is to record data from patients at rest (without performing any specific maneuvers or requiring active collaboration), especially if they are in intensive care. Thus, many recent studies have focused on using only spontaneous fluctuations of ABP. While this approach increases challenges in terms of analyzing the recorded signals and can lead to high intra- and inter-subject variability, its effectiveness has been demonstrated (Panerai, 1998, Panerai et al., 1998, Panerai, 2007, among others).

Algorithms already described in the literature for estimating autoregulation involve system identification (black-box modeling) to represent the relationship between ABP and CBFV. Most of the studies of autoregulation focus on linear methods (Zhang et al., 1998, Birch et al., 1995, Panerai et al., 1999, 2003, Simpson et al., 2001) with the more recent inclusion of some nonlinear approaches

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(Panerai et al., 1999, Marmarelis et al., 2002, Panerai et al., 2004, Angarita-Jaimes et al., 2010). Although nonlinear techniques can provide improved model fits, their benefit in assessing cerebral autoregulation is still unclear with few studies having systematically compared them to linear alternatives.

In the investigation of autoregulation from linear models, the extraction of a small number of parameters from the frequency-, the impulse- or step-response of the models have been studied. Examples of autoregulatory parameters include gain, phase and coherence in selected frequency ranges, (Zhang et al., 1999, Panerai et al., 1999, Birch et al., 1995, Liu et al., 2003), selected features of the step-response (e.g. slopes, amplitudes at selected points) (Simpson et al., 2001, Liu et al., 2003). Alternative methods include the autoregulatory index (ARI) (Tiecks et al., 1995), or the correlation of the ABP and CBFV time series (Piechnik et al., 1999). The majority of published studies have only considered a single -or at most- a couple of measures for the analysis of cerebral blood flow control from spontaneous variations (Liu et al., 2003, Panerai et al., 2001, among others) and no single method for assessing autoregulation has become accepted as a gold standard..

The current paper aims to contribute to optimizing this last, but crucial step in detecting impairment in patients' autoregulation from the recorded signals. In this study, we investigate the performance of both linear and nonlinear models, and compare different measures extracted from the models to assess cerebral autoregulation. In the absence of a gold standard, the autoregulatory parameters are evaluated on a sample of signals recorded from healthy volunteers in whom temporary impairment of autoregulation was induced by hypercapnia. Based on the results, we suggest some autoregulatory measures that are most promising for future physiological and clinical studies.

2 METHODS

2.1 Data Collection and Pre-processing

The study was performed on 13 healthy volunteer subjects (age 32 ± 8.8 years) and was approved by the local Research Ethics Committee. All recordings were made with subjects in the supine position with the head elevated. Middle cerebral artery velocity was measured using a Transcanial Doppler Ultrasound system (Scimed QVL-120) in conjunction with a 2MHz transducer held in position by an elastic headband. Simultaneously arterial blood pressure (ABP) was non-invasively monitored using a finger cuff device (Ohmeda 2300 Finapress Bp monitor). End-tidal CO2 (EtCO2) levels were monitored via an infra-red capnograph (Datex Normocap 200). The experimental protocol for CO2 reactivity test was as follows: each recording began with a period of breathing ambient air for approximately 5 minute, followed by 2 minutes of elevated (EtCO2) due to the inhalation of 5% CO2 in air.

The signals were pre-processed off-line. The maximum velocity envelope from the spectra of the Doppler signal was extracted by fast Fourier transform (FFT) every 5 ms. The ABP signals were digitized at 200 Hz. Short periods of evident artifact as well as any spikes on the signals were removed by linear interpolation. The ABP and CBF signals were low pass filtered (20 Hz). The start of each heart cycle was automatically identified from the ABP signal, after which the average ABP and CBFVs from the right and left MCA were calculated for each heartbeat. This time series was then interpolated with a third-order polynomial, and sampled at a constant rate of 5 Hz. In order to reduce the serial correlation between samples, the signals were further decimated to a new sampling rate of 1Hz, following anti-alias filtering with a cut-off frequency at 0.5 Hz. These recordings were normalized by their mean values, and the mean values of the resultant signals were then removed. In that way, the relative change in each signal was obtained, and will be denoted by %ABP and %CBFV, respectively.

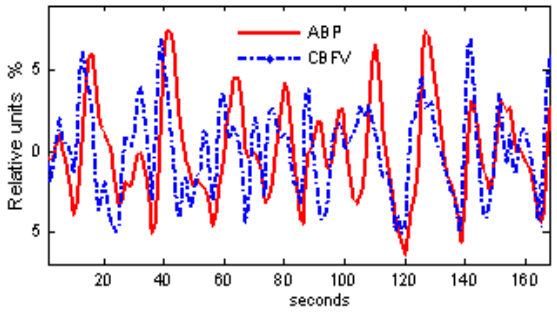

Figure 1: Representative recording, showing%ABP and %CBFV. A phase lead of CBFV indicates a good cerebral autoregulatory response.

2.2 Data Analysis

For each subject a segment of data was selected from before (normocapnia – NC) and during 5%

CO2 breathing (hypercapnia – HC). The former were approx. 300 s long and the latter approx. 100 s.

For both linear and nonlinear models, %ABP was the input and %CBFV the output. Since both signals are normalized, the underlying assumption is that in the absence of autoregulation changes in %CBFV would passively follow those in %ABP (Panerai et al., 1999). All models were estimated according to the usual least-mean-squares approach. A linear sixth order (5 seconds in duration) FIR filter (Liu et al., 2005) was chosen, since the autoregulatory response is largely completed during this time (Panerai et al., 2003, Liu et al., 2003). A non-linear Volterra-Wiener model, as previously proposed (Mitsis et al., 2003, Panerai et al., 1999, Panerai et al., 2003), was also estimated using the Wiener-Laguerre estimation procedure (for more details see for example Panerai et al., 1999). The number of lags used for both the linear and nonlinear kernels was 12.

3 ASSESMENT OF CEREBRAL AUTOREGULATION

3.1 Selection of Autoregulatory Parameters

A commonly used approach (Panerai et al., 1999, Panerai et al., 2003, Liu et al., 2005) to assess cerebral autoregulation is to look at the final value of the models response after applying an idealized step. From physiology, the step response is expected to first show a sharp increase in flow when blood pressure rises, followed by a return towards baseline within a few seconds as autoregulation provokes arteriolar vasoconstriction. In the absence of autoregulation, %CBFV would remain elevated. However, the step response shows large variability across subjects as well as erratic variations and decays to values less than zero that are hardly compatible with physiology (Simpson and Birch, 2008, Liu et al., 2005) – see Fig. 2A. The relatively narrow frequency range of spontaneous oscillations in blood pressure is expected to lead to poor estimation of the frequency response in the very low and very high frequencies where the system is not excited. This in turn probably causes the wide spread in the final values of the step responses and the erratic rapid variations respectively (Figure 2).

Simpson and Birch (2008) therefore proposed an alternative test-input to assess model responses. Instead of the step, a cosine wave modulated by a Gaussian envelope (Fig. 2B and Fig. 3) was chosen. This pulse reflects more closely the characteristics of ABP from spontaneous fluctuations and its shape is visually similar to fluctuations observed in spontaneously varying ABP signals.

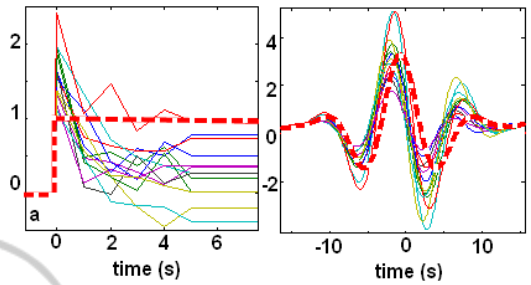

Figure 2: Step (a) and pulse (b) response for thirteen subjects estimated from a 5 seconds-long FIR model. The inputs are shown as the bold-dotted line. Considerably larger dispersion is observed in the step compared to the pulse response.

In order to quantify autoregulation using this response, , four parameters were selected, as shown in Fig. 3: the time of the left shift of the response (**TLS**, in seconds), measured as the difference in time between input and output crossing the abscissa after the main peak, the amplitude of the pulse response at 1.5 seconds (**A1.5**), the amplitude at 6 seconds (**A6**) and the time of the second negative peak (**TP**) - for the input signal this occurs at 3.5 seconds. These parameters were chosen as they reflect the expected left-shift (phase-lead) of the autoregulatory response, and had been found most robust in preliminary work; A1.5 and A6 lie on the steep slopes of the descending and ascending responses, and are therefore likely to be most sensitive to temporal shifts in the response.

We compare these novel parameters with others previously proposed in the literature. First, we estimated the final value of the step response (**FVS**) for both the linear and nonlinear models**.** Then, for

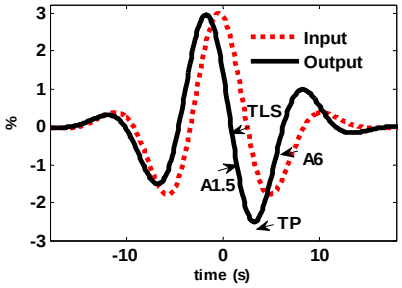

Figure 3: The %ABP test input (dotted line - sinusoid modulated by a Gaussian pulse) and the estimated response (solid line - %CBFV), together with the parameters used to quantify autoregulation.

the linear models, the average phase (**Pha**) was calculated from transfer function analysis in the frequency range from 0.07 Hz to 0.2 Hz (Zhang et al., 1998, Birch et al., 1995), and coherence, (**Coh**) was evaluated over a similar range (Zhang et al., 1998, Panerai et al., 1998). The correlation method (**Mx**) was also estimated from the average Pearson's correlation coefficient of 4 equal segments of the %ABP and %CBFV time series (Piechnik et al., 1999). The Autoregulatory Index **ARI** was calculated from the set of models proposed by Tiecks et al. (1995). For each recording, the set of models was applied to the %ABP, and the model leading to the highest correlation coefficient between the model generated velocity and the measured %CBFV gave the **ARI**. Finally, a parametric model based on the coefficients of a first-order (two taps) FIR filter was evaluated. The second coefficient of the filter **H1** was selected as it has been shown to reflect autoregulatory activity (Simpson et al., 2001).

3.2 Statistical Analysis

The aim of estimating autoregulatory parameters is to be able to distinguish between impaired and normal autoregulation. Since hypercapnia is known to impair autoregulation, changes in the autoregulatory parameters in response to increased pCO_2 were tested using Wilcoxon matched pairs tests. In addition repeatability and intra- and inter-subject variability were also evaluated. Inter-subject variability was assessed by calculating the standard deviation during normo and hypercapnia, and averaging the result (SD). In order to compare the performance of parameters, SD was normalized by the difference in mean value between NC and HC (CVd).

To investigate the effect of noise and as an indication of the repeatability of the autoregulatory parameters, 100 simulated signals were generated from each of the recordings. Additive noise was modeled based on the residual error in %CBFV (i.e. the signal component that cannot be explained by applying the identified models to the %ABP signals) using an AR model of order 8. Surrogate %CBFV signal were then generated by applying the identified models (linear or nonlinear) to the %ABP signals and then adding the random noise to simulate residuals. Autoregulation parameters were then calculated from these simulated signals, and their standard deviation was considered as the intra-subject variability for each recording and parameter. These were also normalized by the parameter's mean difference between normocapnia and hypercapnia, and their average across the subjects was denoted by mCVd. Low values of CVd and mCVd indicate low dispersion and wide separation between groups.

For each model, the predicted velocity response was also compared to the measured data and the model's performance was evaluated using the normalized mean square error (NMSE). Cross-validation, with two equal segments, was used to calculate NMSE**.**

4 RESULTS

Table 1 shows the NMSE in fitting different models to the data. The most sophisticated model has the smallest error on the training data (150 s duration) but on the validation data set performs poorly. The simplest model (1st order FIR) overall shows the poorest model fit, both on training and validation data.

Table 1: Mean ± SD NMSE across 13 subjects for the different models used on baseline recordings.

Model	Training NMSE %	Validation NMSE %
FIR - 2 lags (1st order)	36.4 ± 17.5	47.5 ± 25.4
FIR - 6 lags	27.6 ± 15.5	37.5 ± 21.4
Quadratic Wiener Laguerre - 12 lags	21.4 + 12.1	42 ± 25.9

The performance of the different autoregulatory parameters is shown in Figure 4, and provides a rather different picture of which model might be most appropriate in quantifying autoregulation. CVd and mCVd estimates, indicating inter- and intra-subject variability respectively, are presented for all 10 parameters studied. The last five were evaluated for both the linear (L) and nonlinear models (NL).

Autoregulatory parameters with the smallest CVd indicate best separation between NC and HC, and can thus considered to provide the clearest distinction between normal and impaired autoregulation in terms of inter-subject variability. Amongst the parameters studied **H1, TP** (both for linear and nonlinear models), **A1.5** (linear model) and **A6** (nonlinear model) had the lowest CVd. The latter three show a clear improvement compared to the final value obtained from the step response (**FVS**). Furthermore, Wilcoxon matched pair test showed that the magnitude of these parameters

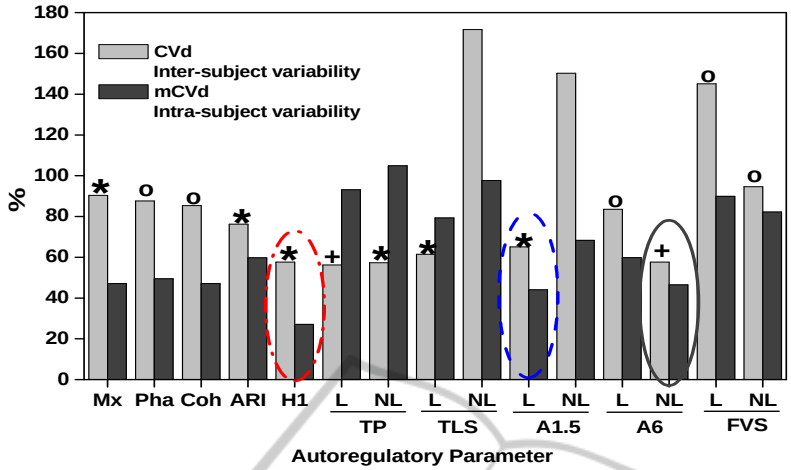

Figure 4: Comparison of the different autoregulatory parameters. L (linear) and NL (non-linear) models, respectively. The different significance levels of the Wilcoxon test comparing parameters during NC and HC are grouped as: + $0.009<p<0.0009$; * $0.09<p\leq 0.009$, **o** $p\leq 0.09$ (inter-subject variability) The parameters showing the strongest distinction between NC and HC for linear and non-linear models, are circled.

changed significantly between NC and HC (**H1**, $p\approx 0.0014$; **TP-L**, $p\approx 0.0006$; **TP-NL** $p\approx 0.002$, **A1.5-L** $p\approx 0.004$; **A6-NL** $p\approx 0.0006$).

The different measures performed differently depending on the models used to characterize the relationship between ABP and CBFV. For example, whilst the amplitude at 1.5 s or **TLS** performed well with the L model, these had very high inter-individual dispersion for the NL approach. Conversely, amplitude at 6 s was the best parameter for the NL and poorer for L. A slight improvement in **FVS** was observed by using the NL approach.

When evaluating the influence of additive noise in the recordings, the highest dispersion in terms of mCVd (see Figure 4, darker bar) was noted for the non-linear models, and especially the time-delay parameters. In some cases the mCVd was larger than CVd, which probably reflects the differences in normalization: in the former dispersions are normalized by the differences for each individual (and then averaged across the cohort), but in the latter it normalization is by the average difference. Conventional parameters extracted from the frequency response (**Pha, Coh**) as well as **Mx** were relatively robust to noise (low mCVd). Overall, the autoregulatory parameters with the lowest variability and best separation between pC02 levels are **H1**, **A1.5** (linear model) and **A6** (nonlinear model). The excellent performance of the simplest parameter, **H1**, is particularly notable, and is shown in more detail in Figure 5, with 12 of 13 subjects showing the expected increase in **H1** during HC.

5 DISCUSSION

In previous work, the high inter-subject variability of a number of measures of cerebral blood flow control and poor repeatability has been noted (Panerai et al., 2003, Simpson et al., 1999). The results in this work showed that the model used to represent the relationship between blood flow and blood pressure, and how the models are then used (the calculation of autoregularory parameters), can notably increase the uncertainty in the estimates. The current work is probably the most extensive comparison between different parameters of autoregulation published to date. In some of the earlier work (Panerai et al., 1999, Panerai et al., 2003, Mitsis et al., 2004, Angarita-Jaimes et al., 2010) the primary concern has been with how well different models fit the data. This however is only an intermediate step in addressing the main challenge: quantifying autoregulation when only spontaneous fluctuations in ABP and CBFV are present. In the continued absence of a gold-standard measure of autoregulation, we take as criteria for assessing performance the ability to distinguish between normal (during normo-capnia) and impaired (during hyper-capnia) autoregulation. The current work also moves beyond the more established ‘test inputs’ that give impulse, step or frequency (i.e. sine-wave) responses, recommending a ‘test input’ that is physiologically more realistic, in the form of a broad-band pulse.

Larger dispersion was observed in the traditional autoregulatory parameters, particularly in the final

value of the step response, compared to some of the measures extracted from the pulse response, as indicated by CVd (see Figure 4). The simulations indicate that intra-subject variability, due to assumed additive noise in the recordings is a large contributor the overall dispersion in results. However in this respect, **H1** outperformed all other measures. **H1** was also among the best in terms of inter-subject variability. It should also be noted that model fit (Table 1) alone clearly is not a good indicator of what makes for the best method in the assessment of autoregulation.

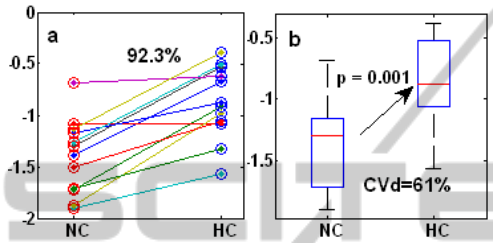

Figure 5: a) Magnitude of **H1** during normocapnia (NC) and hypercapnia (HC). b) Box plots representation of the median, quartile, minimum and maximum of **H1**.

A number of other parameters for assessing autoregulation, including parameters taken directly from the model (as **H1** for the first order FIR filter) were also investigated, but none proved superior to the ones presented. The relatively small sample of recordings available and relatively large number of parameters tested is a limitation of the current study. It is possible that the relative performance of the methods reflects peculiarities or random effects in the particular data set available. Given that parameters estimated are not independent, the usual methods for determining statistically significant differences between the approaches are not appropriate. However, the large differences observed between methods, probably do indicate which approaches are most promising to be taken on in a further study on a larger data set.

6 CONCLUSIONS

In this work we have compared a number of measures to evaluate autoregulatory activity. Some of the parameters extracted from the proposed pulse input show less variability compared with the more conventional parameters extracted from the frequency and step responses. Thus relatively small variations across as well as within subjects were found for the amplitude of the pulse response at certain lags (**A1.5, A6**). These also showed a clearer distinction between the different levels of autoregulation (quantified by the p value). In particular, for linear models **A1.5** would be recommended whereas **A6** seemed to perform well for nonlinear models. However, the results obtained from **H1** suggest that this parameter from a very simple model might be the method of choice, with small coefficients of variation (CVd, mCVd). This method also allows the analysis of relatively short data segments and thus lends itself to further studies of time-varying (adaptive) estimates of dynamics in cerebral blood flow control.

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