Detection of autoregulation in the brain of premature infants using a novel subspace-based technique

G. Morren[1], P. Lemmerling[1], S. Van Huffel[1], G. Naulaers[2], H. Devlieger[2] and P. Casaer[2]
[1]SISTA/COSIC Division, Electrical Engineering Dept. (ESAT), K.U.Leuven, Belgium
[2]Neonatal Intensive Care Unit, Dept. of Paediatrics, University Hospital Leuven, Belgium

Abstract— **A recent study [1] suggests that, under certain circumstances, concordant changes in cerebral intravascular oxygenation and mean arterial blood pressure reflect impaired cerebrovascular autoregulation. In this paper, we propose a new measure to quantitate this concordance, derived from the common subspace of these signals. The method is compared to correlation and coherence analysis with respect to our application, but it is also suited for other biomedical signals. Furthermore, this model-based approach is not restricted to applications involving only 2 signals.**

Keywords— **subspace-based modeling, correlation, coherence, cerebrovascular autoregulation, near-infrared spectroscopy**

I. Introduction

The most important forms of brain injury in premature infants (germinal matrix-intraventricular hemorrhage (GMH-IVH) and periventricular leukomalacia (PVL)) are caused in considerable part by disturbances in cerebral blood flow (CBF). Premature infants have a particular propensity for development of disturbances in CBF for 2 major reasons. First, because alterations in mean arterial blood pressure (MAP) are very common in such infants. And second, because cerebral autoregulation, the mechanism by which CBF is maintained constant despite alterations in MAP, is either defective or absent in at least some infants. So, there is a relationship between impaired autoregulation and the occurence of brain injury.

Two studies [2] [3] showed a relationship between CBF and MAP and concluded that autoregulation may be defective in some premature infants. Different authors did not find any correlation between CBF and MAP, however they used singular measurements and not continuous measurements. A recent study suggests [1] that concordant changes in cerebral intravascular oxygenation (HbD) and MAP reflect impaired cerebrovascular autoregulation in continuous measurements. A previous study [4] showed a strong correlation between HbD, measured non-invasively by near-infrared spectroscopy (NIRS) as the difference between the concentration changes of oxygenated hemoglobin (HbO_2) and deoxygenated hemoglobin (Hb), and volemic CBF, determined by radioactive microspheres if the arterial oxygen saturation (SaO_2) does not change appreciably during the measurement. Thus, under such conditions, HbD is a measure of CBF.

Consequently, premature infants with impaired cerebrovascular autoregulation could be identified by simultaneous, continuous measurements of HbD, assessed by NIRS, and MAP, assessed by intravascular catheterisation. If, in this way, infants at high risk for GMH-IVH/PVL can be identified before the occurence of the lesions, it might be possible to correct the cerebral circulatory disturbance and prevent the lesions.

The mathematical problem is thus the quantitation of the concordance between HbD and MAP. For this purpose, three different measures are described and compared. Furthermore, some preliminary results obtained from measured data are given.

II. Methods

A. Correlation

The most straightforward way to quantitate the concordance between two signals $x(t)$ and $y(t)$ is the correlation coefficient COR, estimated as:

$$COR = \frac{\sum_{t=1}^{N}(x(t)-\bar{x})(y(t)-\bar{y})}{\sqrt{\sum_{t=1}^{N}(x(t)-\bar{x})^2 \sum_{t=1}^{N}(y(t)-\bar{y})^2}} \qquad (1)$$

where N is the number of samples considered and $\bar{x}, \bar{y}$ stands for the mean of $x(t)$, respectively $y(t)$. If one is only interested in the correlation in a specific frequency band, the signals should be filtered with a band-pass filter containing the frequency band of interest before calculating the correlation coefficient.

B. Coherence

Another way to quantitate the correlation in a frequency specific manner is based on the coherence function, defined as:

$$C_{xy}(f) = \frac{|P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)} \qquad (2)$$

where $P_{xy}(f)$ is the cross power spectral density of $x(t)$ and $y(t)$, and $P_{xx}(f)$, $P_{yy}(f)$ the power spectral densities of $x(t)$, respectively $y(t)$. The spectral density functions are estimated using Welch's method [5] as follows:

- $x(t)$, $y(t)$ are divided in overlapping sections of n points;
- each section is detrended and windowed;
- the length n fast Fourier transform (FFT) is calculated of each section (these FFTs are called periodograms);
- the pointwise products of the spectra of $x(t)$ and $y(t)$ are averaged over the overlapping sections to form $P_{xy}(f)$;
- the pointwise squared FFTs of $x(t)$ and $y(t)$ are averaged over the sections to form $P_{xx}(f)$, respectively $P_{yy}(f)$;
- C_{xy} is calculated by means of (2).

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Abstract

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The coherence function is a measure of the linear dependance between the signals $x(t)$ and $y(t)$ at a given frequency. A coherence of 1 indicates perfect frequency specific correlation, a coherence 0 indicates a complete lack of frequency specific correlation. To obtain a measure of the coherence over a specific frequency band, the coherence function is averaged over that frequency band.

C. HTLS-SEP

This method was first described in [6] and is briefly described in this section. The goal of the HTLS-SEP method is to fit one linear model to two signals. Only if the two signals have the same dynamical properties (or, in other words, have common signal poles), the determined system will be able to explain both signals sufficiently well. Let us start from the hypothesis that the two signals have the same dynamical properties. Mathematically this is reflected in the proposed model of $x(t)$ and $y(t)$ as follows:

$$x(t) = \sum_{k=1}^{K} c_k^x z_k^t + n_1(t),\ t = 0, 1, \ldots, N-1 \tag{3}$$

$$y(t) = \sum_{k=1}^{K} c_k^y z_k^t + n_2(t),\ t = 0, 1, \ldots, N-1 \tag{4}$$

where $n_1(t)$ and $n_2(t)$ represent the noise, and $z_k,\ k = 1, \ldots, K$ the so-called signal poles:

$$z_k = e^{(j2\pi f_k - d_k)\Delta t} \tag{5}$$

where $f_k, k = 1, \ldots, K$ represent the frequencies, $d_k, k=1, \ldots, K$ the dampings and Δt the constant sampling interval; furthermore, $c_k^x,\ k = 1, \ldots, K$ represent the so-called complex amplitudes associated with $x(t)$:

$$c_k^x = a_k^x e^{j\phi_k^x} \tag{6}$$

where $a_k^x,\ k = 1, \ldots, K$ stands for the amplitude and $\phi_k^x,\ k = 1, \ldots, K$ for the phase. In a similar way the complex amplitudes $c_k^y,\ k = 1, \ldots, K$ of $y(t)$ are defined as a function of $a_k^y,\ k = 1, \ldots, K$ and $\phi_k^y,\ k = 1, \ldots, K$.

From (3) and (4), it is clear that the two signals $x(t)$ and $y(t)$ are modeled with the same signal poles $z_k,\ k = 1, 2, \ldots, K$ (meaning that they share the dynamical properties of one linear system) but with different complex amplitudes. To determine the common poles, a subspace-based approach is used. First, Hankel matrices H_x and H_y are constructed from $x(t)$, respectively $y(t)$, as follows:

$$H_x = \begin{bmatrix} x(0) & x(1) & \ldots & x(N-m+1) \\ x(1) & x(2) & \ldots & x(N-m+2) \\ \vdots & \vdots & \ddots & \vdots \\ x(m-1) & x(m) & \ldots & x(N-1) \end{bmatrix} \tag{7}$$

Then, to determine the common subspace C of H_x and H_y, matrices X and Y must be calculated such that:

$$H_x X = H_y Y \equiv C \tag{8}$$

Since this condition can also be written as:

$$[H_x \ -H_y] \begin{bmatrix} X \\ Y \end{bmatrix} = 0 \tag{9}$$

it is clear that X and Y can easily be derived from the null space of the block Hankel matrix $[H_x\ H_y]$.

The common poles are thus estimated from the common subspace C by means of the HTLS algorithm[1] [8], giving the pole estimates $\hat{z}_k,\ k = 1, \ldots, K$. This is possible because the column spaces of H_x and H_y possess the shift invariance property. Multiplying them with a matrix to the right does not change this property.

After estimation of the common poles, the phases and the amplitudes are estimated for $x(t)$ and $y(t)$ separately as the least squares solutions to (3), respectively (4), with z_k replaced by the estimates $\hat{z}_k$.

Using (3) and (4) with all parameters replaced by their estimates, we reconstruct the part of $x(t)$ common to $x(t)$ and $y(t)$, giving $\hat{x}_c(t)$. The residual $x_r(t)$ can then be defined as:

$$x_r(t) \equiv x(t) - \hat{x}_c(t) \tag{10}$$

Note that if $x(t)$ and $y(t)$ do not have many components in common, $\hat{x}_c(t)$ will be a very bad fit to $x(t)$. Therefore, the ratio of the energy of the common part to the sum of the energy of the common part and the energy of the residual, is used as a measure of the importance of the common part in the original signal $x(t)$:

$$x_r(t) \equiv x(t) - \hat{x}_c(t) \tag{11}$$

$$CPC_x = \frac{\sum_{t=0}^{N-1} (\hat{x}_c(t))^2}{\sum_{t=0}^{N-1} (\hat{x}_c(t))^2 + \sum_{t=0}^{N-1} (x_r(t))^2} \tag{12}$$

If the signals consist only of common poles than CPC_x approaches one, if there are no common poles CPC_x will be close to zero. If the signals are normalized (standard deviation=1), CPC_x can also be regarded as a measure of the mean square error of $\hat{x}_c(t)$ with respect to $x(t)$, since:

$$CPC_x \approx 1 - \frac{1}{N} \sum_{t=0}^{N-1} x_r(t)^2 \tag{13}$$

In a similar way $\hat{y}_c(t)$, $y_r(t)$ and CPC_y can be defined.

[1] HTLS is a subspace-based pole estimation method that exploits the shift invariance property. It is an alternative to the TLS-ESPRIT method [7]: HTLS uses the singular value decomposition of the data matrix, whereas TLS-ESPRIT uses the eigenvalue decomposition of the sample covariance matrix.

III. Experimental results

A. Measurements

From several premature infants, MAP, SaO_2 and HbD were measured simultaneously at the University Hospital Leuven. HbD was calculated as the difference between the concentration changes of HbO_2 and Hb. These changes were acquired using near-infrared spectroscopy (NIRO-300®, Hamamatsu). The data are recorded at a sampling frequency of 100 Hz by a data acquisition system Codas (CODAS®, Dataq Instruments, USA) and stored on a PC. The MAP- and SaO_2- signals are analog and digitized afterwards by the CODAS-system. The NIRO-300 signals are digital with a sampling rate of 6 Hz. They are converted to analog signals with a sample-and-hold function before their introduction in the CODAS-system. From this 100 Hz data, the average values for non-overlapping 5-second intervals were calculated (0.2 Hz). This sampling frequency is still high enough, since major physiological importance can be attributed to the frequency band of 0-0.01Hz (i.e. changes occuring over several minutes) [1].

B. Results

Since the concordance between the signals might vary as a function of time, a sliding window approach was used: the presented measures were calculated on 30-minute recordings (i.e. 360 samples), and plotted against the starting time of the 30-minute window. In this way it is possible to track the changes of the measures over time.

For the correlation coefficient, we used the 5-second averaged values without filtering. When the signals are low-pass filtered to the frequency range of interest (0-0.01Hz), the correlation coefficient is only slightly higher in highly correlated windows, but also higher in uncorrelated windows. Therefore, the correlation coefficient of the unfiltered signals is more sensitive to discriminate between correlated and uncorrelated windows.

Several parameters have an influence on the estimation of the spectra for the calculation of the coherence function. In the first place, the length n of the sections, used for the calculation of the FFTs, and the number of overlapping points between consecutive sections. The smaller the value of n, the more periodograms can be averaged and hence the lower the variance of the estimates of the spectra. On the other hand, the smaller n, the lower the frequency resolution. Experiments with varying n showed that $n=144$ gives the best results (the frequency resolution is then 0.0014Hz). In order to average as much as possible, we used maximum overlap between the sections (i.e. $n–1=143$ data points). The average of the coherence function over the frequency band of interest (0-0.01Hz) was used as measure, and is called COH in the remainder of this paper. Before calculating the FFT of each section, the mean was removed and a Hanning window applied.

The main problem for the HTLS-SEP method is the determination of the model order of the common subspace K, which is twice the number of frequency components. Since K is not known a priori, the following approach is used. First, $x(t)$ and $y(t)$ are modeled with $K=2$. Then, as long as e_x, being the mean of $|x(t)-\hat{x}(t)|$ over the 30-minute window, and e_y, being the mean of $|y(t)-\hat{y}(t)|$ over the same period, decreases, K is increased with 2. If either e_x or e_y increases, the algorithm is stopped. The model of HbD with the previous value of K is then used to calculate CPC by means of (12). Before modeling, the signals of the 30-minute windows were normalized (such that mean=0, standard deviation=1).

An example of the measurements on a premature infant are shown in Fig. 1, together with the corresponding measures. The total length of the measurement was four hours. The MAP signal shows only modest fluctuations during the first two hours. There is also modest variability in HbD during the first two hours, except between the 40th and 60th minute, where HbD clearly decreases. However, this decrease is accompanied by a decrease in SaO_2, as can be seen in Fig. 2. Fig. 2 also shows MAP and HbD during the 30-minute window containing this decrease, together with the models of MAP and HbD. Since the condition of constant SaO_2 does not hold, HbD can not be assumed to be proportional to CBF during this period, and therefore the results should be interpreted carefully. The analysis of this 30-minute window results in low COR and COH values (0.26 and 0.39 respectively); on the other hand, CPC is high (0.86). The latter indicates that the dynamics of the SaO_2 is not only reflected in HbD, but also in MAP although to a lesser degree. A possible explanation of this finding is that the patient might have had an open ductus Botalli. This causes decreases in oxygenation which are often accompanied by decreases in blood pressure. However, further research is necessary to clarify this hypothesis. During the last two hours of the recording, large (spontaneous) fluctuations in MAP are associated with parallel changes in HbD, while SaO_2 remains constant. This is a case of impaired cerebrovascular autoregulation. During this period, CPC (close to 1) and COR (about 0.8) are higher than COH, suggesting that CPC and COR are more sensitive in order to detect impaired autoregulation. To evaluate the predictive value of the measures with respect to subsequent brain injuries statistically, a larger follow-up study is necessary.

IV. Conclusions

A new measure to quantitate how similar the dynamics in two (or more) signals are, was presented. It is derived from the common subspace of the signals. The measure was used to quantitate the concordance between cerebral intravascular oxygenation and mean arterial blood pressure, which reflects impaired cerebrovascular autoregulation. The recordings analyzed so far indicate that the new method and correlation are better measures to detect impaired autoregulation than coherence analysis. A larger follow-up study is needed to confirm the performance of the new measure, and to evaluate the predictive value

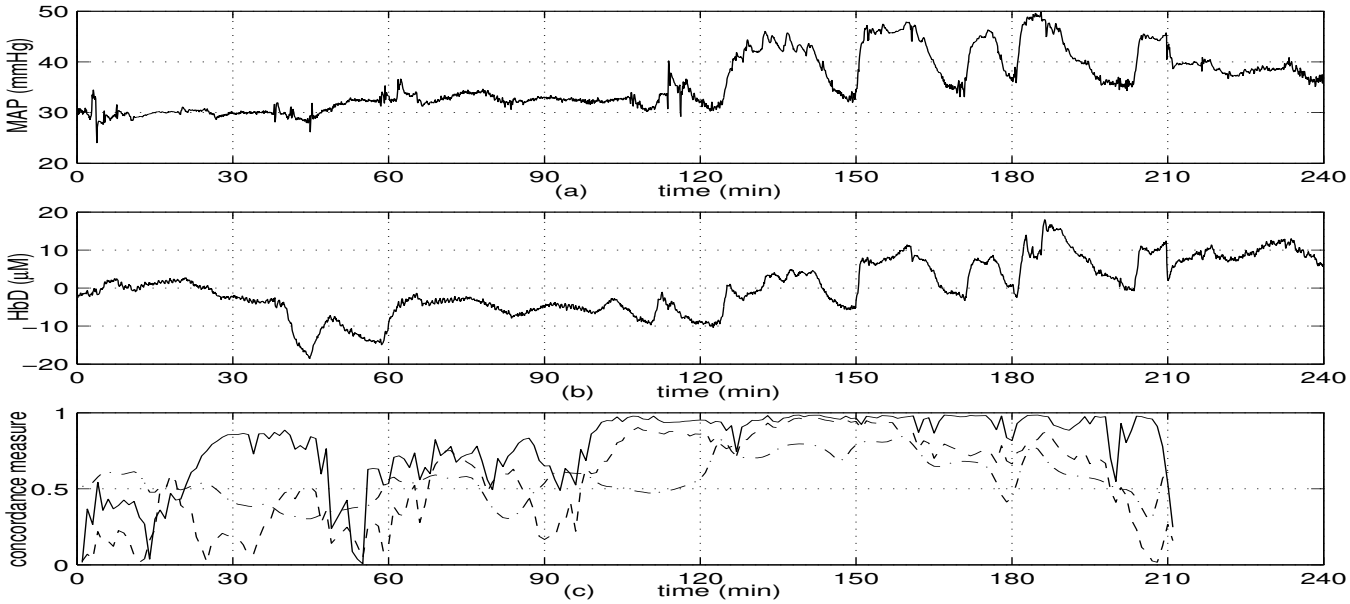

Fig. 1. Simultaneous changes in MAP (a) and HbD (b) in a premature infant, with corresponding measures (c): COR (dashed line), COH (dash-dotted line) and CPC (solid line).

of the different measures with respect to possible brain damage statistically. Furthermore, the new measure truly looks for similarity of the dynamics between signals and should therefore be better suited to see whether the signals are generated by one and the same biomedical process. Another advantage of the new method is that it allows to analyze the dynamical properties of more than two signals simultaneously. This will allow us in the future to include other relevant physiological parameters like the arterial carbon dioxide tension (PCO_2) in the analysis.

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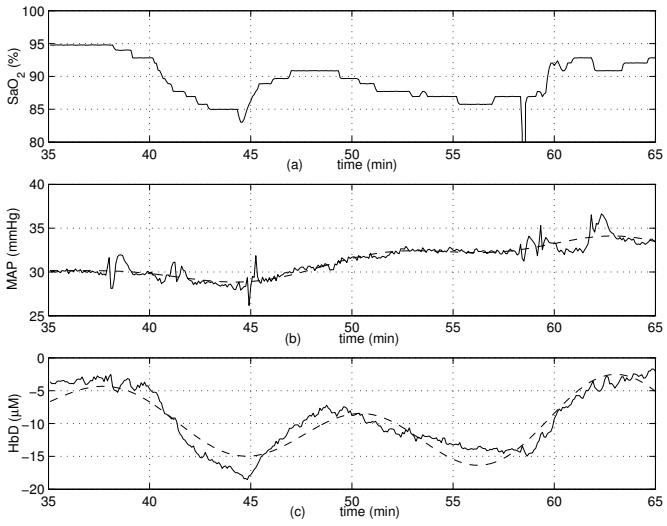

Fig. 2. Simultaneous changes in SaO_2 (a), MAP (b) and HbD (c) in the premature infant of Fig.1 between the 35th and 65th minute. The original signals (solid line) are displayed together with the modeled signals (dashed line). The model order K was 4. The different measures are: COR=0.26, COH=0.39 and CPC=0.86.

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