DETECTION OF AUTOREGULATION IN THE BRAIN OF PREMATURE INFANTS

D. De Smet[1], S. Van Huffel[1], J. Vanderhaegen[2], G. Naulaers[2], E. Dempsey[3]

[1]Katholieke Universiteit Leuven, Department of electrical engineering, ESAT-SCD, Belgium
[2]Katholieke Universiteit Leuven, University Hospital Gasthuisberg, Belgium
[3]McGill University Montreal, University Hospital, Canada

In *Proc. of the Belgian Day on Biomedical Engineering - IEEE/EMBS Benelux Symposium*, Brussels, Belgium, Dec. 2006, pp. 215-218.
Paper available at :
ftp://ftp.esat.kuleuven.be/sista/ddesmet/reports/0612.pdf

Contact : dominique.desmet@esat.kuleuven.be

DETECTION OF AUTOREGULATION IN THE BRAIN OF PREMATURE INFANTS

D. De Smet[1], S. Van Huffel [1], J. Vanderhaegen [2], G. Naulaers[2], G. Dempsey[3]
[1]Katholieke Universiteit Leuven, Department of electrical engineering, ESAT-SCD, Belgium
[2]Katholieke Universiteit Leuven, University Hospital Gasthuisberg, Belgium
[3]McGill University Montreal, University Hospital, Canada

1 Introduction

Brain injury in premature infants are caused in a considerable part by disturbances in the cerebral blood flow (CBF). Alterations in mean arterial blood pressure (MAP) are very common in such infants and otherwise the CBF can consequently often not be maintained constant. Some studies [4] have showed that an inadequate autoregulation of the CBF occurs with concordant variations between MAP and CBF. A important point is also that there exists a strong correlation between the CBF and the cerebral intravascular oxygenation (HbD), under the condition that the arterial oxygen saturation (SaO_2) does not change appreciably. Several mathematical algorithms were implemented to detect such concordant variations between HbD, MAP and SaO_2.

2 Methods

We have mainly used two ways to study the concordance between some input signals : static methods and dynamic ones. The static methods - coherence (COH), correlation (COR), partial coherence (PCOH) and principal autopower spectra (PAPS) - can be applied between two (COH and COR) or three (PCOH and PAPS) signals. The dynamic methods, HTLS-SEP [1] and MUSCLE [2], applied can process two (HTLS-SEP and MUSCLE) or three (MUSCLE) signals simultaneously.

COH and COR are the more simple ways to study the concordance between two signals. HTLS-SEP is a measure to quantitate how similar the dynamics of two signals are. It is derived from the common subspace of the signals, and its goal is to fit one linear model to two signals. MUSCLE is also derived from the common subspace of the signals, but makes use of semi-unitary matrices to determine the number of common signal poles. The PCOH measures the degree of linear dependence between the spectra of two signals after having eliminated the contribution of some other signals. PAPS is a measure of the linear independence of the signals.

An important problem for the HTLS-SEP and MUSCLE methods is the determination of the model order of the input signals. For this purpose several methods were studied, e.g. SAMOS [3] which is a subspace-based method.

3. Experiments

HbD, MAP and SaO_2 were measured at a frequency of 4Hz on 6 premature babies, susceptible to suffer from an impaired autoregulation, during a recording time ranging from 8 to 16 hours for each. The babies were aged from 24 to 28 weeks, and their weights range from 675g to 1155g. The six methods presented were implemented on these datasets.

4. Results and discussion

COR seems to be a stronger measure to detect impaired autoregulation than COH. PCOH and PAPS allow the consideration of a third signal. HTLS-SEP and MUSCLE allow a dynamic analysis of the measured signals, sometimes highlighting a dynamic concordance between HbD and MAP even if COR and COR are low.

References

[1] Morren, G.; P. Lemmerling; S. Van Huffel; G. Naulaers; H. Devlieger; and P Casaer. Detection of autoregulation in the brain of premature infants using a novel subspace-based technique. *Proceedings 23rd Annual International Conference IEEE Engineering in Medicine and Biology Society*, Istanbul, Turkey. Paper 4.5.1-7, 4 pages (CD-rom). October 25-28, 2001.

[2] Papy, J.-M.; L. De Lathauwer; and S. Van Huffel. Common pole estimation in multi-channel exponential data modelling. *Signal Processing*, vol. 86, pp. 846-858. 2006.

[3] Papy, J.-M.; L. De LathauWer; and S. Van Huffel, A shift invariance-based order selection technique for the exponential data modeling. *IEEE Signal Processing Letters*, 2006, to appear.

[4] Tsuji, M.; J. Saul; A. du Plessis; E. Eichenwald; J. Sobh; R. Crocker;and J. Volpe. Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. *Pediatrics*, vol. 106, no. 4, pp. 625-632. October 2000.

Detection of autoregulation in the brain of premature infants

D. De Smet[1], S. Van Huffel[1], J. Vanderhaegen[2], G. Naulaers[2], E. Dempsey[3]
[1] Katholieke Universiteit Leuven, Department of electrical engineering, SISTA, Belgium
[2] Katholieke Universiteit Leuven, University Hospital Gasthuisberg, Belgium
[3] McGill University Health Centre, Montreal, Canada
Dominique.DeSmet@esat.kuleuven.be

1 Introduction

The most important forms of brain injury in premature infants are partly caused by disturbances in cerebral blood flow (CBF). Such infants have a propensity for development of disturbances in CBF for two major reasons : alterations in mean arterial blood pressure (MABP) are common in such infants and cerebral autoregulation, the mechanism by which CBF is maintained constant despite alterations in MABP, is either defective or absent in at least some infants. So, there is a relationship between impaired autoregulation and the occurrence of brain injury.
Studies showed a relationship between CBF and MABP and concluded that autoregulation may be defective in some premature infants. A recent study suggests that concordant changes in cerebral intravascular oxygenation (HbD) and MABP reflect impaired autoregulation in continuous measurements. A strong correlation was also found between HbD and volemic CBF if the arterial oxygen saturation ($Sa0_2$) 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 near-infrared spectroscopy (NIRS), and MABP, assessed by intravascular catheterisation. If, in this way, infants at high risk for brain injuries can be identified prior to 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 MABP. For this purpose, six different measures are described and compared : four of them give a *static* concordance between the signals of interest : coherence, correlation, partial coherence and principal power spectral density [2]. The two last measures are new and give a *dynamic* concordance between the signals : HTLS-SEP [3] and MUSCLE [5].

2 Methods

Correlation

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

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

with N the number of samples considered and $\bar{x}$, $\bar{y}$ stands for the mean of $x(t)$, respectively $y(t)$.

Coherence

Another way to quantify the signal concordance in a frequency specific manner is based on the coherence function, defined as :

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

with $P_{xy}(f)$ the crosspower spectral density (CSD) of $x(t)$ and $y(t)$ at a given frequency f, and $P_{xx}(f)$, $P_{yy}(f)$ the power spectral densities (PSD) of $x(t)$, respectively $y(t)$. The spectral density functions are estimated using Welch's method.

Partial coherence

If the ordinary coherence function measures the degree of linear dependence between the spectra of two signals, the partial coherence function (PCOH), described in [2], acts in a similar way, but after having eliminated in a least squares sense the contribution of some other signals.
Let us consider p signals $x_1, \ldots, x_p$. Let us choose x_1 as the reference signal, and let us eliminate out of $x_2, \ldots, x_p$ the linear dependence on x_1 (hypothesis of a *black-box model*). For this, we first have to compute the Fourier transform of the signals at a particular frequency, respectively $X_1, \ldots, X_p$. The signals are correlated at this frequency when the autopower matrix P is singular :

$$P = \begin{pmatrix} P_{11} & \cdots & P_{1p} \\ \vdots & \ddots & \vdots \\ P_{p1} & \cdots & P_{pp} \end{pmatrix} \quad (3)$$

where P_{ii} is the PSD of signal x_i, and P_{ij} with $i \neq j$ is the CSD between signal x_i and signal x_j.
For X_2, the pertinent equations are the followings :

$$X_2^1 = X_2 - \frac{P_{12}}{P_{11}} X_1 \quad (4)$$

In this equation, X_2^1 represents what is left from X_2 after having eliminated the hypothetic linear dependence on X_1 in a least squares sense.
The PSD of X_2^1 can then be computed :

$$P_{22}^1 = P_{22} - \frac{|P_{12}|^2}{P_{11}} \quad (5)$$

$$= P_{22}(1 - COH_{12}) \quad (6)$$

These equations also define the first step of a Gauss elimination on P applied to element P_{22}. If X_1 and X_2 are linearly dependent, then COH_{12} equals 1. From the former equations, it follows that P^1_{22} equals 0 : a zero diagonal element is generated during the first step of the Gauss elimination in matrix P^1. Therefore P^1 is singular, thus so is P, and $X_1,\ldots,X_p$ are correlated. If COH_{12} is smaller than 1, X_1 and X_2 are not linearly dependent. Gradually a total of maximum $p-1$ partial coherence functions of the form (here pertinent for X^1_2 and X^1_3) :

$$COH^1_{23} = \frac{|P^1_{23}|^2}{P^1_{22}P^1_{33}} \tag{7}$$

can be generated. If any of these coherence function equals 1, then P is a singular matrix.

pPSD

As an alternative technique to the latter one, let $X'_1,\ldots,X'_p$ represent the basis of p independent, fully non-correlated input signals (named *principal* signals) from which the basis of the real input signals $X_1,\ldots,X_p$ can be derived by linear combinations as follows :

$$[X_1 \cdots X_p] = [X'_1 \cdots X'_p]U \tag{8}$$

and thus :

$$P = U^h P' U \tag{9}$$

where U is a complex square matrix, h denotes the Hermitian transpose of matrix U, and P' is a diagonal matrix with the PSD of the principal signals on its diagonal. The diagonal elements are referred to as *principal power spectral densities* (pPSD) [2].
Let us notice that 9 also defines the eigenvalue decomposition of P. From this point of view, P' represents the eigenvalues, and U the corresponding eigenvectors of P. This eigenvalue decomposition is always defined since P is Hermitian. The eigenvectors are independent, so that U is not a singular matrix. Therefore when some of the eigenvalues of P equal 0 or are negligible, which means that the corresponding principal input signals are insignificant, P is singular. Calculating the pPSD's is thus usable as a diagnostic tool to evaluate the concordance between the input signals. For X_3, the pertinent equation is :

$$(P')^{12}_{33} = (P')^1_{33}(1-(COH')^1_{23}) \tag{10}$$

HTLS-SEP and MUSCLE

These two methods were used to quantify and extract the common information present in several signals in the case where the channels are contaminated by different undesired harmonics. The developments are here carry out for the two-signal case, but can be extended using MUSCLE for the three-signal case, and even more. Let us start from the hypothesis that the two signals have the same dynamical properties. Mathematically this is reflected in the proposed EDS model (Exponentially Damped Sinusoid) of $x(t)$ and $y(t)$ as follows :

$$x(t) = \sum_{k=1}^{K} c^x_k z^t_k + n_x(t), \quad t=0,1,\ldots,N-1 \tag{11}$$

$$y(t) = \sum_{k=1}^{K} c^y_k z^t_k + n_y(t), \quad t=0,1,\ldots,N-1 \tag{12}$$

with $n_x(t)$ and $n_y(t)$ represent the noise, and z_k, $k=1,\ldots,K$ the so-called signal poles :

$$z_k = e^{(j2\pi f_k - d_k)T_{Samp}} \tag{13}$$

with f_k, $k=1,\ldots,K$ represent the frequencies, d_k, $k=1,\ldots,K$ the dampings, and T_{Samp} the constant sampling interval. Furthermore, c^x_k, $k=1,\ldots,K$ represent the so-called complex amplitudes associated with $x(t)$:

$$c^x_k = a^x_k e^{j\phi^x_k} \tag{14}$$

with a^x_k, $k=1,\ldots,K$ stands for the amplitude and ϕ^x_k, $k=1,\ldots,K$ for the phase. In a similar way the complex amplitudes c^y_k, $k=1,\ldots,K$ of $y(t)$ are defined.
From 11 and 12, it is clear that the two signals $x(t)$ an $y(t)$ are modeled with the same signal poles z_k, $k=1,\ldots,K$ but with different complex amplitudes. To determine the common poles, subspace-based approaches like the HTLS-SEP or MUSCLE algorithms are used : these consist in a set of operations applied to the Hankel matrices H_x and H_y of the signals $x(t)$, respectively $y(t)$. These matrices are constructed as follows :

$$H_x = \begin{pmatrix} x(0) & x(1) & \cdots & x(N-m+1) \\ x(1) & x(2) & \cdots & x(N-m+2) \\ \vdots & \vdots & \ddots & \vdots \\ x(m-1) & x(m) & \cdots & x(N-1) \end{pmatrix} \tag{15}$$

Once the common subspace C has been determined, the common poles can be estimated from this common subspace by means of the HTLS algorithm[1] [6]. Finally the total least squares (TLS) solution of this system is computed and yields the frequencies and damping factors, giving the pole estimates $\hat{z}_k, k=1,\ldots,K$. 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 (LS) to 11, respectively 12, with z_k replaced by the estimates $\hat{z}_k$. Using 11 and 12 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 ratio of the energy of the common part to the sum of the energy of the common part and the energy of the residual part is then used as a measure of the importance of the common part in the original signal $x(t)$:

$$CPC_x = \frac{\sum_{t=0}^{N-1}(\hat{x}_c(t))^2}{\sum_{t=0}^{N-1}(\hat{x}_c(t))^2 + \sum_{t=0}^{N-1}(x(t)-\hat{x}_c(t))^2} \tag{16}$$

[1] HTLS consists in first computing the singular value decomposition of the Hankel data matrix. Then a system of equations is built via a similarity transformation of the dominant subspace to a Vandermonde vector basis by means of the shift-invariance property.

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. In a similar way, $\hat{y}_c(t)$ and CPC_y can be defined.
The goal of the HTLS-SEP method is to fit one linear model to two signals. Only if the two signals have common signal poles, the determined system will be able to explain both signals sufficiently well. Such a system is obtained by calculating the following matrices X and Y :

$$H_x X = H_y Y \quad (17)$$
$$\equiv C \quad (18)$$

Since this condition can also be written as :

$$[H_x - H_y] \begin{bmatrix} X \\ Y \end{bmatrix} = 0 \quad (19)$$

it is clear that X and Y can easily be derived from the null space of the block Hankel matrix $[H_x - H_y]$. Such a linear model could also be fitted to more than two signals, but than the information given by the CPC parameter would be less easy to exploit. The MUSCLE algorithm does not rely on such a linear model, therefore it can be extended to more than two signals. It consists of using unitary matrices for determining a set of linearly independent vectors spanning the common space.
Concerning the estimation of the order of the EDS-model, three methods were investigated. The two first ones, the model-based methods ESTER [1] and SAMOS [4] both using a property called *shift-invariance property*, are respectively based on LS and singular value decomposition (SVD) approaches. SAMOS is shown to be more general, flexible and robust than ESTER. The third method is a classic iterative one based on the computation of an error on the difference between the signal and a model of it computed from a particular order.

3 Experimental results

From several premature infants, MAP, SaO_2 and HbD were measured simultaneously at the McGill University Health Centre (6 babies aged from 24 to 28 weeks, with a weight ranging from 675 to $1155g$, for a recording time ranging from 8 to 16 hours) and at the University Hospital Leuven (39 babies aged from 24 to 31.6 weeks, with a weight ranging from 570 to $1470g$, for a recording time ranging from $1h30$ to $23h35$). HbD was calculated as the difference between the concentration changes of HbO_2 and Hb, and was acquired at the frequency of $6Hz$. MABP and SaO_2 were recorded at a sampling frequency of $4Hz$ at the McGill University Health Centre and at $10Hz$ at the University Hospital Leuven. For this reason HbD was upsampled to respectively 4 and $10Hz$. From this data, the average values for non-overlapping 5-second intervals were calculated ($0.2Hz$). This sample 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) [7].
Since the concordance between the signals might vary as a function of time, a sliding window approach was used : the presented measures were calculated over 30-minute recordings (i.e. 360 samples), and plotted against the halftime of the 30-minute window. Several parameters have an influence on the estimation of the spectra for the calculation of COH, PCOH and pPSD : the length n of the sections, used for the calculation of the FFT's, and the number of overlapping points between consecutive sections. Experiments [3] with varying n showed that $n = 144$ gives the best results. In order to average as much as possible , we used maximum overlap between the sections (i.e. $n - 1 = 143$ data points). The averages of COH, PCOH and pPSD over the frequency band of interest ($0 - 0.01Hz$) were used as measure. Before calculating the FFT of each section, the mean was removed but no temporal window function was applied. pPSD was also normalized by two times its mean. Before computing COR and the CPC's, the signals were low-pass filtered to the frequency range of $0 - 0.01Hz$. Otherwise, HbD is the signal having been considered to compute the CPC's. As said in the introduction, HbD is indeed supposed to represent CBF. As this latter signal varies with varying MABP, a high CPC computed from HbD means that HbD and MABP are correlated. MUSCLE has been implemented for two and three signals. In the case of the 3-input MUSCLE, the third signal considered is SaO_2. Before building the EDS model, 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 (age: 27.6 weeks, weight: $840g$) are shown in Fig. 1, together with the corresponding measures. The total length of the measurement was four hours. We have further filtered all the signals to keep only the recording intervals during which the variation of SaO_2 around its mean does not exceed 5%. In this way the condition of constant SaO_2 is satisfied. During the first two hours of the recording, fluctuations in MABP seem at first sight not to be associated with parallel changes in HbD. The analysis of this period results in low COH (0.31), COR (0.51), PCOH (0.3) and high pPSD (0.61, wich means a low $1 - pPSD = 0.39$) values. During the same period, the CPC values of HTLS-SEP (0.91), 2-input MUSCLE (0.77) and 3-input MUSCLE (0.73) are higher suggesting that the CPC's are more sensitive in order to detect impaired autoregulation. During the last two hours of the recording, fluctuations in MABP are associated with parallel changes in HbD. This is a case of impaired cerebrovascular autoregulation. We obtained higher COH (0.54), COR (0.63), PCOH (0.49), 2-input MUSCLE (0.81) and $1 - pPSD$ (0.71), and still high values for HTLS-SEP (0.83) and 3-input MUSCLE (0.66). Now if we consider the last 45 minutes, HbD presents still parallel changes with the ones of MABP, even if slightly delayed. COH (0.31), COR (0.57), PCOH (0.46) and $1 - pPSD$ (0.67) are decreasing while HTLS-SEP (0.98), 2-input MUSCLE (0.98) and 3-input MUSCLE (0.98) are increasing. The CPC values are then more sensitive to detect an impaired autoregulation.

4 Conclusion

First COR seems to be a more sensitive measure to detect impaired autoregulation than COH. Secondly, the methods PCOH and pPSD were presented. They quantify in the frequency domain how similar three signals are. The hypothesis of these methods concerning the linearity between the signals seems to be validated. Furthermore, two other measures - HTLS-SEP and MUSCLE - were implemented. They quantify how similar the dynamics of the signals are, and are able to highlight a dynamic concordance between the considered signals in contrast to the others methods. Also MUSCLE can be generalized to study more than two signals. All these measures were used to quantitate the concordance between cerebral intravascular oxygenation and mean arterial blood pressure, which reflects impaired cerebrovascular autoregulation. A larger follow-up study is needed to confirm the performance of the newly implemented measures, and to evaluate statistically the predictive measure values with respect to possible brain damage.

Acknowledgements Dominique De Smet made a Master on Biomedical Engineering at the Katholieke Universiteit Leuven, Belgium. The topic of his master thesis was the detection of autoregulation in the brain of premature infants. Dr. Sabine Van Huffel is a full professor at the KULeuven. The research was supported by Research Council KUL: GOA-AMBioRICS, CoE EF/05/006 Optimization in Engineering, IDO 05/010 EEG-fMRI, several PhD/postdoc & fellow grants; by Flemish Government: FWO: PhD/postdoc grants, projects, G.0407.02 (support vector machines), G.0360.05 (EEG, Epileptic), G.0519.06 (Noninvasive brain oxygenation), FWO-G.0321.06 (Tensors/Spectral Analysis), G.0341.07 (Data fusion), research communities (ICCoS, ANMMM); and IWT: PhD Grants; by Belgian Federal Science Policy Office IUAP P5/22 ('Dynamical Systems and Control: Computation, Identification and Modelling'); by EU: BIOPATTERN (FP6-2002-IST 508803), ETUMOUR (FP6-2002-LIFESCIHEALTH 503094), Healthagents (IST-2004-27214, FAST (FP6-MC-RTN-035801) and by ESA: Cardiovascular Control (Prodex-8 C90242)

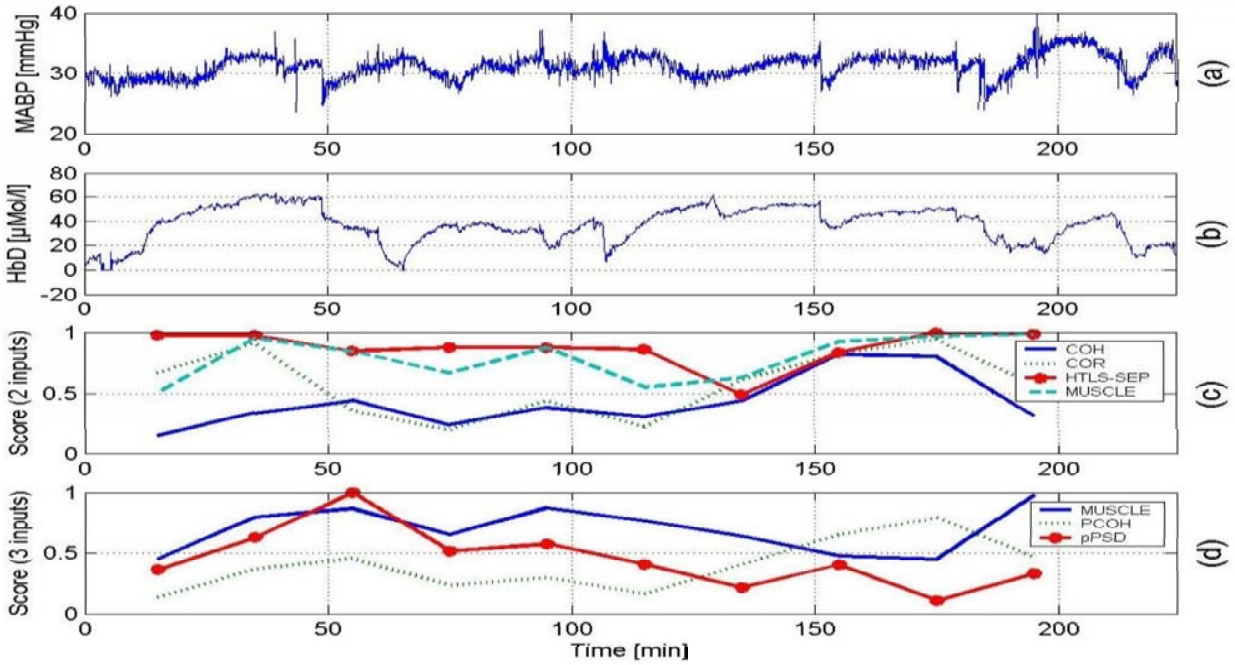


FIGURE 1: Simultaneous changes in MABP (a) and HbD (b) in a premature infant, with corresponding measures for two (c) and three (d) input signals

References

[1] Badeau, R.; B. David; and G. Richard. 2004. Selecting the modeling order for the ESPRIT high resolution method : an alternative approach. *Proc. Int. Conf. Acoust. Speech Signal Process.*, vol. II, pp. 1025-1028.

[2] Leuridan, J.; and B. Rost. September 1985. Multiple input estimation of frequency response functions : diagnostic techniques for the excitation. *ASME design engineering division conference and exhibit on mechanical vibration and noise*, Cincinnati, Ohio, USA.

[3] Morren, G.; P. Lemmerling; S. Van Huffel; G. Naulaers; H. Devlieger; and P. Casaer. October 25-28, 2001. Detection of autoregulation in the brain of premature infants using a novel subspace-based technique. *Proceedings 23rd Annual International Conference IEEE Engineering in Medicine and Biology Society*, Istanbul, Turkey. Paper 4.5.1-7, 4 pages (CD-rom).

[4] Papy, J.-M.; L. De Lathauwer; and S. Van Huffel. 2006. A shift invariance-based order selection technique for the exponential data modeling. *IEEE Signal Processing Letters*, to appear.

[5] Papy, J.-M.; L. De Lathauwer; and S. Van Huffel. 2006. Common pole estimation in multi-channel exponential data modelling. *Signal Processing*, vol. 86, pp. 846-858.

[6] Van Huffel, S.; H. Chen; C. Decanniere; and P. Van Hecke. February 1994. Algorithm for time-domain NMR data fitting based on total least squares. *J. Magn. Res.*, vol. 110, pp. 228-237.

[7] Tsuji, M.; J. Saul; A. du Plessis; E. Eichenwald; J. Sobh; R. Crocker; and J. Volpe. October 2000. Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. *Pediatrics*, vol. 106, no. 4, pp. 625-632.