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Nonlinear Multivariate Analysis of Dynamic Cerebral Blood Flow Regulation in Humans

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Abstract: **The dynamic relationship between cerebral blood flow, arterial blood pressure and arterial CO_2 is studied using the Laguerre-Volterra network methodology for modeling multiple-input nonlinear systems. Spontaneous beat-to-beat cerebral blood flow velocity and mean arterial blood pressure fluctuations, as well as breath-to-breath end-tidal CO_2 fluctuations are analyzed and the Volterra kernels of the system are obtained. It is found that, while pressure changes explain most of the blood flow velocity variations, the inclusion of end-tidal CO_2 fluctuations as an additional input variable can improve the prediction accuracy of the model output considerably. The model includes also nonlinear interactions between pressure and end-tidal CO_2 and their impact on cerebral blood flow.**

Keywords- **Cerebral autoregulation, Laguerre-Volterra network, Nonlinear modeling.**

I. INTRODUCTION

Cerebral blood flow (CBF) regulation maintains a relatively constant cerebral blood flow (CBF) over a wide range of mean arterial blood pressure (MABP) changes. In addition to pressure, blood flow regulation is affected by other exogenous variables. One such variable is arterial pCO_2, since the reactivity of cerebral vessels to CO_2 affects CBF regulation (hypercapnia causes vasodilation, while hypocapnia causes vasoconstriction). The effect of CO_2 on autoregulation can be assessed by breath-to-breath measurements of end-tidal CO_2 ($EtCO_2$).

Dynamic cerebral autoregulation is a frequency dependent and nonlinear phenomenon [1]. MABP changes occurring in the low frequency range, where the nonlinearities are also more prominent, are attenuated more effectively than high-frequency MABP changes. However, whereas the dynamic relationship between MABP and CBF has been studied extensively using spontaneous fluctuations of the two variables (following the advent of Doppler ultrasound), the same has not been done for the CO_2-CBF relationship, except in a limited number of studies [2]-[3].

In order to address this issue, the dynamic relationship between CBF, MABP and pCO_2 is examined in a nonlinear context, by using a recently developed nonlinear system identification method [4], extended here to multiple-input systems.

II. METHODOLOGY

The Laguerre-Volterra network (LVN) combines artificial neural networks with the Laguerre expansion technique and has been shown to be effective in modeling nonlinear systems from short input-output data records [4]. It is extended to multiple-input systems, in order to study the MABP, CO_2-CBF relation.

According to the method, each of the two inputs is fed into a different discrete-time Laguerre filter-bank, whose outputs are fully connected to a layer of hidden units with polynomial activation functions. The output of the network is given by a non-weighted summation of the hidden unit outputs and an offset parameter.

This representation is equivalent to the Volterra representation of a nonlinear system of order equal to the degree of the activation functions. The Volterra kernels of the system can be expressed in terms of the network parameters. Hence, after training the network from input-output data, we can obtain the kernel estimates from the resulting values of the trained parameters. The network training is performed using a gradient descent algorithm. In the multiple-input case, we extract self-kernels, describing the linear and nonlinear effects of each input on the output, as well as cross-kernels, describing the nonlinear interactions between different inputs.

The experimental data were obtained from 14 healthy subjects under normal conditions (around 40 minutes of data from each). CBF velocity (CBFV), which represents CBF well in all practical cases, was monitored in the middle cranial artery using transcranial Doppler ultrasonography. MABP was monitored noninvasively with a finger cuff device and $EtCO_2$ was measured with an end-tidal forcing system (nasal catheter). The measurement values were preprocessed appropriately (i.e., resampled and high-passed at 0.005 Hz). Six-minute data segments are employed, MABP and $EtCO_2$ values being the input signals of the LVN and CBFV values being the output of the network. The LVN model order was determined with a minimum description length criterion, by taking both in-sample and out-of-sample prediction performance into consideration.

III. RESULTS

The average achieved (in-sample) output prediction NMSEs using first and second-order LVN models are given in Table I, for one-input (MABP) and two-input (MABP and $EtCO_2$) LVN models. It is found that incorporating $EtCO_2$ as an additional input to the system improves the Normalized Mean Square Error (NMSE) of the LVN model prediction considerably, compared to the single-input (MABP) case. Moreover, the inclusion of $EtCO_2$ improves the out-of-sample model predictions. The reduction of the prediction NMSE from the first-order (linear) model to the second-order (nonlinear) model is significant (over 25%),

demonstrating the strongly nonlinear nature of CBF regulation.

TABLE I: LVN model predictions

Model inputs	MABP	MABP& $EtCO_2$
	NMSE(%)	
First-order	63.7 ±27.2	45.1±13.1
Total	27.3±10.4	19.4±6.7

The relative contributions of the linear and nonlinear terms of the model are illustrated in Fig. 1 for a typical data segment in the frequency domain, where the output spectrum and the spectra of the first-order and second-order residuals (output prediction errors) are shown. The shaded area corresponds to the difference between the first and second-order model residuals in the frequency domain, indicating that the nonlinearities are found below 0.1 Hz and are prominent below 0.04 Hz. This observation is consistent throughout all the data segments.

Averaged first-order kernels for MABP and $EtCO_2$ for one subject are shown in Figs. 2 and 3 respectively. The frequency responses of the MABP kernels show that low-frequency MABP changes are attenuated more effectively and that at high frequencies CBF follows MABP changes [1]. The $EtCO_2$ kernels show that the effect of CO_2 is slower, as expected, and the high variance of the initial kernel values is viewed as a pure delay of around 5 sec, which agrees with previous findings [3], possibly due to CO_2 transport phenomena.

The second-order self and cross-kernels reveal that nonlinearities are significant and inherent to the system and that they act mainly in low frequencies (below 0.1 Hz). Their frequency responses can provide a wealth of information about the different mechanisms (neural, myogenic, endothelial) influencing CBF regulation and acting in different frequencies, as well as about their interactions.

A critical observation concerns the issue of nonstationarity of CBF regulation, which is addressed by performing the analysis for overlapping six-minute segments with a five-minute overlap. It is found that nonstationarities are present and do not exhibit a clear pattern. The nonlinear dynamics exhibit considerably more nonstationary behavior than their linear counterparts.

IV. Conclusion

The contribution of MABP and $EtCO_2$ spontaneous fluctuations on CBF changes can be studied with the LVN methodology in a nonlinear context. The largest fraction of CBF variations is explained by MABP changes but including $EtCO_2$ can lead to more accurate models of CBF regulation, which could be clinically valuable for the evaluation of patients with cerebrovascular disorders (i.e., impaired CBF regulation).

References

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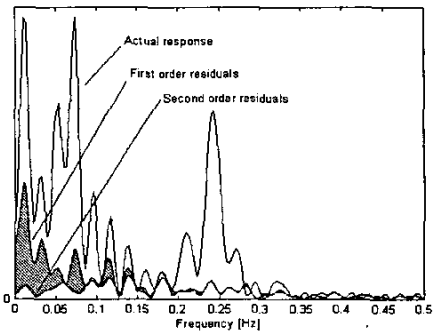

Figure 1: Spectra of the output (CBFV), first and second-order model residuals. The shaded area shows the effect of the nonlinear term.

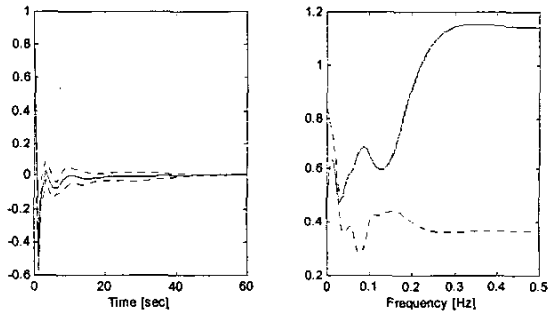

Figure 2: Averaged first-order MABP kernels in time and frequency domains. Solid: average, Dotted: Std. Deviation.

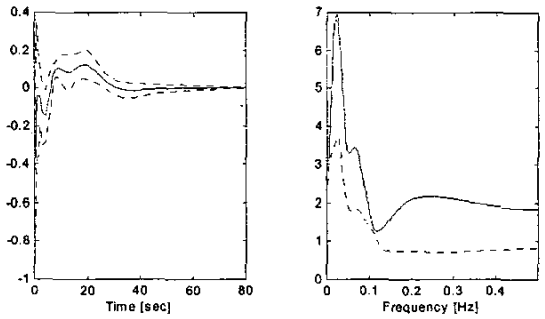

Figure 3: Averaged first-order $EtCO_2$ kernels in time and frequency domains. Solid: average, Dotted: Std. Deviation.