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Nonlinear Analysis of Dynamic Cerebral Autoregulation in Humans under Orthostatic Stress

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Abstract - **The effects of orthostatic stress on cerebral autoregulation are assessed by examining the dynamic relationship between spontaneous fluctuations of cerebral blood flow and arterial blood pressure under various levels of Lower Body Negative Pressure (LBNP) in healthy humans. The Laguerre-Volterra network methodology for modeling nonlinear systems is employed to this purpose. Results are obtained in the form of Volterra kernels as well as in the form of the dynamic modes of the system. Three significant modes are identified, one of them residing mostly in the linear system dynamics, and the other two residing in the nonlinear system dynamics. The obtained results reveal that the latter are affected mainly in the low frequency range (below 0.04 Hz), whereas they remain unaffected in the intermediate frequency range (between 0.04 and 0.08 Hz) and are affected moderately above 0.08 Hz.**
Keywords - **Cerebral autoregulation, Laguerre-Volterra network, Nonlinear modeling, Orthostatic stress.**

I. INTRODUCTION

Orthostatic syncope is a common problem that affects patients with autonomic dysfunction, as well as normal individuals after bed rest or spaceflight. The specific mechanism of orthostatic syncope may not always be clear and is probably multifactorial. However, the final event leading to syncope must be ultimately a reduction in cerebral perfusion sufficient to cause loss of consciousness. It has recently been shown that, even without a significant change in Mean Arterial Blood Pressure (MABP), steady-state Cerebral Blood Flow Velocity (CBFV) decreases substantially during LBNP-induced orthostatic stress [1]. In the same study, based on transfer function and coherence analysis, it was suggested that cerebral autoregulation becomes impaired during orthostatic stress, contributing possibly to the occurrence of orthostatic syncope.

However, the dynamic and strongly nonlinear nature of cerebral autoregulation has been revealed by the recent advance of high-temporal resolution measurement techniques and the study of the dynamic interactions between spontaneous fluctuations of MABP and Mean CBFV (MCBFV) [2]. In order to assess the effects of orthostatic stress conditions on autoregulation in an appropriate (i.e., dynamic and nonlinear) context, the dynamic relationship between MABP and MCBFV under various levels of LBNP is studied by using a novel variant of the general Volterra-Wiener approach, termed the Laguerre-Volterra Network (LVN) [3].

II. METHODOLOGY

The Laguerre-Volterra network (LVN) combines Volterra-equivalent networks with the Laguerre expansion technique and has been shown to be effective in modeling nonlinear systems from short input-output data records [4]. In order to account for the multiple mechanisms with different time scales affecting autoregulation, an alternative formulation of the LVN with two Laguerre filter banks (LVN-2), introduced in [4], is employed here and is shown in Fig. 1. The system input is fed into two distinct discrete-time Laguerre filter-banks, characterized by different Laguerre parameters, 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. By assigning different values to the Laguerre parameters of the filter banks, we can model the fast and slow dynamics of a nonlinear system effectively.

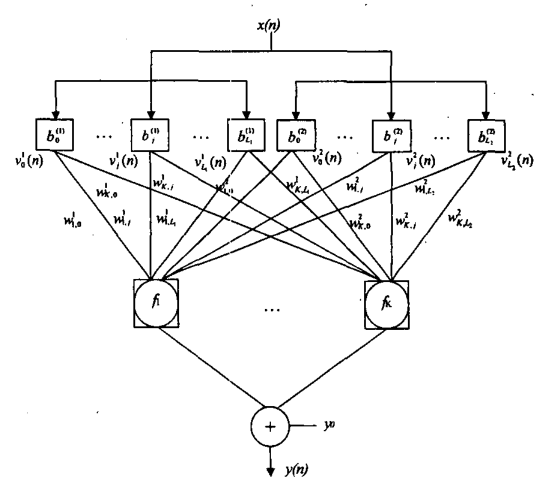

Fig. 1: The Laguerre-Volterra Network with two Laguerre filter-banks $\{b_j^{(1)}\}$ and $\{b_j^{(2)}\}$ that preprocess the input $x(n)$ (LVN-2). The hidden units in the second layer have polynomial activation functions $\{f_k\}$ and receive input from all Laguerre filters. The output $y(n)$ is formed by summation of the outputs of the hidden units $\{z_k\}$ and the output offset y_0.

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 an iterative gradient descent scheme.

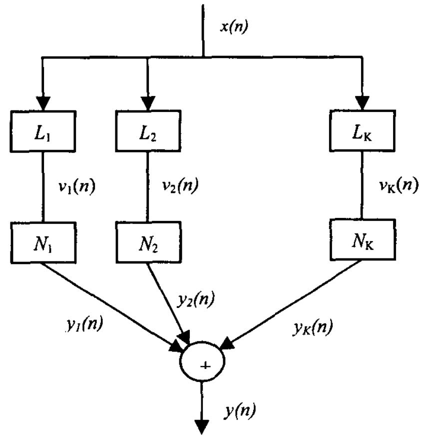

Figure 2. Dynamic mode representation of a nonlinear system.

The LVN-2 can be also expressed in the form of Fig. 2, whereby $L_1,\ldots,L_K$ are linear filters given by the linear combinations of the discrete-time Laguerre functions weighted by $w^{i}_{k,j}$, and constitute the dynamic modes of the system, and $N_1,\ldots,N_K$ are static nonlinearities, given by the hidden unit activation functions. Therefore, the number of the system modes is equal to the number K of the LVN-2 hidden units.

Beat-to-beat values of MABP and mean Cerebral Blood Flow Velocity (MCBFV) were obtained from five healthy subjects under various levels of LBNP. MCBFV, which represents blood flow well in all practical cases, was measured in the middle cranial artery using transcranial Doppler ultrasonography and MABP was measured noninvasively with a finger cuff device (FinaPres). LBNP was maintained by placing the subjects in a supine position in a Plexiglas LBNP box, sealed at the iliac crests and vacuum controlled by a pressure monitoring system. The subjects were allowed to rest for at least 30 minutes. Following this stage 6 minutes of beat-to-beat heart rate, MABP and MCBFV were collected. This formed the baseline data. After a gap of 2 minutes (for stabilization of cardiovascular hemodynamics) -15mm Hg LBNP was applied. Following this, the pressure was increased by a magnitude of -15 mm Hg. Post this reading, pressure was consistently reduced by 10 mm of Hg at each stage and data were recorded. This was continued until the patient felt nausea or uneasiness.

The measurement values were preprocessed appropriately (i.e., resampled at 1 Hz and high-passed at 0.005 Hz). The six-minute data segments are used to train the network, MABP being the input of the LVN-2 and MCBFV being the output. The LVN-2 model order was determined with a minimum description length criterion, by taking both in-sample and out-of-sample prediction performance into consideration. Following this procedure, an LVN-2 model with 7 Laguerre functions in each filter-bank, followed by three hidden units with third-order activation functions was selected.

III. Results

The average achieved (in-sample) output prediction Normalized Mean Square Errors (NMSEs) using linear and nonlinear (third-order) LVN-2 models are given in Table I. It is evident that the performance of nonlinear models is significantly better, as shown by the reduction achieved in the prediction NMSE, which is over 30%, demonstrating the strongly nonlinear nature of autoregulation. The nonlinearities are mainly active in the low-frequency range (i.e., below 0.04 Hz).

TABLE I: LVN-2 MODEL PERFORMANCE

[illegible]	[illegible]
First-order	48.0±9.9
Third-order	15.3±6.6

Representative data segments from one subject, used for model estimation are shown in Fig. 3 for baseline conditions, LBNP=-15 mmHg and LBNP=-30 mmHg. The averaged values of MABP and MCFV over the 6 min recordings are given in Table II for the same subject, along with their corresponding standard deviations. The mean value and variability of MABP is not affected much under orthostatic stress, whereas the mean value of MCBFV decreases for high LBNP values (i.e., above 30 mm Hg) and its variability increases considerably for increasing LBNP values. This was observed for all subjects consistently.

TABLE II: AVERAGED MABP AND MCBFV DURING LBNP

[illegible]	[illegible]	[illegible]
0 (Baseline)	67.2±3.5	58.9±2.1
-15	67.6±3.3	60.8±3.3\
-30	71.1±2.8	60.0±3.8
-40	71.1±3.3	56.7±4.3
-50	69.6±5.5	53.5±6.5

The obtained first-order Volterra kernel estimates for the same subject and under the same conditions are shown in Fig. 4. For the baseline conditions, the first-order kernel has a high-pass (differentiating) characteristic, which was also reported in previous studies [2], with peaks at 0 Hz, 0.02 Hz, 0.08 Hz and 0.25 Hz. The form of the frequency response implies that changes in MABP occurring between 0.01 and 0.1 Hz are attenuated more effectively. For LBNP=-30mm Hg and LBNP=-50 mm Hg, it is evident that the power of the first-order kernel is significantly increased in the low frequency range (below 0.04 Hz), giving rise to two significant peaks at 0.01 and 0.025 Hz (while the peaks at 0.08 Hz and 0.2 Hz remain), yielding the first-frequency response a low-pass characteristic. The linear frequency response is not affected between 0.04 and 0.08 Hz and is affected, but to a smaller extent, above 0.08 Hz, especially for LBNP=-50 mm Hg. Equivalently, in the time domain, the slow dynamics become more pronounced.

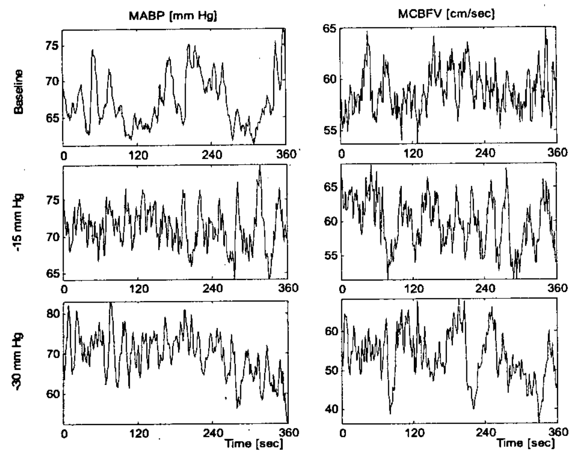

Figure 3. Representative MABP and MCFV data used for LVN-2 model estimation, for baseline, LBNP=-30 mmHg and LBNP=-50 mmHg conditions.

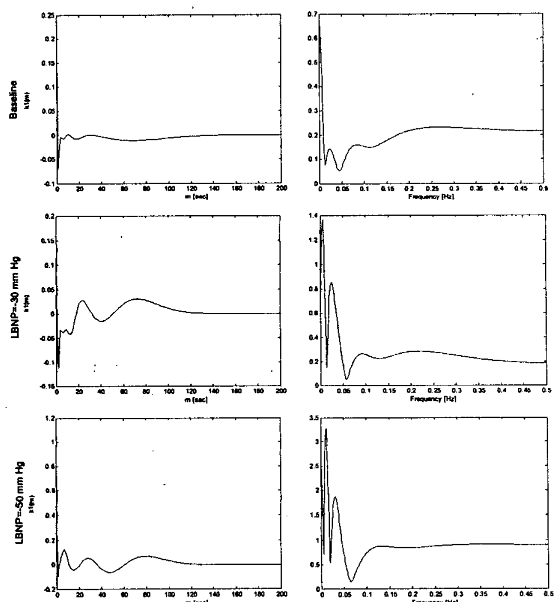

Figure 4. Estimated first-order kernels for the subject of Fig. 3 for baseline, LBNP=-30 mmHg and LBNP=-50 mmHg conditions. Left panel: Time domain, Right panel: Frequency domain.

The equivalent dynamic mode representation of the system is shown in Figs 5-7 in the frequency domain, for the subject of Fig. 4. Three significant modes are identified. Mode 2 has a high-pass component and resembles the first-order kernel more, whereas modes 1 and 3 have low-pass characteristics and reside mainly in the nonlinear dynamics of the system. The frequency domain characteristics of all three modes are affected mostly in the low frequency range. The output magnitude of the corresponding nonlinearities, which indicates the effect of each mode on the output, is markedly increased for Modes 1 and 3. Regarding the second mode, while the magnitude of its nonlinearity is not affected much, its sign is reversed for negative values of the mode output v_2 (i.e., it becomes positive).

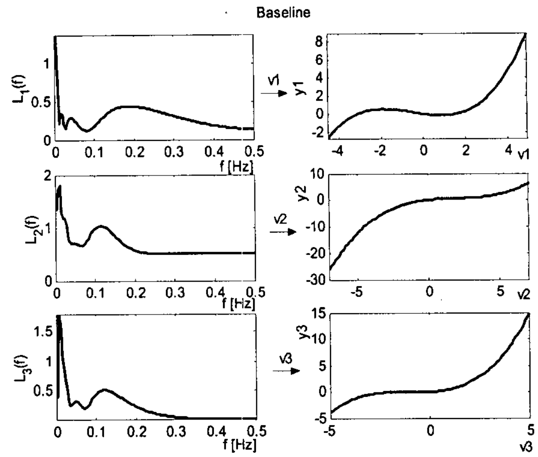

Figure 5. Estimated dynamic modes and corresponding nonlinearities for baseline conditions.

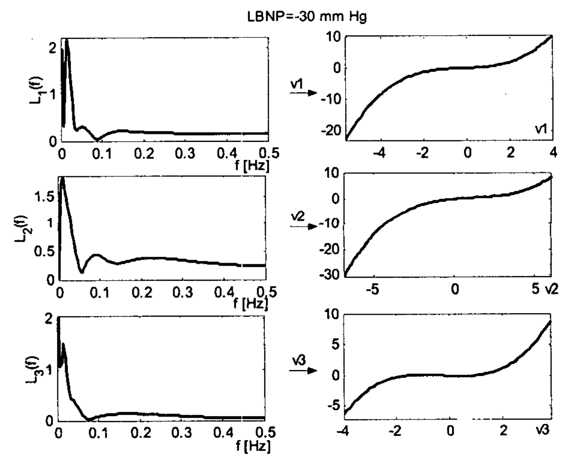

Figure 5. Estimated dynamic modes and corresponding nonlinearities for LBNP=-30 mm Hg.

IV. Discussion

The presented results exhibit the strongly nonlinear nature of cerebral autoregulation under baseline and LBNP conditions. The contribution of the nonlinear model terms was found to be varying and its relative significance is not consistently affected in the presence of orthostatic stress. The frequency domain characteristics of the first-order Volterra kernels are affected mostly below 0.04 Hz. Specifically, the low-frequency power of the linear dynamics increases markedly, giving the first-order kernel a low-pass characteristic rather than the high-pass characteristic observed usually under baseline conditions [2]. This effect becomes more pronounced for increasing values of LBNP. For frequencies above 0.04 Hz, the linear dynamics are affected less.

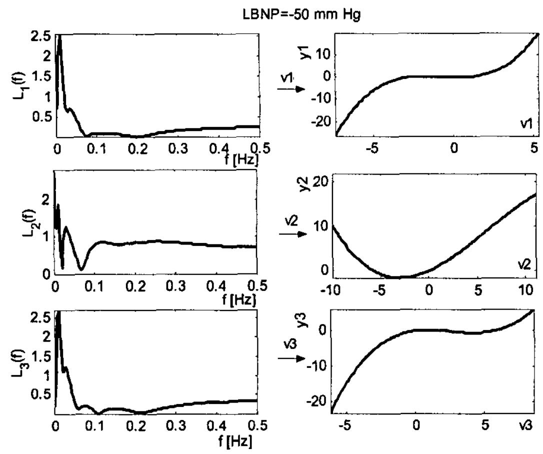

Figure 7. Estimated dynamic modes and corresponding nonlinearities for LBNP=-50 mm Hg.

Of the three modes that were determined to describe the system dynamics (linear and nonlinear), the second mode has a high-pass component and resides mainly in the first-order kernel, while the rest exhibit low-pass characteristics and are associated with the nonlinear dynamics. The frequency domain characteristics of the three modes are also affected mostly in the low frequency range under orthostatic stress. The magnitude the nonlinearity outputs corresponding to the first and third modes increases significantly with increasing LBNP values, indicating that their effect on blood flow in response to blood pressure changes is larger and implying that autoregulation may not be as effective. The magnitude of the second mode nonlinearity is affected less but its sign is reversed for high values of LBNP.

It should be also noted that in some cases, the effects of orthostatic stress were saturated for high LBNP values, i.e., the dynamics of the system were not affected further above a specific LBNP level, the value of which was subject-specific. In general, the effects of orthostatic stress on the system dynamics are similar qualitatively among different subjects, but quantitative differences exist.

V. CONCLUSION

The preliminary results presented here reveal the efficiency of the proposed approach in obtaining accurate nonlinear models of dynamic cerebral autoregulation during orthostatic stress and in detecting changes in the system dynamics. However, more work needs to be done in order to associate the obtained dynamic components (modes) of the system to specific underlying physiological mechanisms and quantify the effect of orthostatic stress on each one of them.

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