Supplementary Material

Dysregulation of CO2-Driven Heart-Rate Chemoreflex Is Related Closely to Impaired CO2 Dynamic Vasomotor Reactivity in Mild Cognitive Impairment Patients

Outline of Kernel-Based Input-Output Modeling Methodology

The advocated kernel-based modeling methodology is founded on the general Volterra-Wiener theories of input-output nonlinear system identification (applicable to all finite-memory stationary dynamic systems) and their elaborations over the last 50 years [1]. For the present study, this methodology is placed in the context of *linear* models of parts of the cerebral hemodynamic system expressing an output signal of interest (CFV: Cerebral Flow Velocity, measured at the middle cerebral arteries via Transcranial Doppler; TOI: Tissue Oxygenation Index, measured at the lateral prefrontal Cortex via Near Infrared Spectroscopy; or HR: Heart Rate) in terms with two time-series input signals (ABP: beat-to-beat mean Arterial Blood Pressure and CO2: breath-to-breath end-tidal CO2). If we denote the output signal as $y(t)$, and the two input signals, ABP and ETCO2, as $p(t)$ and $x(t)$ respectively, then the general linear predictive dynamic has the form:

$$y(t) = k_0 + \int_0^\infty k_p(\tau)\, p(t-\tau)\, d\tau + \int_0^\infty k_x(\tau)\, x(t-\tau)\, d\tau \qquad (1)$$

The dynamic characteristics of this model are described by the kernels k_p and k_x, which are estimated from the given input-output data (along with the zero-order kernel k_0), by means of Laguerre expansions of the kernels [1]:

$$k_p(\tau) = \sum_{j=1}^{L} C_p(j)\, b_j^p(\tau) \qquad k_x(\tau) = \sum_{j=1}^{L} C_x(j)\, b_j^x(\tau) \qquad (2)$$

where $\left\{b_j^i(\tau)\right\}$ denotes the orthogonal Laguerre basis for the i-th input. These kernel expansions transform the input-output relation (1) into Eq. (3) that involves *linearly* the unknown Laguerre expansion coefficients (which must be estimated from the data as shown below):

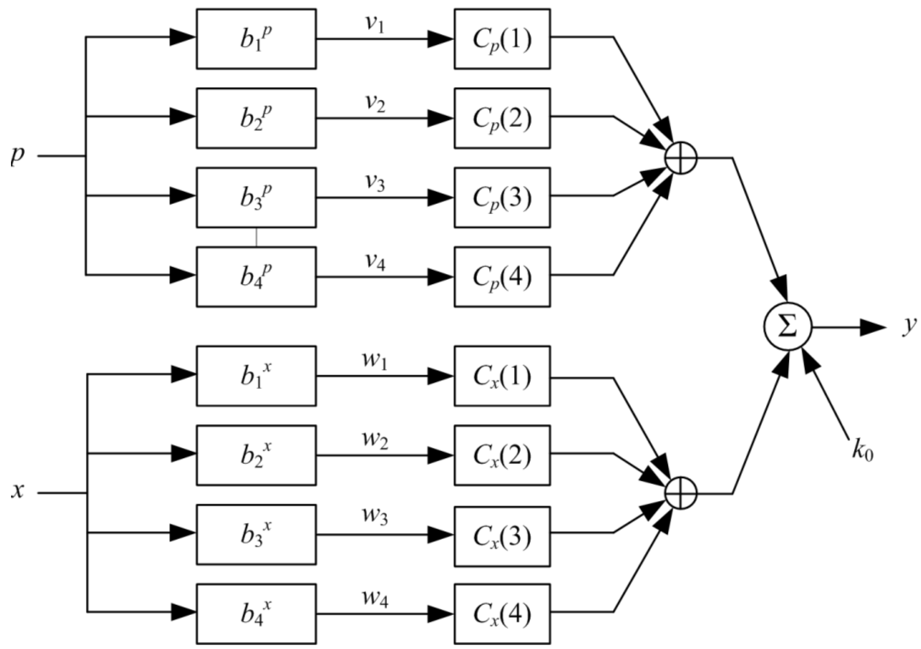
$$y(t) = k_0 + \sum_{j=1}^{L} C_p(j)\, v_j(t) + \sum_{j=1}^{L} C_x(j)\, w_j(t) \tag{3}$$

where:

$$\begin{aligned} v_j(t) &= \int_0^{\infty} b_j^p(t-\tau)\, p(\tau)\, d\tau \\ w_j(t) &= \int_0^{\infty} b_j^x(t-\tau)\, x(\tau)\, d\tau \end{aligned} \tag{4}$$

Since the Laguerre expansion coefficients enter linearly in the input-output model of Eq. (3), their estimation can be achieved via least-squares regression (a simple and robust numerical procedure). Following estimation of the Laguerre expansion coefficients, we can construct the kernel estimates using Eq. (2) and compute the model prediction for *any* given input using Eq. (1) or (3). Key parameters in the application of the Laguerre expansion technique are the number of employed Laguerre basis functions *L*, as well as the Laguerre parameter “alpha” that defines the relaxation dynamics of these Laguerre functions for each input. These parameters are selected on the basis of a search procedure that seeks to minimize the Bayesian Information Criterion that takes into account the normalized mean-square error (NMSE) of the model prediction and the number of free parameters in the respective model. In this study, the appropriate number L of Laguerre functions for both inputs, ABP or CO2, was found to be L=4 when the output is CFV (with Laguerre parameters “alpha” of 0.7 and 0.85, respectively); L=4 when the output is TOI (with Laguerre parameters “alpha” of 0.9 and 0.9, respectively) and L=3 when the output is HR (with Laguerre parameters “alpha” of 0.5 and 0.85, respectively).

The kernel-based model of a two-input/one-output system using the Laguerre expansion has the structure depicted in the block-diagram of Supplementary Figure 1.



Supplementary Figure 1. Block-diagram of the kernel-based linear model of a two-input/one-output system using the Laguerre expansion that is employed in this study for three different outputs (CFV, TOI, HR) in combination with the two inputs (ABP and CO2). Each model output is composed of the weighted summation of the convolutions of the Laguerre basis functions with each input (see Eq. (3) above).

REFERENCE

[1] Marmarelis VZ (2004) *Nonlinear Dynamic Modeling of Physiological Systems*. Wiley-Interscience & IEEE Press.