**Supplementary Material**

The advocated PDM-based modeling approach has its foundation in the general nonparametric Volterra modeling methodology that is applicable to all finite-memory dynamic nonlinear systems (i.e., almost all physiological systems, with the exception of chaotic systems or non-dissipating oscillators) [1]. For instance, the 2nd order Volterra model of the aforementioned dual-input system of cerebral hemodynamics expresses the output CBFV or TOI *y*(*t*) signal in terms of the following functionals of the two input signals, *p*(*t*) and *x*(*t*), denoting the ABP and ETCO2 input respectively:

 (1)

where *ε*(*t*) denotes possible measurement or modeling errors. The dynamic characteristics of this system/model are described by the kernels: *kp* , *kx* , *kpp* , *kxx* , *kpx* , which are estimated using given input-output data (along with the zero-order kernel *k0*), by means of Laguerre expansions of the kernels [2]:

 (2)

where  denotes the orthogonal Laguerre basis for the *i*-th input. The kernel expansions transform the input-output relation (1) to Eq. (3) that involves *linearly* the Laguerre expansion coefficients:

 (3)

where:

 (4)

Since the Laguerre expansion coefficients enter linearly in the nonlinear 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 Volterra 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 parameters that define 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 number of free parameters in the respective model. This search procedure yielded *L*=4 for both inputs and outputs, however the Laguerre parameters alpha were 0.55 and 0.85, for the ABP and ETCO2 inputs respectively, when the output was CBFV, or 0.75 and 0.9, for the ABP and ETCO2 inputs respectively, when the output was TOI.

Although the Laguerre expansion technique brings considerable model estimation efficiencies, it does not remove the “curse of dimensionality” associated with the multi-dimensional structure of high-order kernels. In order to overcome this latter practical limitation, we have introduced the concept of Principal Dynamic Modes (PDM), which aims at identifying the minimum set of basis functions for each input (distinct and characteristic for each system) that is capable of representing adequately the system dynamics (i.e., provide satisfactory approximations of the kernels) while minimizing the contributions of possible cross-terms [1]. The computation of the PDMs for each input is based on Singular Value Decomposition (SVD) of a rectangular matrix that can be composed of all 1st order kernel estimates in the cohort (for linear analysis) or the 1st and 2nd order kernel estimates properly weighted by the root-mean-square values of the respective input (i.e., for nonlinear analysis) [1]. The resulting PDMs form a filter-bank that receives the respective input signal and generates (via convolution) signals that are subsequently transformed by the "Associated Nonlinear Function" (ANFs) to form additively the system output. Thus, the PDM-based model separates the dynamics (PDMs) from the nonlinearities (ANFs).

Since the “separability” of the system nonlinearities cannot be generally assumed, we may include in the PDM-based model cross-terms that are selected on the basis of a statistical significance test using the Fisher statistic on the computed correlation coefficient between each cross-term (i.e., the pair product of PDM outputs) and the output signal.

As mentioned above, the present study is limited to *linear* modeling in order to enhance the robustness of the obtained results for the available, relatively short, data records (5-6 min). The *linear* model reduces the ANFs to simple scalars (termed “Gains” in the sequel) multiplying the respective PDM outputs, and excludes possible cross-terms. Thus, the resulting model output equation is:

 (5  
where {*uj*} and {*wm*} are the PDM outputs (i.e. convolutions of each input with the respective PDM) for the ABP and ETCO2 inputs, respectively, and {*Aj*} and {*Cm*} are the scalar Gains associated with each PDM output. These Gains are estimated, along with *c*0 via least-squares regression of Eq. (5).

In this linearized modeling study, we obtain the “global” PDMs via SVD of a rectangular matrix that contains all the 1st order kernel estimates for each input (as column vectors) for all the control subjects. *Four global PDMs* were found to be adequate for each input in this application, whether the output is CBFV or TOI. The block-diagram of the structure of the linearized PDM-based model of the two-input/one-output cerebral hemodynamics system is shown in Supplementary Figure 1.

**REFERENCES**

[1] Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B (2001) Current concepts in mild cognitive impairment. *Arch Neurol* **58**, 1985-1992.

[2] Marmarelis VZ (1993) Identification of nonlinear biological systems using Laguerre expansions of kernels. *Ann Biomed Eng* **21**, 573–589.



**Supplementary Figure 1:**Block-diagram of the employed PDM-based two-input/one-output model of cerebral hemodynamics with four global PDMs for each input, p: ABP and x: ETCO2. The output up,j of the j-th PDM, Pp,j , for input p, or the output wx,m of the m-th PDM, Px,m , for input x ,is the convolution of the PDM with the respective input signal. In this application, the ANFs are replaced by linear Gains: {Aj}for the ABP components and {Cm} for the ETCO2 components to generate the mode output prediction: y= c0 + Σ Aj uj + Σ Cm wm , which is either CBFV (measured via TCD) or TOI (measured via NIRS).