Published in final edited form as:

Ann Biomed Eng. 2013 May ; 41(5): 1029–1048. doi:10.1007/s10439-012-0736-8.

Closed-Loop Dynamic Modeling of Cerebral Hemodynamics

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Abstract

The dynamics of cerebral hemodynamics have been studied extensively because of their fundamental physiological and clinical importance. In particular, the dynamic processes of cerebral flow autoregulation and CO₂ vasomotor reactivity have attracted broad attention because of their involvement in a host of pathologies and clinical conditions (e.g. hypertension, syncope, stroke, traumatic brain injury, vascular dementia, Alzheimer's disease, mild cognitive impairment etc.). This raises the prospect of useful diagnostic methods being developed on the basis of quantitative models of cerebral hemodynamics, if cerebral vascular dysfunction can be quantified reliably from data collected within practical clinical constraints. This paper presents a modeling method that utilizes beat-to-beat measurements of mean arterial blood pressure, cerebral blood flow velocity and end-tidal CO₂ (collected non-invasively under resting conditions) to quantify the dynamics of cerebral flow autoregulation (CFA) and cerebral vasomotor reactivity (CVMR). The unique and novel aspect of this dynamic model is that it is nonlinear and operates in a closed-loop configuration.

Key terms

Cerebral Autoregulation; Nonlinear Modeling; Modeling Cerebral Hemodynamics; Closed-Loop Modeling; Cerebral Flow Autoregulation; Cerebral Vasomotor Reactivity

Introduction

Cerebral flow autoregulation (CFA) and cerebral vasomotor reactivity (CVMR) are two fundamental aspects of cerebral hemodynamics that are implicated in a host of pathologies and clinical conditions (e.g. hypertension, syncope, stroke, traumatic brain injury, vascular dementia, Alzheimer's disease, mild cognitive impairment etc.). With increasing evidence of significant vascular components in many neurodegenerative diseases, the prospect of useful model-based diagnostic methods emerges if cerebral vascular dysfunction can be quantified reliably within practical clinical constraints. For this reason, many studies have sought such quantification of these two functional aspects (CFA and CVMR) of cerebral hemodynamics using subject-specific models based on beat-to-beat measurements of mean arterial blood pressure, cerebral blood flow velocity and end-tidal CO₂ [1–2,5–7,11–23]. The requisite data can be collected non-invasively and safely under resting conditions in a clinical setting. The study of CFA and CVMR in cerebral hemodynamics has revealed the presence of multiple physiological control or regulatory mechanisms that maintain variations of cerebral blood flow within narrow bounds during physiological changes of perfusion pressure in healthy humans. In addition to perfusion pressure, variation in blood CO₂ tension is viewed as a key factor affecting changes in cerebral blood flow [3–4,11–15]. Quantification of these physiological mechanisms has been pursued with models that describe the “open-loop” causal relationship between these measured variables [11–23]. This modeling task has been

confounded by many intrinsic complexities of this system: dynamics, nonlinearities, multiple nested interactions etc.

Our previous work has focused, in particular, on deriving nonlinear dynamic models of the causal “open-loop” relationship between an “output” variable: the cerebral blood flow velocity, and two “input” variables: the arterial blood pressure and the end-tidal CO₂. This has been pursued by use of the Volterra approach and Laguerre expansions that exhibit good predictive capability [8–15]. Recently, we utilized the concept of Principal Dynamic Modes (PDMs) to achieve more compact representations of this model and to facilitate its physiological interpretation [11]. In these “open-loop” modeling studies, beat-to-beat measurements of the aforementioned variables were used that are reliably collected under resting conditions in a clinical setting. Using these open-loop models, simple CFA and CVMR indices have been derived that may eventually have clinical utility by quantifying specific physiological mechanisms, disease progress or the effect of medication in each subject.

These previous studies have yielded useful results, but they do not take into account the “closed-loop” nature of the subject system – i.e. the fact that changes in blood flow may also affect the blood pressure of cerebral perfusion, and not only the other way around – which is expressed herein as our “working hypothesis”. If this working hypothesis becomes validated, the “open-loop” studies and the previously obtained results are not invalidated. However, they must be interpreted in the open-loop context, which is distinct from the “closed-loop” context discussed in this paper. We maintain that there is considerable scientific value (and potential clinical utility) in studying and understanding the closed-loop characteristics of the CFA-CVMR system, as elaborated below. This paper presents a general methodology with which physiological closed-loop systems can be studied in general and, in particular, it demonstrates its application to the closed-loop analysis of the CFA-CVMR system of cerebral hemodynamics.

Materials and Methods

Experimental Methods

Fifteen control subjects participated voluntarily in this study and signed the Informed Consent Form that has been approved by the IRB of the University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas, where the data were collected at the Institute for Exercise and Environmental Medicine. Demographic characteristics of the study participants have been reported previously [23]. Arterial blood pressure was measured continuously and non-invasively with finger photoplethysmography (Finapres) and cerebral blood flow velocity was measured in the middle cerebral artery using a 2 MHz transcranial Doppler (TCD) probe (Multiflow, DWL) placed over the temporal window and fixed at constant angle with a custom-made holder. Heart rate was monitored via electrocardiogram (ECG) and end-tidal CO₂ tension was measured via a nasal cannula using capnography (Criticare Systems). All experiments were performed in the morning in a quiet, environmentally controlled laboratory under resting conditions. After 20 minutes of supine rest, 5–6 minutes of recordings were made in supine position under resting conditions.

Data Preprocessing

Continuous recordings of arterial blood pressure, end-tidal CO₂ and cerebral blood flow velocity were reduced to beat-to-beat time-series data by averaging the signals over each R-R interval of the ECG to yield three time-series data of the physiological variables of interest: mean arterial blood pressure (MABP), end-tidal CO₂ (ETCO₂) and mean cerebral blood flow velocity (MCBFV), after re-sampling of the computed beat-to-beat values every

0.5 sec via cubic-spline interpolation. Occasional measurement artifacts were removed by applying a threshold criterion on the maximum change that is physiologically possible from beat to beat in these variables. The resulting time-series data were de-trended via high-pass filtering to remove the constant offset (average) and the very low frequencies below 0.008 Hz, and were clipped at $\pm$ two standard deviations to mitigate the effects of occasional outliers. The ETCO₂ data were shifted by 2 sec to compensate for the latency of the measurement apparatus. Figure 1 shows illustrative time-series data over 6 min and the respective spectra for a typical control subject (#11).

Modeling methods

The first step in the closed-loop analysis (CLA) of the CFA-CVMR system is the estimation of the open-loop models (as done previously) in both causal directions (see diagram of Figure 2): Component **A**, when MCBFV is considered the output (with MABP and ETCO₂ the two inputs) and Component **B**, when MABP is considered the output (with MCBFV and ETCO₂ the two inputs). We note that the model-predicted internal signals, $F_d(t)$ and $P_d(t)$, from the closed-loop model components **A** and **B** respectively, are only portions of the measured signals $F(t)$ and $P(t)$ – with the residuals, $F_d(t)$ and $P_d(t)$, representing blood flow and systemic pressure disturbances caused by cardio-vascular and neural factors that have yet to be identified. The open-loop models **A** and **B** are obtained using Principal Dynamic Modes (PDMs) and the procedure outlined in Appendix I. For the many mathematical and technical details of Volterra-type modeling and related issues, the reader is referred to the comprehensive monograph [10]. In brief, the output of the dual-input PDM-based model is formed by additive signal components that are generated through cascaded operations on the input signals – i.e. polynomial (typically cubic) transformation of the convolution of each input with each respective “global” PDM. The global PDMs are derived from the data as outlined in Appendix I. The coefficients of the polynomial nonlinearity associated with each PDM, termed “Associated Nonlinear Function” (ANF), are estimated via regression of the PDM outputs on the system output, along with the coefficients of the significant cross-terms (pair-products of PDM outputs from the two inputs) and a constant offset.

The structure of PDM-based model of the two-input/one-output CFA-CVMR system is shown in the block-diagram of Figure 3. Three global PDMs were found to be adequate for each input. We note that the global PDMs represent an efficient set of “basis” functions (distinct and characteristic for each class of systems) that are capable of representing adequately and compactly the dynamics of this class of systems. The global PDMs are computed via Singular Value Decomposition of a rectangular matrix containing all PDMs from a representative set of this class of systems, as described in Appendix I. The global PDMs represent a common “functional coordinate system” (i.e. basis of functions) for efficient representation of all kernels of the CFA-CVMR system for all subjects. However, the ANFs associated with the global PDMs and the coefficients of the cross-terms are *subject-specific* and can be used to characterize uniquely the CFA-CVMR process of each subject (i.e. they have potential diagnostic value). In Figure 3, the output $u_{j,m}(t)$ of the j -th PDM, $p_{j,m}$ for the m -th input, x_m ($m=1,2$), is the convolution of the PDM with the respective input. The ANFs are taken in this application to be cubic polynomials: $z_{j,m} = f_{j,m}(u_{j,m}) = a_{1,j,m} u_{j,m} + a_{2,j,m} u_{j,m}^2 + a_{3,j,m} u_{j,m}^3$. The selected cross-terms, $\{c_{i,j} u_{i,j}(n) u_{j,j}(n)\}$, have significant correlation with the output (correlation coefficient > 0.1 , based on the w -statistic for a null hypothesis of zero correlation). The output MCBFV is the sum of all ANF output components $\{z_{j,m}\}$, the selected significant cross-terms and a constant offset value c_0 which represents the baseline output value when the input signals are zero.

The proposed methodology commences with the estimation of the dual-input PDM-based models (like the one shown in Figure 3) for the open-loop components **A** and **B** in Figure 2,

following the procedure outlined in Appendix I. The disturbance signals $F_d(t)$ and $P_d(t)$ are computed in each case as the model-prediction residuals and can be examined for their spectral or statistical characteristics, since they are viewed as the physiological “drives” of the closed-loop system $\mathbf{A} \leftrightarrow \mathbf{B}$. Observing Figure 2, we have two equivalent closed-loop equations:

$$\begin{aligned} F(t) &= \mathbf{A}\{P, C\} + F_d(t) \\ &= \mathbf{A}\{B[F, C] + P_d(t), C\} + F_d(t) \end{aligned} \quad (1)$$

$$\begin{aligned} P(t) &= \mathbf{B}\{F, C\} + P_d(t) \\ &= \mathbf{B}\{A[P, C] + F_d(t), C\} + P_d(t) \end{aligned} \quad (2)$$

which are nonlinear stochastic integral equations, since from Figure 2 and Appendix I we have:

$$F(t) = F_0 + \sum f_i^{PF} [u_i^{PF}(t)] + \sum f_j^{CF} [u_j^{CF}(t)] + \sum c_{k,\ell}^{PC} u_k^{PF}(t) u_\ell^{CF}(t) + F_d(t) \quad (3)$$

$$P(t) = P_0 + \sum f_i^{FP} [u_i^{FP}(t)] + \sum f_j^{CP} [u_j^{CP}(t)] + \sum c_{k,\ell}^{FC} u_k^{FP}(t) u_\ell^{CP}(t) + P_d(t) \quad (4)$$

where the signals $u(t)$ are convolution integrals of the input signals with the PDMs, the functions $f[\cdot]$ are polynomials (cubic in this case), and F_0, P_0 are the baseline values of MABP and MCBFV respectively (i.e. their values when there are no systemic disturbances). In the case of discretized data (as for beat-to-beat time-series data here), Equations (1) and (2) are tantamount to nonlinear auto-regressive equations in $F(t)$ or $P(t)$ with *stochastic* coefficients and an exogenous variable $C(t)$. Note that the signals $F(t)$, $P(t)$ and $C(t)$ represent *deviations* from their respective baseline (reference) values – i.e. they are zero at the reference “operating point” of each subject – and they are caused by the systemic disturbance signals $F_d(t)$ and $P_d(t)$.

The operators $\mathbf{A}$ and $\mathbf{B}$ denote the dynamic nonlinear PDM-based models of the respective transformations in Figure 2. Since the latter operators are estimated from the data, either of the closed-loop system equations (1) or (2) can be simulated to generate the blood pressure signal $P(t)$ or the flow velocity signal $F(t)$ for given $C(t)$ and systemic disturbances $F_d(t)$ and $P_d(t)$. These simulations can reveal the closed-loop dynamic nonlinear characteristics of the subject system. For instance, broadband (band-limited white-noise) systemic disturbances can be used to examine the *spectral characteristics of the closed-loop model* for various power levels under isocapnic conditions ($C(t) = 0$) or under hypercapnic ($C(t) > 0$) and hypocapnic ($C(t) < 0$) conditions (see Discussion). Another informative simulation is to set the systemic disturbances equal to zero and use a pulse $C(t)$ to examine the *CO₂ vasomotor reactivity of the closed-loop model*. Likewise, the *pressure autoregulation* can be examined under isocapnic conditions by simulating Eq. (1) for a pulse $P_d(t)$ while setting $C(t) = F_d(t) = 0$. Note that the resulting $F(t)$ in this latter example will be different from the resulting $F(t)$ in the open-loop model simulation where $P(t)$ is a pulse, instead of $P_d(t)$, while $C(t)$ and $F_d(t)$ are still set equal to zero. Specifically, the isocapnic flow-velocity response to a pulse-pressure change $p(t)$ for the open-loop model is:

$$F_{OL}(t) = \mathbf{A}\{p(t), 0\} \quad (5)$$

while the flow-velocity response to a pulse-pressure change $p(t)$ for the closed-loop model is:

$$F_{CL}(t) = \mathbf{A}\{\mathbf{B}[F_{CL}(t), 0] + p(t), 0\} \quad (6)$$

when no systemic random disturbances exist. This potentially important difference between open-loop and closed-loop dynamics of the CFA-CVMR system is the thrust of this paper.

It is instructive to examine the particular case where the operators $\mathbf{A}$ and $\mathbf{B}$ are linear – i.e. described by Transfer Functions in the frequency domain. Then, Eq. (1) yields the following relation in the Laplace domain (i.e. the variables are described by their Laplace Transforms):

$$F = \frac{H_{PF} H_{CP} + H_{CF}}{1 - H_{PF} H_{FP}} \cdot C + \frac{H_{FP} P_d + F_d}{1 - H_{PF} H_{FP}} \quad (7)$$

where H_{XY} denotes the Transfer Function from input X to output Y. This expression indicates that, under the linear assumption, the dynamics and stability of the closed-loop model are determined by the poles (i.e. the roots) of the expression: $(1 - H_{PF} H_{FP})$. To maintain stability, the product $H_{PF} H_{FP}$ in the complex Laplace domain must remain away from 1. The resonances of the closed-loop system are defined by the troughs of the function $|1 - H_{PF} H_{FP}|$ expressed in the Fourier domain. With regard to the aforementioned difference of model-predicted flow-velocity response to a pulse of pressure between open-loop and closed-loop models under isocapnic conditions and without random disturbances (see Eqs. (5) and (6)), the relations under the linear assumption become: $F_{OL} = H_{FP} P$ and $F_{CL} = [H_{FP} / (1 - H_{PF} H_{FP})] P$, where P is the Fourier Transform of the pressure pulse. It is evident that the two simulated responses are significantly different, since the latter formulation takes into account the “loop recycling effects” (see Discussion). To prevent confusion, we emphasize that in the open-loop formulation the pressure pulse is presented at the input of operator $\mathbf{A}$, while in the closed-loop formulation the pressure pulse is presented as the “pressure disturbance” signal (see Figure 2).

The results of nonlinear closed-loop modeling of the CFA-CVMR process in 15 control subjects are presented in the following section. The following structural parameters of the PDM-based models were used after proper search: 5 Laguerre basis functions for the MABP or MCBFV inputs and 3 Laguerre basis functions for the ETCO₂ input, with Laguerre parameter $\alpha = 0.7$ for all, three PDMs for each input and cubic ANFs for all PDMs. The presented results include the obtained global PDMs, illustrative ANFs, and comparisons of open-loop/closed-loop flow responses to imposed pulse changes in pressure or CO₂, when no random systemic disturbances exist. The latter simulations yield measures of CFA and CVMR in each subject, which may attain clinical utility in the future. The set of global PDMs used for all control subjects as a common reference set, were obtained from five control subjects randomly selected. Surprisingly, it was found that the form of the global PDMs did not change appreciably when a different set of five subjects was selected among the 15 control subjects to determine the global PDMs.

Results

We first estimate the global PDMs for the open-loop models $\mathbf{A}$ and $\mathbf{B}$, following the procedure outlined in Appendix I. The obtained “global” PDMs from a set of 5 randomly chosen control subjects (CS) are shown in Figure 4 for the PDM-based model of $\mathbf{A}$ (in the time and frequency domains) and in Figure 5 for the PDM-based model of $\mathbf{B}$. As noted above, three “global” PDMs were found to be adequate for each input and their form remained practically unchanged when a different set of 5 control subjects (out of a separate set of 10) was randomly selected for their computation, corroborating the notion that these six global PDMs can be used for reliable modeling of the CFA and CVMR dynamics of all

subjects. Of course, the ANFs of these global PDMs are distinct and characteristic for each subject and may prove useful for diagnosis of pathologies or assessment of clinical conditions that impact the dynamics of the CFA-CVMR system.

As shown in Figure 4, the 1st PDM of the MABP input for the **A** model component exhibits a high-pass characteristic, consistent with the Windkessel model as applied to the cerebral vasculature, where arterial flow is viewed as the output [23] – not the initial application of the Windkessel model to aortic pressure, where the ventricular flow is viewed as the input. However, this PDM also exhibits a blunt resonant peak around 0.15 Hz which is likely associated with active autoregulation. The 2nd PDM exhibits a broad resonant peak around 0.08 Hz and the 3rd PDM exhibits a sharp resonant peak around 0.04 Hz. The physiological origin of these resonant peaks ought to be explored in future studies, as they may be related to myogenic, endothelial and/or autonomic mechanisms (see Discussion). The nonlinear characteristics of the CFA-CVMR process are expected to be associated primarily with the 2nd and 3rd PDMs, since our previous studies have shown that most of the nonlinearities are found in the range 0.01 – 0.08 Hz, where linear coherence is low [11–15]. The 1st PDM of the ETCO₂ input exhibits a low-pass characteristic, indicating weighted integration of the ETCO₂ past values over ~ 20 sec, with maximum weight applied for lags of about 5 s. The 2nd PDM of the ETCO₂ input exhibits a broad resonant peak around 0.08 Hz and the 3rd PDM exhibits a sharp resonant peak around 0.04 Hz, suggesting functional coupling with the respective PDMs of the MABP input with possible common origin of these resonances due to the same physiological mechanisms (see Discussion).

Figure 5 shows the global PDMs for the **B** component of the closed-loop model that has MABP as its output (top row: MCBFV input; bottom row: ETCO₂ input). The 1st PDM of the MCBFV input for the **B** model component exhibits an all-pass characteristic with mild low-frequency integration below 0.02 Hz; the 2nd PDM exhibits resonant peaks around 0.02 Hz and 0.08 Hz (similar to its counterpart for the MABP input of model component **A**); the 3rd PDM exhibits strong integrative characteristics over ~30 sec and a resonant peak around 0.08 Hz. For the ETCO₂ input of the **B** model component, the 1st and 3rd PDMs exhibit low-pass characteristics but, interestingly, only the 3rd PDM has integrative characteristics in the time-domain (over ~15–20 sec) while the 1st PDM has a biphasic time-domain profile with two positive and one negative segment (see blue line in the bottom left panel of Figure 5) – i.e. this is a “non-minimum phase” filter. The 2nd PDM of the ETCO₂ input exhibits a resonant peak around 0.04 Hz, similar to the 3rd PDM of the ETCO₂ input for model component **A** (see Figure 4). Although the detailed physiological interpretation of these global PDMs will require careful and extensive future study, it is evident that these waveforms contain potentially useful functional information about the CFA and CVMR processes (see Discussion).

To complete the estimation of each PDM-based open-loop model (**A** and **B** in Figure 2), we must estimate the ANFs of each global PDM for each subject that describe the nonlinear characteristics of the CFA-CVMR process, as well as the coefficients of the significant cross-terms that describe the interactions of the two inputs as they impact the output. Each ANF is a static nonlinear function (cubic in this case) that is applied to the output of the respective PDM to generate an additive contribution to the model output (see Figure 3). For illustrative purposes, we show the ANFs of model **A** component for the six global PDMs (three for each input) of all control subjects in Figure 6 (MABP input) and Figure 7 (ETCO₂ input). On the abscissa are the values of the respective PDM output $u_{j,m}$ (the range in this plot is adjusted to one standard deviation of the respective PDM output as computed from the available data, since each subject has its own range of physiological variations for each input) and on the ordinate is the corresponding additive contribution to the model output $z_{j,m}$. It is evident in Figure 6 that the ANFs for the 1st PDM of the MABP input are

dominant (i.e. with largest slope) and almost linear, while the ANFs for the other two PDMs of the MABP input are curvilinear and make smaller (but occasionally significant) contributions. The observation about the ANF of the 1st MABP-PDM is consistent with passive fluid dynamics in a compliant vessel (Windkessel model) and with the absence of nonlinearity in the high frequencies where autoregulation is less effective. The curvilinear forms or the occasional negative trends of the 2nd and 3rd MABP-PDM suggest the presence of active mechanisms of cerebral flow autoregulation (see Discussion).

It is observed in Figure 7 that the ANFs for the 1st PDM of the ETCO₂ input have positive trend but they are not always dominant (i.e. with the largest slope), while the ANFs for the other two PDMs are curvilinear and make comparable (but variable) contributions to the model output. This observation is consistent with the view that all ETCO₂-PDMs are influenced by active autoregulatory mechanisms that are nonlinear (see Discussion).

With regard to the cross-terms of the PDM-based models that account for interactions between the two inputs, we select the significant cross-terms based on their correlation with the system output and estimate their coefficients following the procedure outlined in Appendix I. In this study, the selected significant cross-terms never exceeded four and their contribution to the model prediction varied among subjects. To assess the relative contributions of the two inputs (when all three PDM-ANF channels are combined for each input) and of the cross-terms to the model output, we provide in Table 1 the mean-square values of these separate contributions to the model prediction of the output, along with the normalized mean-square error (NMSE) of the total model prediction for each subject. An illustrative example of the predictive capability of the PDM-based open-loop model of **A** is presented in Figure 8, where the output MCBFV signal is plotted against the model prediction, along with the residuals and their spectrum.

A simple way to examine the functional characteristics of the obtained dual-input PDM-based nonlinear model is to compute the model response to pulse changes of one input while the other input is kept constant (simulated clamping). An illustrative example is given in Figure 9 for a typical control subject, where each input has a positive pulse change over 20 sec equal to one standard deviation (SD) of the respective input data (left panels) or a negative pulse change of the same size (right panels), while the other input stays at zero (baseline reference value). As expected under normal physiological conditions, the MABP component of the dual-input PDM-based model correctly predicts the CFA-CVMR processes by showing: (1) a return of MCBFV close to baseline after an initial transient caused by the positive or negative pulse change of MABP (normal CFA); and (2) an increase (above baseline) of MCBFV in response to a positive pulse change of ETCO₂ and a decrease (below baseline) in response to a negative pulse change of ETCO₂ (normal CVMR).

In order to reduce to a single index the CFA and CVMR characteristics of each subject, as quantified by the dual-input PDM-based model, we compute the average value of the model-predicted MCBFV response over the first 20 sec following the onset of the pulse change (see Figure 9). When this average value is divided by the respective pulse value (equal to +1 or -1 SD of the respective input data), we obtain a measure of the **CFA average gain** (for the MABP input) and of the **CVMR average gain** (for the ETCO₂ input). When the average gain for the negative pulse is subtracted from the average gain for the positive pulse, then we have the index of **average gain difference** that can be used to quantify the CFA and CVMR characteristics of each subject. The computed values of the average CVMR and CFA gain differences for the 15 control subjects are reported in Table 2 and indicate **strictly positive values of the average CVMR gain difference and small values of the average CFA gain difference** for all subjects. These indices may prove clinically useful for the diagnosis of

pathologies or clinical conditions that alter consistently and significantly the CFA and/or CVMR characteristics of patients (see Discussion).

The results illustrated in Figure 9 for a typical control subject and summarized for all subjects in Table 2 are obtained for the open-loop model component **A** in Figure 2. As indicated in Methods, these results are expected to be different for the **closed-loop model** of Figure 2, when the pulse change of MABP is delivered as extra-loop “pressure disturbance” P_d (while the flow-velocity disturbance F_d and the ETCO₂ are set to zero) or the pulse change of ETCO₂ is delivered to both closed-loop model components **A** and **B** (while the pressure disturbance P_d , flow-velocity disturbance F_d and the ETCO₂ are set to zero). The MCBFV responses predicted by the closed-loop model for the same control subject of Figure 9 are shown in Figure 10 and illustrate the anticipated differences. The values of “average gain differences” computed via the closed-loop model are given in Table 3 and exemplify the main point of this paper: the closed-loop effects can be significantly larger and with distinct dynamics.

Another important aspect of closed-loop dynamics that may be examined concerns the spectral/resonant characteristics of the closed-loop system. As indicated in Methods, the spectral characteristics of the closed-loop system are different from, but depend on, the characteristics of the open-loop system components **A** and **B**. To examine the spectral characteristics of the closed-loop system under isocapnic conditions, we simulate the closed-loop model of Figure 2 with independent white-noise pressure and flow-velocity disturbances P_d and F_d while the ETCO₂ input is kept at zero (baseline value), and examine the spectrum of the resulting in-the-loop signals P and F , especially with respect to resonant peaks which may attain clinical importance (see Discussion). This simulation can be repeated for various power levels of the two systemic disturbances and the closed-loop spectral characteristics can be examined with respect to physiological vulnerabilities – e.g. at which frequencies or power level of systemic disturbances, P_d and F_d , the closed-loop CFA-CVMR process of a specific subject becomes unstable. This may prove a valuable measure of vulnerability of cerebral autoregulation or perfusion to various pathologies and clinical conditions for each subject (see Discussion). A potentially useful aspect of this study concerns the effects of changes in ETCO₂ on the closed-loop spectral characteristics. As an illustrative example, Figure 11 shows the spectra of the in-the-loop signals F and P (see Figure 2) for independent white-noise systemic disturbances, P_d and F_d , when the ETCO₂ input is kept at zero (baseline value) or at 1 SD above baseline. Spectral peaks around 0.04 Hz and 0.15 Hz are evident for F under both isocapnic and hypercapnic conditions, with a low-frequency peak around 0.02 Hz evident only for isocapnic conditions. These spectral peaks indicate resonances of the closed-loop model at the respective frequencies, since the driving disturbances of pressure and flow are broadband (white noise). The spectral characteristics of P are different and exhibit a peak around 0.06 Hz and increased power at very low frequencies (<0.02 Hz) for isocapnic conditions. These characteristics are not evident for hypercapnic conditions, where arterial pressure appears broadband (see Discussion).

Finally, in order to compare the results of the presented nonlinear analysis with linear analysis, we present in Figure 12 the predicted MCBFV responses by the **linear closed-loop** model of the same control subject as in Figure 10 (blue line) to a 20-sec pulse (purple line) of the MABP disturbance P_d or ETCO₂ input equal to +1 SD of the measured data, when the subsystems **A** and **B** are represented by linear PDM-based models (left panels) or traditional linear dynamic models (right panels). As in Figure 10, the other input/disturbance in either case is kept at baseline zero (simulated clamping). Only the onset responses are shown for the linear analysis, since the offset responses are simply with reverse polarity (no asymmetric on/off responses as in the nonlinear analysis). The traditional linear dynamic

model is obtained via Transfer Function computation in the frequency domain, followed by inverse Discrete Fourier Transform to obtain the respective Impulse Response Function for each sub-system **A** and **B**. The linear PDM-based model is obtained by estimating the best linear ANFs of the general PDM-based model and eliminating the cross-terms. It is evident in Figure 12 that some differences exist between the PDM-based linear and nonlinear closed-loop predictions, but not dramatic. The differences are more pronounced between the results from PDM-based linear or nonlinear and traditional linear analysis (especially for the MABP response in this subject, although other subjects exhibited significant differences in the ETCO₂ response as well). The relative evaluation of the closed-loop results of these methods is not possible in the absence of a meaningful criterion, since the prediction errors based on the experimental data are the same in closed-loop and open-loop analysis. Possible differences between open-loop and closed-loop analysis can be evaluated through correlation with clinical data in the case of a specific disease (not relevant to this study) or through model predictions of data collected in specialized experiments where specific external disturbances are imposed as stimuli (not available in this study). The importance of the impact of these differences on the corresponding model-based CFA and CVMR indices will have to be assessed when the means for clinical evaluation of these indices become available.

Discussion

This paper proposes a methodology for closed-loop analysis (CLA) of cerebral hemodynamics with respect to the nonlinear dynamics of Cerebral Flow Autoregulation (CFA) and CO₂ Vasomotor Reactivity (CVMR), using beat-to-beat time-series data of Mean Arterial Blood Pressure (MABP), End-Tidal CO₂ (ETCO₂) and Mean Cerebral Blood Flow Velocity (MCBFV) under resting conditions (in supine position). The proposed approach utilizes the concept of Principal Dynamic Modes (PDMs) and Associated Nonlinear Functions (ANFs) to facilitate the estimation of the dual-input open-loop models of the components **A** and **B** of the closed-loop diagram shown in Figure 2. Simulation of this closed-loop model may advance our quantitative understanding of the CFA and CVMR processes, as well as allow the computation of simple, yet reliable, model-based indices with potential clinical utility in improving diagnosis of cerebrovascular diseases. Simulations of the obtained closed-loop models for 15 control subjects reproduced the expected physiological responses of normal CFA and CVMR, as well as allowed a novel glimpse into the closed-loop spectral characteristics of this system, with potential clinical implications in revealing potential vulnerabilities of cerebral autoregulation (see below). Future experiments should seek to interpret the specific features (e.g. PDMs and ANFs) of this model and reveal the underlying physiological mechanisms.

Each of the open-loop models **A** and **B** was validated through its predictive capability and deemed capable of predicting its output for *any* given pair of its inputs within the dynamic range of the analyzed data. Three “*global*” PDMs for each of the two inputs were found to constitute an adequate and consistent “functional coordinate system” for representing the dynamics of each open-loop component for all subjects in the study. These global PDMs were obtained from the time-series data of five randomly selected control subjects within the available set of 15 subjects. Interestingly, the overall form of the global PDMs did not change appreciably when a different subset of 5 subjects was used for their estimation. The existence of such a set of global PDMs facilitates this formidable modeling task in a practical context and assists the physiological interpretation of the modeling results. The form of the global PDMs contains functional information regarding the physiological mechanisms that define the *dynamics* of the CFA-CVMR process. The ANFs are estimated from the data of each individual subject and used to describe quantitatively the *nonlinearities* of the CFA-CVMR process specifically for this subject. Future studies should explore the

specific mechanisms that give rise to the global PDM waveforms and the form of the subject-specific ANFs. The main findings of this study are summarized below.

1. The PDM-based approach is generally applicable for input-output modeling

The employed canonical formulation of dynamic nonlinear Volterra models with the use of “global” PDMs for open-loop input-output modeling is generally applicable across subjects and cerebrovascular pathologies pertinent to the modeled cerebral hemodynamics. It is useful for the dual purpose of model compaction and physiological interpretation. The specific physiological mechanisms that influence the waveforms of the global PDMs and the subject-specific ANFs require careful examination in future studies. We emphasize that the global PDMs serve as a common “functional coordinate system” – thus they are the same for all subjects – but the ANFs are subject-specific and can be used for interpretation of measurement variability or diagnostic purposes. The PDM-based approach can be used for modeling the open-loop input-output components of closed-loop models, like the components **A** and **B** in Figure 2, whereby the residuals of each model prediction attain the role of “systemic disturbances” that essentially drive the closed-loop system in its spontaneous operation. The resulting closed-loop model can be studied through appropriate simulations to reveal the nonlinear dynamic functional properties of the closed-loop system in a manner that has not been possible heretofore (see below). We note that the PDM approach is more constrained than traditional frequency-domain analysis in terms of identifying pure delays.

2. Closed-loop analysis offers useful insights into the CFA and CVMR processes

Previous studies have shown that the CFA and CVMR processes are dynamic and nonlinear [11–15]. It is posited herein as a working hypothesis that the system of cerebral hemodynamics operates in “closed-loop” (i.e. changes in cerebral perfusion pressure affect cerebral blood flow and vice-versa, and CO₂ tension affects both blood flow and blood pressure). Since direct physiological evidence of such a closed-loop operation in cerebral hemodynamics is heretofore limited (e.g. the modulation of blood pressure by flow-mediated changes in cerebrovascular impedance and/or a possible “central baroreflex” in response to oscillations in blood flow), the presented closed-loop analysis is intended to generate, rather than to test, our key working hypothesis of closed-loop operation in cerebral hemodynamics. We note that the model-predicted internal signals, $F_p(t)$ and $P_p(t)$, from the closed-loop model components **A** and **B** respectively, are only portions of the measured signals $F(t)$ and $P(t)$. Previous studies have focused on “open-loop modeling” of this system, whereby changes in arterial pressure were thought to cause changes in cerebral blood flow, and they did not take into account possible closed-loop dynamics of this system – i.e. the possibility that changes in cerebral blood flow also cause changes in arterial pressure. This presents no problem as long as the study is limited to discovering/understanding the “forward” causal relation from pressure changes to flow changes. However, the open-loop analysis may be misleading when a question is addressed that is affected by the closed-loop operation of this system (provided, of course, our working hypothesis is correct). The prediction of the internal (in-the-loop) variables for an externally imposed change in arterial pressure, blood flow or CO₂ tension is significantly affected under the closed-loop arrangement, since the latter has effects that are “recycled” through the closed-loop system. For example, an imposed pulse change in the unobserved pressure disturbance signal, $P_d(t)$, of Figure 2 may transform to a different waveform by the time it “shows up” as a change in the measured arterial pressure signal, $P(t)$, that is the input to the forward model **A** in Figure 2. In the case of an imposed change in CO₂ tension, the difference is also clear, because in the closed-loop model of Figure 2 this change will affect the output of component **A** as one of its inputs but it will also affect the other input of **A** via component **B**. These differences

were explained and described mathematically in Methods (see Eqs. (5) – (6)) and demonstrated in Figures 9–10, as well as in Tables 2 and 3.

The closed-loop analysis also affords novel insights into the spectral characteristics of the closed-loop system which may reveal valuable characteristics pertinent to clinical applications. Figure 11 illustrates the spectral characteristics of the closed-loop model for a typical control subject and suggests possible physiological vulnerabilities (i.e. closed-loop resonances) that may attain critical clinical importance for certain pathologies. For example, it is evident in Figure 11 that the cerebrovascular impedance (the ratio of P to F values) under isocapnic conditions varies by one order of magnitude across frequency (with maximum impedance of ~ 1 at very low frequencies and a minimum of ~ 0.1 around 0.03 Hz), thus raising the possibility that a sudden (albeit intermittent) driving disturbance at the “wrong” frequency band (0.03 Hz in this example) may induce large oscillations in blood flow and thus have hazardous consequences for cerebral homeostasis. Under hypercapnic conditions, the frequency locations of the minimum and maximum impedance remain approximately the same for this subject (perhaps with a slight shift to higher frequencies). However, as expected with hypercapnic cerebral vasodilation, the minimum impedance value is raised considerably (approximately tripled). It is important to note that the “apparent” impedance estimate, as the ratio of the pressure/flow spectra, is different for the actual data (see Figure 1) or for the simulated internal variables (see Figure 11). We take the view that the latter is closer to the actual cerebrovascular impedance because it separates the internal (intra-loop) from the external (extra-loop) variables. We also note that the variance (or dynamic range) for P and F remain about the same under hypercapnic conditions (i.e. the integrated spectrum) for this subject, although the average value of both internal variables rises (data not shown), as physiologically expected. However, for hypocapnic conditions (data not shown in the interest of space), the variance of P increases (but not for F) exhibiting sudden pressure drops that make its distribution skewed towards lower pressure values, while the average values of both variables decrease as expected.

Therefore, excessive closed-loop gain at a resonant peak (due to pathology or a clinical condition) may lead to wide oscillations of the internal variables and cause clinical symptoms (e.g. wide oscillations of cerebral blood flow may cause fainting or syncope-like symptoms in response to ordinary changes in orthostatic stress, such as changes in body posture in daily life). These spectral characteristics, as well as the dynamic range of the in-the-loop variables, may be affected significantly by changes in CO₂ tension. We take the view that the effect of external or “imposed” changes must be studied in the context of closed-loop modeling to retain a realistic understanding of physiological states (e.g. for simulating the effect of a pulse change in arterial pressure or CO₂ tension upon the cerebral flow velocity – a simulation that was used herein to quantify the CFA and CVMR processes in cerebral hemodynamics. In connection with this point, we note that the systemic disturbances, $P_d(t)$ and $F_d(t)$, may be physiologically correlated – an issue that deserves further study in the future. The closed-loop effects are also likely to affect the assessment of the impact of possible hemodynamic alterations caused by pathologies, clinical conditions or the administration of drugs. The presented approach affords this type of quantitative analysis for individual subjects separately and the examination of hemodynamic characteristics via simulation. This may have important clinical implications (see #3 below).

3. Model-based indices of CFA and CVMR with potential clinical utility

The PDM-based closed-loop model of the CFA-CVMR process has the potential to yield clinically useful indices for improved diagnosis of cerebrovascular diseases. One such set of indices can be defined on the basis of the model-predicted MCBFV changes in response to imposed pulse changes of arterial pressure under isocapnic conditions (CFA index) or imposed pulse changes of CO₂ tension under isobaric conditions (CVMR index). We have

proposed a model-based “average gain difference” index that quantifies the MCBFV response difference between an increase and a decrease of arterial pressure (CFA index) or CO₂ tension (CVMR index) in each subject over a 20 sec time-horizon following the onset of the pulse change equal to ± 1 SD of the respective input data. These indices may prove valuable as “functional biomarkers” for improved diagnosis of cerebrovascular or neurodegenerative diseases. For example, it has been suggested that CO₂ vasomotor reactivity may be impaired in Alzheimer’s patients [7]. Based on this observation, the breath holding index (BHI) was initially proposed as a diagnostic tool. However, the BHI approach exhibited high variability and yielded ambiguous results due to baseline variations among subjects and experimental uncertainties related to the level of CO₂ tension that develops in each subject during breath holding. An index based on the aforementioned open-loop dual-input model under *isobaric* conditions may hold promise in connection with improved diagnosis. The use of a closed-loop model for this purpose may allow further improvements in this regard. This will be examined in future studies. This approach may have potential utility in the context of personalized medicine or “physiological fingerprinting” that attract recently considerable attention with regard to the future directions of clinical practice. However, the presented results should not be taken as definitive conclusions regarding the actual physiology of this system or its clinical implications, until more extensive studies have been completed with additional data. Finally, the closed-loop analysis offers novel insights into the resonant characteristics of physiological autoregulation which may prove valuable in clinical applications where sporadic wide-amplitude oscillations may have catastrophic effects.

Acknowledgments

This work was supported in part by the Biomedical Simulations Resource at the University of Southern California under NIH/NIBIB grant P41-EB001978 and NIA R01AG033106-01 grant to the UT-Southwestern Medical Center.

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APPENDIX I: Basics of Volterra and PDM modeling

The proposed modeling methodology is based on the general nonparametric Volterra approach that is applicable to all finite-memory dynamic nonlinear systems and covers almost all physiological systems (with the exception chaotic systems or non-dissipating oscillators). In the proposed methodology, the modeling task commences with the estimation of a 2nd order Volterra model of the two-input CFA-CVMR system using Laguerre expansions of the kernels of the dual-input 2nd order Volterra model [8–10] :

$$\begin{aligned}
 y(t) + k_0 + \int_0^\infty k_p(\tau) p(t-\tau) d\tau + \int_0^\infty k_x(\tau) x(t-\tau) d\tau \\
 + \int \int_0^\infty k_{pp}(\tau_1, \tau_2) p(t-\tau_1) p(t-\tau_2) d\tau_1 d\tau_2 + \int \int_0^\infty k_{xx}(\tau_1, \tau_2) x(t-\tau_1) x(t-\tau_2) d\tau_1 d\tau_2 \\
 + \int \int_0^\infty k_{px}(\tau_1, \tau_2) p(t-\tau_1) x(t-\tau_2) d\tau_1 d\tau_2 + \varepsilon(t)
 \end{aligned} \quad (A1)$$

where $p(t)$ denotes the MABP input, $x(t)$ denotes the ETCO₂ input, $y(t)$ denotes the mean cerebral blood flow velocity (MCBFV) output and $\varepsilon(t)$ denotes possible measurement or modeling errors. The modeling task involves the estimation of the unknown Volterra kernels of the model from given input-output data $p(t)$, $x(t)$ and $y(t)$. Thus, in the proposed modeling

approach, the output is initially expressed in terms of a functional expansion that represents the hierarchical nonlinear interactions among different parts of the input epochs as they affect the output (i.e. a 2nd order Volterra functional between two inputs represents the quantitative pattern in which all values in the epochs of the two inputs interact in order to influence the output). The specific pattern of these nonlinear interactions for a given system is codified by the respective Volterra “kernel” (i.e. the 2nd order self-kernel codifies the interactions between two values of the epoch of the respective input, and the 2nd order cross-kernel codifies the interactions between two values of the epochs of the two inputs). Each kernel convolves the respective input(s) as many times as its order stipulates (a 2nd order kernel performs a double convolution) to form the corresponding Volterra functional. The 1st order kernel quantifies the linear dynamics of the system and the respective 1st order functional (single convolution) represents the linear component of the Volterra model. Thus, a hierarchy of functionals (defined by the respective kernels) is built in each case as appropriate. It has been proven that the Volterra model can represent (almost) all nonlinear causal relationships between arbitrary input and output signals, with the exception of chaotic processes and non-dissipating nonlinear oscillators [10].

In spite of the conceptual and mathematical appeal of the Volterra formulation, practical problems arise from the high dimensionality of high-order kernels which makes their estimation difficult and their physiological interpretation daunting. For this reason, most applications to date have been limited to 2nd order, with only a few attempts for 3rd order modeling. To mitigate this practical limitation, we have utilized kernel expansions on the Laguerre basis that simplify the kernel estimation and yield significant computational benefits [8–9]. For instance, the Laguerre expansion of the r -th order kernel :

$$\begin{aligned} k_{p,\dots,p,r}(\tau_1, \dots, \tau_r) &= \sum_{j_1=1}^L \dots \sum_{j_r=1}^L a_r(j_1, \dots, j_r) b_{j_1}(\tau_1) \dots b_{j_r}(\tau_r) \\ k_{x,\dots,x,r}(\tau_1, \dots, \tau_r) &= \sum_{j_1=1}^L \dots \sum_{j_r=1}^L c_r(j_1, \dots, j_r) b_{j_1}(\tau_1) \dots b_{j_r}(\tau_r) \end{aligned} \quad (A2)$$

where $\{b_j(\tau)\}$ denotes the orthonormal basis of L Laguerre functions, yields the following nonlinear input-output relation which involves *linearly* the Laguerre expansion coefficients $\{a_r\}$ and $\{c_r\}$:

$$y(t) = c_0 + \sum_{r=1}^Q \sum_{j_1=1}^L \dots \sum_{j_{r-1}=1}^{j_{r-1}} a_r(j_1, \dots, j_r) v_{j_1}(t) \dots v_{j_r}(t) + \sum_{r=1}^Q \sum_{j_1=1}^L \dots \sum_{j_{r-1}=1}^{j_{r-1}} c_r(j_1, \dots, j_r) z_{j_1}(t) \dots z_{j_r}(t) + \varepsilon(t) \quad (A3)$$

where the signals $v_j(t)$ and $z_j(t)$ are the convolutions of the Laguerre basis function b_j with the respective input and Q is the nonlinear order of the model. Note that in the model equation (A3) the cross-kernel contribution has been suppressed in the interest of simplifying the model. Possible effects of input interactions upon the output are subsequently accounted by the inclusion of significant cross-terms (see below). The fact that the Laguerre expansion coefficients enter linearly in the nonlinear Volterra model of Equation (A3) allows their estimation via least-squares linear regression (a simple and robust numerical procedure). Having estimated the Laguerre expansion coefficients, we can construct the Volterra kernel estimates using Equation (A2) and compute the model prediction for *any* given input using Equation (A1) or (A3). This procedure applies to higher order Volterra models as well, possibly including cross-kernels.

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 practical limitation,

we have introduced the concept of Principal Dynamic Modes (PDM), which aims at identifying the minimum set of “basis” functions (distinct and characteristic for each system) that are capable of representing adequately the system dynamics (i.e. provide satisfactory expansions of the kernels). The computation of the PDMs from the self-kernel estimates, for each input separately, employs Singular Value Decomposition (SVD) of a rectangular matrix composed of the 1st order kernel estimate (as a column vector) and the 2nd order self-kernel estimate weighted by the standard deviation of the respective input (as a square block matrix). The Singular Vectors corresponding to the top Singular Values that account for a cumulative 95%, are selected as global PDMs.

The resulting PDMs form a filter-bank that receives the respective input signal and generates (via convolution) signals that are subsequently transformed by properly defined nonlinear functions to form additively the system output [46], as depicted schematically in Figure 2. Each PDM has its own “Associated Nonlinear Function” (ANF) which represents the nonlinear characteristics of the system for the respective PDM dynamics. The ANFs are typically represented by polynomials and their coefficients are estimated via regression on the output signal [10, 11]. The degree of the ANF polynomial is constrained by the length of the available data to prevent over-fitting problems (i.e. cubic degree is the maximum in this application).

Thus, the PDM-based model separates the dynamics (PDMs) from the nonlinearities (ANFs). Since the “separability” of the system nonlinearity cannot be generally assumed, we include in the PDM-based model cross-terms that are properly selected to capture the most significant interactions among the inputs. This also obviates the need for the inclusion of cross-kernels in the initially estimated 2nd order Volterra model of Equation (A3), with considerable practical benefits – especially when the number of model inputs is further increased. The validity of this practical approach to the representation of input interactions must be checked in each application. In this particular application, it was found to yield results comparable to the formal inclusion of cross-kernels (or the associated cross-PDMs [11]) with improved model compactness. The selection of the significant cross-terms is based on a statistical significance test on the computed correlation coefficient between each cross-term (i.e. the pair product of ANF outputs from each of the inputs) and the output signal. Each computed correlation coefficient was subsequently tested for statistical significance using the w-statistic. Three PDMs for each input and up to four cross-terms were found to be adequate in this application.

It was found that it is more efficient in this application to exclude the cross-kernel from the initial estimation of the 2nd order Volterra model and account for input interactions by the subsequent inclusion in the model of the selected significant cross-terms using a statistical procedure. We obtain the global PDMs from a reference set of 5 control subjects (randomly chosen) using the estimated self-kernels and then we estimate the ANFs associated with each global PDM of each input and the coefficients of the selected significant cross-terms that account for the interaction effects between the two inputs. The model output prediction is composed of the sum of all ANF outputs and cross-terms, along with the estimated constant baseline value. In this study, it was found that cubic ANFs and up to four multiplicative cross-terms are adequate for the CFA-CVMR system. The total number of free parameters for this two-input global PDM-based model is ≤ 23 (including the constant baseline term), which implies a minimum required data-record of approximately 2 minutes. By comparison, the Laguerre-based 2nd order Volterra model (for $L_1=5$, $L_2=3$) has 45 free parameters when the 2nd order cross-kernel is included and 30 free parameters when the cross-kernel is excluded.

The structure of the PDM-based model of the two-input/one-output CFA-CVMR system is shown in Figure 2. The employed “global” PDMs represent a common reference “functional coordinate system” (i.e. basis of functions) for efficient representation of *all* kernels of the CFA-CVMR system for *all* subjects. These “global” PDMs are obtained from the time-series data (over 5–6 min) of a reference set of control subjects in supine position. We emphasize that, although the global PDMs in the model are common for all subjects, the estimated ANFs associated with each global PDM and the coefficients of the cross-terms are *subject-specific* and can be used to characterize uniquely and differentially the CFA-CVMR process for each subject. The use of PDMs allows us to write the output Equation (A3) as:

$$y(t) = c_0 + \sum f_h [u_h(t)] + \sum f_m [w_m(t)] + \text{Cross-Terms} + \varepsilon(t) \quad (\text{A4})$$

where $\{u_h\}$ and $\{w_m\}$ are the PDM outputs (i.e. convolutions of the input with the respective PDM) for the MABP and ETCO₂ inputs, respectively, and $\{f_h\}$ and $\{f_m\}$ are the ANFs associated with each PDM. The ANFs are typically given polynomial form (cubic in this application). The “Cross-Terms” in Equation (A4) are composed of pair products of $\{u_h\}$ and $\{w_m\}$ that have significant correlation with the output. The coefficients of the selected Cross-Terms are estimated, along with c_0 and the coefficients of the (cubic) ANFs via least-squares regression of Equation (A4).

Figure 1.

Top panel: illustrative time-series data over 6 min for a typical control subject, representing beat-to-beat spontaneous variations of MCBFV (red line), MABP (green line) and ETCO2 (blue line). The units on the ordinate axis are: cm/s for MCBFV and mm Hg for MABP and ETCO2. Bottom panel: the respective spectra of the time-series data up to 0.25 Hz.

Figure 2.

Block-diagram of the closed-loop model for the CFA-CVMR system, where $F(t)$ denotes the MCBFV beat-to-beat data, $P(t)$ denotes the MABP beat-to-beat data, $C(t)$ denotes the ETCO₂ data, $F_p(t)$ denotes the MCBFV prediction of the PDM-based model **A** and $P_p(t)$ denotes the MABP prediction of the PDM-based model **B**. The signals $F_d(t)$ and $P_d(t)$ are the residuals of the respective model predictions (**A** and **B**) and they are viewed as the systemic blood flow and pressure “disturbances” that drive this closed-loop physiological system.

Figure 3.

Block-diagram of the PDM-based model of the CFA-CVMR system with MCBFV output and three global PDMs for each of the two inputs, x_1 (MABP) and x_2 (ETCO₂). The output $u_{j,m}(t)$ of the j -th PDM, $p_{j,m}$, for the m -th input, x_m , is the convolution of the PDM with the respective input. The ANFs are cubic polynomials: $z_{j,m} = f_{j,m}(u_{j,m}) = a_{1,j,m} u_{j,m} + a_{2,j,m} u_{j,m}^2 + a_{3,j,m} u_{j,m}^3$. The selected cross-terms, $\{c_{i,j} u_{i,1}(t) u_{j,2}(t)\}$, have significant correlation with the output. The output y (MCBFV) is the sum of all ANF output components $\{z_{j,m}\}$, the selected significant cross-terms and a constant offset value c_0 .

Figure 4. The three global PDMs of the **A** component of the closed-loop model in Figure 2 for the MABP input (top panels) and ETCO2 input (bottom panels). Left column: time-domain representations. Right column: frequency-domain representations.

Figure 5. The three global PDMs of the **B** component of the closed-loop model in Figure 2 for the MCBFV input (top panels) and ETCO2 input (bottom panels). Left column: time-domain representations. Right column: frequency-domain representations.

Figure 6.

The cubic ANFs of the global PDMs for the MABP input of model component **A** for all 15 control subjects, corresponding to the 1st (blue), 2nd (green) and 3rd (red) PDM. The range of the abscissa is one standard deviation of the respective PDM output (variable among subjects). The ANFs of the 1st PDM are almost linear and make the dominant contribution to the model output (MCBFV).

Figure 7.

The cubic ANFs of the global PDMs for the ETCO₂ input of model component **A** for all 15 control subjects, corresponding to the 1st (blue), 2nd (green) and 3rd (red) PDM. The range of the abscissa is one standard deviation of the respective PDM output (variable among subjects). The ANFs of the 1st PDM have consistently positive trend (although generally curvilinear) but they do not always make the dominant contribution to the model output (MCBFV).

Figure 8.

Top panel: Prediction of the dual-input PDM-based nonlinear model (red line) and the actual MCBFV output (blue line) for CS#11. Bottom panel: Spectra of the actual MCBFV output (black line) and of the prediction residuals for the MABP terms (red line), both MABP and ETCO₂ terms (blue line) and all terms, including cross-terms (green line). The blue and green lines nearly overlap, indicating that the cross-terms make minimal contributions in CS#11.

Figure 9.

For CS#1, The predicted MCBFV response by the PDM-based model of the **open-loop** component **A** for a typical control subject (blue line) to a 20-sec pulse (purple line) of the MABP input (top panels) or ETCO₂ input (bottom panels) equal to +1 SD (left panels) or -1 SD (right panels) when the other input is kept at zero (baseline value). As expected under normal physiological conditions, the model autoregulates the MCBFV response with respect to pressure changes (positive or negative) by returning close to the baseline after an initial transient (normal CFA), while showing an increasing/decreasing MCBFV response for a positive/negative change of ETCO₂, respectively (normal CVMR).

Figure 10.

The predicted MCBFV response by the **closed-loop** PDM-based model of the same control subject as in Figure 9 (blue line) to a 20-sec pulse (green line) of the MABP disturbance P_d (top panels) or ETCO₂ input (bottom panels) equal to +1 SD (left panels) or -1 SD (right panels) when the other input/disturbance is kept at baseline zero (see text). The resulting “in-the-loop” pressure signal is also shown (red line) in all cases.

Figure 11.

The spectra of the simulated in-the-loop signals F (blue line) and P (red line) in the **closed-loop** model of Figure 2 for the same control subject as in Figure 9 when the systemic disturbances, P_d and F_d , are independent white-noise processes and the ETCO₂ is kept at zero baseline value (top) or at 1 SD above baseline (bottom). Spectral peaks are evident for F around 0.04 Hz and 0.15 Hz under both isocapnic and hypercapnic conditions, with a low-frequency peak around 0.02 Hz evident only for isocapnic conditions. The spectral characteristics of P exhibit a peak around 0.06 Hz and increased power at very low frequencies (<0.02 Hz) for isocapnic conditions, but appear broadband for hypercapnic conditions.

Figure 12.

The predicted MCBFV responses by the **linear closed-loop** model of the same control subject as in Figure 10 (blue line) to a 20-sec pulse (green line) of the MABP disturbance P_d (top panels) or ETCO₂ input (bottom panels) equal to +1 SD of the measured data, when the sub-systems **A** and **B** are represented by linear PDM-based models (left panels) or traditional linear dynamic models (right panels). As in Figure 10, the other input/disturbance in either case is kept at baseline zero (see text) and the resulting “in-the-loop” pressure signal is also shown (red line).

Table 1

Percent normalized mean-square errors (NMSE) of the total model prediction and the contributions of model terms to the MBCFV output prediction for 15 control subjects.

Supine CS	NMSE values of model prediction	Mean-square contributions of model terms in %		
		MABP input	ETCO2 input	Cross-Terms
1	25.17	53.41	27.18	13.07
2	21.78	91.04	21.22	8.68
3	48.10	42.27	37.82	12.89
4	17.93	40.07	35.97	5.02
5	40.71	83.38	40.19	8.06
6	28.16	21.41	99.82	1.25
7	62.69	67.12	27.54	5.09
8	42.82	50.32	34.80	11.71
9	53.56	187.64	33.21	45.69
10	36.38	36.03	59.04	8.22
11	38.11	54.96	47.64	0.72
12	68.32	37.04	78.66	7.74
13	46.05	68.58	20.63	20.11
14	31.20	33.54	50.63	8.46
15	45.40	77.85	21.70	2.02
μ (σ)	40.42 (0.1442)	62.98 (39.89)	42.40 (22.36)	10.58 (10.96)

Table 2

Average gain differences for the CFA and CVMR processes of 15 control subjects computed via the **open-loop** model of component **A** in Figure 2 (see text).

CS ID	CFA Gain Difference [cm/s/mmHg]	CVMR Gain Difference [cm/s/mmHg]
1	0.10	4.35
2	1.53	1.35
3	0.44	1.49
4	0.55	1.39
5	-0.31	3.94
6	-0.01	9.73
7	1.17	1.12
8	1.31	0.72
9	0.06	1.79
10	-0.50	2.64
11	0.19	2.58
12	0.10	1.17
13	0.60	1.56
14	0.43	3.87
15	0.53	2.16
μ (σ)	0.41 (0.57)	2.66 (2.26)

Table 3

Average CFA and CVMR gain differences computed via the **closed-loop** model.

CS ID	CFA Gain Difference [cm/s/mmHg]	CVMR Gain Difference [cm/s/mmHg]
1	0.05	8.40
2	2.70	1.34
3	0.57	1.57
4	2.14	3.05
5	-0.30	3.96
6	-0.03	9.68
7	1.48	2.07
8	1.26	0.40
9	0.51	1.76
10	-0.53	3.00
11	0.26	2.92
12	0.12	1.19
13	0.69	2.22
14	0.75	5.40
15	0.48	2.12
μ (σ)	0.68 (0.89)	3.27 (2.65)