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Modeling Methodology for Nonlinear Physiological Systems

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Abstract—A general modeling approach for a broad class of nonlinear systems is presented that uses the concept of principal dynamic modes (PDMs). These PDMs constitute a filter bank whose outputs feed into a multi-input static nonlinearity of multinomial (polynomial) form to yield a general model for the broad class of Volterra systems. Because the practically obtainable models (from stimulus-response data) are of arbitrary order of nonlinearity, this approach is applicable to many nonlinear physiological systems heretofore beyond our methodological means. Two specific methods are proposed for the estimation of these PDMs and the associated nonlinearities from stimulus-response data. Method I uses eigendecomposition of a properly constructed matrix using the first two kernel estimates (obtained by existing methods). Method II uses a particular class of feedforward artificial neural networks with polynomial activation functions. The efficacy of these two methods is demonstrated with computer-simulated examples, and their relative performance is discussed. The advent of this approach promises a practicable solution to the vexing problem of modeling highly nonlinear physiological systems, provided that experimental data be available for reliable estimation of the requisite PDMs.

Keywords—Principal dynamic modes, Artificial neural networks, Volterra systems, Volterra kernels, Polynomial activation functions, Nonlinear modeling.

INTRODUCTION

Mathematical modeling of physiological systems from stimulus-response data is the rigorous process by which knowledge acquired from experimental observations (data) is organized in a concise form that facilitates scientific articulation, interpretation, and dissemination, as well as new experiment design. In this sense, modeling provides the means of summarizing vast amounts of data into relatively compact mathematical (or computational) form that allow the formulation and testing of scientific hypotheses by specially designed experiments—an iterative process that should lead to successive refinement and evolution of the model. Thus, modeling attains a central role in the scientific process of generation and dissemination of knowledge, consistent with the credo "model or muddle." Models can be applied to arbitrary levels of system decomposition or integration, depending on the availability of appropriate data—thus providing the conceptual and methodological means for integrative systems physiology.

Most modeling methods and studies to date have focused on the limited class of linear systems, due to their relative simplicity of analysis. Nonlinearities, however, are ubiquitous in physiology and often essential in serving critical aspects of physiological function. Although few will argue with the importance and necessity of addressing the nonlinear dynamic aspects of physiological systems, most will view this task as a daunting challenge owing to its considerable complexity.

The purpose of this paper is to present a practicable modeling methodology for a broad class of nonlinear dynamic systems (the Volterra class), using stimulus-response data, that extends the boundary of feasibility over a vast domain of physiological applications. Because of the immense variety of nonlinear systems, the approach presented herein must be viewed as a modeling methodology suitable only for finite-memory Volterra systems (defined in the following section) that involve the nonlinear dynamic relation between a sufficiently broadband known stimulus signal and its corresponding stable response signal. Thus, it cannot be used to model autonomous oscillatory or chaotic systems that lack an observable input or do not satisfy the requirement of finite memory.

The proposed methodology has its mathematical underpinnings in the theory of functional expansions (Volterra and Wiener series) of nonlinear dynamic systems operators (1,4,12–15). It was facilitated by the advent of an efficient kernel estimation technique that uses Laguerre expansions to yield accurate low-order

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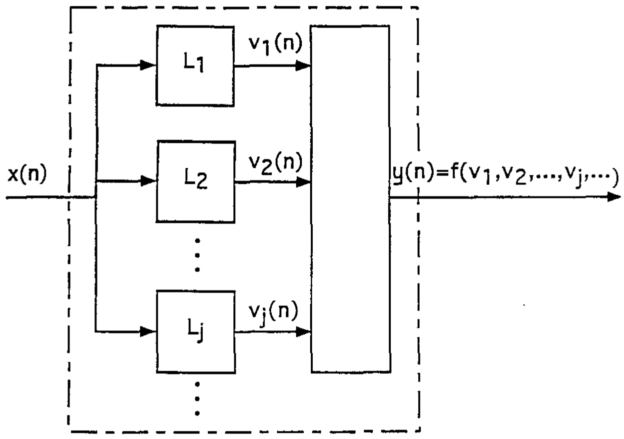

FIGURE 1. Block-structured model of the discrete-time Volterra-Wiener class of systems. The linear filter bank $\{L_j\}$ has impulse responses $\{b_j(m)\}$ that form a basis for the system kernels. The nonlinear function $f(\cdot)$ has a multinomial (polynomial) or power series form that maps the filter-bank outputs $(v_1, v_2, \ldots, v_j, \ldots)$ onto the output values $y(n)$ at each discrete-time n.

kernel estimates from short experimental data records, even in the presence of considerable noise (9). The advantages accrued by the use of this technique are realizable only in those cases where compact representation of the system kernels by Laguerre expansions is feasible. Although this cannot be guaranteed in general and must be examined in each particular application, it seems likely that many physiological systems with exponential relaxation properties will be amenable to this treatment owing to the asymptotically exponential form of the Laguerre functions.

The parsimonious representation afforded by this kernel expansion technique has also suggested the use of eigendecomposition of a symmetric matrix composed of the practically obtainable Laguerre expansion coefficients of first and second order to derive the principal dynamic modes (PDMs) of the system. If the number of selected PDMs is small, then the task of obtaining a complete nonlinear model is greatly simplified. This model makes use of a filter bank comprised of the selected PDMs that receive the stimulus signal as input and produce outputs that feed into a "multi-input static nonlinearity" that, in turn, generates the response signal (Fig. 1). The mathematical and physiological bases of this modeling approach were originally introduced in connection with neural systems generating action potentials (8,11). The novel contribution of this paper is in extending the PDM modeling approach to high-order nonlinear systems with continuous outputs (beyond the binary outputs of neural systems) and in introducing the use of artificial neural networks for this purpose. Note that the formal decomposition of a nonlinear dynamic system into a linear filter bank (representing the dynamics) and a multi-input static nonlinearity is valid for all systems that have square-integrable kernels (5). In discrete-time representations, this condition becomes one of square summability, which is satisfied by the condition of absolute summability defining the Volterra class of systems.

Despite the generality of this modeling representation, its efficiency (parsimony) naturally depends on the characteristics of each particular system defined by the chosen stimulus and response variables. Thus, if such parsimony (*i.e.*, small number of required PDMs) cannot be achieved for a given set of experimental data, it is advisable to search for different model representations or additional experimental stimulus and/or response locations that define component subsystems admitting such parsimonious representation. An example of this is the study of a long cascade of linear and static nonlinear components (*e.g.*, a neuronal chain) where, although the entire long cascade may elude a parsimonious PDM representation, intermediate recordings along the cascade allow its segmentation into component subsystems, each amenable to parsimonious representation. A class of systems that lacks efficient PDM representation is the one wherein a static nonlinear transformation precedes the dynamic transformations in the system (Hammerstein models) (12). However, this class is easily detected by the diagonal values of the second-order kernel estimate and can be modeled efficiently when it is possible to remove the effects of this nonlinearity by transforming first the input with the proper inverse static nonlinearity. Inability to do this is expected to lead to a large number of PDMs required for adequate modeling accuracy. Thus, the efficacy of the proposed general PDM representation must be viewed in the context of feasible experimental measurements and appropriate preliminary analysis of the data.

The key practical issue is how to determine the minimum number of PDMs required in a given modeling application and how to estimate the corresponding static nonlinearities (of arbitrary order) from stimulus-response data. This is the subject of this paper.

Two practical methods are presented for estimating the PDMs of a system from given stimulus-response data, as well as the associated multi-input static nonlinearity, leading to parsimonious models for a broad class of nonlinear systems. The first method is based on eigendecomposition of a matrix composed of the first- and second-order kernel estimates obtained from the data. The second method uses a class of feedforward artificial neural networks with a single hidden layer and polynomial activation functions. This method yields a model form with superficial resemblance to the previously proposed "parallel cascade model" (3); but, it is entirely different methodologically and conceptually (*i.e.,* the parallel cascade model is composed of numerous parallel branches estimated sequentially via vector orthogonalization). Comparisons between the two proposed methods will be made using simulated data that allow relative performance evaluation, because ground truth is available only in simulated examples. It must be emphasized that the critical value of the proposed methodology is found in the case of high-order systems (higher than second order), wherein high-order nonlinear models can be obtained by using static (polynomial or multinomial) nonlinearities of arbitrary degree.

The methodology of nonlinear modeling of dynamic systems using functional expansions and kernels has its origin in Wiener's pivotal monograph that suggested the use of Gaussian white noise (GWN) as the effective test input for nonlinear system identification based on a hierarchy of nonlinear functionals (the Wiener series) (16). Volterra's pivotal contribution was in suggesting, much earlier, the use of functional expansions (the Volterra series) to represent unknown analytic functionals implicated in studies of nonlinear mechanics and population dynamics (14). Wiener's critical contributions were: (a) placing the functional expansion approach in a nonlinear system identification context, wherein the system nonlinear dynamics are fully described by kernel functions of various orders; and (b) using GWN test inputs to obtain estimates of the (unknown) system kernels via orthogonalization of the functional expansion (Wiener series) and covariance computations. Numerous theoretical and practical considerations were left as challenges to the investigative zeal of subsequent generations of scientists and engineers. As the Volterra-Wiener theories were gradually adapted to actual applications, discrete-time representations of the functionals and finite-bandwidth approximations of the input GWN signals became practically necessary. The fundamental importance of this problem and the generality of the Volterra-Wiener approach gave rise to a host of innovative variants and implementations of this approach; for partial review, see Refs. 4–7,12,13. Applications to physiological system modeling were among the first, commencing in the late 1960s and blossoming in the 1970s and beyond; for partial review, see Refs. 4–7.

The most serious obstacle to expanding applications has been the practical inability to identify highly nonlinear systems—*i.e.,* to estimate high-order kernels in a practical context—a limitation that this paper seeks to relax by using model forms incorporating static nonlinearities of arbitrary order. The latter can be estimated from stimulus-response data. Thus, high-order nonlinear models can be obtained without need for explicit estimation of high-order kernels. Although the PDM approach was developed to overcome practical limitations in estimating high-order Volterra models, it has also demonstrated excellent noise resistance in test cases, even for low-order models—an important collateral benefit in practice.

METHODOLOGY

In discrete time, the general input-output relation of a stable (finite-memory) nonlinear time-invariant dynamic system is given by the discrete-time Volterra series:

$$y(n) = k_0 + \sum_m k_1(m)\, x(n-m) + \sum_{m_1}\sum_{m_2} k_2(m_1, m_2)\, x(n-m_1)\, x(n-m_2) + \ldots, \quad (1)$$

where $x(n)$ is the input and $y(n)$ is the output of the system. The ith term of the series is an i-tuple convolution of the ith-order kernel k_i, with i versions of x. The Volterra kernels (k_0, k_1, $k_2, \ldots$) describe the dynamics of the system at each order of nonlinearity and constitute a complete and canonical representation of the system nonlinear dynamics. For a uniformly bounded input, the output remains uniformly bounded if and only if the system kernels are absolute-summable and form a convergent series (Volterra class of systems). Note that k_0 represents a constant value (output offset), and k_1 represents the linear dynamics of the system. Kernels of higher order represent a hierarchy of system nonlinearities (of the respective order), and they are symmetric functions (*i.e.,* invariant under permutation of their arguments). For causal systems, the kernels are zero for negative values of their arguments.

Expansion of the Volterra kernels on a complete basis $\{b_j(m)\}$ transforms Eq. 1 into the multinomial expression:

$$\begin{aligned} y(n) &= c_0 + \sum_j c_1(j)\, v_j(n) + \sum_{j_1}\sum_{j_2} c_2(j_1, j_2)\, v_{j_1}(n)\, v_{j_2}(n) + \ldots \\ &= f(v_1, v_2, \ldots, v_j, \ldots) \end{aligned} \quad (2)$$

where,

$$v_j(n) = \sum_m b_j(m)\, x(n-m), \quad (3)$$

and $c_1(j)$, $c_2(j_1, j_2), \ldots$ represent the expansion coefficients of the respective kernels. Note that $c_0 = k_0$ and the symmetries are preserved in the high-order terms [*e.g.,* $c_2(i, j) = c_2(j, i)$].

The unknown expansion coefficients can be estimated in practice by linear regression of the output data $y(n)$ on the terms of the multinomial expression of Eq. 2, as long as the expression is finite and its terms do not lead to ill-conditioning of the regression matrix inversion. The latter condition can be secured when the input is sufficiently broadband. Note that for a white noise input and an orthogonal basis, the signals $\{v_j(n)\}$ have zero covariance. This fact was used by Wiener in his original suggestion for kernel estimation using covariance computations. He also suggested the use of Laguerre functions as an appropriate orthonormal basis, owing to their built-in exponential term that makes them suitable for physical systems with asymptotically exponential relaxation dynamics. This suggestion was first implemented in Ref. 15 and recently adapted to discrete-time for improved kernel estimation (9) allowing, for the first time, accurate estimation of third-order kernels from short experimental data records (10).

The use of the kernel expansion basis implies that a general model of the Volterra class of systems can take the block-structured form of Fig. 1, wherein the basis functions $\{b_j(m)\}$ constitute the impulse responses of a filter bank whose outputs are feeding into the multi-input static nonlinearity $f(v_1, \ldots, v_j, \ldots)$. For a selected basis (*e.g.,* Laguerre functions), the modeling problem reduces to estimating the multivariate function $f(\cdot)$. Of course, the latter will be different for different bases.

The proposed modeling methodology rests on the fact that, among all possible choices of expansion bases (orthogonal or nonorthogonal), there are some that require the minimum number of basis functions (*i.e.,* filters in the filter bank of Fig. 1) to achieve a given mean-square approximation of the system output. Such a minimum set of basis functions is termed PDMs of the nonlinear system and correspond to an associated multivariate nonlinear function $f(\cdot)$ generating the system output. The term "principal modes" has been also used in linear systems analysis, but in a different context (*i.e.,* to denote the eigenfunctions associated with the significant eigenvalues of a state-space formulation). No claim of uniqueness can be made for these PDMs, because their form depends on the associated nonlinearity. However the associated nonlinear function $f(\cdot)$ is unique for a selected set of PDMs for a given system and vice versa.

The particular method of selecting (estimating) PDMs from given stimulus-response data determines the form of PDMs in each application. Selected PDMs are expected to capture the important dynamic characteristics of the system, but in conjunction with the system nonlinearities. For instance, in an action potential-generating neuron, PDMs reflect the integrated effects of all axodendritic and axosomatic synaptic inputs (including conduction effects) on the formation of the transmembrane potential at the axon hillock, preceding the generation of an action potential. Static nonlinearity $f(\cdot)$ represents all of the nonlinear static transformations applied on the outputs of the PDMs to produce the action potential (8).

Two practical methods are proposed in this paper for the estimation of the PDMs and the output nonlinearity $f(\cdot)$ from stimulus-response data. The first method uses eigendecomposition of properly constructed matrices using estimated first- and second-order kernel values. A variant of this method using Laguerre expansions of the kernels in connection with neuronal modeling and coding has been previously reported (11). The second method makes use of a class of feedforward artificial neural networks with a single hidden layer and polynomial activation functions to accomplish the same objective by training the network parameters with the given stimulus-response data. Brief outlines of the two methods are given herein, and illustrative computer-stimulated examples are given in the following section.

Method I is based on previously obtained first- and second-order kernel estimates (in addition to k_0), because in most practical applications kernel estimation is limited to second order. The obtained kernel values up to a maximum lag M (kernel memory) can be combined to form a real symmetric $(M + 2) \times (M + 2)$ square matrix:

$$Q = \begin{bmatrix} k_0 & \frac{1}{2}k_1(0) & \frac{1}{2}k_1(1) & \cdots & \frac{1}{2}k_1(M) \\ \frac{1}{2}k_1(0) & k_2(0,0) & k_2(0,1) & \cdots & k_2(0,M) \\ \frac{1}{2}k_1(1) & k_2(1,0) & k_2(1,1) & \cdots & k_2(1,M) \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \frac{1}{2}k_1(M) & k_2(M,0) & k_2(M,1) & \cdots & k_2(M,M) \end{bmatrix} \quad (4)$$

that can be used to express the second-order Volterra model response, $y_2(n)$ in a quadratic form:

$$y_2(n) = \underline{x}^T(n) Q \underline{x}(n), \quad (5)$$

where the $(M + 2)$-dimensional vector $\underline{x}^T(n) = [1\ x(n)\ x(n-1) \ldots x(n-M)]$ is composed of the stimulus $(M + 1)$-point epoch at each time n and a constant 1 that allows incorporation of the zeroth- and first-order kernel contributions in Eq. 5. Because Q is a real symmetric square matrix, there exists always an orthonormal matrix R such that $Q = R^T \Lambda R$, leading to the expression:

$$y_2(n) = \underline{u}^{\mathrm{T}}(n)\, \Lambda\, \underline{u}(n), \qquad (6)$$

where Λ is the diagonal eigenvalue matrix and

$$\underline{u}(n) = R\underline{x}(n) \qquad (7)$$

is the vector of transformed inputs by the orthonormal eigenvector matrix R. Inspection of the real eigenvalues in Λ allows selection of the significant ones on the basis of relative magnitude (a selection that calls for appropriate threshold criteria) and subsequent selection of the corresponding orthonormal eigenvectors that become the PDMs of this system.

For each significant eigenvalue λ_i, the values of the corresponding eigenvector (with the exception of $\mu_{i,0}$) $\underline{\mu}_i^{\mathrm{T}} = [\mu_{i,0} \quad \mu_{i,1} \quad \ldots \quad \mu_{i,M+2}]$, define the ith PDM:

$$p_i(m) = \sum_{j=1}^{M+1} \mu_{i,j}\, \delta(m - j + 1), \qquad (8)$$

where $\delta(\cdot)$ denotes the discrete impulse function (Kronecker delta). The obtained ith PDM generates the ith mode output $u_i(n)$ via convolution with the stimulus $x(n)$. Note that a constant offset value $\beta_i = \mu_{i,o}$ must be added to the ith mode output u_i to express the second-order model response in terms of the mode outputs (see equivalent Eq. 6):

$$y_2(n) = \lambda_1[u_1(n) + \beta_1]^2 + \lambda_2[u_2(n) + \beta_2]^2 \ldots + \lambda_{M+2}[u_{M+2}(n) + \beta_{M+2}]^2. \qquad (9)$$

Nonzero offset values $\{\beta_i\}$ give rise to linear terms in $\{u_i\}$ in the model output equation.

Equation (9) indicates that the relative importance of $u_i(n)$ for the second-order model response $y_2(n)$ is determined by the relative magnitude (absolute value) of the corresponding eigenvalue λ_i. Note that the matrix Q is not positive definite and, therefore, negative and positive eigenvalues are possible. By selecting only those eigenvectors of the matrix R that correspond to eigenvalues of significant magnitude, we concentrate on those linear combinations of the elements of the stimulus vector $\underline{x}(n)$ that contribute most to the second-order model response. This is the essence of the PDM model for a second-order system, extendable to higher order.

In practice, the selection of the significant eigenvalues/eigenvectors must take into account signal-to-noise ratio (SNR) considerations (*i.e.*, setting the selection threshold higher for lower SNR) and trade-offs between prediction accuracy and model complexity (*i.e.*, significant improvement in accuracy is needed to justify increasing the number of PDMs).

Clearly, when the actual system is of higher than second order, the search for PDMs based on the quadratic form of Eq. 5 may be unduly confined. Nonetheless, the final model (which includes the estimated multi-input static nonlinearity) is not limited to the second order of the employed quadratic form, because the multivariate nonlinear function of the model (receiving as inputs the outputs of the J selected PDM filters) can be estimated up to any degree of nonlinearity. There is no guarantee that the PDMs selected from the quadratic model will be adequate for the high-order model; their adequacy will be assessed ultimately by the predictive ability of the resulting model. Thus, for every time instant n, we have:

$$y = F(u_1, \ldots, u_J) + \varepsilon, \qquad (10)$$

where ε is an error term and $F(\cdot)$ represents the nonlinear function of the model with the selected PDMs in the filter bank [*i.e.*, an approximation of the associated system nonlinearity $f(\cdot)$, in general]. The error term ε includes noise effects, measurement errors, and modeling errors due to the omission of less significant terms associated with small eigenvalues or the omission of PDMs residing only in kernels of order higher than second. Estimates of $F(\cdot)$ can be obtained from the data, either analytically or graphically.

Analytical evaluation of $F(\cdot)$ requires the introduction of a postulated mathematical structure (form) for F, containing certain unknown parameters that are subsequently estimated from the data via least-squares fitting. For instance, a multinomial structure of specified degree can be imposed on F (consistent with the modified Volterra expansion of Eq. 2), and its coefficients can be estimated from the data through linear regression (because the unknown parameters enter linearly in this expression). Other mathematical structures or bases of functions of $(u_1, \ldots, u_J)$ can be used that are compatible with the specific characteristics of the system at hand (*e.g.*, exponential, sigmoidal, etc.). They can be related to the multinomial (polynomial) forms of the nonlinearity through truncated Taylor expansions (if analytic) or Weierstrass approximations (if not analytic).

Graphical evaluation of $F(\cdot)$ is feasible when there are only two PDMs generating the outputs (u_1, u_2). Then, a surface can be computed in (u_1, u_2, y) space by averaging all the data y that correspond to each specified two-dimensional bin in the (u_1, u_2) plane. These averaged values form the discretized surface

$\hat{y} = \hat{F}(u_1, u_2)$, where $\hat{F}$ is a discretized approximation of F. In the presence of noise, there are the usual trade-offs between spatial resolution [the bin size in the (u_1, u_2) plane] and estimation variance or estimation bias (*i.e.,* a larger bin size typically affords lower estimation variance but higher estimation bias). This graphical approach is particularly useful in the case of spike-output neural systems, where we can define the "trigger regions" of the system as the locus of points (u_1^*, u_2^*) that correspond to an output spike (2,11).

Method II uses a suitable class of feedforward artificial neural networks and does not require previously obtained kernel estimates. The given stimulus-response data are used to train (via a back-propagation algorithm) a feedforward artificial neural network with a single hidden layer of K hidden units, and with a single output unit simply adding the outputs of the hidden units. A threshold may be appended to the output unit if the system response is binary. The network has (M + 1) input units, receiving values corresponding to the stimulus epoch at each time instant (tapped-delay network). The novel features of this class of artificial neural networks are that the activation functions of the hidden units are polynomial (instead of the conventional sigmoidal), and the output unit is a simple adder (*i.e.,* it has in-bound weights fixed to unity). This type of network, termed polynomial artificial neural network (PANN), has been studied in connection with the questions of how do Volterra models relate to feedforward artificial neural networks and what is the equivalence between these two types of nonlinear mapping (7)?

The PANN architecture is shown in Fig. 2 and takes the form of a tapped-delay fully connected feedforward network, wherein the hidden units form weighted sums of the corresponding input values and then subject them to polynomial transformations distinct for each hidden unit. Although the weighted-sum operation performed by each hidden unit on the input values (input epoch) is equivalent to a discrete-time convolution, it is evident that the general model of Fig. 1 becomes equivalent to the PANN configuration of Fig. 2 if and only if a set of PDMs can be found for which the associated multivariate nonlinear function $f(\cdot)$ can be decomposed as the sum of univariate polynomial functions. Clearly, this equivalence remains valid (owing to the possibility of Taylor series expansions) when the polynomial form of these univariate functions is replaced by other nonlinear analytic forms (exponential, trigonometric, etc.) or combinations thereof. A special case is the traditional neural network choice of analytic sigmoidal activation functions.

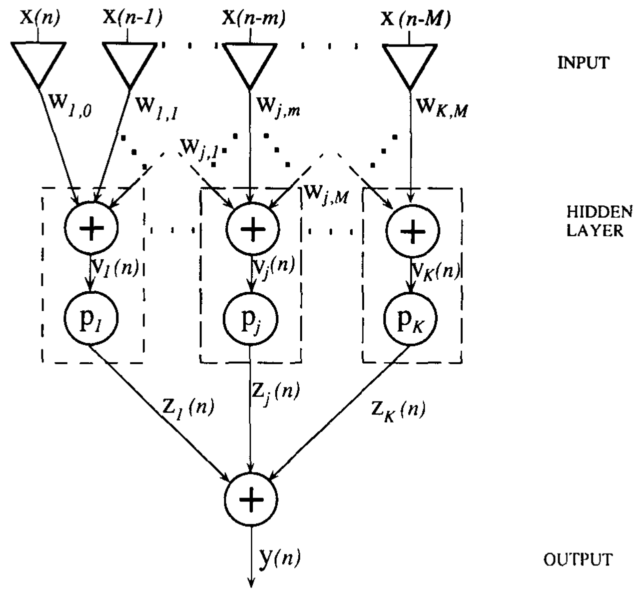

FIGURE 2. Basic architecture of a PANN. Input units receive a finite input epoch [0, M] (tapped-delay network). Hidden units have polynomial activation functions $\{p_j\}$. The in-bound weights vector $[w_{j,0}, w_{j,1}, \ldots, w_{j,M}]^T$ for each hidden unit j is normalized to unity Euclidean norm. The output unit is a simple adder.

According to Method II, the PANN with the smallest number of hidden units, trained successfully with the given stimulus-response data, yields a set of nonorthogonal PDMs of the system in the form of the in-bound weight vectors of the hidden units. Note that the latter are normalized to unity Euclidean norm by convention of our method to make them comparable in scale with the eigenvectors of Method I. This approach can yield accurate estimates of the desired PDMs when the number of hidden units and the degree of the polynomial activation functions are correctly specified. These parameters can be determined in practice by successive trials with various polynomial degrees and increasing number of hidden units or by rank evaluation of the matrix composed by the in-bound weight vectors of a large number of hidden units. The use of PANN offers an attractive alternative for obtaining PDM estimates through back-propagation training without requiring any kernel estimation.

The use of these two method for PDM estimation is illustrated in the following section, with data obtained from computer simulations.

EXAMPLES

The efficacy of the methodologies presented in the previous section is illustrated herein with computer-simulated examples. To this purpose, we begin with

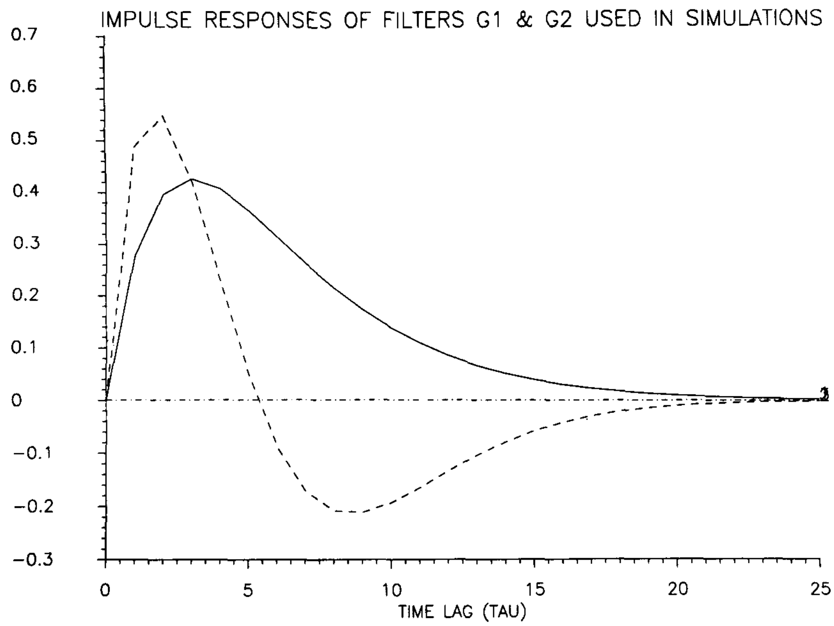

FIGURE 3. Impulse responses of the two nonorthogonal modes $\{g_1, g_2\}$ used in the simulation example.

a two-mode, second-order system described by the output equation:

$$y(n) = 1 + v_1(n) + v_2(n) + v_1(n)\, v_2(n), \quad (11)$$

where $y(n)$ is the system output and (v_1, v_2) are the convolutions of the system input $x(n)$—a 1,024-point GWN signal in this simulation, with the two impulse response functions, g_1 and g_2, respectively, shown in Fig. 3. The first- and second-order kernels of this system are shown in Fig. 4 and can be precisely estimated from these data via the Laguerre expansion technique (7). As anticipated by theory, these kernels can be expressed as (note that $k_o = 1$):

$$k_1(m) = g_1(m) + g_2(m) \quad (12)$$
$$k_2(m_1, m_2) = \tfrac{1}{2}[g_1(m_1)g_2(m_2) + g_1(m_2)g_2(m_1)]. \quad (13)$$

Equation 11 can be viewed as the static nonlinearity of a two-mode system with nonorthogonal PDMs g_1 and g_2 (and their corresponding outputs v_1 and v_2) having a bilinear cross-term: $v_1 \cdot v_2$. This nonlinearity can be also expressed without cross-terms using the "decoupled" orthogonal PDMs: $(g_1 + g_2)$ and $(g_1 - g_2)$, and their corresponding outputs: $u_1 = (v_1 + v_2)$ and $u_2 = (v_1 - v_2)$, with offsets $\beta_1 = 2$ and $\beta_2 = 0$, respectively (see Eq. 9) as:

$$y = \tfrac{1}{4}(u_1 + 2)^2 - \tfrac{1}{4}u_2^2 = 1 + u_1 + \tfrac{1}{4}u_1^2 - \tfrac{1}{4}u_2^2. \quad (14)$$

Note that, owing to the convention of normalizing the PDMs to unity Euclidean norm, the resulting normalized PDMs are: $p_1 = 0.60(g_1 + g_2)$, $p_2 = 0.92(g_1 - g_2)$, in this case, and have an associated nonlinearity:

$$y = 1 + 1.67u_1 + 0.69u_1^2 - 0.30u_2^2. \quad (15)$$

Application of the eigendecomposition approach (Method I outlined in the previous section) yields the two orthogonal PDMs shown in Fig. 5. Note that the first PDM (solid line) has the same form as the first-order kernel in this case. As indicated previously, these two PDMs are the normalized sum and difference of g_1 and g_2 of Fig. 3. After the linear regression method outlined previously, the estimated nonlinear function for these PDM estimates is precisely the one given by Eq. 15.

Using the same data, we now train a PANN with two hidden units having quadratic activation functions (Method II outlined previously) and obtain PDM estimates that are precisely the same as the PDMs obtained via eigendecomposition (not shown in the interest of space). This coincidence of resulting PDMs will not hold in a case where the cross-terms cannot be avoided in the nonlinear output function via linear combinations of the PDM outputs. Inclusion of a third hidden unit in this PANN results in a "redundant" in-bound weight vector associated with a negligible activation function (*i.e.,* negligible polynomial coefficients) that does not affect the model response or prediction accuracy. Nonetheless, it was observed that the inclusion of the third "redundant" hidden unit facilitated considerably the convergence of the training algorithm (back-propagation) in this example, requir-

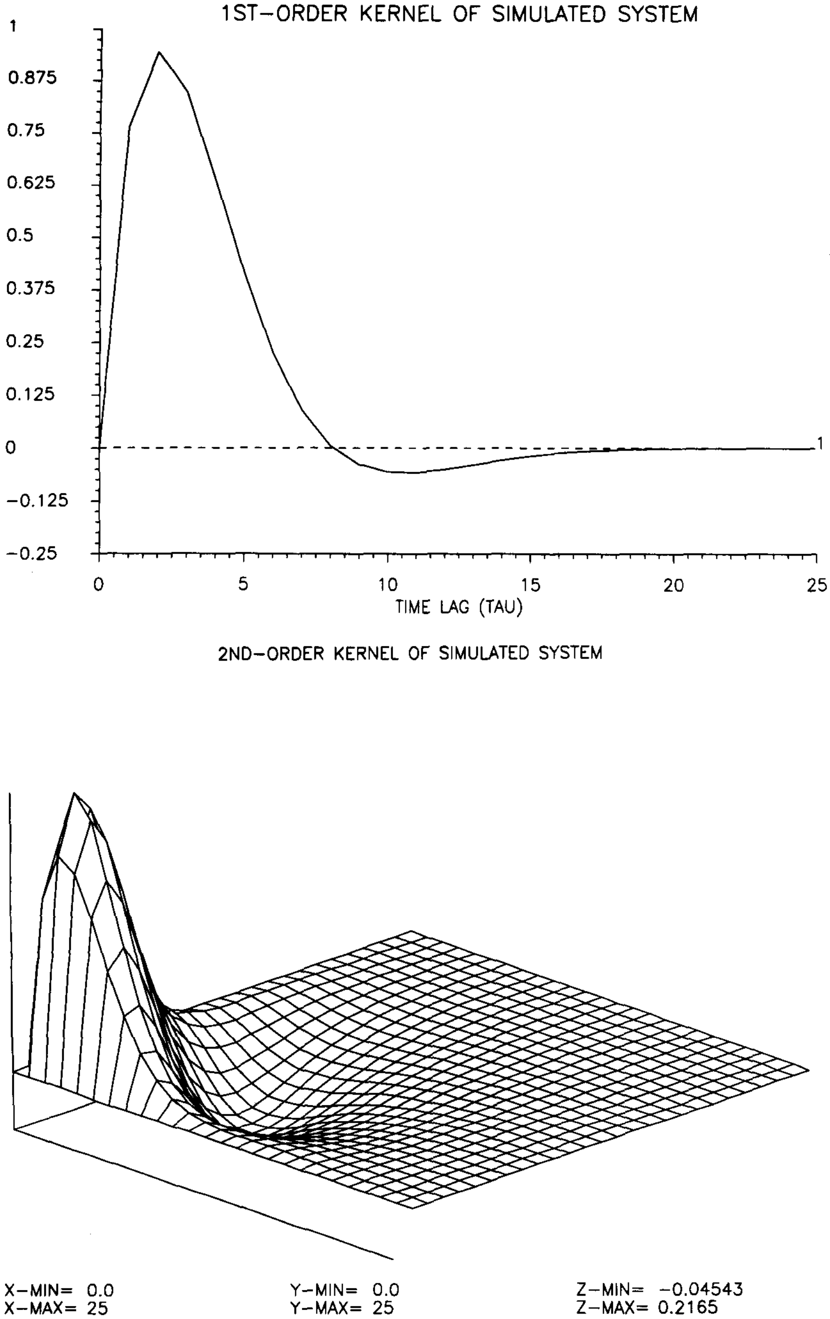

FIGURE 4. First-order (top) and second-order (bottom) kernels of the simulated system described by Eq. 11.

ing less than 100 iterations for satisfactory convergence!

The presence of contaminating noise may introduce considerable estimation errors (random fluctuations) in the obtained PDMs. This point is illustrated by adding independent GWN to the output signal for an SNR of 6 dB and, subsequently, estimating the PDMs using both Methods I and II. The results are shown in Figs. 6 and 7, for Methods I and II, respectively, and show comparable effects of noise in the two cases. We observe slightly better noise resistance of the eigendecomposition approach (Method I) for the first PDM (solid line) that corresponds to the highest eigenvalue. The obtained normalized output nonlinearities associated with the PDMs estimated via the two methods are: $\hat{y} = 1.02 + 1.66u_1 + 0.70u_1^2 - 0.32u_2^2$ (Method I); $\hat{y} = 0.99 + 1.68u_1 + 0.71u_1^2 - 0.29u_2^2$. (Method II); demonstrating the robustness of both methods by comparing with the precise output nonlinearity of Eq. 15. Although these estimates are somewhat affected by the noise in the data, the estimation accuracy of the resulting nonlinear models in the presence of consider-

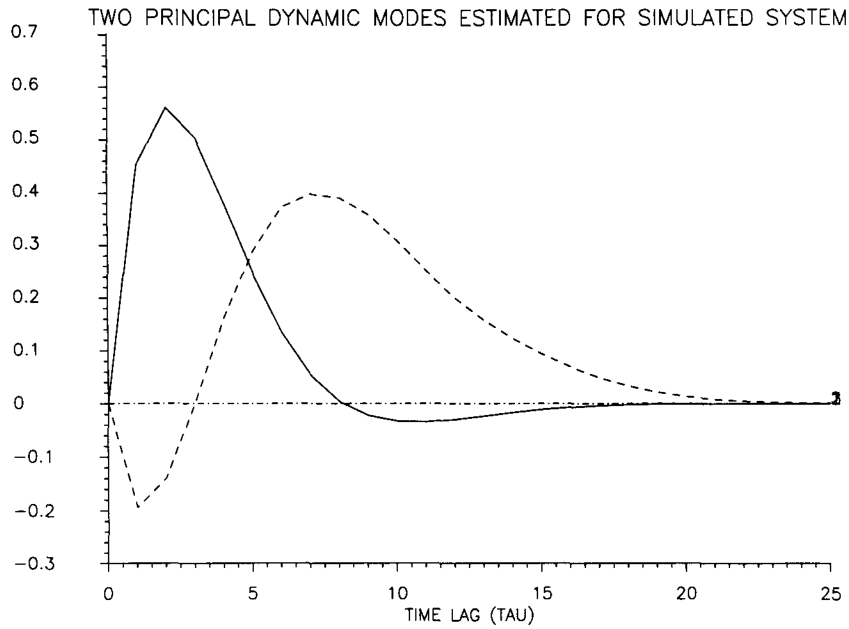

FIGURE 5. Two orthogonal PDMs obtained via eigendecomposition (Method I) using the first two kernel estimates. They correspond to the normalized functions: $0.60(g_1 + g_2)$ and $0.92(g_1 - g_2)$, associated with the nonlinearity of Eq. 15 (see text).

able noise (SNR = 6 dB) represents a notable demonstration of efficacy for the proposed approach, even for low-order systems.

Next, we examine the efficacy of this approach for high-order systems by considering first the fourth-order system described by the output nonlinearity:

$$y = \nu_1 + \nu_2 + \nu_1\nu_2 - \tfrac{1}{3}\nu_1^3 + \tfrac{1}{4}\nu_2^4, \qquad (16)$$

where (ν_1, ν_2) are as defined previously. This example serves to demonstrate the relative performance of the two methods in a high-order case where it is not feasible to estimate all of the system kernels, whereas the proposed methods may yield a complete model (*i.e.*, one containing all nonlinear terms present in the system).

Note that the quadratic part of Eq. 16 is identical to the output nonlinearity of the previous example given by Eq. 11. The addition of the third- and fourth-order terms will introduce some bias into the first- and second-order kernel estimates obtained for the truncated second-order model with existing estimation

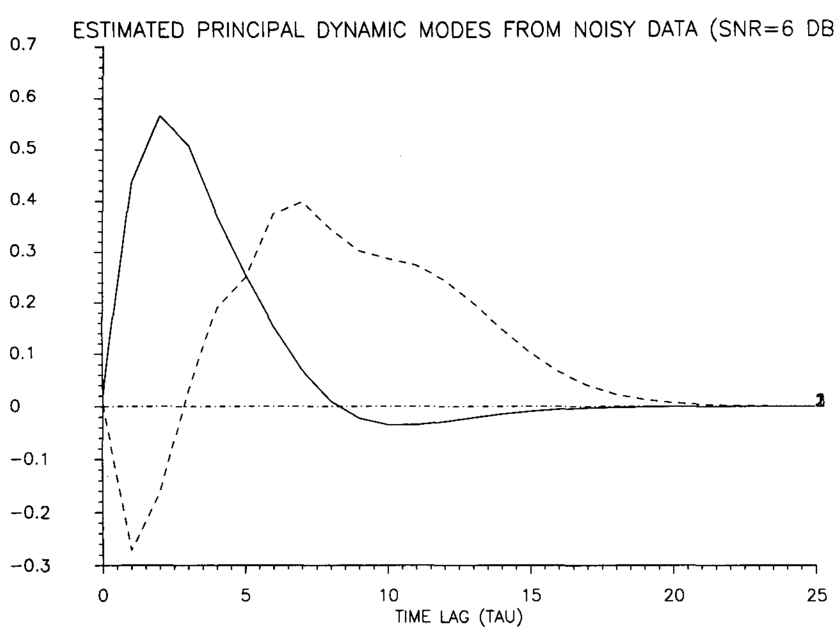

FIGURE 6. Estimated PDMs from noisy data (SNR = 6 dB) using Method I (eigendecomposition).

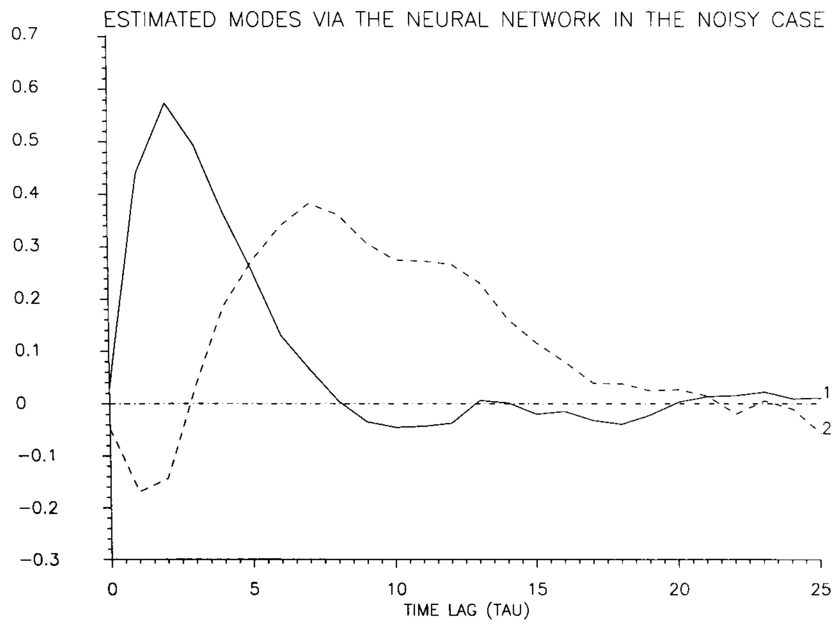

FIGURE 7. Estimated PDMs from noisy data (SNR = 6 dB) using Method II (PANN).

methods (9). This bias is likely to prevent precise estimation of the previous orthogonal PDMs $[(g_1 + g_2)$ and $(g_1 - g_2)]$ via eigendecomposition based on the first two kernel estimates. Furthermore, more than two PDMs will be required for a model of this system without cross-terms in the output nonlinearity (*i.e.*, for a representation consistent with a precise PANN model of fourth degree). For instance, the use of three PDMs corresponding to g_1, g_2 and a linear combination $(g_1 + \alpha g_2)$ should be adequate, because g_1 and g_2 give rise to ν_1 and ν_2, respectively, and the cross-term $(\nu_1\nu_2)$ can be expressed in terms of these three PDMs as: $1/2\alpha[(\nu_1 + \alpha\nu_2)^2 - \nu_1^2 - \alpha^2\nu_2^2]$. Thus, the three polynomial activation functions corresponding to these three PDMs are: $[\nu_1 - 1/2\alpha\nu_1^2 - 1/3\nu_1^3]$, $[\nu_2 - \alpha/2\nu_2^2 + 1/4\nu_2^4]$, and $[1/2\alpha(\nu_1 + \alpha\nu_2)^2]$. The results of eigendecomposition based on the first two kernel estimates cannot be anticipated with the same clarity, owing to the aforementioned kernel estimation bias introduced by the practically imposed truncation of the Volterra model.

These issues are explored with the simulated data. Use of the eigendecomposition method (based on the first two kernel estimates) still yields two PDMs corresponding to two significant eigenvalues: $\lambda_1 = 2.38$, $\lambda_2 = -0.65$ (with the subsequent eigenvalues being $\lambda_3 = 0.14$, $\lambda_4 = -0.12$, etc.). Note that the sign of the eigenvalues signifies how the respective PDM output contributes to the system output (excitatory or inhibitory). The obtained PDMs for λ_1 and λ_2 are shown in Fig. 8, and resemble the PDMs of the previous example, although considerable distortion (estimation bias) is evident due to the aforementioned influence of the high-order nonlinearities. These two PDMs correspond to a two-mode output nonlinearity that only yields an approximation of the system output. This problem can be overcome by using the PANN approach that does not limit the order of estimated nonlinearities and allows estimation of nonorthogonal PDMs.

To this purpose, a PANN with four hidden units having fourth-degree polynomial activation functions is trained with these data. The error diminished below 0.5% after 5,000 iterations, yielding the three PDMs shown in Fig. 9 that correspond to g_1, g_2 and a linear combination of g_1 and g_2 that is close to their sum; the fourth hidden unit had negligible activation function (*i.e.*, polynomial coefficients on the order of 10^{-4}). These results corroborate our theoretical expectations discussed earlier. Note that any linear combination of g_1 and g_2 is admissible for the third PDM, leading to appropriate adjustments in the second-degree coefficients of the activation functions of all PDMs (see previously described data). The computational burden associated with Method II (PANN) is considerably heavier than Method I (~50 times more in this example), but still remains within the capabilities of a pentium-based PC.

To examine the accuracy of the estimated models in the two cases, we can compare the overall predictive accuracy of the two nonlinear models (PDMs and their respective output nonlinearities) for a segment of data that was not used in obtaining the models. Results are shown in Fig. 10, corresponding to prediction-normalized mean-square errors of 2.4% and 0.3% for Methods

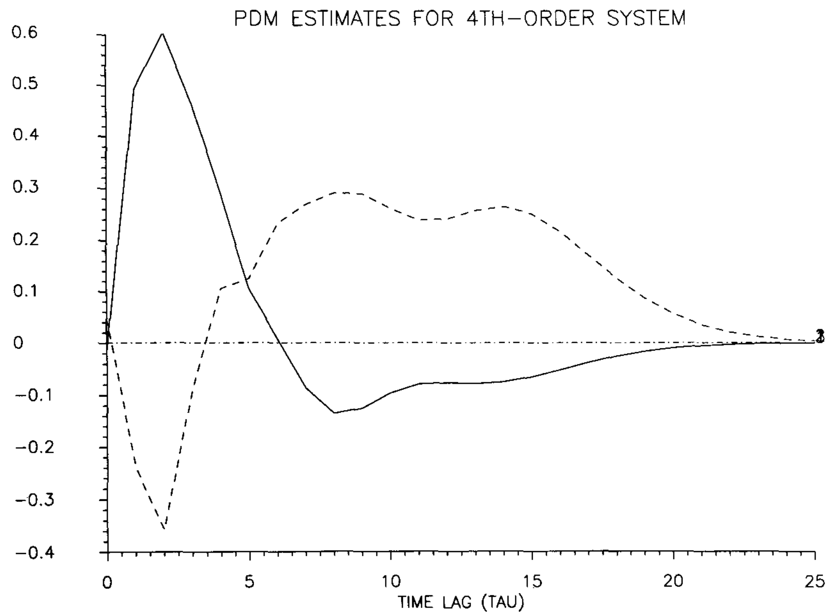

FIGURE 8. Estimated PDMs for the fourth-order system described by Eq. 16 using Method I (eigendecomposition). Only two PDMs are still obtained, corresponding to two significant eigenvalues: $\lambda_1 = 2.38$, $\lambda_2 = -0.65$. Considerable distortion relative to the previous two PDMs is evident, due to the influence of the higher order terms (third and fourth order).

I and II, respectively. Although the prediction of the Method I model is better than the corresponding PDM estimates might have suggested, the first- and second-order kernel estimates are considerably worse than their counterparts obtained by Method II.

These results are extendable to multimode systems of arbitrary order of nonlinearity, endowing this approach with unprecedented power for modeling applications of highly nonlinear systems. An illustrative example is provided by the infinite-order Volterra system described by the output nonlinearity:

$$y = \exp[\nu_1]\sin[(\nu_1 + \nu_2)/2], \tag{17}$$

where ν_1 and ν_2 are as defined previously. This Volterra system has kernels of all orders, with declining magnitudes as the order increases. This becomes evident when the Taylor expansions of the exponential and trigonometric functions are used in Eq. 17. Application of Method I yields only two PDMs (*i.e.,* only two significant eigenvalues: $\lambda_1 = 1.86$ and $\lambda_2 = 1.09$, with the remaining eigenvalues being at least one order of magnitude smaller). The prediction of the fifth-order PDM

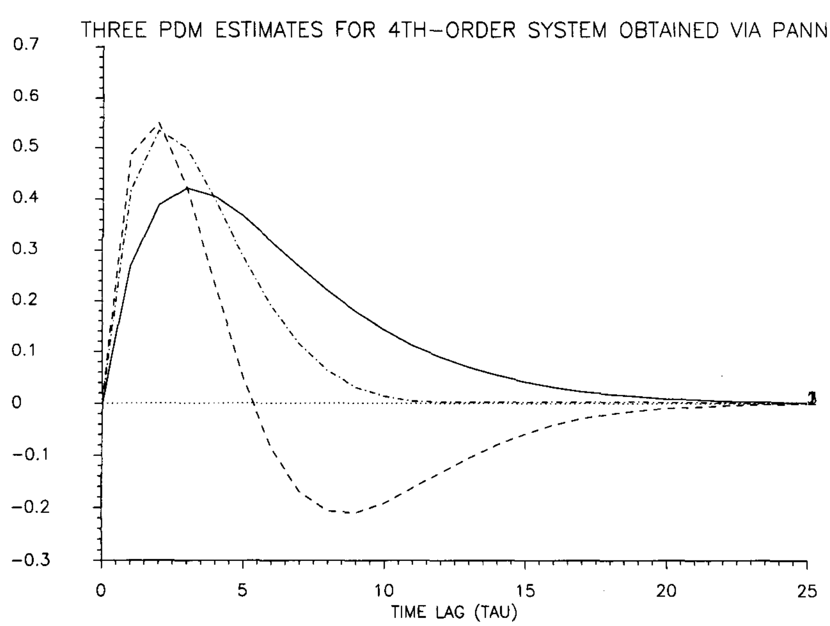

FIGURE 9. Estimated PDMs for the fourth-order system described by Eq. 16 using Method II (PANN). Three nonorthogonal PDMs are obtained corresponding to g_1, g_2, and a linear combination of g_1 and g_2, as anticipated by theory.

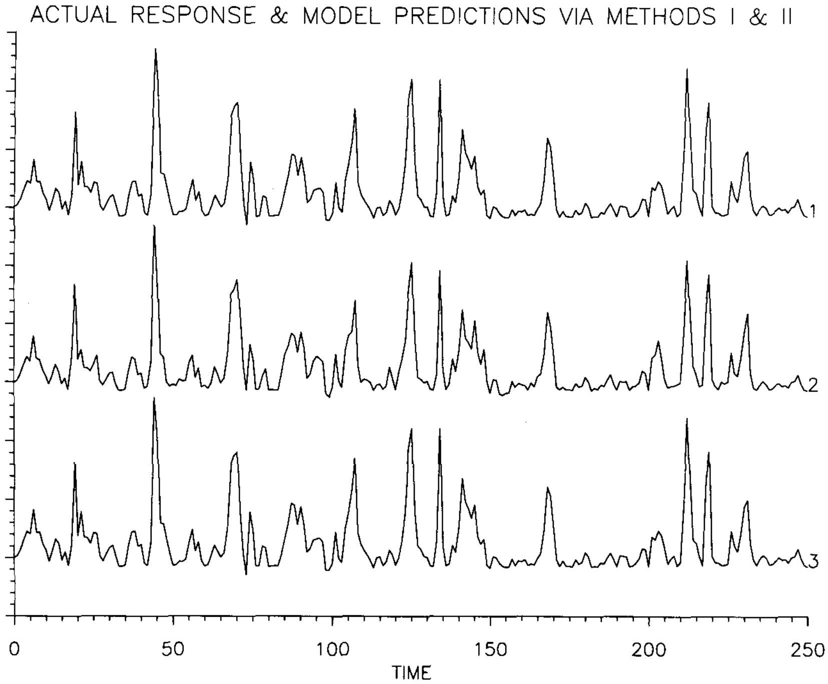

FIGURE 10. Model predictions by the two methods for the fourth-order system. The actual system output (trace 1) and the predicted outputs by the models obtained via Method I (trace 2) and Method II (trace 3).

model (based on two PDMs obtained by use of PANN) is shown in Fig. 11, along with the exact system output. Note that the corresponding normalized mean-square error of the model prediction is 6.8% for the fifth-order PDM-based model, demonstrating the benefits of the PDM approach in this case of an infinite-order Volterra system.

Although the efficacy of Method I cannot be guaranteed, in general, because it depends on how well the PDM estimates (obtained from the second-order model) extend to higher order models, the efficacy of Method II is ensured whenever successful training of a high-order PANN is possible via the back-propagation technique.

CONCLUSIONS

The study of highly nonlinear physiological systems can benefit from the presented general modeling ap-

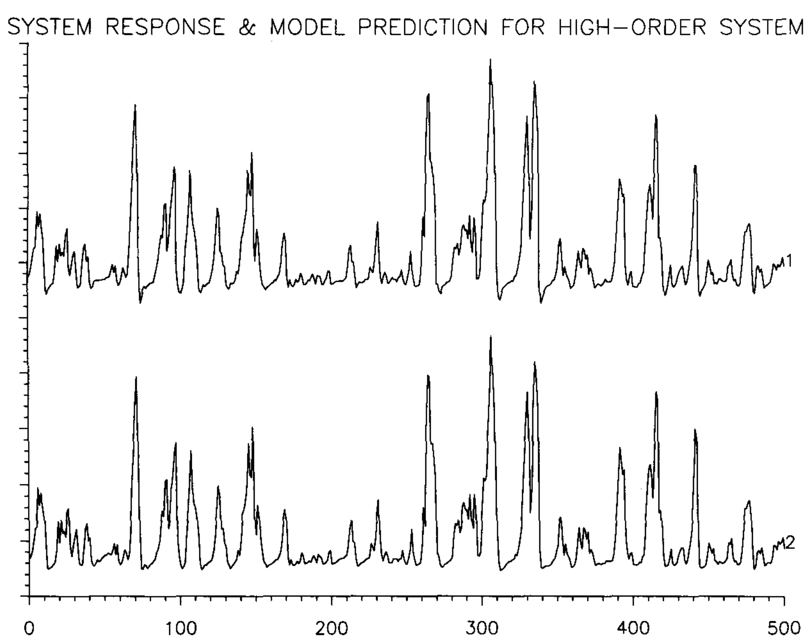

FIGURE 11. Actual output of infinite-order Volterra system (trace 1) and model prediction by a fifth-order PANN-based model using two PDMs (trace 2).

proach that uses PDMs to obtain accurate models of nonlinear systems of the Volterra class in a practical context (*i.e.*, from relatively short input-output data records contaminated by noise). The key to the successful application of this new approach is the ability to represent adequately the system dynamics with a small number of PDMs. This paper presents two practicable methods by which this may be accomplished: one base on eigendecomposition of low-order kernel estimates (typically of first and second order) and the other using feedforward artificial neural networks with polynomial activation functions. The quality of the obtained kernel estimates and of the associated nonlinear predictive models is demonstrated for short data records (1,024 data points), even under significant data contaminating noise (SNR = 6 dB).

The presented simulation examples demonstrate rough parity between the two methods for low-order systems. However, for high-order systems, Method II (which is based on a new class of artificial neural networks) seems to yield superior results and to render solvable a class of problems that have long been viewed as nearly intractable.

It is hoped that this approach may provide the effective tools for modeling complex nonlinear physiological systems that cannot be adequately modeled by use of the first two or three kernels. In the context of physiological system modeling, the obtained PDMs may also afford greater scientific insight and interpretability of the obtained nonlinear models (*e.g.*, the obtained PDMs may represent distinct pathways of dynamic transformations of the stimulus into the response signal, corresponding to distinct physiological mechanisms).

Conceptual forerunners of the proposed approach were first introduced in the study of spike-output neural systems (8,11). By extending this approach to cover the broader class of continuous-output systems, it is hoped that the range of applications of nonlinear modeling to biomedical systems will be expanded and generate new scientific insights by proper physiological interpretation of the obtained PDMs and associated models.

REFERENCES

1. Barrett, J. F. The use of functionals in the analysis of nonlinear physical systems. *J. Electron. Control* 15:567–615, 1963.
2. French, A. S., and V. Z. Marmarelis. Nonlinear neuronal mode analysis of action potential encoding in the cockroach tactile spine neuron. *Biol. Cybern.* 73:425–430, 1995.
3. Korenberg, M. J. Parallel cascade identification and kernel estimation for nonlinear systems. *Ann. Biomed. Eng.* 19:429–455, 1991.
4. Marmarelis, P. Z., and V. Z. Marmarelis. Analysis of Physiological Systems: The White-Noise Approach. New York: Plenum, 1978, pp. 1–487. (Russian translation: Mir Press, Moscow, 1981, pp. 1–480. Chinese translation: Academy of Sciences Press, Beijing, 1990, pp. 1–561.)
5. Marmarelis, V. Z., ed. Advanced Methods of Physiological System Modeling, vol. I. Los Angeles: Biomedical Simulations Resource, University of Southern California, 1987, pp. 1–336.
6. Marmarelis, V. Z., ed. Advanced Methods of Physiological System Modeling, vol. II. New York: Plenum, 1989, pp. 1–302.
7. Marmarelis, V. Z., ed. Advanced Methods of Physiological System Modeling, vol. III. New York: Plenum, 1994, pp. 1–272.
8. Marmarelis, V. Z. Signal transformation and coding in neural systems. *IEEE Trans. Biomed. Eng.* 36:15–24, 1989.
9. Marmarelis, V. Z. Identification of nonlinear biological systems using Laguerre expansions of kernels. *Ann. Biomed. Eng.* 21:573–589, 1993.
10. Marmarelis, V. Z., K. H. Chon, Y. M. Chen, D. J. Marsh, and N. H. Holstein-Rathlou. Nonlinear analysis of renal autoregulation under broadband forcing conditions. *Ann. Biomed. Eng.* 21:591–603, 1993.
11. Marmarelis, V. Z., and M. Orme. Modeling of neural systems by use of neuronal modes. *IEEE Trans. Biomed. Eng.* 40:1149–1158, 1993.
12. Rugh, W. J. Nonlinear System Theory: The Volterra/Wiener Approach. Baltimore: Johns Hopkins University Press, 1981, pp. 1–325.
13. Schetzen, M. The Volterra and Wiener Theories of Nonlinear Systems. New York: Wiley, 1980, pp. 1–531.
14. Volterra, V. Theory of Functionals and of Integral and Integro-differential Equations. New York: Dover, 1930, pp. 1–232.
15. Watanabe, A., and L. Stark. Kernel methods for nonlinear analysis: identification of a biological control system. *Math. Biosci.* 27:99–108, 1975.
16. Wiener, N. Nonlinear Problems in Random Theory. New York: Wiley, 1958.