

# Nonlinear modeling of glucose metabolism: comparison of parametric vs. nonparametric methods

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**Abstract**— This paper presents the results of computational studies that compare simulated parametric and nonparametric models in terms of their ability to obtain reliable quantitative descriptions of the dynamic effects of variable infusions of insulin on blood glucose concentration in human subjects. In the nonparametric modeling approach, we employ the general class of Volterra-type models that are estimated from input-output data. The parametric models considered are the extensively studied “minimal model” and an augmented variant of the latter that incorporates the process of insulin secretion by the pancreas in response to elevated blood glucose. This model represents the actual closed-loop operating conditions of the system. The presented results demonstrate the feasibility of obtaining data-driven (i.e. inductive) nonparametric models in a realistic operating context, without resorting to the restrictive prior assumptions of model structure that are necessary for the numerous parametric (compartmental) models proposed previously. The rationale underpinning the nonparametric approach is that prior assumptions regarding the model structure may lead to results that are improperly constrained or biased by preconceived notions. Thus, it may be preferable to let the data guide the inductive selection of the appropriate model within the general class of Volterra-type models that imposes no such constraints.

## I. INTRODUCTION

Diabetes mellitus represents a major threat to public health, exhibiting alarmingly rising trends of incidence in recent years. There is, therefore, need for improved diagnostic methods that provide more quantitatively precise clinical assessments at earlier stages of the disease. This task may be facilitated by the utilization of advanced mathematical models that describe reliably and quantitatively the dynamic interrelationships among the key physiological variables implicated in the underlying pathophysiology (i.e., blood glucose concentration and its causal interrelationships with insulin, glucagon etc.). Such models could also prove instrumental in achieving long-term glucose regulation in diabetics through closed-loop model-reference control by variable insulin micro-infusions, administered by programmable micro-pumps, preventing the onset of pathologies caused by elevated blood glucose.

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Prolonged hyperglycemia is usually caused by defects in insulin production or action; therefore, the effects of insulin are considered to be the most important. Consequently, most modeling studies to date have focused on the causal relationship between insulin and glucose (as the “input” and “output” of a system representing this causal relationship respectively), relying often on the concept of compartmental modeling. In this context, the minimal model (MM) of glucose disappearance, combined with the intravenous glucose tolerance test (IVGTT), has been the most widely used method to study whole body glucose metabolism *in vivo* [1]-[2]. The accuracy of the estimates obtained from the MM has been questioned; therefore, two-compartmental models for glucose kinetics [3] have been also proposed. Other approaches include artificial neural networks and probabilistic models [4]-[5].

The aforementioned compartmental models rely on *a priori* assumptions and are often linked to specific experimental protocols; therefore, their ability to quantify glucose metabolism under normal operating conditions remains limited. Recent technological advances in the development of continuous long-term glucose sensors and insulin micro-pumps have enabled the nonparametric (i.e., data-true) approach, providing new opportunities of obtaining reliable models of the insulin-glucose interrelationships in a broader operating context.

The present paper examines the relation between existing parametric (compartmental) and nonparametric (Volterra-type) models. The analytical and simulation results demonstrate the feasibility of obtaining accurate nonparametric models of insulin-glucose dynamics that are generated by widely used parametric models. Since the nonparametric modeling approach does not require prior assumptions about the model structure, it can provide the effective means for obtaining accurate patient-specific and data-true models in a clinical context – thus overcoming the limitations of current parametric models.

## II. METHODS

The causal relationship between infused insulin and blood glucose concentration is nonlinear and dynamic. Therefore, the present study concerns modeling methodologies (parametric and nonparametric) that belong to this category. Among parametric models, we selected the MM as well as an augmented version of the latter, incorporating an insulin-secretion equation (closed-loop operation). Among nonparametric models, we selected a variant of the general Volterra-Wiener approach. The descriptors of the Volterra model (first and second-order kernels) were estimated from

broadband input-output data generated from the simulated parametric models.

#### A. The minimal model of glucose disappearance

The MM is described by the following two differential equations, which describe the nonlinear dynamics of the insulin-to-glucose relationship during an IVGTT [1]:

$$\frac{dg(t)}{dt} = -p_1g(t) - x(t)[g(t) + g_b] \quad (1)$$

$$\frac{dx(t)}{dt} = -p_2x(t) + p_3i(t) \quad (2)$$

where  $g(t)$  is the deviation of glucose plasma concentration from its basal value  $g_b$  (in  $mg/dl$ ),  $x(t)$  is the state variable of insulin action (in  $min^{-1}$ ),  $i(t)$  is the deviation of insulin plasma concentration from its basal value  $i_b$  (in  $\mu U/ml$ ),  $p_1$  and  $p_2$  are parameters describing the kinetics of glucose and insulin action respectively (in  $min^{-1}$ ) and  $p_3$  is a parameter (in  $min^{-2} \cdot ml/\mu U$ ) affecting the clinically important attribute of insulin sensitivity.

The MM is nonlinear, due to the presence of a bilinear term between insulin action  $x(t)$  and glucose concentration  $[g(t)+g_b]$  in (1). This term describes the modulation of the effective kinetic constant of glucose dynamics by insulin action. The physiological interpretation of the MM parameters can be made in terms of insulin-dependent and insulin-independent processes that enhance glucose uptake and suppress net glucose output. The parameter  $p_1$ , termed glucose effectiveness  $S_G$ , represents the insulin-independent effect, while the insulin-dependent effect is represented by the ratio  $p_3/p_2$  (in  $min^{-1}/\mu U \cdot ml^{-1}$ ) and is termed insulin sensitivity  $S_I$ . Both  $S_G$  and  $S_I$  are of clinical importance and are estimated from IVGTT data.

From a physiological point of view, the most obvious limitation of the MM described by (1)-(2) is the absence of an equation describing the secretion of insulin from pancreatic beta cells in response to an elevation in blood glucose concentration (i.e. it is an open-loop model). This limitation can be removed through the inclusion of an insulin-secretion equation that renders this ‘‘augmented MM’’ a closed-loop model.

#### B. Closed-loop parametric model: the augmented MM

The closed-loop nature of glucose metabolism can be accounted for (in first approximation) by incorporating an equation describing insulin secretion dynamics in the MM. Of several models that have been proposed for modeling insulin secretion, we select one that utilizes a threshold function [6]. The resulting closed-loop model becomes:

$$\frac{dg(t)}{dt} + p_1g(t) = -x(t)[g(t) + g_b] \quad (3)$$

$$\frac{dx(t)}{dt} = -p_2x(t) + p_3[i(t) + r(t)] \quad (4)$$

$$\frac{dr(t)}{dt} = -ar(t) + \beta T_h[g(t)] \quad (5)$$

where  $r(t)$  is the secreted insulin in response to an elevation in plasma glucose concentration, with the threshold function  $T_h[g(t)]$  defined as:

$$T_h[g(t)] = \begin{cases} g(t) - \theta, & g(t) \geq \theta \\ 0, & \text{otherwise} \end{cases} \quad (6)$$

The parameter  $\alpha$  (in  $min^{-1}$ ) is the kinetic constant of the dynamics of secreted insulin and the parameter  $\beta$  (in  $\mu U \cdot min^{-2}/ml$  per  $mg/dl$ ) determines the rate of insulin secretion (i.e. the strength of the feedback pathway of this closed-loop system).

#### C. Nonparametric Volterra-type modeling

The Volterra-Wiener framework has been employed extensively for nonparametric modeling of nonlinear physiological systems. In this context, the input-output dynamic relationship of a causal, nonlinear system of order  $Q$  and memory  $M$  is described by the Volterra functional expansion:

$$g(t) = \sum_{n=0}^Q \int_0^M \dots \int_0^M k_n(\tau_1, \dots, \tau_n) i(t-\tau_1) \dots i(t-\tau_n) d\tau_1 \dots d\tau_n \quad (7)$$

where  $i(t)$  and  $g(t)$  are the input and output of the system at time  $t$  (deviations of plasma insulin and glucose concentrations from basal values). The first-order ( $n=1$ ) and higher-order ( $n>1$ ) Volterra kernels  $k_n$  form a hierarchy of the linear and nonlinear dynamics of the system.

In order to estimate  $k_n$  from input-output data, we employ the Laguerre-Volterra Network (LVN) methodology, which combines Laguerre functional expansions and networks with polynomial activations, yielding accurate representations of high-order systems from short input-output records [7]. The LVN is trained on the basis of input-output data with an iterative gradient descent scheme. Its structural parameters are selected on the basis of the normalized mean-square error (NMSE) of the output prediction, defined as the sum of squares of the model residuals (the difference between the model prediction and the true output) divided by the sum of squares of the de-measured true output.

#### D. Equivalence between parametric and nonparametric models

The mathematical relationship between the aforementioned parametric and nonparametric models is examined by employing the generalized harmonic balance method, as outlined below for the second-order case of the nonparametric model. This procedure can be extended to any order of interest [8]. By setting the input  $i(t)$  equal to 0,  $e^{st}$  and  $e^{s_1t} + e^{s_2t}$  in (7) successively, the output  $g(t)$  becomes equal to  $k_0$ ,  $k_0 + e^{st}K_1(s) + e^{2st}K_2(s,s)$  and  $k_0 + e^{s_1t}K_1(s_1) + e^{s_2t}K_1(s_2) + e^{(s_1+s_2)t}K_2(s_1,s_2) + \dots$ , where  $K_1(s)$  and  $K_2(s_1,s_2)$  are the Laplace transforms of  $k_1(\tau)$  and  $k_2(\tau_1,\tau_2)$ . If we substitute these three input-output pairs into (1)-(2) and (3)-(5) for the open and closed-loop models respectively and equate the coefficients of the resulting exponentials of the same kind, we can obtain analytical expressions of the Volterra kernels in terms of the parameters of the respective parametric model.

To define the computational equivalence between the two model forms and demonstrate the feasibility of obtaining accurate nonparametric models of insulin-glucose dynamics from input-output data, we simulated the parametric models with broadband insulin data and estimated the kernels of the equivalent nonparametric model.

### III. RESULTS

#### A. Analytical open-loop Volterra kernels

The bilinear term between insulin action and glucose concentration in (1) gives rise to an equivalent Volterra model of infinite order. However, it was found that for parameter values within the physiological range, a second-order Volterra model offers an adequate approximation. Specifically, as shown below, the magnitude of the  $n$ -th order kernel is proportional to the  $n$ -th power of  $p_3$ , with the latter being on the order of  $10^{-5}$ - $10^{-4}$ . In order to derive the Volterra kernels of the MM analytically we solve (2):

$$x(t) = p_3 \int_0^{\infty} \exp(-p_2 \tau) i(t - \tau) d\tau \quad (9)$$

and substitute into (1):

$$\dot{g}(t) + p_1 g(t) + p_3 (g(t) + g_b) \int_0^{\infty} \exp(-p_2 \tau) i(t - \tau) d\tau = 0 \quad (10)$$

Upon application of the generalized harmonic balance method outlined above, we derive the following analytical expressions for the first-order and second-order Volterra kernels of the MM in the Laplace domain ( $k_0 = 0$ ):

$$K_1(s) = -p_3 g_b \frac{1}{(s + p_1)(s + p_2)} \quad (11)$$

$$K_2(s_1, s_2) = \frac{g_b p_3^2}{2} \frac{1}{(s_1 + p_1)(s_1 + p_2)} \frac{1}{(s_2 + p_1)(s_2 + p_2)} \left[ 1 + \frac{p_2}{s_1 + s_2 + p_1} \right] \quad (12)$$

The resulting expression for the first-order kernel in the time domain is:

$$k_1(\tau) = -g_b \frac{p_3}{p_2 - p_1} [\exp(-p_1 \tau) - \exp(-p_2 \tau)] \quad (13)$$

The first and second-order Volterra kernels are plotted in Figure 2 for typical MM parameter values ( $p_1 = 0.024 \text{ min}^{-1}$ ,  $p_2 = 0.033 \text{ min}^{-1}$ ,  $p_3 = 1.783 \cdot 10^{-5} \text{ min}^{-2} \cdot \text{ml}/\mu\text{U}$ ,  $g_b = 80 \text{ mg/dl}$  and  $S_I = p_3/p_2 = 5.403 \cdot 10^{-4} \text{ min}^{-2} \cdot \text{ml}/\mu\text{U}$ ) [9]. The positive values of the second-order Volterra kernel indicate that the actual glucose drop caused by the insulin infusion will be slightly less than the first-order prediction (sublinear response).

#### B. Analytical closed-loop Volterra kernels

To derive the analytical expressions of the kernels in the closed-loop case, we approximate the threshold function of (6) with a polynomial, assuming that  $\theta$  is equal to zero (i.e. assuming that secretion is triggered when glucose concentration rises above its basal value):

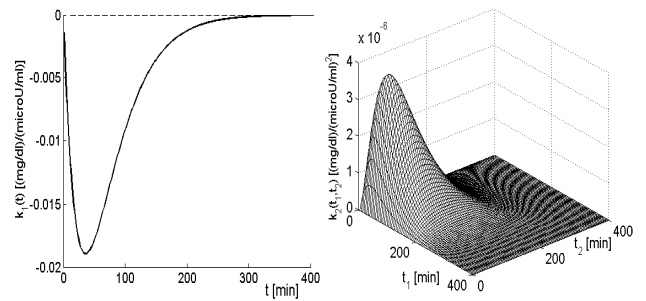


Fig. 1. The first-order (left) and second-order (right) Volterra kernels of the minimal model for typical values of its parameters within the physiological range.

$$\beta T_h[g(t)] \equiv \beta_1 g(t) + \beta_2 g^2(t) + \dots \quad (14)$$

Equation (5) can be rewritten as:

$$\frac{dr(t)}{dt} = -ar(t) + \beta_1 g(t) + \beta_2 g^2(t) + \dots \quad (15)$$

The solution of (15) is given by:

$$r(t) = \beta_1 f(t) * g(t) + \beta_2 f(t) * g^2(t) + \dots \quad (16)$$

where the asterisk denotes convolution and  $f(t) = e^{-at}u(t)$ .

Also, from (4) we have:

$$\frac{dx(t)}{dt} = -p_3 h(t) * [i(t) + r(t)] \quad (17)$$

where  $h(t) = e^{-p_2 t}u(t)$ . Equation (3) becomes:

$$\frac{dg(t)}{dt} + p_1 g(t) = -p_3 g(t) \cdot [h(t) * i(t) + \beta_1 h(t) * f(t) * g(t) + \beta_2 h(t) * f(t) * g^2(t) + \dots] \quad (18)$$

Equation (18) can be used to obtain the equivalent Volterra kernels of the closed-loop model, following the procedure outlined before for the open-loop model. The resulting expression for the first-order kernel in the Laplace domain is ( $k_0 = 0$ , second-order kernel not shown):

$$K_1(s) = -p_3 g_b \frac{H(s)}{s + p_1 + p_3 g_b \beta_1 H(s) F(s)} \quad (19)$$

where  $F(s)$ ,  $H(s)$  are the Laplace transforms of  $f(t)$ ,  $h(t)$ . Equation (18) was inverted numerically to yield the first-order kernel in the time-domain, shown in Fig. 2 for different values of  $\alpha$ ,  $\beta$ , keeping the rest of the parameters constant to the values used in the open-loop case.

#### C. Simulation results

In order to demonstrate the feasibility of estimating the Volterra kernels directly from input-output measurements, we simulated the open-loop MM by numerical integration of (1)-(2) for the typical values of MM parameters used above. The input signal was a Gaussian white noise (GWN) sequence of insulin infusions (i.e., independent samples every 5 min) with standard deviation of  $10 \mu\text{U/ml}$  superimposed on a constant baseline of  $25 \mu\text{U/ml}$ . Due to the low-pass dynamic characteristics of the model, one sample every 5 min is sufficient for representing the input-

output data. An input-output record of 360 sample points was used to perform the training of a second-order LVN model and the estimation of the equivalent Volterra kernels.

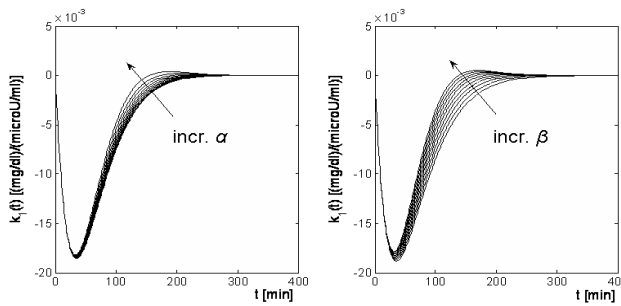


Fig. 2. The first-order kernels of the closed-loop MM for  $\alpha$  between 0.1 and 0.3  $\text{min}^{-1}$  ( $\beta = \text{constant} = 0.05$ -left panel) and for  $\beta$  between 0.01 and 0.1 ( $\alpha = \text{constant} = 0.15 \text{ min}^{-1}$ -right panel).

The estimated first- and second-order kernels were almost identical to the true kernels shown in Fig. 1 (prediction NMSE below 0.01%) and are not shown separately. In order to examine the robustness of the kernel estimates in the presence of output noise, we repeated the procedure after adding independent noise to the output for an SNR of 10 dB (10 different noise samples). The estimated first and second-order kernels are shown in Fig. 3 (mean  $\pm$  SE) and demonstrate the robustness of this approach. The average prediction NMSE in this case was around 10%, as expected due to the SNR value. Finally, the augmented MM was simulated by integrating (3)-(5) for a 360-point GWN insulin input. The prediction NMSE was below 1%, with the kernel estimates being also very close to their analytically derived counterparts of Fig. 2 (data not shown), though higher-order LVN models were required in this case.

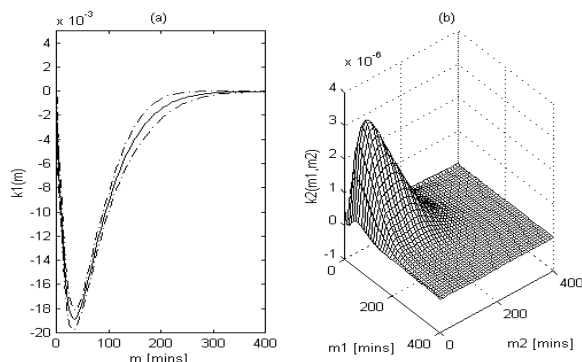


Fig. 3. Estimated kernels for ten different noisy output runs (SNR=10 dB) (a) Average first-order kernel (solid line) and corresponding standard error bounds (dashed lines) (b) Average second-order kernel.

#### IV. DISCUSSION

The relation between parametric (differential) and nonparametric (Volterra-Wiener) models of glucose metabolism was examined analytically in the present study. Their equivalence was demonstrated and Volterra kernels of first and second-order were derived in terms of the parameters of both the MM as well as an augmented version of the latter that reflects the closed-loop nature of glucose metabolism.

The simulation results demonstrated the feasibility of obtaining accurate nonlinear models from insulin-glucose data generated from open-loop and closed-loop parametric models, which were robust under conditions of output-additive noise. Such models may be estimated with the use of current technology, i.e., measurements from continuous glucose sensors in combination with insulin micropumps, suggesting that prior, constricting assumptions are not necessary in order to model the dynamic effects of insulin on glucose. These data-true models are furthermore amenable to adaptive and patient-specific estimation, which could prove critical in the implementation of model-based control algorithms. The proposed approach is currently evaluated with clinical data (infused insulin and glucose) from diabetic patients. Preliminary results, as well as simulation results from multiple-infusion stimuli (data not shown), agree with the results presented above, suggesting that adequate variability is provided by non-random inputs and that this approach is feasible in more general situations.

Finally, Volterra models may be used to extract parameters of clinical importance. For example, the minimum value or the integrated area of the first-order kernel is a measure of how much an insulin infusion will affect plasma glucose concentration. In the case of the MM, the integrated area under the first-order kernel is equal to  $g_b \cdot S_I/S_G$ . Also, the slope of the first-order kernel at the origin (a measure of how rapidly glucose drops in response to an insulin infusion) is equal to  $-(g_b p_3)$ . A quick estimate of  $p_3$  may be obtained from the slope of the first-order kernel.

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