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ORIGINAL ARTICLE

Analysis of Intravenous Glucose Tolerance Test Data Using Parametric and Nonparametric Modeling: Application to a Population at Risk for Diabetes

Vasilis Z. Marmarelis, Ph.D.,[1] Dae C. Shin, Ph.D.,[1] Yaping Zhang, M.S.,[1]
Alexandra Kautzky-Willer, M.D.,[2] Giovanni Pacini, D.Sc.,[3] and David Z. D'Argenio, Ph.D.[1]

Abstract

Background:

Modeling studies of the insulin–glucose relationship have mainly utilized parametric models, most notably the minimal model (MM) of glucose disappearance. This article presents results from the comparative analysis of the parametric MM and a nonparametric Laguerre based Volterra Model (LVM) applied to the analysis of insulin modified (IM) intravenous glucose tolerance test (IVGTT) data from a clinical study of gestational diabetes mellitus (GDM).

Methods:

An IM IVGTT study was performed 8 to 10 weeks postpartum in 125 women who were diagnosed with GDM during their pregnancy [population at risk of developing diabetes (PRD)] and in 39 control women with normal pregnancies (control subjects). The measured plasma glucose and insulin from the IM IVGTT in each group were analyzed via a population analysis approach to estimate the insulin sensitivity parameter of the parametric MM. In the nonparametric LVM analysis, the glucose and insulin data were used to calculate the first-order kernel, from which a diagnostic scalar index representing the integrated effect of insulin on glucose was derived.

Results:

Both the parametric MM and nonparametric LVM describe the glucose concentration data in each group with good fidelity, with an improved measured versus predicted r^2 value for the LVM of 0.99 versus 0.97 for the MM analysis in the PRD. However, application of the respective diagnostic indices of the two methods does result in a different classification of 20% of the individuals in the PRD.

Conclusions:

It was found that the data based nonparametric LVM revealed additional insights about the manner in which infused insulin affects blood glucose concentration.

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Author Affiliations: [1]Department of Biomedical Engineering, University of Southern California, Los Angeles, California; [2]Medical University of Vienna, Endocrinology & Metabolism, Gender Medicine Unit, Vienna, Austria; and [3]Metabolic Unit, Institute of Biomedical Engineering, Italian National Research Council, Padova, Italy

Abbreviations: (CNT) controls, (GDM) gestational diabetes mellitus, (IM) insulin modified, (IVGTT) intravenous glucose tolerance test, (LVM) Laguerre based Volterra model, (MM) minimal model, (PRD) population at risk of developing diabetes, (T2DM) type 2 diabetes mellitus

Keywords: diabetes risk, intravenous glucose tolerance test, minimal model, nonparametric volterra model

Corresponding Author: David Z. D'Argenio, Ph.D., Department of Biomedical Engineering, 1042 Downey Way/DRB 154, University of Southern California, Los Angeles, CA 90089; email address dargenio@bmsr.usc.edu

Introduction

Type 2 diabetes mellitus (T2DM) is an emerging threat to public health worldwide, with symptoms that are not easily discernible and multiple long-term surreptitious pathological effects, including many life-threatening complications.[1] This creates an urgent need for reliable tests that can assist clinical diagnosis at the early stages before the damage becomes irreversible. This important task can be facilitated by the use of advanced mathematical/computational models of the dynamic relationship between insulin and glucose concentration.[2] Although blood glucose concentration is influenced by a multitude of physiological variables other than insulin, we posit that its causal relationship to infused insulin can provide reliable diagnostic information because of its cardinal importance in glucose homeostasis.

Since the pioneering work of Bolie[3] and Ackerman and coauthors,[4] modeling studies of the insulin–glucose relationship have mainly utilized parametric models described by differential equations. Among them, the minimal model (MM) of glucose disappearance[5] has been the most widely used to interpret data from the intravenous glucose tolerance test (IVGTT). Subsequently, to increase the dynamics of the test and allow more accurate parameter estimation, an infusion of insulin was added to the IVGTT protocol; this test has been termed insulin-modified (IM) IVGTT.

Parameters of the MM, including those representing insulin-dependent and insulin-independent components of glucose utilization, are typically estimated using the measured plasma glucose and insulin concentrations from individual subjects via nonlinear least-squares methods.[6] Hierarchical population methods, including Bayesian approaches, have also been used for estimation of MM parameters.[7–10] While parameters derived from the MM have been explored for their clinical importance with considerable success, limitations of the MM model have also prompted the introduction of other parametric model extensions.[11–16]

Nonparametric modeling approaches have also been explored, including artificial neural networks,[17] probabilistic models,[18] and Volterra models.[19,20] However, their utilization for clinical studies has been hindered by the perception that they are not amenable to physiological interpretation. Since this perception is only partly deserved, we explore in this article the possibility of utilizing a certain type of nonparametric model in conjunction with IM-IVGTT data for clinical diagnostic purposes and also investigate whether this nonparametric approach provides additional information about insulin's regulation of glucose that is not available from the MM analysis.

This article presents a comparative study between parametric (MM using population estimation) and nonparametric (Volterra) models used for the analysis of IM-IVGTT in a population of subjects at risk for developing T2DM. The population studied is women who exhibited gestational diabetes mellitus (GDM), in whom the signs detected during pregnancy are predictive of 50–70% later maternal T2DM.[21–23] Thus, the ability to accurately diagnose the level of impairment of glucose utilization in these women, representative of a wider category of subjects at high risk for T2DM, may help in identifying those prone to develop the overt disease. The results presented in this article demonstrate the feasibility of nonparametric modeling for this purpose and offer some physiological interpretation that can be used for potential clinical benefit.

Methods

Participants

A total of 125 women with prior GDM [population at risk of developing diabetes (PRD)] and 39 women with normal pregnancy [control subjects (CNT)] were recruited from the outpatient department of the University Clinic of Vienna. Their clinical and anthropometric characteristics, the rationale of the study protocol, and ethical committee approvals have been reported elsewhere.[23] The mean age and body mass index of the PRD were 32 ± 6 years and 25 ± 6 kg/m^2, while the corresponding values of the CNT were 33 ± 5 and 27 ± 5, respectively.

Insulin-Modified Intravenous Glucose Tolerance Test Protocol

All women were tested 8 to 10 weeks postpartum. Blood samples were taken at 3, 4, 5, 6, 8, 10, 14, 19, 22, 27, 30, 35, 40,

50, 70, 100, 140, and 180 min after intravenous glucose injection (0.3 g/kg). Insulin infusion (1 min) of 0.03 U/kg was given at 20 min post-glucose injection. Plasma glucose and insulin were measured using an automated glucose analyzer and radioimmunoassay method, respectively. For nonparametric modeling, the glucose and insulin time series data were divided into two distinct phases: before and after the insulin injection, referred to as phase 1 and phase 2 data, respectively. The data segments for these two phases were subjected to distinct analysis via nonparametric modeling. In the parametric analysis, the data from both phases were analyzed together. All available data were used in the modeling analyses.

Modeling Methods

Parametric Minimal Model

The MM of glucose disappearance is described by the following two differential equations:

$$\begin{aligned} \frac{dg(t)}{dt} &= -p_1 \cdot g(t) - x(t)[g(t) + g_b],\ g(0) = D/V_G \\ \frac{dx(t)}{dt} &= -p_2 \cdot x(\mathrm{t}) + p_3 \cdot i(t),\ x(0) = 0 \end{aligned} \quad , \tag{1}$$

where $g(t)$ is the deviation of glucose plasma concentration from its basal value g_b (in mg/dl), $x(t)$ is the internal variable of insulin action (in min^{-1}), $i(t)$ is the deviation of insulin plasma concentration from is basal value i_b (in μU/ml) and is treated as a known input obtained by linear interpolation of the measured plasma insulin, p_1 (glucose effectiveness, often denoted S_G) and p_2 are parameters describing the kinetics of glucose *per se* and insulin action, respectively (in min^{-1}), and p_3 is a parameter (in $min^{-2}ml/\mu U$) related to insulin sensitivity. Initial condition $g(0)$ represents the glucose concentration above baseline immediately following the injection (D = 0.3 g/kg); V_G is glucose distribution volume (in dl). The diagnostic index from MM that is used as a measure of insulin action on glucose disappearance is referred to as the insulin sensitivity index; it is defined as $SI = p_3/p_2$ (in $min^{-1}/\mu Uml^{-1}$).

To estimate the model parameters, a population analysis approach was employed in which the parameters were treated as random variables and assumed to follow a lognormal distribution, thus constraining the distribution of all parameters to positive values. For each of the two groups, the complete data record from all women in that group were pooled to simultaneously estimate the mean and covariance of the population lognormal distribution, as well as the parameters of each individual participant. To estimate the population mean and covariance as well as the individual subject's parameters, the joint likelihood for all subjects in a group was maximized using the expectation-maximization algorithm with a sampling-based method to calculate the needed conditional means parameters for each individual. The maximum-likelihood expectation-maximization algorithm in the ADAPT 5 software implementing this approach was used in the analysis.[24] The model is parameterized in terms of p_1, p_2, SI, and V_G.

Nonparametric Volterra Modeling

The nonparametric modeling approach seeks to estimate a hierarchy of kernel functions $\{k_0, k_1, k_2,\ldots\}$ of a Volterra model of the appropriate order that map the epoch of input (insulin) values onto the present value of the output (glucose) through a hierarchy of convolutional functional of various nonlinear orders:[25]

$$g(t) = k_0 + \Sigma\ k_1(\tau)\ i(t-\tau) + \Sigma\ \Sigma\ k_2(\tau_1,\tau_2)\ i(t-\tau_1)\ i(t-\tau_2) + \ldots\ , \tag{2}$$

where summation symbol Σ sums over all values of lags $\{\tau,\tau_1,\tau_2,\ldots\}$ of the kernel "memory" and replaces the integration symbol of the original mathematical expression of the Volterra model for sampled data. The mathematical foundation of the discretized Volterra model is the Weierstrass theorem stipulating that a continuous function of many variables can be approximated to any desired accuracy by a multinomial expression of these variables (the variables in this case are the past epoch values of the input). It is evident in **Equation (2)** that all the linear terms (following constant term k_0) form a convolution that is the general input–output relation for all linear time-invariant systems (i.e., equivalent to the "particular solution" of any linear differential equation with constant coefficients). The estimation of the Volterra kernels was accomplished by making this mapping as accurate as possible according to a least-squares criterion.[25]

The relative advantage of the nonparametric approach is that it does not require the postulation of a particular parametric model form (such as the MM or other parametric models in the field) and can be extended to dynamic nonlinearities. Its relative limitation is that the estimation of the kernels requires adequate input–output data, depending on the dynamic characteristics of the system and, most critically, on whether nonlinearities are included in the model.[26] In this particular application, it was found that the available IM-IVGTT data were able to support only the estimation of a first-order Volterra model (i.e., the best linear approximation of the actual insulin-to-glucose causal relationship), which was obtained by use of a Laguerre expansion of the Volterra kernel.[27]

In order to perform the estimation of the first-order Volterra kernel of the nonparametric input–output model, we must first interpolate the insulin measurements using Laguerre functions to generate time-series data every 1 min. We further assume that, prior to the insulin injection; the glucose concentration is relaxing exponentially under the influence of the normal processes of insulin-independent uptake and clearance of glucose. This allows the estimation of the exponent of this exponential relaxation process, along with the initial value of glucose phase 1 data and the basal glucose value, using least-squares fitting of the phase 1 glucose data. The assumption of exponential glucose relaxation prior to insulin injection is consistent with the first equation of the MM when there is no insulin action. The extrapolated values of this estimated exponential function were subsequently subtracted from the phase 2 glucose data in order to remove the insulin-independent portion of the phase 2 measurements:

$$g_r(t) = g(t) - g_0\, exp(-p_1 t). \tag{3}$$

The observed changes in the residual glucose phase 2 data were viewed as dependent on the insulin injection and, therefore, can be used for the estimation of the nonparametric input–output (insulin-to-glucose) model:

$$g_r(t) = k_0 + \Sigma\, k_1(\tau)\, i(t - \tau), \tag{4}$$

where k_0 is a constant offset and $k_1(\tau)$ is the first-order Volterra kernel. In the proposed methodology, we use phase 2 glucose residual $g_r(t)$ as the output variable and, as input the variable, $i(t) = I(t) - i_b$, where $I(t)$ denotes the insulin measurements and i_b denotes the basal values of insulin that were estimated as $i_b = \{I(0) + I(180)\} / 2$. For the estimation of first-order kernel $k_1(\tau)$ of this nonparametric model, we employ a Laguerre expansion of the kernel on two Laguerre basis functions $\{b_1, b_2\}$:

$$k_1(\tau) = c_1\, b_1(\tau) + c_2\, b_2(\tau), \tag{5}$$

where the Laguerre basis functions were defined for the optimal value of the Laguerre parameter alpha.[25–27] The latter is selected through a search procedure that seeks to minimize the mean-square error of the model prediction. An illustrative example of a pair of Laguerre basis functions is shown in **Figure 1**. By substituting **Equation** (**5**) into **Equation** (**4**), the glucose residual values can be expressed as

$$g_r(t) = k_0 + c_1\, v_1(t) + c_2\, v_2(t), \tag{6}$$

where

$$v_j(t) = \Sigma\, b_j(\tau)\, i(t - \tau)\ (j = 1,2). \tag{7}$$

Kernel expansion coefficients $\{c_1, c_2\}$ can be estimated from **Equation** (**6**) through linear regression, since variables $\{v_1(t), v_2(t)\}$ can be computed from **Equation** (**7**). The kernel estimate is constructed with the expansion coefficient estimates using **Equation** (**5**).

We note that the number of free parameters is the same (three) for the parametric and nonparametric models. For the latter, the free parameters are the two coefficients of the Laguerre basis functions that are used for the expansion of the first-order kernel and the constant zeroth-order kernel in **Equation** (**6**). Therefore, the nonparametric approach

offers different "structural flexibility" for the model using the same number of free parameters during model estimation. This implies that the two types of models are comparable in terms of fitting a training set of data but offer distinct insights into the system dynamics.

The relationship between the parametric and nonparametric approach can be explored by seeking the equivalent nonparametric Volterra model of the parametric MM, using either analytical methods or computational methods based on simulations with broadband insulin inputs.[19,25] The analytical methods yielded the following expression of the first-order Volterra kernel of the MM:

$$k_1(t) = -g_b \frac{p_3}{p_2 - p_1} [e^{-p_1 t} - e^{-p_2 t}]. \quad (8)$$

Equation (8) provides the rigorous means for comparing (in the first order) the parametric and the nonparametric modeling results. The same can be done in the second (or higher) order if data of sufficient length were available for the reliable estimation of the second-order kernel. Since the second-order kernel estimation can be accomplished via two-dimensional expansion on the same Laguerre basis, three additional free parameters would be required for inclusion of this kernel in the nonparametric model and four additional parameters for the inclusion of a cross-kernel accounting for the second-order interactions between insulin and glucose.[25] Therefore, the number of required data samples is approximately tripled for the second-order model. Hence, in this application, we were limited by the available IM-IVGTT data to a first-order insulin-to-glucose Volterra model:

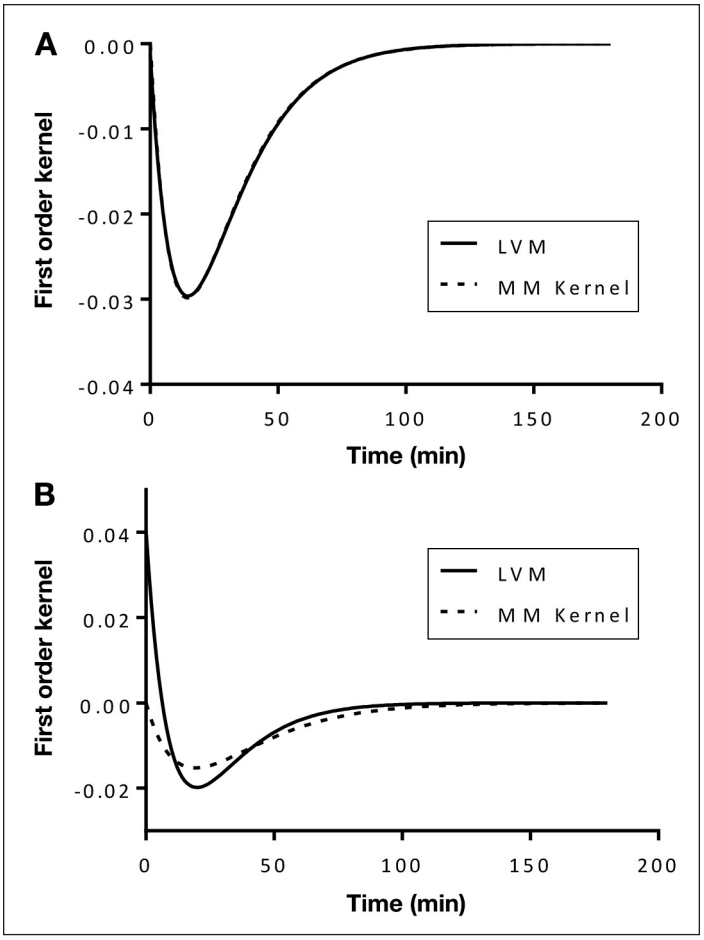

Figure 1. Illustrative kernel estimates using the nonparametric LVM approach (solid lines) and the parametric MM kernel fit of **Equation (8)** (dashed lines). **(A)** Entirely negative kernel, consistent with the mathematical constraints of the MM. **(B)** Kernel with large early positive region.

$$g(t) = g_0\, e^{-p_1 t} + \Sigma\, k_1(\tau)\, i(t - \tau) + g_b\ . \quad (9)$$

Results

Glucose and Insulin Response to Insulin-Modified Intravenous Glucose Tolerance Test

Figure 2 shows the mean and standard deviation of the measured plasma glucose (**Figure 2A**) and insulin (**Figure 2B**) concentrations for all PRD (n = 125) and CNT (n = 39). Following intravenous bolus administration of glucose and throughout phase 1, mean plasma glucose concentrations (**Figure 2A**) in PRD remain higher than those in CNT. After the insulin infusion at 20 min, the mean glucose concentrations of PRD continue to exceed that in CNT until approximately 100 min, following which the mean concentrations in the two groups are similar. **Figure 2B** shows that the mean insulin concentrations in PRD are lower than those in CNT early in phase 1. However, in phase 2, the mean insulin levels in PRD are higher than those in CNT (falling less rapidly than those in CNT from a similar peak), even though the phase 2 mean glucose concentrations in PRD continue to exceed those in CNT. The insulin concentrations in the two groups return to a similar level by the end of the protocol.

A complete data record for one individual from CNT is shown in **Figure 3A**, illustrating the time course of the glucose–insulin response following the initial glucose bolus and subsequent insulin infusion. The data for the two phases of the response in this individual are illustrated separately in **Figure 3B** (phase 1) and **Figure 3C** (phase 2).

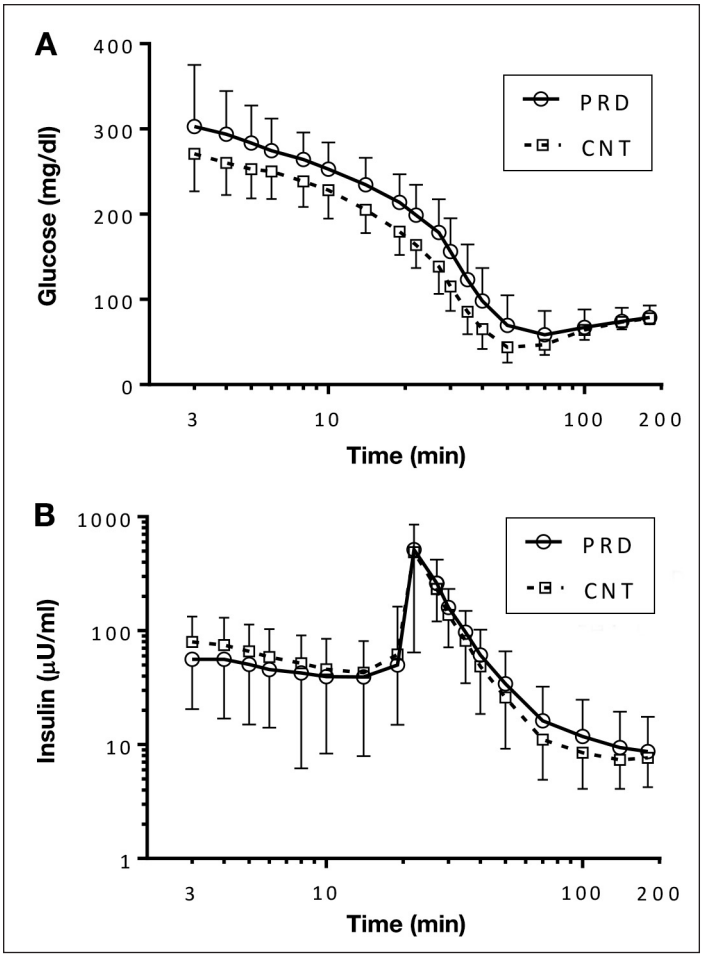

Figure 2. (A) The mean and standard deviation of glucose concentrations in PRD (solid line) and CNT (dashed line) groups. The abscissa is plotted on a log scale to illustrate the differences in glucose between the two groups during the first 60 min of the protocol. **(B)** The mean and standard deviation of insulin concentrations in PRD (solid line) and CNT (dashed line). Here the ordinate is also shown on a log scale to illustrate the differences in insulin concentrations between the two groups observed at the lower concentrations (below 100 μU/ml).

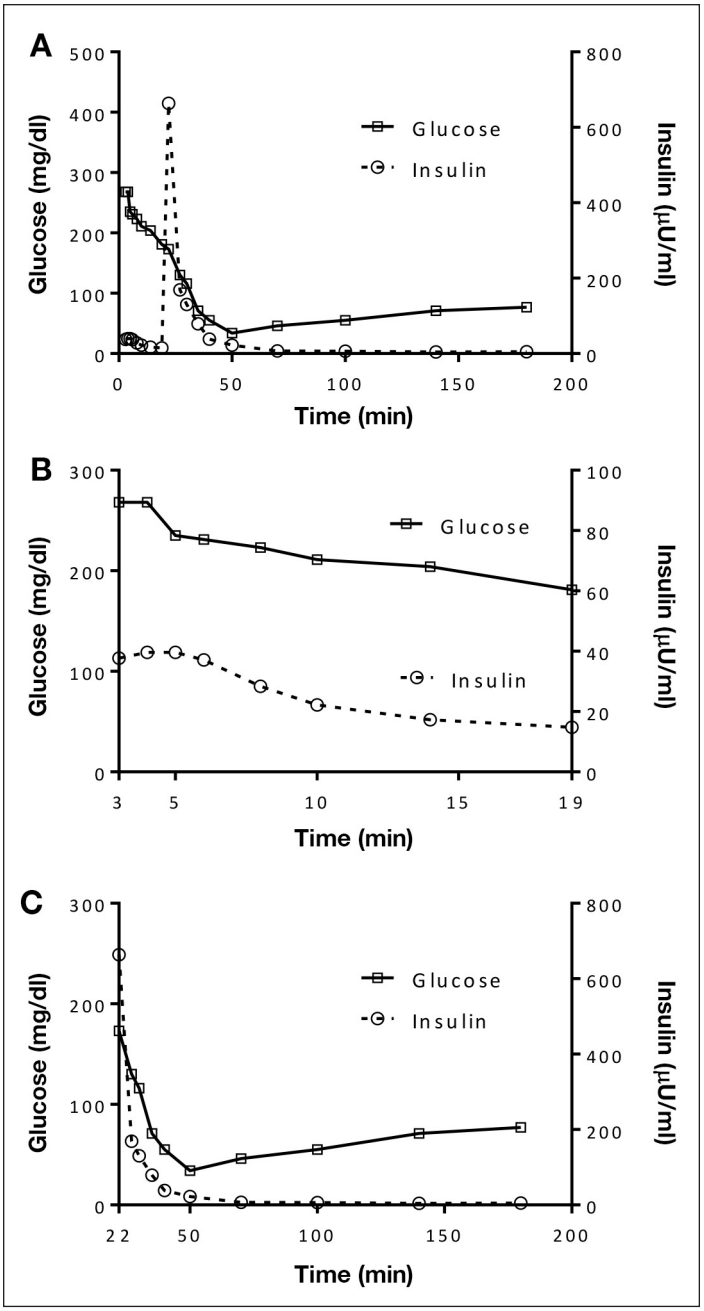

Figure 3. (A) The measured glucose (solid line) and insulin (dotted line) concentrations for a representative individual in CNT (these time series data are analyzed in parametric modeling). The **(B)** phase 1 and **(C)** phase 2 measured glucose (solid line) and insulin (dotted line) concentrations area also shown separately (the data in these panels are analyzed separately in nonparametric modeling; see Methods).

Estimation of the Nonparametric Infused Insulin-to-Glucose Kernel

Following the procedure outlined earlier, we can estimate the kernel of the first-order (linear) Volterra model that has input the infused insulin signal (potentially of arbitrary waveform) and output the insulin-dependent blood glucose concentration signal, $g_r(t)$. Two illustrative kernel estimates are shown in **Figure 1** that exemplify the cases of agreement (to the first order) between the nonparametric model and the kernel of the MM (**Figure 1A**) and significant deviation between the two models (**Figure 1B**). We observe that the equivalent first-order kernel of the MM [dashed line; from Equation (8)] is entirely negative by virtue of the mathematical constraints imposed by the structure of the MM model, while the kernel estimate obtained directly from the phase 2 IM-IVGTT data via the nonparametric approach (solid line) may exhibit an early positive portion followed by a negative portion (**Figure 1B**). It is physiologically expected that an insulin infusion will cause a reduction in blood glucose concentration. Thus, the aforementioned kernel ought to be negative to satisfy this requirement (whereby the constraint is imposed by

the structure of the MM). However, a biphasic kernel waveform (with an early positive and late negative portion) may still be physiologically meaningful if the total area of this kernel is negative, indicating that a basal infusion of insulin will cause a steady-state reduction in blood glucose concentration (after an initial transient, which may even take early positive values). This point deserves more attention in future studies. For now, we take the view that the data-based kernel may reveal a physiological characteristic of the system that is real, although counter-intuitive in the context of our present understanding of this system.

Figure 4 shows the areas of positive (A_p) and negative (A_n) portions of the first-order kernel estimates for all CNT and PRD. The mean (standard deviation) values of A_p were 0.0142 (0.0252) and 0.0447 (0.101) for CNT and PRD, respectively, indicating significantly higher values of A_p for PRD. The corresponding values of A_n were 1.09 (0.575) and 1.28 (1.39) for CNT and PRD, respectively, indicating no significant difference of A_n value for the two groups. Since normal subjects are expected to have zero or small A_p value, we may reasonably posit that the efficacy of insulin action on glucose concentration (and the widely used index of "insulin sensitivity") ought to be inversely related to the A_p value or to the difference A_p - A_n or to the ratio A_p/A_n. Therefore, a putative "diagnostic index" can be based on a threshold value of A_p above which the subject may be deemed as having reduced efficacy of insulin action on glucose. For example, if a threshold value of A_p = 0.05 is used as a putative "diagnostic index," then **Figure 4** shows that 2 CNT and 22 PRD were "diagnosed" with "abnormal" insulin action on glucose. We return to the issue of a diagnostic index based on the following nonparametric analysis.

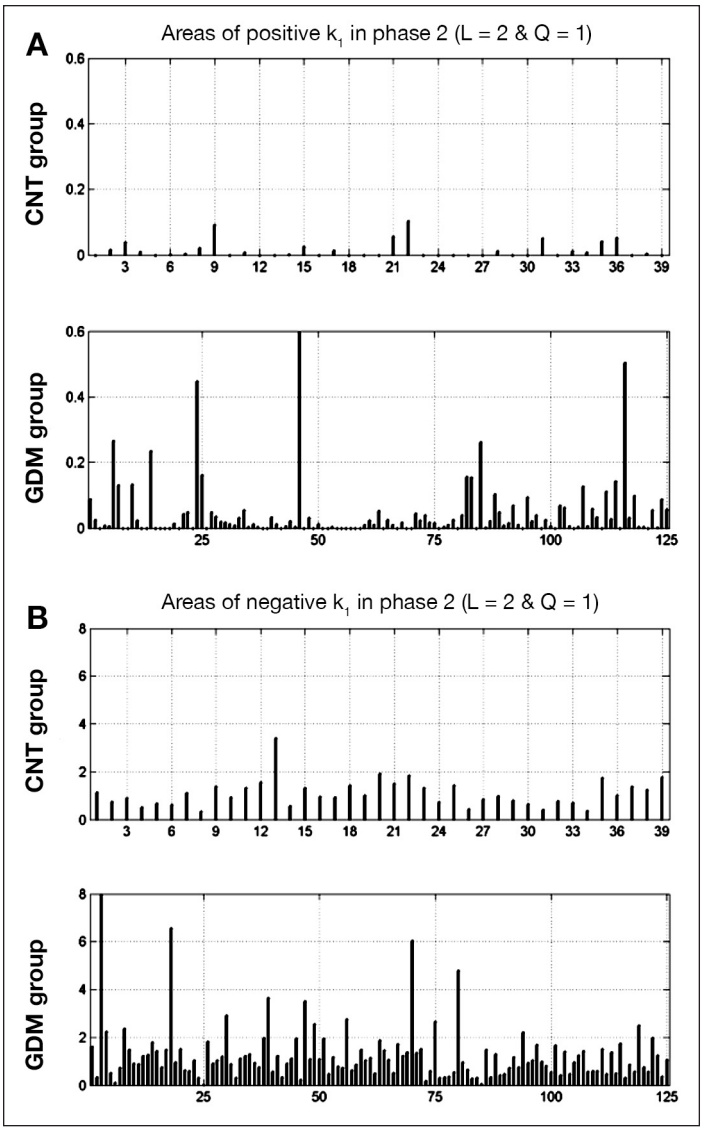

Figure 4. (A) Values of positive areas, A_p, in the first-order insulin to glucose kernel estimates obtained from phase 2 data of CNT (top) and PRD (bottom). **(B)** Values of negative areas, A_n , in the first-order insulin to glucose kernel estimates obtained from phase 2 data of CNT (top) and PRD (bottom).

Comparison of Nonparametric and Parametric Results

An illustration of the "goodness-of-fit" of the parametric and nonparametric model predictions is shown in the scatter plots of the model-predicted values of glucose versus the actual measurements for the phase 2 IM-IVGTT data segment. **Figure 5A** shows the scatter plots from the nonparametric analysis (CNT on the left and PRD on the right), while **Figure 5B** shows the corresponding plots obtained using the individual parameters from the parametric MM analysis. The computed r^2 values of the regression lines from the nonparametric analysis were 0.986 (CNT) and 0.991 (PRD), and those obtained from the parametric MM analysis were 0.956 (CNT) and 0.972 (PRD). To illustrate the time course of glucose predicted by the two modeling approaches, **Figure 6** shows the data and model predictions [nonparametric Laguerre-based Volterra model (LVM), solid line, and parametric MM, dashed line] for one individual from CNT (**Figure 6A**) and one individual from PRD (**Figure 6B**). Overall, the two modeling approaches each describe the time course of the measured glucose from both groups with equally good fidelity, with the nonparametric approach resulting in higher values of the measured versus predicted correlation coefficients compared with those from the MM parametric model.

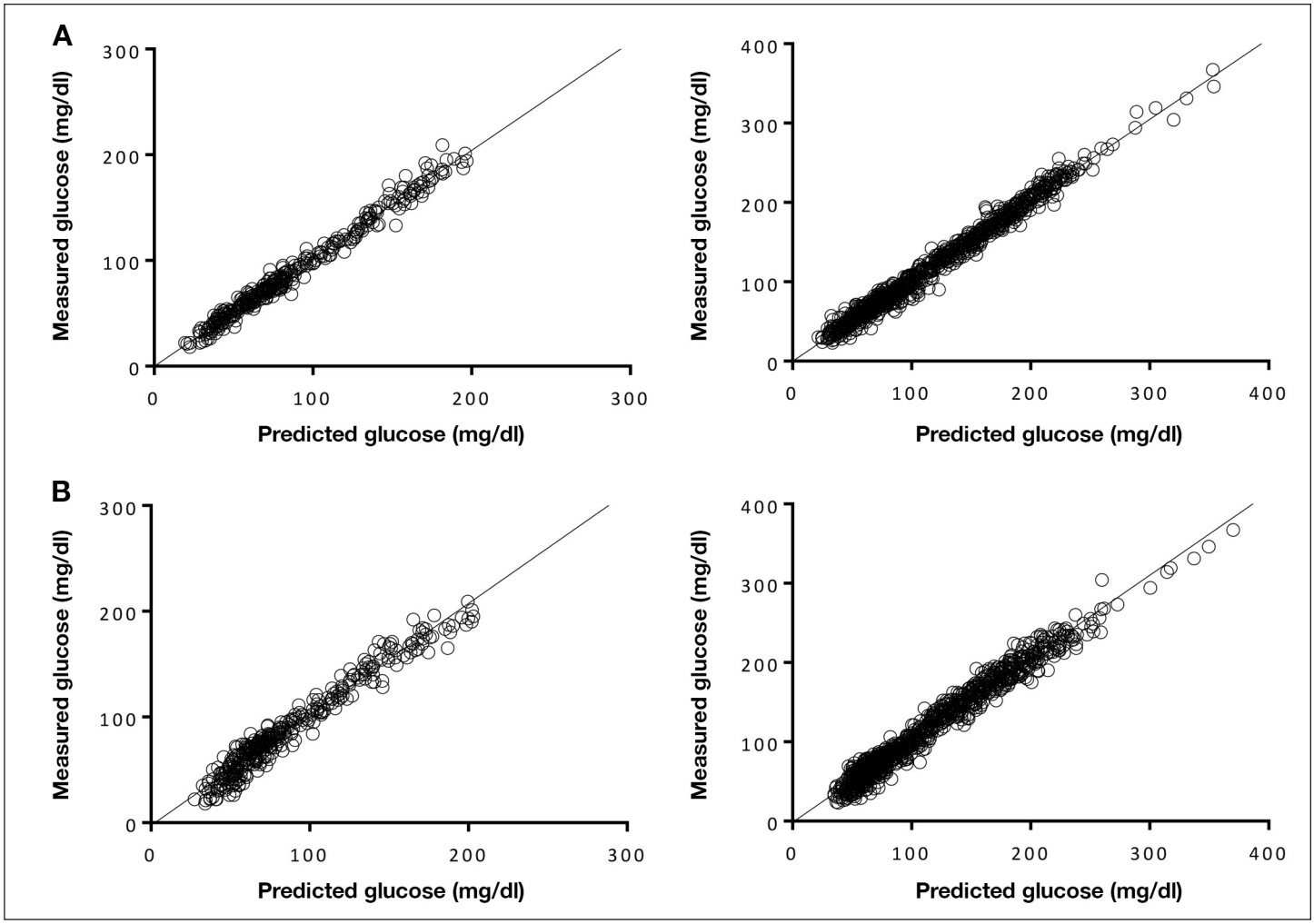

Figure 5. Scatter plots illustrating the "goodness of fit" of the nonparametric (top) and parametric (bottom) model predictions versus the actual phase 2 glucose measurements (CNT on left and PRD on right). The slopes and r^2 values of the displayed regression lines are as follows: nonparametric LVM - CNT slope = 1.02 and r^2 = 0.984 and PRD slope = 1.02 and r^2 = 0.986; parametric MM - CNT slope = 1.05 and r^2 = 0.956 and PRD slope = 1.04 and r^2 = 0.972.

The two modeling approaches can also be compared by examining their respective diagnostic parameters of insulin's action on glucose uptake: *SI* in the case of the parametric MM and A_p for the nonparametric Volterra model. The MM analysis resulted in estimates of *SI* ($min^{-1}/\mu Uml^{-1}$) for CNT of 0.000452 ± 0.000186 (mean ± standard deviation) and a significantly lower value of 0.000339 ± 0.000209 for PRD ($p < .01$; Mann–Whitney). For the LVM analysis, A_p was 0.0142 ± 0.0252 in CNT and had a significantly higher of 0.0447 ± 0.101 for PRD ($p < .02$; Mann–Whitney). **Figure 7A** shows the cumulative distributions of individual estimated *SI* values for CNT (dashed line) and PRD (solid line). The vertical dashed line corresponds to the median *SI* value obtained from pooling the *SI* estimates from both groups (0.000324 $min^{-1}/\mu Uml^{-1}$). Using this median value as a threshold (albeit arbitrary), we find that 70 of the 125 subjects (56%) in the PRD have a lower value of *SI* and presumably at greater risk for T2DM. The corresponding cumulative distributions of A_p obtained from the nonparametric Volterra analysis are also shown in **Figure 7B**, with the median value of A_p (0.00775) from both groups shown by the vertical dashed line. Using this median value as the threshold, 69 of the 125 PRD (55%) have a higher value of A_p, indicating they are at greater risk for T2DM. While these two methods show that essentially the same fraction of PRD is "at risk," a significant number of subjects were identified differently by the two methods. For example, 27 of the subjects who were identified as "at risk" by the MM analysis were classified as "not at risk" by the LVM analysis, while 26 subjects classified as "at risk" by LVM were classified as "not at risk" by MM. We also note that using the same median values indicated earlier for the 39 subjects in the CNT groups yields the following "at risk" results: 28% using *SI* from the MM analysis and 36% using A_p from the LVM analysis.

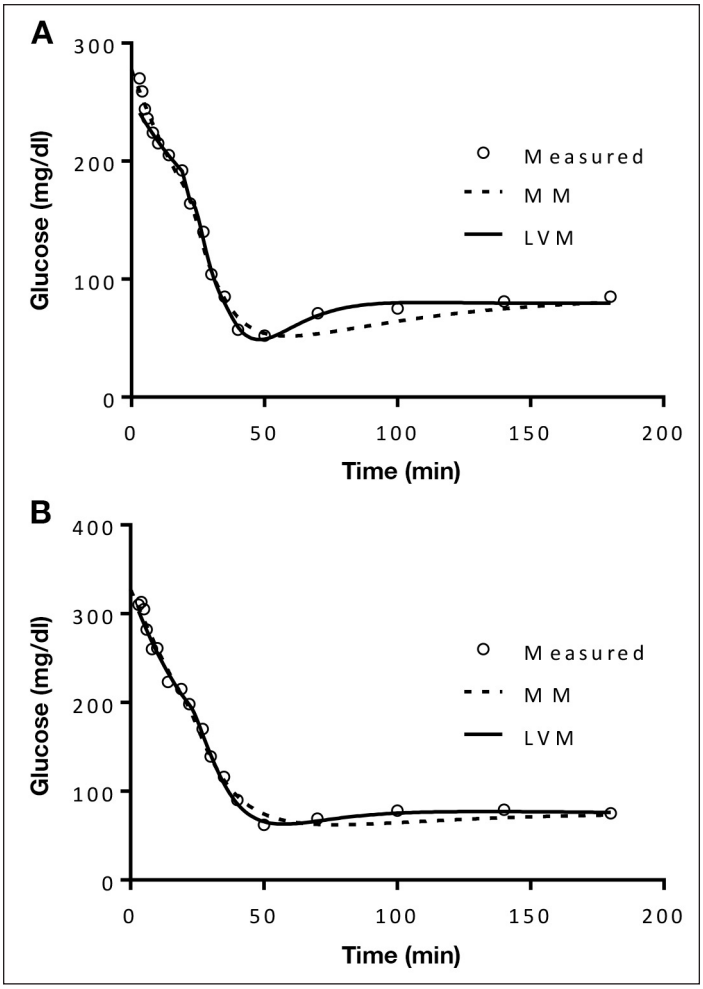

Figure 6. Illustration of the time course of glucose predicted by the two modeling approaches. The graphs show the data (open circles) and model predictions (nonparametric, solid line; parametric, dashed line) for **(A)** one CNT individual and **(B)** one PRD.

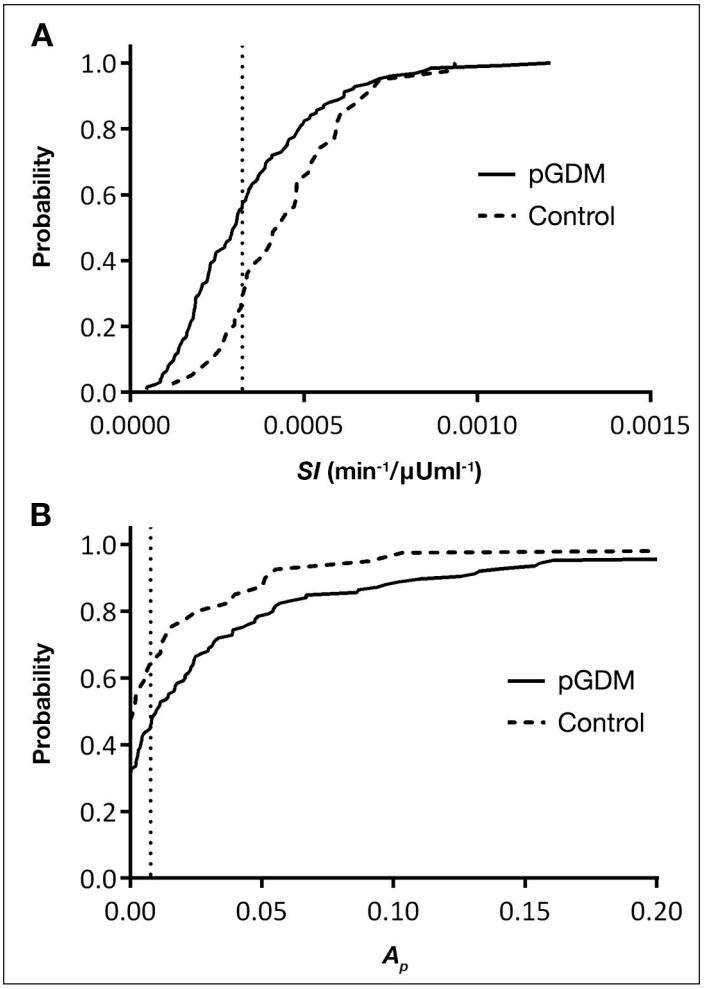

Figure 7. (A) The cumulative distribution of individual estimated *SI* values (parametric MM analysis) for CNT (dashed line) and PRD (solid line). The vertical dashed line corresponds to the median pooled *SI* value (0.00323 $min^{-1}/\mu Uml^{-1}$), with values of *SI* below the median designated as "at risk." **(B)** The corresponding cumulative distributions of A_p obtained from the nonparametric LVM analysis for CNT (dashed line) and PRD (solid line). The vertical dashed line corresponds to the median pooled A_p value (00775), with values of A_p above the median designated as "at risk."

Discussion and Conclusion

We presented the results of a comparative analysis of the response to an IM-IVGTT in a large group of women at risk for T2DM, using both the traditional parametric MM analysis as well as a novel nonparametric LVM method. It was shown that nonparametric LVM of the causal relationship between infused insulin and blood glucose concentration can be obtained from IM-IVGTT data (using only the phase 2 data segment following insulin infusion). This analysis reveals the precise pattern (i.e., the kernel) by which the insulin-to-glucose system weighs the infused insulin signal (input) to generate the glucose concentration signal (output).

Explicit analytical expressions of the equivalent nonparametric model of the MM have been derived. Thus, rigorous comparison of the two model forms is currently feasible. The nonparametric model separates the insulin-dependent from the insulin-independent components of the glucose measurements. The insulin-dependent component of the nonparametric model is defined by the estimated kernel, which occasionally exhibits an early region of positive values—unlike the equivalent kernel of the parametric MM that must be entirely negative according to **Equation (8)**. This fact indicates that the nonparametric model yields innovative insights in the description of the physiological mechanisms of the insulin-to-glucose system. Several new indices of the efficacy of infused insulin action upon blood glucose concentration are also available through the nonparametric LVM analysis, including the positive kernel area A_p.

Since the number of free parameters is kept the same for the two types of models and robust estimation methods exist (and have been demonstrated) for both approaches, the parametric and nonparametric modeling methods are equally applicable in this problem area. The key remaining question is the relative value of the distinct insights into the system dynamics offered by the two methods. The answer to this question pertains to the specific objectives of each study. Analysis of longitudinal data may provide this answer with regard to diagnosis and prognosis.

In conclusion, both the parametric MM and nonparametric LVM describe the glucose concentration data in each group with good fidelity. The measured versus predicted r^2 values from the LVM and MM analyses were similar in both PRD (0.99 versus 0.97, for the LVM and MM analyses) and CNT (0.98 versus 0.96, for the LVM and MM analyses). This result will require further evaluation from other larger IM-IVGTT studies. Of great potential significance, the respective diagnostic indices for the two methods (SI from the MM and A_p from LVM), which describe different aspects of the same important pathophysiological mechanism, each identified some different individuals from PRD as exhibiting higher risk for developing diabetes in the future. This interesting finding needs, however, to be evaluated based on the results from the longitudinal studies in these women that will become available in the future.

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