Nonlinear Modeling of the Dynamic Effects of Free Fatty Acids on Insulin Sensitivity

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Abstract This chapter presents a nonlinear model of the combined dynamic effects of spontaneous variations of plasma insulin and free fatty acids on glucose concentration in a fasting dog. The model is based on the general nonparametric modeling methodology that employs the concept of Principal Dynamic Modes (PDMs) to obtain a Volterra-equivalent nonlinear dynamic model with two inputs (insulin and free fatty acids) and one output (glucose) that are measured experimentally every 3 min in a fasting dog as time-series data over 10 hr. This model is deemed valid and predictive for all input waveforms within the experimental dynamic range. The obtained model is composed of two PDMs for each input and cubic Associated Nonlinear Functions (ANFs), in addition to two cross-terms. The waveform of the obtained PDMs offers potentially valuable interpretation of the implicated physiological mechanisms. The system nonlinearities are described, in turn, by the obtained ANFs. The evaluation of the overall model performance is facilitated by the use of specialized inputs, such as pulses or impulses. For instance, the use of insulin input pulses can yield estimates of "dynamic insulin sensitivity" (as the ratio of the steady-state glucose response to the input pulse amplitude) for various levels of free fatty acids. The obtained result indicates (in a quantitative manner) the widely held view that insulin sensitivity decreases with rising levels of free fatty acids. Furthermore, it indicates that this effect depends on the input insulin strength (dose-dependent insulin sensitivity). Drastic reduction of

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insulin sensitivity is predicted by the model above a critical level of free fatty acids for low-to-moderate values of plasma insulin. This result demonstrates the potential utility of the proposed modeling approach for advancing our quantitative understanding of the processes underpinning obesity and Type II diabetes.

1 Introduction

The multiple effects (direct and indirect) of insulin on blood glucose have been studied extensively in the context of diabetes mellitus, motivated by the need for improved diagnostic procedures and effective treatment of diabetic patients. Parametric/compartmental models (assuming the form of sets of differential and algebraic equations) have been developed for this purpose and seek to describe the causal effect of infused insulin on blood glucose concentration—typically in connection with specific testing protocols, such as the Glucose Tolerance Test [1, 2]. More complex models that take into account the effects of glucagon and free-fatty acids have also been proposed [3, 4]. Nonparametric data-based modeling has also been suggested for this purpose using variants of the Volterra-Wiener approach to input-output system modeling [5, 6]. Our group has pioneered the Laguerre-Volterra network [5] and the Principal Dynamic Modes (PDMs) approaches [6], which both utilize Laguerre expansions of the system kernels. The nonparametric approach has the advantage of being true to the data and not requiring a priori postulation of a specific model form (e.g. differential equations). The PDM-based approach is used in the present study, which seeks to elucidate the dynamic effects of free fatty acids (FFAs) on insulin-glucose interactions. This subject is attracting increasing attention in the context of the relation between obesity and diabetes [7, 8]. Elevated FFAs have been shown to increase plasma glucose and hepatic glucose output, as well as increase peripheral and hepatic insulin resistance in a dose-dependent manner [9–11].

Thus, FFAs are viewed as a major link between obesity and insulin resistance or Type 2 diabetes. In the liver, FFAs cause insulin resistance by inhibiting insulin suppression of glycogenolysis. FFAs also promote glucose-stimulated insulin secretion by the pancreatic beta cells. The latter is viewed as a possible reason preventing the development of Type 2 diabetes in most obese insulin-resistant people. FFAs have also been shown to facilitate inflammatory processes and, therefore, may contribute to the pathogenesis of coronary artery disease [8, 9]. Dysregulation of FFA metabolism may cause insulin resistance because of preferential oxidation of FFA over glucose [10].

In the present study, we examine how spontaneous variations in plasma insulin and FFA (viewed as the "input" variables) jointly affect the level of blood glucose (viewed as the "output" variable) under fasting conditions. To achieve this goal, we quantify the dynamic effects of changes in the two input variables upon the output variable via the Volterra-equivalent PDM-based model estimated from

actual experimental time-series data collected in a fasting dog. The obtained model has predictive capability for arbitrary inputs that remain within the experimental dynamic range. The model is *dynamic* (i.e. it predicts the present value of output glucose concentration on the basis of the entire epoch of insulin and FFA input values) and *nonlinear* (i.e. the effects of input changes upon the output are not additive and do not scale proportionally). The employed modeling methodology is generally applicable to nonlinear dynamic systems and robust in the presence of measurement noise or systemic interference. In addition, this methodology is applicable to short data-records, thereby rendering feasible the estimation of the model with limited number of experimental measurements [12].

The objective of this chapter is to demonstrate the efficacy of the proposed approach with experimental data from a fasting dog and to provide some novel (albeit preliminary) physiological insight into the joint causal effects of plasma insulin and FFA variations on plasma glucose. This insight is offered in the quantitative form of a predictive model that may be used to test rigorously postulated hypotheses within the dynamic range of the available data. It is hoped that the efficacy of this approach will enable fruitful applications in this physiological domain.

2 Methods

Experimental time-series data of plasma glucose, insulin and free fatty acids (FFAs) were collected in a healthy male mongrel dog every 3 minutes over a 10-hour period (200 time-series samples). The data were collected under fasting conditions of spontaneous activity and the animal was judged to be in good health. The University of Southern California Institutional Animal Care Committee approved all surgical and experimental procedures. Details of the experimental procedures can be found in [6].

The collected time-series datasets are shown in the left panel of Fig. 1 and their mean (standard deviation) values are: 81.14 (2.39) mg/dl for glucose; 44.85 (13.81) pM for insulin; and 0.52 (0.07) mM for FFA. Since we are interested in studying the dynamics of this system over time horizons longer than 15 min, we perform moving averaging with a five-point Hanning window (equivalent to low-pass filtering below 0.1 cycles/min) that removes the very rapid variations of the data. We analyze the de-meaned filtered data that have standard deviations (SDs) of 1.84 mg/dl for glucose; 9.68 pM for insulin; and 0.06 mM for FFA, and are shown in the right panel of Fig. 1. The SDs of the filtered data are smaller because sharp peaks are smoothed, especially in the insulin data. We deem this acceptable because we focus on capturing the system dynamics over cyclical changes with periods longer than 10 min per cycle. The random and broadband nature of these datasets is evident. It is difficult to discern visually any consistent correlation between the fluctuations of these signals—a fact that motivates the use of dynamic modeling of the data using our nonlinear methodology. The latter employs the

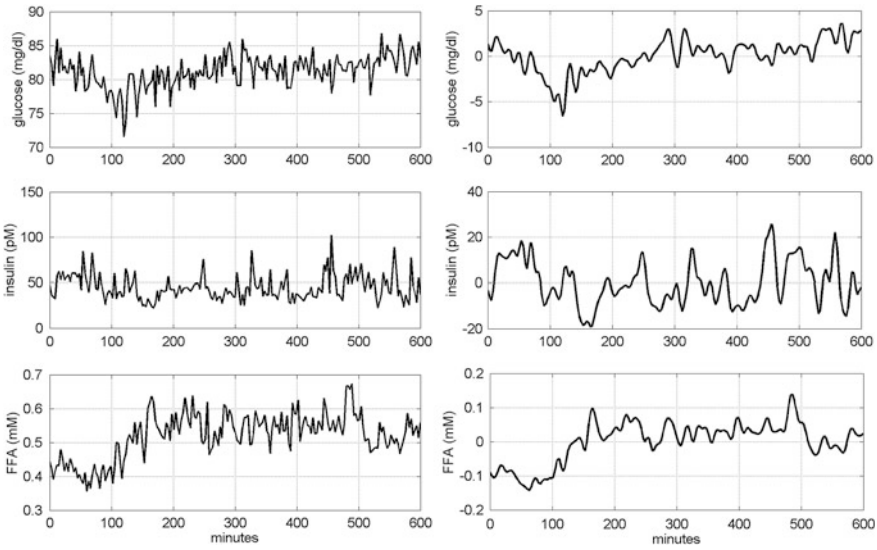

Fig. 1 *Left* the collected experimental time-series data of plasma glucose (*top panel*), insulin (*middle panel*) and free fatty acids (FFAs) (*bottom panel*) from a fasting dog at rest over 10 hours (sampling every 3 min). *Right* the time-series data after mean subtraction and low-pass filtering

concept of Principal Dynamic Modes (PDMs) to obtain a model with two inputs (insulin and FFA) and one output (glucose). The obtained Volterra-equivalent PDM-based nonlinear dynamic model of the input-output relationship does not require a priori model postulates and yields data-based models that have general predictive capability for arbitrary input waveforms within the experimental dynamic range. The employed modeling methodology is summarized in Appendix I. Details can be found in [12].

3 Results

Using the PDM-based modeling methodology outlined in Appendix I with three Laguerre basis functions having alpha parameter 0.4 for the insulin input and 0.8 for the FFA input (determined via a search procedure minimizing the prediction error), we obtain the model shown schematically in Fig. 2 that has two PDMs for each input and two cross-terms (one between the 1st PDM of insulin and the 2nd PDM of FFA, and the other between the 1st and 2nd PDM of FFA). The computed PDMs are shown in Fig. 3 in the time-domain. Each PDM can be viewed as the impulse response function of a linear filter that transforms the respective input epoch into a state variable (the PDM output) that has a contemporaneous nonlinear relationship with the output variable described by the respective ANF [12]. The computed ANFs are shown in Fig. 4, plotted over the abscissa range of ± 1 SD of

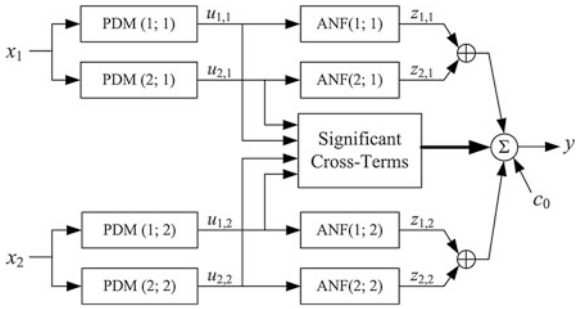

Fig. 2 Schematic of the PDM-based model, which is composed of two PDMs for each input (insulin and FFA deviations from the respective mean values) that can be viewed as impulse response functions of two linear filters receiving the respective input. Each PDM is followed by a static nonlinearity, termed Associated Nonlinear Function (ANF), which transforms the PDM output into an additive component of the model-predicted glucose output (deviation from its mean value). The model also includes the significant cross-terms that are selected on the basis of the statistical significance of their correlation with the output (see Appendix I). Two cross-terms were found significant in this system: one between PDMs of the two inputs (1st of insulin and 2nd of FFA) and the other between the two PDMs of the FFA input. The ordinate of the insulin PDMs is in mg/dl per pM, and in mg/dl per mM for the FFA PDMs. The abscissa of the PDMs is in min. The abscissa and ordinate of the ANFs are both in mg/dl

the PDM output that corresponds to the experimental data. The abscissa of the ANF plot is the PDM output and the ordinate is the corresponding component of the model output prediction (glucose) at the same time instant. Figure 5 shows the PDM-based model prediction (after the initial transient of 120 min that is roughly equal to the system memory), along with the actual glucose-output. The normalized mean-square error of this model prediction is 21 %. We view this low prediction error (relative to what can be achieved with other methods) as validating the obtained model. The specific form of the obtained PDMs and ANFs is discussed in the following section with regard to plausible physiological interpretations.

The output equation of this two-input PDM-based model is:

$$G(t) = G_0 + f_{I,1}\left[P_{I,1} * I(t)\right] + f_{I,2}\left[P_{I,2} * I(t)\right] + f_{F,1}\left[P_{F,1} * F(t)\right] + f_{F,2}\left[P_{F,2} * F(t)\right] + \sum_{j,k} C_{j,k}(t)$$

where * denotes the convolution operation, $G(t)$, $I(t)$ and $F(t)$ denote the demeaned time-series data of glucose, insulin and FFA respectively, f denotes the cubic ANF and P denotes the PDM for the input and rank indicated in the respective subscript, G_0 is the model constant, and $C_{j,k}$ (t) denotes the significant cross-terms of the model (products of PDM outputs that have statistically significant correlation with the glucose-output signal)—in this model, the following cross-term combinations were found to be significant: ($P_{I,1}$, $P_{F,2}$) and ($P_{F,1}$, $P_{F,2}$). This model has 15 free parameters (12 ANF coefficients, 2 cross-term coefficients

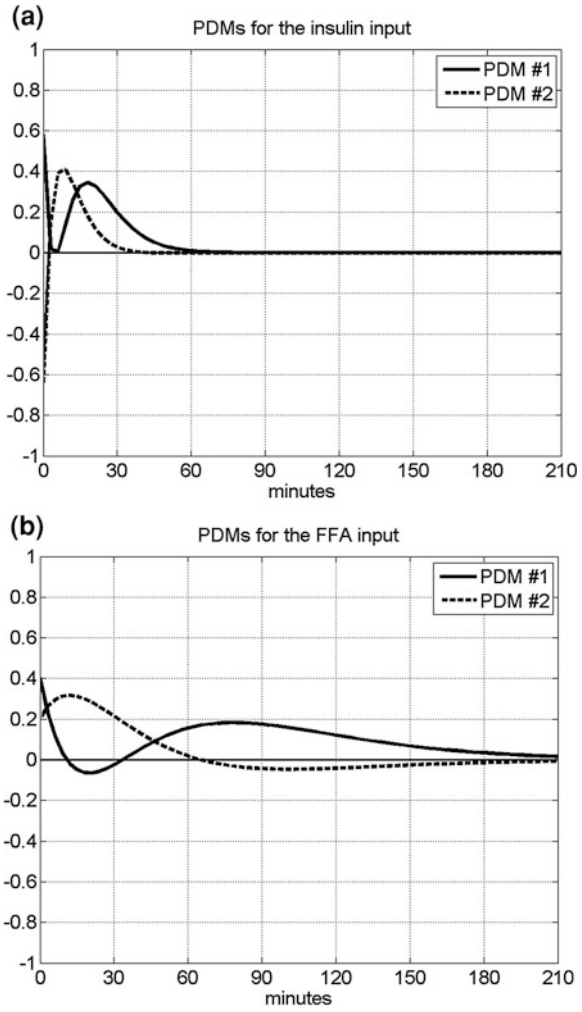

Fig. 3 The computed two PDMs for the insulin input (*left*) and the FFA input (*right*)

and the constant G_0). The PDMs are estimated separately from the kernel estimates via the Laguerre expansion technique (see Appendix I) that requires in this case the least-squares estimation of 28 free parameters (9 for the self-kernels of each of the two inputs, 9 for the cross-kernel and the constant). The available data (200 samples) are deemed adequate for the estimation of these parameters without risk of over-fitting.

Having obtained the PDM-based model, we can use it to advance our understanding of the dynamics of this system. Some discussion on plausible interpretations of the specific form of the obtained PDMs and the respective ANFs are provided in the following section. In this section, we illustrate the model prediction for specialized inputs (i.e. insulin impulse and FFA pulse) that can be evaluated against known physiology. We also explore one important aspect of the system

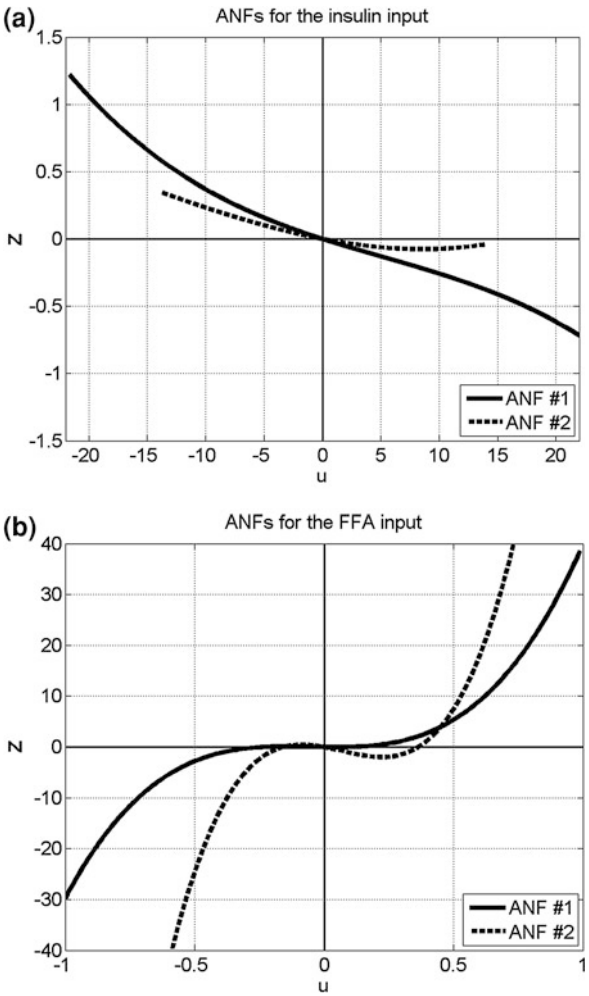

Fig. 4 The computed ANFs for the insulin input (*left*) and the FFA input (*right*)

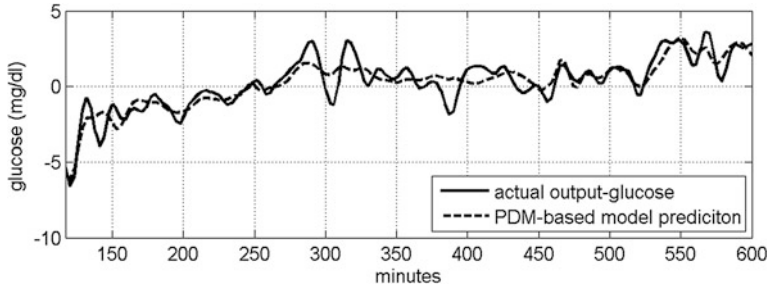

Fig. 5 The PDM-based model prediction of the output (*dashed line*) and the actual output-glucose data (*solid line*) after de-meaning and low-pass filtering. The resulting Normalized Mean-Square Error (NMSE) of this prediction is 21 %

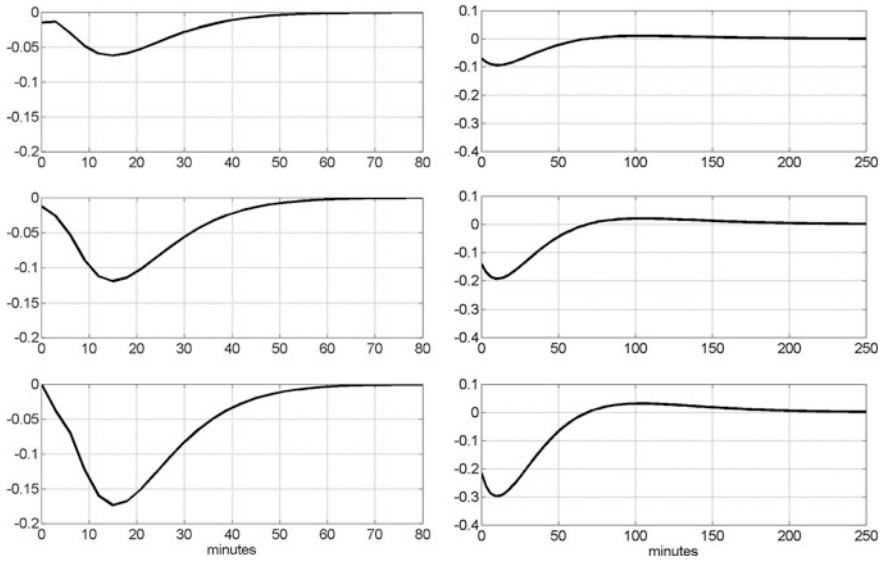

Fig. 6 *Left panels*, *top* to *bottom* the model-predicted glucose responses for three magnitudes of insulin impulses (0.5, 1 and 1.5 SD of the recorded insulin data). *Right panels*, *top* to *bottom* the model-predicted glucose responses for three levels of FFA impulses (0.5, 1 and 1.5 SD of the recorded FFA data). The units of glucose are mg/dl. Evidently, the FFA effect is much larger

dynamics that pertains to the notion of "dynamic insulin sensitivity" (DIS) by utilizing the predictive capability of the PDM-based model to compute the predicted glucose response to an insulin pulse input for a given level of FFA. The insulin and FFA values are deviations from the respective mean values of the experimental data (i.e. relative to the observed operating point of the system). The model predictions for three magnitudes of insulin impulses (0.5, 1 and 1.5 SD of the recorded insulin data) and three levels of FFA impulses (0.5, 1 and 1.5 SD of the recorded FFA data) are shown in Fig. 6 and suggest that glucose is reduced in a sub-linear manner in response to an increase of insulin (consistent with current view), and the glucose response to an FFA increase is biphasic exhibiting an early sub-linear reduction and a later phase of counter-regulation (after about 2 hr) where glucose is increased. The early phase of the glucose response to an FFA increase may be due to the reported facilitation of pancreatic beta-cell secretion (leading to an increase of insulin and subsequent reduction of glucose), whereas the late-phase counter-regulation may be due to the known inhibition of FFA to the insulin facilitation of glucose uptake by tissues and to the insulin inhibition of the processes of glycogenolysis and gluconeogenesis (both leading to glucose increase). It is posited from the different dynamic time-scales that the latter effect takes longer than the former.

As an illustration of the nonlinear interaction between the two inputs as they affect the glucose output, we show in Fig. 7 the model-predicted glucose responses to an insulin pulse input with amplitude equal to 1 SD of the experimental insulin data for four different levels of FFA equal to 0, 0.5, 1 and 1.5 SD of the

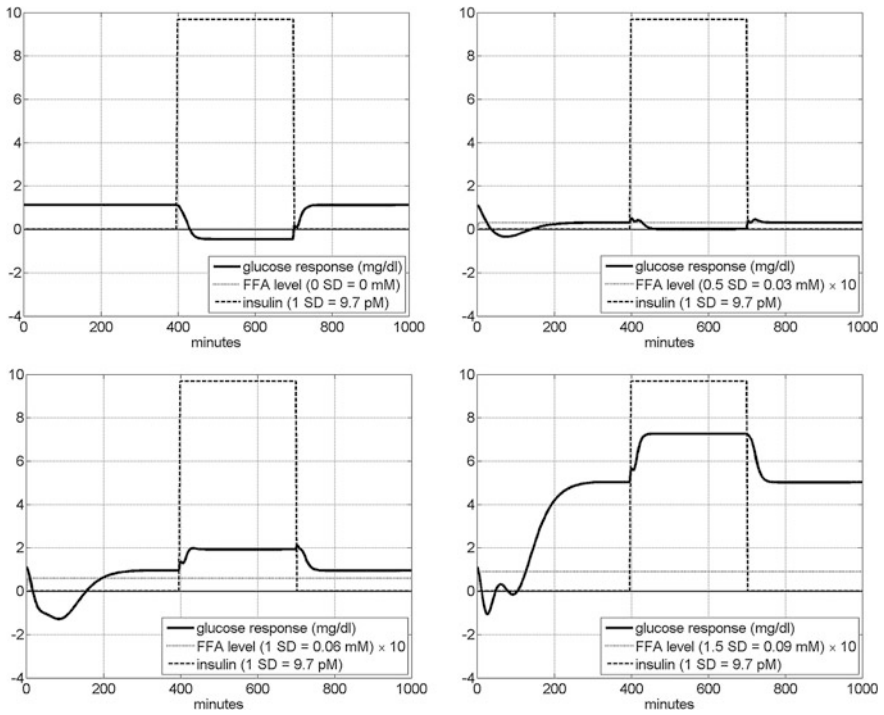

Fig. 7 The model-predicted glucose response in mg/dl to an insulin pulse input equal to 1 SD of the experimental insulin data (9.7 pM) for four different levels of FFA: 0 (*top left*), 0.5 (*top right*), 1 (*bottom left*) and 1.5 (*bottom right*) SD of the experimental FFA data. We observe that the glucose response to insulin is reversed from the normal (increase instead of decrease) for high levels of FFA. The early transient glucose response (reduction) to a non-zero FFA step input (prior to the application of the insulin pulse) is consistent with the response profile presented in Fig. 6

experimental FFA data. It is evident that the steady-state value of the glucose output (in response to the given insulin pulse input) is smaller for higher level of FFA and, surprisingly, it is reversed from the normal (increase instead of decrease) for high levels of FFA. This surprising result must be examined with controlled experiments in the future. The observed early transient glucose response (reduction) to a non-zero FFA step input is consistent with the response profile presented and discussed in Fig. 6.

The Dynamic Insulin Sensitivity (DIS) is defined as the ratio of the predicted steady-state glucose response to the corresponding amplitude of an insulin pulse input (for a given FFA level). The sign is inverted, so that normal DIS (i.e. reduction of glucose for raised insulin) takes positive values. Since the model is nonlinear (3rd order), the computed DIS values will generally follow a nonlinear (cubic) function of the insulin pulse amplitude and of the respective FFA level. These DIS nonlinear functions will be generally different for different operating points of the system.

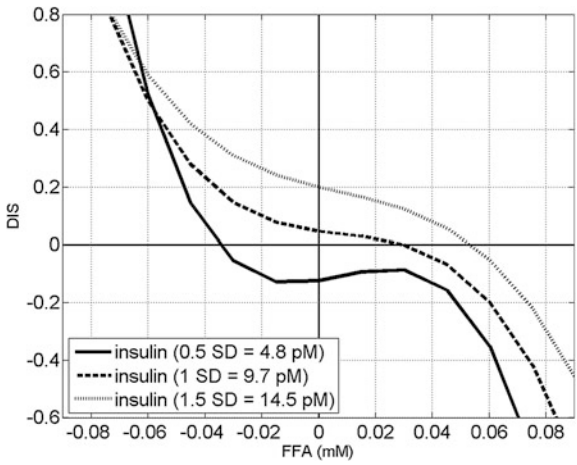

Fig. 8 The computed DIS curves as a function of FFA level for three amplitudes of the insulin input pulse (0.5, 1 and 1.5 SD of the experimental insulin data)

The obtained results of computed DIS values are shown in Fig. 8 for three amplitudes of the insulin input pulse (0.5, 1 and 1.5 SD of the experimental insulin data), plotted over constant FFA levels ranging from −1.5 to +1.5 SD of the actual FFA experimental data. It is evident in Fig. 8 that the DIS is reduced significantly for high FFA levels, with a critical soft-threshold value seen around 0.05 mM. This effect is sharper for lower insulin values. Additional discussion on this result and the relation of DIS to the widely used "insulin sensitivity" (S_I) parameter associated with the "Minimal Model" of the Glucose Tolerance Test is provided in the following section.

Using the model output equation, we can remove, in principle, the dependence of the DIS estimate from the specific operating point of the experimental data (as defined by the mean values) by replacing the deviations from the mean with the data value prior to de-meaning. It can be shown that the 3rd-degree coefficients are not affected, although the ANF coefficients of degree lower than 3rd and the constant term are affected by the mean values. The PDMs remain the same.

As a final illustration of the capability of the predictive model in enhancing our understanding of the system functional characteristics, we plot in Fig. 9 the steady-state value of the glucose output in response to an insulin input pulse for various amplitudes ranging from −2 to +2 SD of the experimental insulin data. This steady-state insulin-glucose relationship is nonlinear and varies for different levels of FFA, as demonstrated in Fig. 9 for five different levels of FFA. It is seen that the insulin-glucose relation exhibits only small changes when the FFA levels remain close to the baseline value (e.g. from −0.05 to 0.05 mM), but changes drastically when the FFA levels take larger values (e.g. ±0.1 mM). In this regard—i.e. high levels of FFA result in drastic reduction of insulin sensitivity (rise of insulin resistance), as indicated by the slope of these curves. It is also seen that increased levels of insulin generally improve the insulin sensitivity (by making the slope of

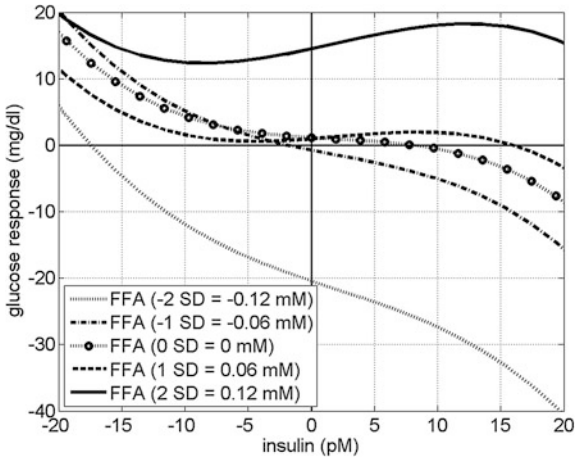

Fig. 9 The computed steady-state insulin-glucose curves (over ±2 SD of the experimental insulin data) for various FFA levels. Insulin resistance is highest for the highest FFA level and is generally reduced as the insulin values increase

these curves more negative) for all FFA levels. A critical value of insulin around 15 pM (i.e. about 1.5 SD of the experimental insulin data) emerges from the results in this regard (see Fig. 9).

4 Discussion

The PDM-based model of Fig. 2 provides insights into the dynamic interrelationships between insulin, FFA and glucose variations during spontaneous fasting conditions in a dog. If analogies hold in human subjects, these insights may have important implications for the in-vivo regulation of these variables in diabetics.

The waveforms of the obtained two PDMs and ANFs for the insulin input indicate a "glucoleptic" effect (i.e. glucose reduction for insulin increase) for both PDMs—with the 1st PDM exhibiting faster dynamics. The 1st ANF (see Fig. 4) exhibits a symmetric and mildly supralinear response characteristic, but the 2nd ANF is asymmetric indicating larger effect for negative PDM output. These findings are consistent with existing qualitative physiological knowledge regarding the process of insulin-facilitated glucose uptake by muscle, adipose and organ tissues, as well as inhibition of the processes of glycogenolysis and lipolysis, all of them leading to reduction in plasma glucose, as described quantitatively by the two glucoleptic PDM-ANF cascades. However, it is not currently known which set of those glucoleptic processes is faster and thus corresponds to the 1st PDM. This question should be resolved with specialized experiments in the future.

The waveforms of the obtained two PDMs for the FFA input indicate mainly glucogenic characteristics (i.e. positive PDM values), probably related to the known inhibitory effects of FFA on insulin facilitation of glucose uptake and the process of glycogenesis. Specifically, the 1st FFA PDM exhibits early positive values indicating immediate rise of glucose in response to an impulsive rise of

FFA (as long as it is of adequate size to exceed the observed dead-zone—which is not the case in the illustration of Fig. 6). The positive values of this PDM rapidly diminish and become slightly negative between 10 and 30 min after input onset. Subsequently, the values of this PDM rise to reach a peak in ∼70 min and remain positive for over three hours. This late positive "hump" is responsible for the late-phase counter-regulation observed in the illustration of Fig. 6 for large FFA pulse input and explains the surprising result of reversed glucose response to insulin (increase instead of decrease) for high levels of FFA that is shown in Fig. 7. This intriguing finding ought to be examined with specialized experiments in the future because, if confirmed, bears huge implications for the understanding of Type 2 diabetes. The 2nd FFA PDM starts positive and reaches a peak within ∼10 min (although its respective ANF exhibits small negative values near the origin, which accounts for the early negative glucose response to FFA pulse input in the illustration of Fig. 6), diminishing afterwards and reaching near-zero levels around 60 min (see Fig. 3). The respective ANFs (see Fig. 4) have nearly symmetric response characteristics with a central dead-zone (i.e. supralinear increase/decrease of glucose for increase/decrease of FFA, as long as the latter has adequate size to exceed the dead-zone). These findings are consistent with existing qualitative physiological knowledge regarding the inhibitory effects of FFA on insulin facilitation of glucose uptake and on the process of glycogenesis. The precise time-constants or the relative magnitudes of these physiological effects are not currently known and, therefore, confirmation of the validity of the PDM analysis of this system with specialized experiments in the future may provide valuable new insights.

One interesting finding that was presented in the previous section is the relation of "dynamic insulin sensitivity" (DIS) to the widely used "insulin sensitivity" (S_I) associated with the "Minimal Model" of the Glucose Tolerance Test [1], which is defined as the ratio of two parameters of that model: $S_I = p_3/p_2$. The computed DIS values using the PDM-based model (see Fig. 8) suggest that DIS is reduced for increasing levels of FFA—a finding consistent with previous observations regarding the effect of elevated FFA on plasma glucose and insulin sensitivity [7]—and this reduction becomes drastic when the FFA level exceeds a critical value (∼0.05 mM). Our findings also suggest that the induction of insulin resistance by elevated FFA is insulin-dose dependent. When our definition of the DIS is applied to the Minimal Model, the following expression is derived between DIS and S_I: $\mathbf{DIS = (G_b{*}S_I) / (p_1 + A\ S_I)}$, where G_b denotes the basal glucose value, p_1 is the glucose disappearance parameter of the Minimal Model and A is the amplitude of the insulin input pulse. It is evident from this expression that the DIS is dependent on the insulin dose A and the operating point (defined by G_b). We note that the Minimal Model does not take into account the effects of FFA.

The presented modeling approach is data-driven and offers quantitative insights into the causal inter-relationships between insulin, glucose and FFA. These insights may prove useful in understanding these critical processes in patho-physiological conditions such as obesity and Type 2 diabetes (with the eventual promise of improved diagnosis and disease management). The presented results

are preliminary and, since they are based on only one dataset, they are simply illustrative of the PDM-based modeling approach and its potential in this field of physiology. The obtained model is not proposed as the definitive dynamic relation among these variables. Nonetheless, the presented results demonstrate the potential of the PDM-based modeling approach to advance our quantitative understanding of the subject system.

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Appendix I: Summary of PDM-Based Modeling Methodology

We follow the general Volterra modeling approach which is applicable to all finite-memory stationary dynamic nonlinear systems [12]. For the two-input system of this study, we begin with the estimation of a 2nd order Volterra model using Laguerre expansions of the kernels [12]:

$$\begin{aligned} G(t) = k_0 &+ \int_0^\infty k_I(\tau)\, I(t-\tau)\, d\tau \;+\; \int_0^\infty k_F(\tau)\, F(t-\tau)\, d\tau \\ &+ \int\int_0^\infty k_{II}(\tau_1,\tau_2)\, I(t-\tau_1) I(t-\tau_2)\, d\tau_1 d\tau_2 \\ &+ \int\int_0^\infty k_{FF}(\tau_1,\tau_2)\, F(t-\tau_1) F(t-\tau_2)\, d\tau_1 d\tau_2 \\ &+ \int\int_0^\infty k_{IF}(\tau_1,\tau_2)\, I(t-\tau_1) F(t-\tau_2)\, d\tau_1 d\tau_2 \;+\; \varepsilon(t) \end{aligned} \tag{A1}$$

where, $G(t)$ denotes the glucose output, $I(t)$ denotes the insulin input, $F(t)$ denotes the FFA input and $\varepsilon(t)$ denotes the model prediction errors. The dynamic characteristics of this system/model are described by the kernels: k_I, k_F, k_{II}, k_{FF}, k_{IF}, which are estimated from given input-output data by means of Laguerre expansions and least-squares fitting as described below. A key step in the use of the Laguerre expansion technique is the proper selection of the Laguerre parameter "alpha", which is accomplished through a search procedure minimizing the mean-square prediction error. The Laguerre expansions of the 1st-order kernels using L Laguerre basis functions $\{b_j\}$ are given by:

$$k_i(\tau) = \sum_j a_i(j)\, b_j(\tau) \tag{A2}$$

where the subscript i denotes the input (I or F), a_j are the Laguerre expansion coefficients and the summation is taken over $j = 1,\ldots, L$. The Laguerre expansions of the 2nd-order kernels are given by:

$$k_{i_1,i_2}(\tau_1,\tau_2) = \sum_{j_1}\sum_{j_2} a_{i_1,i_2}(j_1,j_2)\; b_{j_1}(\tau_1)\; b_{j_2}(\tau_2) \tag{A3}$$

where the subscripts i_1, i_2 denote the inputs (I or F), a_{i_1,i_2} are the Laguerre expansion coefficients and the double summation is taken over j_1 and j_2 from 1 to L. The self-kernels correspond to the case when i_1 and i_2 denote the same input, and the cross-kernel when i_1 is different from i_2. Then, we have the following input-output relation which involves *linearly* the Laguerre coefficients:

$$y(t) = a_0 + \sum_i \sum_j a_i(j)\; v_{j,i}(\tau) \; + \sum_{i_1,i_2}\sum_{j_1}\sum_{j_2} a_{i_1,i_2}(j_1,j_2)\; v_{j_1,i_1}(\tau_1)\; v_{j_2,i_2}(\tau_2) \tag{A4}$$

where a_0 is a baseline constant, and the signals $v_{j,i}(t)$ are the convolutions of the Laguerre basis function b_j with the respective input i. The fact that the Laguerre expansion coefficients enter linearly in the nonlinear input-output model of Eq. (A4) allows their estimation via least-squares fitting. Following estimation of the Laguerre expansion coefficients, we can construct the Volterra kernel estimates using Eqs. (A2) and (A3), which allows computation of the model prediction for *any* given input using Eq. (A1) or (A4).

The concept of Principal Dynamic Modes (PDMs) aims at identifying an efficient basis of functions distinct and characteristic for each system, which is capable of representing adequately the system kernels. The computation of the PDMs for each input is based on Singular Value Decomposition (SVD) of a rectangular matrix composed of the 1st order kernel estimate (as a column vector) and the 2nd order self-kernel estimate (as a block matrix) weighted by the standard deviation of the respective input. The PDMs are defined for the significant singular values (two for each input in this application). The resulting PDMs form a filter-bank that receives the respective input signal and generates (via convolution) signals that are subsequently transformed by the "Associated Nonlinear Function" (ANF), which represents the nonlinear characteristics of the system for the respective PDM dynamics, to form additively the system output, as depicted schematically in Fig. 2. Thus, the PDM-based model separates the dynamics (PDMs) from the nonlinearities (ANFs). Since the "separability" of the system nonlinearity cannot be generally assumed, we include "cross-terms" in the PDM-based model that are properly selected on the basis of a statistical significance test on the computed correlation coefficient between each cross-term (i.e. the pair product of PDM outputs) and the output signal, using the w-statistic. Two cross-terms were found to be adequate in this application.

The structure of the PDM-based model of the two-input/one-output system is shown in Fig. 2. The employed PDMs represent a common "functional basis" for

efficient representation of *all* kernels of the system. Upon selection of the PDMs and the significant cross-terms, we estimate the Associated Nonlinear Functions (ANFs), which are polynomial functions (cubic in this case) transforming the output of the respective PDM into a variable that represents an additive component of the model output, along with the other ANF outputs and the cross-terms:

$$y(t) = c_0 + \sum f_I[u_I(t)] + \sum f_F[u_F(t)] + \text{Cross-Terms} + \varepsilon(t) \qquad \text{(A5)}$$

where $\{u_I\}$ and $\{u_F\}$ are the PDM outputs for the inputs I and F respectively (i.e. convolutions of each input with the respective PDM), and $\{f_I\}$ and $\{f_F\}$ are the ANFs associated with each PDM. The "Cross-Terms" in Eq. (A5) are pair products of $\{u_I\}$ and $\{u_F\}$ that have significant correlation with the output. The coefficients of the cubic ANFs and of the selected Cross-Terms (pair products of PDM outputs with significant correlation with the system output) are estimated, along with baseline constant c_0, via least-squares regression of the output Eq. (A5).

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