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Critical Modeling Issues for Successful Feedforward Control of Blood Glucose in Insulin Dependent Diabetics

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Abstract - **Accurate modeling of the effects of nutrient and activity variables on blood glucose can make a major impact in reducing the complications of diabetes for insulin dependent type 1 and 2 diabetics. These models can be used to design feedforward controllers that can revolutionize blood glucose control. However, to achieve this objective, there are several critical issues in measurement, data collection, and modeling that need to be resolved. This work discusses and presents solutions to resolving these issues.**

Keywords
Feedforward Controllers, Type 1 Diabetics, Type 2 Diabetics, Wiener systems, Glucose Modeling and Control

I. Introduction

The importance of tight glucose control in reducing the complications associated with diabetes is widely recognized [1]. The primary ways that glucose has been managed include diet and exercise, stress management, insulin injections, and different types of drugs. In most cases control has been open loop requiring diabetics to use test strip meters to monitor glucose behavior from just a few readings per day. However, recent technological advancements have produced accurate glucose monitors that measures as often as every five minutes, twenty four hours a day [2], and thus provide a critical component in the realization of continuous closed loop control for insulin dependent diabetic people. Therefore, recent research has focused on using this advancement in measurement technology in feedback control or in the development and exploitation of one-step ahead prediction (OSAP) in model predictive control (MPC). While earlier studies looked at standard feedback controllers [3], several recent studies have considered advanced control techniques like model based controllers [4], robust tracking [5], run-to-run control [6], and the feed forward control for carbohydrate content of the meals [7]. But a major limitation of all these studies is that the control strategies have been developed and tested only in simulation (i.e., not using real subjects). While such studies may lead to significant advancements in tightening glucose behavior in the years to come, accurate anticipatory understanding of the complex effects of food as well as physical and emotional activity on blood glucose can pave the way for further tightening of blood glucose via feedforward control. Thus, this article discusses critical issues in model development for disturbance variables and presents results of a recently developed model involving 11 inputs for a type 2 diabetic (TTD) subject.

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II. Issues and Background

Our basic motivation for the promotion of feedforward control is a belief that feedback control and even MPC will not completely provide the necessary control performance to maintain adequate glucose levels in insulin dependent diabetic subjects. The ability to proactively compensate for variables that change glucose levels such as food consumption, physical activity and stress exists only in feed forward control. When precise models for the effects of all the variables on glucose are not available, a combination of feedback and feedforward control may be preferable. However, to implement feedforward control, these types of variables need to be measured or inferred from other measurements and accurately modeled in terms of their complex effects on blood glucose. To this end we have divided our discussion of the critical issues for successful feedforward control into two categories. These categories are the data requirements and the modeling requirements.

There are several attributes the data must have for accurate modeling for feedforward control. First, since this is dynamic modeling, it is necessary to have accurate and frequent measurements of the glucose concentration. This requirement suggests that lancet test strip sampling will not be practical since it cannot produce more than a few values daily. However, recent technology has produced accurate devices such as the MiniMed Continuous Glucose Monitor, MMT-7102® (Medtronic, Minneapolis, Minnesota), with sampling rates as often as every five minutes, which is adequate for dynamic glucose modeling, as we show later.

Secondly, a set of noninvasive variables need to be defined that provides adequate information to explain a sufficient amount of the variation in glucose to be useful. Our experience tells us that nutrient components alone will not meet this requirement as we will demonstrate in the next section in a type 2 diabetic modeling case. While food consumption has a significant effect on blood glucose, it does not account for major behaviors particularly during times of low food consumption such as during sleep. Furthermore, stress and activity can have as great an impact on glucose levels as eating. Hence, an adequate data set must not only contain frequent and accurate sampling of food but

also variables that measure activity and stress levels. A device that has much promise in meeting this requirement for the latter two is the SenseWear® Pro3 body monitoring system (BodyMedia Inc., Pittsburgh, PA). This device utilizes pattern detection algorithms [8,9] that employ physiologic signals from a unique combination of sensors. The raw physiological data include movement, heat flux, skin temperature, near body temperature, and galvanic skin response (GSR). It collects data using five sensors: heat flux, skin temperature, near body temperature, GSR, and an accelerometer (2-axis). The heat flux sensor measures the amount of heat being dissipated from the body by measuring the heat loss along a thermally conductive path between the skin and a vent on the side of the armband. Skin temperature and near-armband temperature are also measured by sensitive thermistors. The armband also measures GSR, which is the conductivity of the wearer's skin that varies due to physical and emotional stimuli. A two-axis accelerometer tracks the movement of the upper arm and provides information about body position [8, 9]. The study presented in the next section will demonstrate the effectiveness of this device to meet the requirements for activity and stress variables.

Thirdly, to adequately cover the response space that a subject experiences, the input space must adequately cover the changes experienced by the subject. This means that data must be collected under free-living conditions and for a prolonged period of time. Our experience has suggested that this period is of the order of weeks and is another reason for supporting free-living data collection since it would be difficult for anyone to follow a rigid meal and activity protocol for weeks. Moreover, there are other inputs, such as stress, that are uncontrollable and thereby likely to have significant influence in a study involving weeks of data collection. Furthermore, a prescribed (i.e., experimentally designed) set of input changes may not adequately cover the experiences of the subject and thus, further supporting our premise that a free-living study appears to be the only practical data collection approach over weeks.

Finally, the modeling method must be able to achieve high cause and effect accuracy from free-living data with highly nonlinear and interactive behavior. Free-living data have the same nature as chemical plant data where inputs can be highly correlated (e.g., carbohydrates and fats) and the inputs contain limited ranges to keep the output under control, that is, as close to the target as possible. Thus, the signal-to-noise ratio is suppressed and kept to a minimum. In the world of nonlinear dynamic modeling (apart from theoretical modeling) there are really only a few general approaches. In applications with constant and frequent sampling rate, discrete-time (DT) modeling dominates. All of the DT approaches that we are aware of (except the one we will propose in this work) use lag variables which has a major limitation of large parameter sets. The approaches with the linear coefficients can be placed under the general class of nonlinear autoregressive moving average models with exogenous variables (NARMAX) [10]. This modeling approach has two severe drawbacks. First, because the model form is linear in parameters, the values of the fitted model coefficients are tied to the correlation structure of the input. Thus, any change in the input correlation structure can produce large prediction errors. Furthermore, the model can produce highly incorrect results for independent (i.e. uncorrelated) changes in the inputs, which makes it impractical for feedforward control. The second drawback is the strong natural correlation of common lag variables which causes ill conditioning and inflates estimation errors. Moreover, if linear dependencies are too high, lags are forced out of the model by computer packages to enable the determination of a solution. Thus, particularly for cases with a large number of inputs, it may not be possible to model all the dynamic behavior and thereby retain all critical components. We illustrate these limitations in an example shortly.

The popular empirical approach with nonlinear coefficients is the artificial neural network (ANN) [11]. The major limitation of ANN is the lack of phenomenological structure which is crucial when fitting nonlinear behavior. As far as mapping a set of input changes under adjustable parameterization (i.e., training) to a point on the response surface, ANN is excellent, as supported by its success in pattern recognition applications. However, for untrained input combinations, the use of highly nonlinear transfer functions can cause extremely large prediction errors caused by the extrapolation phenomenon of nonlinear models. Thus, there is no doubt that ANN can train well but it is highly doubtful that a trained ANN model could perform well for input combinations not used in training. We will illustrate this limitation of ANN in the example to be given later in this section.

The only approach that we have found with cause and effect capability under free-living data collection is Wiener modeling as Rollins et al. [12] applied it using the method of Bhandari and Rollins [13] for continuous-time (CT) modeling and Rollins and Bhandari [14] for DT modeling. Wiener modeling falls under the general class of block-oriented modeling and specifically is characterized by each input passing through its own linear dynamic block (i.e., function) with the outputs from these blocks being collected and passing through a nonlinear static block [13]. We will use the following mathematical Wiener modeling process with two-inputs and one-output to illustrate the unique strengths of this approach and the weaknesses of NARMAX (and related methods) and ANN discussed above.

True Linear Dynamic Functions:

$$v_{i,t} = \delta_{i1} v_{i,t-1} - \delta_{i2} v_{i,t-2} + \omega_{i1} x_{i,t-1} - \omega_{i2} x_{i,t-2} \qquad (1)$$

True Nonlinear Static Function:

$$\eta_t = \beta_1 v_{1,t} + \beta_2 v_{2,t} + \beta_3 v_{1,t}^2 + \beta_4 v_{2,t}^2 + \beta_5 v_{1,t} v_{2,t} \qquad (2)$$

with $x_{i,t}$ = the input variable i at the time t, $i = 1, 2$; $x_{i,t}$ and $v_{i,t} = 0$ for $t < 0$; η_t is the true response of the output at time t; $\beta_1 = 0.08$; $\beta_2 = 0.20$; $\beta_3 = 0.12$; $\beta_4 = 0.15$; $\beta_5 = 0.11$;

$$\delta_{i1} = \frac{2\tau_i^2 + 2\tau_i \zeta_i \Delta t}{\tau_i^2 + 2\tau_i \zeta_i \Delta t + \Delta t^2} \qquad (3)$$

$$\delta_{i2} = \frac{\tau_i^2}{\tau_i^2 + 2\tau_i \zeta_i \Delta t + \Delta t^2} \qquad (4)$$

$$\omega_{i1} = \frac{(\tau_{ia} + \Delta t)\Delta t}{\tau_i^2 + 2\tau_i\zeta_i\Delta t + \Delta t^2} \quad (5)$$

$\tau_1 = 10$; $\tau_2 = 20$; $\zeta_1 = 0.5$; $\zeta_2 = 0.9$ $\tau_{1a} = 3$; $\tau_{2a} = -2$; and $\omega_{i2} = 1 - \delta_{i1} - \delta_{i2} - \omega_{i1}$ (see [10]), where $\Delta t = 1$ is the sampling time; and Corr($x_{1,t}$, $x_{2,t}$) = 0.994 is the correlation coefficient of input variables 1 and 2 at time t. Note that this true Wiener modeling process depends on only two inputs, x_1 and x_2, that are highly correlated. In Eq. 1, $v_{i,t}$ represents the response of a linear second order dynamic process in discrete form and Eqs. 3-5 give its parameters in terms of the dynamic parameters from a second order CT process using backward difference approximations for the derivative (see [12] for the derivation).

Equations 1-5 are in a form that allows us to present our proposed ***cause and effect*** Wiener model development approach from free-living data. To obtain unique parameter estimates and thus, have cause and effect predictability, the parameter estimates for a model must be unaffected by the correlated dependence of inputs. This can only happen if the terms in a model are uncorrelated. Terms will be uncorrelated if they are uncorrelated with respect to changes in parameters or changes in variables. Our proposed approach uses non-linear regression to ***directly*** estimate the dynamic parameters and obtains Eq. 1 via Eqs. 3-5. Thus, in the way we estimate the dynamic parameters, the terms in Eq. 1 are uncorrelated because each of these terms have separate nonlinear dependence on these parameters. Also, in this approach, the coefficients in Eq. 2 are estimated simultaneously with the dynamic parameters. The terms in Eq. 2 are uncorrelated because the v_i's have their own independent (and often periodic) dynamic behavior. Consequently, our proposed approach is a powerful model building technique since it is uniquely able to obtain cause and effect models under conditions of highly correlated inputs. Moreover, our approach provides a uniquely powerful way to develop cause and effect models from highly correlated plant data in addition to this application of free-living data.

In contrast, NARMAX models do not have this property of uncorrelated terms because the models are linear in parameters. This can be seen by substituting Eq. 1 into Eq. 2, to give the NARMAX form for the true model as:

$$\begin{aligned} y_t = {} & a_1 y_{t-1} + a_2 y_{t-2} + \cdots + a_7 y_{t-7} + a_8 y_{t-8} \\ & + b_1 x_{1,t-1} + \cdots + b_8 x_{1,t-8} \\ & + c_1 x_{2,t-1} + \cdots + c_8 x_{2,t-8} \\ & + d_1 x_{1,t-1}^2 + d_2 x_{1,t-2}^2 + \cdots + d_4 x_{1,t-4}^2 + d_5 x_{1,t-1} x_{1,t-2} \\ & + d_6 x_{1,t-1} x_{1,t-3} + \cdots + d_9 x_{1,t-2} x_{1,t-3} + d_{10} x_{1,t-3} x_{1,t-4} \\ & + e_1 x_{2,t-1}^2 + e_2 x_{2,t-2}^2 + \cdots + e_4 x_{2,t-4}^2 + e_5 x_{2,t-1} x_{2,t-2} \\ & + e_6 x_{2,t-1} x_{2,t-3} + \cdots + e_9 x_{2,t-2} x_{2,t-3} + e_{10} x_{2,t-3} x_{2,t-4} \\ & + f_1 x_{1,t-1} x_{2,t-1} + f_2 x_{1,t-1} x_{2,t-2} + \cdots + f_{12} x_{1,t-3} x_{2,t-4} \\ & + \cdots + f_{15} x_{1,t-4} x_{2,t-3} + f_{16} x_{1,t-4} x_{2,t-4} \end{aligned} \quad (6)$$

In Eq. 6 the linear coefficient are estimated directly. As a result, these terms are correlated in two ways. First, since lag variables are inherently correlated with their family of lag variables, all the terms with the same letter for the coefficients (e.g., a_1 and a_2) in Eq. 6 will be correlated. Secondly, because the inputs are correlated, terms with common inputs will be correlated (e.g., $b_1 x_{1,t-1}$ and $d_1 x_{1,t-1}^2$). Note that since Eq. 6 was derived from Eqs. 1-2 (the derivation is not shown due to space constraints), its form is exact for this mathematical example and gives the parameterization and the lags under NARMAX modeling. This derivation reveals other severe drawbacks of NARMAX modeling. First, even for a small number of inputs (in this case two), the number of terms in a NARMAX model can be quite large (in this case 60). Secondly, since the terms can be significantly correlated, the potential for numerical instability due to linear dependencies is great which means that to reach a numerical result, some of the terms will likely have to be removed. Finally, in the usual way NARMAX modeling is applied, the number of lags for each set of variables is not known and usually determined by trial and error, which can be quite time consuming.

In this study we also evaluated ANN with the same terms as we derived for the NARMAX model. The model is a feedforward ANN model with sixty input nodes (one for each lag in Eq. 6), one hidden layer, and logistic transfer functions [15] (the equations are not shown because of space limitations).

To evaluate cause and effect capability of a model, it is important to test it with a sequence of data under a different input correlation structure. Since we are modeling under correlated inputs, we train the model under a highly correlated input structure (i.e., Corr($x_{1,t}$, $x_{2,t}$) = 0.994) and test it under a very weak correlation structure with Corr($x_{1,t}$, $x_{2,t}$) ≈ 0 to demonstrate how well the model has captured independent input behavior. We now present the results of this comparative study of the proposed Wiener approach and the NARMAX and ANN approaches.

III. Results of the Simulated Data Study

The input sequence for this study is presented in Fig. 1. The changes mimic eating meals as their levels change for a period and then drop to zero a number of times where x_1 and x_2 are meant to mimic carbohydrates and fats, respectively. We also show the dynamic responses (i.e., the v_i's) that correspond to each input. These responses provide information on the periodicity of the inputs as well as their residence times. For example, Fig. 1 shows that x_1 is more oscillatory but that x_2 has the higher residence time. This is also revealed by the values of the parameters which are estimated very accurately by the proposed approach. The high correlation of the inputs for the training data is also very apparent as well as the lack of correlation for the test data. Note also the independent relationship of v_1 and v_2 due to their different dynamic behavior. All the models fit the training data well with the amount of explained variation (R^2) equaling 100.0%, 100.0% and 99.9% for the proposed

method, NARMAX, and ANN, respectively. However, to obtain a solution using linear regression in the statistical program Minitab, 23 of 60 lags were removed from the model.

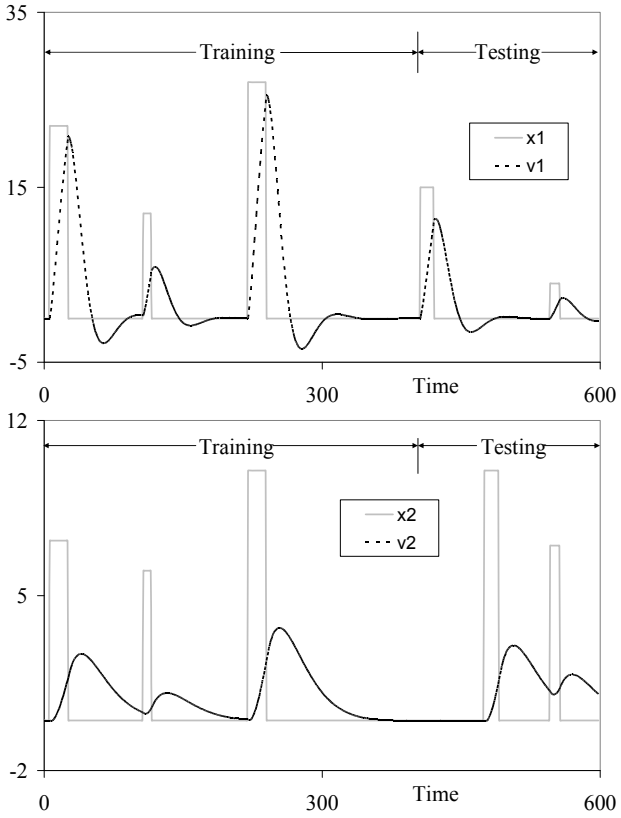

Fig. 1. Training and testing input sequences for x_1 (with v_1) and x_2 (with v_2). Their correlation coefficient for training is 0.994 and zero for testing.

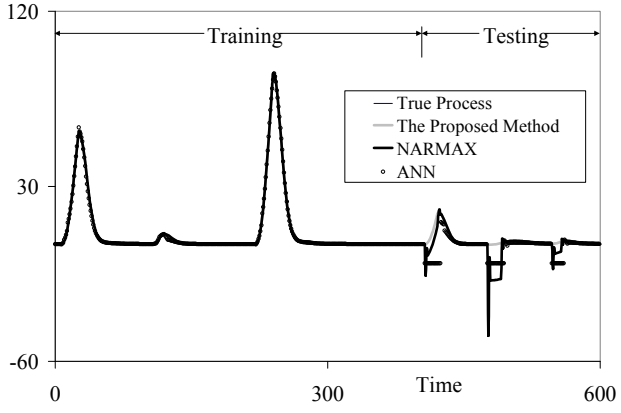

Fig. 2. Training and testing model performance. The proposed Wiener method fits the true process nearly perfectly but the testing performance of NARMAX and ANN is very poor.

As shown by Fig. 2 for the test data, the proposed model fit the data nearly perfectly but the other two methods did very poorly, which supports our discussion above regarding the inability of these methods to predict well under an input correlation structure different than in training. Moreover, this study shows that our proposed Wiener modeling approach could estimate the coefficients accurately under high input correlation and predict accurately for independent changes in the inputs, supporting its ability to determine a cause and effect relationship between the inputs and the output. Thus, this approach appears to have much promise in modeling glucose using free living data. Next, we present results of the application of the proposed method in a glucose modeling study.

IV. Modeling Real Data

We recently applied the proposed Wiener modeling method to data collected on a type 2 diabetic subject controlling blood glucose by diet and exercise only. The training data were collected over a period of 20 days and the next five days of data were the test data set. The MMT-7102® monitor collected the glucose data at five minutes intervals over the 25 days of this study. The SenseWear® Pro3 body monitoring system collected activity and stress data that corresponded to the glucose data. Food data were collected and converted to carbohydrates (carbs), fats and protein using nutrient tables. We also developed an input variable to represent military time to assess the hypothesis that the body has an internal clock for glucose variation. In all there were 24 inputs but after the application of input reduction procedures the final model consisted of eleven (11) inputs. The linear dynamic blocks in the study were second-order-plus-lead-plus-dead-time and the static nonlinear function was a second order regression model with interaction terms similar to Eq. 2 except for the number of inputs. The inputs are given in Table 1 with the values of the dynamic parameters were determined by application of the proposed method. The values for the static parameters are not given here due to space limitation. For these values and for more details of this study see [12].

R^2 and r_{fit} (the correlation coefficient for the observed and fitted values) for the training data were 64.0% and 0.80, respectively. For the five days of testing data, r_{fit} was very good at 0.65. The twenty days of training data were too large to plot but a representative plot of the first four days is shown in Fig. 4. The five days of testing data are plotted in Fig. 5. As shown, the proposed method fits quite well but does not always at the extreme values. As Table 1 shows, of the nutrient components, carbs have the smallest period. Table 1 also gives approximate values for their residence times $\tau_{1i} + \tau_{2i} = 2\tau_i\zeta_i$. From this table we see that the residence times of fats and proteins are more than 4 and 13 times, respectively, greater than carbohydrates, which reflect the relative rates that these three nutrients impact the blood glucose for this subject.

Figure 5 plots the dynamic responses of carbs (v_1) and fats (v_2) over measured glucose for the five days of test data to visually contrast their dynamic behavior. As shown, the fats have a significantly larger residence time and overlaps very strongly with meals eaten on the same day. In contrasts, carbs have a faster residence time and is out of the system (i.e., the blood) typically before the next meal. Thus, fats appear to have more of a "storing" effect than carbs. One

implication is that fats will have a greater long term effect and affects more greatly, for example, the glucose behavior at night during sleep since food is not consumed for several hours. Dynamic plots for the other variables for both training and testing data are given in [12]. Thus, because our proposed Wiener approach is able to determine values with physical meaning, we are able to not only develop models for use in the development of feedforward control laws but also an understanding of the dynamic impact of the inputs.

Table 2. Estimated dynamic parameters (in minutes) for the TTD Wiener model.

Variable	i	τ_i	ζ_i	θ_t	τ_{ai}	$2\tau_i\zeta_i = \tau_{1i} + \tau_{2i}$
Carbs	1	31	1.3	15	-2.8	79
Fats	2	256	0.7	15	15	344
Proteins	3	1621	0.3	15	-2.3	1087
Trans. Accel peaks	4	25	0.06	0	-9.	2.7
Heat flux average	5	91.8	0.06	0	14	10.5
Long. Accel average	6	227	3.5	0	-6.8	1581
Near-body temp average	7	402	0.9	0	6	727
Trans. Accel MAD	8	14	0.5	0	4.6	12.5
GSR average	9	900	0.04	0	7.6	75.6
Energy Expenditure	10	267	2.1	0	-14	1126
Time of Day	11	98	2e-3	25	8	0.39

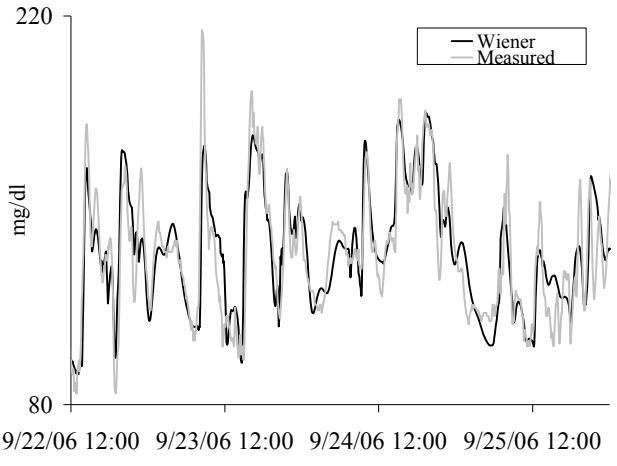

Fig. 3. The first four days of training showing measured glucose response and a representative fit of the proposed Wiener model.

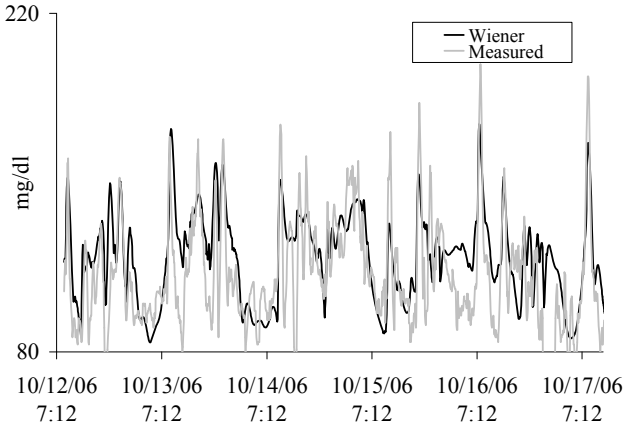

Fig. 4. The five days of testing showing the performance of the proposed Wiener Model for glucose response.

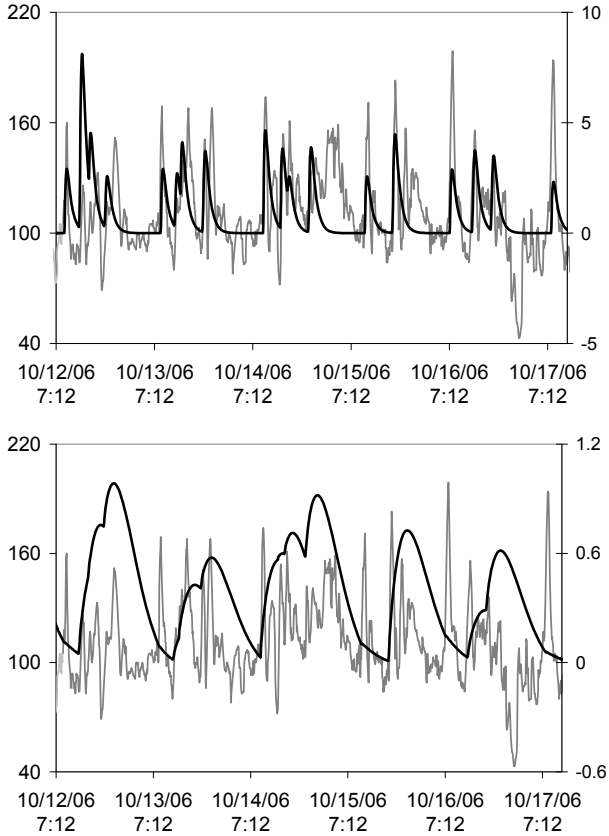

Fig. 5. Dynamic overlay plots for carbs (top) and fats (bottom). The scale on the right is for glucose (mg/dl) and the one on the left is for v_i.

V. Concluding Remarks

The purpose of this article was to demonstrate the unique and powerful ability of the proposed Wiener approach to develop ***cause and effect*** dynamic models of plasma glucose for changes in food, activity, and stress inputs with physically interpretable parameters under free-living conditions. Due to the length of time required to experience a broad enough range of input changes, free-living data collection appears to be the most practical. The main challenge in model development from free-living data is

high correlation of input variables. The proposed method is effective because the parameters are independent nonlinear functions for the terms in the linear dynamic functions and the terms in the static nonlinear functions depend on the variables from the dynamic blocks which are not strongly correlated due to their dynamic behavior. This effect was demonstrated on both simulated and real data in this work. The proposed method maintains its modeling strengths in the presence of noise but we did not show those cases for mathematical model due to space limitations. By application of the proposed method, the successful development of feedforward control appears promising which necessitates cause and effect prediction to make accurate changes in insulin.

NARMAX modeling, a linear empirical approach that uses lags variables, has serious drawbacks due to the strong correlation of lag variables as well as the correlation of terms due to dependence on the same inputs. In addition, it also has the drawback of linear dependencies which requires the elimination of terms to reach a solution as well as the drawback of determining the number and types of lags. For a method to demonstrate cause and effect modeling ability, it must be developed under a strong correlation of inputs and predict well under a very different correlation structure for a set of test data. In a simulation example, this work demonstrated this inability of NARMAX modeling.

ANN modeling, a nonlinear empirical approach that also uses lag variables, has serious drawbacks due to the lack of phenomenological structures and parameters and its strong nonlinear mapping to specific cases of input changes. Input combinations different from the ones in training can predict poorly due to highly nonlinear behavior of models that are not phenomenologically correct. This work demonstrated this drawback of ANN on the simulated mathematical example where it predicted poorly for test data with different input changes than the training data.

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NOMENCLATURE

x	Input variable
v	Intermediate variable, the output from the dynamic block, in a Wiener model
y	Output variable
Δt	Sampling time
η	True response
β	Static gain parameter
δ,ω	Discrete-time dynamic parameters
τ, τ_a	Time constants, continuous-time dynamic parameter
ζ	Damping factor, continuous-time dynamic parameter
θ	Dead time, continuous-time dynamic parameter
a-f	Linear parameters in NARMAX model
i	as subscript denotes a particular input

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