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A NONLINEAR DATA–DRIVEN APPROACH TO TYPE I DIABETIC PATIENT MODELING

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Abstract: Glucose–insulin interactions in the Type I diabetic patient are approximated in an input–output sense using a third–order Volterra series model. Due to the large number of unique coefficients present in a third–order model, efficient parameter identification methods are developed. Several pruned model structures were examined, and maximum dynamic accuracy was obtained when a linear plus nonlinear diagonal model was employed. Increased steady state accuracy could be obtained by including semi–diagonal and off–diagonal coefficients; however, this increase in static accuracy came at a cost of decreased dynamic accuracy. Furthermore, calculation of semi-diagonal and off-diagonal coefficients requires data acquisition times infeasible for clinical applications. Hence, the linear plus nonlinear diagonal Volterra series model is a well–suited structure for approximating Type I diabetic patient glucose–insulin dynamics using input–output methods.

Keywords: Biomedical systems, identification algorithms, nonlinear models, sampled-data systems, Volterra series

1. INTRODUCTION

Type I diabetes mellitus is a chronic condition characterized by the body's destruction of its own pancreatic β–cells and the resulting loss of endogenous insulin production. This inability to secrete insulin leads to glucose concentration deviations from normoglycemia (defined as 70-120 mg/dL) with blood glucose concentrations typically reaching into the hyperglycemic range ($>$120 mg/dL). Extended elevated glucose concentrations are reported to contribute to long-term health problems such as poor circulation and retinopathy based on the findings of the Diabetes Control and Complications Trial Research Group (DCCT) (1993; 1996). Hypoglycemia ($<$60 mg/dL) results from an over-delivery of insulin to the diabetic patient and can lead to coma or death. As a result, blood glucose concentrations must be maintained within a stringent set of physiological limits.

Current treatment of Type I diabetes involves the use of inhalers, direct injections, or continuous infusion pumps. However, these methods rely on patient compliance to effectively regulate blood glucose levels. The patient must adjust doses prior to meals, exercise, or sleep to maintain blood glucose levels within the normoglycemic range. An inaccurate estimate or missed insulin dose could lead to complications as described above (DCCT - The Diabetes Control and Complications Trial Research Group, 1993). An alternative to patient self–care is a closed-loop system that uses periodic samples of blood glucose to establish an insulin dose, thereby eliminating the patient from the control loop.

A closed–loop glucose control device would consist of three primary components: (i) an insulin delivery pump; (ii) a glucose sensor; and (iii) a mathematical algorithm to regulate insulin delivery based on glucose concentration measurements (Parker *et al.*, 1999). This study focuses on diabetic patient model

development, the initial step in the development of a model–based glucose control algorithm. The following sections describe the systematic construction of an empirical relationship between insulin infusion rate and glucose concentration using a control–relevant data–driven model structure.

2. THIRD–ORDER VOLTERRA MODELING

The general Volterra series model has the form:

$$\hat{y}(k) = y_0 + \sum_{i=1}^{N} \sum_{j_1=1}^{M} \cdots \sum_{j_N=1}^{M} h_i(j_1,\ldots,j_N) \times u(k-j_1)\ldots u(k-j_N) \quad (1)$$

This is a single–input single–output discrete–time model that can approximate fading–memory nonlinear systems (Boyd and Chua, 1985). The output of a fading memory system is affected by past input changes over some model memory, M, such that inputs occurring beyond the memory of the model no longer affect the output significantly. A truncated Volterra series model is constructed by selecting the order, N, of the desired model. Using only insulin inputs and the corresponding glucose measurements, an understanding of the empirical relationship between insulin infusion and glucose concentration can be identified and consequently utilized for regulating glucose levels. From the general Volterra series model in equation (1), a third–order structure can be decomposed as :

$$\begin{aligned} y(k) &= h_0 + \mathscr{L}(k) + \mathscr{D}_2(k) + \mathscr{O}_2(k) \\ &\quad + \mathscr{D}_3(k) + \mathscr{S}_3(k) + \mathscr{O}_3(k) \quad (2) \\ \mathscr{L}(k) &= \sum_{i=1}^{M} h_1(i)u(k-i), \\ \mathscr{D}_2(k) &= \sum_{i=1}^{M} h_2(i,i)u^2(k-i), \\ \mathscr{O}_2(k) &= 2\sum_{i=1}^{M}\sum_{j=1}^{i-1} h_2(i,j)u(k-i)u(k-j), \\ \mathscr{D}_3(k) &= \sum_{i=1}^{M} h_3(i,i,i)u^3(k-i), \\ \mathscr{S}_3(k) &= \sum_{i=1}^{M}\sum_{j=1}^{M} h_3(i,j,j)u(k-i)u^2(k-j) \\ \mathscr{O}_3(k) &= \sum_{i=1}^{M}\sum_{j\neq i}^{M}\sum_{p\neq j\neq i}^{M} h_3(i,j,p) \times \\ &\quad u(k-i)u(k-j)u(k-p) \end{aligned}$$

In the above partitioning, $\mathscr{L}$ represents the linear terms, $\mathscr{D}_n$ denote the nonlinear diagonal terms of order n, $\mathscr{S}_3$ are the third–order semidiagonal terms, and $\mathscr{O}_n$ are the off–diagonal terms of order n. Without loss of generality, the coefficients of the above equations (h_i) are assumed to be symmetric. Furthermore, the variables $y(k)$ and $u(k)$ are in scaled deviation form.

In developing a model of this form for the diabetic patient, the sampling rate (T_s) and model memory must be determined. For the present study, the memory and sampling rate were calculated so that a model of memory M at sampling rate T_s would capture $\approx 99\%$ of the patient step response.

The Volterra series is a highly parameterized structure, so significant quantities of data are required for accurate coefficient identification. However, tailored input sequences can be employed to efficiently identify subsets of coefficients within the model. Input sequence properties for focused coefficient identification are developed based on the prediction error variance expression (Heemstra, 1996):

$$\begin{aligned} \sigma_p^2 &= \sigma_0^2 + \sigma_u^2 \sum_{i=1}^{M} \delta_1^2(i) + (\kappa+2)\sigma_u^4 \sum_{i=1}^{M} \delta_2^2(i,i) \\ &\quad + 2\sigma_u^4 \sum_{i=1}^{M}\sum_{j=1}^{i-1} \delta_2^2(i,j) \\ &\quad + (m_6 - \frac{m_4^2}{\sigma_u^2}) \sum_{i=1}^{M} \delta_3^2(i,i,i) \\ &\quad + 9(\kappa+2)\sigma_u^6 \sum_{i=1}^{M}\sum_{j\neq i}^{M} \delta_3^2(i,j,j) \\ &\quad + 6\sigma_u^3 \sum_{i=1}^{M}\sum_{j\neq i}^{M}\sum_{p\neq j\neq i}^{M} \delta_3^2(i,j,p) \quad (3) \end{aligned}$$

where

$$\begin{aligned} \delta_1(i) &= h_1(i) - \hat{h}_1(i) \\ \delta_2(i,j) &= h_2(i,j) - \hat{h}_2(i,j) \\ \delta_3(i,j,p) &= h_3(i,j,p) - \hat{h}_3(i,j,p) \end{aligned}$$

Here, σ_0^2 was the prediction error variance obtained in the absence of parameter estimation errors, and κ was the kurtosis of the input sequence. The variables, δ_i are the deviations between the actual and estimated model coefficients. Input sequences can be developed with particular moment and kurtosis properties that excite certain terms while yielding minimal or zero excitation of other model contributions. This method not only ensures more accurate coefficient identification (Parker *et al.*, 2001), but also allows for a possible reduction in the number of coefficients calculated if pruned model structures are employed.

3. LINEAR/DIAGONAL IDENTIFICATION

The least complicated nonlinear extension of a linear time series model is to include the nonlinear diagonal terms. There are several motivations for this choice. First, calculating only these terms significantly reduces the overall number of coefficients that require estimation. Second, tailored identification sequences can be developed for targeted identification of linear and nonlinear diagonal coefficients, and these

sequences will require less data than traditional cross–correlation identification techniques. Third, all other coefficient calculations have contributions from the linear and/or nonlinear diagonal terms. Calculating these coefficients when there are no other confounding contributions allows for more accurate estimates for *all* model coefficients.

To properly excite a third–order Volterra model, the input sequence must have at least four discrete levels (Nowak and Van Veen, 1994). For the purposes of nonlinear diagonal identification a deterministic 5–level sequence is employed. This can be interpreted as a special case of a continuous switching–pace symmetric random sequence having the following form:

$$u(k) = \begin{cases} \gamma_1 & k = 0 \\ 0 & 1 \le k \le M \\ -\gamma_1 & k = M+1 \\ 0 & M+2 \le k \le 2M+1 \\ \gamma_2 & k = 2M+2 \\ 0 & 2M+3 \le k \le 3M+2 \\ -\gamma_2 & k = 3M+3 \\ 0 & 3M+4 \le k \le 4M+3 \end{cases} \tag{4}$$

This sequence of $4M+4$ points will accurately identify $3M+1$ coefficients (linear, second– and third–order diagonal, plus the bias, h_0). The spacing of M steps between pulses ensures that only linear and nonlinear diagonal terms are excited by the input sequence. Since only one input over the past horizon M has non–zero value at any time, the contribution of the semi– and off–diagonal terms to the output will be zero by definition.

Pulse order and magnitude play a significant role in the resulting model quality. The levels in this sequence represent scaled deviations from the nominal input value, and obey $|\gamma_1| < |\gamma_2|$. The magnitude choice guarantees that larger output deviations resulting from the larger pulses do not interfere with the smaller pulse responses. The initial two pulses in equation (4) primarily serve to excite the linear dynamics, and are also used in the identification of the third–order diagonal coefficients. The larger insulin delivery pulses stimulate nonlinear behaviors, and are explicitly used to estimate the second– and third–order diagonal coefficients. The decision to construct the second–order diagonal estimator using only the larger pulse series is a result of poor dynamic and steady state accuracy of the resulting model when the second–order coefficients were identified using the full 4–pulse sequence.

Coefficient estimators for h_i were constructed that minimize the prediction error:

$$J = \sum_{k=0}^{4M+3} e^2(k) = \sum_{k=0}^{4M+3} [y(k) - \hat{y}(k)] \tag{5}$$

Estimators are calculated by taking $\frac{\partial J}{\partial h_n} = 0$ for $n = 0,1,2,3$. Estimators for the bias term and second–order coefficients are solved for simultaneously and are similar to those used by Parker *et al.* (2001), but with a shift because the second pair of pulses are the only ones used for second–order identification:

$$\hat{h}_0 = \frac{y(0)+y(M+1)}{4} + \frac{y(2M+2)+y(3M+3)}{4} \tag{6}$$

$$\hat{h}_2(k,k) = \frac{(y(k+2M+2)-y(2M+2))}{2\gamma_2^2} + \frac{(y(k+3M+3)-y(3M+3))}{2\gamma_2^2} \tag{7}$$

Likewise, the equations for $\frac{\partial J}{\partial h_1(k)} = 0$ and $\frac{\partial J}{\partial h_3(k,k,k)} = 0$ can be solved simultaneously to yield the estimators:

$$\hat{h}_1(k) = \frac{\gamma_2^3(y(k)-y(k+M+1))}{2\gamma_1\gamma_2(\gamma_2^2-\gamma_1^2)} - \frac{\gamma_1^3(y(k+2M+2)-y(k+3M+3))}{2\gamma_1\gamma_2(\gamma_2^2-\gamma_1^2)} \tag{8}$$

$$\hat{h}_3(k,k,k) = \frac{\gamma_2(y(k)-y(k+M+1))}{2\gamma_1\gamma_2(\gamma_2^2-\gamma_1^2)} - \frac{\gamma_1(y(k+2M+2)-y(k+3M+3))}{2\gamma_1\gamma_2(\gamma_2^2-\gamma_1^2)} \tag{9}$$

Note that the h_1 estimator from (Parker *et al.*, 2001) has changed to include a correction term as a result of using the third–order Volterra model structure. In the noise–free case, the estimators in equations (6) through (9) provide excellent coefficient identification. To eliminate the effects of measurement noise, the input sequence would have to be repeated and the coefficient estimates averaged over the number of pulse repetitions, as in (Parker *et al.*, 2001).

4. DIABETIC PATIENT CASE STUDY

The goal of the current work is to approximate diabetic patient glucose–insulin dynamics in an input–output sense using a Volterra series model. The physiological model in Parker *et al.* (2000) was treated as the "real" patient and was therefore used as a data generator. The steady state locus of the diabetic patient model is shown in Figure 1. This system is linear in a local region of the nominal state ($y_s \approx 81, u_s \approx 22$), but the hyperglycemic and hypoglycemic regions display deviations from linear behavior. To account for this nonlinearity, and because the steady state curve resembles that of a third–order polynomial, a third–order nonlinear model was chosen for describing the insulin/glucose relationship. This empirical method requires minimal physical knowledge of the patient for model identification. A further advantage is the individualizability of the approach, as new parameter values would be identified for each patient. These

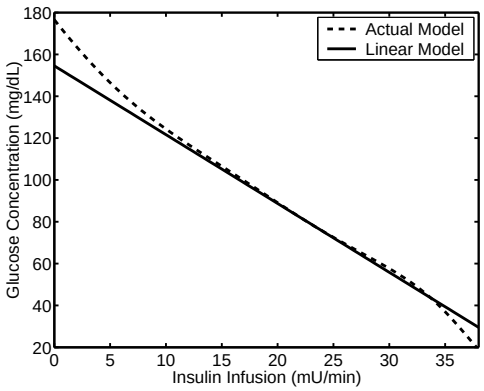

Fig. 1. Steady state locus for the diabetic patient. Nonlinear patient model (dashed), linear model (solid).

patient–specific models would further tailor the resulting control algorithm employed in a closed–loop device. A further advantage of employing Volterra series models is the relative ease with which a standard recursive least–squares algorithm can update the model to match time–varying patient dynamics.

4.1 *Linear/Diagonal Identification*

Prior to model identification, memory and sampling rate were determined. Upper bounds on both parameters ($M \leq 40, T_s \leq 10$ min) were imposed by numerical sensitivity of the parameter identification problem and closed–loop controller performance (based on author experience), respectively. Within these constraints, a sampling rate of 10 minutes and a memory length of 40 provided accurate model approximation. A 5–level sequence is adequate for the identification of linear, second–, and third–order diagonal coefficients. However, the placement of the symmetric pulses in equation (4) must be addressed.

While the output achieves 99% recovery after each pulse input, the 1% remaining from the larger pulse magnitudes has a magnitude equivalent to 5% to 10% of the small pulse magnitude output response. As such, the ordering of large pulses followed by small pulses resulted in models having decreased predictive accuracy. Hence, the 5–level quad–pulse sequence was implemented with small magnitude pulses followed by the larger pulses, as shown in Figure 2. The mathematical representation is given in equation (4), where $\gamma_2 = 7\gamma_1 = 22.3$ mU/min. The spacing of M steps (400 minutes) between pulses ensures that only linear and nonlinear diagonals terms are excited by the input sequence. By limiting the identification to linear plus nonlinear diagonal terms a reduction is achieved in the number of unique unknown coefficients from 12,341 to 121 (for $M = 40$), a $> 99\%$ reduction. The total input sequence (on–line) time for accurate linear/diagonal coefficient calculation using the above estimators is 1630 minutes.

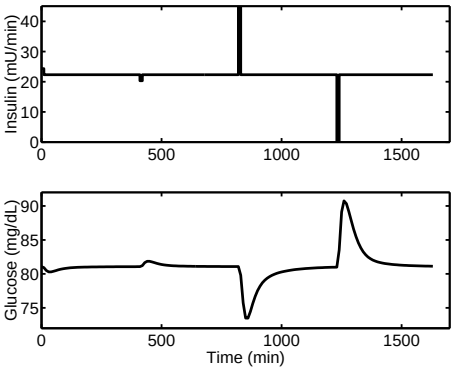

Fig. 2. Input sequence (top) and output response (bottom) for linear plus nonlinear diagonal coefficient identification.

4.2 *Less Complicated Model Structures*

Linear Model: Linear model identification used the 3–level binary pulse sequence from (Parker *et al.*, 2001), with $\chi = \gamma_2 = 22.3$ mU/min. The time required for identification was 810 minutes ($\approx \frac{1}{2}$ that required for linear plus second– and third–order diagonal terms). The performance of this model, shown in Figures 3 and 4, is worse than the nonlinear model in both dynamic (517% worse) and steady state (10% worse) accuracy using sum–squared error (SSE) as the error metric. A controller designed using a linear model

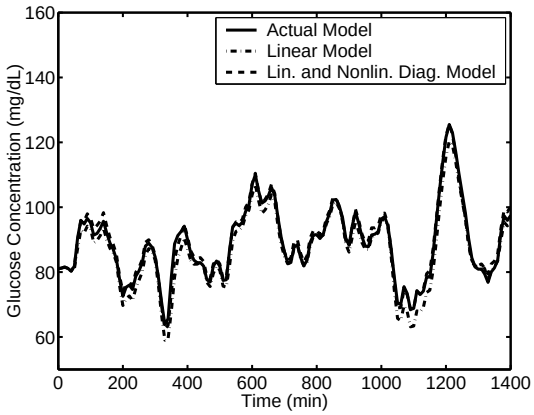

Fig. 3. Dynamic comparison versus a less complicated model. Actual patient (solid), linear plus second– and third–order diagonal model (dashed; nearly overlays solid), and linear model (dash–dot).

would suffer performance penalties due to the decreased dynamic accuracy.

Linear plus second–order diagonal: This model identification used the same sequence as for the linear model alone. When compared to the linear plus second– and third–order diagonal model, a loss of dynamic (37% worse) and steady state (7% worse) accuracy was observed based on SSE. Furthermore, the diabetic patient steady state locus does not possess input multiplicity, a qualitative characteristic of second–order polynomial models. As a result, the

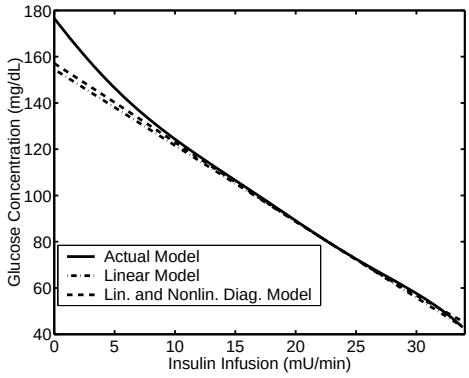

Fig. 4. Steady state comparison versus a less complicated model. Actual patient (solid), linear plus second– and third–order diagonal model (dashed), and linear model (dash–dot).

linear plus second-order diagonal structure is not a viable option for modeling the diabetic patient.

Linear and third–order diagonal: This model requires at least a 4–level input sequence, so the sequence from the top panel of Figure 2 was used. The resulting predictive accuracy of the model was significantly worse in both dynamic (462% worse) and steady state (57% worse) cases based on SSE. This error is primarily associated with the asymmetry observed in the actual patient glucose–insulin interaction that this model structure was unable to capture. Hence, the linear plus second– and third–order diagonal model is the least complex structure that adequately predicts glucose concentration as a function of insulin delivery rate.

4.3 *More Complicated Model Structures*

Nonlinear diagonal (linear plus nonlinear diagonal terms) plus third–order off–diagonal: Off–diagonal coefficients ($\mathscr{O}_2, \mathscr{O}_3$) can be calculated via cross–correlation using a random binary sequence (Pearson *et al.*, 1996), given by:

$$u(k) = \begin{cases} \gamma_2 & 0 \le p < 0.5 \\ -\gamma_2 & 0.5 \le p < 1 \end{cases} \qquad (10)$$

The random variable p takes values between zero and one, meaning that at each sample time the input either stays at its current value, or changes sign. A portion of this input sequence is shown in the top panel of Figure 5. Given the 9880 unique third–order off–diagonal coefficients, the input sequence would be at least 98,800 minutes, or ≈ 69 days, long at a ratio of one data point per coefficient. This is clearly infeasible in a clinical setting. As a computational exercise, this model was evaluated using dynamic and steady state SSE as an error metric. Figure 6 shows the significant improvement in steady state prediction (90% better), but the dynamic accuracy important in closed–loop model–based control was 77% worse as

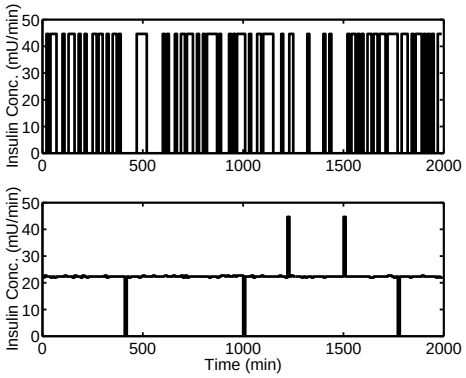

Fig. 5. First 200 samples for the second– and third–order off–diagonal (top) and third–order semi–diagonal (bottom) input sequences.

shown in Figure 7. Overall, the dynamic performance

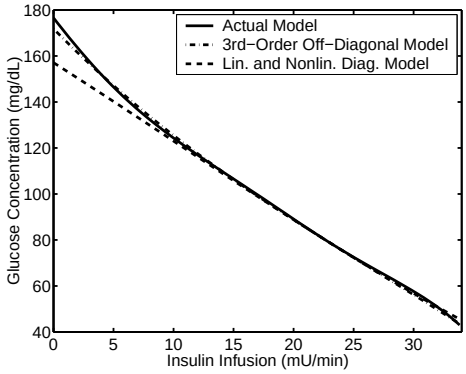

Fig. 6. Steady state comparison versus a more complicated model. Actual patient (solid), linear plus second– and third–order diagonal model (dashed), and nonlinear diagonal plus third–order off–diagonal model (dash–dot).

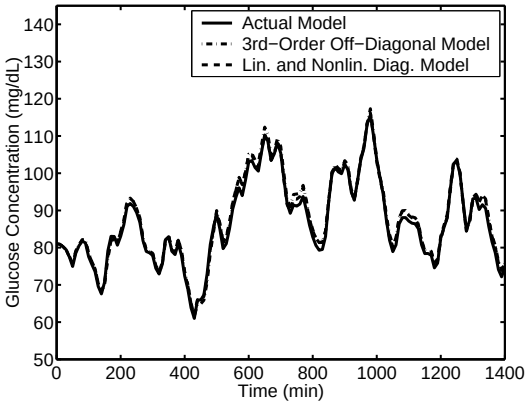

Fig. 7. Steady state comparison versus less complicated models. Actual patient (solid), linear plus second– and third–order diagonal model (dashed), and nonlinear diagonal plus third–order off–diagonal model (dash–dot).

and extended identification time required make this model unacceptable for the diabetic patient problem.

Nonlinear diagonal plus second– and third–order off–diagonal coefficients: The second–order off–diagonal coefficients can be identified using cross–correlation and a random binary input sequence as well. While the steady state accuracy was better than the nonlinear diagonal model (by 53%), this model is inferior to using the third–order off–diagonal coefficients alone. In addition, the dynamic predictive accuracy decreased by 273%. The extended identification time required above is still a significant issue in this case. Hence, this model is a poor choice for modeling this diabetic patient.

Nonlinear diagonal plus third–order semi–diagonal coefficients: An input sequence of at least four levels is required to identify the semi–diagonal coefficients ($\mathscr{S}_3$). The current work used a 5–level input sequence having the following probability distribution:

$$u(k) = \begin{cases} \gamma_2 & 0 \le p < 0.01 \\ \gamma_2/56 & 0.01 \le p < 0.14 \\ 0 & 0.14 \le p \le 0.86 \\ -\gamma_2/56 & 0.86 < p \le 0.99 \\ -\gamma_2 & 0.99 < p \le 1.0 \end{cases} \qquad (11)$$

A portion of this input sequence is shown in the bottom panel of Figure 5. While the steady state accuracy of this model was the best of all models considered (92% better), the dynamic performance was still inferior to the nonlinear diagonal model by 146%. Furthermore, to identify the 1560 unique coefficients requires at least 15,600 min ($\approx$ 11 days) of on–line time at one data point per coefficient, which is clinically unacceptable. Again, the increased complexity requiring significant data acquisition time is not adequate for patient modeling.

5. CONCLUSIONS

This paper presents an identification algorithm for third–order Volterra series models. Using tailored input sequences, specific coefficient contributions were excited and identified from diabetic patient data. A 5–level sequence with M points between each pulse was used to identify the linear and nonlinear diagonal terms. The order of input pulses significantly affected the predictive accuracy of the resulting model, such that the small magnitude pulse pair must precede the larger magnitude pulse pair. Partitioning the data acquisition over two days, as would be necessary in an actual hospital setting, did not significantly effect model accuracy (results omitted due to space constraints).

The nonlinear diagonal model was clearly demonstrated to be superior to all Volterra series alternatives for a variety of reasons. Based on a sum–squared error metric, models of lesser and greater complexity routinely demonstrated performance losses in dynamic accuracy. Steady state model approximations improved (in general) as more contributions were included, but often at the cost of dynamic performance. Even for those processes where steady state approximation accuracy improved, it was often achieved using input sequences that are clinically irrelevant in terms of the required amount of data (up to 69 days). For these reasons, a Volterra series model composed of linear plus nonlinear diagonal contributions offers the best trade–off in terms of: (i) model complexity, (ii) predictive accuracy, and (iii) in–hospital patient time.

6. ACKNOWLEDGMENTS

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