European Journal of Control (2005)11:601–616

European Journal of Control

Empirical Modeling for Glucose Control in Critical Care and Diabetes

J.A. Florian Jr. and R.S. Parker*

Department of Chemical and Petroleum Engineering, University of Pittsburgh, Pittsburgh, PA 15261, USA

Empirical Volterra series models of glucose–insulin behavior were identified from input–output data provided by a physiologically-based nonlinear patient model. While completely identified nonlinear Volterra models provided accurate output prediction, clinical data limitations constrained the structure of the Volterra series to linear plus nonlinear diagonal coefficients. In the absence of measurement noise, the ability of this structurally constrained model to capture process dynamics was very good. The addition of Gaussian distributed measurement noise, having variance 10 mg^2/dL^2, significantly degraded coefficient estimates, but projection onto the Laguerre basis (with subsequent expansion to the Volterra space for analysis) provided excellent noise-filtering and model predictions requiring only 164 measurements to identify 121 Volterra coefficients. Linear and nonlinear model predictive control algorithms were developed from the identified Volterra models. In the absence of measurement noise, nonlinear control algorithms provided mild performance enhancement in rejecting a 50 g glucose challenge. With the addition of measurement noise matching the above noise characteristics, the benefits of nonlinear control were lost. The superiority of the nonlinear empirical model to capture open-loop data did not translate into closed-loop performance enhancement in the presence of measurement noise. Linear model predictive control, with the ability to filter noise effects by proper tuning, provided the best combination of performance and robustness to uncertainty (both measurement and model) in this nonlinear case study.

Keywords: Critical Care; Diabetes; Identification; Laguerre Basis; Model Predictive Control; Volterra Series

1. Introduction

Patient survival and recovery in a critical care setting can be dramatically improved by carefully regulating plasma glucose concentration [11,16,27,58,59]. The cause of elevated glucose levels in critical care patients may be because of changes in insulin sensitivity leading to systemic resistance [54,59,61,62]. In the case of critical care patients, the pancreatic β-cells release an insufficient amount of insulin to maintain normoglycemic plasma glucose levels (usually defined in diabetics as 70–120 mg/dL [6,7]). To counteract this elevation in plasma glucose concentration, a recent study evaluated the effect of infusing exogenous insulin to patients recovering in a critical care setting [60]. Patients in the intensive treatment arm had their insulin infusion rates changed at 1–4 h intervals to maintain glucose in the 80–110 mg/dl range. The standard treatment arm was dosed with insulin only if glucose concentrations exceeded 215 mg/dl, and then glucose was controlled between 180 and 200 mg/dl. The results were dramatic; glucose control in critical care provided reductions in patient mortality by 34%, blood infection by 46% and renal failure by 41%, as well as a 48% decrease in the number of patients

*Correspondence to: R.S. Parker 1249 Benedum Hall, Pittsburgh, PA 15261 USA. Tel.: +1-412-624-7364. E-mail: rparker@pitt.edu

Received 1 June 2004; Accepted 11 October 2005. Recommended by G. Dumont and D.W. Clarke.

spending more than 5 days in the intensive care unit [59]. Other studies have indicated improvements in survival [27], clinical outcomes [11], and mortality rate [16] by controlling glucose concentrations. Currently, glucose is controlled by adjusting insulin infusion rates, and these rates are established using a titration algorithm [58,59]. This means that ICU staff must periodically measure glucose concentrations, calculate a new insulin infusion rate and set the delivery pump. An automated closed-loop algorithm, using a patient-specific model, could reduce the burden on ICU staff while simultaneously improving glucose concentration control.

The development and deployment of a closed-loop glucose control device is one approach to accomplishing these potential performance improvements. This insulin delivery solution would consist of three primary components: a glucose sensor (a topic of intense interest, e.g. Refs [4,20,21,28,46,57]); an insulin delivery mechanism (e.g. Refs [5]); and a mathematical algorithm for calculating insulin delivery amounts based on blood glucose measurements (also a popular research topic). A number of different mathematical approaches have been employed in blood glucose control design, such as nonlinear PID algorithms [56], optimal control theory [13,18,33], adaptive methods [3,12,52], and model predictive control [26,34,36,39,42,45]. The focus of the present work is algorithm development for blood glucose control, and model-based methods are employed because theoretically achievable performance scales directly with model quality [30]. Therefore, the development of a control-relevant, and clinically-relevant, model of patient glucose–insulin dynamics is paramount. Given the breadth of critical care and diabetic patient characteristics, the patient model within the algorithm must be easily customizable to individual patient dynamics. Furthermore, there exist severe data requirements that limit model construction, whereby physiologically-based pharmacokinetic/pharmacodynamic models may not be identifiable. Hence, the present work develops efficient model identification techniques, and a corresponding model-based control algorithm, capable of providing patient-tailored models and maintaining blood glucose control within healthy patient bounds.

2. Clinically-Relevant Model Identification

The model structure used to approximate patient glucose-insulin dynamics in the present work is the nonlinear Volterra series, given by:

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

Here N is the Volterra model order, h_i are the Volterra kernels and M is the model memory. This discrete-time, single-input single-output (SISO) model structure can be used to approximate fading-memory nonlinear systems where it is assumed that the past input effects on the output become less significant as the model memory length, M, is approached.

Identifying the coefficients of a Volterra series model from patient data requires efficient algorithms because the amount of clinical data for a given patient is extremely limited as compared with traditional chemical process data. However, it is reasonable to collect a short window of high-fidelity data that will facilitate model construction, as sampling at 10 min intervals can be accomplished by clinicians or automated devices [2,57]. The quality of a model is measured by prediction error variance, as in Refs [14,43]. This facilitates a decomposition of the Volterra model along particular model contributions as follows:

$$\hat{y}(k) = h_0 + L(k) + D_2(k) + O_2(k) + D_3(k) + S_3(k) + O_3(k), \quad (2)$$

$$L(k) = \sum_{i=1}^{M} h_1(i)u(k-i),$$

$$D_2(k) = \sum_{i=1}^{M} h_2(i,i)u^2(k-i),$$

$$O_2(k) = 2\sum_{i=1}^{M}\sum_{j=1}^{i-1} h_2(i,j)u(k-i)u(k-j),$$

$$D_3(k) = \sum_{i=1}^{M} h_3(i,i,i)u^3(k-i),$$

$$S_3(k) = 3\sum_{i=1}^{M}\sum_{j\neq i}^{M} h_3(i,i,j)u^2(k-i)u(k-j),$$

$$O_3(k) = 6\sum_{i=1}^{M}\sum_{j=1}^{i-1}\sum_{p=1}^{j-1} h_3(i,j,p)u(k-i)u(k-j)u(k-p).$$

Here $L(k)$ represents the linear term, $D_N(k)$ represent the N-th order diagonal terms, $O_N(k)$ represent the N-th order off-diagonal terms, $S_N(k)$ represent the N-th order sub-diagonal terms, and $y(k)$ and $u(k)$ are glucose concentration and insulin infusion rate in deviation form, respectively. Coefficients for off-diagonals and sub-diagonals are assumed to be