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Model Predictive Control of Blood Glucose in Type 1 Diabetes: the Principal Dynamic Modes approach

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Abstract — **This computational study demonstrates the efficacy of regulating blood glucose in Type 1 diabetics with a Model Predictive Control strategy, utilizing a nonparametric / Principal Dynamic Modes model. For this purpose, a stochastic glucose disturbance signal is introduced and a simple methodology for predicting its future values is developed. The results of our simulations confirm that the proposed algorithm achieves very good performance, is computationally efficient and avoids hypoglycaemic events.**

I. INTRODUCTION

Several papers have demonstrated the feasibility of regulating blood glucose in Type 1 diabetics via Model Predictive Control (MPC) [1]-[5]. The vast majority of them adopt a parametric approach to modeling the insulin – glucose dynamics: the available input - output data sets are fitted in a pre-determined model structure. Very few studies till now have used the alternative nonparametric / Volterra modeling approach (e.g. [3]), where the structure of the model is actually driven by the data. However, even there, the nonparametric model utilized is usually constrained in some sense (e.g. it includes only the diagonal terms of the higher order Volterra kernels).

The present computational study attempts to go one step further: we derive a discrete-time, nonparametric model of the insulin – glucose dynamics in Type 1 diabetes, but in the much more intuitive and parsimonious form of the Principal Dynamic Modes (PDM) [6]. We also introduce a stochastic glucose disturbance signal and briefly present the MPC algorithm. The results of our simulations are followed by a discussion and possible future directions of research.

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II. METHODS

A. PDM model of Glucose Metabolism in Type 1 Diabetes

In [7], a new minimal model structure for the metabolism of glucose is introduced. The new model, termed the Augmented Minimal Model (AMM), is described by the following differential equations:

$$\frac{dI}{dt} = -\gamma_I \cdot I(t) + \beta \cdot \max[G(t) - \theta_I, 0] + D_I(t)$$

$$\frac{dN}{dt} = -\gamma_N \cdot N(t) + \alpha \cdot \max[\theta_N - G(t), 0]$$

$$\frac{dX}{dt} = -p_2 \cdot X(t) + p_3 \cdot I(t)$$

$$\frac{dG_I}{dt} = -p_1 \cdot G_I(t) - X(t) \cdot G(t)$$

$$\frac{dG_N}{dt} = -p_4 \cdot G_N(t) + p_5 \cdot N(t)$$

$$G(t) = G_b + G_I(t) + G_N(t) + D_G(t)$$

where I represents plasma insulin, N plasma glucagon and X insulin action (all deviations from basal values). G_I is the deviation of blood glucose from the basal value (G_b=90 mg/dl) due to insulin action, G_N is the deviation of blood glucose from the basal value due to glucagon action and G is the concentration of blood glucose. D_I is the intravenous insulin input and D_G the glucose disturbance (e.g. meals). Based on simulations of Sorensen's model [8] and published data, we have concluded that the following set of parameters can represent the dynamics of Type 1 diabetes: p_1=0.013, p_2=0.063, p_3=9·10^{-6}, p_4=0.04, p_5=0.016, β=0, γ_N=3·10^{-3}, α=8·10^{-4} and θ_N=83 (γ_I and θ_I do not matter since β=0).

By simulating the AMM presented above, we produce discrete-time, broadband input - output data with sampling period equal to 3 minutes. Then we decompose the dynamics captured in that data in a linear filter, the Principal Dynamic Mode (from which quantities like peak value, peak time, time constant and memory of the system are directly observable) and a nonlinearity in series, through which the output of the filter is transformed. The result of this identification procedure is the PDM model of Figure 1: the left panel presents the linear filter whereas the right panel shows the corresponding nonlinearity and its linear approximation, which will be used later on. The normalized mean square error of the identification is 1.36% for the nonlinear PDM model and 5.68% for the linear one.

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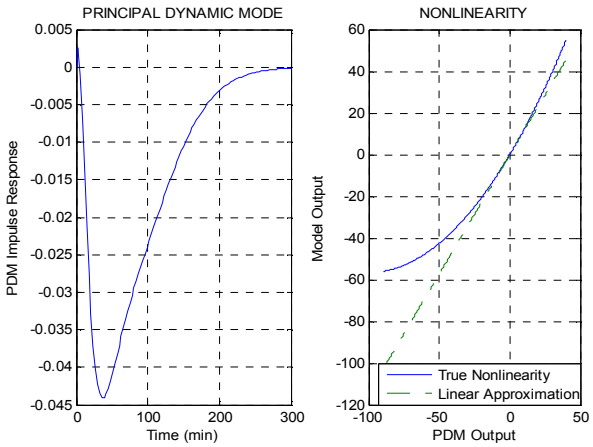
Note that the output of the PDM model of Figure 1 corresponds to the deviation of blood glucose concentration from its basal value (G-G_b).

FIGURE 1
THE NONLINEAR PDM MODEL OF THE INSULIN-GLUCOSE DYNAMICS AND ITS LINEARIZED COUNTERPART



B. Glucose Disturbance

We define as glucose disturbance every factor that causes blood glucose to deviate from its basal value. For the purposes of this study we have considered a glucose disturbance signal D_G, which is additive to the output of the PDM model and includes the following components:

- Three gamma-like functions (of the form $t^3 \cdot e^{-0.4t}$) every 24 hours of simulation, representing the effects of the three daily meals. These gamma-like functions have peak value 40, 60 and 50 mg/dl (breakfast, lunch and dinner), peak time about 80 minutes and random times of occurrence (uniformly distributed within specified periods). The meal forms are roughly equivalent to small Lehmann - Deutsch meals [9].
- Two sinusoids with periods 8 and 24 hours respectively, phases uniformly distributed within [0 , π] and amplitudes 10 mg/dl. These sinusoids attempt to capture the diurnal and circadian rhythms of glucose [10], [11].
- Gaussian White Noise (GWN), additive to the sum of the other two components, with signal-to-noise ratio 20 dB. This term represents small-scale, unknown factors that affect the concentration of blood glucose.

In contrast to the vast majority of similar publications, this computational study considers also stochastic, non-meal disturbance factors, in an attempt to make the glucose disturbance signal more realistic and also more challenging for the controller.

C. Prediction of Glucose Disturbance

In order to apply MPC we must be able to predict accurately the future values of blood glucose concentration. Apart from having a good description of the insulin – glucose dynamics and knowing all the past insulin inputs, this also implies our ability to predict accurately the future values of glucose disturbance. To achieve this we hypothesize that the glucose disturbance signal D_G can be considered as the output of an Auto-Regressive (AR) model:

$$D_G(n) = D \cdot \alpha + w(n)$$
$$D = [\, D_G(n-1)\ D_G(n-2) \ldots D_G(n-K)\,]$$
$$\alpha = [\alpha_1\ \alpha_2\ \ldots\ \alpha_K]^{\mathrm{T}}$$

where α is the vector of coefficients of the AR model, w is an unknown "innovation process" (ideally a white sequence), and K is the order of the AR model.

At a discrete-time instant n, the prediction task consists of estimating the coefficient vector α, which in turn will allow us to estimate the future values of glucose disturbance: a consequence of the Certainty Equivalence Principle is that we can use the already estimated disturbance values as if they were real, in order to compute the glucose disturbance over the desired future horizon using sequentially the AR model. In that way the issue of predicting disturbance is transformed to an equivalent parameter estimation problem. The estimation of the coefficient vector can be performed with the method of linear least-squares as:

$$\alpha = [A^T A]^{-1} A^T b$$

where A is a matrix constructed with the appropriate values of the D vectors over M discrete times ($M>K$) and b is the corresponding vector of disturbance values [12]. Note, however, that we do not know apriori whether the least-squares criterion is appropriate in the AR context; what is most pertinent is the lack of correlation among the residuals. For this reason, we also compute the autocorrelation of the residuals and seek to make its values for all non-zero lags statistically insignificant, a fact indicating that all structured / correlated information in the glucose disturbance signal has been captured by the AR model. A critical part of this procedure is the determination of the best AR model order K, at every discrete-time instant. This is performed using the Akaike Information Criterion (AIC) [13].

D. Model Predictive Control

Having knowledge of the PDM model describing the dynamics between insulin and glucose, all the past insulin inputs and an estimate of the future values of glucose disturbance, the goal of the MPC is at every time instant n to determine the control input value $U(n)$, so that the following cost function is minimized:

$$J(n) = [G(n+p\,|\,n) - R]^T \cdot \Gamma_y \cdot [G(n+p\,|\,n) - R] + \Gamma_U \cdot U(n)^2$$

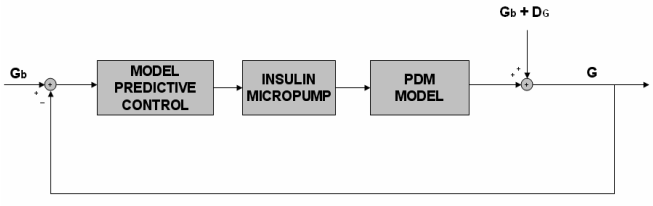
where $G(n+p|n)$ is the vector of predicted output values over a future horizon of p steps (20 samples in the present study), R is the target value for the output (set equal to G_b), Γ_y is a diagonal matrix of weighting coefficients that assigns greater importance to the near-future predictions (negative exponential with time constant of 1 hour) and Γ_U a scalar,

determining how "expensive" is the insulin input (considered 0 here). More details on MPC, the Certainty Equivalence Principle and relevant control issues can be found in [14]. The notion of asymmetric weight is also utilized (see e.g. [15]), as a measure of precaution against hypoglycaemia.

E. Closed-Loop System

In our simulations the PDM model plays the role of the real system. The objective of the MPC is to attenuate the effects of the disturbance signal D_G and keep the error signal (G_b-G) within bounds, defined as the normoglycaemic region (a conservative definition of the normoglycaemic region used in this study is from 70 to 110 mg/dl). The use of an insulin micro-pump is simulated with the imposition of an upper bound of 80 mU/min on the magnitude of the exogenous insulin rate. A block diagram of the closed-loop system considered in this study can be seen in Figure 2.

FIGURE 2
CLOSED-LOOP SYSTEM FOR BLOOD GLUCOSE REGULATION



III. RESULTS

A. Plant – Model Match

We begin this section by examining the case when the MPC algorithm has perfect knowledge of the nonlinear PDM model. The figures presented below aim to give insight into how our algorithm works and the performance it achieves under all conditions stated above.

Figure 3 presents the blood glucose concentration without control and with MPC, in its upper panel. The lower panel shows the intravenous insulin infusion rate (superimposed to the basal rate) as determined by the MPC. Obviously the proposed algorithm can regulate well blood glucose and is able to deal with both positive and negative deviations of glucose from its basal value (the latter by reducing the rate of infusion below the basal).

In Figure 4 we can see how the order of the AR-Model varies with time, as determined by the AIC, for the simulation of Figure 3. Even though several hypotheses can be made about its relation with the glucose disturbance structure, none can be verified by the results we have seen after numerous simulation runs.

Figure 5 demonstrates the autocorrelation function of the innovation process w. The fact that its value for all non-zero time lags is statistically insignificant (smaller than the confidence bounds determined by the null hypothesis that the residuals are uncorrelated with zero mean) implies that most of the structure of the glucose disturbance signal is captured by the AR-Model. This result is very important, considering that we have included a significant level of GWN in our disturbance.

FIGURE 3
BLOOD GLUCOSE WITH AND WITHOUT MPC AND THE CORRESPONDING INSULIN INFUSIONS

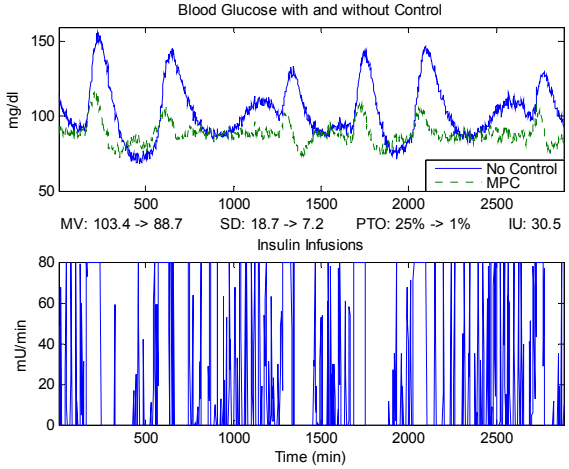
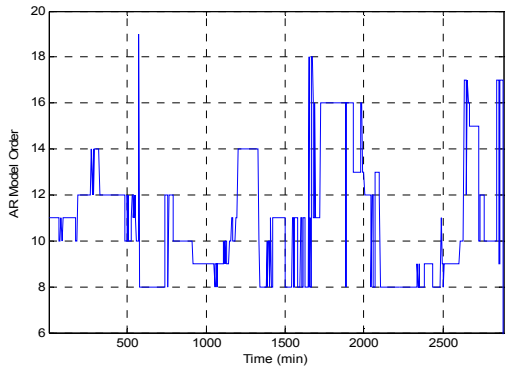


FIGURE 4
THE ORDER OF THE AR-MODEL FOR GLUCOSE DISTURBANCE PREDICTION



In Table 1 we present the average behavior of the MPC algorithm with perfect knowledge of the PDM model (denoted as PM on the Table), based on some widely accepted metrics of performance: the mean value of blood glucose (MV), its standard deviation (STD), the percent of time that glucose is outside the target regions of [70 , 110] mg/dl (PTO) and the average insulin per day required (IU). In the same Table we present the case of "No Control" (only the basal infusion rate) for comparison with MPC. The number of hypoglycaemias that occurred is a good measure of the patients' safety and is also given.

B. Plant – Model Mismatch

Finally, we consider one of the possible cases of plant – model mismatch: we assume that the MPC has access only to the linearized version of the PDM model (dashed line in the right panel of Figure 1) and not the full nonlinear model. The average behavior of the MPC algorithm in the case of plant – model mismatch (denoted as PMM) can be found again in

Table 1. Comparison with the "perfect model" case shows a very slight degradation in performance; the MPC is still able to regulate very well blood glucose and not risk the patients' safety.

FIGURE 5
AUTOCORRELATION OF THE RESIDUALS OF THE AR-MODEL

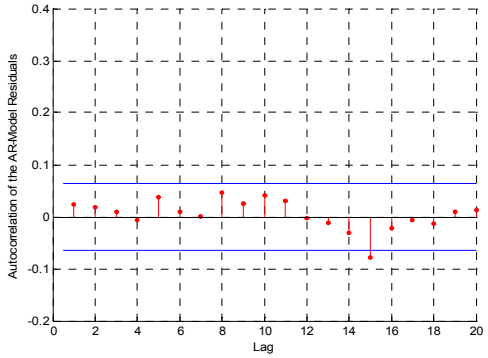


TABLE 1
AVERAGE BEHAVIOR OF THE MPC FOR 30 INDEPENDENT SIMULATION RUNS OF 48 HOURS EACH

	NO CONTROL	MPC (PM)	MPC (PMM)
MV	103.1	89.8	91.4
STD	21	7.8	7.6
PTO	26	2	3
IU	14.8	29.8	27.5
HYPO	0	0	0

IV. DISCUSSION

The present computational study of Model Predictive Control of blood glucose seeks to:

- Demonstrate that the insulin – glucose dynamics of Type 1 diabetes can be captured with a data – driven, nonparametric model in the form of Principal Dynamic Modes. This form provides a parsimonious and intuitive discrete – time representation of the actual system.
- Show the efficacy of utilizing PDM models in model-based strategies for the regulation of blood glucose. The results of our simulations strongly suggest that a PDM - MPC strategy can regulate blood glucose very well under the presence of stochastic, noise - corrupted disturbance, and at the same time avoid dangerous hypoglycaemic events.
- Provide an alternative way for predicting blood glucose disturbance: an Auto-Regressive model, whose order is determined adaptively by the AIC, is able to capture the basic structure of a stochastic disturbance signal, even if it is corrupted by noise. This approach is conceptually simple and provides an alternative to other, more sophisticated techniques (such as the Kalman filter [2]).

A side – conclusion of this study comes up by the results of the "plant – model mismatch" case: in Type 1 diabetics the control design can be based on a linearized version of the model of insulin – glucose dynamics and not necessarily the precise nonlinear one. A look at Figure 3 shows that regulated blood glucose does not exceed ± 20 mg/dl from the basal value. In Figure 1 we can see that for deviations up to this magnitude, the system operates in the linear region anyway.

The results and conclusions of this paper depend critically on the assumption that the model of Sorensen (from which the AMM and the PDM models are derived) is an accurate description of the blood glucose regulation system. Sorensen's model was derived out of numerous real data sets and several computational studies have used it to date, as a representation of the actual metabolic system [1], [2], [16]. Naturally, clinical validation of both the nonparametric model and the performance of the control strategy developed here, are necessary future directions in our research.

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