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Computational Study of an Augmented Minimal Model for Glycaemia Control

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Abstract — **In this paper we introduce a new model structure for the metabolic effects of intravenous insulin on blood glucose in man and derive its parameter values from the widely used model of Sorensen. The proposed model attempts to combine the advantages of the existing comprehensive and minimal models. Validation of the new model is done through deriving equivalent nonparametric nonlinear models in the form of Principal Dynamic Modes. We show that the new structure can represent the insulin – glucose dynamics of healthy subjects as well as Type 1 and Type 2 diabetics, with appropriate adjustment in its parameters.**

I. INTRODUCTION

It is well known that the basic hormones affecting the metabolism of blood glucose in man are insulin and glucagon. Throughout the last 25 years researchers have tried to capture in various models the full complexity of these nonlinear, closed-loop interactions. On one hand, comprehensive models of the glucose metabolism [1]-[3] use a large number of states and parameters and nonlinear metabolic sources and sinks to model the dynamics of the real system. On the other hand, most of the minimal models proposed to date like [4]-[6] try to represent only a part of the actual dynamics, by completely disregarding the effects of glucagon and neglecting the procedure of endogenous insulin production. This computational study seeks to bridge the gap between the existing comprehensive and minimal models of the glucose metabolism by introducing a new model structure, which is capable of capturing all basic factors affecting this procedure, and the corresponding dynamics. Towards a similar direction is the work in [7], even though it focuses on modeling the contribution of free fatty acid and the case of Type 1 diabetes. In some aspects, this paper can be considered as the continuation and generalization of the research efforts in [8].

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II. THE AUGMENTED MINIMAL MODEL

The aim of this study is to introduce a new model of the glucose metabolism, termed the Augmented Minimal Model (AMM) that satisfies the following specifications:

- It models the effects of both insulin and glucagon on blood glucose concentration.
- It includes time-independent sections for endogenous insulin and glucagon production, in agreement with the approach in [8].
- It incorporates the effects of exogenous "disturbance" factors on plasma insulin and blood glucose (e.g. exogenous insulin infusions or meals).

A model structure that satisfies these specifications is the following:

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

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

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

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

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

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

where the implicated variables are:

I: deviation of plasma insulin concentration from its basal value (15 mU/L in healthy subjects)

N: deviation of plasma glucagon concentration from its basal value (75 ng/L in healthy subjects)

X: insulin action (in min^{-1})

G_I: deviation of blood glucose concentration from its basal value due to insulin action (in mg/dL)

G_N: deviation of blood glucose concentration from its basal value due to glucagon action (in mg/dL)

G_b: basal value of blood glucose concentration (assumed 90 mg/dl in this study)

G: concentration of blood glucose (in mg/dL)

D_I: insulin disturbance (in mU/L/min)

D_G: glucose disturbance (in mg/dL)

The insulin disturbance signal D_I can model either exogenous insulin infusions or endogenous oscillations in insulin concentration [9]. The glucose disturbance D_G is meant to capture the factors affecting directly blood glucose, like meals. Note that both D_I and D_G are exogenous variables and represent inputs to the system (in a wider sense) and not states.

A special note on the structure of endogenous glucagon production: it is known that endogenous glucagon production depends not only on the concentration of blood glucose but also on the concentration of plasma insulin. For the sake of simplicity we decide to omit this secondary feedback mechanism (although this effect is captured in Sorensen's Model).

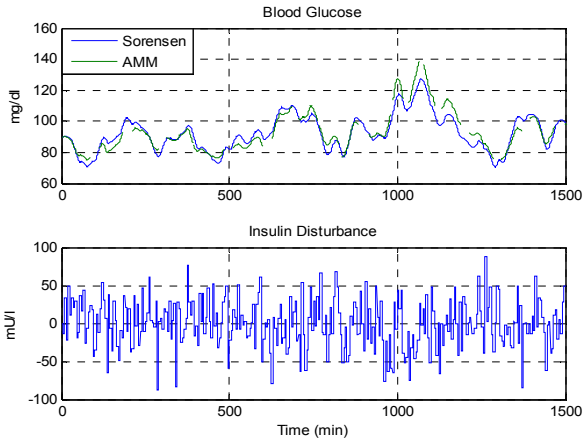
Reference values for the parameters of the AMM are computed, using the comprehensive model of Sorensen [1]. Sorensen's model (SM) was derived out of numerous real data sets and several research groups have used it for their computational studies the last years, as a representation of the actual metabolic system [10]-[12]. Hence, we assume that it is likely to represent well the dynamics of the real system. However we do not make any claims about the model's universal validity; we use it as an analytical tool in order to make an "educated guess" about the AMM parameters.

Since the AMM operates in "closed-loop" (having two feedback loops), in order to estimate its parameters we adopt the strategy of artificially opening-the-loop: each of the four loops of the model (insulin to glucose, glucagon to glucose, glucose to insulin, and glucose to glucagon) is estimated independently of the others. By opening-the-loop artificially in SM we produce appropriate input-output data sets to which every loop of the AMM is fitted. Very briefly, the feedback loops (endogenous insulin and glucagon production) are computed from input-output data generated by the respective metabolic sources in SM. The forward loop of insulin is identified from input-output data after removing the feedback loops and the effects of glucagon from the general model. In a similar way, the forward loop of glucagon is estimated. All input signals used during the identification procedure are broadband (Gaussian White Noise) with carefully selected dynamic ranges, so that they fully excite the dynamics of each loop. The fitting procedure mentioned above is a nonlinear, least squares fitting, performed with the *nlinfit* command in MATLAB. The resulting parameters of the AMM for healthy subjects (since SM, with the parameters given in [1] represents healthy subjects) are shown in Table 1.

Since the AMM is developed for glycaemia control, we focus on its input (D_I) – output (G) properties. In Figure 1 we present the responses of the SM and the AMM (upper panel) to a common broadband insulin input (lower panel). Obviously, the responses of the two models are very close.

A way of gaining insight into the dynamics of the two models (and indirectly confirming the validity of the new model) is by deriving the equivalent nonparametric / Principal Dynamic Modes (PDM) models [13] of SM and the AMM. A common broadband insulin disturbance signal is used to excite the dynamics of both models, and thus create input-output data from which the PDM models are derived. The dynamics of each model are decomposed in a linear filter, the PDM (from which quantities like peak value, peak time, time constant and memory of the system are directly observable) and a corresponding nonlinearity, through which the output of the PDM is transformed. Figure 2 shows that the PDM of the AMM is very similar to that of SM, only slightly scaled. However we also notice an important difference in the nonlinearities of the two models: SM appears to be almost linear whereas the AMM exhibits a convex nonlinearity. Both results are justifiable: the nonlinearities of SM (hypertangent functions of metabolic sources and sinks) are almost linear around the operating point – the convexity and the saturation effect of the AMM is due to its bilinear term. We cannot be positive regarding which nonlinear form "makes more sense" in terms of physiology. Further clinical investigation is required.

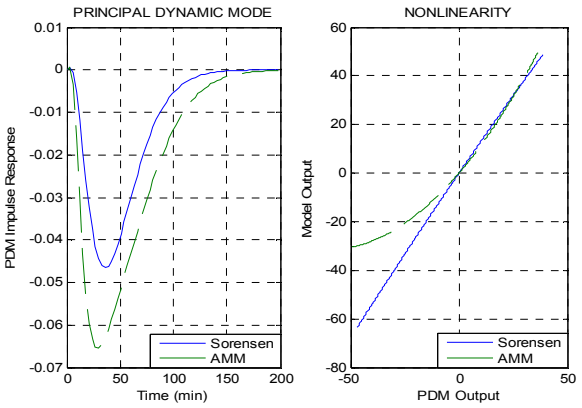
FIGURE 1
COMPARISON OF THE RESPONSES OF THE AMM AND SORENSEN'S MODEL



III. THE AMM FOR DIABETIC PATIENTS

Since the case of Type 1 diabetes is widely studied and its physiological causes are relatively clear, the attention of the academic community has been focused lately on modeling and understanding Type 2 diabetes better (see e.g. [14]). One of the goals of this study is to demonstrate the ability to describe the glucose metabolism of healthy, Type 1 and Type 2 diabetics with a single minimal model (the AMM in our case). Applying some well-known physiological differences between healthy subjects and diabetics to SM, we produce new input-output data sets and then fit the AMM again to these data.

FIGURE 2
COMPARISON OF THE AMM WITH SORENSEN'S MODEL



A. Type 1 Diabetes

Type 1 diabetes is characterized by complete failure of the pancreatic beta cells, decreased (40 - 50% of normal) insulin stimulated hepatic and periphery glucose uptake and impaired, glucose-induced, endogenous glucagon production (assumed 0 – 50% of normal in this study). In Sorensen's terminology these are translated to:

$$r_{PIR} = 0$$

$$M_{HGU}^{I_\infty} = 1.45 \cdot \tanh(0.845 \cdot I_L^N)$$

$$r_{PGU} = r_{PGU}^B \cdot G_{PI}^N \cdot [3.965 + 3.2 \cdot \tanh(0.338 \cdot (I_{PI}^N - 5.82))]$$

$$M_{PTR}^G = x - (x - 0.83) \cdot \tanh[4.18 \cdot (G_H^N - y)]$$

$$x \in [0.92, 1.67]$$

$$y = 1 - \frac{1}{4.18} \tan\left(\frac{x-1}{x-0.83}\right)$$

The parameters of the AMM for the case of Type 1 diabetes are shown in Table 1. Note that the basic differences with the healthy case are in the parameters β (determining endogenous insulin production) and p_1 (the homogeneous dynamics of G_I). For the parameters determining endogenous glucagon production, ranges are given instead of precise values to account for different cases that may arise.

B. Type 2 Diabetes

Type 2 diabetes can be attributed to a large number of different physiological causes, of which the most important are: intermediate to significantly attenuated and delayed pancreatic insulin responsiveness (20 – 60% of normal for this study), decreased insulin stimulated hepatic and periphery glucose uptake (20 – 60% of normal for this study) and impaired, glucose-induced, endogenous glucagon production (20 – 60% of normal for this study). In Sorensen's terminology these are translated to:

$$\alpha = 0.02$$

$$\beta = 0.4$$

$$r_{PIR}^B \in [0, 10.2]$$

$$M_{HGU}^{I_\infty} = x \cdot \tanh(y \cdot I_L^N)$$

$$x \in [1.2, 1.5]$$

$$y = \tan\left(\frac{1}{x}\right)$$

$$\Sigma_{PGU} = \Sigma_{PGU}^B \cdot G_{PI}^N \cdot [u + v \cdot \tanh(0.338 \cdot (I_{PI}^N - 5.82))]$$

$$v \in [1.304, 3.912]$$

$$u = 1 - v \cdot \tan[0.338 \cdot (1 - 5.82)]$$

$$M_{HGP}^{I_\infty} = 1.21 - (1.21 - w) \cdot \tanh[1.66 \cdot (I_L^N - z)]$$

$$w \in [0.442, 0.814]$$

$$z = 1 - \frac{1}{1.66} \tan\left(\frac{1.21-1}{1.21-w}\right)$$

The parameters of the AMM for the case of Type 2 diabetes are also shown in Table 1. Note that a range of values is given for every parameter, as determined by the results of the least, squares fitting procedure to numerous input – output data sets.

TABLE 1
PARAMETERS OF THE AMM FOR HEALTHY AND DIABETIC SUBJECTS (AVERAGE VALUES OVER 20 INDEPENDENT DATA SETS)

	HEALTHY	**TYPE 1**	**TYPE 2**
p_1	0.022	0.013	[0.004 , 0.036]
p_2	0.075	0.063	[0.034 , 0.155]
p_3	$1.3 \cdot 10^{-5}$	$9 \cdot 10^{-6}$	$[3.1 \cdot 10^{-6}$, $1.3 \cdot 10^{-5}]$
p_4	0.04	0.04	[0.027 , 0.05]
p_5	0.016	0.016	[0.015 , 0.017]
γ_I	0.42	N / A	[0.43 , 0.56]
β	0.106	0	$[9 \cdot 10^{-4}$, 0.08]
θ_I	103	N / A	[101 , 114]
γ_N	$5.8 \cdot 10^{-4}$	$[0$, $1.2 \cdot 10^{-3}]$	$[4.5 \cdot 10^{-4}$, $9.5 \cdot 10^{-4}]$
α	0.0037	$[4 \cdot 10^{-4}$, $1.2 \cdot 10^{-3}]$	[0.0023 , 0.0049]
θ_N	83	[75 , 93]	[77 , 91]

In order to gain insight into the dynamics of the three AMM cases mentioned above, we present in Figure 3 their equivalent PDM models. In the case of Type 2 diabetes, where all the AMM parameters can vary significantly, we consider the lower bounds of the ranges given in Table 1.

IV. DISCUSSION

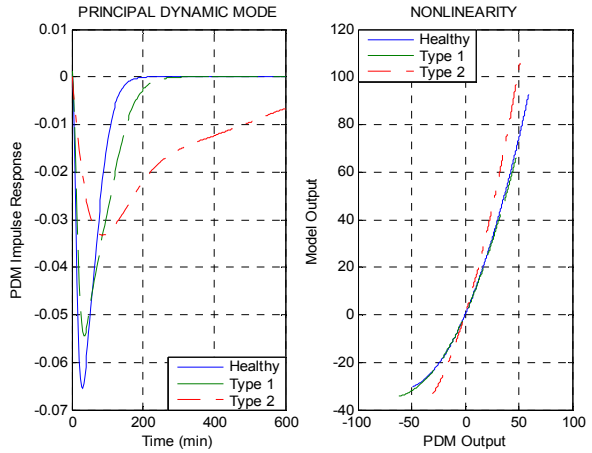
The introduction of the Augmented Minimal Model seeks to:

- Fill the gap between comprehensive models, which are too complicated for practical use, and the existing minimal

models that neglect glucagon action and are usually restricted to Type 1 diabetes.

- Provide direct insight into the closed-loop dynamics of glucose metabolism by incorporating the two main hormones affecting it (insulin and glucagon).
- Offer a meaningful order reduction of the well-known comprehensive model of Sorensen (by reducing the original 22 states and 44 parameters to only 5 states and 11 parameters) that can facilitate the design of glucose control in future computational or clinical studies.
- Represent healthy subjects, as well as Type 1 and Type 2 diabetic patients, with a simple adjustment of a few parameter values.

FIGURE 3
COMPARISON OF THE DYNAMICS OF THE AMM FOR HEALTHY, TYPE 1 AND TYPE 2 SUBJECTS



The presented results show that:

- The effects of glucagon on blood glucose are more direct than the respective effects of insulin, since glucagon does not seem to require a remote compartment from where to act (unlike insulin, which requires the insulin-action compartment). Also for healthy subjects, the endogenous dynamics of G_N are twice faster than the dynamics of G_1 (compare p_1 with p_4).
- The incorporation of the glucose disturbance D_G into the model can be additive to the output of the system and not a "rate disturbance" in the glucose-rate equation, as in several previous studies. With this approach, the effect of disturbance on glucose is independent of the dynamics of the model and of the identification procedure (e.g. does not depend on parameter p_1 like in the Bergman Model context).
- Figure 3 shows that the difference in dynamics between healthy subjects and Type 1 diabetics does not appear significant (i.e. the Type 1 PDM has a slightly smaller peak and a bit longer time constant). This might come as a surprise since Type 1 is considered the most severe type of diabetes. However, the severity of the disease does not necessarily imply great alteration in the system's dynamics. This conclusion, of course, depends critically on the way we have modeled Type 1 diabetes (in terms of the SM).
- The wide variety of symptoms of Type 2 diabetes can be easily discerned by inspecting the estimated parameters of the AMM. This may have important implications for improved diagnostic procedures.

This study also demonstrates the important fact that we can compare the dynamics of very different models and structures using the unified nonparametric / PDM approach.

Future work may be directed towards the clinical validation of the AMM for various cases of clinical interest. The proposed AMM structure is relatively simple and flexible so that easy modifications in parameter values can adjust to the knowledge gained by experimental data. Further analysis may also lead to improved representations of the model structure (e.g. replacing the threshold nonlinearities of endogenous insulin and glucagon production with hypertangent functions, including the "coupling" effect of insulin to glucagon production etc).

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