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A minimal model for glycemia control in critically ill patients

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Abstract— **In this paper we propose a modified minimal model to be used for glycemia control in critically ill patients. For various reasons the Bergman minimal model is widely used to describe glucose and insulin dynamics. However, since this model is mostly valid in a rather restrictive setting, it might not be suitable to be used in a model predictive controller. Simulations show that the new model exhibits a similar glycemia behaviour but clinically more realistic insulin kinetics. Therefore it is potentially more suitable for glycemia control. The designed model is also estimated on a set of critically ill patients giving promising results.**

I. INTRODUCTION

Hyperglycemia (i.e., an increased glucose concentration in the blood) and insulin resistance (i.e., the resistance of the glucose utilizing tissues to insulin) are common in critically ill patients (even if they have not had diabetes before) and are associated with adverse outcomes. Tight glycaemic control (between 80 and 110 mg/dl = target range) by applying intensive insulin therapy in patients admitted to the medical and the surgical intensive care unit (ICU) results in a spectacular reduction in mortality and morbidity ([10], [12]).

Currently, ICU patients are treated through a manual and rigorous administration of insulin ([11]). In order to design a model predictive controller (MPC) that (semi) automatically normalizes glycemia in ICU, it is necessary to develop a model that describes the glucose and insulin dynamics of these patients. In literature several physical models that describe the glucose dynamics and the insulin kinetics of healthy and diabetic subjects exist (e.g., Bergman et al. [2], Hovorka et al. [6], Parker et al. [8], among others). The Bergman model (also well known as "minimal model") is characterized by its low complexity (three state variables) which makes it easy to interpret clinically. It is widely used as reference model for other more complex physical compartmental models [6], [7], [8]. However, it is not valid beyond a certain time horizon.

In this paper we propose a modification of the minimal model so it can be valid for a longer time horizon and applicable in ICU. ICU patients have different clinical features than diabetic patients or healthy persons (who are the subjects of previously described models). With such extension the model can be used in practice to design an MPC for glycemia control in ICU. In the second part of this paper the dynamics of the developed ICU model are compared with those of a real life surgical ICU patient group. A first physical model to describe insulin and glucose dynamics of ICU-patiens has already been introduced in [3].

II. THE MINIMAL MODEL

In this section the original Bergman model and its related model for diabetic patients are presented. In the second part a modified minimal model that is designed for potential use of glycemia control in ICU is proposed.

A. Existing elementary models for glucose dynamics and insulin kinetics

1) The Minimal Model (MM) [2]: The original minimal model consists of a single glucose compartment. Plasma insulin is assumed to act through a so-called remote compartment to influence net glucose uptake [4]. The model reliably describes the plasma glucose disappearance [1] and the insulin kinetics [9] during an intravenous glucose tolerance test (IVGTT) in a healthy person. In this test 300 mg glucose per kg bodyweight is intravenously administered to a person after which the plasma glucose and insulin concentration are measured with a high sample frequency. The minimal model is described as follows:

$$\frac{dG(t)}{dt} = (P_1 - X(t))G(t) - P_1 G_b, \tag{1a}$$

$$\frac{dX(t)}{dt} = P_2 X(t) + P_3(I(t) - I_b), \tag{1b}$$

$$\frac{dI(t)}{dt} = \max(0, \gamma(G(t) - h)t) - nI(t), \tag{1c}$$

where $G(t)$ and $I(t)$ are the glucose and the insulin concentration in the blood plasma, respectively. The variable $X(t)$ describes the effect of insulin on net glucose disappearance and is proportional to insulin in the remote compartment. G_b and I_b are the basal value of plasma glucose and plasma insulin, respectively. The coefficient P_1 represents the glucose effectiveness (i.e., the fractional clearance of glucose) when insulin remains at the basal level; P_2 and P_3 are the fractional rates of net remote insulin disappearance and insulin dependent increase, respectively. The ratio P_3/P_2 is referred to as the *insulin-sensitivity index*. The endogenous insulin release during an IVGTT is composed of two different phases. First-phase insulin release is represented as a bolus of insulin (proportional to the glycemia rise) that enters the plasma compartment when glucose is injected. The first-phase insulin concentration in the plasma is symbolized by I_0. This insulin concentration cannot be estimated directly. Second-phase insulin release (modeled in equation (1c)), however, is represented as the insulin flow that is released in proportion (by γ) to the degree by which glycemia exceeds a glucose threshold level h. The time constant for insulin disappearance is denoted as n. In case glycemia does not

surpass the glucose threshold level h, the first part of this equation (that represents the endogenous insulin production) equals 0. The time that has passed since the administered glucose shot is denoted as t.

2) The Diabetic Minimal Model (D-MM) [4], [5]: In order to describe the glucose dynamics and insulin kinetics of a type 1 diabetic patient the original minimal model has been extended in [5]. Type 1 diabetes is characterized by insulin deficiency caused by an auto-immune destruction of the β-cells of the pancreas. Consequently, the endogenous insulin section (represented in (1c)) is replaced by an exogenous insulin flow (symbolized by F_I in (2c)). In addition, a meal glucose disturbance variable F_G is added to denote the glucose flow that enters the glucose compartment. The full model is described as follows:

$$\frac{dG(t)}{dt} = (P_1 - X(t))G(t) - P_1 G_b + \frac{F_G}{V_G}, \tag{2a}$$

$$\frac{dX(t)}{dt} = P_2 X(t) + P_3 I(t), \tag{2b}$$

$$\frac{dI(t)}{dt} = \frac{F_I}{V_I} - nI(t), \tag{2c}$$

where V_G and V_I are the glucose distribution space and the insulin distribution volume, respectively.

B. Extended minimal model for glucose dynamics and insulin kinetics in ICU: The ICU Minimal Model (ICU-MM)

In this section we present the contribution of this paper, by proposing an extended minimal model for use in an ICU setting. There are two main reasons why an extension of previously presented models may be necessary.

1) *A combined endogenous and exogenous insulin section:* The majority of the patients admitted to ICU are non-diabetic patients. It is the increased (physical) stress level (due to the critical illness) that causes hyperglycemia ([10], [11], [12]). In an ICU model the endogenous and exogenous insulin sections that can be noticed in (1c) and (2c), respectively, need both to be present.
2) *A time-independent endogenous insulin section:* The original minimal model (MM) describes the glucose and the insulin kinetics during one IVGTT (which lasts for approximately three hours [2]). The endogenous insulin equation (1c) is a direct function of time. ICU patients are continuously and (especially during the first phase of their stay) intravenously fed. This administration of calories can be approximated by the delivery of a sequence of small glucose shots (e.g., every minute). One can use an IVGTT model for the evaluation of the individual effects of these shots, with t (see (1c)) set to 0 at the time of administration of the respective glucose shots. In reality, however, a *continuous* flow is administered, such that the resetting of time t to 0 during each sample time is infeasible. Considering the possible use of this model in an MPC, a one-minute reset approach would also significantly increase the complexity level. Therefore, we transformed the plasma insulin equation ((1c) for MM, (2c) for D-MM) into a set of two equations which are not explicit functions of time.

Our proposed ICU minimal model is presented as follows:

$$\frac{dG(t)}{dt} = (P_1 - X(t))G(t) - P_1 G_b + \frac{F_G}{V_G}, \tag{3a}$$

$$\frac{dX(t)}{dt} = P_2 X(t) + P_3 (I_1(t) - I_b), \tag{3b}$$

$$\frac{dI_1(t)}{dt} = \alpha \ \max(0, I_2) - nI_1(t) + \frac{F_I}{V_I}, \tag{3c}$$

$$\frac{dI_2(t)}{dt} = \beta \ \gamma \ (G(t) - h) - nI_2(t), \tag{3d}$$

where G and I_1 are the glucose and the (second-phase) insulin concentration in the blood plasma. The second insulin variable I_2 is introduced in order to describe the endogenous insulin section without any time-dependence while maintaining the second order behaviour of I_1 after glucose administration. It is a purely mathematical manipulation such that I_2 does not have any direct clinical interpretation.

In [2], four different 'healthy' patient groups are described segregated on the bases of body weight and glucose tolerance. The importance of avoiding the explicit time-dependence is clarified in Figure 1 in which several successive IVGTTs are introduced to an obese - low glucose tolerance patient whose characteristics are described in [2]. Glucose dynamics and insulin kinetics are simulated by using both the MM and the ICU-MM. Consider the case of a patient who is administered a sequence of IVGTTs, as is shown in Figure 1 (top). If the general condition of the patient does not change during this sequence, it is intuitive to expect a similar glucose and insulin pattern for each new IVGTT.

The original model (MM), however, does not show similar behaviour, as can be observed in Figure 1. The plasma insulin concentration described by MM increases with every IVGTT due to the explicit dependence on time in equation (1c). Time t cannot be reset to 0 with every new IVGTT as this example approaches the ICU setting (in which the resetting is infeasible due to the continuous calories flow) that is described above. On the contrary, our model (ICU-MM) generates an insulin trajectory that follows the expected behaviour.

Finally, two additional model coefficients (α and β), both without any physiological significance, are also included in the ICU-MM in order to keep the correct units. The coefficient β equals 1 min. The coefficient α is optimized (by using least squares) for the set of patients whose data are described in [2] such that every *single* IVGTT simulation, for insulin kinetics, should give a similar representation as that of MM.

Considering the high insulin resistance that is present in most of the critically ill patients, ICU glucose and insulin dynamics are mostly comparable to those belonging to the

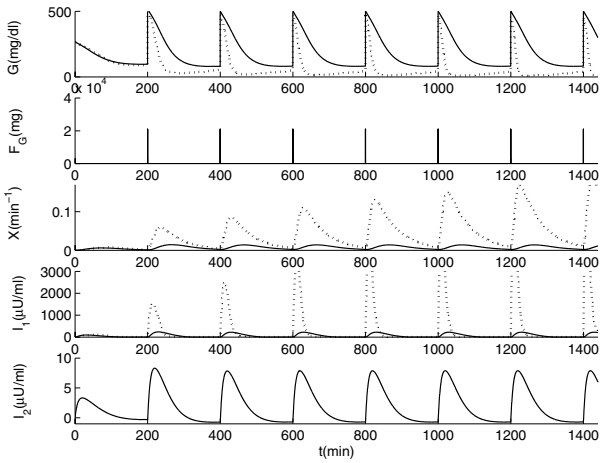

Fig. 1. Presentation of the glucose and insulin dynamics during several successive IVGTTs (F_G, shown in the second panel) for patient 16 (whose data are described in [2]). The solid and dotted line represent the simulated trajectories by using ICU-MM and MM, respectively. Although the glycemia behaviour shows a similar progress after every IVGTT (top panel), the insulin variables (both X and I_1) show exploded trajectories (see the third and fourth panel) after simulating with MM. This phenomenon is clinically infeasible. In contrast, the use of ICU-MM results in an identical behaviour for insulin and glycemia after every IVGTT.

obese and low glucose tolerance patient group described in [2]. The units of all used variables and parameters and their mean coefficient values (for the obese and low glucose tolerance patient group) are represented in Table I.

TABLE I

VARIABLES AND COEFFICIENT VALUES APPLICABLE IN THE ICU MINIMAL MODEL (ICU-MM).

Variables	Units	Variables	Units
G	mg/dl	I_2	μU/ml
X	1/min	F_I	μU/min
I_1	μU/ml	F_G	mg/min
Coefficients	**Units**	**Value** [(1)]	
P_1	1/min	-1.31 10^{-2} [(1)]	
P_2	1/min	-1.35 10^{-2} [(1)]	
P_3	ml/(min$^2\mu$U)	2.90 10^{-6} [(1)]	
V	dl	50	
h	mg/dl	136 [(1)]	
n	1/min	0.13 [(1)]	
α	1/min	3.11	
β	min	1	
γ	$\frac{\frac{\mu U}{ml}\frac{dl}{mg}}{min^2}$	5.36 10^{-3} [(1)]	

[(1)] As an example the mean model coefficient values for the obese - low glucose tolerance patient group (described in [2]), are presented.

III. APPLICATION OF THE ICU MINIMAL MODEL ON A REAL-LIFE CLINICAL DATASET

In this section we applied our proposed ICU-MM to a real-life surgical ICU dataset. The data are firstly described followed by an analysis of complete simulations of the model for every patient.

A. Data Description

In our setting, the Glucoday system (A. Menarini Diagnostics, Florence, Italy), a portable instrument provided with a micro-pump and a biosensor, coupled to a microdialysis system, was used to measure the glucose concentration. After informed consent from the next of kin, we implanted a microfibre in 14 ventilated adult patients who were admitted to the surgical ICU of the University Hospital K.U. Leuven (Belgium) for a variety of reasons (see Table II). After implantation of the fibre in the peri-umbilical subcutaneous tissue, we recorded continuous subcutaneous glucose levels during 48 hours. Every 3 minutes the mean value of the last 3 minutes was exported. During the first 24 hours, arterial blood glucose was measured concomitantly every hour using the ABL machine (Radiometer, Copenhagen, Denmark); during the next 24 hours, arterial blood glucose was measured every 4 hours. A 2-point retrospective calibration was executed at 12 and 20 hours. The administered flows of calories and insulin were also stored.

TABLE II

PATIENT POPULATION.

Variable	Value
Male sex - no (%)	10 (71.4)
Age - yr $(std-dev)$	60.9 (13.8)
Body-mass index - kg/m^2 $(std-dev)$	25.8 (5.2)
Reason for intensive care - no (%)	
Cardiac surgery	7 (50.0)
Noncardiac indication	7 (50.0)
Neurologic disease, cerebral trauma, or brain surgery	3 (21.4)
Abdominal surgery or peritonitis	2 (14.3)
Vascular surgery	2 (14.3)
APACHE II score (first 24 hr) $(std-dev)$	17.9 (6.2)
Mean glycemia - mg/dl $(std-dev)$	111 (26)
Minimal glycemia - mg/dl	50
Maximal glycemia - mg/dl	223

B. Model estimation

The ICU-MM is used as a general template, which is estimated for each individual patient such that the model parameters P_1, P_2, P_3, h, n, α, and γ are patient-specific. This is done by minimizing the (squared) errors between the simulated and observed glycemia trajectories (by using non-linear least squares, Matlab®-function 'fminsearch'). The simulated glycemia is obtained directly from the integration of the ICU-MM over the corresponding time span. In this way, an optimization problem is formulated in such a way that the optimal model parameters are found to be those that give the best possible simulation for the patient.

For this optimization process, the starting parameters are taken from the obese - low glucose tolerance patient group coming from [2] (see Table I). The model performance for each patient p is measured by computing the Mean Squared Error, $\text{MSE}_p = \frac{\sum_{t=1}^{N}(G_{t,p}-\hat{G}_{t,p})^2}{N}$, and the Mean Percentage Error, $\text{MPE}_p = \frac{\sum_{t=1}^{N}\frac{|G_{t,p}-\hat{G}_{t,p}|}{G_{t,p}}}{N}100\%$, where $G_{t,p}$ and $\hat{G}_{t,p}$ are the actual and simulated glycemia value for patient p. The size of each dataset is denoted as N. The resulting values for each patient can be observed in Table III. Figure 2 (top) gives an example of a simulated glucose trajectory for patient 3. A delivery of calories (Figure 2, bottom) results in a glycemia increase whereas insulin (Figure 2, middle) results

in a glycemia decrease. Although the model only takes two input variables into consideration, in comparison with the high number of (un)known additional disturbance inputs (e.g., administration of farmaca) that are present in ICU, the glucose trajectories keep track of the general glucose behaviour.

TABLE III

MEAN SQUARED ERROR (MSE) AND MEAN PERCENTAGE ERROR (MPE) OBTAINED AFTER INTEGRATING THE SYSTEM FOR EVERY PATIENT

Patient no	MSE $(mg/dl)^2$	MPE (%)
1	714.8	20.6
2	184.0	9.2
3	197.0	9.7
4	178.0	10.8
5	127.9	8.6
6	134.8	8.9
7	292.9	13.7
8	1138.8	21.5
9	456.6	14.0
10	1033.9	22.0
11	771.0	22.5
12	149.9	9.1
13	537.2	18.3
14	194.0	10.7

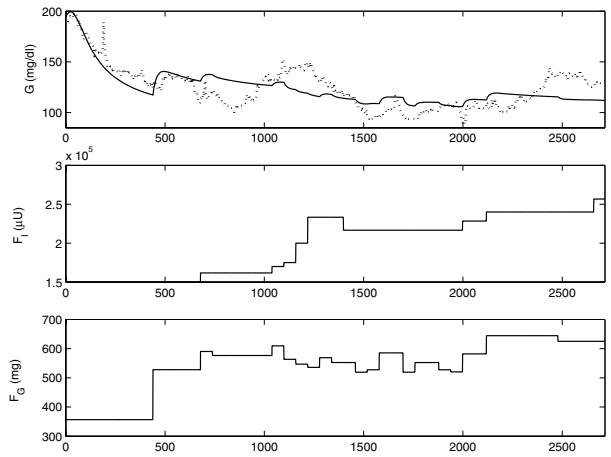

Fig. 2. *Top panel:* Simulated evolution of glucose (solid line) for patient 3 as given by ICU-MM. The dotted line represents the observed continuous glycemia. The *middle* and *bottom* panel show the administered insulin and calories flow, respectively.

IV. CONCLUSION AND FUTURE WORK

In this paper we present a modified minimal model to describe the glucose dynamics and the insulin kinetics of ICU patients. Simulations show that the modified model (ICU-MM) exhibits a similar glycemia behaviour as that of the original minimal model (MM) and clinically more realistic insulin kinetics. Therefore, it is potentially more suitable for glycemia model predictive control (MPC). The modified model is also estimated on a real-life surgical ICU dataset. Although only two input variables are taken into account, the simulated glucose trajectories keep track of the general glycemia behaviour. Future research (among which the possible implementation of other input variables like delivered farmaca) is required to further increase the model performance. Also the validity of the model on patients belonging to the medical (instead of surgical) ICU needs to be investigated.

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