

Linear Periodic Models of Subcutaneous Insulin Absorption: Mathematical Analysis

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Abstract

This work proposes a pair of models for subcutaneous (sc) insulin kinetics. Three sc injections are considered over a 24 hour time period. Each injection delivers both fast and slow insulin, so that a third order system is built, whose components are the fast and slow sc masses of insulin and the plasma insulin concentration. The insulin injections are modeled as impulsive inputs.

ODE (Ordinary Differential Equation) models can be written when neglecting the delays in the absorption of insulin from the sc injections to the plasma circulation. Two linear, time-varying, periodic models have been presented, both taking into account that different absorption rates are associated with different times of a 24 hour time period. One model consists of a variable structure system, switching among three linear working modes, according to the injection times. The other treats the time-varying absorption rate as an harmonic function.

The qualitative behavior of the solutions is investigated in both the cases, showing positivity, boundedness and global stability of solutions. As far as the statistical identifiability of the models is concerned, it has also been proven the global identifiability of the switching linear model, according to a suitably defined set of experiments, while a rank condition is given to check local identifiability of the other periodic model.

Keywords

Insulin absorption, Mathematical modeling, Insulin delivery, Identifiability.

I. INTRODUCTION

The modeling of glucose-insulin homeostasis is an appealing and challenging topic in biomathematics and many different models have been presented in the last decades, mostly referred to the well-known experimental framework of the Intra Venous Glucose Tolerance Test (IVGTT), where a bolus of glucose is administered intra-venously and glucose and insulin concentrations are frequently sampled (see e.g. the ODEs of the Minimal Model [2], [10], or the more recent integro-differential equations models of [3], [6], [8]). An interesting survey on a very wide class of most significative models available in literature and the software tools related to them may be found in [7]. The main role of these models is to evaluate glucose and insulin sensitivity in clinical patients [2], [10].

A widely adopted insulin therapy for type 1 Insulin-Dependent Diabetes Mellitus (IDDM) patients consists of subcutaneous (sc) injections three or four times a day, with the dose adjusted on the basis of three to seven capillary blood glucose concentration measurements. The aim of a closed loop control of the plasma glucose concentration has recently

stimulated the research towards implantable sc actuators/sensors, from a technological point of view [4]; of course, the design of a suitable control law (see e.g. [1] and references therein to take a look at closed and partially-closed loop strategies of recent years) requires an accurate description of the absorption of insulin from the sc injection to the plasma circulation.

Such an issue, dealing with the modeling of the plasma insulin absorption from a sc injection in IDDM patients, has been investigated in this paper. The existing literature is mainly involved in linear, time-invariant models, taking into account one or two compartments (see [9] and references therein, where an interesting comparison has been performed among most of the available models). The novelty of the present contribute is to consider time-varying, periodic models, describing the physiological situation of a different sc absorption according to different periods of a single day. Two models have been presented, dealing with a different approach to the characterization of such a periodicity: one model is a variable structure system, whose dynamics switches among three linear working modes; the other is a more generic periodic system, assuming that the absorption rate of sc insulin is a 24 hour harmonic function.

The experimental framework consists of three sc injections over a 24 hour time period. Each injection delivers both fast and slow insulin, so that a third order system is built, whose components are the fast and slow sc masses of insulin and the plasma insulin concentration. The insulin injections are modeled as impulsive inputs.

Both the models provide positive bounded solutions, continuous w.r.t the initial conditions. Moreover, it has also been proven that the unique equilibrium point, corresponding to the physiological basal values, is globally asymptotically stable. As far as the models identifiability is concerned, the switching model is proven to be globally identifiable, while a condition is given to check local identifiability for the other periodic model.

The paper is organized as follows: the next section describes the equations of a linear, periodic model for the sc absorption; Sections III and V consider the variable structure and the harmonic models, respectively, while Sections IV and VI deal with the corresponding qualitative analysis of the models. Section VII investigates the models identifiability.

II. MODELING THE INSULIN ABSORPTION

The plasma insulin absorption from a subcutaneous injection in an IDDM patient is described according to the following ODE model:

$$\begin{aligned}\dot{Q}_f(t) &= -K_{pf}(t)Q_f(t) + u_f(t), \\ \dot{Q}_s(t) &= -K_{ps}(t)Q_s(t) + u_s(t), \\ \dot{I}(t) &= -K_{xp}I(t) + \frac{K_{pf}(t)}{V_I}Q_f(t) + \frac{K_{ps}(t)}{V_I}Q_s(t),\end{aligned}\tag{1}$$

where Q_f and Q_s are, respectively, the fast and slow sc masses of insulin, I is the plasma insulin concentration, K_{pf} , K_{ps} are the absorption rates of the fast and slow sc masses of insulin, K_{xp} is the rate of plasma insulin disappearance, V_I is the distribution volume. It is assumed that both the time-varying absorption rates K_{pf} , K_{ps} are periodic functions on a 24 hour time period, so that model (1) is a linear, time-varying, periodic system. Moreover, the rate of absorption of the slow sc insulin $K_{ps}(t)$ is assumed to have the same time shape of that of the fast sc insulin, that means:

$$K_{ps}(t) = \alpha K_{pf}(t), \quad \text{with } \alpha \in (0, 1).\tag{2}$$

Initial conditions are:

$$Q_f(t_0) = 0, \quad Q_s(t_0) = 0, \quad I(t_0) = 0,\tag{3}$$

according to the fact that an IDDM patient has zero basal insulinemia.

The inputs u_f , u_s describe the fast and slow sc insulin injections. There are three sc injections each day, at times $t_1 + hT$, $t_2 + hT$, $t_3 + hT$, with:

$$0 \leq t_0 \leq t_1 < t_2 < t_3 < T, \quad T = 24, \quad h \in \mathcal{Z}^+;\tag{4}$$

each injection at time $t_i + hT$, $i = 1, 2, 3$, is an impulsive forcing term, modeled as a Dirac function of weigh D_{f_i} and D_{s_i} for the fast and slow sc insulin, respectively, so that:

$$\begin{aligned}u_f(t) &= \sum_{h=0}^{\infty} \sum_{i=1}^3 D_{f_i} \delta(t - t_i - hT), \\ u_s(t) &= \sum_{h=0}^{\infty} \sum_{i=1}^3 D_{s_i} \delta(t - t_i - hT).\end{aligned}\tag{5}$$

III. VARIABLE STRUCTURE MODEL: SOLUTIONS

According to physiological reasons, a way to model the absorption rate is to assume that $K_{pf}(t)$ switches among three different constant values. The sc insulin masses are injected at the beginning of each period so that, without loss of generality, it is reasonable to assume $t_0 = t_1 = 0$. Taking into account a generic interval $T_h = [hT, (h+1)T)$, for $h \in \mathcal{Z}^+$, and considering the partition:

$$\begin{aligned} T_{h,1} &= [hT, t_2 + hT), \\ T_h &= T_{h,1} \cup T_{h,2} \cup T_{h,3}, & T_{h,2} &= [t_2 + hT, t_3 + hT), \\ & & T_{h,3} &= [t_3 + hT, (h+1)T), \end{aligned} \quad (6)$$

the fast sc insulin absorption rate can be written according to the following formula:

$$K_{pf}(t) = K_{pf1} + K_{pf2}\chi_{T_{h,2}}(t) + K_{pf3}\chi_{T_{h,3}}(t), \quad t \in T_h, \quad (7)$$

with $\chi_{T_{h,i}}(t)$ being unitary for $t \in T_{h,i}$ and zero elsewhere. Note that parameters K_{pf1} , K_{xp} , V_I , α are strictly positive, while K_{pf2} , K_{pf3} , may well be negative, provided that:

$$K_{pf1} + K_{pf2} > 0, \quad K_{pf1} + K_{pf3} > 0. \quad (8)$$

According to (7), system (1) can be written by using the following variable structure model:

$$\dot{X}(t) = A_{\mu(t)}X(t) + Bu(t), \quad (9)$$

where $X = (Q_f \quad Q_s \quad I)^T \in \mathbb{R}^3$ is the state vector, μ is a known switching parameter, taking values in $\mathcal{R}(\mu) = \{1, 2, 3\}$ such that:

$$\mu(t) = \begin{cases} 1, & t \in T_{h,1}, \\ 2, & t \in T_{h,2}, \\ 3, & t \in T_{h,3}, \end{cases} \quad h \in \mathcal{Z}, \quad (10)$$

with:

$$A_i = \begin{bmatrix} -K_i & 0 & 0 \\ 0 & -\alpha K_i & 0 \\ K_i/V_I & \alpha K_i/V_I & -K_{xp} \end{bmatrix}, \quad \begin{aligned} K_1 &= K_{pf1}, \\ K_2 &= K_{pf1} + K_{pf2}, \\ K_3 &= K_{pf1} + K_{pf3}; \end{aligned} \quad (11)$$

$u = (u_f \ u_s)^T \in \mathbb{R}^2$ is the input with:

$$B = \begin{bmatrix} 1 & 0 \\ 0 & 1 \\ 0 & 0 \end{bmatrix}. \quad (12)$$

In the sequel, the explicit solutions of system (9) are achieved. In order to have a more compact notation, the triple $\{K_1, K_2, K_3\}$ will be preferred in the notations w.r.t. $\{K_{pf_1}, K_{pf_2}, K_{pf_3}\}$, as it has been done in (11). Below follow the impulsive responses (i.e. $X(0) = 0$) of Q_f and Q_s for $t \in T_h$, achieved at each $T_{h,i}$ as free evolutions starting from times $t_i + hT$, $i = 1, 2, 3$:

$$Q_f(t) = \begin{cases} \bar{Q}_{f,h} e^{-K_1(t-hT)}, & t \in T_{h,1}, \\ (\bar{Q}_{f,h} e^{-K_1 t_2} + D_{f_2}) e^{-K_2(t-t_2-hT)}, & t \in T_{h,2}, \\ ((\bar{Q}_{f,h} e^{-K_1 t_2} + D_{f_2}) e^{-K_2(t_3-t_2)} + D_{f_3}) e^{-K_3(t-t_3-hT)}, & t \in T_{h,3}, \end{cases} \quad (13)$$

$$Q_s(t) = \begin{cases} \bar{Q}_{s,h} e^{-\alpha K_1(t-hT)}, & t \in T_{h,1}, \\ (\bar{Q}_{s,h} e^{-\alpha K_1 t_2} + D_{s_2}) e^{-\alpha K_2(t-t_2-hT)}, & t \in T_{h,2}, \\ ((\bar{Q}_{s,h} e^{-\alpha K_1 t_2} + D_{s_2}) e^{-\alpha K_2(t_3-t_2)} + D_{s_3}) e^{-\alpha K_3(t-t_3-hT)}, & t \in T_{h,3}, \end{cases} \quad (14)$$

with $\bar{Q}_{f,h} = Q_f(hT)$, $\bar{Q}_{s,h} = Q_s(hT)$ given by:

$$\begin{aligned} \bar{Q}_{f,h+1} &= D_{f_1} + ((\bar{Q}_{f,h} e^{-K_1 t_2} + D_{f_2}) e^{-K_2(t_3-t_2)} + D_{f_3}) e^{-K_3(T-t_3)}, \\ \bar{Q}_{f,0} &= D_{f_1}, \end{aligned} \quad (15)$$

and

$$\begin{aligned} \bar{Q}_{s,h+1} &= D_{s_1} + ((\bar{Q}_{s,h} e^{-\alpha K_1 t_2} + D_{s_2}) e^{-\alpha K_2(t_3-t_2)} + D_{s_3}) e^{-\alpha K_3(T-t_3)}, \\ \bar{Q}_{s,0} &= D_{s_1}. \end{aligned} \quad (16)$$

The plasma insulin concentration is the convolution integral of both the fast and slow insulin masses contributions:

$$I(t) = \frac{1}{V_I} \int_0^t (K_{pf}(\tau) Q_f(\tau) + K_{ps}(\tau) Q_s(\tau)) e^{-K_{xp}(t-\tau)} d\tau, \quad (17)$$

so that, by naming $I_{h,i}(t)$, $i = 1, 2, 3$, the insulin concentration for $t \in T_{h,i}$:

$$\begin{aligned} I_{h,1}(t) &= \bar{I}_h e^{-K_{xp}(t-hT)} + \frac{K_1 \bar{Q}_{f,h}}{V_I(K_{xp}-K_1)} (e^{-K_1(t-hT)} - e^{-K_{xp}(t-hT)}) \\ &\quad + \frac{\alpha K_1 \bar{Q}_{s,h}}{V_I(K_{xp}-\alpha K_1)} (e^{-\alpha K_1(t-hT)} - e^{-K_{xp}(t-hT)}), \end{aligned} \quad (18)$$

$$I_{h,2}(t) = I_{h,1}(t_2 + hT)e^{-K_{xp}(t-t_2-hT)} + \frac{K_2(\bar{Q}_{f,h}e^{-K_1t_2+D_{f_2}})}{V_I(K_{xp}-K_2)}(e^{-K_2(t-t_2-hT)} - e^{-K_{xp}(t-t_2-hT)}) \\ + \frac{\alpha K_2(\bar{Q}_{s,h}e^{-\alpha K_1t_2+D_{s_2}})}{V_I(K_{xp}-\alpha K_2)}(e^{-\alpha K_2(t-t_2-hT)} - e^{-K_{xp}(t-t_2-hT)}), \quad (19)$$

$$I_{h,3}(t) = I_{h,2}(t_3 + hT)e^{-K_{xp}(t-t_3-hT)} \\ + \frac{K_3((\bar{Q}_{f,h}e^{-K_1t_2+D_{f_2}})e^{-K_2(t_3-t_2)+D_{f_3}})}{V_I(K_{xp}-K_3)}(e^{-K_3(t-t_3-hT)} - e^{-K_{xp}(t-t_3-hT)}) \\ + \frac{\alpha K_3((\bar{Q}_{s,h}e^{-\alpha K_1t_2+D_{s_2}})e^{-\alpha K_2(t_3-t_2)+D_{s_3}})}{V_I(K_{xp}-\alpha K_3)}(e^{-\alpha K_3(t-t_3-hT)} - e^{-K_{xp}(t-t_3-hT)}), \quad (20)$$

where:

$$I_{h,i}(t_{i+1} + hT) = \lim_{t \rightarrow t_{i+1} + hT} I_{h,i}(t), \quad i = 1, 2, \quad (21)$$

and $\bar{I}_h = I(hT)$ obeys the equation:

$$\bar{I}_{h+1} = \bar{I}_h e^{-K_{xp}T} + \eta_h, \quad \bar{I}_0 = 0, \quad (22)$$

with:

$$\eta_h = \frac{K_1 \bar{Q}_{f,h}}{V_I(K_{xp}-K_1)}(e^{-(K_1t_2+K_{xp}(T-t_2))} - e^{-K_{xp}T}) + \frac{\alpha K_1 \bar{Q}_{s,h}}{V_I(K_{xp}-\alpha K_1)}(e^{-(\alpha K_1t_2+K_{xp}(T-t_2))} - e^{-K_{xp}T}) \\ + \frac{K_2(\bar{Q}_{f,h}e^{-K_1t_2+D_{f_2}})}{V_I(K_{xp}-K_2)}(e^{-(K_2(t_3-t_2)+K_{xp}(T-t_3))} - e^{-K_{xp}(T-t_2)}) \\ + \frac{\alpha K_2(\bar{Q}_{s,h}e^{-\alpha K_1t_2+D_{s_2}})}{V_I(K_{xp}-\alpha K_2)}(e^{-(\alpha K_2(t_3-t_2)+K_{xp}(T-t_3))} - e^{-K_{xp}(T-t_2)}) \\ + \frac{K_3((\bar{Q}_{f,h}e^{-K_1t_2+D_{f_2}})e^{-K_2(t_3-t_2)+D_{f_3}})}{V_I(K_{xp}-K_3)}(e^{-K_3(T-t_3)} - e^{-K_{xp}(T-t_3)}) \\ + \frac{\alpha K_3((\bar{Q}_{s,h}e^{-\alpha K_1t_2+D_{s_2}})e^{-\alpha K_2(t_3-t_2)+D_{s_3}})}{V_I(K_{xp}-\alpha K_3)}(e^{-\alpha K_3(T-t_3)} - e^{-K_{xp}(T-t_3)}). \quad (23)$$

In the sequel it will be useful also to compute the free evolutions (i.e. $X(t_0) \neq 0$, $u(t) \equiv 0$), denoted by Q_f^0 , Q_s^0 , I^0 . Consider $t_0 \in T_0 = [0, T)$. Then, for $h > 0$:

$$Q_f^0(t) = \begin{cases} \bar{Q}_{f,h}^0 e^{-K_1(t-hT)}, & t \in T_{h,1}, \\ \bar{Q}_{f,h}^0 e^{-[K_1t_2+K_2(t-t_2-hT)]}, & t \in T_{h,2}, \\ \bar{Q}_{f,h}^0 e^{-[K_1t_2+K_2(t_3-t_2)+K_3(t-t_3-hT)]}, & t \in T_{h,3}, \end{cases} \quad (24)$$

$$Q_s^0(t) = \begin{cases} \bar{Q}_{s,h}^0 e^{-\alpha K_1(t-hT)}, & t \in T_{h,1}, \\ \bar{Q}_{s,h}^0 e^{-\alpha[K_1t_2+K_2(t-t_2-hT)]}, & t \in T_{h,2}, \\ \bar{Q}_{s,h}^0 e^{-\alpha[K_1t_2+K_2(t_3-t_2)+K_3(t-t_3-hT)]}, & t \in T_{h,3}, \end{cases} \quad (25)$$

with:

$$Q_f^0(t) = \begin{cases} Q_f(t_0)e^{-K_1(t-t_0)}, & t \in [t_0, t_2), \\ Q_f(t_0)e^{-[K_1(t_2-t_0)+K_2(t-t_2)]}, & t \in T_{0,2}, \\ Q_f(t_0)e^{-[K_1(t_2-t_0)+K_2(t_3-t_2)+K_3(t-t_3)]} \\ & t \in T_{0,3}, \end{cases} \quad (26)$$

$$Q_f^0(t) = \begin{cases} Q_f(t_0)e^{-K_2(t-t_0)}, & t \in [t_0, t_3), \\ Q_f(t_0)e^{-[K_2(t_3-t_0)+K_3(t-t_3)]}, & t \in T_{0,3}, \end{cases} \quad (27)$$

$$Q_f^0(t) = Q_f^0(t_0)e^{-K_3(t-t_0)}, \quad t_3 \leq t_0 \leq t < T, \quad (28)$$

$$Q_s^0(t) = \begin{cases} Q_s(t_0)e^{-\alpha K_1(t-t_0)}, & t \in [t_0, t_2), \\ Q_s(t_0)e^{-\alpha[K_1(t_2-t_0)+K_2(t-t_2)]}, & t \in T_{0,2}, \\ Q_s(t_0)e^{-\alpha[K_1(t_2-t_0)+K_2(t_3-t_2)+K_3(t-t_3)]} \\ & t \in T_{0,3}, \end{cases} \quad (29)$$

$$Q_s^0(t) = \begin{cases} Q_s(t_0)e^{-\alpha K_2(t-t_0)}, & t \in [t_0, t_3), \\ Q_s(t_0)e^{-\alpha[K_2(t_3-t_0)+K_3(t-t_3)]}, & t \in T_{0,3}, \end{cases} \quad (30)$$

$$Q_s^0(t) = Q_s^0(t_0)e^{-\alpha K_3(t-t_0)}, \quad t_3 \leq t_0 \leq t < T, \quad (31)$$

and $\bar{Q}_{f,h}^0 = Q_f^0(hT)$, $\bar{Q}_{s,h}^0 = Q_s^0(hT)$ obeying the following recursive equations:

$$\begin{aligned} \bar{Q}_{f,h+1}^0 &= \bar{Q}_{f,h}^0 e^{-[K_1 t_2 + K_2(t_3-t_2) + K_3(T-t_3)]}, \\ \bar{Q}_{s,h+1}^0 &= \bar{Q}_{s,h}^0 e^{-\alpha[K_1 t_2 + K_2(t_3-t_2) + K_3(T-t_3)]}, \end{aligned} \quad (32)$$

with $\bar{Q}_{f,1}^0$ and $\bar{Q}_{s,1}^0$ coming from (26-28), (29-31), respectively.

As far as the free evolution of the plasma insulin concentration is concerned, it is formally achieved according to the following convolution integral:

$$I^0(t) = I^0(t_0)e^{-K_{xp}(t-t_0)} + \frac{1}{V_I} \int_{t_0}^t (K_{pf}(\tau)Q_f^0(\tau) + K_{ps}(\tau)Q_s^0(\tau))e^{-K_{xp}(t-\tau)} d\tau. \quad (33)$$

In Fig.1, the evolutions of the fast/slow sc masses of insulin together with the plasma insulinemia are reported. The following reasonable set of data has been chosen:

$$\begin{aligned} K_{pf1} &= 0.005 \text{min}^{-1}, & K_{pf2} &= 0.002 \text{min}^{-1}, \\ K_{pf3} &= -0.001 \text{min}^{-1}, & K_{xp} &= 0.020 \text{min}^{-1}, \\ V_I &= 50 \text{ l}, & \alpha &= 0.125, \end{aligned}$$

with

$$\begin{aligned} D_{f_1} &= 49\mu\text{mol}, & D_{s_1} &= 21\mu\text{mol}, & t_1 &= 8\text{h}, \\ D_{f_2} &= 49\mu\text{mol}, & D_{s_2} &= 21\mu\text{mol}, & t_2 &= 13\text{h}, \\ D_{f_3} &= 70\mu\text{mol}, & D_{s_3} &= 30\mu\text{mol}, & t_3 &= 18\text{h}. \end{aligned}$$

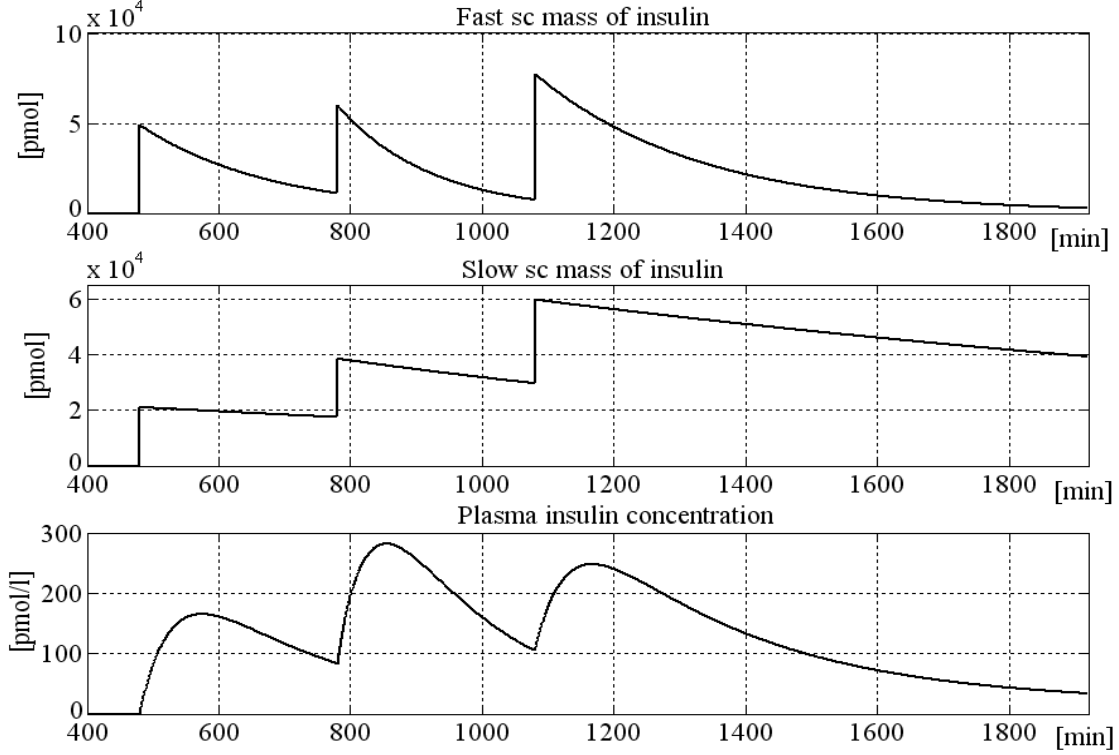


Fig. 1. Q_f, Q_s, I evolutions.

IV. VARIABLE STRUCTURE MODEL: ANALYSIS

According to the previous section, the following propositions are true.

Proposition 1 Solutions of system (9) exist and are unique for any choice of the initial conditions.

Proof: Existence and uniqueness come from the linear feature of the differential system. From a computational point of view, the explicit solutions readily come from the triangular form of matrices A_i , eq. (11), and have been reported in (13-16), (18-23) (the impulsive response) and in (24-33), (the free evolution). ■

Proposition 2 The impulsive and free evolutions of system (1) are positive bounded for any choice of positive initial conditions. Moreover:

$$Q_f^0(t) \leq Q_f^0(t_0), \quad Q_s^0(t) \leq Q_s^0(t_0), \quad (34)$$

and

$$I^0(t) \leq I^0(t_0) + \frac{(Q_f^0(t_0) + Q_s^0(t_0))K_M}{V_I|K_{xp} - \alpha K_m|}, \quad (35)$$

where:

$$K_m = \min \{K_1, K_2, K_3\}, \quad K_M = \max \{K_1, K_2, K_3\}. \quad (36)$$

Proof: According to the explicit solutions, the impulsive and free evolutions are positive bounded because they are given by sums of decreasing exponentials with positive coefficients. Now consider the free evolution of the first component of Q_f^0 , given by (24), (26-28). It consists of an exponential function, whose decaying rate switches among the three values assumed by K_i , so that it is bounded by the following exponential:

$$Q_f^0(t) \leq Q_f^0(t_0)e^{-K_m(t-t_0)}, \quad (37)$$

with K_m as in (36). Analogously for Q_s^0 , from (25), (29-31):

$$Q_s^0(t) \leq Q_s^0(t_0)e^{-\alpha K_m(t-t_0)}. \quad (38)$$

As far as the free evolution of the insulinemia is concerned, eq. (33), according to (37), (38):

$$\begin{aligned} I^0(t) &\leq I^0(t_0)e^{-K_{xp}(t-t_0)} + \frac{(Q_f^0(t_0)+Q_s^0(t_0))K_M e^{-K_{xp}t}}{V_I} e^{\alpha K_m t_0} \int_{t_0}^t e^{(K_{xp}-\alpha K_m)\tau} d\tau \\ &= I^0(t_0)e^{-K_{xp}(t-t_0)} + \frac{(Q_f^0(t_0)+Q_s^0(t_0))K_M e^{-K_{xp}t}}{V_I(K_{xp}-\alpha K_m)} e^{\alpha K_m t_0} (e^{(K_{xp}-\alpha K_m)t} - e^{(K_{xp}-\alpha K_m)t_0}) \\ &= I^0(t_0)e^{-K_{xp}(t-t_0)} + \frac{(Q_f^0(t_0)+Q_s^0(t_0))K_M e^{-\alpha K_m t_0}}{V_I|K_{xp}-\alpha K_m|} |e^{-\alpha K_m(t-t_0)} - e^{-K_{xp}(t-t_0)}| \\ &\leq I^0(t_0)e^{-K_{xp}(t-t_0)} + \frac{(Q_f^0(t_0)+Q_s^0(t_0))K_M}{V_I|K_{xp}-\alpha K_m|} e^{-\bar{K}_m(t-t_0)} \\ &\leq \left(I^0(t_0) + \frac{(Q_f^0(t_0)+Q_s^0(t_0))K_M}{V_I|K_{xp}-\alpha K_m|} \right) e^{-\bar{K}_m(t-t_0)}, \end{aligned} \quad (39)$$

with $\bar{K}_m = \min \{\alpha K_m, K_{xp}\}$ and K_M as in (36). ■

Proposition 3 The impulsive response converges to a periodic bounded evolution.

Proof: Existence of asymptotic solutions is ensured from the free evolutions, which are bounded by decreasing exponentials according to (37-39), so that they exponentially decay to zero. Below the asymptotic solutions are computed. From the impulsive responses of Q_f , Q_s , eq.s (13), (15) and (14), (16) respectively, it comes that $\bar{Q}_{f,h}$, $\bar{Q}_{s,h}$ obey the following recursive equations:

$$\bar{Q}_{f,h+1} = \beta_f \bar{Q}_{f,h} + \gamma_f, \quad \bar{Q}_{s,h+1} = \beta_s \bar{Q}_{s,h} + \gamma_s, \quad (40)$$

with:

$$\begin{aligned} \beta_f &= e^{-(K_1 t_2 + K_2(t_3 - t_2) + K_3(T - t_3))} < 1, \\ \gamma_f &= D_{f_1} + (D_{f_2} e^{-K_2(t_3 - t_2)} + D_{f_3}) e^{-K_3(T - t_3)}, \end{aligned} \quad (41)$$

and

$$\begin{aligned} \beta_s &= e^{-\alpha(K_1 t_2 + K_2(t_3 - t_2) + K_3(T - t_3))} < 1, \\ \gamma_s &= D_{s_1} + (D_{s_2} e^{-\alpha K_2(t_3 - t_2)} + D_{s_3}) e^{-\alpha K_3(T - t_3)}, \end{aligned} \quad (42)$$

so that the asymptotic solutions $\bar{Q}_{f,\infty} = \lim_{h \rightarrow \infty} \bar{Q}_{f,h}$ and $\bar{Q}_{s,\infty} = \lim_{h \rightarrow \infty} \bar{Q}_{s,h}$ exist and satisfy the equations:

$$\begin{aligned} \bar{Q}_{f,\infty} &= \beta_f \bar{Q}_{f,\infty} + \gamma_f \quad \Rightarrow \quad \bar{Q}_{f,\infty} = \frac{\gamma_f}{1 - \beta_f}, \\ \bar{Q}_{s,\infty} &= \beta_s \bar{Q}_{s,\infty} + \gamma_s \quad \Rightarrow \quad \bar{Q}_{s,\infty} = \frac{\gamma_s}{1 - \beta_s}. \end{aligned} \quad (43)$$

Substituting $\bar{Q}_{f,\infty}$, $\bar{Q}_{s,\infty}$ in (13) and (14), respectively, the asymptotic periodic evolutions are obtained.

As far as the insulin concentration is concerned, the asymptotic solution $\bar{I}_\infty = \lim_{h \rightarrow \infty} \bar{I}_h$ of (22) satisfies the equation:

$$\bar{I}_\infty = \bar{I}_\infty e^{-K_{xp}T} + \eta_\infty \quad \Rightarrow \quad \bar{I}_\infty = \frac{\eta_\infty}{1 - e^{-K_{xp}T}}, \quad (44)$$

with $\eta_\infty = \lim_{h \rightarrow \infty} \eta_h$ obtained from (23) by replacing $\bar{Q}_{f,h}$, $\bar{Q}_{s,h}$ with $\bar{Q}_{f,\infty}$, $\bar{Q}_{s,\infty}$, respectively. Then, the asymptotic evolutions I_1^∞ , I_2^∞ , I_3^∞ , are achieved from (18-20), by replacing \bar{I}_h , $\bar{Q}_{f,h}$, $\bar{Q}_{s,h}$ with \bar{I}_∞ , $\bar{Q}_{f,\infty}$, $\bar{Q}_{s,\infty}$, respectively. ■

Proposition 4 There is a unique equilibrium point at the origin: $X_{eq} = (0 \ 0 \ 0)^T$.

Proof: It is the unique solution to the problem:

$$A_{\mu(t)} X = 0, \quad \forall t \geq t_0. \quad (45)$$

■

Lemma 5 The equilibrium point $X_{eq} = (0 \ 0 \ 0)^T$ is globally uniformly asymptotically stable.

Proof: Let X^0 denote the free evolution of X . In order to show uniform stability, it has to be proven that:

$$\forall \epsilon > 0, \exists \delta = \delta(\epsilon) : \quad \|X^0(t_0)\| < \delta \quad \Rightarrow \quad \|X^0(t)\| \leq \epsilon, \quad (46)$$

$\forall t \geq t_0$, with δ independent of t_0 . Recall that, according to Proposition 2:

$$\begin{aligned} |Q_f^0(t)| &\leq |Q_f^0(t_0)| \leq \|X^0(t_0)\|, \\ |Q_s^0(t)| &\leq |Q_s^0(t_0)| \leq \|X^0(t_0)\|, \\ |I^0(t)| &\leq |C^T X^0(t_0)| \leq \|C\| \cdot \|X^0(t_0)\|, \end{aligned} \quad (47)$$

with:

$$C^T = \begin{bmatrix} \frac{K_M}{V_I |K_{xp} - \alpha K_m|} & \frac{K_M}{V_I |K_{xp} - \alpha K_m|} & 1 \end{bmatrix}. \quad (48)$$

Let $\epsilon > 0$. Then:

$$\|X^0(t)\| \leq |Q_f^0(t)| + |Q_s^0(t)| + |I^0(t)| \leq (2 + \|C\|) \|X^0(t_0)\|. \quad (49)$$

By choosing:

$$\delta = \frac{\epsilon}{2 + \|C\|}, \quad (50)$$

the uniform stability is proven. The equilibrium point is also globally asymptotically stable, in that the free evolution of each component is bounded by decreasing exponentials for any choice of $X^0(t_0) \in \mathbb{R}^3$. ■

Proposition 6 Solutions of system (9) are continuous w.r.t. any admissible initial condition.

Proof: Denote $\Phi(t, t_0)$ the state transition matrix of X , i.e.:

$$X^0(t) = \varphi(t, t_0, X_a) = \Phi(t, t_0) X_a, \quad X^0(t_0) = X_a. \quad (51)$$

Then, according to Lemma 5, asymptotic stability for the linear system (9) implies also exponential stability that means [5]:

$$\exists M, \lambda > 0 : \quad \|\Phi(t, t_0)\| \leq M e^{-\lambda(t-t_0)}, \quad \forall t \geq t_0. \quad (52)$$

Continuity w.r.t. any admissible initial condition means that:

$$\exists N > 0 : \quad \|\varphi(\cdot, t_0, X_a) - \varphi(\cdot, t_0, X_b)\|_2 \leq N\|X_a - X_b\|, \quad (53)$$

for any pair of positive initial conditions (X_a, X_b) . The left-hand side of (53) is a suitably defined functional norm. The proof is achieved by using the L_2 norm on a the infinite-horizon interval $[t_0, +\infty)$, that means:

$$\|\varphi(\cdot, t_0, X_0)\|_2^2 = \int_{t_0}^{+\infty} \|\varphi(\tau, t_0, X_0)\|^2 d\tau. \quad (54)$$

From (51) and (52):

$$\begin{aligned} \|\varphi(\cdot, t_0, X_a) - \varphi(\cdot, t_0, X_b)\|_2^2 &\leq \int_{t_0}^{+\infty} \|\Phi(\tau, t_0)\|^2 \cdot \|X_a - X_b\|^2 d\tau \\ &\leq M^2 \|X_a - X_b\|^2 \int_{t_0}^{+\infty} e^{-2\lambda(\tau-t_0)} d\tau = \frac{M^2 \|X_a - X_b\|^2}{2\lambda}, \end{aligned} \quad (55)$$

so that condition (53) is obtained with $N = M/\sqrt{2\lambda}$. ■

V. HARMONIC PERIODIC MODEL

The case of $K_{pf}(t)$ time-varying according to an harmonic function is investigated in this section. All the assumptions of Section 1 remain unchanged. By setting the highest value of K_{pf} (named $K_M > 0$) at time 16h, the lowest ($K_m > 0$) is then fixed at time 4h, so that:

$$K_{pf}(t) = \frac{K_M - K_m}{2} \left[\sin\left(\frac{2\pi(t+14)}{T}\right) + 1 \right] + K_m. \quad (56)$$

According to (56), the system equations (1) may be written as the following linear, time-varying, periodic system:

$$\dot{X}(t) = A(t)X(t) + Bu(t), \quad A(t+T) = A(t), \quad (57)$$

with:

$$A(t) = \begin{bmatrix} -K_{pf}(t) & 0 & 0 \\ 0 & -\alpha K_{pf}(t) & 0 \\ K_{pf}(t)/V_I & \alpha K_{pf}(t)/V_I & -K_{xp} \end{bmatrix}, \quad B = \begin{bmatrix} 1 & 0 \\ 0 & 1 \\ 0 & 0 \end{bmatrix}, \quad (58)$$

and $u = (u_f \ u_s)^T$ with $u_f(t)$, $u_s(t)$ as in (5). Without loss of generality, the impulsive solutions are achieved for $t_0 = t_1 = 0$.

The impulsive response of Q_f is given by the convolution integral of the state transition matrix $\Phi_f(t, \tau)$ with the input $u_f(t)$:

$$\begin{aligned} Q_f(t) &= \int_0^t \Phi_f(t, \tau) \sum_{h=0}^{\infty} \sum_{i=1}^3 D_{f_i} \delta(\tau - t_i - hT) d\tau \\ &= \sum_{h=0}^{\lfloor \frac{t}{T} \rfloor} \sum_{i=1}^3 D_{f_i} \Phi_f(t, t_i + hT) \delta_{-1}(t - t_i - hT), \end{aligned} \quad (59)$$

and:

$$\begin{aligned} \Phi_f(t, \tau) &= e^{-\int_{\tau}^t K_{pf}(\theta) d\theta} = e^{-\left[\frac{(K_M + K_m)\theta}{2} - \frac{(K_M - K_m)T}{4\pi} \cos\left(\frac{2\pi(\theta+14)}{T}\right) \right]_{\tau}^t} \\ &= e^{-\frac{(K_M + K_m)(t-\tau)}{2} + \frac{(K_M - K_m)T}{4\pi} [\cos(\frac{2\pi(t+14)}{T}) - \cos(\frac{2\pi(\tau+14)}{T})]}; \end{aligned} \quad (60)$$

(the symbol $\delta_{-1}(\cdot)$ denotes the unitary step function). Analogously for $Q_s(t)$, so that, according to (2):

$$Q_s(t) = \sum_{h=0}^{\lfloor \frac{t}{T} \rfloor} \sum_{i=1}^3 D_{s_i} \Phi_s(t, t_i + hT) \delta_{-1}(t - t_i - hT), \quad (61)$$

with:

$$\Phi_s(t, \tau) = e^{-\int_{\tau}^t \alpha K_{pf}(\theta) d\theta} = \Phi_f^{\alpha}(t, \tau). \quad (62)$$

Differently from the variable structure model, the plasma insulin concentration does not allow a closed loop form, although it can be readily computed according to (17), where K_{pf} is now given by the harmonic function (56).

As far as the free evolutions are concerned:

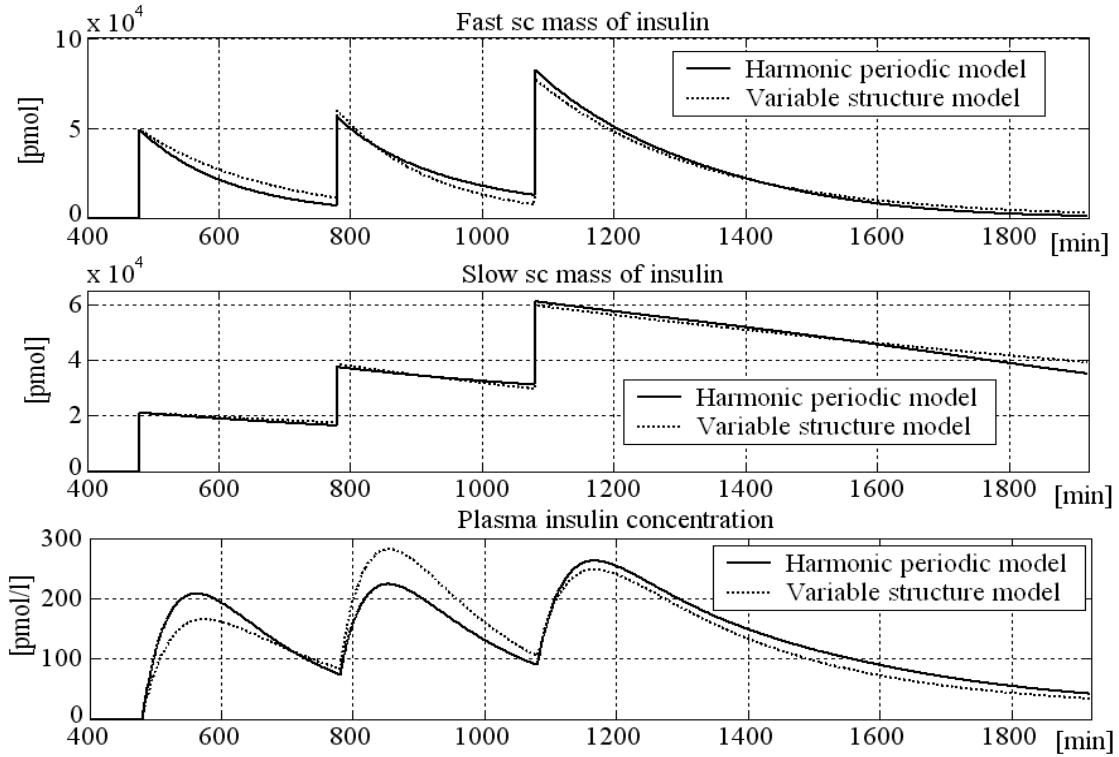
$$Q_f^0(t) = \Phi_f(t, t_0) Q_f^0(t_0), \quad Q_s^0(t) = \Phi_f^{\alpha}(t, t_0) Q_s^0(t_0), \quad (63)$$

while $I^0(t)$ has to be computed according to (33).

In Fig.2, the evolutions of the fast/slow sc masses of insulin together with the plasma insulinemia are reported. Parameters K_{xp} , V_I , α are the ones chosen for the variable structure model of Section III, while K_M and K_m have been chosen as follows:

$$K_M = 0.007 \text{min}^{-1}, \quad K_m = 0.004 \text{min}^{-1}.$$

Also the injected masses of insulin D_{f_i} , D_{s_i} are the same of the previous simulation. Fig.2 shows the evolutions related to the two different models.

Fig. 2. Q_f, Q_s, I evolutions.

VI. HARMONIC PERIODIC MODEL: ANALYSIS

According to the linear feature of the differential system (1), existence and uniqueness of the solutions are ensured. Impulsive and free solutions are positive bounded for any positive initial conditions, in that they are sums of decreasing exponentials with positive coefficients, from which also comes the existence of a periodic asymptotic evolution. Moreover, the following propositions are true:

Proposition 7 The free evolutions of each component are bounded, with:

$$Q_f^0(t) \leq M Q_f^0(t_0), \quad Q_s^0(t) \leq M^\alpha Q_s^0(t_0), \quad I^0(t) \leq \left(I^0(t_0) + \frac{(M Q_f^0(t_0) + M^\alpha Q_s^0(t_0)) K_M}{V_I |K_{xp} - \alpha \frac{K_M + K_m}{2}|} \right), \quad (64)$$

and

$$M = e^{\frac{(K_M - K_m)T}{2\pi}}. \quad (65)$$

Proof: The boundedness of Q_f^0 readily comes by considering the explicit solutions (63) and the boundedness of the state transition matrix (60):

$$\Phi_f(t, t_0) \leq M e^{-\frac{(K_M + K_m)(t - t_0)}{2}}, \quad (66)$$

with M as in (65). Analogously for $Q_s^0(t)$:

$$Q_s^0(t) \leq M^\alpha Q_s^0(t_0) e^{-\frac{\alpha(K_M + K_m)(t - t_0)}{2}}. \quad (67)$$

As far as the insulinemia is concerned, following the same steps of the proof of Proposition 2, it comes that:

$$I^0(t) \leq \left(I^0(t_0) + \frac{(M Q_f^0(t_0) + M^\alpha Q_s^0(t_0)) K_M}{V_I |K_{xp} - \alpha \frac{K_M + K_m}{2}|} \right) e^{-K_{\min}(t - t_0)}, \quad (68)$$

with:

$$K_{\min} = \min \left\{ \alpha \frac{K_M + K_m}{2}, K_{xp} \right\}. \quad (69)$$

■

Lemma 8 The origin is the unique, globally, uniformly asymptotically stable equilibrium point.

Proof: The proof comes by using Proposition 4 and the same steps of Lemma 5. ■

Proposition 9 Solutions of the harmonic periodic model are continuous w.r.t. any admissible initial condition.

Proof: The proof comes by using the same steps of Proposition 6. ■

VII. MODEL IDENTIFIABILITY

This section investigates the identifiability of the models presented, w.r.t. the set of unknown parameters, denoted in the sequel by the vector $\theta \in \mathbb{R}^m$. Denote by $y(t) = h(t, t_0, X_0, u, \theta)$ the measured output of a generic ODE system of the type:

$$\dot{X}(t) = f(t, X(t), u(t), \theta), \quad X(t_0) = X_0. \quad (70)$$

In the sequel $h(\cdot, t_0, X_0, u, \theta)$ will denote an element of a suitably defined L_2 -space, constituted of Lebesgue-measurable, square integrable functions on the interval $[t_0, T)$, with

T possibly equal to $+\infty$. Then, *local* identifiability in a point θ requires the existence of a neighborhood I_θ such that:

$$h(\cdot, t_0, X_0, u, \theta') \neq h(\cdot, t_0, X_0, u, \theta'') \quad \forall \theta' \neq \theta'' \in I_\theta, \quad (71)$$

for a non-empty set of pairs (X_0, u) . Note that such a condition does not depend on the approach followed in order to estimate θ . In case of $I_\theta \equiv \mathbb{R}^m$, then we have *global* identifiability.

As far as the switching model is concerned, it consists of a variable structure model, switching among three linear time-invariant working modes, each depending of a 4-dimensional parameter vector $\theta_i = (K_i \ \alpha \ V_I \ K_{xp})^T$. That means, a sufficient condition for the identifiability is that each of the three linear modes be identifiable w.r.t. θ_i . Such an issue is performed for the initial condition $X_0 = 0$, according to the following theorem:

Theorem 10 Consider a linear system with multiple inputs of the type:

$$\begin{aligned} \dot{X}(t) &= A(\theta)X(t) + \sum_{j=1}^p B_j(\theta)u_j(t), \\ y(t) &= C(\theta)X(t), \end{aligned} \quad (72)$$

with $\theta \in \mathbb{R}^m$ a vector of unknown parameters and y the measured output. Define $R_j(\theta)$ the following vectors (*Markov coefficients vectors*):

$$R_j(\theta) = \begin{bmatrix} C(\theta)B_j(\theta) \\ C(\theta)A(\theta)B_j(\theta) \\ \vdots \\ C(\theta)A^{2n-1}(\theta)B_j(\theta) \end{bmatrix}, \quad j = 1, \dots, p. \quad (73)$$

Assume that the entries of each $R_j(\theta)$ are differentiable w.r.t. $\theta \in \Theta \subseteq \mathbb{R}^m$, with continuous derivative. Then θ is locally identifiable in Θ , if the Jacobian

$$\frac{dR}{d\theta} = \frac{d}{d\theta} \begin{bmatrix} R_1(\theta) \\ \vdots \\ R_p(\theta) \end{bmatrix} \quad (74)$$

has rank m for $\theta \in \Theta$.

Theorem 11 Each working mode of the switching parameter model is globally identifiable.

Proof: Recall that $B_1 = [1 \ 0 \ 0]^T$, $B_2 = [0 \ 1 \ 0]^T$ and the measurements are given by the plasma insulin concentration, so that $C = [0 \ 0 \ 1]$, with $CB_i = 0$, $i = 1, 2$. The theorem is proven by showing that the following vector

$$V(\theta) = \begin{bmatrix} CA(\theta)B_1 \\ CA^2(\theta)B_1 \\ CA(\theta)B_2 \\ CA^2(\theta)B_2 \end{bmatrix} \quad (75)$$

obtained by selecting 4 rows of matrix $R(\theta)$, has a full rank Jacobian matrix, named $J_V(\theta)$. After standard computations, $J_V(\theta)$ is given by:

$$\begin{bmatrix} \frac{1}{V_I} & 0 & -\frac{K_i}{V_I^2} & 0 \\ -\frac{2K_i+K_{xp}}{V_I} & 0 & \frac{K_i(K_i+K_{xp})}{V_I^2} & -\frac{K_i}{V_I} \\ \frac{\alpha}{V_I} & \frac{K_i}{V_I} & -\frac{\alpha K_i}{V_I^2} & 0 \\ -\frac{\alpha(2\alpha K_i+K_{xp})}{V_I} & -\frac{K_i(2\alpha K_i+K_{xp})}{V_I} & \frac{\alpha K_i(\alpha K_i+K_{xp})}{V_I^2} & -\frac{\alpha K_i}{V_I} \end{bmatrix}. \quad (76)$$

According to the fact that each parameter is strictly positive, the rank of the Jacobian $J_V(\theta)$ is equivalent to the rank of the following matrix, obtained after rows and columns manipulations:

$$\text{rank}(J_V(\theta)) = \text{rank} \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & K_i & 1 \\ \alpha & 1 & 0 & 0 \\ 0 & 0 & \alpha^2 K_i & \alpha \end{bmatrix}, \quad (77)$$

whose determinant is $-\alpha K_i(1 - \alpha) \neq 0$, for all $\alpha \in (0, 1)$. ■

As far as the identifiability of the harmonic periodic model is concerned, below is reported a general test in order to check local identifiability. Consider a sequence of discrete measurements, sampled at times $j\Delta$, starting from $t_0 = 0$:

$$y(j\Delta) = h(j\Delta, 0, X_0, u, \theta), \quad j = 0, \dots, N, \quad (78)$$

shortly denoted in the sequel by $\bar{h}(j\Delta, \theta)$. The local identifiability condition (71) is fulfilled for a given $\bar{\theta}$ if the following equations:

$$\mathcal{F}_j(\theta) = \bar{h}(j\Delta, \bar{\theta}) - \bar{h}(j\Delta, \theta) = 0, \quad (79)$$

admit only the trivial solution $\theta = \bar{\theta}$ for all $j = 0, \dots, N$ and θ in a sufficiently small neighborhood of $\bar{\theta}$. That means, by naming:

$$H_N(\theta) = \begin{bmatrix} \bar{h}(0, \theta) \\ \bar{h}(\Delta, \theta) \\ \vdots \\ \bar{h}(N\Delta, \theta) \end{bmatrix}, \quad (80)$$

a test for the local identifiability of $\bar{\theta}$ is to check if the Jacobian $\nabla_{\theta} H_N(\bar{\theta})$ is a full column rank matrix.

VIII. CONCLUSIONS

A pair of ODE models describing the plasma insulin absorption from a sc injection in IDDM patients has been proposed. The novelty of the paper relies on the fact that both the models take into account that different absorption rates are associated with different times of a 24 hour time period, so providing time-varying periodic systems. A complete analysis concerning existence and uniqueness, positive boundedness, stability and continuity of the solutions has been reported. Moreover, global identifiability has been proven for the switching model, while a rank condition is given to check local identifiability of the other. In order to make the proposed models effectively useful in a biological/clinical framework, it would be necessary to show that the model parameters are statistically estimable with sufficient precision from data sets obtained from standard experimental procedures. This is a work in progress by the same authors. Further modeling developments concern the consideration of delays in the absorption of insulin from the sc injections to the plasma circulation.

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