Glucose-Insulin Minimal Model Augmented: Identification and Validation ⋆

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Abstract: In this paper a new mathematical model of the glucose-insulin system is presented. The proposed model represents Type 1 Diabetes Mellitus patients and seeks to give a suitable model of the malfunction of the pancreas. Based on the classic *minimal model*, this new approach takes into account the description of the glucose dynamic in the subcutaneous layer and a meal disturbance term, together with an additional term that represents the insulin injections, which make this proposal a more realistic approach. Virtual data from UVA/Padova T1DMS software are used for first evaluations of the effectiveness of the proposed model.

Keywords: Glucose-insulin system, type 1 diabetes mellitus, minimal model augmented, validation.

1. INTRODUCTION

Type 1 diabetes is a chronic illness where the cells in the pancreas that make insulin are destroyed, and the body is not longer able to produce insulin. Onset most often occurs in childhood, but the disease can also develop in adults in their late 30s and early 40s. Patients with type 1 diabetes require lifelong insulin therapy. Most require two or more injections of insulin daily, with doses adjusted based on self-monitoring of glucose levels. This therapy replaces the continuous insulin secretion, which should be provided by the pancreas.

The body naturally tightly regulates blood glucose levels in a tight range $(70 - 110 mg/dl$ or $3.9 - 6.04 mmol/l$ after overnight fast). If the glucose concentration level is significantly out of this range, it is considered that the person have a plasma glucose problem: hyperglycemia or hypoglycemia. For better understanding of the metabolic system and monitoring adequate of the glucose level, medical and engineers researchers have developed several models that can be found in the literature. Based on the knowledge of the behavior of insulin secretion, different control approaches via mathematical models to mimic it, have been proposed. A technique has been developed in the last four decades consisting of the use of an insulin pump that provides continuous insulin administration, based on information from self-monitoring of glucose levels.

The device consists in a control algorithm which manipulates a pump that supplies insulin to the body when the glucose level is high, this level is monitoring via a subcutaneous sensor that gives the glucose values periodically. The main aim of this system called *artificial pancreas*, is to incorporate a closed loop technology to adjust autonomously and permanently the insulin delivery avoiding the dangerous situations, as blood glucose levels rise and fall. The most critical part of this new approach lies in the development of a feasible, robust and safe algorithm for insulin delivery. Technological challenges are present due to inevitable time delays between glucose level measurement (subcutaneous via) and insulin actuation, as well as should also be considered individual patient responses to disturbances (meals, sport, moods, etc.).

Among the mathematical tools that have been developed to represent the glucose-insulin system, we can find models of ordinary differential equations (Bergman *et al.* (1981); Parker *et al.* (1999)), delay differential equations (Bennett and Gourley (2004)), partial differential equations (Kenner (2001)), stochastic differential equations (De Vries and Sherman (2000)) and integro-differential equations (Li *et al.* (2006)). In like manner it is possible to find models including artificial neural networks (ANNs) (Pérez-Gandía *et al.* (2010)), fuzzy logic (Campos-Delgado *et al.* (2006)) or expert systems approach (Chee *et al.* (2003)).

All these models are the subject of ongoing researches in order to overcome challenges based on previous attempts to control the system. For this, it is important to pay attention on the following issues: model uncertainties, time-varying and/or nonlinear phenomena, natural time delays, actuator saturation, measurement noise, to finally consider a real-time application (Sánchez-Pena *et al.* (2011)).

⋆ The authors would like to thank the National Research Fund Luxembourg (FNR) for the financial support in the developing of the project I2R-DIR-AFR-090000.

As a result, different software packages have been developed from different types of mathematical models for numerical analysis and simulations. Among the most popular it is possible find the UVa/Padova Type 1 Diabetes Mellitus Metabolic Simulator (T1DM), which is used to design and test treatment of in-silico subjects with type 1 diabetes and was developed by The Epsilon Group (Dalla Man *et al.* (2006, 2007)). This software it is based on the glucose-insulin dynamics in human subjects represented by a model developed by Kovatchev *et al.* (2009), which can also be used to test performance of control strategies.

As an alternative solution to these challenges, in the physiological environment, compartmental models based on ordinary differential equations are often employed. The most widely used model is the so-called *minimal model* of Bergman *et al.* (1981) (see Fig. 1), which was designed for the interpretation of the glucose and insulin plasma concentrations following the intravenous glucose tolerance test (IVGTT). The purpose of this model is to provide a description of the insulin/glucose dynamic in the simplest way possible, using a minimum number of known or identified parameters.

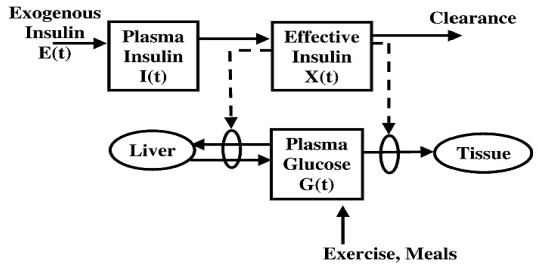

Fig. 1. Minimal model schematic.

In this work, it is proposed an extension of the minimum model that takes into account three main characteristics of the real system, which must be considered for successful treatment of the T1DM disease. First, it is important to consider that in reality all insulin-dependent diabetic subjects live with a conventional or intensified insulin therapy regimen; i.e., insulin is injected subcutaneously repeatedly by day and the dose is adjusted based on glucose concentration measurements continuously monitored by an implanted glucose sensors (Bellazzi *et al.* (2001)). Considering this, a description of the glucose level in the subcutaneous layer is considered in the proposed model, i.e., with an additional dynamic equation it is possible take into account the time delay in absorption by subcutaneous route in a simplest form.

Second, the ingested food, directly impacts blood glucose level. Furthermore, the glucose level is a variable difficult to control because the quantity and the timing of the meals are unknown. With this intention, this model includes a term to describe the meals as a disturbance that helps to improve the glucose dynamic representation.

Third, in order to establish a suitable insulin therapy, a term that represents the insulin dose considering its type is included on the proposed model (see Fig. 2). Pharmaceutical research has produced various types of insulin to mimic the appearance of insulin in plasma occurring in a normal individual. These insulin types ranging from short to long acting, then the insulin is classified according to how long it works in the body. Consequently, considering these aspects, our model gives an approach more realistic that facilitates the future control strategies implementation in real-time. Finally in this paper, we use a scenario designed for an adult in-silico-patient via UVa/Padova T1DM metabolic simulator, in order to validate our proposed model.

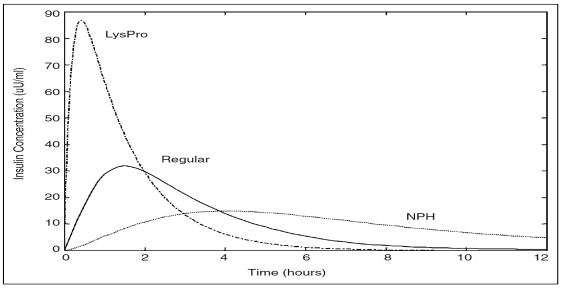

Fig. 2. Time course of plasma insulin concentration after a subcutaneous injection (10 U) of different types of insulin.

This paper is organized as follows: the minimal model and their basic properties are presented in Section 2. Section 3 contains the proposed changes in order to obtain a simple model but more complete, compared to the minimal model of Bergman *et al.* (1981). In Section 4, simulations to identify the parameters and validate the proposed model are presented and discussed. Section 5 provides the conclusions of present work.

2. MINIMAL MODEL

The authors in Bergman *et al.* (1981), from analysis of the complex dynamic relationship between plasma glucose and insulin, have concluded that the resulting data can be described as a stimulus-response model of the extra pancreatic tissues that utilize glucose, giving rise to the minimal model. This model has become in the tool currently most used in physiological research on the metabolism of glucose and the insulin regulation, in a normal person (without T1DM). Such model it is considered simple enough to measured glucose, however makes possible, using mathematical techniques, to estimate all the characteristic parameters of the model from a single data set (Bergman (2006)).

Minimal model involves two physiological compartments: a glucose compartment and a plasma insulin compartment, which is assumed acting through a *remote form* to influence net glucose uptake. The first is represented by Eqs. (1-2) describing the glucose plasma concentration, and the second by Eq. (3) that describes the time course of plasma insulin concentration. These equations are given as follows:

$$\frac{dG(t)}{dt} = -(p_1 + X(t))G(t) + p_1 G_b \tag{1}$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3(I(t) - Ib) \tag{2}$$

$$\frac{dI(t)}{dt} = -nI(t) + \gamma(G(t) - h)^{+}t \tag{3}$$

where G is the blood glucose concentration (mg/dL), X is the effect of active insulin (min^{-1}), I is the plasma insulin concentration (mU/L), G_b and I_b are the basal values of glucose and insulin concentration, p_1 is the glucose clearance rate independent of insulin (min^{-1}), p_2 is the rate of clearance of active insulin (min^{-1}) and p_3 increase in uptake ability caused by insulin $((\mu U/mL)^{-1}min^{-2})$, n is the fractional disappearance rate of insulin (mU/L), γ is the rate of pancreatic release after glucose bolus $(\frac{mU*dL}{L*mg*min})$, h is the the target glucose level (mg/dL) and t represents the time interval from the glucose injection (min).

The function given by Eq. (3) was first presented by Bergman *et al.* (1981) and adjusted by De Gaetano and Arino (2000). Only the positive part of the term $(G(t) - h)$ is taken, otherwise the value is zero. Therefore h is considered a threshold level to decide when the pancreas should produce more insulin and when to stop, finally the difference between $G(t) - h$ determines how much it should be produced. The effect to multiply by t is because the pancreas response, is proportional not only to the hyperglycemia attained but also to the time elapsed from the glucose stimulus.

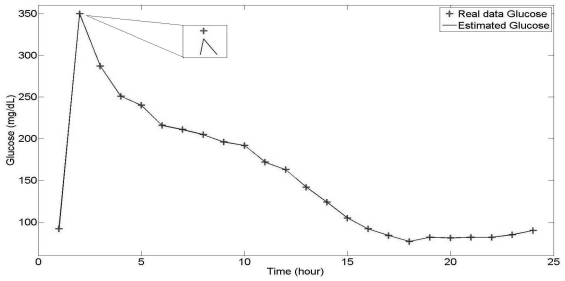

Fig. 3. Blood glucose level using the identified parameters for minimal model for a normal individual.

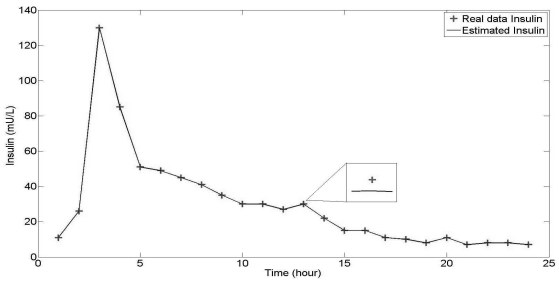

Fig. 4. Blood insulin level using the identified parameters for minimal model for a normal individual.

This model is useful to represent a normal individual, because describes the pancreas as the source of insulin. In a healthy person a small amount of insulin is always created or cleared. This helps to keep the insulin basal concentration I_b. If the insulin level is above basal concentration the clearance increases, if the insulin level is below basal concentration the basal production increases.

2.1 Parameter identification

In order to validate the minimal model, the authors Pacini and Bergman (1986) have provided the FSIGT test data (see Table 1) that describe glucose and insulin measurements that were taken during three hours from a normal individual. Based on these data, numerical simulations have been implemented in MATLAB to estimate the parameters (p_1, p_2, p_3) via the Levenberg-Marquardt algorithm, which is a standard technique used to solve nonlinear least squares problems.

Let $\dot{x} = f(p)$ be the parameterized model function. The minimization starts after an initial guess for the parameters when vector p is provided. The algorithm is locally convergent; namely, it converges when the initial guess is close to the true values. In each iteration step, the parameter vector p is updated by a new estimate $p + \varepsilon_p$ where ε_p is a small correction term that can be determined by a Taylor Series expansion which leads to the following approximation:

$$f(p + \varepsilon_p) \simeq f(p) + J\varepsilon_p \tag{4}$$

where $J = \frac{\partial f(p)}{\partial p}$ is the Jacobian of f at p. Levenberg-Marquardt iterative initiates at the starting point p_0 and produces a series of vectors p_1, p_2, p_3, that converge towards a local minimizer p^{+} of f. At each step, it is required to find the small correction factor ε which minimizes the value of:

$$\| x - f(p + \varepsilon_p) \| \simeq \| x - f(p) - J\varepsilon_p \| \tag{5}$$

That gives the following:

$$\| x - f(p + \varepsilon_p) \| \simeq \| x - \dot{x} - J\delta_p \| = \| e - J\varepsilon_p \| \tag{6}$$

where ε_p is the solution to a linear least squares problem. The process iterates until a value of ε_p that reduces error is found (see Hariri and Wang (2011) for more details).

Via the Optimization Toolbox of MATLAB, a function called *Lsqnonlin* is used to solve this algorithm and the parameters can be estimated with lower and/or upper bounds. The values of the parameters found minimize the difference between the measured time course of plasma glucose and the parameter-dependent solution to the glucose minimal model from Eqs. (1-3). Figs. 3-4 shown the glucose and insulin levels of both experimental data (see Pacini and Bergman (1986)) and simulated data for a normal individual.

3. MINIMAL MODEL AUGMENTED

However, to use the minimal model for a diabetic patient Type 1 it is necessary to consider some additional terms, which are variables and functions that should be added in order to contribute with the design of a complete model that can be used in closed- or partially closed-loop strategies of insulin control.

The aim in this section is to present an augmented model to be used to represent human diabetic patients with Type 1 diabetes.

Table 1. G(t) and I(t) levels of a normal individual

Time (min)	Glucose (mg/dL)	Insulin (mU/L)
1	92	11
2	350	26
4	287	130
6	251	85
8	240	51
10	216	49
12	211	45
14	205	41
16	196	35
19	192	30
22	172	30
27	163	27
32	142	30
42	124	22
52	105	15
62	92	15
72	84	11
82	77	10
92	82	8
102	81	11
122	82	7
142	82	8
162	85	8
182	90	7

3.1 Include a meal disturbance

It is possible to increase the functionality of the glucose minimal model by additions of functions describing the patient conditions. The first of these additions corresponds to meals that directly impacts on blood glucose levels. This is done by adding a meal disturbance term $D(t)$ into Eq. (1). To represent a person in a diabetic state, the original minimal model is described by the following differential equations:

$$\frac{dG}{dt} = -p_1 G - X(G - G_b) + D(t) \tag{7}$$

$$\frac{dX}{dt} = -p_2 X + p_3(I - I_b) \tag{8}$$

where $D(t)$ is the meal disturbance and can be represented by a function as follows:

$$D(t) = \frac{R_{abs}}{m_{BW} V_G} \tag{9}$$

where R_{abs} is the rate of absorption of exogenous glucose (mg/min) and is scaled by the glucose distribution volume V_G and for the body weight m_{BW}. Eq. (9) is adapted to change basal blood glucose concentrations according to body mass, i.e., the model is adapted to each patient (Lunze *et al.* (2012)).

The description of process of exogenous glucose (meals) absorption was suggested by Fisher (1991). The author points that the glucose absorption description should be a function which rapidly increases after the meal, and then decays to 0 in 2-3 hours, as follows:

$$R_{abs}(t) = B \cdot e^{(\theta \cdot t)} \tag{10}$$

where B represents the carbohydrates quantity ingested (grams) and $\theta = 0.05$ is a constant suggested by Fisher (1991).

3.2 Include a exogenous insulin infusion

Similarly, on insulin model (Eq. (3)) a function $U_I(t)$ representing the exogenous insulin infusion instead of $[\sigma(G(t) - h)t]$, it is added as follows:

$$\frac{dI}{dt} = -n(I - I_b) + U_I(t) \tag{11}$$

where $U_I(t)$ can be modeled as the rate of insulin absorption after a subcutaneous insulin injection according to authors in Berger and Rodbard (1989), as follows:

$$U_I(t) = \frac{s_i t^{s_i} T_{50}^{s_i} D_I}{t[T_{50}^{s_i} + t^{s_i}]^2 V_I} \tag{12}$$

where t is the time elapsed from the injection (t^s means t raised to the power s_i), T_{50} is the time at which 50% of the insulin dose D_I has been absorbed and s_i is a parameter which defines the insulin absorption pattern depending of types of insulin (regular, intermediate, slow, etc.),. V_I is the distribution volume of insulin in blood that should be estimated. The linear dependency of T_{50} on dose is defined by:

$$T_{50} = a_i D_I + b_i \tag{13}$$

where a_i and b_i are preparation-specific parameters the values of which are given in Berger and Rodbard (1989) along with values for s_i.

3.3 Glucose level in the subcutaneous layer

In order to obtain a useful model according to the non-invasive monitoring techniques, the description of the glucose level in the subcutaneous layer is considered in this work. A patient with T1DM, usually test their blood glucose frequently (3 to 10 times per day), both to assess the effectiveness of their prior insulin dose and to help determine their next insulin dose. For this reason, it is easier to do the blood glucose concentration monitoring through the subcutaneous layer measurements and not via intravenous.

For this purpose, $G_{sc}(t)$ is introduced, which describes the glucose concentration in the subcutaneous layer via the following dynamic function:

$$\frac{dG_{sc}}{dt} = \frac{G(t) - G_{sc}}{5} - R_{utl} \tag{14}$$

where the initial condition is defined as $G_{sc}(0) = (G(0) - 5)R_{utl}$. This equation represents a first-order delay (5 minutes) between the blood glucose concentration and the subcutaneous glucose concentration measurements. The R_{utl}, is the rate of utilization, which is the difference between the two concentrations in steady state Fisher (1991). One of the major problems concerning automatic control of glucose level is the proper estimation of this delay.

4. RESULTS

Numerical simulations are presented in order to show how the proposed model can describe the meals and insulin injection effects and the delay of subcutaneous layer, into the glucose-insulin system. For this, the data

of an adult diabetic patient are used via the UVa/Padova T1DM metabolic simulator. One day scenario (24 hours) is designed using the realistic computer data derived from clinical trials reflecting the body metabolism for a patient with Type 1 Diabetes Mellitus.

Via the GUI scenario creator, parameters corresponding to one day scenario is designed with 3 potential meals: breakfast, lunch and dinner with associated boluses in insulin Units. The timing of the meals is fixed at 7a.m., 12p.m. and 6p.m. and the length of simulation is automatically set to 24 hours. The meal amount in grams is fixed at $45g$, $70g$ and $80g$ of carbohydrates each one and insulin injections exogenous of $3U$, $4.7U$ and $5.3U$ respectively.

The constant parameters p_1, p_2, p_3 are estimated via the Levenberg-Marquadt algorithm. The body weight $102.32kg$, the basal values $G_b = 138.56mg/dL$ and $I_b = 100.25U/hr$, and volumes $V_g = 1.9152dL/kg$, $V_I = 0.0549L/kg$ are supplied by the UVa/Padova T1DM metabolic simulator.

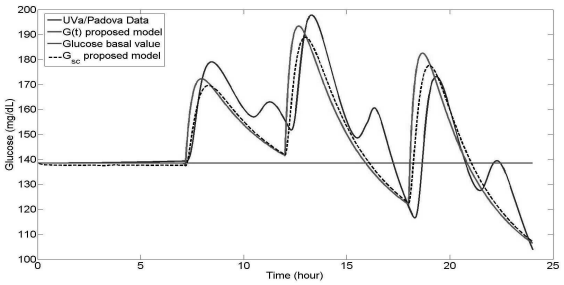

Fig. 5. Blood and subcutaneous glucose level using the minimal model augmented.

Fig. 5 shows that glucose level rises from basal value, it can be seen the increase of glucose levels in each meal and return it to basal glucose level three hours after approximately. With the modified model using the $U_I(t)$ function with insulin regular type it is possible to see how the model reacts to exogenous insulin injections. With this in mind, it is assumed that the three insulin doses were injected at the meal times. The larger the dose of regular insulin, the faster the onset of action, but the longer the time to peak effect and the longer the duration of the effect.

The proposed augmented minimal model gives a good approximate estimation of $G(t)$ (see red line) compared with that obtained from the UVa/Padova T1DM metabolic simulator (see blue line), using the same adult subject data, and correlation was satisfactory. Importantly, the UVa/Padova T1DM software uses a complex model with more than 10 differential equations, and a lot of parameters are taken into consideration. So, for this reason, in the Fig. 5 can be seen that the blue line represents a more accurate estimation of the blood glucose level behavior. Instead the proposed model, keeps the simplicity of the minimal model with some additional parameters, which are considered indispensable to customize it to each patient and make it more suitable for the development of observation and control strategies. The dotted black line represents the subcutaneous glucose level, that can be seen as more approximate estimation to real glucose level.

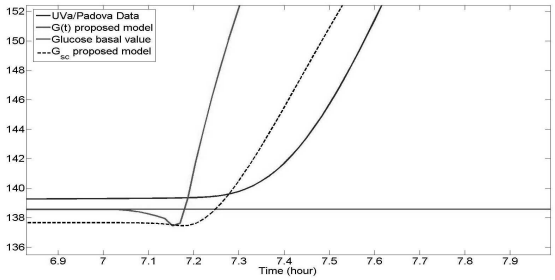

Fig. 6. Zoom of blood and subcutaneous glucose level at first meal disturbance (7 a.m.).

In addition, a zoom (Fig. 6) shows the delay between two models (15 min approx. between blog glucose level and software data), due to that the proposed model approximates the time differences in the dynamics of blood glucose and subcutaneous glucose. This difference should be analyzed to consider its effect on the insulin treatment represented by a closed loop control. It is expected that this offset will be compensated in the estimation step (via state observers) and / or control step, which will be presented on future publications.

Additionally can be seen that the deviation from basal value depends on the quantity of carbohydrate presents in the meals. The speed of clearance of glucose also depends of values of estimated parameters, i.e., if p_1 have a lower value, slows the decay.

The figures showed that the meal disturbance is an external variable that causes important deviations from the normal glucose level. In the real system, this perturbation is considered as a completely unknown and individual, which should be detected and its size should be estimate with the intention of calculate the adequate insulin dose.

5. CONCLUSIONS

The Bergman's model is considered to be the simplest and has been usually used to identify important issues in systems biology as they relate to carbohydrate metabolism. For this reason, in this paper, new functions were included based on the minimal model in order to obtain a representation more realistic of metabolism of T1DM patients.

These additional functions represent unmeasurable meal disturbances, the insulin type and delays for glucose subcutaneous measurements. As has been noted, in trying to represent such conditions several complex models have been developed. Therefore in this work, an alternative that seeks to obtain an more realistic and simplest model taking into account these issues is presented.

In essence, a function to represent the meals disturbance scaled by weight body, was aggregated. This function allows personalize the model to each T1DM patient, and at the same time monitor the direct impact of meals in the glucose level for each one. In like manner, the type of insulin in a subcutaneous injection dose was considered in the proposed model, which enabled to establish an insulin therapy adequate to each individual. Finally, an additional

dynamic equation representing the subcutaneous glucose level was taken into consideration. This equation represents the subcutaneous layer glucose level, which is a way more easy to monitoring instead via intravenous, that is an invasive techniques requiring medical supervision.

To summarize, the additional functions turn the proposed model into an interesting tool, because gives an approximate representation of human body behavior, which is one of the greatest issues in the diabetes treatment. As a result, the model extended will collaborate to development of monitoring and control strategies under those circumstances (meal disturbance, subcutaneous layer monitoring and insulin injections), which contributes and promotes to research of the artificial pancreas.

Our results indicate that the minimal model augmented proposed, provides a good approximate estimation of the glucose level compared with data from clinical trials for an adult patient provided by UVa/Padova T1DM metabolic simulator. Thus, this minimal model augmented can be presented as a candidate model, which is simple, cost-effective, and reliable tool to measure the glucose level from subcutaneous glucose tests without employing complex invasive devices.

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