TYPE 1 DIABETES MELLITUS MODEL: SIMULATION STUDY

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Abstract

This paper deals with Type 1 Diabetes Mellitus (T1DM) minimal model identification. Minimal model is extended with the model of insulin pharmacokinetics. Identification data sets are obtained from IVGTT (Intravenous Glucose Tolerance Test) and data of pharmacokinetics test of a healthy subject. Identified model is subjected to various simulation experiments to verify its validity.

1 Introduction

Diabetes is a serious life-long health condition where the concentration of blood glucose is not regulated as a contrast to a healthy subject. Blood glucose is often above the normal levels because pancreas doesn't produce any insulin, or not enough insulin, to help glucose enter body cells – or the produced insulin doesn't work correctly (this condition is called insulin resistance).

According to the International Diabetes Federation, more than 56.3 million people are suffering from diabetes in Europe only. We are expecting growth of prevalence to 68.9 million in 2025. More than 6.8% of adults have diagnosed diabetes. In 2013, more than 619 000 people died from diabetes in European region and more than 147 billion USD (estimated) was spent for diabetes treatment. [1]

If we focus on the global statistical data, there are over 382 million people living with diabetes in 2013 worldwide. Up to one half of the population with diabetes remains undiagnosed. In 2013, more than 5.1 million people died from diabetes and 548 billion USD was spent for diabetic patients healthcare. [1]

There is no ultimate cure for diabetes yet. Type 1 Diabetes Mellitus (T1DM) patients deal with the disease by taking several blood glucose measurements a day and administering insulin by injections or manual insulin pumps. Accurate amount of insulin and right time of administration can be difficult to determine considering affecting factors like meal intake or exercise. The goal is to keep blood glucose concentration at the normoglycemic levels, avoiding hypoglycemic and hyperglycemic excursions.

Control theory and automation with the help of continuous glucose monitoring (CGM) and insulin pumps bring us a possibility of automatic insulin dose calculation and administration without the need of patient involvement. Closed-loop device that consists of CGM, insulin pump and control algorithm is called artificial pancreas because it mimics glucose concentration regulation of a real human pancreas. Artificial pancreas is not supposed to be the ultimate cure for T1DM, but it has a potential to improve the quality of life of those suffering from the disease until the cure is found. More information on artificial pancreas can be found in the publications [2] and [3].

Design of the control algorithm of the closed-loop system relies heavily on the relevant mathematical model of insulin and glucose kinetics, therefore extended minimal model is presented and its parameters are identified in this paper.

2 T1DM minimal model

Common treatment of T1DM uses information about the most recent blood glucose concentration (using CGM or fingerpick measurements); and information about upcoming meal intake. Patients normally administer two types of insulin doses – basal and bolus. Basal insulin keeps glucose concentration on its basal level when there is no meal intake present (state without disturbance). On the other hand, bolus insulin is administered in the time of meal intake to increase glucose uptake during and after meals.

The mathematical model based on the Bergman's minimal model [4] [5] [6] (Figure 1) presented and identified in this paper consists of two inputs – insulin concentration $I(t)$ [μU/ml] and glucose rate of appearance in plasma $R_a(t)$ [mg/kg/min] (based on meal announcement information, e. g. meal intake); and one output – glucose concentration G [mg/dl].

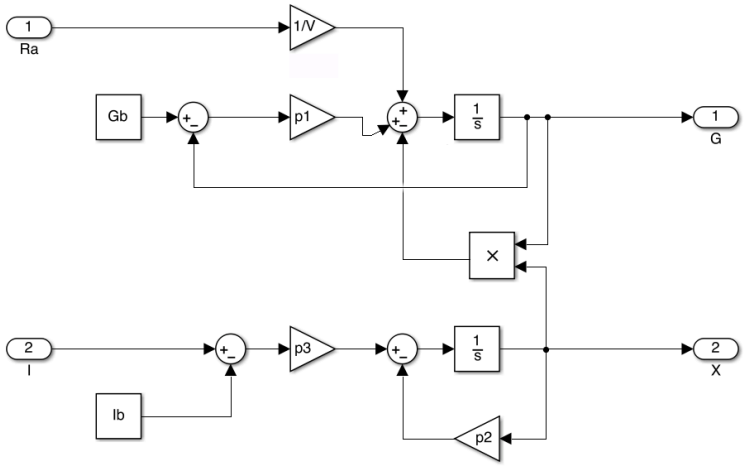

Figure 1: T1DM minimal model scheme

Equations describing the model are:

$$\frac{dG(t)}{dt} = -[p_1 + X(t)]G(t) + p_1 G_b + Ra(t) \quad (1)$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3[I(t) - I_b] \quad (2)$$

$$S_G = p_1, S_I = \frac{p_3}{p_1} \quad (3)$$

where G_b [mg/dl] and I_b [μU/ml] are basal values of glucose and insulin respectively. Identification parameters of the model are p_1 $[1/min]$, $p_2[1/min]$ and $p_3[ml/\mu U/min^2]$. S_I is insulin sensitivity, S_G is glucose effectiveness and X [1/min] is remote insulin.

Described minimal model is extended with the model of insulin pharmacokinetics and pharmacodynamics.

3 Insulin pharmacokinetics and pharmacodynamics

Exogenously administered insulin is unable to mimic the exact effect of the insulin released by healthy pancreas into the portal vein. Insulin pharmacokinetics describes how the plasma insulin concentration reacts to external insulin after its subcutaneous administration and pharmacodynamics describes the resulting effect on glucose concentration over time.

When assessing insulin pharmacokinetics and pharmacodynamics, insulin dose is administered to a fasting healthy subject. Subsequently regular blood samples are taken for glucose and insulin concentrations analysis and glucose concentration is kept on its basal level by glucose infusion during the time of experiment.

Equations of the insulin pharmacokinetics model (Figure 2) are [7]:

$$\frac{dS_1(t)}{dt} = -\left(\frac{1}{t_I}\right) S_1(t) + v(t) \quad (4)$$

$$\frac{dS_2(t)}{dt} = -\left(\frac{1}{t_I}\right) S_2(t) + \left(\frac{1}{t_I}\right) S_1(t) \quad (5)$$

$$\frac{dI(t)}{dt} = -k_I I(t) + \left(\frac{1}{t_I}\right)\left(\frac{1}{V_I}\right) S_2(t) \quad (6)$$

Where $v(t)$ $[\mu U/kg/min]$ is the rate of subcutaneously administered insulin, $S_1(t)$ $[\mu U/kg]$ and $S_2(t)$ $[\mu U/kg]$ are state values, t_I $[min]$ is a time constant, $k_I[1/min]$ is the rate of naturally disposed insulin and V_I $[dl/kg]$ is the distribution volume per kilogram of body weight.

The input $v(t)$ has the form:

$$v(t) = v_b + v_B\delta(t) \tag{7}$$

where v_b $[\mu U/kg/min]$ is the basal value, causing the output of this subsystem being on I_b $[\mu U/ml]$ in the basal state and v_B $[\mu U/kg]$ is the insulin dose, $\delta(t)$ is the approximation of Dirac impulse.

Basal values can be calculated as follows:

$$S_1(0) = S_2(0) = \frac{k_I I_b}{\frac{1}{t_I}\frac{1}{V_I}} \tag{8}$$

$$v_b = \frac{1}{t_I} S_1(0) \tag{9}$$

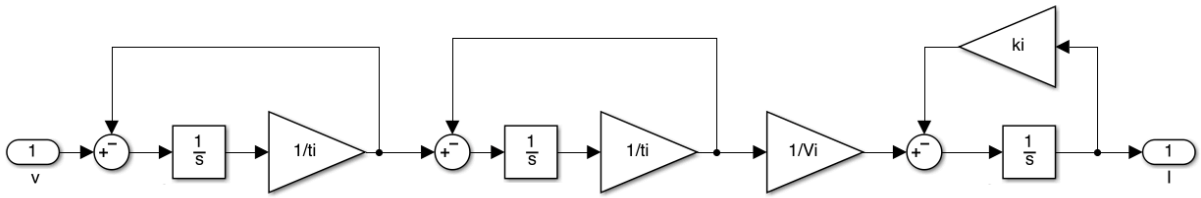

Figure 2: Pharmacokinetics model scheme

The next chapter summarizes the results of the identification process carried out using extended minimal model of T1DM.

4 Experiments and results

Using data from pharmacokinetics measurements [8] with the help of Non-linear least square optimization, the following parameters of pharmacokinetics model were identified. (Table 1)

Table 1: MODEL OF INSULIN PHARMACOKINETICS – IDENTIFIED PARAMETERS

Parameter	*Value*	*Dimension*
$S_1(0) = S_2(0)$	9294.9	$[\mu U/kg]$
v_b	182.3085	$[\mu U/kg/min]$
V_I	87	$[dl/kg]$
t_I	50.9847	$[min]$
k_I	0.1905	$[1/min]$

When the model of pharmacokinetics is identified, it can be used as a base for minimal model identification. Bolus insulin input was 15 U, which corresponds to $v_B = 40000\ \mu U/kg/min$ over the period of 5 minutes.

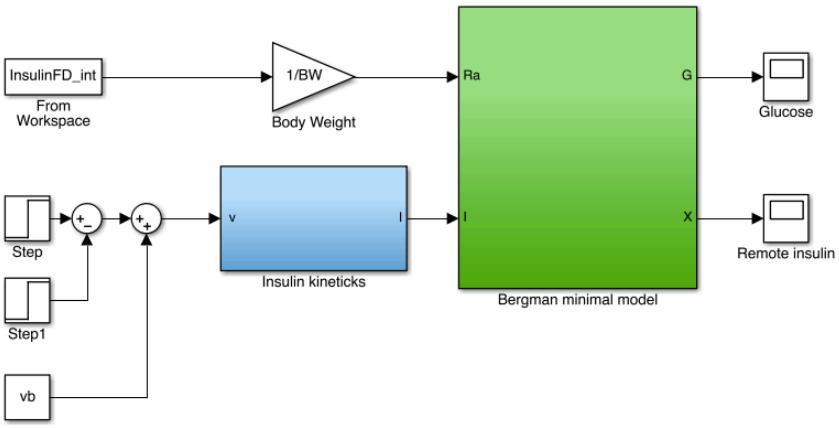

Figure 3: Extended T1DM minimal model scheme

Data from pharmacodynamics represent glucose rate of appearance $R_a(t)$ signal while glucose concentration G_b basal level is maintained during the experiment.

The equation (1) can be rewritten in the form:

$$\dot{G}(t) = -p_1 G(t) + p_1 G_b + \frac{1}{V}\left(Ra(t) - V \cdot X(t) \cdot G(t)\right) \tag{10}$$

Considering glucose concentration $G(t) = G_b$ when $Ra(t) = V \cdot X(t) \cdot G(t)$, (see the Figure 5) parameters of the minimal model were identified (see Table 2).

Table 2: MINIMAL MODEL – IDENTIFIED PARAMETERS

Parameter	*Value*	*Dimension*
G_b	92	$[mg/dl]$
I_b	11	$[\mu U/ml]$
BW	75	$[kg]$
V	1.7	$[dl/mg]$
p_1	0.7683	$[1/min]$
p_2	0.0131	$[1/min]$
p_3	1.7822e-05	$[ml/\mu U/min^2]$

Simulation experiment results are shown in Figure 4.

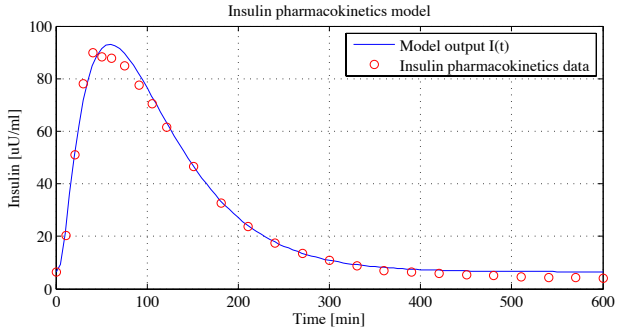

Figure 4: Insulin pharmacokinetics model

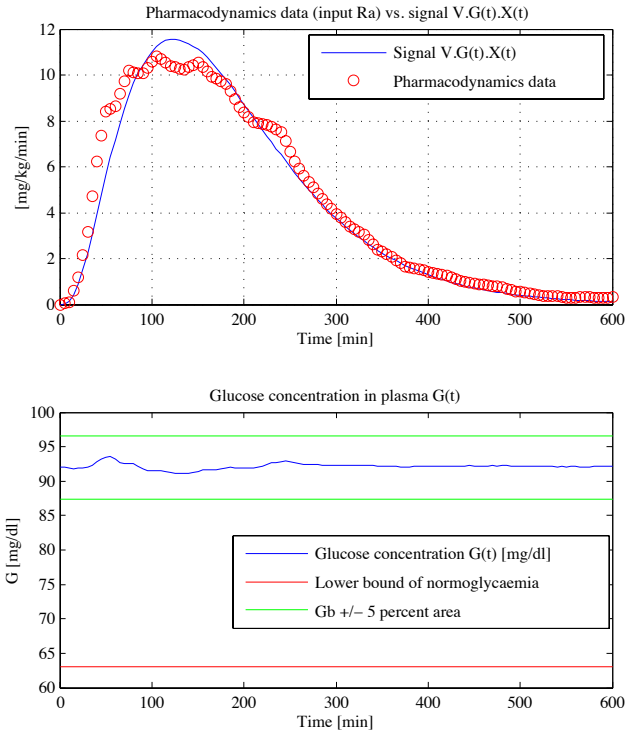

Figure 5: Pharmacodynamics data and glucose concentration in plasma

5 Conclusion

This paper presents the identification of T1DM minimal model extended with the model of insulin pharmacokinetics. Insulin pharmacokinetics describes how the plasma insulin concentration reacts to the external insulin after its subcutaneous administration, which is a common way of insulin injection in T1DM treatment using insulin pumps. When T1DM is treated without the use of insulin pumps, more types of insulin are administered. Therefore, additional research on insulin with different pharmacodynamics and pharmacokinetics could be beneficial. Identification of extended T1DM minimal model is based on the Non-linear least square optimization and identified model is evaluated using simple experiment. Described minimal model can be used as a foundation for further extension with the gastrointestinal absorption subsystem.

Acknowledgment

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