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Identification of T1DM minimal model using non-consistent data from IVGTT

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Abstract

Type 1 diabetes mellitus identification using inconsistent data from IVGTT (Intravenous Glucose Tolerance Test) of healthy subject is presented in this paper. Simple PID (Proportional – Integral – Derivative) controller is applied to the identified minimal model to maintain normoglycemia.

Keywords: Type 1 diabetes mellitus; Identification; IVGTT; Linearization; PID

1. Introduction

According to the IDF (International Diabetes Federation), there are over 371 million people living with diabetes in 2012 worldwide. This number is growing in every country. Up to one half of population with diabetes remains undiagnosed. In 2012, more than 4.8 million people died from diabetes and 471 billion American dollars were spent for diabetic patients healthcare (IDF, 2012).

The cure for diabetes does not exist yet. In Type 1 diabetes mellitus (T1DM) patients deal with this disease by several blood glucose measurements a day and insulin administration using insulin injections or manual insulin pump. Correct amount of insulin and precise time of administration can be difficult to determine taking into account variety of affecting factors, e.g. meal intake, exercise, illness and many others. Blood glucose hypoglycaemic and hyperglycaemic excursions need to be avoided, keeping blood glucose concentration at the normoglycemic levels.

Artificial pancreas, or closed-loop control system, is a device consisting of continuous glucose monitoring (CGM) system, insulin pump and control algorithm. The term artificial pancreas comes from the possible ability of this device to mimic glucose concentration regulation of a real human pancreas. Closed-loop system may revolutionize T1DM management in the next one to two decades (Hovorka, 2013).

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Crucial part of the closed-loop system is a design of its control algorithm that often relies on appropriate mathematical model of glucose and insulin kinetics. Therefore, the minimal model is presented and identification of the model parameters based on input–output data from in vivo tests on healthy subject is carried out.

Identified model is used as a base for a simple in silico experiment applying PID control algorithm.

2. Preliminaries and problem formulation

For the identification purposes frequent subject measurements at the exact time intervals are needed. Input–output data can be obtained in several ways. Data from unsupervised tests might be not consistent as people tend to forget, they measure their blood glucose at other time than needed, or might skip several measurements.

Another example of obtaining non-consistent data is the result of the IVGTT. The IVGTT consists of two phases. In the first phase, a test amount of glucose is administered intravenously to the subject. In the second phase, blood samples are taken at specified time intervals (usually not consistent) and glucose and insulin plasma concentration is analyzed.

2.1. Model description

The minimal model of the glucose kinetics has the form of these two differential equations:

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

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

where

$$G(0) = \frac{D}{V}; \quad X(0) = 0; \quad Ra(t) = \frac{D}{V}\delta(t) \tag{3}$$

$G(t)$ represents plasma glucose concentration (mmol/l); $I(t)$ is plasma insulin concentration (mU/l); $X(t)$ is remote insulin (min^{-1}); $Ra(t)$ represents the glucose rate of appearance in blood $\delta(t)$ is the Dirac delta function, i.e. unity amplitude impulse signal. G_b and I_b are the basal plasma glucose and insulin concentrations and D (mmol/kg) is the administered glucose dose. The remaining parameters are used to represent insulin sensitivity $S_I = (p_3/p_2)$ (mU/l) and glucose effectiveness $S_G = p_1$ (min^{-1}) (more in Cobelli et al. (2009) and Tarnik (2012)).

2.2. Linear approximation of minimal model

The first two terms of Taylor series in the set point ξ_e (plasma insulin concentration remains on its basal state) were used to obtain a linearized model of the glucose–insulin kinetics.

$$F(\xi) \approx F(\xi_e) + \left.\frac{\partial F}{\partial \xi}\right|_{\xi_e} (\xi - \xi_e)$$
$$\xi_e = [G_b \quad 0] \tag{4}$$

Finally, the linear approximation of the introduced minimal model at the basal state has the form:

$$\begin{bmatrix} \dot{G}(t) \\ \dot{X}(t) \end{bmatrix} = \begin{bmatrix} -p_1 & -G_b \\ 0 & -p_2 \end{bmatrix} \begin{bmatrix} \Delta G(t) \\ \Delta X(t) \end{bmatrix} + \begin{bmatrix} 1/V & 0 \\ 0 & p_3 \end{bmatrix} \begin{bmatrix} D \cdot \delta(t) \\ \Delta I(t) \end{bmatrix}$$
$$y(t) = \begin{bmatrix} 1 & 0 \end{bmatrix} \begin{bmatrix} \Delta G(t) \\ \Delta X(t) \end{bmatrix} \tag{5}$$

The model (5) has two inputs ($D \cdot \delta(t)$ and $\Delta I(t)$), one output $\Delta G(t)$ and it consists of two transfer functions. There are four parameters which need to be identified – p_i, $i = \{1, 2, 3\}$ and parameter V. The forth parameter represents

Table 1
Identified model parameters.

p_1 (min^{-1})	p_2 (min^{-1})	p_3 (min^{-1} mU/l)
3.7219	0.0329	0.00073

the distribution volume and was identified during clinical testing (Hovorka, 2013; Hovorka et al., 2002; Tarnik and Miklovicova, 2012). For this experiment we consider this parameter as known:

$$V = 1.88\,\text{dl/kg}$$

The corresponding continuous transfer functions are as follows:

$$\Delta G(s) = \frac{-p_3 G_b}{S^2 + (p_1 + p_2)s + p_1 p_2}\Delta I(s) + \frac{1/V}{s + p_1} D \cdot \delta(s) \tag{6}$$

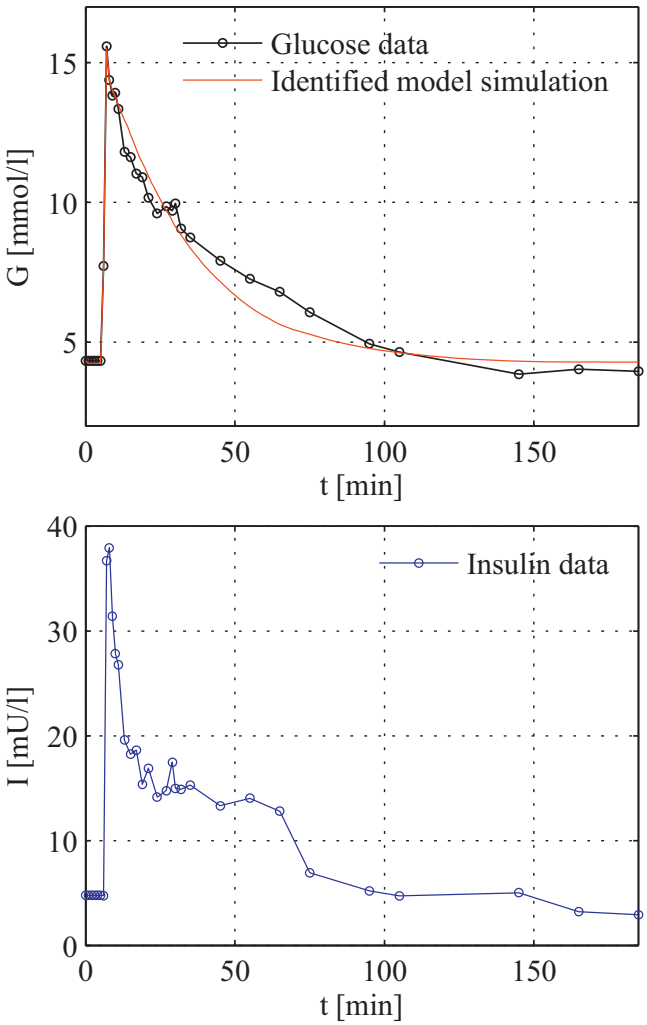

Fig. 1. Glucose (G) and insulin (I) data from IVGTT compared to identified model output.

3. Main results

3.1. Identification

For identifying the parameters of given minimal model, we used data collected from three healthy subjects, which underwent IVGTT. A glucose shot of different amount was administered intravenously to each subject and blood samples were taken each minute at the beginning of the test, then the time interval increased to 2, 10, 20 and 40 min. The blood was analyzed for glucose and insulin concentrations. It is obvious, that the resulting data are not regularly sampled. The minimum time between two samples was 1 min, which was chosen as our sampling period.

Matlab ARX routine requires periodically sampled data. We used a linear interpolation algorithm, to calculate the missing samples.

The resulting discrete time model has the following form:

$$A(z^{-1})\Delta G(z^{-1}) = B_1(z^{-1})\Delta I(z^{-1}) + B_2(z^{-1})D \cdot \delta(z^{-1}) \tag{7}$$

where the polynomial $A(z^{-1})$ has the form $A(z^{-1}) = 1 + a_1 z^{-1} + a_2 z^{-2}$ and polynomials $B(z^{-1})$ and $B_2(z^{-1})$ are $B_1(z^{-1}) = b_{11} z^{-1} + b_{12} z^{-2}$, $B_2(z^{-1}) = b_{21} z^{-1} + b_{22} z^{-2}$. Coefficients in these polynomials have no direct interpretation in the minimal model. Therefore, a backward transformation to continuous transfer functions (TFs) needs to be done. Because the backward transformation is not straightforward, we got the following forms of transfer functions:

$$\Delta G(s) = \frac{b_{11}s + b_{12}}{s^2 + a_1 s + a_2}\Delta I(s) + \frac{b_{21}s + b_{22}}{s^2 + a_1 s + a_2} D \cdot \delta(s) \tag{8}$$

Zeros appeared in both TF, after the backward transformation. They do not affect the systems dynamics, so it is possible to model the system without them. The first order TF in (6) does not represent the glucose intake well;

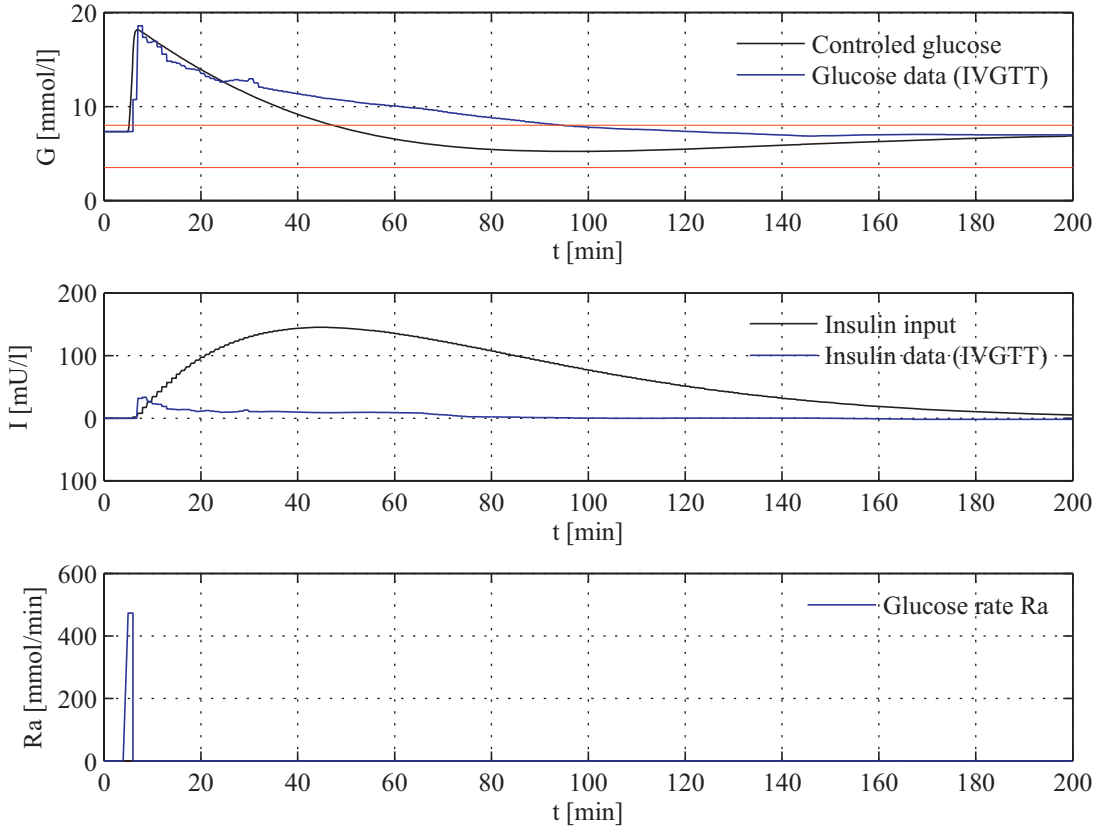

Fig. 2. Simulation experiment results.

therefore, we use TF of the second order. Finally we could calculate the missing parameters needed for the minimal model (Table 1).

3.2. Control algorithm

In this section we briefly describe discrete PID algorithm which was used to control blood glucose concentration of T1DM model presented in the previous section.

For the purpose of the simple experiment, we have decided to use built-in Matlab PID Tuner interface to set the parameters of discrete PID controller. PID Tuner automatically evaluates a linear model of the plant. Plant is considered to be the combination of all Simulink blocks between controller input and output ports. PID Tuner computes an initial controller design balancing between robustness and performance.

We have carried out a simple simulation experiment of PID control algorithm applied to the identified T1DM minimal model trying to emulate insulin secretion of a healthy pancreas. The simulation conditions as present during IVGTT have been replicated – identified model received the equal amount of glucose.

The primary objective of glucose concentration control is keeping its level between 3.8 mmol/l and 10 mmol/l. Hypoglycaemic excursions have to be avoided.

Results of the simulation experiment can be seen in Fig. 2. At the time of initial glucose peak, PID controller tries to keep glucose concentration within normoglycemic range resulting in insulin rise with the peak of about 140 mU/l. In the comparison to the reaction of healthy human pancreas it is almost four times higher amount of insulin. Hypoglycaemic excursions are not present.

Second simulation experiment represents regulation process of T1DM subject in 24 h. Three meals during a day are considered – breakfast at 8 am, lunch at 12 am and dinner at 8 pm. Results can be seen in Fig. 3.

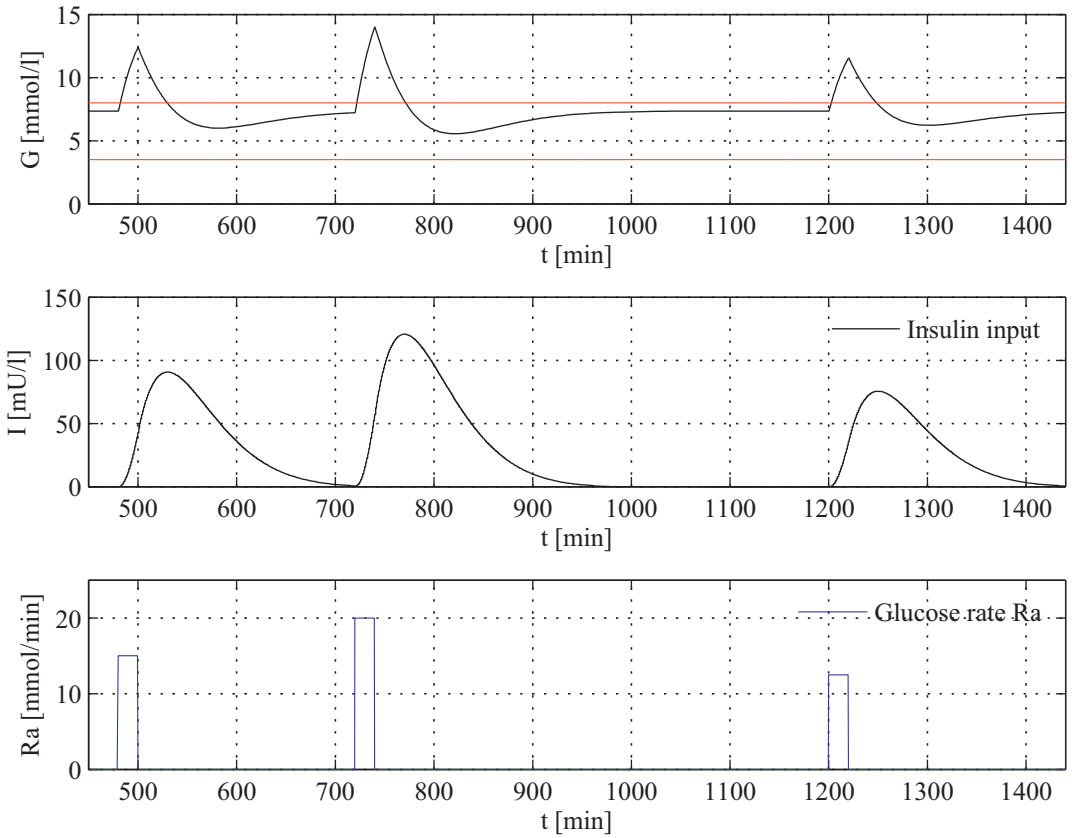

Fig. 3. Glucose regulation during a day.

Identification of the minimal model is limited to IVGTT data and does not consider delays in glucose level measurements and insulin infusion caused by subcutaneous tissues. Extending the minimal model with submodels of subcutaneous tissues should be performed before applying it in practical use.

4. Conclusion

In this paper identification of T1DM minimal model using IVGTT data has been presented. Simple simulation experiment of PID control algorithm application has been carried out. IVGTT provides inconsistent data, therefore linear interpolation algorithm has been used to calculate missing samples. ARX routine has been applied to evaluate parameters of minimal model. Graphical results of the identification can be seen in Fig. 1. Simulation experiment with simple PID controller showed possible emulation of a healthy pancreas glucose regulation function, although further research on alternative control algorithms is necessary.

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