Dynamic simulation of insulin-glucose interaction in type 1 diabetes with MATLAB Simulink®

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Abstract. Diabetes is a complex multifactorial disease where a person endures hyperglycemia in a long period. There have been large interest to perform dynamic simulation of insulin-glucose interaction to obtain a new insight of glucose homeostasis in a diabetic patient. Type 1 diabetes is characterized by the inability of β-cell in the pancreas to produce insulin and hence type 1 diabetes patient needs continuous insulin injection throughout their lives. Here, an educational module for process control in chemical engineering education has been developed to describe the insulin-glucose interaction. The model used an extended version of the minimal model (Bergman model) to simulate the interaction of insulin-glucose using state-space and SIMULINK. The state-space model development through classic linearization method followed by open-loop as well as a closed-loop simulation in SIMULINK was presented. The model was then used to simulate the meal disturbance over 24 h of simulation time. Various PI parameters were compared based on ITAE tuning methods in order to evaluate the dynamics of insulin-glucose interaction.

Keyword: diabetes, dynamic, simulation, minimal model

1. Introduction

Diabetes is a chronic disease which occurs when β-cell in the pancreas does not produce enough insulin or when the body cannot effectively utilize insulin. World Health Organization reported that diabetes prevalence has been rising tremendously in middle- and low-income countries. Type 1 diabetes is characterized by the inability of β-cell in the pancreas to produce enough insulin. It usually occurs in younger age which makes it called “juvenile diabetes” [1]. According to WHO, diabetes currently considered as a burden of our civilization with more than 1 million children were living with type 1 diabetes in 2017 [2], [3]. Type 1 diabetes patient needs continuous insulin supply by administrating exogenous insulin injection. Without proper treatment, the fluctuation of insulin-glucose in their body may harm their heart, blood vessels, eyes, kidneys, nerves, or even leading to disability and premature death [2].

The same as a normal person, the dynamic of blood glucose level in a person with type 1 diabetes is very important to maintain. In a regular person without diabetes, the insulin produced in the pancreas is used to conserve their blood glucose. On the contrary, a person with diabetes struggles to maintain their blood glucose. A slight excess of glucose level (hyperglycemia) may cause cerebral blood flow problems. On the contrary, too low glucose (hypoglycemia) will result in palpitations and tremors [4], [5]. Therefore, it is important to develop an injection device that maintains the glucose level in a ‘normal’ level through understanding the dynamic interaction of insulin-glucose in the blood.

One way to understand the dynamics of blood glucose level in a person with type 1 diabetes is by making a mathematical model of insulin-glucose interaction. In the ‘80s, Bergman and colleagues successfully made
a model called the Minimal Model to describe pancreatic responsiveness and insulin sensitivity of a diabetic type-1 patient by conducting research on 8 male and 18 females with various bodyweight [6]. Furthermore, an extension of the Bergman Minimal Model was proposed by Hovorka and colleagues in 2002 with an additional partition of compartments in their model. In addition, Gonzales has included the meal disturbance in the system to the extended version of the minimal model [7], [8]. Despite massive development in diabetes modeling, to some extends, most of the model in the works of literature were developed from or compared with the Bergman Minimal Model [9].

Diabetes modeling is an attractive and largely investigated subject in process control course in chemical engineering [10]. It is generally accepted that chemical engineers should also play a role in developing technology in biology and medical subjects. Thus, as a part of the modernization of the process control module in Chemical Engineering at UGM, it is important to develop a diabetes model as a part of the process control module in undergraduate education. This expansion may lead chemical engineers to produce a more novel approach to the topic and facilitate collaborative works with a medical doctor who specialized in the field such as endocrinology.

The objective of the present work is to develop a process control module for process control course in chemical engineering by introducing diabetes modeling problem. This is conducted by using the extended version of the Bergman Minimal Model to facilitate engineering students to understand the basic principle of insulin-glucose interaction in the blood. Here, we elaborate on the diabetes model for type-1 diabetes with state-space modeling in MATLAB Simulink®. Both open-loop and closed-loop systems were investigated. Eventually, we also present a tuning method of P and PI parameters based on the ITAE method to obtain reasonable injection rate of insulin under meal disturbances in 24 h of simulation time.

2. Methodology

Bergman Minimal Model
The extended model of the Bergman minimal model has been used in the present study as depicted by equation 1 to 6. The model has been adapted from Hedengren as presented in AP Monitor website [11]. Several parameters to describe the insulin-glucose interaction includes plasma insulin (μU/mL), remote insulin (μU/mL), and plasma glucose (mg/dL). The model also considers insulin injection into the body to countermeasure the glucose increase. The list of notations is presented in notation table. The extended version of the Bergman Minimal Model [11] that has been used in the present study is presented as follows:

\[ \frac{dG}{dt} = -p_1 \cdot (G - G_b) - \psi_1 \cdot X \cdot G + \int \frac{k_{abs}}{v_g} \cdot G_{gut} + \int \frac{d}{v_g} \cdot d \]  \hspace{1cm} (1)

\[ \frac{dx}{dt} = p_2 \cdot (I - X) \]  \hspace{1cm} (2)

\[ \frac{dl}{dt} = -k_{c} \cdot l + k_1 \cdot U_l \]  \hspace{1cm} (3)

\[ \frac{dQ_1}{dt} = k_2 \cdot U_l - k_{emp} \cdot Q_1 \]  \hspace{1cm} (4)

\[ \frac{dQ_2}{dt} = k_{emp} \cdot (Q_1 - Q_2) \]  \hspace{1cm} (5)

\[ \frac{dG_{gut}}{dt} = k_{emp} \cdot Q_2 - k_{abs} \cdot G_{gut} \]  \hspace{1cm} (6)
The ordinary differential equations as presented in equation 1-6 were used to calculate the dynamic of insulin-glucose. The model was built based on the mass balance of glucose and insulin. The blood glucose level (G) is typically the output parameter that will be monitored (controlled variable). For closed-loop simulation, the manipulated variable (MV) in this case is the insulin injection rate which is represented by $U_I$. Meal intake (d) here acts as a system disturbance.

**Simulation Method**

The dynamic simulation of insulin-glucose interaction is conducted by solving equation 1-6 in MATLAB Simulink. For this purpose, these equations should be converted to linearized forms in deviation variables and followed by Laplace transform to obtain the transfer functions. The linearization technique was conducted by a classic approach using Taylor Series expansion as presented in equation (7).

$$f(t) = f(t_0) + \frac{f'(t_0)}{1!}(t - t_0)$$  \hspace{1cm} (7)

In process control simulation environment, typically we are interested in the change of variables from its steady-state values. As a result of the Taylor Series, we automatically obtained the deviation variables in the model. Deviation variable stands for time-dependent variable subtracted by its steady-state value as follow:

$$G'(t) = G(t) - G(t_0)$$  \hspace{1cm} (8)

Form of deviation variable already present in equation (7). As a result, linearization and conversion to deviation variables can be carried out simultaneously. Subsequently, after those 2 steps the form of Extended Bergman Minimal Model can be described as follows:

$$\frac{dG'}{dt} = -G'(p_1 + \psi.X'), \psi.Gv, X' + \frac{f}{v_g} k_{abs} G_{gut} + \frac{f}{v_g} d'$$  \hspace{1cm} (9)

$$\frac{dX'}{dt} = p_2 \cdot (I' - X')$$  \hspace{1cm} (10)

$$\frac{dI'}{dt} = -k_{e}.I' + k_{i}.U_I$$  \hspace{1cm} (11)

$$\frac{dQ_1'}{dt} = k_{e}.U_I - k_{emp}.Q_1'$$  \hspace{1cm} (12)

$$\frac{dQ_2'}{dt} = k_{emp}.(Q_1' - Q_2')$$  \hspace{1cm} (13)

$$\frac{dG_{gut}}{dt} = k_{emp}.Q_2' - k_{abs}.G_{gut}$$  \hspace{1cm} (14)

The state-space model allows us to obtain a compact system to simulate Multiple Input and Multiple Output (MIMO) system as demonstrated here. The general form of state-space model for any differential equations can be converted into a matrix form as follows:

$$\frac{dx}{dt} = Ax + Bu$$  \hspace{1cm} (15)

$$y = Cx + Du$$  \hspace{1cm} (16)
Where $x$ is the state-variable or $t$ in this study, $u$ as input or the insulin and meal intake, $A$ as process matrix, $B$ as input matrix, $C$ as output matrix, and $D$ as feedthrough matrix. The form of our Extended Bergman Minimal Model after being transferred into the state-space follow these equations:

$$
\frac{d}{dt} \begin{bmatrix} G' \\ X' \\ l' \\ Q'_1 \\ Q'_2 \\ G_{out} \\ \end{bmatrix} = \begin{bmatrix} -(p_1 + \psi_{xu}) & \psi_{xu} & G_{out} & 0 & 0 & 0 & f \cdot k_{abs} \\
0 & -p_2 & p_2 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & -k_{emp} & 0 & 0 & 0 \\
0 & 0 & 0 & k_{emp} & -k_{emp} & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & -k_{abs} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\end{bmatrix} \begin{bmatrix} G' \\
X' \\
l' \\
Q'_1 \\
Q'_2 \\
G_{out} \\
\end{bmatrix} + \begin{bmatrix} \frac{L}{v_0} & 0 \\
0 & 0 \\
0 & k_1 \\
0 & k_2 \\
0 & 0 \\
0 & 0 \\
\end{bmatrix} \begin{bmatrix} d' \\
U'_1 \\
U'_2 \\
\end{bmatrix} \tag{17}
$$

For process control simulation, especially for the closed-loop system, the simulation is typically conducted in the Laplace domain. The Laplace domain of these equations is the result of Laplace Transform according to:

$$\tilde{f}(s) = \int e^{-st} f(t) \, dt \tag{19}$$

In this study, the resulting state-space model was converted into the Laplace domain by ss2tf function in MATLAB.

**Controller Tuning**

Maintaining the blood glucose level is very important in a person with type 1 diabetes. In this study, the controller of insulin injection is represented in the form of Proportional and Integral Controller or PI Controller. The PI Controller has 2 main parameters: $K_c$ for proportional and $\tau_I$ for the integral controller part. Determining the value of those two parameters by guessing or trial-and-error is not efficient. Therefore, we have proposed the use of the standard method of Integral of the Time-weighted Absolute Error (ITAE) in this study. The use of ITAE in this simulation backed by ITAE’s behavior which gives a substantial penalty on continuous or prolongs errors, rather than IAE’s behavior which only weight the absolute error. As we know, we do not want the hyperglycemia or hypoglycemia state to linger. ITAE can be defined as in the equation (20) which represents the total error area of the controlled variable difference to its set point under disturbance rejection mechanism. The aim of tuning was to find the $K_c$ and $\tau_I$ that give the minimum value of ITAE. Here, we not only scanned various combination of $K_c$ and $\tau_I$ that produced the minimum ITAE but also ensuring the insulin injection rate to be a positive value.

$$ITAE = \int_0^t t \left| e(t) \right| dt \tag{20}$$

**3. Result and Discussion**

The equations as presented in equation (17) and (18) were solved in MATLAB Simulink. In MATLAB Simulink, the equations were converted to block diagram to represent the MIMO system. Figure 1 displays
the Open Loop simulation of blood glucose dynamics on a person with type-1 diabetes in the absence of controlled insulin injection. Here, $\text{insulinINJ}$ represents an input of the insulin injection rate to the body. The $\text{mealsDIS}$ corresponds to the food reserves available in the system which enters the body system. The $\text{State-Space_openloop}$ represents a set of equations which attributable to the human metabolism and the insulin-glucose interaction. At the right side of Figure 1, the outputs of the model are blood glucose, remote insulin, plasma insulin, gut blood glucose, and two native glucose in the two compartments represented by $G_{\text{openloop}}, X_{\text{openloop}}, I_{\text{openloop}}, G_{\text{gut_openloop}}, Q_{1_{\text{openloop}}}, Q_{2_{\text{openloop}}}$, respectively.

![Figure 1. Block Diagram of Open-loop System](image1)

The meal disturbance of the system as presented in Figure 1 is characterized by a normal daily intake of food for a normal individual. Figure 2a shows the dynamics of meal disturbances or food reserves in a body for 24 hours of simulation. As seen in Figure 2a, at c. 6-7 AM in the morning, a sudden increase in meals is caused by an additional meal intake such as breakfast. Similarly, the increase at c. 1 PM (slightly above 12 hours) and 7 PM (slightly above 18 hours) show the meals uptake during the lunch and dinner, respectively. Our simulation shows that the meal disturbance has a strong correlation to increase blood glucose as shown in figure 2c. The drop in meals a few moments after meal intake infers body metabolism and insulin-glucose interaction.

![Figure 2. Open-loop System Dynamic of a) Meals Disturbances, b) Insulin Injection Rate, c) Blood Glucose Level](image2)
Figure 2b shows that type 1 diabetes needs continuous insulin injection to maintain their blood glucose level. As observed from 0-6 hours where no meals disturbance was introduced, the sudden decrease in insulin injection rate caused an increase of blood glucose level as seen in Figure 2c. For the open-loop simulation, following meal consumption around 6 hours (or breakfast) since the beginning of the simulation, the blood glucose of the person increases higher than 120 mg/dL (target value for blood glucose control). Similar behavior is also recorded following meal intake around 12 hours and 18 hours since the start of the simulation. It could be inferred that suitable insulin injection rate is important for those with type 1 diabetes and a constant value of injection rate as demonstrated in the open-loop model may harm the patient. Hence, a better control system using a PID controller may play an important role to maintain the blood glucose level.

Figure 3. Block Diagram of Closed-loop System

In the second simulation, a Proportional and Integral controller was used to yield a suitable amount of insulin injection rate with the same meal intake. Figure 3 shows the MATLAB Simulink® block diagram of the closed-loop system. The main distinction between the closed-loop and the open-loop system shown in the previous Figure 1 lies in the feedback stream of blood glucose to the controller block. Nevertheless, as a controlled variable, blood glucose firstly compared to its setpoint or the intended value ($G_{setpoint}$). The rest of the system block diagram acts identically as in the open-loop system.

The algorithm to tune the Proportional and Integral Controller value follows as in subchapter 0 with an additional constraint of $U_I$ or the insulin injection rate should not be under 0 mU/min. The result of the PI Controller tuning in Figure 4a shows that the value of $K_c$ and $t$ that produces the smallest number of ITAE lies between 2 to 3 and 0 respectively which resulted in the use of Proportional-only Controller. However, in Figure 4b, the value of $U_I$ in system with $K_c$ a value of 0.3 and above is below 0 which is not possible at all. After further tuning, the suitable value of $K_c$ used is 0.22.
Other than technical constraints, the health constraints also had to be involved to tune the controller value. The first constraint is the lower limit of the blood glucose level that lies at 70 mg/dL. Lower blood glucose value than 70 mg/dL put the individual with diabetes in a hypoglycemia state which may cause injuries or even death [12]. One more constraint is the upper limit of 120 mg/dL or where the hyperglycemia state starts, and the prediabetes state ends [13], [14]. As the controlled insulin injection aims to help a diabetes type 1 patient, the tuned controller should not give a value of maximum blood glucose beyond this 120 mg/dL mark.

The previous tuning resulted in maximum blood glucose value below 120 mg/dL which is suitable. However, the minimum value of blood glucose in the same controller configuration measured below 70 mg/dL which is not acceptable. In Figure 5, the proportional controller value configuration that able to give a suitable maximum and minimum value of blood glucose level metered between 0.05 to 0.1. After further tuning of the proportional controller value, the suitable $K_c$ computed at 0.08 which gave the minimum and maximum value of blood glucose at 70.05 mg/dL and 111.21 mg/dL respectively, ITAE at 1.18x10$^{-3}$, and the minimum insulin injection rate at 2.52 mU/min.

The result of the simulation with the help of Proportional Controller of insulin injection in Figure 6 shows the result of blood glucose level between 70 and 112 mg/dL with the same meal input. This blood glucose level is much lower than the result without a manipulated insulin injection as seen in Figure 6c. Subsequently, the use of manipulated insulin injection rate with a proportional-only controller with this certain configuration would avoid a person with type 1 diabetes to be in a hyperglycemia or hypoglycemia state.
Figure 6. Closed-loop System Dynamic of a) Insulin Injection Rate, b) Blood Glucose Level, (c) Blood Glucose Level Comparison of Each System

From a technical standpoint, the slight change of a proportional controller configuration may significantly affect the dynamic of personal health. In this study, important parameters that should be carefully weighted are the upper and lower limit of the blood glucose level and the insulin injection rate. Furthermore, using a proportional-only controller gave proof that applying a suitable controller is very pivotal. Using a complete Proportional, Integral, and Derivative Controller might do the job in one case but will not really be the wise option for all cases.

4. Conclusion
The simulation of blood glucose dynamics and its interaction with insulin injection rate and meals intake shown above gave us a small insight about one possibility of how to produce these dynamics. State-space modeling gave an easier and elegant route to achieve a Laplace form of the equations and ITAE parameter helps to find the appropriate controller configuration to manipulate the insulin injection rate and maintain the blood glucose to the accordance level.

The tuning of the controller configuration for the blood glucose dynamics in type 1 diabetes patient resulted in a proportional-only controller with the value of \( K_c \) at 0.08. This configuration gave a proper result by avoiding hypoglycemia or hyperglycemia state that dangerous for the user.

5. Reference
[1] W. P. You and M. Henneberg, “Type 1 diabetes prevalence increasing globally and regionally: The role of natural selection and life expectancy at birth,” BMJ Open Diabetes Res. Care, vol. 4, no. 1, pp. 1–7, 2016.
[2] World Health Organization, “Global Report on Diabetes,” 2016.
[3] International Diabetes Federation, “Diabetes facts & figures,” International Diabetes Federation, 2019. [Online]. Available: https://idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html. [Accessed: 05-Aug-2019].
[4] M. Nowaczewska, A. Kamińska, B. Kukulska-Pawłuczuk, R. Junik, and K. Pawlak-Osińska, “Effect of hyperglycemia on cerebral blood flow in patients with diabetes,” Diabetes Res. Clin. Pract., vol. 153, no. 1, pp. 1–5, 2019.
[5] M. C. Rossi et al., “Impact of severe and symptomatic hypoglycemia on quality of life and fear of hypoglycemia in type 1 and type 2 diabetes. Results of the Hypos-1 observational study,” Nutr. Metab. Cardiovasc. Dis., vol. 29, no. 7, pp. 736–743, 2019.
[6] R. N. Bergman, L. S. Phillips, and C. Cobelli, “Physiologic Evaluation of Factors Controlling Glucose Tolerance in Man from The Response to Intravenous Glucose,” J. Clin. Invest., vol. 68, no.
December 1981, pp. 1456–1467, 1981.

[7] R. Hovorka et al., “Partitioning glucose distribution/transport, disposal, and endogenous production during IVGTT,” Am. J. Physiol. Metab., vol. 282, no. 5, pp. E992–E1007, 2002.

[8] A. A. Gonzalez, H. Voos, and M. Darouach, “Glucose-Insulin System Based on Minimal Model: A Realistic Approach,” Proc. - UKSim-AMSS 17th Int. Conf. Comput. Model. Simulation, UKSim 2015, pp. 55–60, 2016.

[9] R. N. Bergman, “Minimal model: Perspective from 2005,” Horm. Res., vol. 64, no. SUPPL. 3, pp. 8–15, 2005.

[10] T. F. Edgar, B. A. Ogunnaiké, J. J. Downs, K. R. Muske, and B. W. Bequette, “Renovating the undergraduate process control course,” Comput. Chem. Eng., vol. 30, no. 10–12, pp. 1749–1762, 2006.

[11] J. D. Hedengren, “Maintain Glucose in Type-I Diabetic,” 2017. [Online]. Available: https://apmonitor.com/pdc/index.php/Main/DiabeticBloodGlucose. [Accessed: 30-May-2019].

[12] E. R. Seaquist et al., “Hypoglycemia and diabetes: A report of a workgroup of the american diabetes association and the endocrine society,” J. Clin. Endocrinol. Metab., vol. 98, no. 5, pp. 1845–1859, 2013.

[13] R. K. Mahat, N. Singh, M. Arora, and V. Rathore, “Health risks and interventions in prediabetes: A review,” Diabetes Metab. Syndr. Clin. Res. Rev., 2019.

[14] V. Vichaibun, K. Khananurak, and T. Sophonnithiprasert, “Comparative analysis of plasma total antioxidant capacity in patients with hyperglycemia and hyperglycemia plus dyslipidemia,” Diabetes Metab. Syndr. Clin. Res. Rev., vol. 13, no. 1, pp. 90–94, 2019.

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7. Notation List

### Table 1. Notation of Parameters Used

| Notation | Description | Unit |
|----------|-------------|------|
| $G$ | Blood glucose (Controlled Variable) | mg dL$^{-1}$ |
| $\chi$ | Remote insulin | $\mu$U mL$^{-1}$ |
| $I$ | Plasma insulin | $\mu$U mL$^{-1}$ |
| $Q_1$ | Mass of native glucose in the first intermediate compartments | mg dL$^{-1}$ |
| $Q_2$ | Mass of native glucose in the second intermediate compartments | mg dL$^{-1}$ |
| $G_{nat}$ | Gut blood glucose | mg dL$^{-1}$ |
| $U_I$ | Exogenous insulin injection (Manipulated Variable) | $\mu$U min$^{-1}$ |
| $d$ | Meals (Disturbance) | mg dL$^{-1}$ min$^{-1}$ |

### Table 2. Value of Fixed Parameters Used

| Notation | Value | Unit |
|----------|-------|------|
| $G_R$ | 291 | mg dL$^{-1}$ |
| $p_1$ | 3.17x10$^{-2}$ | min$^{-1}$ |
| $p_2$ | 1.23x10$^{-2}$ | min$^{-1}$ |
| $k_e$ | 9x10$^{-2}$ | min$^{-1}$ |
| $k_{emp}$ | 0.18 | min$^{-1}$ |
| $k_{abs}$ | 1.2x10$^{-2}$ | min$^{-1}$ |
| Parameter | Value 1 | Unit 1 |
|-----------|---------|--------|
| $k_1$     | 1       | dL⁻¹   |
| $k_2$     | 1       | mg μU⁻¹ dL⁻¹ |
| $f$       | 0.8     | L      |
| $v_0$     | 12      | L      |
| $\psi$    | 2.9x10⁻² | mL μU⁻¹ min⁻¹ |