Kinetics modeling studies of type 1 diabetes mellitus treatment with the function of exogenous glucose and insulin injection

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Abstract. Mathematical modeling on dynamics system of glucose-insulin in the human body was one of the interesting researches in the complex system of physics. This research could be used as a treatment simulation of type 1 diabetes mellitus (T1DM). In this study, the function of exogenous glucose and insulin would be studied because of these were important factors to describe the maintaining of metabolism in the T1DM subject, especially were the blood glucose concentration in the human body. The modified minimal model would be combined with the functions of exogenous glucose and insulin injection. To control the glucose concentration in the T1DM subject was very dependent depend on the administration time of exogenous glucose and an insulin injection since these could affect the kinematics of the glucose-insulin system in the blood. Based on these simulation results, the optimum treatment was obtained by the first injection of the exogenous insulin of 560 μU/(mL.min) from 0 to 16 min. The administration of exogenous glucose was given by the amount of 47 and 23 mg at time 7 min and 15 min. Later, an injection of the exogenous insulin was given by 38.1 μU/(mL.min) from 35 to 180 min. In this treatment scheme, the intravenous glucose tolerance test (IVGTT) curve during 200 min, the value of $R^2$ was 0.98. It indicates that the treatment simulation results are agreed. Setting the timing and amount of glucose intake and insulin injection affects the glucose concentration in the blood on T1DM subjects so no occur condition of hyperglycemia or hypoglycemia.

1. Introduction
A disease characterized by blood glucose levels in the human body bloodstream consistently rise too high compared to basal glucose, this condition is called hyperglycemia and this disease generally is called Diabetes Mellitus (DM). However, patients with T1DM unable production of endogenous insulin by the pancreas so that will cause hyperglycemia. T1DM is characterized by chronic hyperglycemia syndrome due to the absence of insulin secretion. Symptoms of this disease are appearance the disturbance of carbohydrate, protein and fat metabolism so as the human body is disturbed too in use digested food for growth and energy. The conditions of chronic hyperglycemia are the most common endocrine disorder which will be followed with long term damage, dysfunction, and failure of various body organs, as especially blood vessels, nerves, heart, eyes, and kidneys. This chronic medical condition will last a lifetime if it cannot be controlled [1, 2].

The T1DM is an autoimmune disorder, the pancreas will experience an autoimmune attack by the human body itself so that the pancreas is unable to make insulin. The immune system in the human body with T1DM will attack the beta cells in the islets of Langerhans of the pancreas itself so destroy and damage them significantly to decrease insulin production. The pancreas just produces little or no insulin.
This case occurs most often in children or young adults but also it can occur at any age. Sufferers of T1DM is riskier when not diagnosed and treated with exogenous insulin. The sufferers will lapse into a life-threatening diabetic [1, 2].

Subject with T1DM must be controlled by an insulin level monitoring to inject exogenous insulin every day of their lives because the Langerhans island already destroyed by its own immune system in the body of T1DM. Treatment for T1DM is performed by administrating insulin shots or an insulin pump to inject insulin in the human body bloodstream and administrating enough food. The T1DM is also known as insulin dependent diabetes mellitus (IDDM) [1, 2].

Most subjects with T1DM should self-monitor blood glucose before and after meals, and sometimes before and after exercise. Self-monitoring of blood glucose (SMBG) data is used to prescribe for subjects with T1DM and also to adjust therapy. Insulin is the therapy fundamental for T1DM. The starting total daily insulin dose is typically weight-body based. A typical total daily starting dose in subjects with T1DM who are metabolically stable must be managed through the life span to provide a thorough overview of T1DM treatment and associated recommendations [3].

An auto-immune disease has a significant impact on subjects’ health care systems in everyday life. Because of their bodies cannot control their blood glucose concentrations, so that subjects need to take over this cumbersome task manual daily to avoid the hypoglycemia and hyperglycemia. Counting glucose in meals and injecting insulin is part of their daily routine. This is known as a standard treatment leads a glucose controlling. Calculation of the insulin per the carbohydrate ratios can help in adjusting the mealtime dose of insulin since the insulin doses can be calculated [4]. However, many clinical cases have proven that this treatment of insulin injection per glucose ratios cannot solve all problems. Therefore, insulin-producing cells transplants must be done in T1DM patients, but this method will require more intensive and costly research to ensure, this is an efficient and safe treatment method in T1DM [5].

This paper will focus on mathematical modeling of controlled continuous subcutaneous infusion of insulin in T1DM. This process usually occurs in T1DM subjects to control levels of sugar is entirely dependent on external infusion of insulin. This study will model the glucose concentration in the subjects with T1DM and use it to treat these subjects using a previously glucose concentration curve. This curve model can aid how much the continuous infusion of insulin which is given based upon an individual’s requirements in terms of the curve of decay of glucose concentration in a prescribed time. For each subject, a prescription is made of the desired curve begins the highest level of a glucose concentration to the desired lowest level in a given period of time. This model can fine-tune the delivery amounts of insulin given intermittently or continuously. An SMBG device will infuse insulin continuously to reduce the prescribed curve of glucose concentration. The treatment described will intense clinical research work. Numerical simulations will be used to analysis based on experimental data since it can be more effective in terms of costs and amount of time used. The treatment simulations approach the subjects with T1DM have been previously reported in the literature. Because of these computer algorithms for insulin dosage adjustment.

2. Mathematical model

The minimal model has been applied most frequently to analysis the intravenous glucose tolerance tests (IVGTT) with the main aim of measuring glucose effectiveness and insulin sensitivity. An extension of this model to describe physiological actually, such as oral glucose tolerance tests (OGTT) and mixed meal tests (MTT). The insulin sensitivities that are determined by the OGTT model are well correlated to those obtained by the IVGTT model. The minimal model is also particularly relevant nowadays in the treatment simulation area of T1DM, specifically in those subjects treated with continuous subcutaneous insulin infusions (CSII) coupled with SMBG device [6].

Subjects with T1DM are usually controlled for glucose levels using exogenous insulin injections due to decreased insulin production or without endogenous insulin. The amount of exogenous insulin to be injected needs to be carefully considered because insulin overdose causes hypoglycemia. Simulations
to predict blood glucose concentrations in the treatment of subjects with T1DM are challenging but very important studies.

The models’ development of blood glucose prediction actually can be used to the calculator of bolus glucose, algorithms of the exogenous insulin injection pump, and controller of closed-loop blood glucose level. These research still a very active research field. As proof, many prediction models have been developed now, it was shown in previous literature. These complexities model’s growth up from the simplicity of the Bergman minimal model [7] to the complexity of the Hovorka model [2], all models show potentially good prediction capabilities [8].

2.1. Modified minimal model for representing of glucose-insulin dynamics

A model for predicting the dynamics system of glucose-insulin concentrations in the blood can be given by the equations (1)-(3). These equations have been introduced from the work of Kartono and Kartono et al. [9, 10] and usually called to as a modified minimal model. In this model, a physiologically is verified by the three-compartment model with identifiable parameters. This model can calculate the effect of glucose effectiveness and insulin sensitivity in the human body:

\[
\frac{dG(t)}{dt} = p_1 \left( G_b - G(t) \right) - X(t)G(t), \quad G(t = 0) = G_0, \tag{1}
\]

\[
\frac{dX(t)}{dt} = -p_2 X(t) + p_3 \left( I(t) - I_b \right), \quad X(t = 0) = X_0, \tag{2}
\]

\[
\frac{dI(t)}{dt} = \begin{cases} 
\gamma \left( G(t) - G_b \right) t - k \left( I(t) - I_b \right), & G(t) > G_b, \\
-k \left( I(t) - I_b \right), & G(t) < G_b, 
\end{cases} \quad I(t = 0) = I_0, \tag{3}
\]

where \( G(t) \) defines blood glucose concentration, \( X(t) \) defines the concentration of infused insulin, and \( I(t) \) defines plasma insulin concentration. \( G_b \) defines basal plasma glucose and \( I_b \) defines basal plasma insulin concentration. Notation \( p_1 \) represents absorption or cleansing of glucose does not depend on increased insulin (glucose effectiveness), \( p_2 \) represents the rate of active insulin used, \( p_3 \) represents an increased absorption ability caused by insulin, \( \gamma \) represents fractional disappearance rate and \( k \) represents the insulin delay rate.

The modified minimal model can also provide information about glucose effectiveness (\( S_G \)) and insulin sensitivity (\( S_I \)), as two important parameters. The \( S_G \) from an individual can be explained as a quantitative increase in the loss of glucose in response to an increase in plasma glucose concentration. The \( S_I \) in a steady state is a quantitative influence of insulin to increase its ability to process glucose loss. The \( S_G \) and \( S_I \) equations take the following form:

\[
S_G = p_1, \quad S_I = \frac{p_3}{p_2} \tag{4}
\]

2.2. Mathematical model of a continuous subcutaneous insulin infusion and a glucose input source

A model has been modified for predicting the plasma concentration of glucose and insulin when the normal fasting level of plasma glucose in the range 70-120 mg/dl. This model is introduced by Nilam et al. [1] and assumed that glucose disappearance as a linear function of both glucose and insulin. The secretion and disappearance of insulin are proportional to glucose and plasma insulin concentration linearly. The main objective of this model is to prescribe a more accurate but simple. This method has been arranged the function of administration of bolus glucose for a diabetic subject. These model equations can be represented by:

\[
\frac{dG(t)}{dt} = -l_1 hG(t) + l_2 \left( G_b - G(t) \right) U \left( G_b - G(t) \right) + l_3 F(t) \tag{5}
\]
\[
\frac{dl(t)}{dt} = l_4(G(t) - G_b)U(G_b - G(t)) - l_5h_0 + l_6I_{in}(t) 
\]

(6)

\[
I_{in}(t) = \frac{\rho(t-t_o)}{t-t_o} 
\]

(7)

where \(G(t)\) defines plasma glucose concentration, \(I(t)\) defines insulin concentration, \(l_i\) defines sensitivity constants, \(i = 1, 2, 3, 4, 5, 6...\), \(F(t)\) defines food source input for plasma glucose, \(I_{in}(t)\) defines insulin input and \(U(G_0-G(t))\) defines unit step function, \(\bar{t}\) is the maximum value of time delay from injection, parameter \(\rho\) in \(I_{in}(t)\) may be defined as the quantity of injection. The injection input of external insulin \(I_0(t)\) will be injected through a subcutaneous level interval periodically. The source for food input, \(F(t)\), will be modeled to describe the plasma glucose concentration, so that function \(F(t)\) may be modeled as:

\[
F(t) = \begin{cases} 
Se^{-\alpha(t-t_o)}, & t > t_0 \\
0, & t \leq t_0 
\end{cases} 
\]

(8)

where \(S\) defines a quantity constant of a glucose and \(\alpha\) defines a delay parameter. For non-diabetic case, if time \(t > t_0\) then \(F(t) \neq 0\) and \(I_{in}(t) = 0\) while for diabetes cases then \(F(t) \neq 0\) and \(I_{in}(t) \neq 0\).

| Parameter | Value | Unit |
|-----------|-------|------|
| \(G_0\)  | 310-360 | mg/dL |
| \(G_b\)  | 92-200  | mg/dL |
| \(X_0\)  | 0      | l/min |
| \(I_0\)  | 0-300  | \(\mu\)U/mL |
| \(I_b\)  | 0-10   | \(\mu\)U/mL |
| \(p_1\)  | 0.03-0.05 | l/min |
| \(p_2\)  | 0.005-0.04 | l/min |
| \(p_3\)  | \(1.7 - 5.0 \times 10^{-3}\) | L/(min².\(\mu\)U) |
| \(\gamma\) | 0.001-0.005 | l/min |
| \(k\)    | 0.1-0.5 | l/min |
| \(\rho\) | 2-10   | \(\mu\)U/mL.min |
| \(\alpha\) | 0.03-0.05 | l/min |
| \(S\)    | 20-100 | mg |

2.3. Modified minimal model for treatment of Type 1 Diabetes Mellitus

A modified minimal model for describing the dynamics of glucose concentration in subjects with T1DM will be combined with treatment a continuous subcutaneous insulin infusion and a food source input that has been developed by Nilam et al. [1]. This present model will attempt to describe the release effect of an external insulin source to glucose concentration as a prescribed function of time. Then, this model will be used to assess the optimal insulin release profile and also the threshold amount required of external insulin to bring the level of glucose concentration to within a normal physiological range.
In this model, the delivery of external insulin considers two main factors that are (1) the total amount of insulin released over a specific period associated with (2) the glucose concentration so that the pump will stop releasing insulin when the glucose concentration is the normal subject range. The amount of external insulin source will be proportional to the total amount of glucose from the food input source. This model can represent the human body characteristics of the subjects with T1DM which will require how much insulin is needed to control the glucose concentration to be in the normal physiological range after each meal. This present model extends the minimal model to incorporate the two main factors above, which leads to the following coupled differential equations:

\[ \frac{dG(t)}{dt} = p_1(G_b - G(t)) - X(t)G(t) + r_G F(t), \quad G(t = 0) = G_0 \]  
\[ \frac{dX(t)}{dt} = -p_2 X(t) + p_3 (I(t) - I_b), \quad X(t = 0) = 0 \]  
\[ \frac{dI(t)}{dt} = \begin{cases} y(G(t) - G_b) - k(I(t) - I_b) + I_{in}(t), & G(t) > G_b, \quad I(t = 0) = I_0 \\ -k(I(t) - I_b) + I_{in}(t), & G(t) < G_b, \quad I(t = 0) = I_0 \end{cases} \]  

where \( r_G \) (1/dL.min) distribution per time times per body volume and value ranges are 0.30-0.70.

3. Results and discussion
This research will try to vary some treatments which carried out on subjects with T1DM through this model simulation. However, the characteristics of a normal subject and a T1DM subject were introduced without a continuous subcutaneous insulin infusion and a food input source. These results can be seen in Figure 1. Numerical solutions are obtained by substituting values parameters to equations (1)-(4) so that the curve of the relationship between glucose concentration and time is obtained. Furthermore, model validation is carried out between the simulation results and experimental data obtained from the published literature. Numerical solutions will be used as a control of the correlation between simulation and experimental data.

![Figure 1](image-url)
The simulation results were validated through comparison with normal experimental data. These data were obtained from previously published journals. Simulation validation is calculated using the coefficient of determination \( R^2 \) to compare the simulation results and the experimental data, \( R^2 \) equation given as follows:

\[
R^2 = 1 - \frac{X^2}{SST} \quad (12)
\]

\[
X^2 \equiv \sum_{i=1}^{N} \left\{ \frac{y_i - y(t_i, \theta_1, ..., \theta_M)}{\sigma} \right\}^2 \quad (13)
\]

\[
SST \equiv \sum_{i=1}^{N} \left\{ \frac{y_i - \bar{y}}{\sigma} \right\}^2 \quad (14)
\]

where \( y_i \) is the experimental data with the standard deviation of \( \sigma \), \( y(t_i, \theta_1, ..., \theta_M) \) is the model results, \( N \) is the amount of data, and \( \bar{y} \) is the average value of the experimental data.

The curve of glucose concentration as the time function between T1DM subject and experiment data of normal subject [11] is shown in Figure 1. Parameter values of T1DM subject for simulating is labeled in Table 1. The higher glucose concentration of T1DM subject than the normal subject is caused by T1DM subject has the ability to use glucose without insulin assistance slightly lower than the ability possessed by normal subject. Since glucose absorption to produce energy with insulin assistance occurs just in the brain, red blood cells, and muscle tissue.

![Figure 2. The first scheme simulation results of the glucose concentration as a time function with glucose consumption and without insulin injections treatment.](image-url)
3.1. First scheme treatment for T1DM subjects

In the first scheme, T1DM subjects were administered glucose intake without insulin injections. The simulation results are obtained by substituting parameter values in Table 1 into equations (8)-(11). Later, the curve of the relationship between glucose concentration and time is shown in Figure 2.

Administration of glucose intake will be done using the three following conditions: (1) the first simulation is given glucose intake at time 5 min with $S$ value of 50 mg; (2) the second simulation is given glucose intake at time 5 min with $S$ value of 25 mg and at time 45 min with $S$ value of 25 mg; (3) the third is given glucose intake at time 5 min with $S$ value of 20 mg, at time 60 min with $S$ value of 15 mg, and at time 120 min with $S$ value of 15 mg. The constant values of $r_G$ and $\alpha$ are given at 0.67 dL$^{-1}$ min$^{-1}$ and 0.039 min$^{-1}$, respectively. All parameters have been represented in Table 1, these values are used in all treatment conditions.

First simulation results show that glucose intake will be absorbed by the body and enter the bloodstream so that the glucose concentration in the blood increases to form a peak then drops sharply to touch the basal glucose and then rises again to 200 min. Subjects will experience hyperglycemia at time interval 10-30 min and after time 100 min. Furthermore, the second simulation results are shown that glucose intake will increase glucose concentration but not as large as the first simulation, then decrease at the time when 40 min and rise again to form a second peak and decrease slowly until 200 min. The subjects have experience excess of two peaks of glucose concentration in the blood. Finally, the third simulation results inform that glucose intake is absorbed by the body and enters the bloodstream so that blood glucose concentrations increase to form the first peak but not as large as the second simulation. Then blood glucose concentration drops at the time when 60 min then glucose concentration rises again due to glucose intake at a second time at 120 min and returns to increase due to glucose intake third forms a peak then drops sharply touch basal glucose up to the time at 200 min. These results have shown the process of hyperglycemia that caused by glucose intake because of the role of insulin in converting glucose into energy or glycogen is not significant.

![Figure 3. The second scheme simulation results of the glucose concentration as a time function without glucose consumption and insulin injections treatment.](image)
3.2. Second scheme treatment for T1DM subjects

In the second scheme, the T1DM subject is treated with insulin injections without glucose intake. The administration of insulin injections is given at following time 3-5 min, 5-10 min, 10-15 min, 15-35 min, 35-60 min and 60-90 min with $\rho$ values of 21, 26, 20, 20, 15, and 10 μU/ mL. min, respectively.

The simulation results show that insulin injections will be absorbed by the body so that the glucose concentration in the blood decreases significantly starting from time 5 to 70 min then glucose concentration increased again. The T1DM subjects experience decreasing in glucose concentration (hypoglycemia) which is below the basal glucose range because there is no glucose intake that enters the body. These results can be seen in Figure 3.

3.3. Third scheme treatment for T1DM subjects

In the third scheme, the first time of the T1DM subjects are given glucose intake and then administered insulin injections. Administration of glucose intake is given at time 1 min, at time 31 min, and at time 61 min with $S$ values of 5, 20 and 5 mg, respectively. Later, the administration of the insulin injection was done at time 75 to 100 min and at time 100 to 135 min, and then at time 135 to 170 min with each $\rho$ values of 10, 3.5, and 2.5 μU/(mL.min). These simulation results are shown in Figure 4.

These simulation results show that glucose intake 3 times shows the amount of glucose concentration above the T1DM simulation results and decreases steeply at time 30 min and continues with decreasing to time 60 min. Later, the glucose concentration rose again slowly and continued a significant decrease to time 140 min due to giving 3 times the insulin injection in the body and then the glucose concentration rose again shortly after touching basal glucose up to time 200 min. The T1DM subjects experience excess glucose (hyperglycemia) over a period of 30 to 90 min. These results can be seen in Figure 4.

![Figure 4](image-url)
3.4. Fourth scheme treatment for T1DM subjects

Figure 5. The fourth scheme simulation results of the glucose concentration as a time function with glucose consumption and insulin injections treatment.

In this fourth scheme, the T1DM subject is given an insulin injection at time 0 to 4 min, 4 to 10 min, 10 to 15 min, 15 to 20 min, and 20 to 60 min with each $\rho$ values of 35, 25, 15, 10 and 5 $\mu$U/mL.min. Later, the administration of glucose intake was done at time 60 min and at time 120 min, each glucose intakes are 20 and 10 mg. These simulation results are shown in Figure 5.

The simulation results show that the glucose concentration in the blood drops dramatically to below basal glucose in an interval of 2 to 56 min, this meaning that T1DM subjects experience hypoglycemia or lack of glucose in the blood. The glucose concentration rises again significantly to form the first peak in the span of 60 to 80 min and rises again to form a second peak in the span of 120 to 150 min due to the administration of glucose that enters the body. Subjects have excess glucose or hyperglycemia because they were above the basal glucose range also above the T1DM simulation results.

3.5. Fifth scheme treatment for T1DM subjects

In this last scheme, insulin injections are administrated firstly, then followed by administration of glucose intake and finally the administration of insulin injections is done again. Firstly, the insulin injection was carried out at time 0 to 2 min, 2 to 4 min, 4 to 6 min with each $\rho$ values of 350, 125, and 85 $\mu$U/mL.min, respectively. Later, administration of glucose intake was done at time 7 min and 15 min with each $S$ values of 47 and 23 mg. Finally, administration of insulin injection is done at time 35 to 40 min, 40 to 45 min, 50 to 60 min, 60 to 80 min, 80 to 120 min, and 120 to 180 min with each $\rho$ values of 10, 9, 8, 4, 4.3, and 2.8 $\mu$U/mL.min, respectively. These simulation results are shown in Figure 6.

These simulation results show that a decrease in the amount of glucose concentration of the T1DM subjects caused by the number of insulin injections enter the body. The glucose concentration decreases slowly and is quite gentle until it touches its basal glucose up to time 200 min. The amount of glucose intake that enters after injection of insulin will control glucose concentration and is maintained with the number of subsequent insulin injections up to time 200 min. Figure 6 shown that the simulation results coincide with the experiment data of normal subjects which means that the optimal combination between
the amount of glucose intake and the insulin injection is obtained. $R^2$ value obtained is 0.981 from the curve, this indicates that the simulation results in this condition are agreed.

![Graph showing the fifth scheme simulation results of the glucose concentration as a time function with glucose consumption and insulin injections treatment.](image)

**Figure 6.** The fifth scheme simulation results of the glucose concentration as a time function with glucose consumption and insulin injections treatment.

4. Conclusions

The application of insulin treatment simulation on T1DM subjects very affects the dynamics of glucose and insulin systems in the body. In this study, the modified minimal model can explain the characteristic of treatment kinematics in T1DM subjects. This can be seen that the functions of glucose intake and insulin injections are interrelated and affect the kinematics of glucose and insulin in the body. If the amount of glucose intake is higher than the number of insulin injections needed by the body then the T1DM subjects will experience hyperglycemia, on the contrary, if the amount of glucose intake is lower than the insulin injections required by the body then T1DM subjects will experience hypoglycemia.

Based on the simulation results have been obtained that the correct timing and quantity of exogenous glucose and insulin injection would produce a good treatment so T1DM subjects are not experiencing hyperglycemia or hypoglycemia. The simulation results have proposed that the fifth scheme match the experimental data of the normal subject. In these treatments, a good treatment sequence is insulin injections firstly then glucose intake and insulin injections again consecutively.

For future work, the functions of glucose intake and insulin injections need to be modified again to obtain a better physical picture of the body's metabolism actually.
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