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Simulation of physical activities effect and treatment exogenous insulin for managing plasma glucose concentration in type 1 diabetes mellitus

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Abstract. The simulation model of glucose level dynamics system during physical activity is important to represent an actually of the normal living conditions. These simulation results can be to accelerate the development of the artificial pancreatic design because of an administration of glucose through the oral according to the actual conditions then followed by administering insulin through infusion is following the actual conditions. In this study, the effects of insulin injection and physical activity on the glucose concentration level of type 1 diabetes mellitus (T1DM) will be simulated. A modified oral minimal model using the effects of physical activity and external insulin treatment was developed in the present study. Based on this simulation study, the main objective of this study was to vary insulin injections while carrying out physical activities that could validate the effects of decreased blood glucose levels in T1DM patients. These simulation results showed that the greater the injection of insulin during physical activity, the faster the rate of blood glucose concentration decreases. The optimum experiment simulation has been obtained to represent a treatment accurately by comparing the experimental data of a normal glucose concentration.

1. Introduction

The T1DM disease is caused by the loss of pancreatic insulin secretion, therefore is called generally a metabolic disease. This disease must always maintain the plasma glucose concentration within the normoglycemic range (70–120 mg/dl) to prevent complications with the other diseases. The effects of T1DM subjects in the long-term are the plasma glucose concentration exceeds 120 mg/dl, it is known as hyperglycemia. This disease can also cause hypoglycemia, this condition is marked by a plasma glucose concentration below 70 mg/dl. Therefore, T1DM subjects must be treated by the subcutaneous insulin injection intensively still corresponding to after or before meal times daily.

Physical activities are beneficial for the health of T1DM patients since regular physical activities will increase cardiovascular health, respiratory fitness, lowers cholesterol and especially decreases external insulin requirements. Physical activities of T1DM patients can also reduce the risk of complications with other diseases, also extend and improve life expectancy. Therefore, clinical management should incorporate physical activity regularly program for subjects with T1DM to reduce cardiovascular risk because this is one of the main benefits of physical activities. In patients with T1DM, the other main benefits of physical activity regularly that is to reduce the risk of severe hypoglycemia and mainly to reduce total daily insulin needs [1].



Patients with T1DM are often unable to change endogenous insulin levels properly, this will result in them experiencing normal hormonal glucose counter-regulation during physical activity. This condition will be caused risk of hypoglycemia early or hypoglycemia late, it might also cause hyperglycemia. Glycemic control process during physical activity will experience complexity, this is caused that the different insulin delivery systems of every patient with T1DM. Therefore, insulin pumps that used insulin analog must be programmed in order to deliver small doses of insulin appropriately to control to be on the basal glucose level. Programming of bolus amounts of meals also must be done based on the need to manage the basal glucose levels. In a clinical study, subjects with T1DM using insulin pump treatment and performing regular moderate-to-heavy physical activity intensity will experience less post-exercise hyperglycemia after is delivered multiple daily insulin injections. This program will also not increase the risk of post-exercise hypoglycemia [2].

Modeling of dynamics system of glucose plasma concentration for T1DM patients is research challenging, moreover related to physical activities complexity. The beneficial effects from physical activity are to improve the rate of glucose absorption by the working tissues, to improve the release of hepatic glucose to control overall glucose homeostasis and to reduce plasma insulin concentration [3]. During physical activity, glucose concentration levels will decrease significantly due to the drop in hepatic glucose production [4].

The effects of physical activity on glucose concentration of T1DM subjects known can control the glucose level to be always at an interval of the normal level. The ability to predict these effects is very helpful when be add the administration of an insulin infusion during physical activity. Because this is one of the main challenges to developing an artificial pancreas that can be working in normal living conditions [5]. To predict precisely glucose concentration during physical activity in living every day requires detailed information on the influence of physical activity on the glucose level [6]. Because of this physical activity will also improve physical health and strength in T1DM patients and also significantly reduce external insulin requirements. These information results can be sufficient evidence for clinicians to advocate that physical activity can manage the glucose level of patients with T1DM [7, 8].

The main goal of the present research that is the development of the various simulation of insulin delivery system operating under physical activity conditions, especially making model is capable of predicting blood glucose concentration during physical activity. In this study, early experiment simulation will be used to validate this present model without physical activity, then some possible scenarios to test exogenous insulin infusion algorithms which combined with physical activity alone or physical activity coupled with bolus glucose will also be simulated.

2. Mathematical model

Mathematical models using a three-compartment model that used to describe the dynamics system of glucose-insulin level have been introduced by Bergman and co-worker [9]. This model is used to analyse glucose disappearance and insulin sensitivity during an intravenous glucose tolerance test (IVGTT). This model is commonly called the minimal model. Modifications of this Bergman minimal model have been developed to incorporate many other physiological effects of glucose and insulin [10-13].

Roy and Parker [3] have introduced the effects of physiological physical activity that incorporated into the Bergman minimal model [9] in order to describe the dynamics of the plasma glucose and insulin levels during periods of mild-to-moderate physical activity. An IVGTT minimal model previously has been developed and extended to incorporate the major effects of physical activity on ordinary differential equations of glucose and insulin [4].

In this research study, the IVGTT minimal model results from Roy and Parker [3] research studies which included the physical activity effects on insulin sensitivity on lifestyle and glycaemic control will be combined with an oral minimal model when an oral glucose tolerance test (OGTT). The OGTT protocols for assessing insulin sensitivity or glycaemic control includes the administration of a standard glucose bolus (75 g) and then followed by plasma glucose levels monitoring for the subsequent 2 hours. If the blood glucose levels of above 110 mg/dl at 2 hours indicates an impaired glycaemic control while if the blood glucose levels above 120 mg/dl indicates diabetes.

2.1. Bergman minimal model during an IVGTT

Bergman and co-worker [3] have used a three-compartmental mathematical model that is $I(t)$ represents plasma insulin compartment ($\mu\text{U/ml}$), $X(t)$ represents remote insulin compartment ($\mu\text{U/ml}$) and $G(t)$ represents plasma glucose compartment (mg/dl). This model shows the pancreatic responsiveness and insulin sensitivity of diabetic subjects quantitatively. This model also assumes that all the exogenous insulin is administered by infusion (u_{1b}) for modeling the insulin-dependent diabetes mellitus (IDDM) subjects. A function of the insulin injection has been combined into the remote compartment ($X(t)$) from the circulatory blood system of ($I(t)$) because of the remote insulin compartment ($X(t)$) actively takes part in promoting the uptake of plasma glucose compartment ($G(t)$). The Bergman minimal model can be given mathematically by:

$$\frac{dG(t)}{dt} = -p_1 G(t) - X(t)G(t) + p_1 G_b + \frac{u_2(t)}{Vol_g} \quad G(0) = G_0 \quad (1)$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3 (I(t) - I_b) \quad X(0) = 0 \quad (2)$$

$$\frac{dI(t)}{dt} = -nI(t) + p_4 u_1 \quad I(0) = I_0 = \frac{p_4}{n} u_{1b} \quad (3)$$

Table 1. Parameter estimates of the Bergman minimal model.

Abbreviation	Name	Value	Unit
p_1	the glucose rate is removed from the plasma space independent of the influence of insulin	0.025 - 0.040	1/min
p_2	the disappearance rates of the remote insulin compartment	0.04 - 0.06	1/min
p_3	the appearance rates of insulin in the remote insulin compartment	$2 - 3 \times 10^{-5}$	$\text{ml}/\mu\text{U} \cdot \text{min}^2$
p_4	the rate constant of reduction control in glucose levels	0.08 - 0.10	1/min
G_b	the basal plasma glucose concentrations	80 - 160	mg/dl
I_b	the basal plasma insulin concentrations	0 - 15	$\mu\text{U/ml}$
n	the clearance rate constant of plasma insulin	0.10 - 0.20	1/min
u_{1b}	the rate of exogenous insulin infusion to maintain I_b	10 - 40	mU/min
$u_2(t)$	absorption or infusion of external glucose	50 - 100	mg/min
Vol_g	the glucose distribution volume	110 - 130	dl

2.2. Bergman minimal model with physical activities effect and treatment exogenous insulin

An individual during physically active will consume the oxygen, the maximum rate of oxygen consumption can be represented by $VO_2^{\max}$ (ml/kg/min). Oxygen consumption will be converted to the energy released by an individual, its conversion approximately is proportional linearly. Because this condition is possible to indirectly measure an individual's maximum capacity to be physically active by measuring oxygen consumption. Since physical activity can be represented as a $VO_2^{\max}$ percentage that represented by $PVO_2^{\max}$. In general, the average $PVO_2^{\max}$ for an individual in the basal state around 8%. Therefore, the equation for $PVO_2^{\max}$ is expressed with:

$$\frac{dPVO_2^{\max}(t)}{dt} = -0.8PVO_2^{\max}(t) + 0.8u_{ex}(t) \quad PVO_2^{\max}(0) = 0$$

(4)

where $PVO_2^{\max}$ represented the physical activity level as done by an individual, and $u_{ex}(t)$ represented the ultimate physical activity intensity above the basal level. The physical activity model has been developed by Roy and Parker [3] to quantify $PVO_2^{\max}$. The energy released must be appropriate critical threshold value (A_{TH}) as a function of exercise intensity and duration. An A_{TH} function is mathematically given as follows:

$$A_{TH} = -1.1521[u_{ex}(t)]^2 + 87.471u_{ex}(t) \quad (5)$$

Because of during physical activity, the glycogenolysis rate depends on the depletion of liver glycogen stores, then the glycogenolysis rate during physical activity can be represented as a dynamics system as follows:

$$\frac{dG_{gly}(t)}{dt} = \begin{cases} 0 & A(t) < A_{TH} \\ k & A(t) \geq A_{TH} \\ -\frac{G_{gly}(t)}{T_1} & u_{ex} = 0 \end{cases} \quad (6)$$

where $A(t)$ represent the physical activity intensity, $u_{ex}(t)$, which is calculated by the equations as follows:

$$\frac{dA(t)}{dt} = \begin{cases} u_{ex} & u_{ex} > 0 \\ -\frac{A(t)}{T_2} & u_{ex} = 0 \end{cases} \quad (7)$$

When the onset of physical activities ($u_{ex}(t) > 0$), then the rate of $A(t)$ value will increase which is directly proportional to $u_{ex}(t)$. Later at the end of physical activity ($u_{ex}(t) = 0$) until $A(t)$ will be back returned to its basal condition. During $A(t)$ will be a decline than the critical threshold value (A_{TH}), however, glycogen is still available to be used to maintain the rate of hepatic glucose release. When the value of $A(t)$ has reached A_{TH} , then the rate of change in glycogenolysis will begin to decrease because there is a depletion of available liver glycogen stores. This rate function of glycogenolysis is expressed by k . Physical activity will end when the $u_{ex}(t)$ returns to zero, this condition is also the initial recovery period which is marked by the beginning of the depletion of glycogen storage.

The Bergman minimal model when combined with the physical activities effects to describe glucose and insulin dynamics are given mathematical equation as follows:

$$\frac{dG(t)}{dt} = -p_1[G(t) - G_b] - X(t)G(t) + \frac{\{W[G_{prod}(t) - G_{gly}(t) - G_{upt}(t)] + u_2(t)\}}{Vol_g} \quad (8)$$

$$G(0) = G_b$$

$$\frac{dI(t)}{dt} = -nI(t) - I_e(t) + p_4u_1(t) \quad I(0) = I_b = \frac{p_4}{n}u_{1b} \quad (9)$$

$$\frac{dX(t)}{dt} = -p_2X(t) + p_3[I(t) - I_b] \quad X(0) = 0 \quad (10)$$

$$\frac{dG_{prod}(t)}{dt} = a_1PVO_2^{\max}(t) - a_2G_{prod}(t) \quad G_{prod}(0) = 0 \quad (11)$$

$$\frac{dG_{upt}(t)}{dt} = a_3PVO_2^{\max}(t) - a_4G_{upt}(t) \quad G_{upt}(0) = 0 \quad (12)$$

$$\frac{dI_e(t)}{dt} = a_5PVO_2^{\max}(t) - a_6I_e(t) \quad I_e(0) = 0 \quad (13)$$

The insulin dynamics equation of Bergman minimal model has been modified by adding the function $I_e(t)$ ($\mu\text{U/ml/min}$) which represented the rate of removal of insulin from the circulatory system caused by physiological changes in physical activity. The plasma glucose dynamics equation of the Bergman minimal model also has been modified by the addition of the variables, $G_{upt}(t)$ (mg/kg/min) and $G_{prod}(t)$ (mg/kg/min), which represented the rates of glucose uptake and hepatic glucose production induced by physical activity.

Table 2. Constant estimates of the Bergman minimal model with physical activities effect and treatment of exogenous insulin.

Abbreviation	Name	Value	Unit
a_1	the dynamics constant of G_{prod}	0.0013 - 0.0019	mg/kg. min^2
a_2	the dynamics constant of G_{prod}	0.0441 - 0.0679	1/min
a_3	the dynamics constant of G_{upt}	0.0015 - 0.0024	mg/kg. min^2
a_4	the dynamics constant of G_{upt}	0.0355 - 0.0617	1/min
a_5	the dynamics constant of I_e	0.001 - 0.0015	$\mu\text{U/ml. min}$
a_6	the dynamics constant of I_e	0.0588 - 0.0912	1/min
W	the weight of the subject	60-90	kg

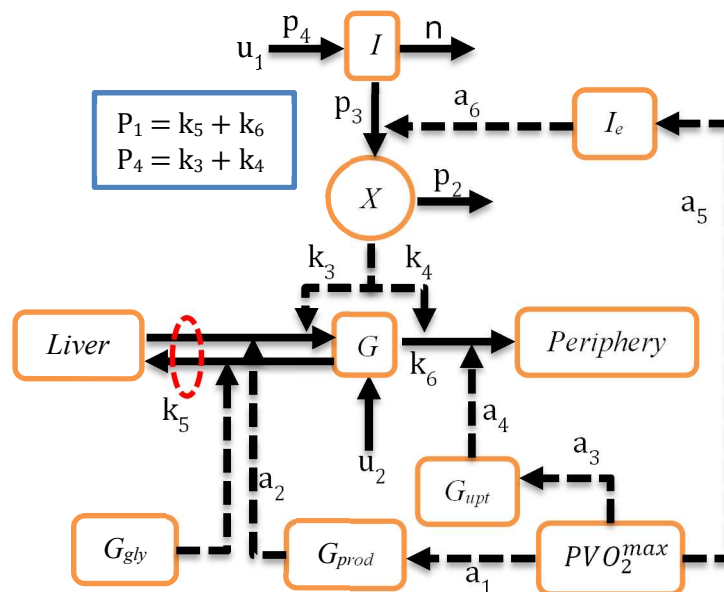


Figure 1. Mechanism of Bergman minimal model with physical activities effect and treatment of exogenous insulin.

2.3. The modified oral minimal model with physical activities effect and treatment exogenous insulin

Actual and most common diagnostic tests for the assessment of insulin secretion and insulin resistance are tests carried out by oral administration such as OGTT and meal tolerance test (MTT). In this study, the mathematical model that has been introduced by Roy and Parker [3] will be modified. In the previous study, glucose consumption has been given directly (at once) before physical activity, whereas in

everyday life, glucose is consumed slowly. This modified model is expected according to the real conditions of T1DM subjects. The modified equations that are as follows:

$$\frac{dG(t)}{dt} = -p_1[G(t) - G_b] - p_4X(t)G(t) + \frac{\{W[G_{prod}(t) - G_{gly}(t) - G_{upt}(t)] + \}}{Vol_g} + \frac{dD(t)}{dt} \quad (14)$$

$$G(0) = G_b$$

$D(t)$ represents the glucose absorption level in the human body that comes from meal or drink. This equation can be described as the following equation:

$$\frac{dD(t)}{dt} = -R_a(t) \quad (15)$$

$$R_a(t) = \begin{cases} \alpha_{i-1} + \frac{\alpha_i - \alpha_{i-1}}{t_i - t_{i-1}}(t - t_{i-1}), & t_{i-1} \leq t \leq t_i, i=1 \dots 8 \\ 0, & \text{others} \end{cases} \quad (16)$$

To analysis the fitting of the model, then the model should be assessed by a calculation of the statistical correlation between experimental data and model results using the R^2 methods. An R^2 value can be defined as:

$$R^2 = 1 - \frac{X^2}{SST} \quad (17)$$

$$X^2 \equiv \sum_{i=1}^N \left[\frac{y_i - y(t_i, \theta_1, \dots, \theta_M)}{\sigma} \right]^2 \quad (18)$$

$$SST \equiv \sum_{i=1}^N \left[\frac{y_i - \bar{y}}{\sigma} \right]^2 \quad (19)$$

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

3. Results and discussion

This study will vary some insulin administrations which is given when T1DM performed physical activities. These variations will be used for testing the present model in the experiment simulation schemes as shown in Table 3. In these experiment simulations, T1DM subject is assumed to carry out the physical activity for 180 to 300 min while the T1DM subject's weight is 80 kg. The constants and parameters used of these experiment simulations in this research are listed following in Table 1 and 2. An experiment data from the OGTT test for the normal subject was used as controls that subject will experience a decrease due to physical activity and administration of exogenous insulin. The experimental data used are listed in Table 4 and 5.

Table 3. The experiment simulation used in this research.

Condition	Condition of experiment simulations	
	Administration of insulin ($\mu\text{U} \cdot \text{min}^{-1}$)	Physical activity
1	10	X
2	10	$\checkmark$
3	20	$\checkmark$
4	30	$\checkmark$
5	40	$\checkmark$

Table 4. An experimental data from T1DM subject [14].

Time (min)	Glucose concentration ($\text{mg} \cdot \text{dL}^{-1}$)
0	140.54
10	158.95
20	180.18
30	216.22
60	275.27
90	284.70
120	270.30
150	237.84
180	198.20
240	148.52
300	121.71

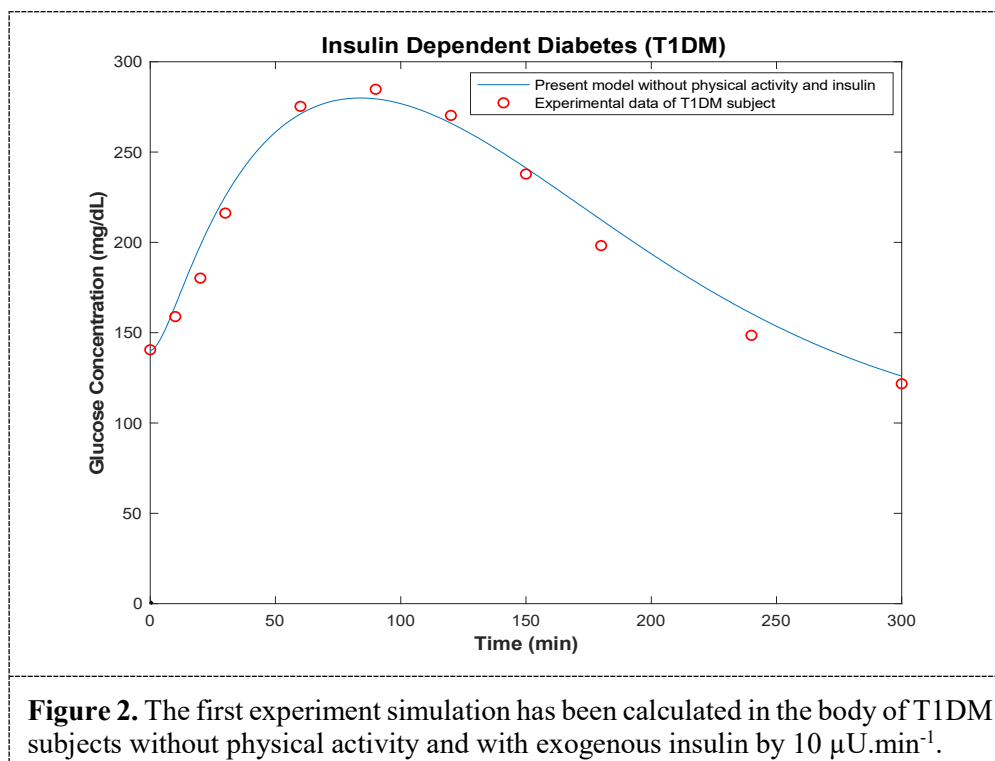
Table 5. An experiment data from normal subject [14].

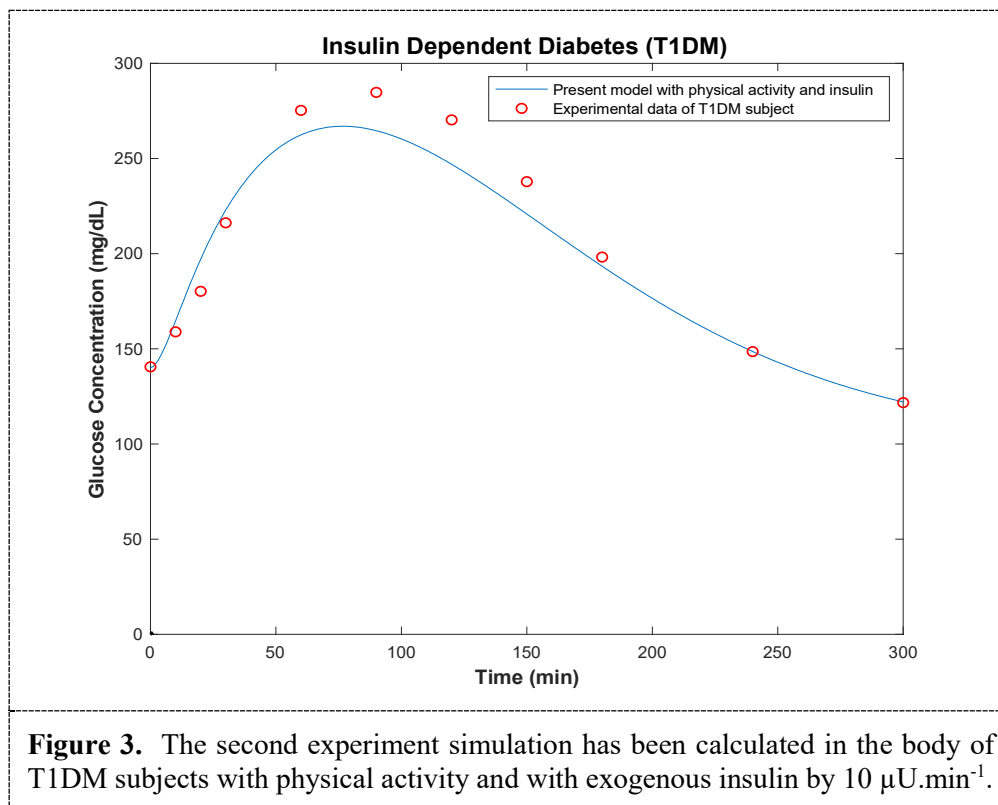
Time (min)	Glucose concentration ($\text{mg} \cdot \text{dL}^{-1}$)
0	106.31
10	147.75
20	160.55
30	179.37
60	187.39
90	170.18
120	149.55
150	138.54
180	121.72
240	106.31
300	107.75

In condition 1, first experiment simulation has been done to describe the blood glucose concentration levels in the body of T1DM subjects without physical activity but given insulin by $10 \mu\text{U} \cdot \text{min}^{-1}$. The simulation results of glucose concentration can be seen in Figure 2. Figure 2 shows that the simulation results approach the experimental data. An increase in the curve at the range of 0 to 100 min indicates the presence of glucose entering and absorbed by the blood body of T1DM subjects. Later, in the range of 100 to 300 min, a decrease in the curve indicates a decrease in blood glucose concentration levels caused by external insulin injection. The R^2 value obtained of first experiment simulation is 96%. The R^2 value is used to validate the experimental data. This shows that the first experiment simulation can describe the condition of blood glucose levels in T1DM according to actual conditions.

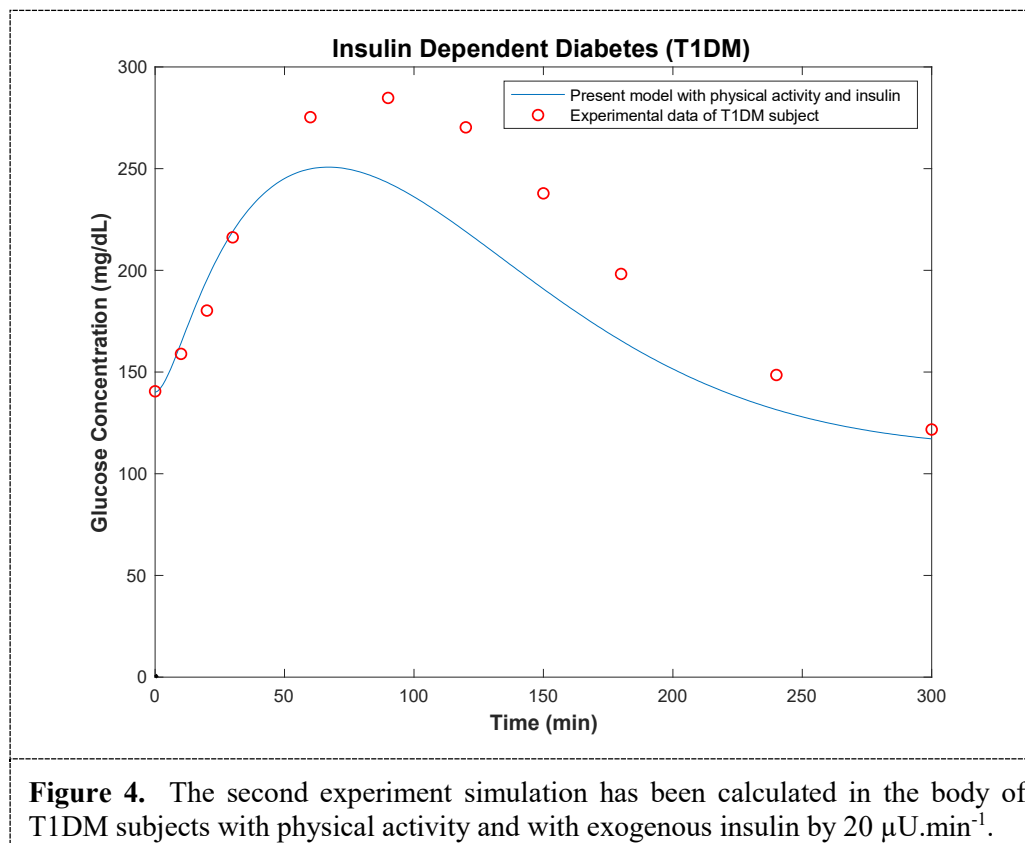
In condition 2, the second experiment simulation describes the condition of blood glucose levels in the body of T1DM subject by administration of insulin injection at $10 \mu\text{U} \cdot \text{min}^{-1}$ and carry out physical

activity. The curve of the Second experiment simulation can be seen in Figure 3. There is an indication of the increase in the curve in the range of 0 to 80 min describe that the presence of glucose entering and absorbed by the body of T1DM subject. Later, the curve decreases in the range of 80 to 300 min. The decreased curve indicates a decrease in blood glucose levels in the body caused by the administration of insulin by $10 \mu\text{U} \cdot \text{min}^{-1}$ and physical activity carried out by T1DM. The curve of the second experiment simulation is lower than the first experiment simulation. This occurs because the administration of insulin when carrying out physical activity has an effect on the rate of decrease in blood glucose levels in T1DM. This shows that the experiment simulation was successful in describing the dynamics system of blood glucose levels and proving that the rate of decrease in blood glucose levels is indicated by a physical activity effect.





In condition 3, this simulation results describes the condition of blood glucose levels in the body of a subject with T1DM by the administration of insulin injection amount $20 \mu\text{U} \cdot \text{min}^{-1}$ and also carry out physical activity. The curve of condition 3 can be seen in Figure 4. Increasing the blood glucose levels in the range of 0 to 70 min indicates the presence of glucose entering and absorbed by the body of a subject with T1DM. Later, glucose concentration decreases in the range of 70 to 300 min due to the administration of external insulin amount $20 \mu\text{U} \cdot \text{min}^{-1}$ and also done the physical activity. As the previous curve, this curve has also shown that this present model successfully describes the previous prediction. Because of the administration of external insulin affects the rate of decrease in blood glucose in T1DM subjects while doing physical activity.



The results of experiment simulation in condition 4 and 5 also have been calculated to describe the concentration of blood glucose levels in the body of a subject with T1DM by the administration of insulin injection amount 30 and $40 \mu\text{U} \cdot \text{min}^{-1}$ when carrying out physical activity. The curve of condition 4 and 5 can be seen in Figure 5 and 6.

Subjects with T1DM generally cannot change overall endogenous insulin levels. However, normal hormonal glucose regulation during and after exercise will occur, because endogenous insulin levels will be processed into energy. But this condition, T1DM subjects can also be at risk of hypoglycemia. The risk of hypoglycemia follows an increase in physical activity with the duration of physical activity, if physical activity lasting more than 180 minutes will double the risk of hypoglycemia.

The duration of physical activity can have a significant impact, a longer period of physical activity will usually lead to greater use of blood glucose. This will also lead to accelerated glucose absorption rates; this process will give rise to compensation for increasing liver glucose production to maintain normoglycemia conditions. In T1DM subjects, endogenous insulin secretion is insufficient. Therefore, this condition will generally be replaced by exogenous insulin injections. Intensive insulin treatment every day is a major factor in maintaining normoglycemia levels in blood glucose. Many researchers have identified that administering insulin during physical activity is the main barrier to optimal control of diabetes. Therefore, the simulation ability to predict the effect of physical activity on blood glucose levels in T1DM is very helpful to adapt how much insulin injection should be given during physical activity is one of the main advantages of developing an artificial pancreas that works in normal living conditions.

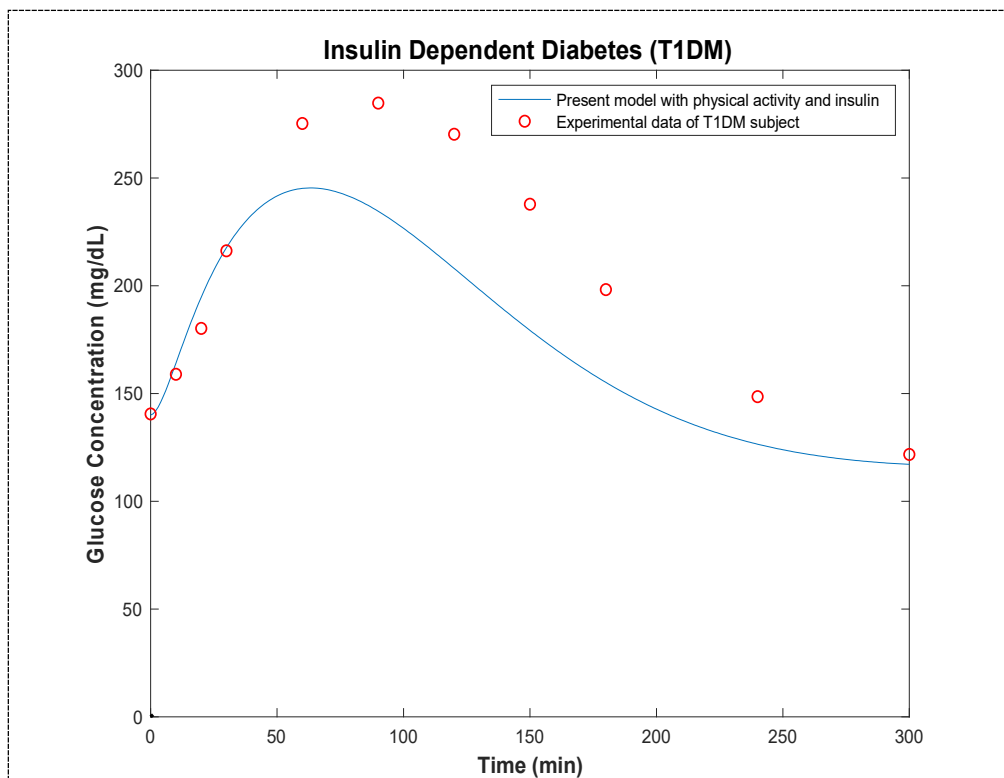


Figure 5. The third experiment simulation has been calculated in the body of T1DM subjects with physical activity and with exogenous insulin by $30 \mu\text{U} \cdot \text{min}^{-1}$.

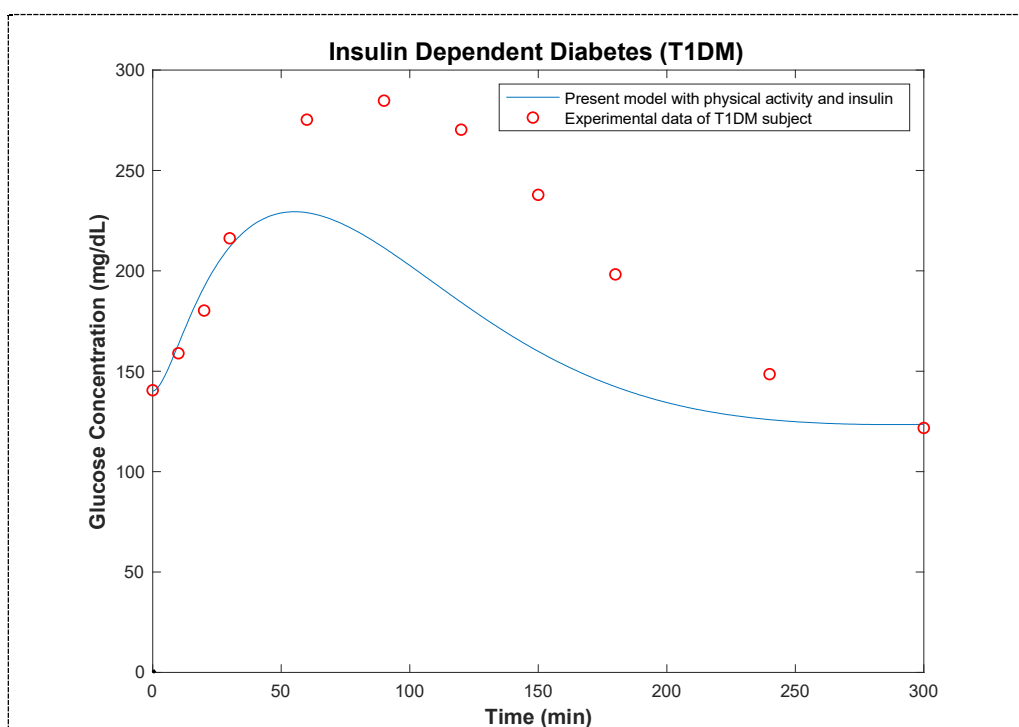
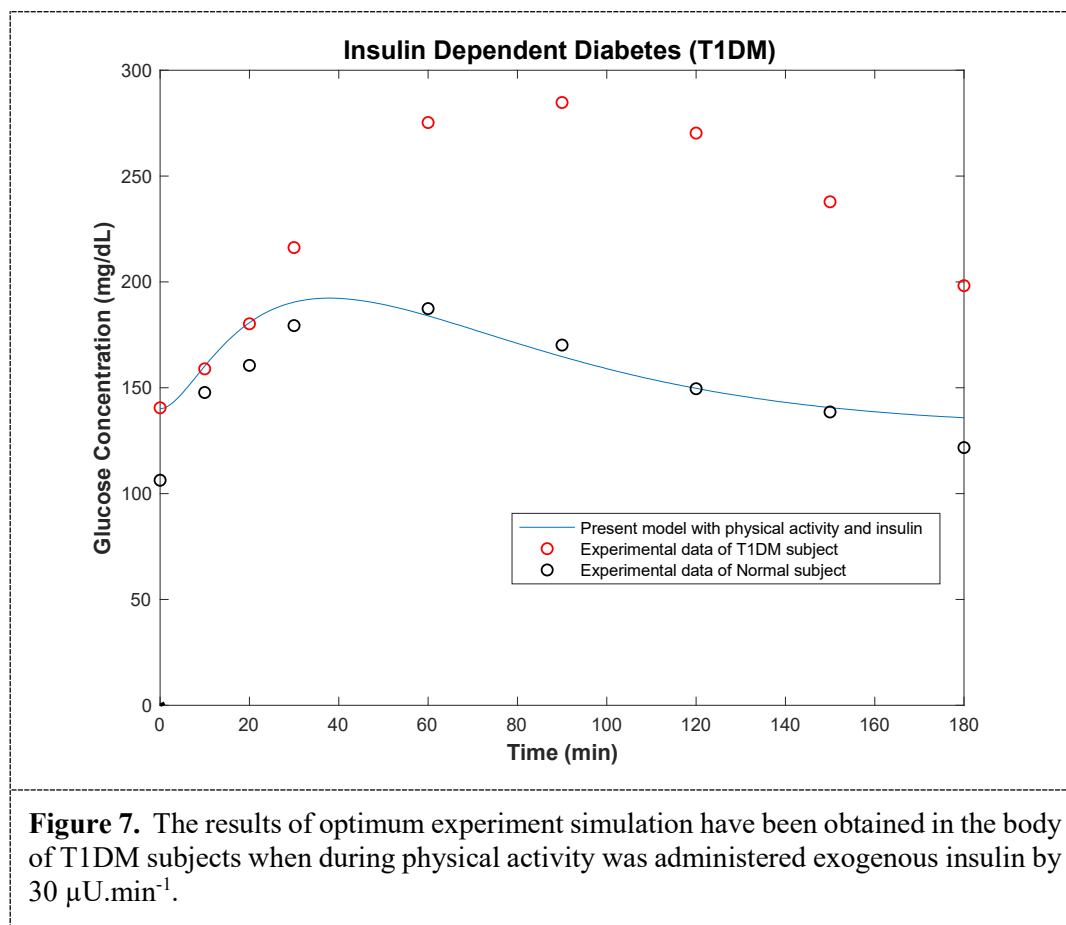


Figure 6. The fourth experiment simulation has been calculated in the body of T1DM subjects with physical activity and with exogenous insulin by $40 \mu\text{U} \cdot \text{min}^{-1}$.

These studies have combined the physical activity model proposed by Roy and Parker [3] into an oral minimal model of the glucose-insulin system. Four experiment simulations differently have been calculated and tested in this simulation. Experiment simulation in condition 4 assumes that physical activity during 180 min with insulin injections amount of $30 \mu\text{U}\cdot\text{min}^{-1}$ in accordance with the normal experimental data. Comparison of between simulation prediction of glucose concentration and experimental data of normal subjects is shown in Figure 7. The prediction results of this present model that have been developed in this research are expected to help the designing of an artificial pancreas. The simulation results of plasma glucose concentration are obtained from combination values of constant and parameters that have been estimated optimally from Table 1 and 2.



4. Conclusions

In conclusion, the modified mathematical model has been used to describe the physical activity effect and also the administration effect of exogenous insulin on blood glucose levels in T1DM patients. Physical activity affects decreasing blood glucose levels in the body of subjects with T1DM. However, the addition of exogenous insulin during physical activity will also increase the process of decline in blood glucose levels. But the combination of an insulin injection during physical activity can be used treatment accurately. These simulation studies can be used to develop the design of artificial pancreatic.

The modified oral minimal model with physical activity effect and treatment external insulin has been used to describe the effect of physical activity and administration of insulin injections on blood glucose levels of T1DM proven successful. However, these modified equations have not considered other aspects, such as variations of physical activity. Because of the influence of physical activity, such as mild, moderate, and heavy physical activity, also will affect physical activity. These variations can represent clearly in everyday living.

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