Simulation Work on Blood Glucose Control for Type1 Diabetes using Modified Hovorka Equations

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Abstract — **The failure of pancreas can cause uncontrolled blood glucose level in the body. This research focuses on type 1 diabetes patients which depend on external insulin injection. In previous studies, Hovorka models are used as the mathematical models in the artificial pancreas controller. However, the models showed lacking of interaction on glucose-insulin dynamic system. The improvement of Hovorka models had been done, but no work was carried out to simulate the proposed equations. The objectives of this research are to simulate the Modified Hovorka equations using Matlab and to compare the simulation results between the reference and modified one. This study shows different interaction of all the variables and parameters on glucose-insulin dynamic system between both cases. The lower administered amount of insulin (16.7mU/min and 20mU/min) can regulate the blood glucose level at normoglycemia condition.**

Keywords- Type 1 diabetes, Mathematical model, Matlab simulation

I. INTRODUCTION

Diabetes is a chronic disease which is caused by insufficient insulin in the body or the excessive insulin in the blood stream. Pancreas acts as the producer of the insulin. The failure of pancreas to produce enough insulin to the human body can lead to the diabetes problem. The development of diabetes also occurs when the body is not able to use the insulin effectively. An irregular insulin amount in the human body will cause the problem such as low blood glucose and high blood glucose. Thus, the uncontrolled blood glucose level in the body will be faced by the diabetes patient.

Diabetes can be divided into two categories which are Type 1 and Type 2. Type 1 diabetes is usually suffered by children and young adults in European region. This type of diabetes is also known as insulin dependent. Meanwhile, Type 2 diabetes is usually suffered by adults and also known as insulin resistant. Both types of diabetes occur when the pancreas fails to produce insulin in the sufficient amount to the body.

Recently, artificial pancreas is developed to help patients to get the sufficient insulin and to control their blood glucose level [1]. Artificial pancreas or closed-loop system consists of insulin pump, continuous glucose monitoring (CGM) sensor, CGM receiver and control algorithm device to measure the current glucose level to supply the sufficient amount of insulin to the body [2]. Therefore, the automated insulin supplied to the body can reduce the insulin injection.

This research focuses on the control algorithm of artificial pancreas for Type 1 diabetes. The control algorithm is a heart of the system which is very important to estimate the amount of insulin needed by the body in order to control blood glucose level.

Hovorka equations are the suitable mathematical model for this control algorithm. However, the equations are being modified to improve the relationship between insulin and glucose variables. In order to identify the behaviours of parameters and variables of the Modified Hovorka Equations, the simulation works need to be done in order to obtain their performance and userabilities.

Type 1 diabetes is a major disease that is suffered by children in the European country. The failures of pancreas to produce the sufficient insulin to the body have led the patients to supply their insulin from the external source. Several amount of insulins needed to their body are introduced by an insulin injection. Usually, injection of insulin is done by themselves or their family before meal taking. The dependency on the insulin injection can reduce the patient life style and routines.

The artificial pancreas is used by the patient to control blood glucose level. However, the current artificial pancreas devices are not fully automated [3]. Hence, the patients still need to manually inject themselves to introduce the insulin into their body. This is caused by the low efficiency of the control algorithm in terms of interrelations and interactions among various parameters in the artificial pancreas device.

The device is needed to function as fully automated in order to reduce the dependency on insulin injection by the patients. The mathematical equations of Hovorka model are used in the control device [4]. However, the model has showed some lacking of interaction on glucose-insulin dynamic system. The modified Hovorka equations have been proposed in order to improve the interaction and interrelation of the parameters in glucose-insulin dynamics [5]. However, presently there is no work carried out to simulate the proposed equations. Thus, this study attempts to show the simulation works by using the improved equations.

II. METHODOLOGY

A. Improvement of Hovorka Model

The mathematical equations from Hovorka model [6] had been changed and transformed into a set of equations. The transformation of modified Hovorka model is developed due to lack of the interaction between insulin and glucose system dynamics in the Hovorka model [5]. By developing the new sets of Hovorka equations using system identification techniques, the interaction between the insulin and glucose system is expected improve tremendously.

The improvement in glucose and insulin interactions of modified Hovorka models can be proved by glucose-insulin dynamics as shows in the Fig 1(a) which shows that the insulin action subsystem does not fully interact with the glucose mass compartment. In this model, it seems that only insulin on action transport (x_1) and insulin on endogenous production (x_3) have the interaction in mass of glucose in the accessible compartment (Q_1). Meanwhile, the mass of glucose in the non-accessible compartment (Q_2) interaction only occurs with insulin on action transport (x_1) and insulin on action disposal (x_2).

However, by modifying the Hovorka model all insulin action subsystems completely interact with the equations of mass of glucose in the accessible compartment and mass of glucose in the non-accessible compartment. Insulin on action transport (x_1), insulin on action disposal (x_2) and insulin on endogenous production (x_3) can

reach the mass of glucose in the accessible compartment (Q_1), and non-accessible compartment (Q_2) interactions as shown in the Fig 1 (b).

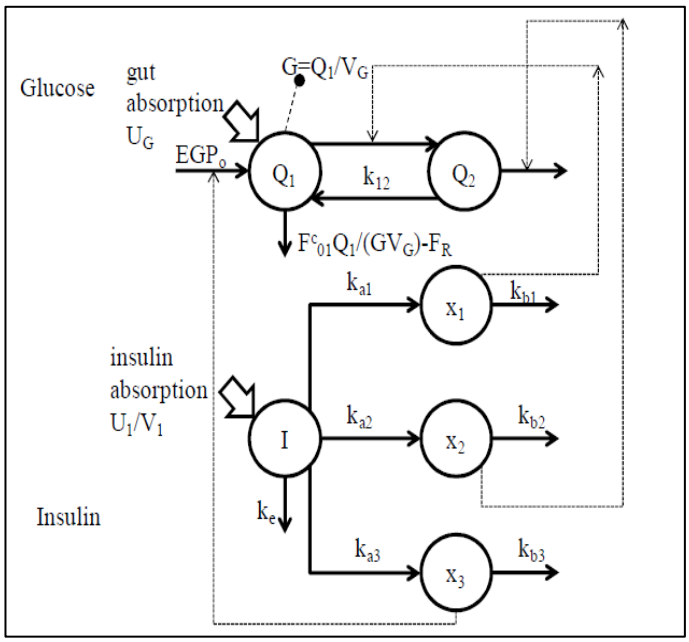

Fig 1(a): Hovorka Model

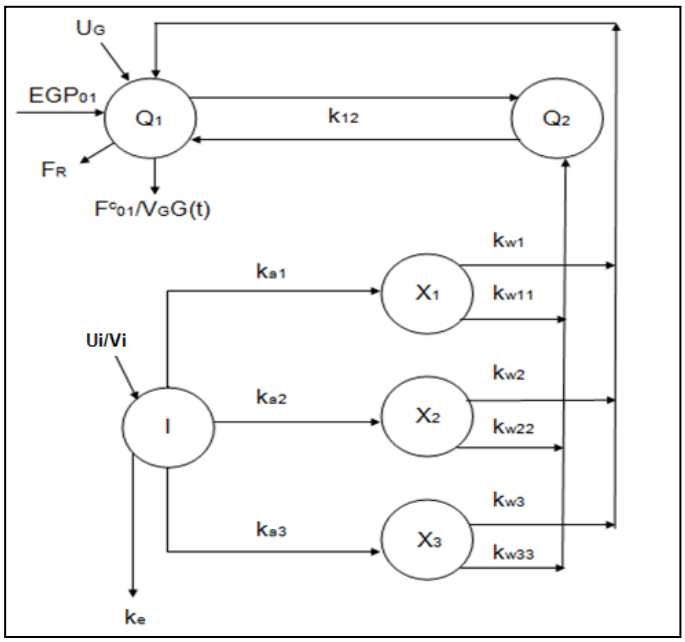

Fig 1(b): Modified Hovorka Model

B. *Modified Hovorka Model*

The equations in the Hovorka model have been modified in the certain subsystem of the models. The modified equations take place namely in glucose subsystem, plasma insulin concentration, and insulin subsystem. Meanwhile, the other equations remain unchanged.

Glucose subsystem has been improved by adding all insulin action variables in the equations for accessible compartment and non-accessible compartment as shown in the equation (1) and equation (2) as follows:

$$\frac{dQ_1}{dt} = EGP_o + U_G + 0.01\,Q_2 + [x_1k_{w1} + x_2k_{w2} + x_3k_{w3}] - F_RQ_1 - \left[\frac{F^c_{01}}{V_GG(t)}\right]Q_1 - 0.002Q_1 \quad (1)$$

$$\frac{dQ_2}{dt} = [k_{w11}x_1(t) + k_{w22}x_2(t) + k_{w33}x_3(t)] + EGP_o[k_{w1}x_1(t) + k_{w2}x_2(t) + k_{w3}x_3(t)]k_{12}Q_2 \quad (2)$$

Q_1 and Q_2 represent the glucose mass in the accessible and non-accessible compartments, respectively. The constants of k_{w1}, k_{w2}, k_{w3}, k_{w11}, k_{w22} and k_{w33} represent the transfer rate constants of insulin action subsystem. Meanwhile, the constant of k_{12} is represented as transfer rate from non accessible to accessible compartment. EGP_0 represents endogenous glucose production (EGP) that is extrapolated to the zero insulin concentration. U_G is represented as the absorption amount of glucose into the blood vessel. The parameter of F_c^{01} is the total of non-insulin dependent glucose flux and F_R is represented as the renal glucose clearance [6].

$$F_C^{01} = \begin{cases} F_{01} if G \geq 4.5\ mmolL^{-1} \\ \dfrac{F_{01}G}{4.5} otherwise \end{cases}$$

$$F_R = \begin{cases} 0.003\,(G-9)V_G if G \geq 9\ mmolL^{-1} \\ 0 \qquad\qquad otherwise \end{cases}$$

The equations in the insulin subsystem remain the same as the Hovorka model. Equations (3) and (4) show the insulin subsystem in the accessible and non accessible compartments.

S_1 and S_2 represent as the insulin sensitivity in the accessible and non accessible compartments, respectively.

$$\frac{ds_1(t)}{dt} = u(t) - \frac{s_1(t)}{t_{max,I}} \quad (3)$$

$$\frac{ds_2(t)}{dt} = \frac{s_1(t)}{t_{max,I}} - \frac{s_2(t)}{t_{max,I}} \quad (4)$$

The variables of insulin action are also added in plasma insulin concentration equation. The plasma insulin concentration I(t) is changed as shown in equation (5) where k_e is the fractional elimination rate, V_I is the distribution volume and U_I is represented as the production amount of insulin required into the blood vessel.

$$\frac{dI(t)}{dt} = \left[\frac{U_I(t)}{V_I}\right] - k_eI(t) - [k_{w1}x_1(t) + k_{w2}x_2(t) + k_{w3}x_3(t)] \quad (5)$$

Meanwhile, equations (6) to (8) represent as insulin action subsystem equations on action transport, action disposal and endogenous production, respectively. The constant of k_{a1}, k_{a2},k_{a3}, k_{w1}, k_{w11}, k_{w2}, k_{w22}, , k_{w3}, and k_{w33} are the deactivation and activation rates of insulin action.

$$\frac{dx_1}{dt} = -k_{a1}x_1(t) + k_{w1}I(t) + k_{w11}I(t) \quad (6)$$

$$\frac{dx_2}{dt} = -k_{a2}x_2(t) + k_{w2}I(t) + k_{w22}I(t) \quad (7)$$

$$\frac{dx_3}{dt} = -k_{a3}x_3(t) + k_{w3}I(t) + k_{w33}I(t) \quad (8)$$

The constants and parameters are included in the equations to represent the glucose absorption for type 1 diabetes conditions. The constants and parameters in the equations are determined by its specific values. The constant values and parameters are defined as shown in Tables1 and 2, respectively.

Table 1 : The constant values for modified Hovorka models

Symbol	Constant	Value & Unit
k_{12}	Transfer rate	0.066 min^{-1}
k_{a1}	Deactivation rate	0.006 min^{-1}
k_{a2}	Deactivation rate	0.06 min^{-1}
k_{a3}	Deactivation rate	0.03 min^{-1}
k_{w1}	Activation rate	50.1 min^{-1}
k_{w11}	Activation rate	-10 min^{-1}
k_{w2}	Activation rate	50.1 min^{-1}
k_{w22}	Activation rate	-0.01 min^{-1}
k_{w3}	Activation rate	50.1 min^{-1}
k_{w33}	Activation rate	-0.01 min^{-1}
k_e	Insulin elimination from plasma	0.138 min^{-1}
V_I	Insulin distribution volume	0.12 L kg^{-1}
V_G	Glucose distribution volume	0.16 L kg^{-1}
A_G	Carbohydrate(CHO) bioavailability	0.8 (unit less)
$t_{max,G}$	Time-to-maximum of CHO absorption	40 min

Source : Modified Hovorka Model [5][6]

C. *Matlab Simulation*

Matlab is a software package that has many built-in tools for solving problems and for graphical illustrations. The simplest method for using the Matlab is by entering the expression in the command window. The program will immediately responds and provide the results [7].

In this study, Matlab program is used to run the simulations. M-files from the Matlab are created by opening text editor. The file has ".m" extension, and consists of the commands that are used as input. Script M-files are ideal for repeating a calculation, but with some parameters changed. All related statement parameter and constant used in the equations are written into the script file. Then, the equations of modified Hovorka model are written as the mathematical expression into the M-files with correct operators. The plot function is used to obtain the graphical results. After the coding of the equation is correctly inserted, the experiment is run by the simulation. To shows the graph, the M-files is called in the command window.

Table 2 : The parameter values for modified Hovorka models

Symbol	Parameter	Value & Unit
$S^{'}_{IT}$	Insulin sensitivity of distribution/ transport	51.2 x 10^{-4} min^{-1} per mU L^{-1}
$S^{'}_{ID}$	Insulin sensitivity of disposal	8.2 x 10^{-4} min^{-1} per mU L^{-1}
$S^{'}_{IE}$	Insulin sensitivity of EGP	520 x 10^{-4} min^{-1} per mU L^{-1}
EPG_o	EGP extrapolated to zero insulin concentration	0.0161 $mmolkg^{-1}$ min^{-1}
F_{01}	Non-insulin-dependent glucose flux	0.0097 $mmolkg^{-1}$ min^{-1}
$t_{max,1}$	Time-to-maximum of absorption of subcutaneously injected short-acting insulin	55 min

Source : Modified Hovorka Model [5][6]

III. RESULTS AND DISCUSSIONS

A. *Plasma Glucose Concentration*

The simulation on plasma glucose concentration is simulated due to the amount of insulin administered, U_t. The behaviour of plasma glucose concentration of 16.7 mU/min, 20 mU/min, 50 mU/min, 75 mU/min and 100 mU/min amount of U_t are showed in the Fig 3.

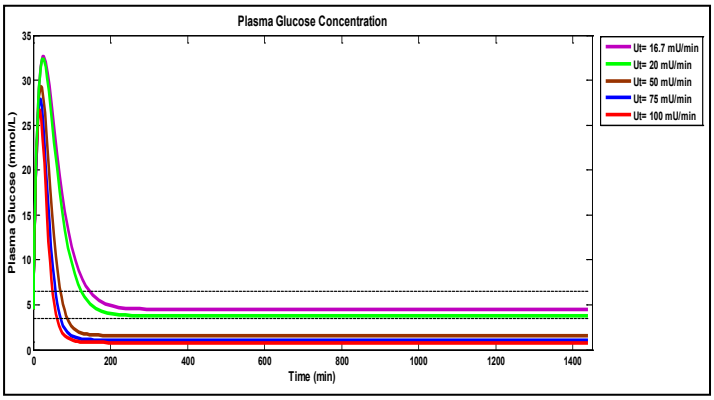

Fig 3: Plasma Glucose concentration

The Fig 3 shows the plasma glucose concentration was initialized at 4.5 mmol/L of plasma glucose. The concentration of plasma glucose was increase rapidly to the peak point. At the certain time, the glucose concentration is reduced and become constant.

The concentration of plasma glucose is achieve normoglycemia condition (4 mmol/L – 6 mmol/L) when the U_t = 16.7 mU/min and U_t = 20 mU/min. In contrast, from the previous study, the simulation of plasma glucose concentration by using Hovorka equations with U_t = 16.7 mU/min shows that the concentration was too high and can cause hyperglycemia [3]. The different of simulation results is due to the improved model from glucose subsystem in accessible compartment and non-accessible compartment by Yusof et al (2012) [5].

Both U_t = 16.7 mU/min and U_t = 20 mU/min was regulated at constant blood glucose level at different time. When U_t = 16.7 mU/min is infused to the body, the blood glucose level of 5 mmol/L is achieved constant at 343 min. However, the infusion of insulin to the body at U_t = 20 mU/min shows that the blood glucose level is achieved constant at 4 mmol/L at 210 min. Thus, the 20 mU/min of insulin administered are achieved constant blood glucose level faster than 16.7 mU/min of insulin.

The plasma glucose concentration for 50 mU/min, 75 mU/min and 100 mU/min of insulin administered was reach lower peak glucose concentration compared to 16.7 mU/min and 20 mU/min. These amounts of insulin are also reach stable blood glucose control earlier than the lower administered amount of insulin infused to the body. However, the blood glucose was remained constant at less than 4 mmol/L of glucose plasma concentration. This condition can lead to hypoglycaemia which is the blood glucose is too low [9].

From the previous Hovorka equations simulation, the higher administered insulin amount shows the blood glucose level was regulated in normoglycemia level [3]. In this study, it shows that the lower administered insulin amount can regulate at normoglycemia level but it takes some time.

B. *Plasma Insulin Concentration*

The plasma insulin concentration was identified by simulated 16.7 mU/min, 20 mU/min, 50 mU/min, 75 mU/min and 100 mU/min of insulin administered. The pattern of plasma insulin concentration is shows in the Fig 4.

Fig 4 shows the plasma insulin concentration was start at 15 mU/L of plasma insulin. The concentration of plasma insulin was increased with respect to time and remained constant at a certain time for all insulin administered amount.

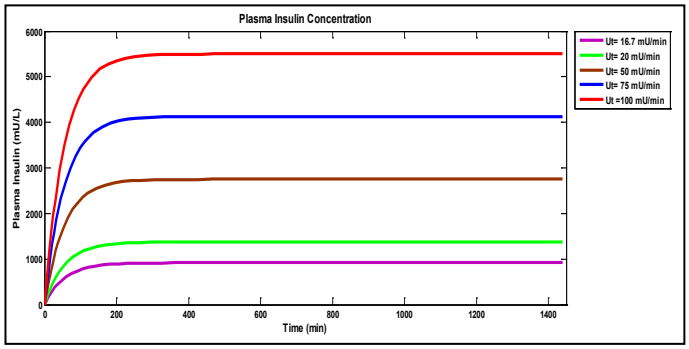

Fig 4: Plasma Insulin concentration.

The plasma insulin concentration was reach 900 mU/L and remained constant after 300 minutes for 16.7 mU/min of insulin. Meanwhile, the simulation for plasma insulin concentration at 100 mU/min was achieved constant at 400 minutes and reach 5500 mU/L of plasma insulin concentration. Thus, the lower amount of insulin infused to the body will cause the plasma insulin concentration is lower than the higher amount of insulin. In addition, the time taken for plasma insulin concentration is achieved constant to low when the insulin administered amount is low.

All results showed the different performance. It is because of the different amount of insulin infuse to the body. When the infusion rate of insulin is higher, the plasma insulin is become higher and the plasma concentration is reach constant slower compared to the low infusion rate of insulin.

The trend showed is same as the previous study by simulating Hovorka equations [3]. The plasma insulin concentration is increasing with respect to time. However, the plasma insulin concentration was achieved at different point. Plasma insulin concentration for modified Hovorka equations was reaching lower than Hovorka equations [3]. This result is same as Yusof et al (2012) when the plasma insulin concentration modified Hovorka equations is comparatively low. It is because of the additional parameters of action subsystem in the equation of plasma insulin concentration [5].

IV. CONCLUSIONS

A present study shows the simulation works for the modified Hovorka equations to show the interaction and interrelation on the glucose-insulin dynamic system among parameters and variables in modified Hovorka equations. The administered of insulin is the most active parameter. Thus, two different insulin administered amounts was used to show the effect of glucose-insulin system.

The analysis shows the lower insulin administered amount which are 16.7 mU/min and 20 mU/min can regulate at 5 mmol/L and 4 mmol/L respectively of plasma glucose concentration. These conditions are called normoglycemia when the blood glucose levels are in the safe range. Meanwhile, the higher administered amount of insulin may lead to hypoglycemia condition due to lower glucose level although they are achieved constant blood glucose level faster than the higher administered amount of insulin.

In addition, the plasma insulin concentration was increased with respect with time when the administered amount of insulin was infused to the body and achieved constant after 300 minutes and 400 minutes for 16.7 mU/min and 100 mU/min of insulin respectively. The higher amount of insulin infused to the body will cause the plasma insulin is higher.

According to the overall result, it can be concluded all the parameter and variables in the modified Hovorka equations are takes part in the simulation. The interactions between variables in glucose and insulin system are different from the Hovorka equations. The simulation result shows that the plasma glucose concentration was control in the constant state when the modified Hovorka equations is applied in the simulation works.

The modified Hovorka equations shows that the lower administered amount of insulin (16.7 mU/min and 20 mU/min) can reach the normal range of blood glucose level compared to the original Hovorka equations. The lower infusion of insulin to the body is also can regulate lower concentration of plasma insulin.

For further studies, it recommended to do the simulations with meal using modified model to see how it reacts to meal disturbances.

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References

[1] Thabit, H., & Hovorka, R. (2012). Closed-loop insulin delivery in type 1 diabetes. *Endocrinol Metab Clin North Am*, *41*(1), 105-117.

[2] Elleri, D., Dunger, D. B., & Hovorka, R. (2011). Closed-loop insulin delivery for treatment of type 1 diabetes. *BMC Medicine*, *9*(1).

[3] Yusof, N. F., Md Som, A., Abdulbari Ali, S., & Abdul Halim Anuar, A. L. (2015). Simulation Work for the Control of Blood Glucose Level in Type 1 Diabetes Using Hovorka Equations. *AMR*, *1113*, 739-744.

[4] Thabit, H., & Hovorka, R. (2016). Coming of age: the artificial pancreas for type 1 diabetes. *Diabetologia*, *59*(9), 1795-1805.

[5] Yusof, N. F., Som, A. M., Ibrehem, A. S., & Ali, S. A. (2012). Parameter addition in interaction of glucose and insulin for type 1 diabetes. *2012 IEEE EMBS Conference on Biomedical Engineering and Sciences*.

[6] Hovorka, R., Canonico, V., Chassin, L. J., Haueter, U., Massi-Benedetti, M., Federici, M. O., … Wilinska, M. E. (2004). Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiological Measurement*, *25*(4), 905-920.

[7] Attaway, S. (2011). *MATLAB: A practical introduction to programming and problem solving*. Waltham, MA: Butterworth Heinemann.

[8] Forbes, J. M., & Cooper, M. E. (2013). Mechanisms of Diabetic Complications. *Physiological Reviews*, *93*(1), 137-188.

[9] Bilous, R. W., Donnelly, R., & Williams, G. (2010). *Handbook of diabetes* (4th ed.). Chichester: Wiley Blackwell.