Simulation Work on Blood Glucose Control for Type 1 Diabetes using Modified Hovorka Equations

Ayub Md Som[1,2]*, Nur Farhana Mohd Yusof[1], Sherif Abdulbari Ali[1] and Nurafiqah Zawawi[1]

[1]*Faculty of Chemical Engineering, Universiti Teknologi MARA, 40450 UiTM, Shah Alam, Selangor, Malaysia*
[2]*Accounting Research Institute, Universiti Teknologi MARA, 40450 UiTM, Shah Alam, Selangor, Malaysia*

ABSTRACT

Failure of pancreas can cause uncontrolled blood glucose levels in the body. This research focuses on type 1 diabetes patients who depend on external insulin injection. The Hovorka model was used as the mathematical model in the development of control algorithm for artificial pancreas. However, the model showed a lack of interaction on selected parameters and variables in its glucose-insulin dynamic system. An improvement on the Hovorka equations was done, but no work was carried out to simulate the proposed equations. The objectives of this study are to simulate the modified Hovorka equations using MATLAB and to compare the simulation results between the reference and modified ones. This study showed better interaction among all variables and parameters on its glucose-insulin dynamic system using the modified equations compared to the original equations. The lower administered amount of insulin, U_t at 16.7mU/min and 20mU/min could regulate the blood glucose level at normoglycemic condition throughout the study.

ARTICLE INFO

INTRODUCTION

Artificial pancreas or closed-loop system consists of continuous subcutaneous insulin infusion (CSII) pump, continuous glucose monitoring (CGM) sensor, CGM receiver and control algorithm which measure and regulate current blood glucose level of type

1 diabetes patients in an automated manner so as to minimise hyperglycaemia without increasing hypoglycaemia (Elleri et al., 2011; Forlenza et al., 2016; Messori et al., 2015; Thabit & Hovorka, 2012; Thabit & Hovorka, 2016). As control algorithm is one of the most important components which act as a heart of the system, the controller should be able to communicate with all components in the device to control insulin infusion activity and blood glucose level in the patient's body (Hovorka et al., 2006; Hovorka et al., 2010).

The device is needed to function as a fully automated device in order to reduce the dependency on manual insulin injection by the patients. The mathematical equations of Hovorka model (Hovorka et al., 2004) are used in the control algorithm; however, the model somewhat lacks interaction and interrelation of selected parameters in its glucose-insulin dynamics, specifically involving its glucose subsystem, plasma insulin subsystem, and insulin action subsystem (Yusof et al., 2012; Yusof et al., 2013; Yusof et al., 2014; Yusof et al., 2015). In the Hovorka model as shown in Figure 1, it seems that only insulin on action transport (x_1) and insulin on endogenous production (x_3) interact 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). As such, the modified Hovorka equations have been proposed by Yusof et al. (2012) in order to improve the interaction and interrelation of all related parameters in the glucose-insulin dynamics system. However, at present no work has been carried out to simulate the proposed equations in order to obtain its performance and user-ability. Thus, this study attempts to show the simulation work by using the improved equations.
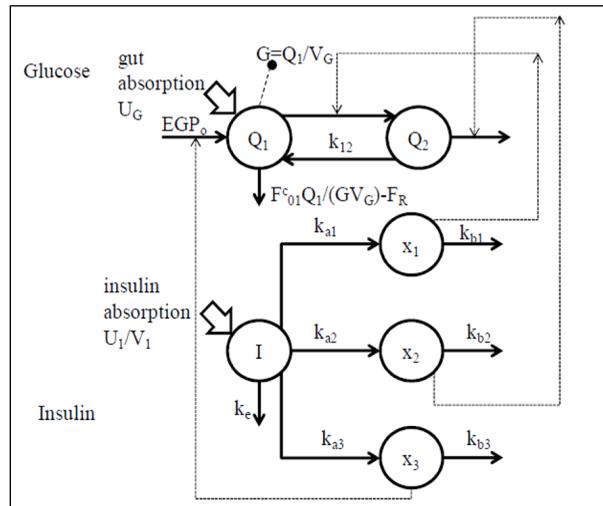

Figure 1. Schematic diagram of Hovorka model

METHODOLOGY

Hovorka Model with Modified Equations

Some of the mathematical equations from the Hovorka model (Hovorka et al., 2004) had been changed and transformed into a set of equations. The transformation of modified Hovorka equations using system identification techniques as previously stated by Yusof et al. (2014) can be clearly seen in Figure 2. As shown in the figure, it depicts a solid improvement in interactions and interrelations of all parameters and variables involved in glucose-insulin dynamics system using the modified Hovorka equations. By employing the system identification technique and modifying related equations, 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.
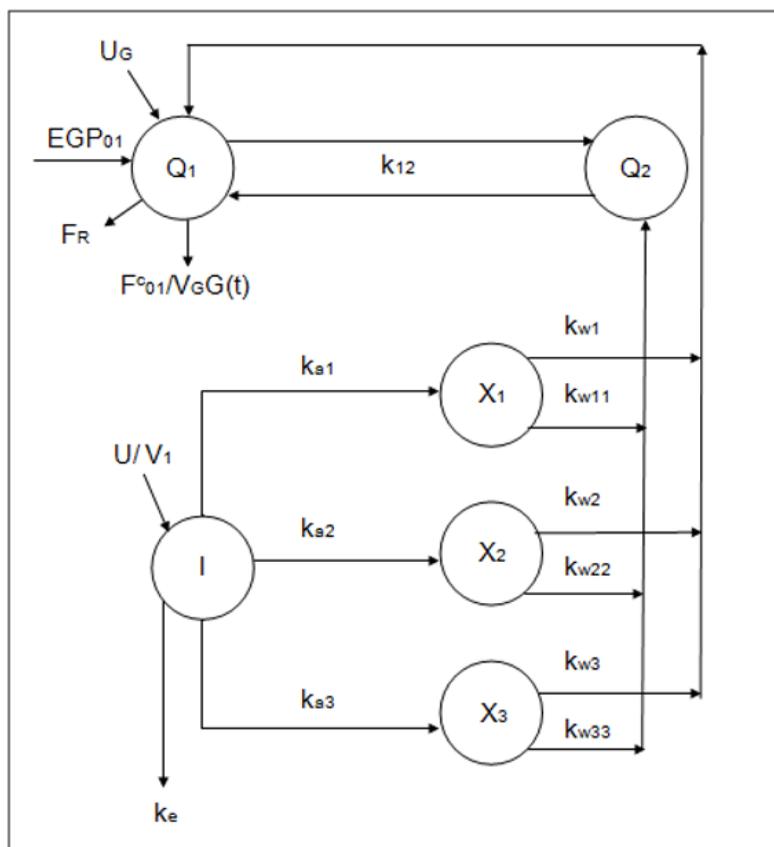

Figure 2. Schematic diagram of Hovorka model with modified equations

Subsequently, some related equations in the Hovorka model have been modified in certain subsystems of the model. The modified equations take place, namely in glucose subsystem, plasma insulin concentration, and insulin action 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 equations (1) and (2) as follows:

$$\frac{dQ_1}{dt} = EGP_o + U_G + 0.01\,Q_2 + [x_1 k_{w1} + x_2 k_{w2} + x_3 k_{w3}] - F_R Q_1 - \left[\frac{F_{01}^C}{V_G G(t)}\right] Q_1 - 0.002 Q_1 \qquad [1]$$

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

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 (Hovorka et al., 2004).

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

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

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.

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

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

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) in which 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.

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

Meanwhile, equations (6) to (8) represent 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.

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

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

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

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 Tables 1 and 2, respectively (Yusof et al., 2012; Yusof et al., 2013; Yusof et al., 2014).

Table 1

The constant values used for modified hovorka equations

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

Table 2

The parameter values used for modified hovorka equations

Symbol	Parameter	Value & Unit
S^f_{IT}	Insulin sensitivity of distribution/ transport	51.2 x 10^{-4} min^{-1} per mU L^{-1}
S^f_{ID}	Insulin sensitivity of disposal	8.2 x 10^{-4} min^{-1} per mU L^{-1}

Table 2 (Continued)

Symbol	Parameter	Value & Unit
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

RESULTS AND DISCUSSION

Simulation work has been done through MATLAB programming as discussed in this section.

Plasma Glucose Concentration

The plasma glucose concentration is simulated based on the amount of insulin administered, U_t. The trends of plasma glucose concentration simulated at U_t of 16.7 mU/min, 20 mU/min, 50 mU/min, 75 mU/min and 100 mU/min are shown in Figure 3.

As shown in Figure 3, the plasma glucose concentration is initialized at 4.5 mmol/L of plasma glucose. The concentration of plasma glucose increased rapidly to the peak point. At certain times, the glucose concentration reduced and became constant. The concentration of plasma glucose achieved normoglycemic condition (4 mmol/L – 6 mmol/L) when the U_t = 16.7 mU/min and U_t = 20 mU/min. On the contrary from the previous study as shown in Figure 4, the simulation of plasma glucose concentration by using Hovorka model with U_t = 16.7 mU/min showed that the concentration was too high and could cause hyperglycaemia (Yusof et al., 2015). The difference in both simulation results was due to the improved model from glucose subsystem in accessible compartment and non-accessible compartment as stated by Yusof et al. (2012).

Both U_t = 16.7 mU/min and U_t = 20 mU/min were regulated at constant blood glucose level at different times. When U_t = 16.7 mU/min was infused to the body, the blood glucose level of 5 mmol/L was achieved at 343 minutes and it remained constant throughout the simulation work. However, the infusion of insulin to the body at U_t = 20 mU/min showed that the blood glucose level of 4 mmol/L was achieved at 210 minutes and it remained constant thereafter. Thus, the 20 mU/min of insulin administered had achieved constant blood glucose level faster than the 16.7 mU/min of insulin. The plasma glucose concentrations for 50 mU/min, 75 mU/min and 100 mU/min of insulin administered had reached lower peak glucose concentrations compared to 16.7 mU/min and 20 mU/min. These amounts of administered insulin had reached constant blood glucose level at earlier times than the lower administered insulin. However, this condition could lead to prolonged hypoglycaemia due to constantly lower blood glucose levels (less than 4 mmol/L)

throughout the simulation work (Bilous et al., 2010). From the previous Hovorka model simulation as shown in Figure 4, the higher administered insulin amount showed that the blood glucose level was regulated at normoglycemia level (Yusof et al., 2015). In this study, it shows that the lower administered insulin amount can regulate at normoglycemia level but it takes some time.
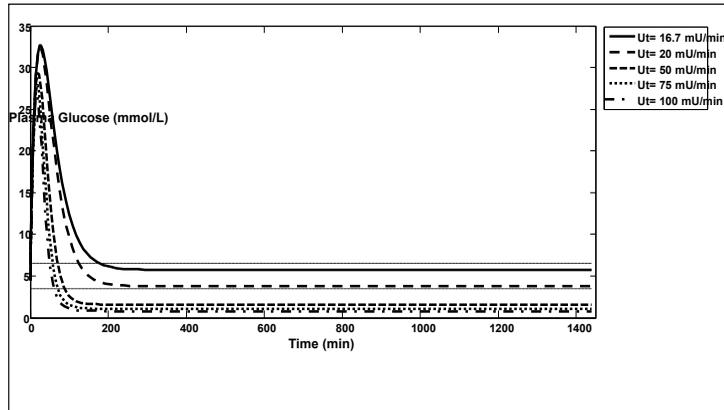

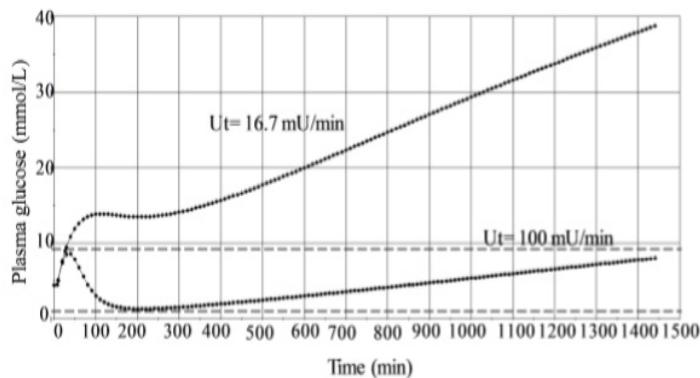*Figure 3.* Plasma glucose concentration using modified Hovorka equations

Figure 4. Plasma glucose concentration using Hovorka model

Plasma Insulin Concentration

The plasma insulin concentration was identified by simulating U_t at 16.7 mU/min, 20 mU/min, 50 mU/min, 75 mU/min and 100 mU/min, respectively. The trends of plasma insulin concentration simulated at these administered U_t are shown in Figure 5.

As shown in Figure 5, the plasma insulin concentration started at 15 mU/L of plasma insulin. The concentration of plasma insulin increased with time and it remained constant thereafter at certain times for all the administered insulins under study.

The plasma insulin concentration reached 900 mU/L and remained constant after 300 minutes for U_t at 16.7 mU/min. Meanwhile, the simulation work for plasma insulin concentration for U_t at 100 mU/min achieved its steady state (remained constant) at 400 minutes and reached as high as 5500 mU/L of its plasma insulin concentration. Thus, the lower amount of insulin infused to the body would cause the plasma insulin concentration to be lower than when the higher amount of insulin was administered. In addition, the time taken for plasma insulin concentration to achieve its steady state was lower when the insulin administered amount was low.

Different administered insulin amounts have shown different performances as depicted in Figure 5. This was due to the different amount of insulin infused in the body. When the infusion rate of insulin was higher, the plasma insulin concentration became higher and the time taken for the plasma insulin concentration to reach its steady state was longer.

The trend shown was the same as previously studied by Yusof et al. (2015) through simulation works using the Hovorka equations as shown in Figure 6. Plasma insulin concentration increased as the time increased. However, the plasma insulin concentration for the modified Hovorka equations reached its steady state at a shorter time as compared to the one in the previous work by Yusof et al. (2015). This result was in agreement with the simulation work as carried out by Yusof et al. (2012) using the modified Hovorka equations for x_1, x_2 and x_3 as shown in Figures 7, 8 and 9, respectively.
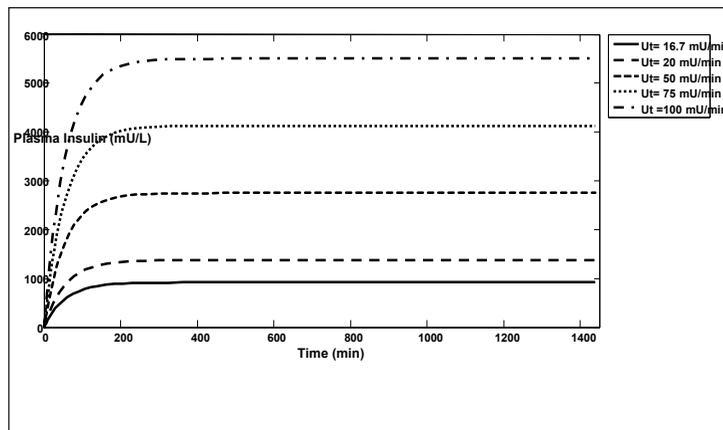

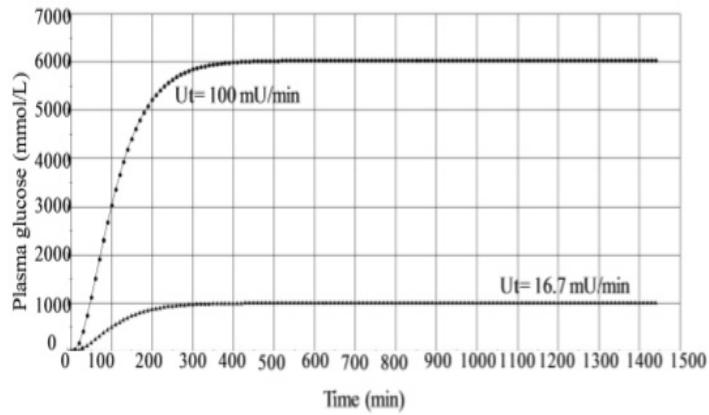*Figure 5*. Plasma Insulin concentration using modified Hovorka equations

Figure 6. Plasma insulin concentration using Hovorka model equations

Hovorka model   Modified Hovorka
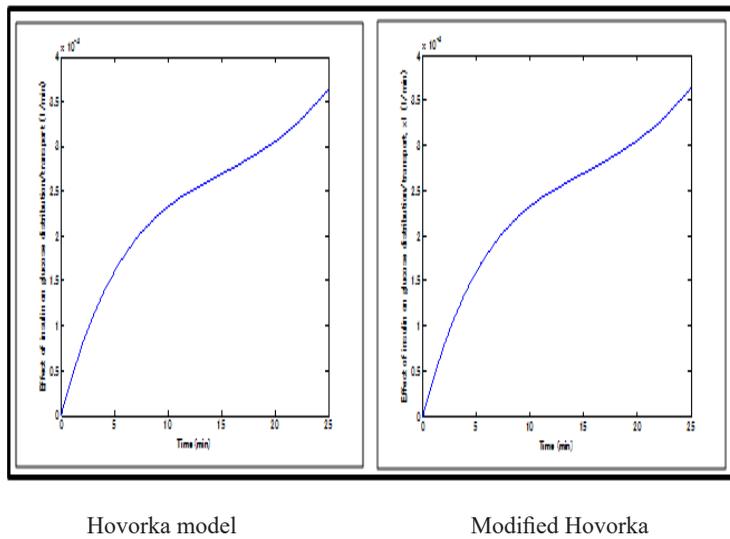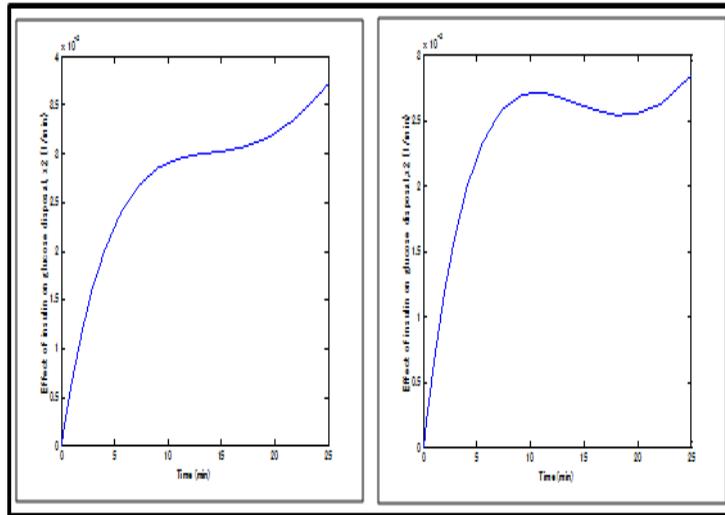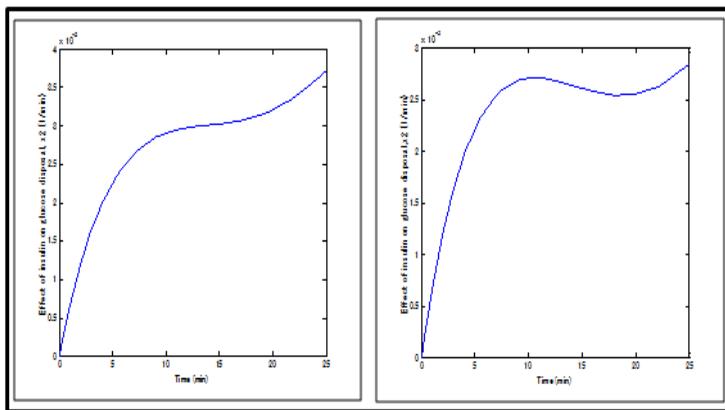
Figure 7. Effect of insulin on glucose distribution/transport, x_1 between Hovorka model and modified Hovorka equations

Hovorka model   Modified Hovorka

Figure 8. Effect of insulin on glucose disposal, x_2 between Hovorka model and modified Hovorka equations

Hovorka model   Modified Hovorka equations

Figure 9. Effect of insulin on endogenous glucose production, x_3 between Hovorka model and modified Hovorka equations

CONCLUSION

The present study showed simulation work for the modified Hovorka equations so as to improve the interaction and interrelation among all parameters and variables on the glucose-insulin dynamic system. The U_t was the most active parameter. Thus, two insulins administered, U_t namely at 16.7 mU/min and 20 mU/min were chosen as they gave the best effect on glucose-insulin dynamic system.

The analysis showed that these lower U_t at 16.7 mU/min and 20 mU/min could regulate the blood glucose level at 5 mmol/L and 4 mmol/L, respectively. This condition was called

normoglycemia in which the blood glucose level was in the safe range. Meanwhile, the higher U_t might have led to hypoglycaemia due to lower blood glucose level, although they had achieved a constant blood glucose level faster than the higher U_t. In addition, the plasma insulin concentration increased as time increased when the U_t was infused to the body. It achieved its steady state after 300 minutes and 400 minutes for U_t at 16.7 mU/min and 100 mU/min, respectively. The higher U_t infused to the body would cause the plasma insulin concentration to be relatively higher.

Based on the overall results, it can be concluded that all parameters and variables in the modified Hovorka equations took part in the simulation work. Hence, the interaction among the parameters and variables in glucose-insulin dynamic system was much better as compared to the original Hovorka equations. The simulation results showed that the blood glucose level was better controlled in its steady state when the modified Hovorka equations were applied in the simulation work. The modified Hovorka equations showed that the lower U_t at 16.7 mU/min and 20 mU/min could achieve a safe range of blood glucose level and lower plasma insulin concentration compared to the original Hovorka equations. For future work, it is recommended to conduct simulation works with meal disturbance using the modified Hovorka equations so as to observe its performance and applicability.

ACKNOWLDGEMENTS

REFERENCES

Bilous, R. W., Donnelly, R., & Williams, G. (2010). *Handbook of diabetes* (4th Ed.). Chichester, England: Wiley Blackwell.

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

Forlenza, G. P., Buckingham, B., & Maahs, D. M. (2016). Progress in diabetes technology: developments in insulin pumps, continuous glucose monitors, and progress towards the artificial pancreas. *The Journal of Pediatrics*, *169*, 13-20.

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.

Hovorka, R., Wilinska, M. E., Chassin, L. J., & Dunger, D. B. (2006). Roadmap to the artificial pancreas. *Diabetes Research and Clinical Practice*, *74*, S178-S182.

Hovorka, R., Allen, J. M., Elleri, D., Chassin, L. J., Harris, J., Xing, D., & Dunger, D. B. (2010). Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. *The Lancet*, *375*(9716), 743-751.

Messori, M., Cobelli, C., & Magni, L. (2015). Artificial pancreas: from in-silico to in-vivo. *IFAC-PapersOnLine*, *48*(8), 1300-1308.

Thabit, H., & Hovorka, R. (2012). Closed-loop insulin delivery in type 1 diabetes. *Endocrinology and Metabolism Clinics, 41*(1), 105-117.

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

Yusof, N. F., Som, A. M., Ibrehem, A. S., & Ali, S. A. (2012, December 17-19). Parameter addition in interaction of glucose and insulin for type 1 diabetes. In *2012 IEEE EMBS Conference on Biomedical Engineering and Sciences (pp.* 273-278). Langkawi, Malaysia.

Yusof, N. F. M., Som, A. M., Ibrehem, A. S., & Ali, S. A. (2013). A review of mathematical model describing insulin delivery system for type 1 diabetes. *Journal of Applied Sciences, 14*, 1465-1468.

Yusof, N. F. B. M., Som, A. M., Ibrehem, A. S., & Ali, S. A., (2014). System identification in modified diabetic model for nanochip controller. *Advanced Materials Research, 938*, 299-304.

Yusof, N. F., Som, A. M., Ali, S. A., & Anuar, A. L. A. H. (2015). Simulation work for the control of blood glucose level in type 1 diabetes using hovorka equations. *Advanced Materials Research, 1113*, 739-744.