In-Silico Works on the Control of Blood Glucose Level for Type 1 Diabetes Mellitus (T1DM) Using Improved Hovorka Equations

Ayub Md Som, Nur Farhana Mohd Yusof, Sherif Abdulbari Ali, Nur'Amanina Mohd Sohadi, and Amar Mohd Maarof
Faculty of Chemical Engineering, Universiti Teknologi MARA (UiTM), 40450 Shah Alam, Selangor, Malaysia
Email: {ayub522, abdulbari}@uitm.edu.my, {ninasohadi, amarmohdmaarof}@gmail.com, nurfarhana2002@yahoo.com

Noor Shafina Mohd Nor
Paediatric Department, Faculty of Medicine, Universiti Teknologi MARA (UiTM), Sungai Buloh Campus, Jalan Hospital, 47000 Sungai Buloh, Selangor, Malaysia
Email: drshafina@uitm.edu.my

***Abstract*—Artificial pancreas technology has been continuously developed over the past few years. However, there are still weaknesses found in recent technology in relation to injection of insulin subcutaneously into Type 1 Diabetes Mellitus (T1DM) patient. The injection of insulin into the patient's body must be specific, exact and precise to ensure that the blood glucose level is between normoglycemic ranges, i.e. 4.5 mmol/L to 6.0 mmol/L so as to avoid hypoglycemia and hyperglycemia episodes. Therefore, this study aims to find the optimum insulin infusion rate into the patient's body for the blood glucose level (BGL) to be maintained at a safe glycemic range. The study mainly focuses on computer simulation in MATLAB using improved Hovorka equations coupled with an enhanced model predictive control (eMPC) as its control scheme in order to control the BGL in T1DM. Only meal disturbance factor is included and it varies in carbohydrate (CHO) intake during breakfast, lunch and dinner times. The simulation was successfully carried out and its findings indicated that the safe glycemic range was able to be reached at shorter time and maintained for a prolonged period as compared to previous workers.**

***Index Terms*—type 1 diabetes mellitus, Hovorka model, in silico works, model predictive control**

I. Introduction

Type 1 Diabetes Mellitus (T1DM) is a chronic illness that is characterized by chronic immune-mediated destruction of pancreatic β-cells and hence leads to partial, or in most cases, absolute insulin deficiency [1]. T1DM patients have to depend on exogenous insulin injection multiple times daily in order to bring down their blood glucose level (BGL). A correct dosage of insulin has to be determined to prevent the occurrence of hypoglycemia and hyperglycemia as both conditions are unfavourable for the patient. Hypoglycemia can be clinically diagnosed through symptoms such as sweating, tachycardia and blurred vision. Severe hypoglycemia could lead to severe morbidity and mortality if not treated immediately. Symptoms of hyperglycemia can be seen when the patient experiences increased thirst, polydipsia and polyuria. Developing an Artificial Pancreas (AP) will help in automating Continuous Subcutaneous Insulin Infusion (CSII) task to prevent both episodes in a closed loop manner. The control algorithm in AP should be able to measure and predict the accurate flow rate and amount of insulin infusion to regulate BGL within normoglycemic range in the closed loop system. Established glucose-insulin dynamic models such as Bergman minimal model [2], Dalla Man model [3] and Hovorka model [4] have been used to describe glucose-insulin dynamics system for T1DM patient.

A modification of Hovorka model equations, also known as improved Hovorka equations, was carried out as in [5]-[8] using system identification techniques. In the improved model, the interrelations between parameters and its specific subsystems (i.e. glucose subsystem, insulin action subsystem and plasma insulin subsystem) were improvised [8], [9] which gave better performance in controlling BGL fluctuations for T1DM.

Handfuls of controller system such as Artificial Neural Network (ANN) [10]-[14], Fuzzy Logic Control (FLC) [15]-[19], and Proportional Integral Derivative (PID) controller were initially employed in AP research. However, Model Predictive Control (MPC) has nowadays started gaining more attention than others as the most suitable control scheme used in regulating BGL for T1DM [20]-[24]. The main objectives of this study are namely: 1) to simulate the BGL of T1DM patients based on variations in their meal intake using the improved equations, and 2) to determine the optimum insulin infusion rate so as to achieve BGL at shorter time and maintain it at

Manuscript received July 12, 2020; revised September 1, 2020.

doi: 10.18178/ijpmbs.9.4.144-151

normoglycemic range for a prolonged period. The study limitations include single hormone used i.e. insulin and only meal intake was taken as a disturbance.

II. Methodology

The model used is Hovorka model with modified Hovorka equations [8], [9]. Parameters, constant values and CHO intakes were taken from Hovorka Model [4], Modified Hovorka equations and real life T1DM patients' data are as defined respectively in Table I, Table II and Table III. Using system identification techniques, the original mathematical equations from Hovorka Model were firstly enhanced into a new set of equations to improve the interrelation between glucose and insulin action subsystem. Schematic diagram depicting Hovorka equations and modified Hovorka equations are shown in Fig. 1 and Fig. 2, respectively. The modified Hovorka equations improve the parameters interaction within its glucose subsystem, insulin action subsystem and plasma insulin subsystem by adding the insulin on action transport (x1), insulin on action disposal (x2) and insulin on endogenous production (x3) in both accessible compartment, Q1 and non-accessible compartment, Q2 [8], [9].

TABLE I. List of Parameters

Parameter's symbol	Descriptions	Value & Unit
S^f_{IT}	Insulin sensitivity of distribution/transport	51.2×10^{-4} min^{-1} per mU L^{-1}
S^f_{ID}	Insulin sensitivity of disposal	8.2×10^{-4} min^{-1} per mU L^{-1}
S^f_{IE}	Insulin sensitivity of Endogenous Glucose Production (EGP)	520×10^{-4} min^{-1} per mU L^{-1}
EGP_0	EGP extrapolated to zero insulin concentration	0.0161 mmol kg^{-1}min^{-1}
F_{01}	Non-insulin-dependent glucose flux	0.0097 mmol kg^{-1}min^{-1}
$t_{max,I}$	Time-to-maximum of absorption of subcutaneously injected short acting insulin	55 min

TABLE II. List of Constants

Constant's symbol	Descriptions	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_{w2}	Activation rate	50.1 min^{-1}
k_{w3}	Activation rate	50.1 min^{-1}
k_{w11}	Activation rate	−10 min^{-1}
k_{w22}	Activation rate	−0.01 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 (dimensionless)
$t_{max,G}$	Time-to-maximum of CHO absorption	40 min

TABLE III. Carbohydrate (CHO) Intake

Item	g CHO	mol CHO	mmol CHO
Breakfast	60	2.068	2068
Lunch	90	3.102	3102
Dinner	90	3.102	3102

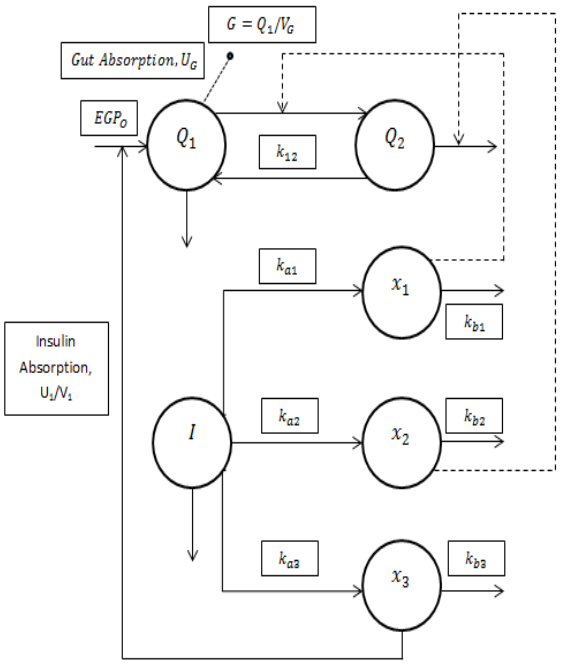

Figure 1. Schematic diagram of Hovorka model.

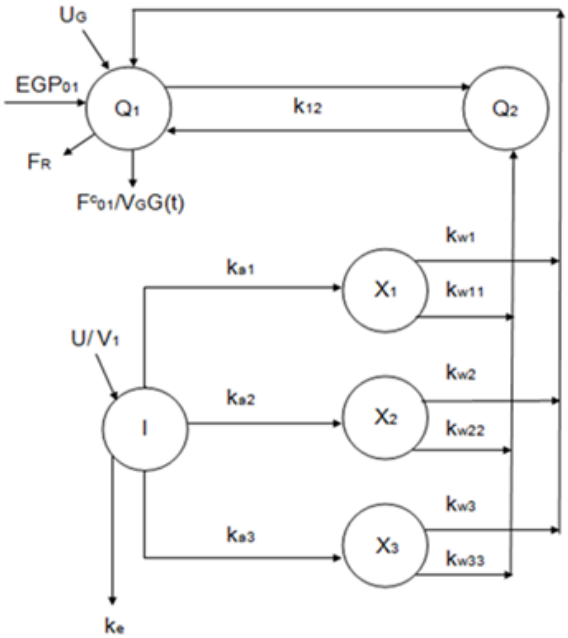

Figure 2. Schematic diagram of improved Hovorka equations from Hovorka model.

The flowchart of the research methodology is described and shown in Fig. 3.

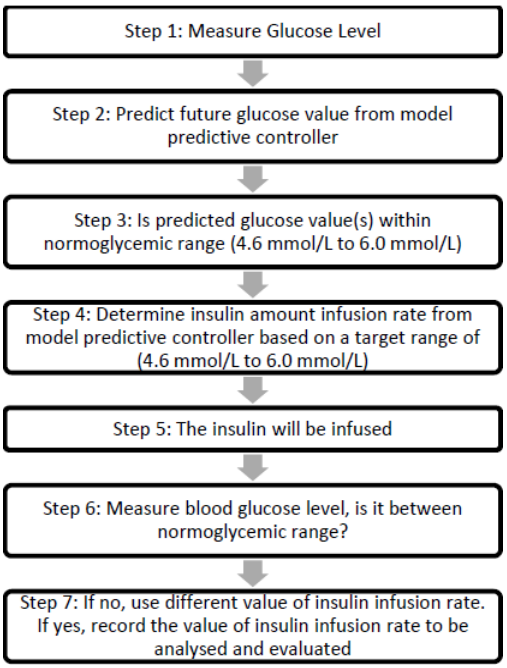

Figure 3. Flowchart of the research methodology.

The equations used in the improved Hovorka model are as follows:

$$\frac{dQ_1}{dt} = EGP_0 + U_G + 0.01Q_2 + [x_1 kw_1 + x_2 kw_2 + x_3 kw_3] - F_R Q_1 - \left[\frac{F_C^{01}}{V_G G(t)}\right] Q_1 - 0.002Q_1 \quad (1)$$

$$\frac{dQ_2(t)}{dt} = [k_{w11}x_1(t) + k_{w22}x_2(t) + k_{w33}x_3(t)] + EGP_0[k_{w1}x_1(t) + k_{w2}x_2(t) + k_{w3}x_3(t)] - k_{12}Q_2 \quad (2)$$

Equations (1) and (2) are the modified Hovorka equations in which the insulin action variables have been added. Q_1 and Q_2 constitute the mass of glucose in the accessible and non-accessible compartments for the glucose subsystem respectively. k_{w1}, k_{w2}, k_{w3}, k_{w11}, k_{w22}, and k_{w33} are the transfer rate constants for the insulin action subsystem. k_{12} is the transfer rate constant from non-accessible compartment to accessible compartment. EGP_0 is the endogenous glucose production that was extrapolated to the zero insulin concentration. U_G is the quantity of glucose absorbed into blood vessel.

Other than that, F_R is renal glucose clearance while F_c^{01} is the total of non-insulin dependent glucose flux.

$$F_C^{01} = \begin{cases} F_{01} \text{ if } G \geq 4.55 \text{ mmolL}^{-1} \\ \frac{F_{01}G}{4.5} \quad \text{otherwise} \end{cases}$$

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

Equations (3) and (4) are the equations for insulin subsystem in the accessible and non-accessible compartment. S_1 and S_2 are insulin sensitivity in the accessible and non-accessible compartment respectively.

$$\frac{dS_1(t)}{dt} = u(t) - \frac{S_1(t)}{t_{max,I}} \quad (3)$$

$$\frac{dS_2(t)}{dt} = \frac{S_1(t)}{t_{max,I}} - \frac{S_2(t)}{t_{max,I}} \quad (4)$$

In plasma insulin concentration equation (5), insulin action variables have also been added. I(t) is the plasma insulin concentration while k_e is the fractional elimination rate. V_I is the distribution volume and U_I is the production amount of insulin required into the blood vessel.

$$\frac{dI(t)}{dt} = \left[\frac{U_1(t)}{V_I}\right] - k_e I(t) - [kw_1 x_1(t) + kw2x_2(t) + kw_3 x_3(t)] \quad (5)$$

$$U_G = \frac{D_G A_G t e^{\frac{t}{t_{max,G}}}}{{t_{max,G}}^2} \quad (6)$$

where:
U_G = two-compartment chain with identical transfer rates $1/t_{max,G}$ (mmol/min)
D_G = meal intake (mmol CHO)
A_G = carbohydrate bioavailability (dimensionless)

The equations (7), (8) and (9) are the insulin action subsystem (I) equations on action transport, action disposal, and endogenous production respectively.

$$\left[\frac{dx_1}{dt}\right] = ka_1 x_1(t) + kw_1 I(t) + kw_{11} I(t) \quad (7)$$

$$\left[\frac{dx_2}{dt}\right] = ka_2 x_2(t) + kw_2 I(t) + kw_{22} I(t) \quad (8)$$

$$\left[\frac{dx_3}{dt}\right] = ka_3 x_3(t) + kw_3 I(t) + kw_{33} I(t) \quad (9)$$

III. Results and Discussion

Fig. 4 shows the simulation results carried out and evaluated using the data from real life patient which include patient's body weight (BW), the instantaneous time during the meal taken (meal time in 24-hour system) and the total amount of meal taken (CHO rate in bolus size, mmol/min).

Other data collected covers the time of insulin injection (Insulin time in 24-hour system) and the amount of insulin dose (Insulin rate in bolus size [mU/min]). Glucose-insulin dynamic was analysed and therefore the simulation was evaluated based on the amount and time of insulin being administered as well as meal intakes (meal disturbance) and how these parameters influence the BGL of the patient.

A. Effect of Insulin Administration on BGL during Meals

As shown in Fig. 4, the first peak is the meal disturbance for breakfast followed by lunch and dinner, respectively. For our simulation, only single hormone (insulin) instead of dual hormone (glucagon) is used to regulate blood glucose level. The hormone that helps in regulating blood glucose level is the insulin which is produced by β-cell of the pancreatic islet of the pancreas. Due to inability of Type 1 diabetes patient to produce insulin because of their malfunctioning pancreas, the glucose inside their body cannot be broken into energy thus increasing BGL within a period of time until they react in a state called hyperglycemia. For our simulation, hyperglycemia is a condition in which the BGL exceeds 6 mmol/L. For three

meal intakes in bolus size per day, a total of three insulin injections in bolus size was administered. The amount of carbohydrate (CHO) intake was taken from real life patient data with the insulin infusion rate was determined manually using semi-closed control loop system. The data was summarised as in Table IV.

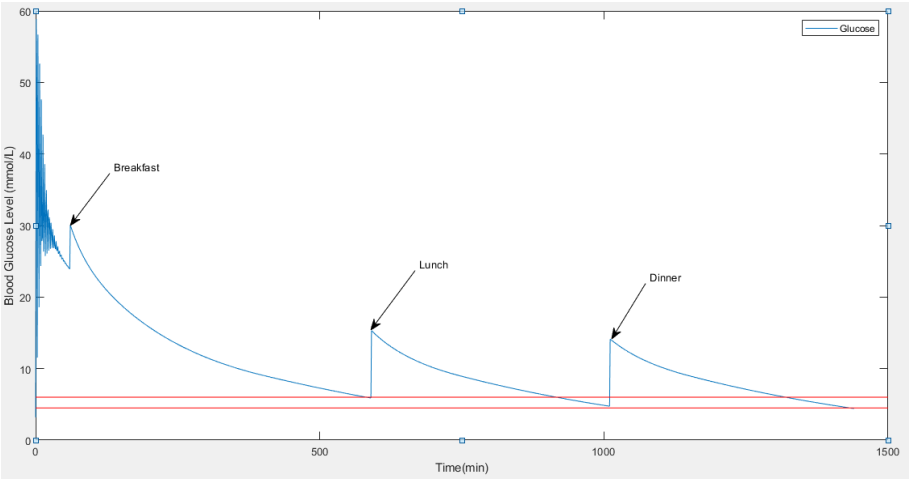

Figure 4. Simulation results for BGL versus insulin infusion rate at 1440 min (24 hours).

TABLE IV. AMOUNT OF MEAL INTAKE AND INSULIN INFUSED

Meal Time (24-hour system)	Meal Time (min)	CHO in bolus size (g)	CHO rate in bolus size (mmol)	Insulin time (24-hour system)	Insulin Time (min)	Insulin rate in bolus size (U/min)
6:00 am	60	60	2068	5:00 am	0	0.0529
3:00 pm	420	90	3102	1:10 pm	420	0.0010
10:00 pm	720	90	3102	9:30 pm	720	0.000001

Bolus insulin is the insulin taken specifically at meal time to keep blood glucose level within normoglycemic range for that particular meal intake. The insulin was taken before meal in this simulation. From Fig. 4, it was observed that the BGL with the insulin administration is more stable than those without insulin administration periodically. However, if no insulin was administered at neither at any time for the day, the BGL will rise up until it reaches hyperglycemia range with no sign of going down. Thus, it will be highly dangerous for the patient as they risk a lot of serious complications due to extremely high BGL. The BGL was compared with previous research, see [8]. However, the meal intake values were not the same as they used meal values from [25].

1) Determining BGL during breakfast

During breakfast as observed in Fig. 5, the patient consumed a lesser amount of CHO compared to lunch and dinner. Therefore, only a little spike of graph indicating that the person had meal intake during that instantaneous time. However, the BGL exceeded the 6 mmol/L range and fluctuated at the beginning because the patient had already experienced the state of hyperglycemia in the morning. This followed the record of the real patient from which the meal data was extracted that the person actually experienced hyperglycemia early in the morning. Comparing the data with [8], the graph seems to fall rightly on the normoglycaemic range whereas the prior research fell short of 10 mmol/L from the normoglycemic range and recorded hyperglycemic state. This is because in current research, we have extended the time gap between breakfast and lunch so as to enable the curve to be in desired range just before lunch. Even though the amount of insulin infused into the patient can be controlled, the ability of the insulin itself to be absorbed fast or slow is highly dependent on the patient itself.

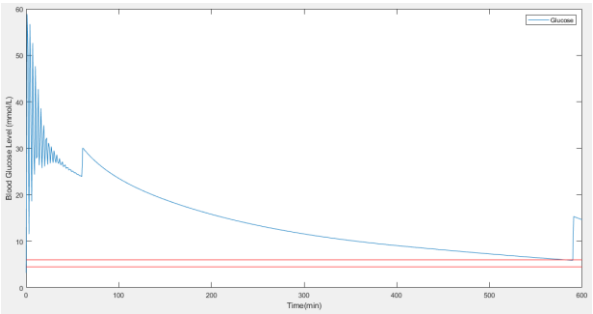

Figure 5. Simulation BGL versus time during breakfast.

2) Determining BGL during lunch

During lunch as observed in Fig. 6, the patient consumed a higher amount of CHO compared to breakfast. Therefore, a higher peak of curve was observed as compared to breakfast when there was a meal disturbance. The amount of insulin infused was lower than those at breakfast time. This is because the amount of insulin as calculated from the algorithm has not been fully utilised. Therefore, it is being used in the next round of meal disturbance. Thus, the graph will keep falling until it reaches normoglycemic range. Prior to the patient experiencing the state of hypoglycemia, there will be another meal disturbance that will eventually increase the BGL. Comparing the result from previous research [8],

previous research had the curve more consistent as compared to current research. This might be due to the low amount of insulin infused during breakfast which leads to more stable curve during dinner. The value of insulin infused could have been more precise as compared to current research. The drawback of this occurrence is that the patient will stay in hyperglycemic state before lunch which is an undesirable and could be in dangerous condition.

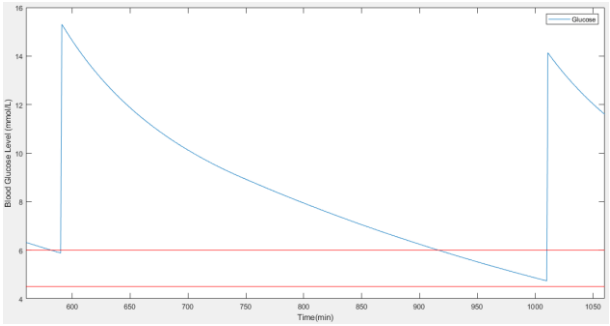

Figure 6. Simulation BGL versus time during lunch.

3) Determining BGL during dinner

During dinner as observed in Fig. 7, the patient consumed relatively the same amount of CHO as in lunch. The peak of curve of the dinner was lower because at the beginning of meal time, the BGL was already at decreased level compared to meal time before lunch. The simulations were done at 24-hour time. Thus, the patient was already backing at 5:00 am (time for another insulin infusion) at the end of dinner time. The patient was supposed to be in state of hyperglycemia according to data; however, it did not happen due to the probability of excess insulin being infused during the simulation. It could also be one of the reasons why BGL keeps falling until the patient wakes up the next morning as the insulin absorption is still ongoing within given period of time. Thus, the simulation might have to be extended to more than one day or one full week to observe the complete change of BGL of the virtual patient.

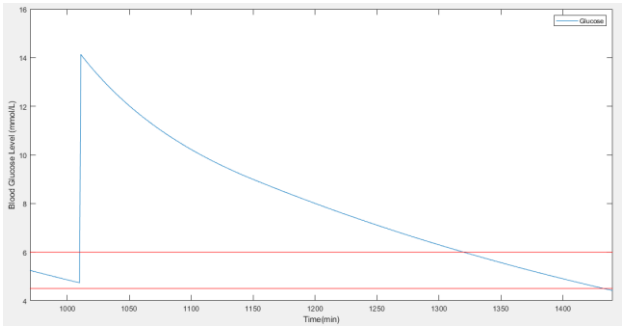

Figure 7. Simulation BGL versus time during dinner.

B. *Effect of Insulin Administration during and after Meal Times on BGL*

The insulin administered time is very important in managing blood glucose level. The time taken for insulin infusion and the time when it is administered, will affect the smoothness of the graph pattern in retaining BGL within normoglycemic range. The insulin administered for the first meal disturbance simulation is 60 minutes before meal time. The second one is during meal and third one is after meal. As shown in Fig. 4, the BGL profile looks better with prior injection of insulin before any meal intake. Although the BGL did not drop immediately, the time taken for BGL to reach normoglycemic range was also quite lengthy. The results have to be compared with the data of real time patient BGL corresponding to their insulin infusion as in the simulation. We need to take note that for continuous subcutaneous insulin injection, the time taken for insulin absorption is much higher as compared to CHO absorption. Therefore, there is a need to prior injection of insulin before meal is taken. There are variety types of insulin in the market today and the accessibility of each patient to specific type of insulin might vary from one to the other in terms of fast or slow acting insulin. These variations would have affected the value of glucose absorption rate, U_G. For the purpose of this simulation, the insulin we are currently using is a slow acting type of insulin. For the slow acting, the longer the gaps between meal intake and insulin infusion, the better control we have on making and retaining the BGL within normoglycemic range.

1) Insulin infusion during meal time

As shown in Fig. 8, the graph had shown undesirable outcome whereas none of the BGL dropped to normoglycemic range for infusion of insulin during meal. This is because the insulin needs some time to react. The insulin inside the body has to react with the components of glucose, which in turns take an undefined condition although predictable amount of time required to convert them into energy. The graph however shows steady and consistent flows although it exceeds normoglycemic range between 9 to 12 mmol/L. It is still unknown why the graph had been more stable when the insulin was injected during meal time. Theoretically, it could have been the presence of CHO during meal which allows more insulin to react at a higher rate compared to infusion before meal. To compensate the inconsistency in the profile of the graph, it is recommended to increase the amount of insulin infusion rate during meal.

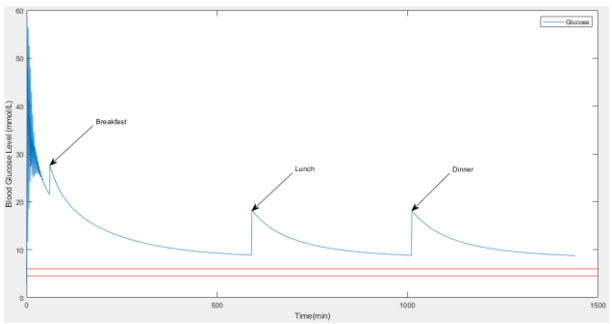

Figure 8. Insulin infusion during meal time.

2) Insulin infusion after meal time

From Fig. 9, it was seen that the addition of insulin after meal time did not show any significant difference after comparing it with the graph during meal time as shown in Fig. 8. The difference is very slight therefore it can be concluded that both profiles during and after the meal are

the same. The insulin design for these equations and its parameter values are meant for short acting insulin. It is therefore recommended that for sensitivity towards insulin absorption, these equations might need to be modified for simulation purposes that use quick or fast acting insulin in the future works.

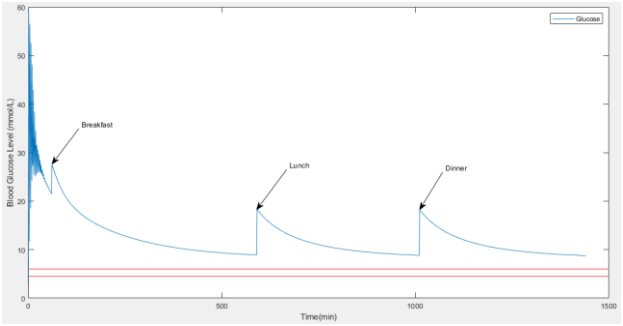

Figure 9. Insulin infusion after meal time.

C. Effect of Meal Disturbance during Snack Time

There are possible meal disturbances at snack time which need to be observed in order to have better control on a BGL curve since insulin is the only hormone simulated to control the BGL in this simulation study with the improved equations. In addition, there is currently no real time artificial pancreas that is capable of delivering dual hormones (i.e. insulin and glucagon) other than the 4th generation artificial pancreas which uses insulin and pramlintide hormones (substitute hormone that acts such as glucagon). Table V shows the amount of CHO consumed during snack times 1 and 2 taken after lunch and dinner, respectively. Table VI shows the insulin time and insulin infusion rate during the snack times. The profile of BGL curve after meal disturbance during the snack times is shown in Fig. 10.

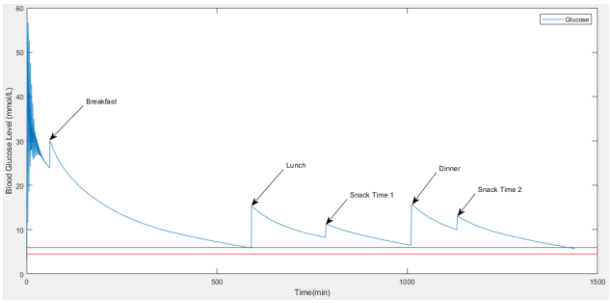

Figure 10. Addition of snack time after lunch and dinner.

From Fig. 10, the graph shows that the curve of the BGL is slightly changed due to addition of snack times. The addition of snack time has improved the BGL curve for dinner by letting not to be so near to below normoglycemic range as compared to the graph profile without snack time. However, the BGL curve for lunch was slightly deviated by exceeding normoglycemic range at mmol/L. The change is not significant and not far from ideal range which is between 4.5 mmol/L until 6.0 mmol/L. Thus, it can be said that the additions of snack times do improve the BGL curve significantly for dinner while not deviating the BGL curve part during breakfast and lunch meal intakes. An improvement is suggested by adjusting the value of insulin infusion during breakfast or lunch that are not carried out in this simulation study.

TABLE V. SNACK TIME AND SNACK BOLUS RATE

Snack time (24-hour system)	Snack time (min)	CHO in bolus size (g)	CHO rate in bolus size (mmol)
6:00 pm	785	30	1033
12:00 pm	1130	30	1033

TABLE VI. INSULIN TIME AND INSULIN INFUSION RATE

Insulin time (24-hour system)	Insulin time (min)	Insulin rate in bolus size (U/min)
5:30 pm	725	0.001
11:30 pm	1070	0.000

D. Effect of Semi-closed Model Predictive Control Loop System on BGL

In this simulation work, a semi-closed loop system of Model Predictive Control (MPC) was implemented in order to obtain better control of BGL of the virtual TID patient body. The outcome for this control is seen as in the graphs for which the BGL's were within normoglycemic range prior to next meals. However, the BGL value before meal was slightly hypoglycemic by 0.1 decimal points for breakfast and lunch. The time window before the next meal was highly important because the BGL would not have dropped to a desired range if the time window had not been extended from its usual range. It is however managed to predict the right dose for insulin in order to lower the BGL within normoglycemic range by reducing the errors ± 0.9 in 24-hours simulation time.

E. Effect of Simulation in MATLAB Using ODE45, ODE23s and ODE 15

For this simulation work, the equations used are modified Hovorka equations instead of original Hovorka equations. Hovorka equations were classified as non-stiff equations [26]. The simulations were first run using ODE Solver of ODE45 and ODE23s which are frequently used for stiff ordinary differential equations (ODE). A smoother curve plot was obtained when the simulations were run using ODE15. ODE15 is an ODE Solver that is used for stiff equations. It can be said that the equations of original Hovorka were partly modified and the improved equations may be suggested as stiff ODE rather than non-stiff ODE.

IV. RESULTS AND DISCUSSION

In summary, the simulation work was successfully carried out in different conditions to observe and evaluate the differences in blood glucose control (BGC) under a wide variety of conditions. Other than that, the implementations of Model Predictive Control in semi-closed loop system can contribute to better control of BGL for the virtual patients that use real life data for meal disturbance parameters in the simulation. Glucose-insulin dynamics were being observed as having smoother although demonstrated lengthy curve when the equations

used were modified Hovorka equations in the simulation study. For future works, it is recommended to study the impact of using different values of initial variables or parameters to control BGL in the simulation for the virtual patient. It is also high time for a comparative study to be carried out to compare results obtained between clinical and simulation works in treating T1DM patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Amar Mohd Maarof, Nur'Amanina Mohd Sohadi and Nur Farhana Mohd Yusof conducted the programming works; Ayub Md Som, Noor Shafina Mohd Nor and Sherif Abdulbari Ali analysed the data and supervised the overall research works; Ayub Md Som and Amar Mohd Maarof wrote the paper; all authors had approved the final version of the paper.

ACKNOWLEDGMENT

The authors wish to acknowledge and extend their gratitude to the Malaysian Ministry of Higher Education and Institute of Research Management & Innovation (IRMI), Universiti Teknologi MARA (UiTM) for the financial support (600-IRMI/DNA 5/3/BESTARI (060/2017)). The authors would also like to thank the Faculty of Chemical Engineering and Faculty of Medicine, UiTM for all the support and assistance given in conducting this study.

REFERENCES

[1] J. Mayer-Davis, A. Kahkoska, C. Jefferies, D. Dabelea, N. Balde, C. Gong, *et al.*, "ISPAD clinical practice consensus guidelines 2018: Definition, epidemiology, and classification of diabetes in children and adolescents," *Pediatr. Diabetes*, vol. 19, suppl. 27, pp. 7-19, June 2018.

[2] S. M. Lynch and B. W. Bequette, "Model predictive control of blood glucose in type I diabetics using subcutaneous glucose measurements," in *Proc. Am. Control Conf.*, 2002, pp. 4039-4043.

[3] C. D. Man, R. A. Rizza, and C. Cobelli, "Meal simulation model of the glucose-insulin system," *IEEE Trans. Biomed. Eng.*, vol. 54, no. 10, pp. 1740-1749, 2007.

[4] R. Hovorka, V. Canonico, L. J. Chassin, U. Haueter, M. Massi-Benedetti, M. O. Federici, *et al.*, "Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes," *Physiol. Meas.*, vol. 25, no. 4, pp. 905-920, 2004.

[5] N. F. M. Yusof, A. M. Som, A. S. Ibrehem, and S. A. Ali, "Parameter addition in interaction of glucose and insulin for type 1 diabetes," in *Proc. IEEE-EMBS Conf. Biomed. Eng. Sci.*, 2012, pp. 273-278.

[6] N. F. M. Yusof, A. M. Som, A. S. Ibrehem, and S. A. Ali, "A review of mathematical model describing insulin delivery system for type 1 diabetes," *J. Appl. Sci.*, vol. 14, no. 13, pp. 1465-1468, 2014.

[7] N. F. M. Yusof, A. Md Som, A. S. Ibrehem, and S. Abdulbari Ali, "System identification in modified diabetic model for nanochip controller," *Adv. Mater. Res.*, vol. 938, pp. 299-304, 2014.

[8] A. M. Som, N. F. M. Yusof, S. A. Ali, and N. S. Fuzil, "Meal disturbance effect on blood glucose control for type 1 diabetes using improved Hovorka equations," *Key Eng. Mater.*, vol. 797, pp. 158-167, 2019.

[9] A. M. Som, N. F. M. Yusof, S. A. Ali, and N. Zawawi, "Simulation work on blood glucose control for type 1 diabetes using modified hovorka equations," *Pertanika J. Sci. Technol.*, vol. 27, no. 4, pp. 1527-1538, 2019.

[10] M. I. D. Bock, A. Roy, M. N. Cooper, J. A. Dart, C. L. Berthold, A. J. Rettrath, *et al.*, "Feasibility of outpatient 24-hour closed-loop insulin delivery," *Diabetes Care*, vol. 38, no. 11, pp. e186-e187, 2015.

[11] A. K. El-Jabali, "*Neural* network modeling and control of type 1 diabetes mellitus," *Bioprocess Biosyst. Eng.*, vol. 27, no. 2, pp. 75-79, 2005.

[12] J. F. D. Canete, S. Gonzalez-Perez, and J. C. Ramos-Diaz, "Artificial neural networks for closed loop control of in silico and ad hoc type 1 diabetes," *Comput. Methods Programs Biomed.*, vol. 106, no. 1, pp. 55-66, 2012.

[13] P. G. Jacobs, J. E. Youssef, J. Castle, P. Bakhtiani, D. Branigan, M. Breen, *et al.*, "Automated control of an adaptive bihormonal, dual-sensor artificial pancreas and evaluation during inpatient studies," *IEEE Trans. Biomed. Eng.*, vol. 61, no. 10, pp. 2569-2581, 2014.

[14] G. M. Steil, C. C. Palerm, N. Kurtz, G. Voskanyan, A. Roy, S. Paz, *et al.*, "The effect of insulin feedback on closed loop glucose control," *J. Clin. Endocrinol. Metab.*, vol. 96, no. 5, pp. 1402-1408, 2011.

[15] S. M. Gharghory and D. A. El-Dib, "Fuzzy control system for regulating the blood glucose level of diabetes patients implemented on FPGA," *J. Circuits. Syst. Comput.*, vol. 25, no. 12, pp. 1-17, 2016.

[16] P. Grant, "A new approach to diabetic control: Fuzzy logic and insulin pump technology," *Med. Eng. Phys.*, vol. 29, no. 7, pp. 824-827, 2007.

[17] M. S. Ibbini and M. A. Masadeh, "A fuzzy logic based closed-loop control system for blood glucose level regulation in diabetics," *J. Med. Eng. Technol.*, vol. 29, no. 2, pp. 64-69, 2005.

[18] R. Mauseth, S. M. Lord, I. B. Hirsch, R. C. Kircher, D. P. Matheson, and C. J. Greenbaum, "Stress testing of an artificial pancreas system with pizza and exercise leads to improvements in the system's fuzzy logic controller," *J. Diabetes Sci. Technol.*, vol. 9, no. 6, pp. 1253-1259, 2015.

[19] M. Phillip, T. Battelino, E. Atlas, and O. Kordonouri, "Nocturnal glucose control with an artificial pancreas at a diabetes camp," *N. Engl. J. Med.*, vol. 368, no. 9, pp. 824-833, 2013.

[20] A. Chakrabarty, S. Zavitsanou, F. J. Doyle, and E. Dassau, "Event-triggered model predictive control for embedded artificial pancreas systems," *IEEE Trans. Biomed. Eng.*, vol. 65, no. 3, pp. 575-586, 2018.

[21] G. P. Forlenza, F. M. Cameron, T. T. Ly, D. Lam, D. P. Howsmon, N. Baysal, *et al.*, "Fully closed-loop multiple model probabilistic predictive controller artificial pancreas performance in adolescents and adults in a supervised hotel setting," *Diabetes Technol. Ther.*, vol. 20, no. 5, pp. 335-343, 2018.

[22] J. B. Lee, E. Dassau, R. Gondhalekar, D. E. Seborg, J. E. Pinsker, and F. J. Doyle, "Enhanced model predictive control (eMPC) strategy for automated glucose control," *Ind. Eng. Chem. Res.*, vol. 55, no. 46, pp. 11857-11868, 2016.

[23] L. Magni, D. M. Raimondo, L. Bossi, C. D. Man, G. De Nicolao, B. Kovatchev, *et al.*, "Model predictive control of type 1 diabetes: An in silico trial," *J. Diabetes Sci. Technol.*, vol. 1, no. 6, pp. 804-812, 2007.

[24] J. E. Pinsker, J. B. Lee, E. Dassau, D. E. Seborg, P. K. Bradley, R. Gondhalekar, *et al.*, "Response to comment on pinsker *et al. randomized* crossover comparison of personalized MPC and PID control algorithms for the artificial pancreas. diabetes care 2016; 39:1135-1142," *Diabetes Care*, vol. 40, no. 1, pp. e4-e5, 2017.

[25] N. Atikah, M. Daud, F. Mahmud, and M. H. Jabbar, "Meal simulation in glucose-*insulin* reaction analysis using hovorka model towards system-on-chip implementation," *Arpn J. Eng. Appl. Sci.*, pp. 1-8, 2015.

[26] D. Boiroux, M. Hagdrup, Z. Mahmoudi, N. K. Poulsen, H. Madsen, and J. B. Jørgensen, "Model identification using continuous glucose monitoring data for type 1 diabetes," *IFAC-Papers OnLine*, vol. 49, no. 7, pp. 759-764, 2016.

Ayub Md Som (PhD CEng FIChemE) was born in Selangor, Malaysia in 1964. He received his BSc Degree in Chemical Engineering from Mississippi State University in USA (1986), MSc Degree in Chemical Engineering from University of Manchester (formerly known as UMIST) in 1995 and PhD in Environmental Engineering from University of Southampton, United Kingdom in 1998. His research interest includes artificial pancreas algorithm, process systems engineering, decision support system, plant-based coagulants, natural antioxidants, and wastewater engineering. He is currently attached as an Associate Professor at the Faculty of Chemical Engineering, Universiti Teknologi MARA (UiTM), Shah Alam, Selangor, Malaysia.

Noor Shafina Mohd Nor (MB BCh BAO BMedSc (Ireland), MRCP Paediatrics (Ireland)) was born in Penang, Malaysia in 1980. She graduated with a medical degree from National University of Ireland (2005). She was awarded Membership of the Royal College Physicians of Ireland in Paediatrics (2009) and National Specialist Register (NSR) in General Paediatric (2010) and Paediatric Endocrinology (2015). She is currently an Associate Professor and Consultant Paediatric Endocrinologist at the Faculty of Medicine, UiTM Sungai Buloh Campus, Malaysia.

Nur Farhana Mohd Yusof was born in Pahang, Malaysia in 1983. She obtained her PhD in Chemical Engineering from Universiti Teknologi MARA (UiTM) in 2019, Bachelor of Engineering (Hons.) in Materials and Life Science System Engineering (2008) from University of Toyama, Toyama, Japan, and Diploma in Chemical and Biochemical Engineering in 2006 from Toyama National College of Technology, Toyama, Japan. She studied the Japanese Language in Pusat Persediaan Kajian Teknikal Ke Jepun, Universiti Teknologi Malaysia, Kuala Lumpur in 2001 and continued her Japanese preparation course in The Japanese Language School of the International Students Institute, Shinjuku, Japan in 2002.

Sherif Abdulbari Ali was born in Cairo, Egypt in 1977. He received his BSc in Computer Science major in computer science (1999) from The Higher Institute for Specific Research, Cairo, Egypt. Then, he attended Universiti Putra Malaysia (UPM), where he was awarded a Master's degree in Computer Security major in cryptography (2006) and PhD in Artificial Intelligence major in natural language processing (2010). His main area of research interest includes artificial intelligence, computer security, control processing, safety risk assessment, and waste management. Presently, he is a Senior Lecturer of the Faculty of Chemical Engineering, UiTM Shah Alam.

Nur'Amanina Mohd Sohadi was born in Selangor, Malaysia in 1994. She received her Bachelor of Engineering (Hons.) Chemical in 2019 from Universiti Teknologi MARA (UiTM) Shah Alam. She is currently pursuing her Master's degree in chemical engineering by research at UiTM Shah Alam since early 2019.

Amar Mohd Maarof was born in Kuala Lumpur, Malaysia in 1996. The author possesses a Bachelor degree in Engineering (Chemical) from Universiti Teknologi MARA (UiTM) at Shah Alam, Selangor.