IN-SILICO WORKS ON CONTROL OF BLOOD GLUCOSE LEVEL FOR TYPE 1 DIABETES (T1D) USING IMPROVED HOVORKA EQUATIONS AND ENHANCED MODEL PREDICTIVE CONTROL (eMPC)

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Abstract

Artificial pancreas technology has been continuously developed over the past few years. However, there are still flaws found in recent technology in relation to injection of insulin subcutaneously into type 1 diabetes patient. The injection of insulin into the patient boy must be specific, exact and precise to ensure that the blood glucose level is between the normoglycemic ranges, 4.5 mmol/L to 6.0 mmol/L. If the blood glucose level (BGL) were below or over normoglycemic range, patients will experience effects caused by hyperglycemia or hypoglycemia. Therefore, the research seeks to find optimum insulin infusion rate into the patient for the blood glucose level to be at safe glycemic range. The research on development of artificial pancreas is mainly focusing on the algorithm that will be programmed into controller system. This research will use enhanced Model Predictive Controller (eMPC) and improved Hovorka equations for in-silico works for controlling blood glucose level for Type 1 Diabetes (T1D). The simulation will be run on MATLAB software. Only meal disturbance factor is include and varies in CHO intake during breakfast, lunch and dinner. Reference data to be substituted into related parameter value in the equation for meal disturbance are taken from real life patient data. The simulation was successfully carried out and the result was observed, evaluated and discussed.

I. Introduction

Types of diabetes are Type 1 Diabetes (T1D), Type 2 Diabetes (T2D) and gestational diabetes. The research focus on controlling blood glucose between normoglycemic range (4.5 mmol/L to 6.0 mmol/L) for Type 1 Diabetes Patient (T1D). T1D is a chronic type disease that causes the body to not produce insulin hormone or enough insulin hormones to be able in converting blood glucose into energy at optimum level. T1D patients have to depend on intravenous insulin injection multiple times daily in order to bring down their blood glucose level. A correct dosage has to be determined to prevent occurrence of hypoglycemia (blood glucose level below 2.4 mmol/L) and hyperglycemia (blood glucose level exceeds 6.0 mmol/L).

Both conditions are unfavorable for the patient. Hypoglycemia can be diagnosed through symptoms such as sweating, rapid pulse and blurred vision. Severe hypoglycemia could lead to death if not treated right away with insulin injection. Symptoms of hyperglycemia can be

seen when the patient is experiencing increased thirst, headaches and frequent peeing. Developing an Artificial Pancreas (AP) will help in automating subcutaneous insulin infusion task to prevent both episodes of hyperglycemia and hypoglycemia in a closed loop system. AP consists of continuous subcutaneous insulin infusion (CSII) pump, continuous glucose monitoring (CGM) sensor, CGM receiver and the control algorithm which is what this research is currently developing. The control algorithm should be able to measure and predict the accurate flow rate and amount of insulin infusion to regulate blood glucose level (BGL) within normoglycemic range in closed loop control system. A lot of glucose-insulin dynamic model such as Bergman Minimal Model, Man Rizza Cobelli and Hovorka has been used to describe glucose-insulin system for type 1 diabetes patient. A modification of Hovorka model was carried out by (Ayub et. al, 2013).

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 $mmolkg^{-1}min^{-1}$
F_{01}	Non-insulin-dependent glucose flux	0.0097 $mmolkg^{-1}min^{-1}$
$t_{max,I}$	Time-to-maximum of absorption of subcutaneously injected short acting insulin	55 min

The model linked insulin action subsystem variables to glucose subsystem variable which what is lacking in original Hovorka equations, the interrelation between parameters between its subsystems. The research was conducted using Modified Hovorka Equations and parameters used in the equation were from Hovorka model. The meal disturbances however were taken from real life T1D patients in Malaysia ranging from 15 to 17 years old. A lot of controller system such as Artificial Neural Network (ANN), Fuzzy Logic Control (FLC) and Proportional Integral Derivative (PID) controller were first researched and based on our findings; we had found that Model Predictive Control (MPC) as the most suitable type of controls in regulating blood glucose level. Objectives of this study is to simulate the variation of meal intake according to data collected from real life T1D patients and determine the optimum insulin infusion rate to decrease and maintain BGL within normoglycemic range. The limitations involved include that the model used only incorporate meal disturbance when there are other factors such as stress, exercise and also daily routines that influences the variations of blood glucose level in a given period of time. In addition, single hormone (insulin) is used to manipulate blood glucose level instead of dual hormone (insulin and glucagon).

II. Methodology

The model used is Hovorka Model with Modified Hovorka Equations. Parameters, constants value and CHO intake were taken from Hovorka Model, Modified Hovorka equations and real life T1D patients with the data is as defined respectively in Table 1, Table 2 and Table 3. Using system identification techniques, the original mathematical equations from Hovorka Model were firstly enhanced into a new set of equation to improve interrelation between glucose and insulin action subsystem. Schematic diagram depicting Hovorka equations and modified Hovorka equations are shown as in Figure 1 and Figure 2 respectively. The modified Hovorka equations improve the interaction between insulin action subsystem and glucose mass compartment by adding the insulin on action transport (x_1), insulin on action disposal (x_2) on the non-accessible compartment (Q_1) while on the accessible compartment (Q_2) only insulin on action transport (x_1) and insulin on endogenous production (x_3) were added towards the glucose subsystem equations.

Table 1: List of Parameters

Table 2 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	0.138 min^{-1}

plasma

$$\left[\frac{dx_1}{dt}\right] = ka_1x_1(t) + kw_1I(t) + kw_{11}I(t) \quad (6)$$

$$\left[\frac{dx_2}{dt}\right] = ka_2x_2(t) + kw_2I(t) + kw_{22}I(t) \quad (7)$$

$$\left[\frac{dx_3}{dt}\right] = ka_3x_3(t) + kw_3I(t) + kw_{33}I(t) \quad (8)$$

$$U_G = \frac{D_G A_G t e^{\frac{t}{t_{max,G}}}}{{t_{max,G}}^2} \quad (9)$$

$\boldsymbol{V_I}$	Insulin distribution volume	0.12 L kg^{-1}
$\boldsymbol{V_G}$	Glucose distribution volume	0.16 L kg^{-1}
$\boldsymbol{A_G}$	Carbohydrate (CHO) bioavailability	0.8 (dimesionless)
$\boldsymbol{t_{max,G}}$	Time-to-maximum of CHO absorption	40 min

Table 3: CHO intake

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

Equations of modified Hovorka equations

$$\frac{dQ_1}{dt} = EGP_0 + U_G + 0.01Q_2 + [x_1kw_1 + x_2kw_2 + x_3kw_3] - F_RQ_1 - \left[\frac{{F_C}^{01}}{{V_G}^{G(t)}}\right]Q_1 - 0.002Q_1 \quad (1)$$

$$\frac{dQ_1}{dt} = [kw_{11}x_1(t) + kw_{22}x_2(t) + kw_{33}x_3(t)] + EGP_o [kw_1x_1(t) + kw_2x_2(t) + kw_3x_3(t)]k_{12}Q_2 \quad (2)$$

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

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

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

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

$$\frac{dI(t)}{dt} = \left[\frac{U_1(t)}{V_I}\right] - k_eI(t) - [kw_1x_1(t) + kw_2x_2(t) + kw_3x_3(t)] \quad (5)$$

Where:

U_G = Two compartment chain with identical transfer rates $\frac{I}{t_{max,G}}\left(\frac{mmol}{min}\right)$

D_G = meal intake (mmol CHO)

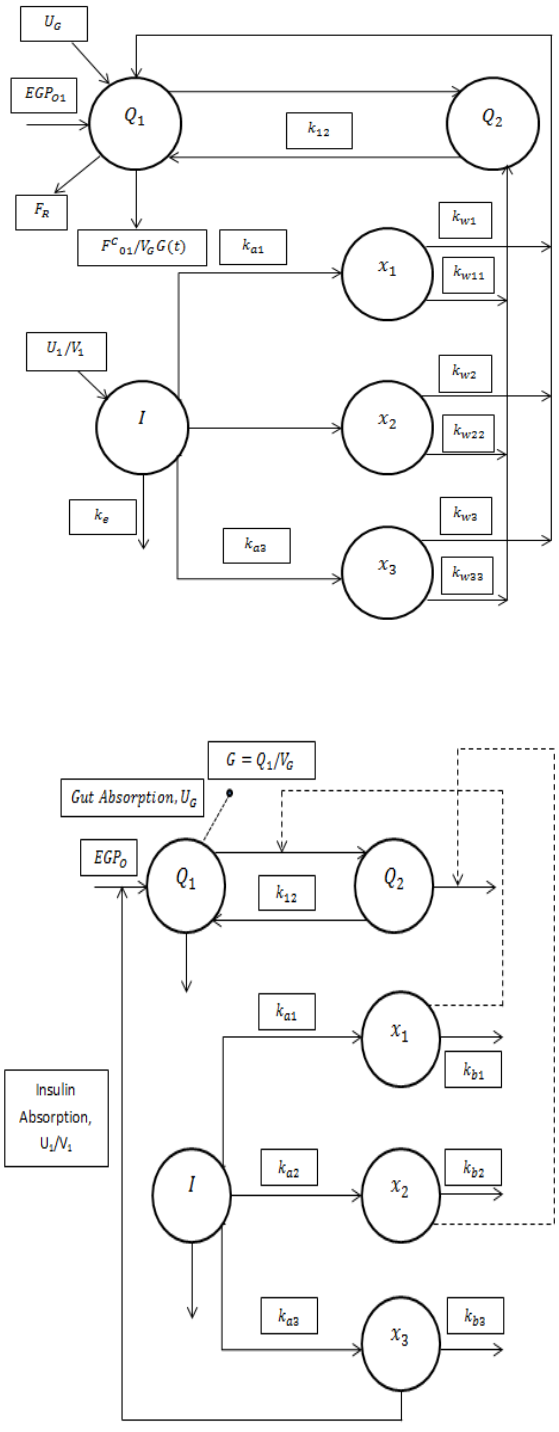
A_G = carbohydrate bioavailability (dimensionless)

Equation (1) and (2) are the modified Hovorka equations where the insulin action variables have been added into. 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}, 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_O 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. Equation (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.

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.

The equation (6), (7) and (8) are the insulin action subsystem (I) equations on action transport, action disposal, and endogenous production respectively. The constants are defined as in Table 1 and also Table 2.

II.1 Schematic Diagram



II.2 Iteration steps

Step 1: Measure Glucose Level

↓

Step 2: Predict future glucose value from model predictive controller

↓

Step 3: Is predicted glucose value(s) within normoglycemic range (4.6 mmol/L to 6.0 mmol/L)

↓

Step 4: Determine insulin amount infusion rate from model predictive controller based on a target range of (4.6 mmol/L to 6.0 mmol/L)

↓

Step 5: The insulin will be infused

↓

Step 6: Measure blood glucose level, is it between normoglycemic range?

↓

Step 7: If no, use different value of insulin infusion rate. If yes, record the value of insulin infusion rate to be analysed and evaluated

III. Results and Discussion

As seen in Figure 4.1, the simulation was carried out and evaluated using the data from real life patient and it include patient's body weight (BW), the instantaneous time during the meal taken (meal time [24-hour system]) and the total amount of meal taken (CHO rate in bolus size [mmol/min]). Other covers the time of insulin injection (Insulin time [24-hour system]) and the amount of insulin dose (Insulin rate in bolus size [mU/min]). Glucose-insulin dynamic was analyzed and therefore the simulation will be evaluated based on the parameter of amount and time of insulin, amount and time of meal disturbance on how it influences the BGC in the virtual patient.

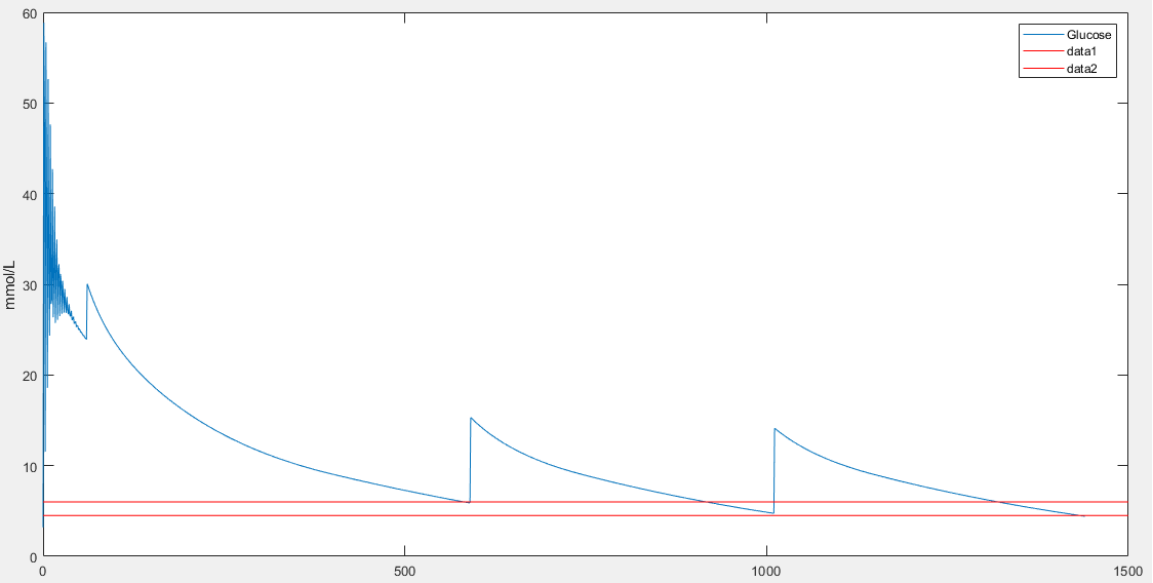


Figure III-1: Simulation for insulin infusion for 1440 min

As seen in figure 12, the simulation was carried out and evaluated using the data from real life patient and it include patient's body weight (BW), the instantaneous time during the meal taken (meal time [24-hour system]) and the total amount of meal taken (CHO rate in bolus size [mmol/min]). Other covers the time of insulin injection (Insulin time [24-hour system]) and the amount of insulin dose (Insulin rate in bolus size [mU/min]). Glucose-insulin dynamic was analyzed and therefore the simulation will be evaluated based on the parameter of amount and time of insulin, amount and time of meal disturbance on how it influences the BGC in the virtual patient.

III.1 Outcome of insulin administration on the Blood Glucose Level (BGL)

Inside figure 12, 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 (glycogen) is used to regulate blood glucose level. The hormone that helps in regulating blood glucose level is the insulin which produced by β-cell of the pancreatic islet of the pancreas. Due to inability of type1 diabetes patient to produce insulin hormone because of their malfunctioning pancreas, the glucose inside their body cannot be broken into energy thus increasing blood glucose level within a period of time until they react a state called hyperglycemia. For our simulation, hyperglycemia is a condition where the blood glucose level is exceeding 6 mmol/L. For three meal intake in bolus size per day, a total of three insulin injection 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 summarized as in Table. Bolus insulin is the insulin that was taken specifically at meal time to keep blood glucose level within normoglycaemic range for that particular meal intake. The insulin was taken before meal in this simulation.

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	9:300 pm	720	0.000001

Table III-1 Meal Intake and Insulin Infused

Figure 4.3, 4.4 and 4.5 shows the graph for meal intake with insulin administered before the meal is taken. From Figure 12, 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 blood glucose level 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 risking a lot of serious complications due to extremely high blood glucose level. The BGL was compared with previous research made by (Ayub et. al, 2019).

III.1.1 BGL FOR BREAKFAST

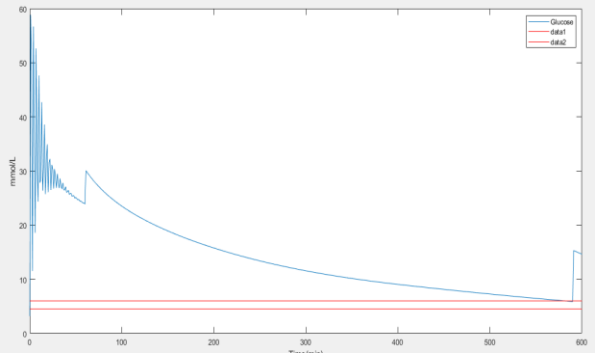


Figure III-2: BGL during breakfast time

For breakfast as observed in Figure 13, 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 graph is already passing the 6 mmol/L range and fluctuating at the beginning because of the patient is actually already in the state of hyperglycemia in the morning. This follows the record of the real patient where the meal data is extracted that the person is actually experiencing hyperglycemia early in the morning. Comparing the data with (Ayub et. al, 2019), the graph seems to fall rightly on the normoglyvemic range whereas the prior research had it had it miss by about 10 mmol/L from the normoglycaemic range in the hyperglycemic state. This is because in current research, we extended the time gap between breakfast and lunch therefore the curve in desired range just before lunch. Even though we can control the amount of insulin infused into the patient, the ability of the insulin itself to be absorbed fast or slow is highly dependent on the patient itself.

III.1.2 BGL FOR LUNCH

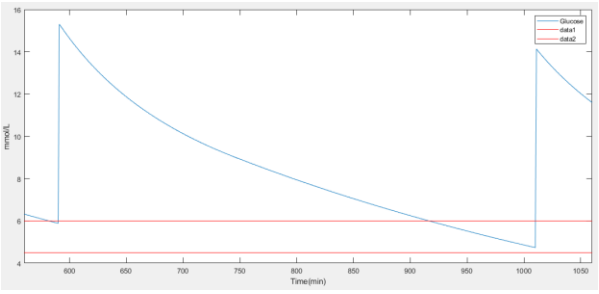


Figure III-3: BGL during lunch time

For lunch as observed in Figure 14, 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 is meal disturbance. The amount of insulin infused is lower than those in before breakfast. This is because the amount of insulin as calculated from the algorithm has not been fully utilized. Therefore, it is being used in the next round of meal disturbance. Thus, the graph will keep falling until it reaches normoglycaemic range and before the patient be in the state of hypoglycemic, there will be another meal disturbance that will increase the BGL. Comparing the result from previous research by (Ayub et. al, 2019), (Ayub et. al, 2019) had it more consistent compared to the current research, this might 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 dangerous condition.

III.1.3 BGL FOR DINNER

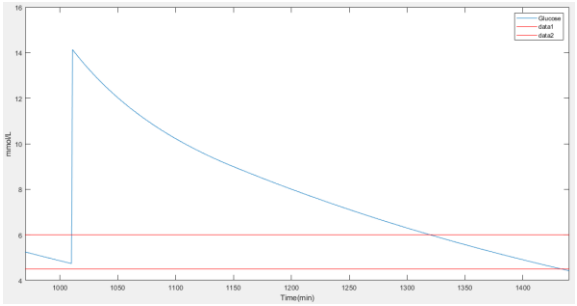


Figure III-4: BGL during dinner time

For dinner as observed in Figure 15, the patient consumed relatively the same amount of CHO as in lunch. The peak of curve of the dinner is 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, for this simulation, due to the probability of excess insulin infused. It could be the reason 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 day or one full week to observe the change of BGL of the virtual patient.

III.2 Outcome of insulin time administration on the Blood Glucose Level (BGL)

The insulin administered time is very important in managing blood glucose level. The time taken for insulin

infusion and the time where it is administered will affect the smoothness of the graph pattern in retaining BGL within normoglycaemic 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. It is shown in the graph that the blood glucose control is better with prior injection of insulin before any meal intake. Although the BGL did not dropped immediately, the time taken for BGL to reach normoglycaemic range is also quiet lengthy. The results have to be compared with the data of real time patient BGL corresponding to their insulin infusion as in the simulation. Take note that for 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 is variety types of insulin in today market, the access for each patient to it 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 this simulation, the insulin we are currently using is 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 normoglycaemic range.

III.2.1 Insulin infusion during meal time

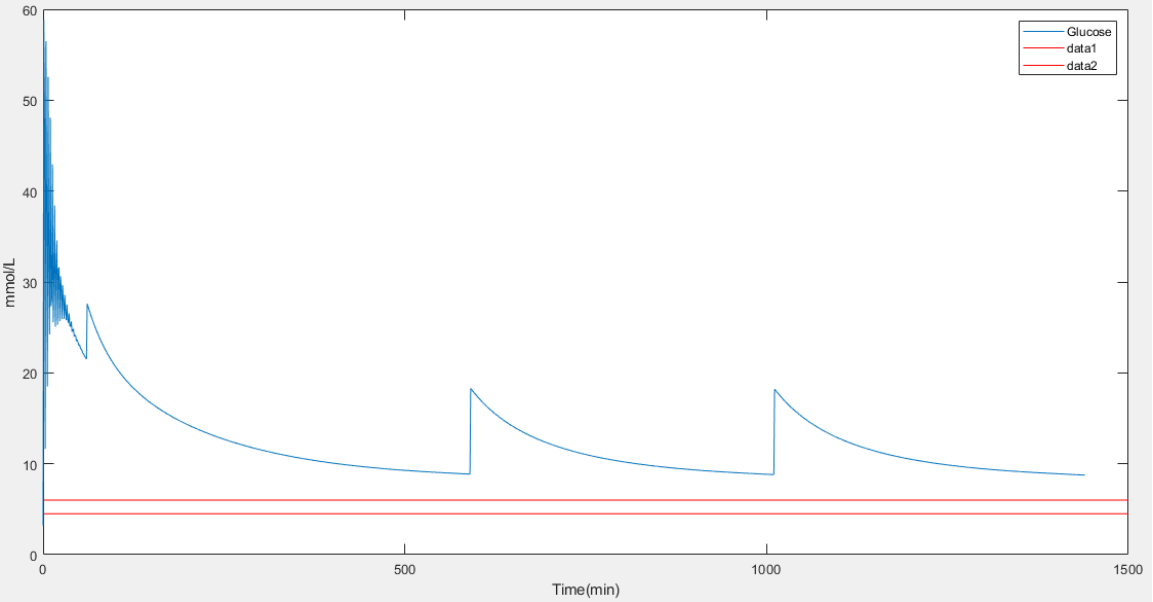


Figure III-5: BGL graph for insulin infusion during meal time

As in Figure 16, the graph had shown undesirable outcome whereas none of the BGL dropped to normoglycaemic 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 although predictable amount of time to convert them into energy. The graph however shows steady and consistent flows although it exceeds normoglycaemic range to the range between 9 to 12 mmol/L. It is still unknown why the graph had been more stable when the insulin injected during meal time. Theoretically, it could have been the presence of CHO during insulin allows the insulin to react at a higher rate compared to infusion before meal. To compensate the flunk of the graph, it is recommended to increase the amount of insulin infusion rate.

III.2.2 Insulin infusion after meal time

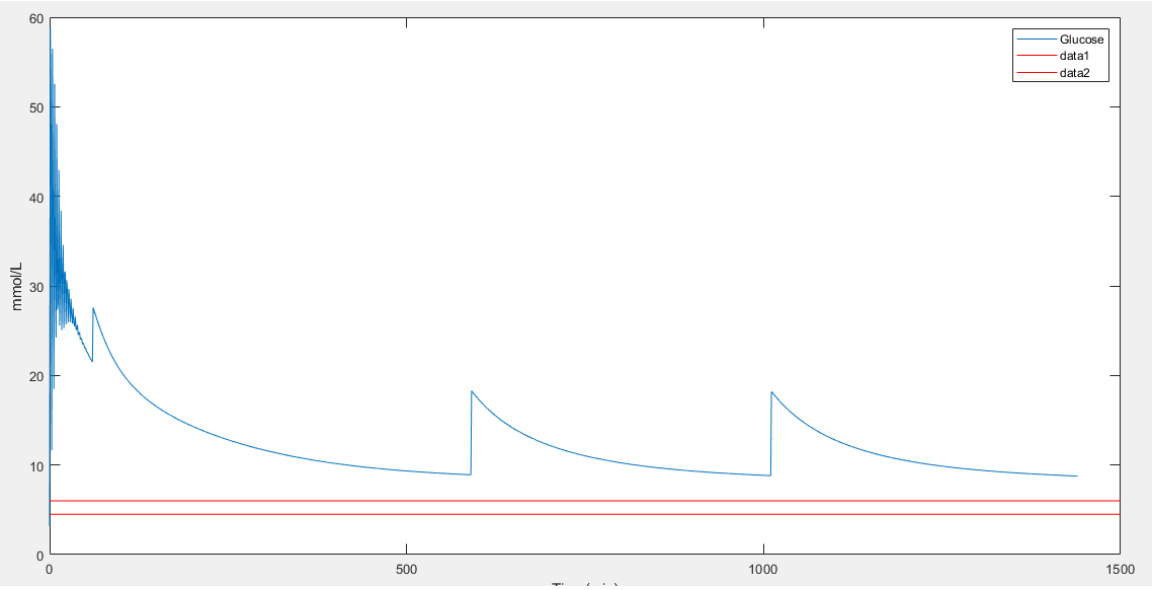


Figure III-6: BGL graph for insulin infusion after meal time

From Figure 17, it was seen that the addition of insulin after meal time is not significantly difference after comparing it with the graph from Figure 16, addition of insulin during meal time. The difference is very slight therefore the outcome can be concluded as indifferent when compared to insulin infusion after meal time graph. The insulin design for this equation and parameters value are for short acting insulin. Sensitivity towards insulin absorption may be modified for simulation that uses quick or fast acting insulin.

III.3 Outcome of addition of Snack Time

There are additions of snack time in order to have better control on BGL curve since insulin is the only hormone simulates to control the BGL in this simulation and also the equations. In addition, currently in real time there are no artificial pancreases that are capable of delivering dual hormone (Insulin and Glucagon) other than 4th generation artificial pancreas which is hormone insulin and hormone pramlintide (substitute hormone that acts such as glucagon). Table 4-1 shows the amount of CHO consumed during snack time 1 and 2 for after lunch and after dinner respectively. Figure 16 shows the BGL curve after addition of snack time.

Snack Time (24-hour system)	Snack 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 pm	785	30	1033	5:30 pm	725	0.001
12:00 pm	1130	30	1033	11:30 pm	1070	0.000

Table III-2: Snack bolus size and insulin infusion rate

From Figure 18, the graph shows that the curve of the BGL is slightly changed due to addition of snack time. The addition of snack tie has improved the BGL curve for dinner by letting not to be so near to below normoglycaemic range as compared to graph without snack time. However, the BGL curve for lunch was slightly deviated by exceeding normoglycaemic range by ± 0.5 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 addition of snack time do improves the BGL curve significantly for dinner while not deviates the BGL curve part during breakfast and lunch meal intake. An improvement is suggested by adjusting the value of insulin infusion during breakfast or lunch that are not carried out in this simulation.

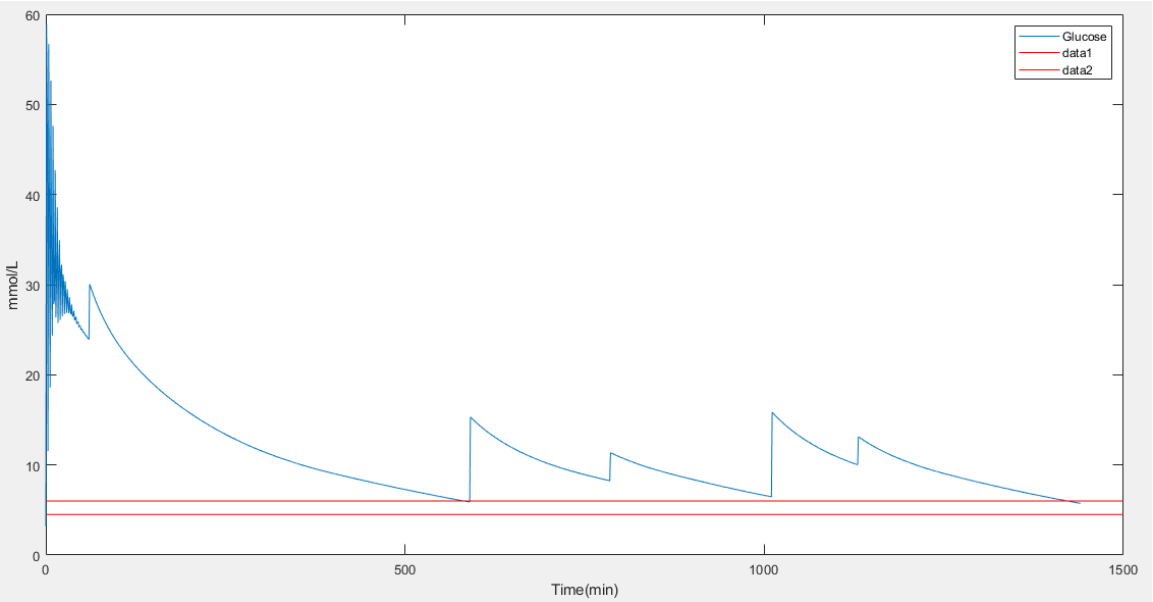


Figure III-7: Addition of snack time after lunch and dinner

III.4 Outcome of Semi-Closed Model Predictive Control Loop System

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

III.5 Outcome of simulation in MATLAB using ODE45 and ODE23s and ODE 15

For this simulation, the equations that were used are modified Hovorka equations instead of original Hovorka equations. Hovorka equations were classified as non-stiff equations by (Boiroux et. al, 2010). 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 say as the equations of original Hovorka were partly modified, the modified Hovorka may be suggest as stiff ODE rather than non-stiff ODE.

IV. CONCLUSION

In sum, the simulations was successfully carried out in different condition to observed and evaluate the difference in blood glucose control (BGC) under 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 patient that use real life data for meal disturbance parameters in the simulation. Glucose-insulin dynamic were being observed as having smoother although lengthy curve when the equation used is modified Hovorka equations. In another attempt of new studies by implementing a part of this simulation, it is recommended to studies the impact of initial variables values to the control of BGL in the simulation for the virtual patient.

V. ACKNOWLEDGEMENT

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