Simulation-Based Analysis System of Glucose-Insulin Dynamics in Type 1 Diabetes Mellitus

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***Abstract*—This project presents the development of an analysis system via simulation approach of glucose-insulin dynamics in a virtual Type 1 Diabetes Mellitus (T1DM) patient: Hovorka diabetic model using MATLAB Graphical User Interface (GUI). This analysis system is developed for a convenient technique in studying the interaction of insulin on blood glucose level based on meal and insulin taken. Several simulations of glucose-insulin dynamics have been conducted using the developed system to study the effect of patient body weight, a number of meal intake and amount and timing of insulin injection to the changes of blood glucose concentration.**

***Index Terms*—Glucose-insulin Dynamics; Mathematical Modeling; Matlab; T1DM.**

I. INTRODUCTION

A survey conducted by the Institute for Public Health Malaysia in 2015 shows that there were 17.5% of Malaysian adults range from 18 years old and above suffering diabetes with 8.3% were known to have diabetes while 8.0% were undiagnosed with diabetes [1]. In addition, every ten seconds, two persons in the world develop diabetes and a person dies from diabetes [2].

Generally, diabetes can be categorized into two; Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM). The T1DM results from an absolute lack of insulin production in the pancreas that required insulin replacement therapy whereas, the T2DM results from insufficient insulin secretion from the pancreas or insulin resistance increment in the body that is basically not required insulin injection [3]. The management of T1DM requires a lot of concern to various aspects such as insulin administration, blood glucose monitoring, balancing food intake and diabetes-related complications [4]. The goal of T1DM care is to regulate the blood glucose concentration within a normoglycemic range between 4 and 8 millimoles per liter (mmol/L) [5] in order to avoid the risks of hyperglycemia (high blood glucose concentration) and hypoglycemia (low blood glucose concentration) through exogenous insulin administration. When a patient accidentally is injected with too much insulin, the blood glucose concentration will be highly reduced. This leads to abnormally low blood glucose levels (hypoglycemia) which particularly affects the brain and causes symptoms such as dizziness, confusion and even coma in severe cases [6]. Thus, the injection of the insulin with respect to the present blood glucose concentration must be very accurate because any miscalculation of insulin dosage will bring about severe problems.

Recently, a comprehensive mathematical modeling managed via in-silico simulation is useful and preferably performed in helping researchers in enhancing the knowledge on the glucose-insulin dynamic system rather than evaluation and testing of medical treatment delivery in humans which are inordinate, exorbitant and confounded by ethical issues [7]. There are a number of mathematical models available in modeling the glucose-insulin system such as linear dynamic models [18], glucose-insulin compartmental models [8,9] and progressed to large-scale in-silico experiments through non-linear model predictive control [10] and artificial intelligence (AI) tools [11] and automated closed-loop control (artificial pancreas) for insulin prediction and glucose control [12].

Therefore, in this study, a model simulation based analysis system for blood glucose-insulin interaction based on the Hovorka diabetic model [11] for T1DM will be developed using GUI MATLAB towards a convenient use in studying the interaction between the insulin and the blood glucose based on body weight, number of meal intake and the amount of insulin injected.

The paper is outlined as follows. The methodology of the overall process in developing the simulation-based analysis system of glucose-insulin dynamics in T1DM is stated in Section II. While in Section III, the results together with the discussions are presented. Finally, the concluding remarks and future planning are stated in Section IV.

II. METHODOLOGY

In this research, the GUI for the analysis of glucose-insulin dynamics based on the Hovorka diabetic model has been designed using MATLAB software. Moreover, the Hovorka model which is represented by nonlinear Ordinary Differential Equations (ODEs) is basically solved using MATLAB ODE solver function of ode23 with the relative tolerance setting of 1e-6.

A. Hovorka Diabetic Model

Hovorka model used in this study has ten nonlinear ordinary differential equations (ODEs) which include three subsystems; carbohydrate (CHO) absorption system, subcutaneous insulin absorption system and gluco-regulatory system. It accurately represents patients with type 1 diabetes [13]. Figure 1 illustrates the block diagram of the model, where the U_G and U_I are time-dependent inputs representing CHO absorption and insulin absorption, respectively. The model will be producing two outputs; glucose concentration, $G(t)$ and plasma insulin concentration, $I(t)$. In this project, we

are focusing on the glucose concentration level as the output from the system. The equations involved in each of the subsystems can be referred in the previous works [11, 14]. Where,

D1 : Amount of glucose in compartment 1, stomach [mmol]
D2 : Amount of glucose in compartment 2, colon [mmol]
U_G : Glucose absorption rate [mmol/min]
S_1 : Amount of insulin in compartment 1, stomach [mU]
S_2 : Amount of insulin in compartment 2, colon [mU]
U_I : Insulin absorption rate into the bloodstream [mU/min]
Q_1 : Amount of glucose in the bloodstream [mmol]
Q_2 : Amount of glucose in the peripheral tissue [mmol]
G(t) : Blood glucose concentration [mmol/L]
x_1 : Insulin dependent state: transport and distribution
x_2 : Insulin dependent state: glucose disposal
x_3 : Insulin dependent state: endogenous production of glucose
I(t) : Plasma insulin concentration [mU/L]

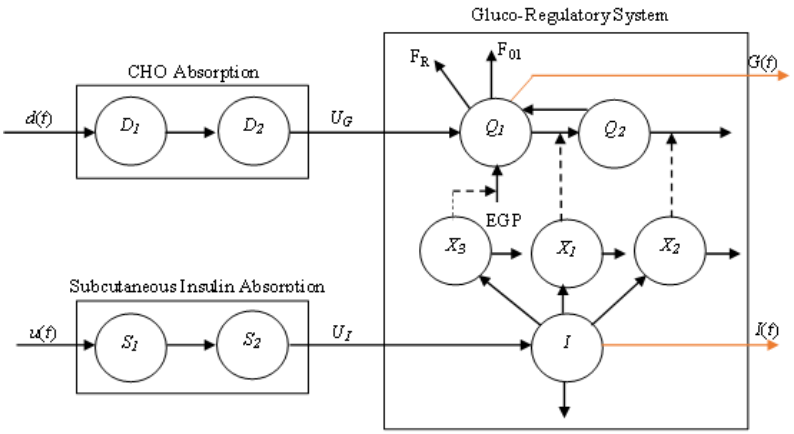

Figure 1: Block diagram of Hovorka diabetic model representation [15]

B. *System Operation of the GUI for the Analysis of Glucose-Insulin Dynamics*

Figure 2 illustrates the block diagram of the GUI system for simulation-based glucose-insulin analysis system. This simulation begins with by key in process of patient data which are the body weight of a patient, the time to consume each meal and insulin administration consume per day and the amount of CHO and the insulin intake to the simulation program. Next, the results from the simulation have analyzed to find out the Blood Glucose Concentration (BGC).

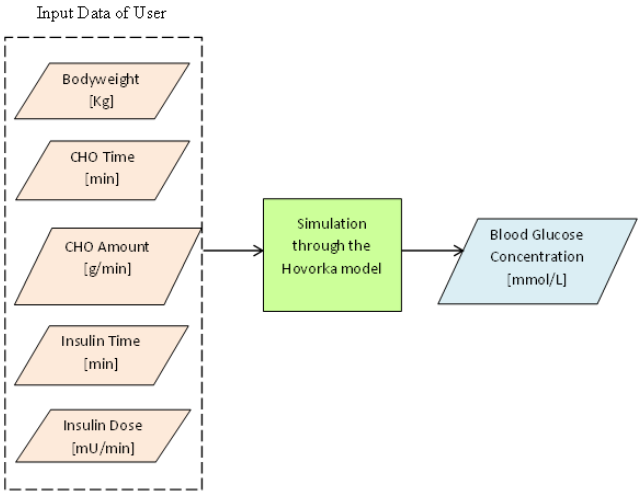

Figure 2: Flow of the GUI analysis system of glucose-insulin dynamics

III. Results and Discussion

A. *GUI Analysis System of Glucose-Insulin Dynamics*

Figure 3 shows the constructed GUI for the analysis of glucose-insulin dynamics based on the Hovorka diabetic model. This GUI analysis system is able to perform several simulation tests related to the glucose-insulin dynamics in a convenient way by comprehensively input related parameters. In order to simulate the glucose concentration, the GUI system needs the data from a user to key in into the system. The data include the type 1 diabetes patient's body weight (BW), the time of meal taken (Meal Time [24-hour system]), the amount of meal taken (CHO Rate in Bolus Size), the time of insulin injection (Insulin Time[24-hour system]) and the amount of insulin dose (Insulin Rate in Bolus Size).

B. *Analysis Studies using the GUI*

The performance of the developed GUI system is evaluated by conducting analysis on the glucose-insulin dynamics. In this paper, the results presented are based on the analysis of the amount of insulin, the insulin intake time and the bodyweight influences on the BGC with a five-time meal disturbance to represent a full course of meals per day; breakfast, lunch, tea-time, dinner and supper.

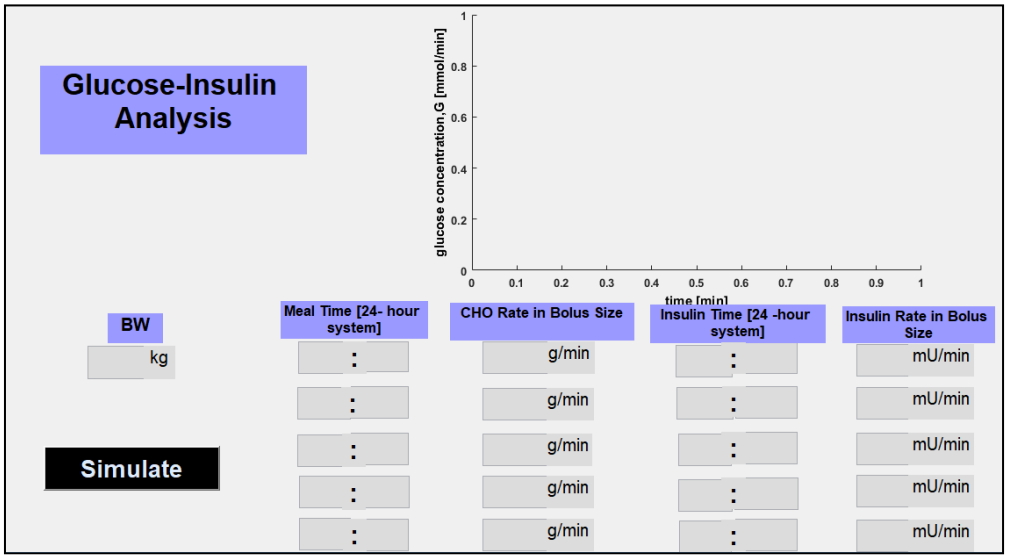

Figure 3: Graphical User Interface (GUI) for the analysis of glucose-insulin dynamics based on the Hovorka diabetic model

C. Effect of the Insulin Administration on the BGC

A hormone that helps to regulate the blood glucose concentration is the insulin secreted by the β-cell of the pancreatic islets of the pancreas. The malfunction of the pancreas to produce an adequate amount of insulin can cause hyperglycemia state. This simulation has been done to analyze the effect of the insulin on the blood glucose concentration, by using five meal intakes per day in a bolus size input. The amount of CHO rate and insulin rate used for the simulation are based on the data from the previous work [16] and summarized in Table 1.

Table 1
The Summary of the CHO and Insulin Input Data of The GUI System for The Analysis of Insulin Administration [16]

Meal time (24-hour system)	CHO rate in bolus size (g/min)	Insulin time (24-hour system)	Insulin rate in bolus size (mU/min)
09:30	24.84	09:30	700
12:30	7.32	12:30	250
16:00	6.9	16:00	200
18:45	15.4	18:45	490
21:00	6.9	21:00	210

The simulation has been carried out according to two conditions. The first condition used only a basal insulin infusion rate input, U_{basal} at 5.06 mU/min with no administration of insulin and it is calculated according to the normoglycemia at 5 mmol/L. While the second condition is using an insulin infusion rate of a bolus size input added at the same time as each meal as in Table 1.

Figure 4 shows the superimposed graphs of the BGC dynamics changes in the 24-hour simulation according to the two conditions mentioned above. From the figure, it is found that the BGC with insulin intake is much lower and stable compared to the glucose concentration with the basal insulin only which causes the hyperglycemia since the insulin intake helps to regulate the blood glucose from hyperglycemia state into the normal state. The pattern of graph showed in [16] also emphasized the importance of insulin intake when the patient is suffering from diabetes. If no insulin is administered, the patient blood glucose will be high throughout a day and may lead to serious complications.

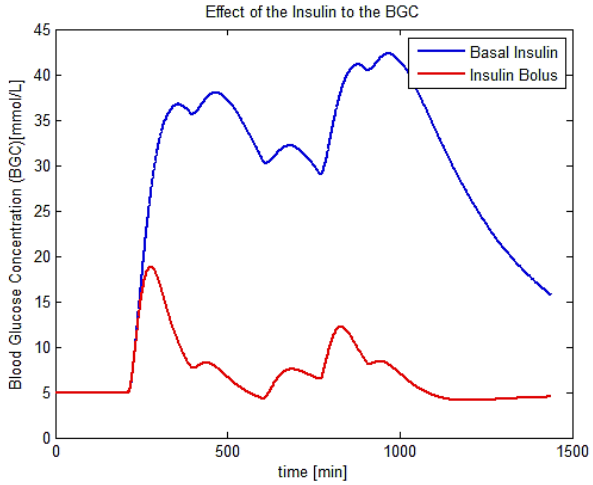

Figure 4: Comparison between the BGC with the basal insulin only and the BGC with the insulin bolus for the virtual diabetic patient bodyweight of 53 kg

D. Effect of the Insulin Intake Time to the BGC

In this simulation, the insulin intake time has been varied between five minutes until 30 minutes before and after meal consumed. Besides, a few meal has been set to five meals per day and the input value for the insulin intake dose and CHO are referred to the previous research in [17] as shown in Table 2. Figure 5 shows the GUI during the simulation of the BGC when the insulin injection time is 30 minutes before each of the meals. Meantime, Figure 6 shows the superimposed graph of the BGC results based on the insulin injection time varies every five minutes from 5 to 30 minutes before and after each of the meal. From the results, it can be understood that the BGC control is much better when the insulin is taken before the meal compared to after the meal since for the subcutaneous insulin injection, the insulin absorption time is larger than the meal absorption time. The longer the insulin intake time before having the meal, the better the BGC level can be controlled. This is because the insulin is administered into the patient body will take time to get effective to respond to any changes in the blood glucose level [19]. However, according to the analysis conducted, the insulin intake time before having a meal is longer than 30 minutes will cause the insulin to react too early and affects the BGC level to hypoglycemia.

Table 2
The Summary of the CHO and Insulin Input Data of the GUI System for The Analysis of The Insulin Intake Time [17]

Meal time (24-hour system)	CHO rate in bolus size (g/min)	Insulin time (24-hour system)	Insulin rate in bolus size (mU/min)
09:30	17.4	09:00	650
12:30	31.54	12:00	900
16:00	5.9	15:30	275
18:45	12.08	18:15	505
21:00	6.64	20:30	185

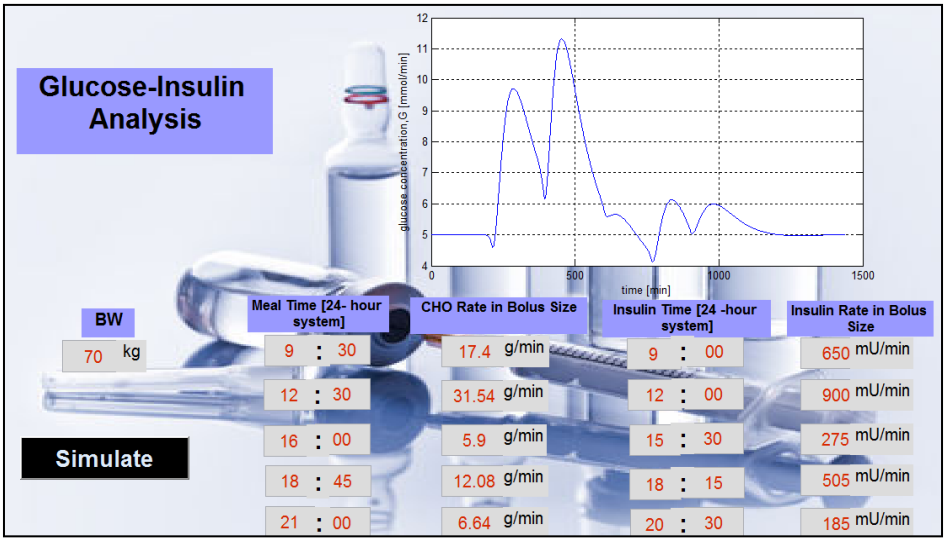

Figure 5: The BGC result when the insulin injection time is 30 minutes before each of the meals for the virtual diabetic patient bodyweight of 70 kg

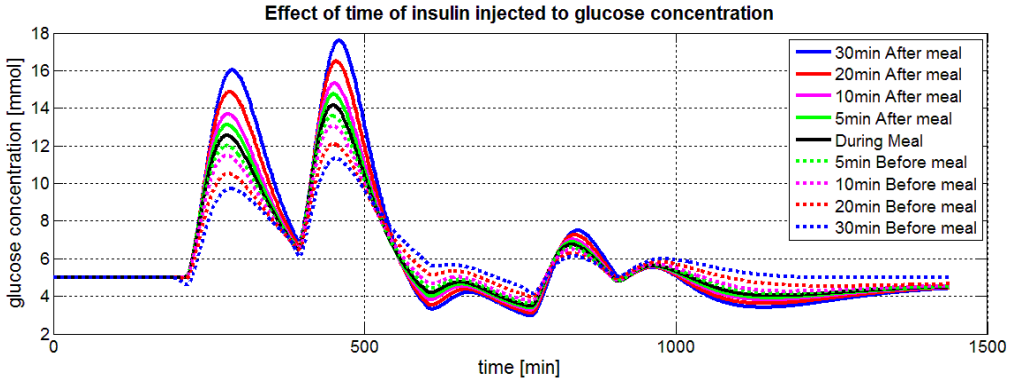

Figure 6: The BGC results when the insulin injection time is given from 30 minutes before to 30 minutes after each of the meal

E. Effect of the Bodyweight to the BGC

The weight of a person is normally stable over time as a result of the everyday food consumption and conducted activities [20]. Therefore, diabetes can be experienced either by a person with overweight or underweight [21]. As the patient undergo insulin therapy, he or she may result in weight gain as a factor to avoid hypoglycemia. An increase in body weight will result in increasing insulin dosing because the insulin dose may require more time to give effect to the blood glucose concentration as the insulin sensitivity decreasing [22].

In other words, the sensitivity of the insulin to lower the blood glucose value will increase by the decrease in the body weight [23]. This trend can be seen in the results shown in Figure 7 which shows the superimposed graph from the BGC level of five different bodyweights which are 60 kg, 70 kg, 80 kg, 90 kg and 100 kg. As the bodyweight is increasing, the body becomes less sensitive to the insulin effect and this causes the changes of blood glucose to a much lower value in the low body weight compared to the high bodyweight. Here, the insulin time has been set to 30 minutes before a meal where the insulin dose and CHO input are kept constant through five different bodyweights according to Table 2.

IV. Conclusion

In conclusion, the development of the GUI for Hovorka Diabetic model based glucose-insulin analysis system has been successfully done by using MATLAB. Moreover, the result produced from this system of simulation-based analysis of glucose-insulin dynamics are comparable to several related previous studies [14-18]. For future recommendation, this system can be further developed for the analysis based on the model prediction control in the glucose-insulin dynamics. The system would attempt to analyze the regulation of the BGC for type 1 diabetes patient by manipulating the insulin infusion rate based on a certain control algorithm.

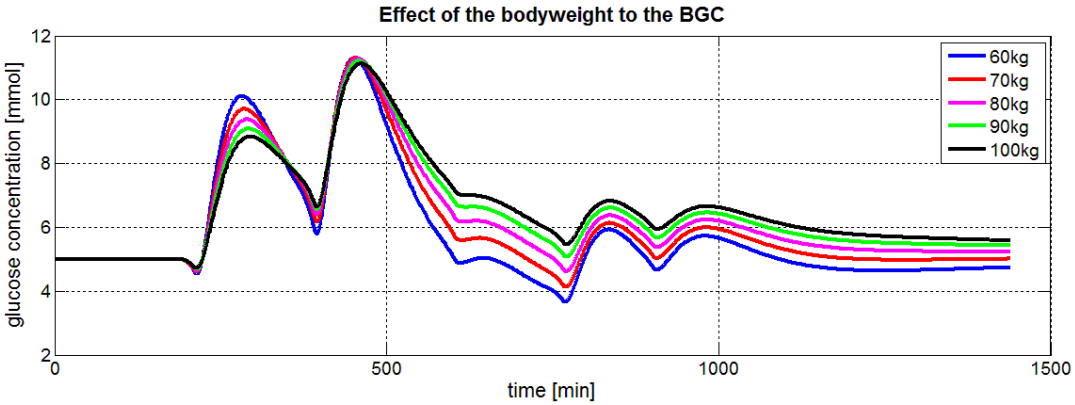

Figure 7: The BGC results based on various T1DM patient's bodyweights varied from 60 to 100 kg

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