Glycemic Control Systems and Complications in Type I/II and Gestational Diabetes

D. Chen, A. Fitzgerald, R. Hailu, D. Manalastas, and V. Rohrer

***Abstract*— An accurate model of insulin-glucose dynamics is paramount when regulating glycemic disorders in which the body has an inadequate response to hyperglycemia. In this paper, we develop an insulin-glucose dynamics model that is an extension of the Bergman Minimal Model and can account for concentration changes that occur if the patient ingests a meal during the simulation. We simulate glucose dynamics for healthy individuals, Type-I diabetics, and Type-II/gestational diabetics. For Type-I diabetics, we propose a PID controller that can regulate the release of exogenous insulin. Comparing the value of the steady-state glucose concentration from the original Bergman model simulation with its expected value (determined by parameter p_5) resulted in a 0.85% steady-state error for healthy patients and a 6.78% error for Type-II diabetics. Comparing steady-state insulin concentration with its expected value I_b resulted in a 0.36% error for healthy patients and a 1.13% error for Type-II diabetics. Due to negligible insulin dynamics, we omit error calculations from the original Bergman simulation for Type-I diabetics. However, applying a PID controller to the original Bergman model for a Type-I diabetic yielded a steady-state error of 0.74%, suggesting that implementing a PID control paired with an insulin pump could be an effective therapy for diabetes regulation.**

I. INTRODUCTION

There are three types of diabetes: Type I, Type II, and gestational diabetes. Type I diabetes corresponds to the body's inhibition of pancreatic insulin production and it makes up approximately 5-10% of diabetic cases. Type II diabetes occurs when the body has a resistance to the effects of insulin or improper insulin storage; making up 90-95% of diabetic cases [9]. Lastly, gestational diabetes is caused by high blood glucose levels during pregnancy. Gestational diabetes patients have limited insulin production and insulin resistance due to the fact that during pregnancy, the need for insulin increases and some expecting mothers' bodies cannot account for this need. There are several causes of gestational diabetes, but for the most part, the diabetes subsides after the patient gives birth; however, they are at higher risk of obtaining Type-II diabetes [7]. It is essential for the human body to maintain blood glucose concentrations in order to properly function [1]. The standard physiological ranges for blood glucose and insulin are 0.39-0.59 g/L and 2-50 mU/L respectively. These three glycemic disorders are characterized by malfunctioning glucose and insulin control, often resulting in elevated (hyperglycemic) or reduced (hypoglycemic) blood glucose levels. Without treatment, complications such as kidney damage, eye damage, heart disease, or stroke can occur in Type II diabetics and fetal complications can occur in gestational diabetics. In this report, Type II and Gestational diabetes are modeled by the same control system, due to similarities in their physiological effects and negligible differences between the two control systems.

II. THE BERGMAN MINIMAL MODEL

Glucose-insulin dynamics in the body are very complex, but Bergman's minimal model is a simple, widely used representation that is often sufficient for analytical purposes [2]. The minimal model contains two submodels to describe both insulin and glucose kinetics within a compartment of a certain volume, which represents the blood volume of the system of interest (i.e. human body). The flow of glucose in and out of this volume V_G results in a base glucose concentration G_b. At concentrations greater than G_b, glucose is taken up by the liver and surrounding tissues. In concentrations below G_b, glucose is produced and released by the liver. Glucose uptake is facilitated by "active insulin" (designed I_2) that is placed in a "remote pool," and whose entry into V_G is delayed by "transport across capillaries" [2]. This ultimately results in two differential equations (1) and (2):

$$\frac{dG(t)}{dt} = -[p_1 + X(t)]\,G(t) + p_1 G \qquad G(0) = G_0 \qquad (1)$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3\,[I(t) - I_b] \qquad X(0) = 0 \qquad (2)$$

Where p_i are parameters describing glucose effectiveness or insulin sensitivity, $G(t)$ is blood glucose concentration, G_b is baseline glucose concentration, $X(t)$ describes the effects of active insulin, $I(t)$ is blood insulin concentration, and I_b is baseline insulin concentration [2].

The Insulin Minimal Model is given by the differential equation (3):

$$\frac{dI(t)}{dt} = p_6\,[G(t) - p_5]^{+}t - p_4[I(t) - I_b] \quad I(0) = I_0 \qquad (3)$$

The *p*-parameters are described in more detail in Table 1, found in the Appendix [2]. Together, Equations (1), (2), and (3) comprise the Bergman Minimal Model.

A Simulink model for glucose-insulin dynamics was created based on the Bergman Equations. The following assumptions are made: the biosystem is modeled as a single compartment with homogenous concentrations of glucose and insulin; the concentrations of glucose and insulin do not drop below their basal values; and model parameters are approximately constant.

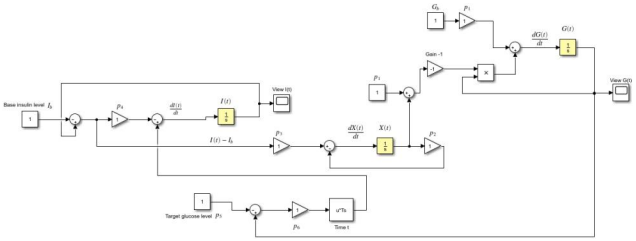

Fig. 1 Simulink block diagram for a healthy individual based on the three Bergman Equations. There is no external control system; the whole diagram represents the biosystem. The parameters and their values are described in Table 1.

For Type-I diabetics, this system would be turned into a closed-loop model with an insulin pump that acts as a controller, which affects an exogenous supply of insulin denoted by $u(t)$ [2]. Such closed-loop systems typically consist of a glucose concentration monitor, a delivery pump, and a digital controller, eliminating the need for manual injection of insulin. An open-loop system, which is not sensitive to feedback, could also be used where the amount of exogenous insulin delivered is set at a predetermined value [1]. For healthy individuals during meals, adding an element of feedforward control based on the size of a meal can lower glucose concentration peaks and result in a more gradual release of bolus [3]. Thus, a combined feedforward-feedback control could be considered for closed-loop systems, though our controller will use only feedback.

III. OUR MODEL: AN EXTENSION OF BERGMAN'S MINIMAL MODEL

Some significant flaws with the Bergman model include its sensitivity to variation in the p parameters and the fact that the concentration of insulin in the plasma with respect to time must be known [11]. The original version also examines only periods of fasting.

Our model, which is an extension of Bergman's Minimal Model, takes into account the effects of ingested glucose on $G(t)$ and incretins that are released during digestion on $I(t)$ [5]. To account for the release of incretins, we use the insulin appearance rate value, k = 0.005 mU min^{-1} ng^{-1}, which was used in a model of glucose-insulin dynamics by Brubaker et al. and add the term $k\,L(t)$ to Bergman Equation (3) as in a paper by Kabul et al., where $L(t)$ is the concentration of incretins in the biosystem in mU/L, resulting in (6) [4][5]. To account for the effects of ingested glucose, we add $R_a(t)$, the rate of appearance of exogenous glucose in the blood in mg/min, which will be simplified as a "pulse" function to represent the entry of glucose after a meal, resulting in (4). The entry rate of incretins to the system is also simplified as a "pulse" function. This results in the following equations:

$$\frac{dG(t)}{dt} = -[p_1 + X(t)]\,G(t) + p_1 G_b + \frac{R_a(t)}{V_G} \qquad G(0) = G_0 \qquad (4)$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3\,[I(t) - I_b] \qquad X(0) = 0 \qquad (5)$$

$$\frac{dI(t)}{dt} = p_6\,[G(t) - p_5]^{+}t - p_4[I(t) - I_b] + k\,L(t) \quad I(0) = I_0 \qquad (6)$$

$$R_a(t) = \frac{meal\,mass}{meal\,time} \qquad \text{for } t = [t_{begin\ meal},\ t_{end\ meal}] \qquad (7)$$

A Simulink model was created based on these equations.

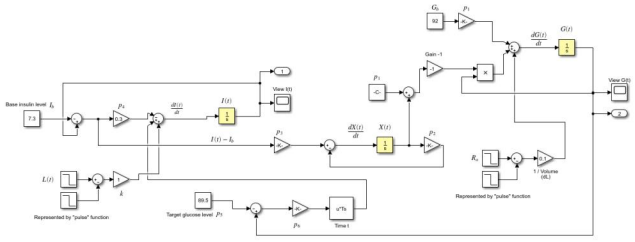

Fig. 2. Simulink block diagram for a healthy individual based on our extended Bergman model. The whole diagram represents the biosystem, with no external control.

We had insufficient information about the concentration of incretins that would result from a given amount of ingested glucose, thus we opted not to use our extended version of the Bergman Minimal Model for the simulations. This was not detrimental to our modeling of diabetes, however, as a spike in $G(t)$ during the simulation due to ingested glucose would have complicated the results unnecessarily. The extended model is simply a proof of concept that additional sources of glucose can be accounted for during a simulation.

V. RESULTS OF SIMULATIONS

The following simulations were based on the Bergman Minimal Model for three different patient-types: healthy, Type-I diabetic, and Type-II/gestational diabetic. It was assumed that the patients did not ingest any additional glucose during the simulation, so our original Bergman Minimal Model block diagram was used to produce the simulated concentration dynamics of $G(t)$ and $I(t)$.

Fig. 3 shows that in a healthy individual, glucose and insulin concentrations display a clear exponential decay. Glucose concentration begins at the designated G_0 value and settles at a value of 90.264 mg/dL, close to the target value of p_5 = 89.5 mg/dL. Likewise, insulin begins at I_0 and settles at 7.326 mU/L, which is close to the basal concentration I_b = 7.3 mU/L.

One advantage of Bergman-based models is that the parameters can be easily adjusted in order to simulate glucose-insulin dynamics in individuals with glycemic disorders. For individuals with Type-I diabetes, basal values of insulin are very low and can be assumed to be 0 for the simulation. Since there are no insulin dynamics, parameters p_4 and p_6 can also be set to 0 [2]. Basal glucose values are higher than in healthy patients due to the lack of insulin production.

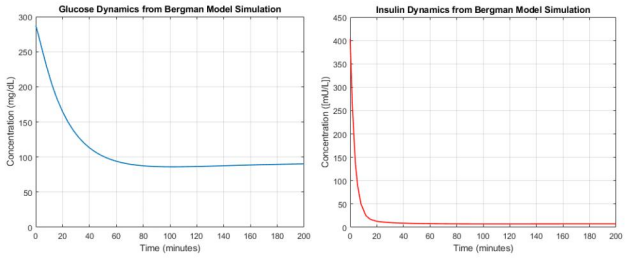

Fig. 3. Results of Bergman model simulation for a healthy individual. The top figure shows glucose dynamics, and the bottom figure shows insulin dynamics.

Type-II and gestational diabetics can display more variability in their models, but generally have parameter values that similarly reflect decreased sensitivity to insulin. For example, p_1 (glucose clearance rate) is typically lower than in healthy individuals. Two new parameters φ_1 and φ_2 can be introduced to represent pancreas sensitivity to insulin. Equations (8) and (9) show ranges of these values for patients with Type-II diabetes.

$$\phi_1 = \frac{I_{max} - I_b}{p_4(G_0 - G_b)} < 2\,\frac{mU\,dL}{mg\,min\,L} \qquad (8)$$

$$\phi_2 \frac{p_3}{p_2} < 75 \times 10^4 \qquad (9)$$

Parameters for the diabetic simulations were chosen based on values found in literature— normal and Type-I parameters come from Friis-Jensen's *Modeling and Simulation of Glucose-Insulin Metabolism*, and Type-II/gestational parameters come

from Kartono's study on the effects of physical exercise on Type-II diabetes, which are shown in Table 1 and inserted in the Bergman's model [2][6].

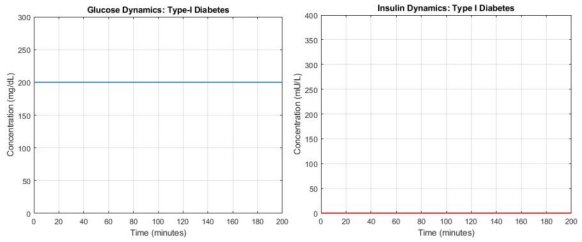

Fig 4. Results of Bergman model simulation for an individual with Type-I diabetes during fasting.

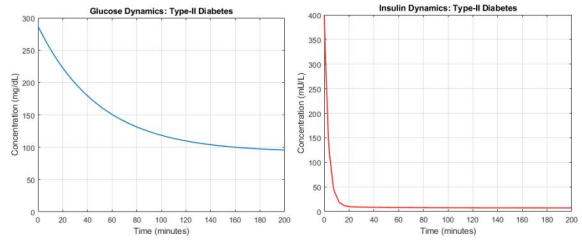

Fig. 5. Results of Bergman model simulation for an individual with Type-II or gestational diabetes.

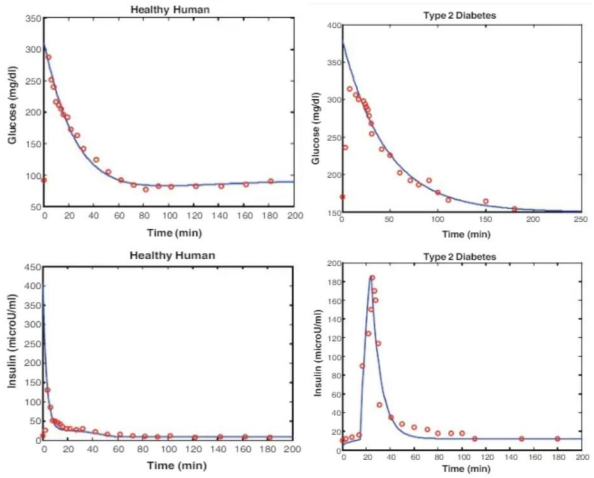

Fig. 6. Data from Kartono's study shows similar dynamics for healthy and Type II patients to our simulation results [6].

These results were compared to those from a study by Kartono, assuming these results represent what a graph of insulin and glucose regulation should look like. Overall, the differences are slight. Below are the results from Kartono's study, which can be compared to our results with the results from the Bergman Model shown in Fig. 3 and Fig. 5 [6].

Parameter p_5, the target glucose level, is the expected value, which was compared to the steady-state values of $G(t)$ from the original Bergman model simulations. The healthy patient model had a steady-state error of 0.85%, and the Type-II patient model had a steady-state error of 6.78%. For insulin concentration dynamics, the expected steady-state value is determined by I_b, the basal blood insulin concentration. The healthy patient model had a steady-state insulin error of 0.36%, and the Type-II patient model had an error of 1.13%.

These results, especially when compared against similar models in the literature, imply that the original Bergman models used here are fairly accurate representations of the body's self-regulation of its glucose levels. Because healthy and Type-II patients produce and respond to insulin, $G(t)$ settles back fairly accurately to its target value after a given period of time. It can be seen from Fig. 3 and Fig. 6 that the Type-II glucose model has an increased time constant (as compared to the healthy model) that slows its exponential decay. The reduced sensitivity of Type-II patients to insulin means their settling time is longer, and the higher steady state errors seen in our simulations could be because the simulation was not run long enough for the system to settle completely. For healthy patients, 200 minutes was more than enough time to reach the target determined by p_5.

The Type-I patient, who was assumed to produce approximately 0 insulin, experienced no dynamic changes in their $G(t)$ and $I(t)$ values, which remained at a constant G_0 = 200 mg/dL and I_b = 0 mU/L, respectively. Therefore, the steady-state errors for this model were technically 0.

V. PID CONTROL FOR DIABETIC PATIENTS

The following model includes PID-controlled IV insulin delivery and was derived from the Bergman Model. It includes an extension of glucose absorption from the gut in Equation (10a), $G_M(t)$, as well as IV insulin delivery in Equation (12) [1].

$$\frac{dG'}{dt} = -p_1 G'(t) - G(t)'X(t) + G_M(t) \tag{10a}$$

$$\frac{dX}{dt} = -p_2 X(t) + p_3 I'(t) \tag{11}$$

$$\frac{dI(t)}{dt} = -p_4[I(t) - I_b] + u(t) \tag{12}$$

All of the above equations are linear except for Equation (10a), which needed to be linearized in order for this model to be accurate. Linearizing the equation about the basal glucose concentration yields the equation below [10].

$$\frac{dG'}{dt} = -p_1 G'(t) - G_b X(t) + G_M(t) \tag{10b}$$

Note that in Type-I diabetics, there is no internal insulin regulation, so the term $p_6\,[G(t) - p_5]^+ t$ in Equation (6) is omitted when we rewrite it as Equation (12). Note also that $u(t)$ denotes an exogenous supply of insulin from a pump.

It is assumed that the initial insulin concentration I_0 and basal insulin concentration I_b are 0 for a Type-I diabetic. Performing the Laplace transform on Equation (12) and rearranging to solve for $I(s)$, as done in the paper by Ul-Hassan et al., yields the equation below [1].

$$\begin{aligned} s\,I(s) &= -p_4 I(s) + u(s) \\ I(s)\,[s + p_4] &= u(s) \\ I(s) &= \frac{u(s)}{s + p_4} \end{aligned} \tag{13}$$

A Laplace transform is then performed on (11) and (13) is substituted for $I(s)$.

$$\begin{aligned} s\,X(s) &= -p_2 X(s) + p_3 I(s) \\ X(s)[s - p_2] &= \frac{p_3 u(s)}{s + p_4} \\ X(s) &= \frac{p_3 u(s)}{(s + p_4)(s + p_2)} \end{aligned} \tag{14}$$

Lastly, a Laplace transform is performed on the linearized version of Equation (10b), substituting Equation (14) for $X(s)$.

$$s\,G(s) = -p_1 G(s) - G_b X(s) + G_M(s)$$

$$G(s) = \frac{-G_b X(s) + G_M(s)}{s + p_1}$$

$$G(s) = \frac{-G_b p_3 u(s) + G_M(s)}{(s + p_4)(s + p_2)(s + p_1)} \quad (15)$$

The overall input to the biosystem is the exogenous insulin supply $u(s)$, and the output is glucose concentration $G(s)$. Therefore, the overall transfer function $H(s)$ of the biosystem is given by the ratio of $G(s)$ to $u(s)$. The $G_M(t)$ is omitted under the assumption that the patient will not be exercising or ingesting any glucose during the simulation [1].

$$H(s) = \frac{G(s)}{u(s)} = \frac{-G_b p_3}{(s + p_4)(s + p_2)(s + p_1)} \quad (16)$$

$$or,\ H(s) = \frac{-G_b p_3}{s^3 + (p_1 + p_2 + p_4)s^2 + (p_1 p_4 + p_2 p_4 + p_1 p_2)s + p_1 p_2 p_4}$$

From this transfer function, it can be concluded that the biosystem has poles at $s = -p_4$, $-p_2$, and $-p_1$ [1]. Referencing Table 1 in the appendix for the values from the uncontrolled Type-I diabetic simulation, the poles are then located at $s = -0.3$, -0.02093, and -0.0287 min^{-1}, respectively. This system has all negative, real poles, indicating that the closed-loop system is *stable*. The error function input to the PID controller is defined as $e(t) = G_{meas}(t) - G(t)$ (an inversion of ordinary control action due to the diminishing effect insulin has on glucose levels).

There are no simple, systematic ways to formulate parameters for a third-order system, so K_p and K_d were both set to be 1 via trial and error, which resulted in a steady-state value $G_b = 82.5$ mg/dL. Setting $K_i = 0.01$ brought the steady-state value much closer to the target, but made the system slightly underdamped. By increasing $K_p = 5$, this resulted in more of a critically damped response.

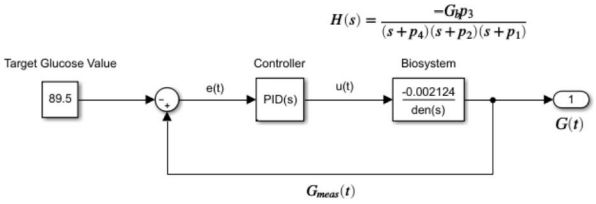

Fig. 7. Simulink diagram used to simulate a PID controlled insulin pump for Type-I diabetic patients. The parameters for the biosystem are in Table 1.

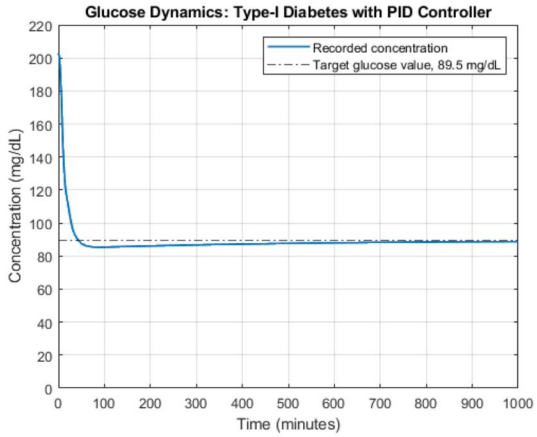

Fig. 8. The resulting glucose concentration dynamics from the simulation represented in Fig.7. The simulation was run for 1000 minutes.

The target glucose concentration was set to 89.5 mg/dL. Setting the PID parameters to the aforementioned values of $K_p = 5$, $K_i = 0.01$, and $K_d = 1$, the steady-state glucose value from the simulation was found to be 88.83 mg/dL, resulting in a 0.74% error. With some more tuning, this small error may even be reduced further, suggesting that PID control could be an effective way to modulate the administration of an insulin supply for a patient with Type-I diabetes.

This simulation could be used as an alternative to actual physiologic experimentation because of how accurate we were able to get our system to be. Although our simulation had small steady state errors, the limitations of this are that starting values are not always the same from patient to patient and insulin sensitivity levels also vary from patient to patient. Additionally, the concentration of insulin in the plasma with respect to time must be known, which our simulation did not include. In order for the simulation to be completely successful, our simulation would have to take these into account.

VI. CONCLUSION

The Bergman Model was able to successfully model insulin and glucose kinetics using differential equations. We were able to integrate a PID controller to the system in order to characterize the effects of an insulin pump on blood glucose regulation. From the poles found from Equation (16) we saw that our Simulink simulation was stable, indicated by all negative poles. Based on our percent errors from all simulations, healthy and diabetic patients, we showed that our simulation had many benefits of use and much accuracy. Although there were limitations to our simulation, we determined that altering the Bergman Model and adding a PID control shows a realistic representation of blood glucose levels.

VII. APPENDIX

TABLE 1: PARAMETER VALUES FOR ORIGINAL BERGMAN MODEL SIMULATIONS [2][6]

Parameter	Healthy Value	Type-I Value	Type-II Value	Unit	Description
$G(0)$	287	200	287	[mg/dL]	Initial blood glucose concentration
$X(0)$	0	0	0	[min^{-1}]	Initial effect of active insulin
$I(0)$	403.4	0	403.4	[mU/L]	Initial blood insulin concentration
G_b	92	200	92	[mg/dL]	Basal blood glucose concentration
I_b	7.3	0	7.3	[mU/L]	Basal blood insulin concentration
p_1	0.03082	0.0287	0.02	[min^{-1}]	Glucose clearance rate (independent of insulin)
p_2	0.02093	0.02093	0.025	[min^{-1}]	Active insulin clearance rate (decrease of uptake)
p_3	1.062×10^{-5}	1.062×10^{-5}	10^{-9}	[L/(min^2 mU)]	Increase in uptake ability caused by insulin
p_4	0.3	0.3	0.315	[min^{-1}]	Decay rate of blood insulin
p_5	89.5	89.5	89.5	[mg/dL]	Target glucose level
p_6	0.3349×10^{-2}	0	0.001	$[\frac{mUdL}{Lmgmin}]$	Rate of pancreatic release after glucose bolus

VIII. ACKNOWLEDGEMENT

On behalf of the entire group, we would like to thank Dr. Cauwenberghs for his guidance and knowledge this quarter. We would also like to thank all of the TAs, Austin Doughty, Ismael Munoz, and Nishant Mysore for their hard work and counsel throughout the quarter. We appreciate everything they have all done to make this quarter successful and memorable.

IX. REFERENCES

[1] Ul-Hassan, F., Adil, M., Ali, K., Shuja, S., Tiwana, M.I., ul-Hassan, Q., Malik, S., & Ali Riaz, R. (2017). "Closed loop blood glucose control in diabetics." *Biomedical Research*, *28*(16). Retrieved December 1, 2020.

[2] Friis-Jensen, E. (2007). *Modeling and Simulation of Glucose-Insulin Metabolism*. Technical University of Denmark. Retrieved December 1, 2020.

[3] Marchetti, G., Barolo, M., Jovanovic, L., Zisser, H., & Seborg. D.E. (2008). "A Feedforward—Feedback Glucose Control Strategy for Type 1 Diabetes Mellitus." *Journal of Process Control*, *18*(2). Retrieved December 1, 2020.

[4] Brubaker, P.L., Ohayon, E.L., D'Allesandro, L.M., & Norwich, K.H. (2007). "A mathematical model of the oral glucose tolerance test illustrating the effects of the incretins." *Annals of Biomedical Engineering*, *35*(7). Retrieved December 1, 2020.

[5] Kabul, R.S.E., Pratiwi, A., Setiawan, A.A., Dahlan, K., & Kartono, A. (2015). "Mathematical model of glucose-insulin system using the modified oral minimal model and the incretin effects." *International Journal of Pharmacy and Pharmaceutical Sciences*, *7*(9), 451-454. Retrieved December 1, 2020.

[6] Kartono, A. (2012). "Modified minimal model for effect of physical exercise on insulin sensitivity and glucose effectiveness in type 2 diabetes and healthy human." *Theory in Biosciences*, *132*(3): 195-206.

[7] *Diabetes During Pregnancy | Maternal Infant Health | Reproductive Health | CDC*. (2020). Centers for Disease Control and Prevention.

[8] Mahmud, F., Isse, N. H., Daud, N. A. M., & Morsin, M. (2017). Evaluation of PD/PID controller for insulin control on blood glucose regulation in a Type-I diabetes. *AIP Conference Proceedings*, 1–8.

[9] *National Diabetes Statistics Report, 2020 | CDC*. (2020). Centers for Disease Control and Prevention

[10] Percival, M. W., Zisser, H., Jovanovic, L., & Doyle, F. J. (2008). Closed-Loop Control and Advisory Mode Evaluation of an Artificial Pancreatic β Cell: Use of Proportional-Integral-Derivative Equivalent Model-Based Controllers. *Journal of Diabetes Science and Technology*, *2*(4), 636–644.

[11] Kovacs, L. (2006). "Extension of the Bergman minimal model for the glucose-insulin interaction." *Periodica Polytechnica Ser. El. Eng.,* 50(1-2): 23-32.