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Optimization of a PID Controller System for Cobelli Diabetic Model Based Glucose-Insulin Control

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Abstract: A clinical study has aided in the development of novel treatments and research for a variety of disorders. Unfortunately, clinical trials are time and expense intensive due to the development of numerous new technologies. Diabetes disease requires long- term testing to have a better knowledge of the disease. For that reason, Cobelli model, a virtual diabetic model is recommended, as it allows for more detailed analysis on the disease. Cobelli model, which is based on a Type I diabetes simulator, is the first computer simulator to be approved by the Food and Drug Administration (FDA). It has paved the door for a new method of comprehending diabetes mellitus. The purpose of this research is to conduct a simulation study using MATLAB Simulink on a PID controller-based insulin-glucose closed loop regulation system based on the Cobelli model for a 24-hour simulation system. In this research, a PID controller-based glucose-insulin closed-loop regulation system based on the Cobelli model Type 1 diabetic was designed using MATLAB Simulink blocks and the PID controller was also optimized using the MATLAB transfer function-based tuning technique. The results of the meal disturbance analysis by reducing carbohydrate (CHO) intake by around 20% and on the analysis of 100%, 70% and 50% of insulin sensitivity have shown a promising outcome in understanding the glucose and insulin dynamics for the insulin-glucose closed loop regulation.

Keywords: PID Controller System, Cobelli Model, Glucose-Insulin Control

1. Introduction

Diabetes mellitus is characterized by high blood glucose levels and low insulin production. Generally, there are two types of diabetes, type 1 and type 2 diabetes. Type 1 diabetes is a progressive

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condition caused by progressive degeneration of beta cells in the pancreas [1] and it is known as insulin-dependent diabetes since people with type 1 diabetes need to take insulin every day to stay alive. While the condition mostly affects children, it can affect adults as well. Type 2 diabetes is known as adult-onset diabetes. Type 2 diabetes is more common than type 1 diabetes [2] since type 2 diabetes is caused by lifestyle and it has high blood sugar and the same hazards as type 1 diabetes. Insulin's natural impact of insulin resistance drives glucose from the blood into the cells, causing type 2 diabetes. As a result, glucose builds up in the blood. However, not everyone with type 2 diabetes needs to take insulin.

Due to mealtimes and exercise, glucose control continues to be difficult, necessitating increased user interaction and an ongoing diabetes management burden. Many researchers have studied closed-loop insulin infusion therapy to avoid insulin stacking, which can cause hypoglycemia [3][4]. Modern insulin therapy uses insulin on board (IOB) calculations in conjunction with continuous subcutaneous insulin infusion (CSII) and other automated glucose-regulating approaches (i.e., artificial pancreas products) [4][5][6]. The ultimate goal is a closed-loop system that does not require any input from the user, but this is still difficult to achieve in practice, and postprandial hyperglycemia and hypoglycemia are the two main problems in fully closed-loop systems [7]. In a study comparing fully closed-loop (FCL) and hybrid closed-loop (HCL) systems, Weinzimer et al. found that the use of HCL of adding small manual priming bolus doses of insulin had increased time in range for incremental insulin response and decreased postprandial peak glucose levels [8]. Meanwhile, a PID controller is widely used for blood sugar control due to its simplicity, ease of implementation, adaptability, and robustness [3][9] [10]. In research conducted by R. Hu and C. Li [3], an improved PID controller algorithm based on onboard insulin estimation was presented using UVa/Padova virtual patient software and the results were simulated. The simulation results showed that the modified PID controller algorithm works effectively in a variety of carbohydrate and insulin sensitivity scenarios.

Therefore, a study on the PID controller for a closed-loop glucose-insulin regulation based on the Cobelli model of type 1 diabetes and its optimization in MATLAB Simulink has been conducted and presented in this paper to further investigate the potential of the PID controller in improving the glucose regulation. The objectives of this project are to analyze Cobelli model of type 1 diabetes mellitus, optimize the parameters of the PID controller for glucose-insulin control in type 1 diabetes mellitus and to evaluate the performance of the optimized PID control system. This could be used as a simulation-based analysis tool of glucose-insulin dynamics that may contribute to a better understanding of type 1 diabetes and its treatment.

2. Materials and Methods

Cobelli's model used in this study is a type 1 diabetic model that is made up of six compartments which are the glucose subsystem, insulin subsystem and the unit process of the gastrointestinal tract, liver, muscle adipose tissue beta-cellcell in the pancreas which is replaced by subcutaneous tissues for type 1 diabetes [11] [12] [13]. This model is composed of 12 nonlinear ordinary differential equations (ODEs) that demonstrate the interplay of glucose and insulin in Type 1 diabetes mellitus.

Figure 1 shows the block diagram of the PID controller system design for glucose-insulin closed-loop regulation based on the Cobelli Type 1 diabetic model. A negative feedback block diagram is utilized to demonstrate the concept of this project in Figure 1. The negative feedback block diagram is made up of three distinct components: the plant, the sensor, and the controller. The controller generates the system's input, the system is the controlled subject, and the sensor measures the output system. By comparing its output to the desired value and using the error signal to dynamically adjust the output to bring it closer to the intended value. For this project, the PID controller will assist in maintaining an optimal glucose concentration rate, as the meal disturbance will cause blood glucose levels to fluctuate. Then the system's reference value is set. The Cobelli model, which is composed of 12 ODEs, was solved using MATLAB Simulink. The constant parameters and the initial values of ODE variables for Cobelli type 1 diabetic model used in this study are shown in Table 1 and Table 2, respectively. The system is

a closed-loop system, which means that the output of the system is fed back into the system's input. The system will also include meal disturbance, which functions as carbohydrate (CHO) input component to the Gastro-Intestinal Tract Unit process in the Cobelli model.

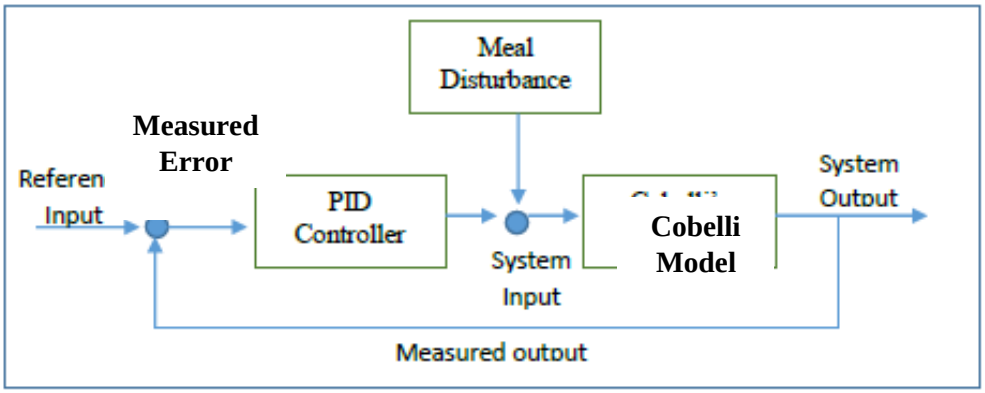


Figure 1: Block diagram of PID controller-based glucose-insulin closed-loop regulation system

Table 1: Parameters for Cobelli type 1 diabetic model [11][12][13].

Process	Parameter	Type 1 Diabetic value	Unit
Rate of appearance	k_{gri}	0.031	min^{-1}
	d	0.129	dimensionless
	k_{abs}	0.111	min^{-1}
	f	0.90	dimensionless
	a	0.00013	mg^{-1}
	b	0.82	dimensionless
	c	0.00236	mg^{-1}
	d	0.010	dimensionless
	k_{max}	0.0080	min^{-1}
	k_{min}	0.0558	min^{-1}
	BW	-	kg
	Q_{sto1}	-	mg
	Q_{sto2}	-	mg
	Q_{gut}	-	mg
Glucose utilisation	F_{cns}	1	$mg\ kg^{-1}\ min^{-1}$
	V_{m0}	4.65	$mg\ kg^{-1}\ min^{-1}$
	V_{mx}	0.030	$mg\ kg^{-1}\ min^{-1}\ per\ pmol\ /l^{-1}$
	K_{m0}	199.5	$mg\ kg^{-1}$
	p_{2u}	0.015	min^{-1}
	G_{tb}	151.3	$mg\ kg^{-1}$
	EGP_b	3.001	$mg\ kg^{-1}\ min^{-1}$
	I_b	90.56	$pmol\ l^{-1}$
	X	-	$pmol\ l^{-1}$
Glucose Kinetics	k_1	0.053	min^{-1}
	k_2	0.098	min^{-1}
	G_p	-	$mg\ kg^{-1}$
	G_t	-	$mg\ kg^{-1}$
	V_G	1.748	$dl\ kg^{-1}$
	k_{p1}	2.90	$mg\ kg^{-1}\ min^{-1}$
	k_{p2}	0.004	min^{-1}

Endogenous glucose production (EGP)	k_{p3}	0.008	$mg\ kg^{-1}\ min^{-1}\ per\ pmol\ /l^{-1}$
	k_i	0.006	min^{-1}
	l_1	-	$pmol\ l^{-1}$
	l_d	-	$pmol\ l^{-1}$
Renal excretion	k_{e1}	0.0007	min^{-1}
	k_{e2}	269	$mg\ kg^{-1}$
Insulin kinetics	k_d	0.017	min^{-1}
	k_{a1}	0.001	min^{-1}
	k_{a2}	0.007	min^{-1}
	m_1	0.156	min^{-1}
	m_2	0.579	min^{-1}
	m_3	1.5*m_1	min^{-1}
	m_4	0,232	min^{-1}
	V_l	0.059	$l\ kg^{-1}$
	I_l	-	$pmol\ kg^{-1}$
	I_p	-	$pmol\ kg^{-1}$
	I_{sc1}	-	$pmol\ kg^{-1}min^{-1}$
	I_{sc2}	-	$pmol\ kg^{-1}min^{-1}$

Table 2: Initial values of 12 ODE variables for Cobelli type 1 diabetic model [11][12][13]

Variable	Initial Value	Unit
$G_p(0)$	157.32	$mg\ kg^{-1}$
$G_t(0)$	151.30	$mg\ kg^{-1}$
$I_p(0)$	5.343	$pmol\ kg^{-1}$
$I_l(0)$	7.93	$pmol\ kg^{-1}$
$Q_{sto1}(0)$	0	mg
$Q_{sto2}(0)$	0	mg
$Q_{gut}(0)$	0	mg
$I_1(0)$	90.56	$pmol\ l^{-1}$
$I_d(0)$	90.56	$pmol\ l^{-1}$
$X(0)$	0	$pmol\ l^{-1}$
$I_{sc1}(0)$	172	$pmol\ kg^{-1}min^{-1}$
$I_{sc2}(0)$	417.71	$pmol\ kg^{-1}min^{-1}$

This system design was done by using MATLAB-Simulink software to simulate the PID controller with the Cobelli model. The controller was used to control the input insulin rate to maintain the glucose concentration at a normoglycemia level. The simulation started at the minute of 0 and stopped at 1440, which represent 24 hours or one-day simulation. Figure 2 shows the designed MATLAB-Simulink block diagrams of the PID controller system for insulin control on blood glucose concentration in the Cobelli diabetic model. Generally, this MATLAB Simulink based PID controller system consists of several parts. They are the S-function block to represent the ODE based mathematical descriptions from the Cobelli model which were then solved using MATLAB ODE solver function, the controller block that was used to control insulin amount to be injected based on the error signal from the blood glucose feedback, the glucose set point as the reference value for the glucose control mechanism, the signal builder block to represent inputs for the meal disturbance of breakfast, lunch, evening snack, dinner and night snack. Lastly, the blood glucose displays, blood glucose displays, input insulin display and data storage to analyze the outcome of the system.

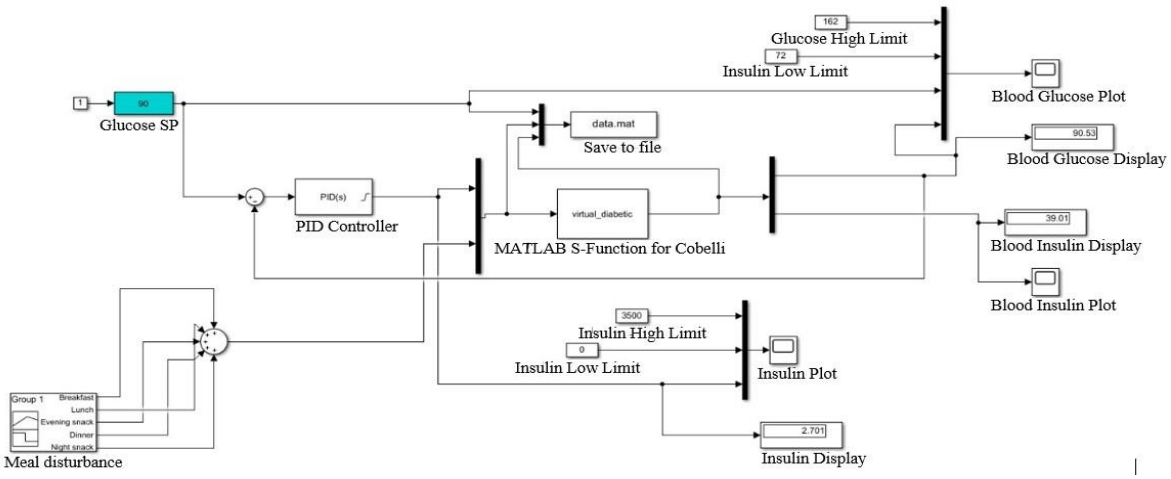
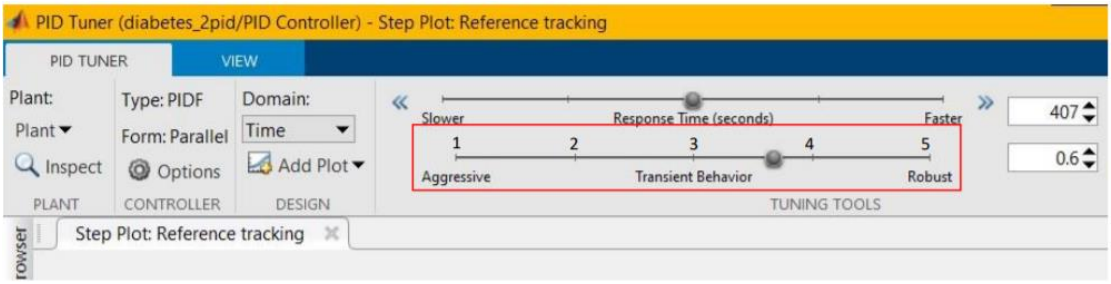


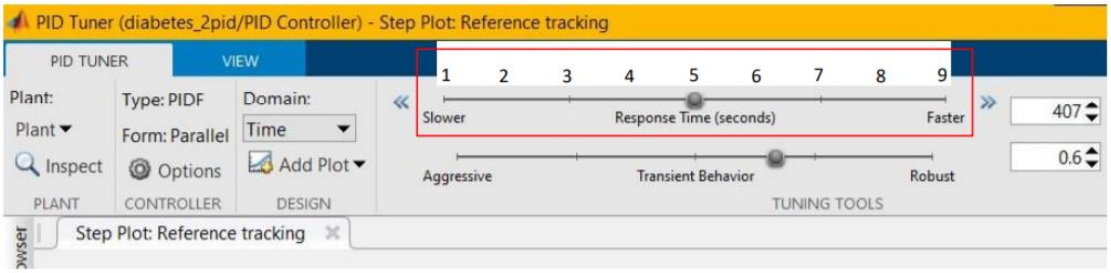
Figure 2: **MATLAB-Simulink block diagrams of the PID controller system for insulin control on blood glucose regulation in Cobelli diabetic model**

The PID controller optimization was done using the transfer function-based tuning technique from the MATLAB PID Tuner application. It was based on the tuning of Transient Behavior and Response Time sliders in MATLAB as shown in Figure 3 and Figure 4 to determine the optimum PID controller parameter values in obtaining the best results for the glucose-insulin regulation. Here, Transient Behavior is the functional unit of the PID controller system which reacts when it is disturbed from equilibrium or a steady state, where *Aggressive* is referred to as a fast rise time reaction and *Robust* is aimed to achieve performance or stability when bounded modelling errors are present. While Response Time is the time functional unit of the PID system to respond to a given input.



1: *Aggressive*
2: *Mid Aggressive*
3: *Normal*
4: *Mid Robust*
5: *Robust*

Figure 3: A segment of PID Tuner interface showing Transient Behavior slider set in five conditions



1: *Slower*
2: *Slower_Slow*
3: *Slow*
4: *Slow_Normal*
5: *Normal*
6: *Normal_Fast*
7: *Fast*
8: *Fast_Faster*
9: *Faster*

Figure 4: A segment of PID Tuner interface showing Response Time slider set in nine conditions

The PID controller optimization was conducted based on nine Response Time conditions of *Slower*, *Slower_Slow*, *Slow*, *Slow_Normal*, *Normal*, *Normal_Fast*, *Fast*, *Fast_Faster* and *Faster*. and five Transient Behavior conditions of *Aggressive*, *Mid Aggressive*, *Normal*, *Mid Robust*, and *Robust*. Firstly, the system was tuned based on the five Transient Behavior conditions with the response time of Slower. Then, based on the simulation results of the blood glucose concentration and blood insulin concentration plots, one optimum setting was selected among the five Transient Behavior conditions. Next, based on the one selected Transient Behavior setting, the system was again tuned with the nine Response Time conditions to find the optimum setting among the nine Response Time conditions before the optimum settings based on Transient Behavior and Response Time were determined.

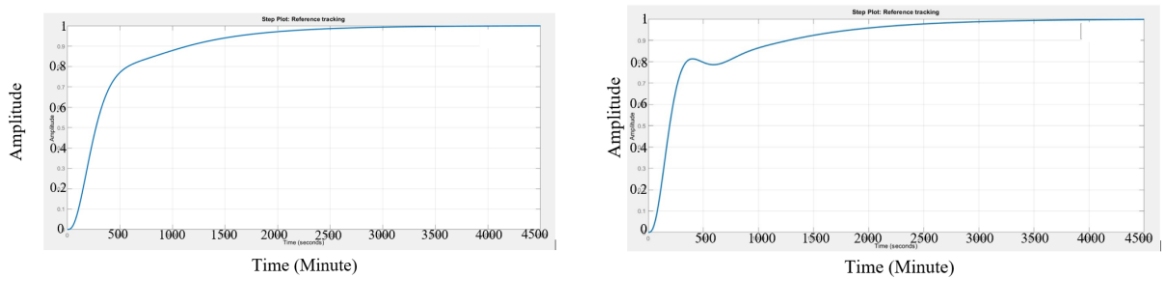
With the optimum parameter setting of the PID controller, a simple analysis on the meal disturbance based on the CHO intake and insulin sensitivity analysis also were conducted as case studies using the PID controller system for the glucose-insulin closed-loop regulation based on Cobelli type 1 diabetic model. For the analysis based on the CHO meal disturbance, the bolus size (mg/min) for lunch was reduced to prove with the reduction of the CHO intake, a diabetic patient can control the blood glucose better with a lower amount of the input insulin. For the insulin sensitivity analysis, the system made use of both 100%, 70%, and 50% of insulin sensitivity to analyze the behavior of the blood glucose concentration, the input insulin, and the blood insulin concentration changes.

3. Results and Discussion

Based on the PID controller optimization, the PID controller's optimum settings for the insulin-glucose closed loop regulation based on the Cobelli Type 1 diabetic model were within *Slow-Normal* and *Normal* conditions for Response Time and *Robust* condition for Transient Behavior. The settings have given better results of the blood glucose plots compared to the other conditions. Table 3 shows the parameter values of the PID controller for *Slow_Normal-Robust* and *Normal-Robust* setting conditions. While Figure 5 (a) and (b) show the PID controller response graphs *Slow_Normal-Robust* and *Normal-Robust* setting conditions. By comparing the response between *Slow_Normal-Robust* and *Normal-Robust* setting conditions in Figure 5 (a) and (b), the prior shows a shorter rise time than the latter, but both reached the steady-state at an almost similar time. In the *Normal-Robust* condition, there is a small fluctuation right after the rising response as it settled gradually at the final value.

Table 3: Parameter values of the PID controller for *Slow_Normal-Robust* and *Normal-Robust* setting conditions

Insulin Sensitivity	*Slow_Normal - Robust*	*Normal - Robust*
P	-0.05897	-0.0780
I	-9.0067	-9.6753
D	-8.7981	-15.5195



(a) (b)

Figure 5: Transfer-function tuning. (a) *Slow_Normal-Robust.* (b) *Normal-Robust*

Figure 6 (a) to (c) and Figure 7 (a) to (c) for the simulation results with *Slow-Normal-Robust* and *Normal-Robust*, respectively. According to Figure 5 and Figure 6, with regular changes in the blood insulin concentration and the input insulin control, the blood glucose concentration changes manage to stay within the hyperglycemic and hypoglycemic levels and near the normoglycemic level at the end of the simulations which show a good regulation of blood glucose [9][11].

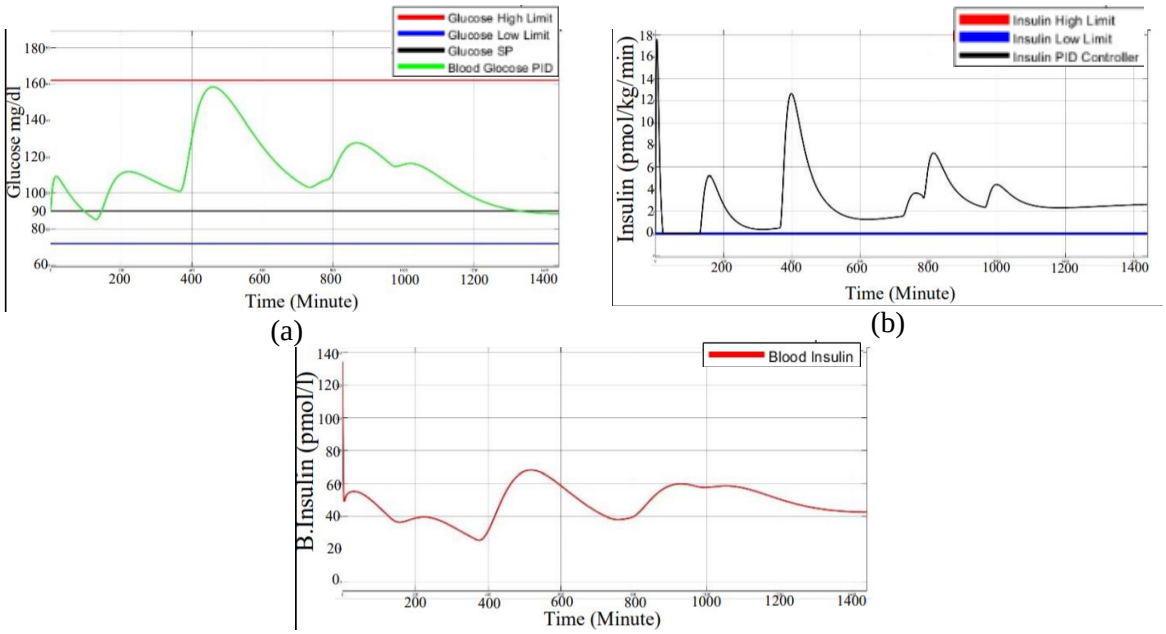


Figure 6: Simulation results for *Slow_Normal-Robust*. (a) Blood glucose plot. (b) Input insulin plot. (c) Blood insulin plot

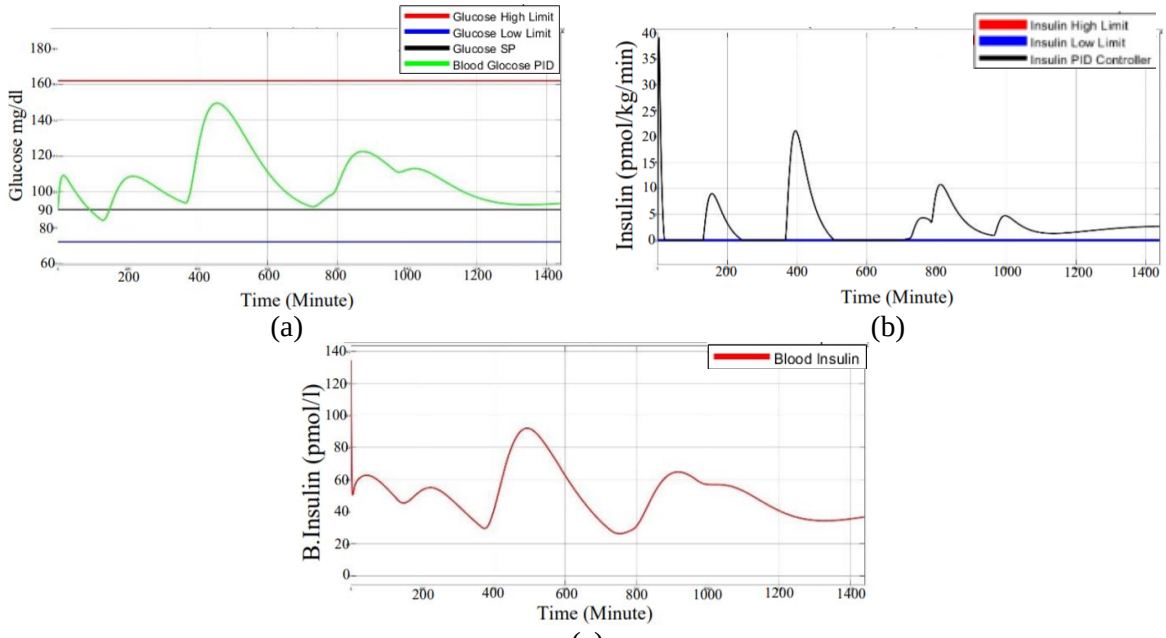


Figure 7: Simulation results for *Normal-Robust*. (a) Blood glucose plot. (b) Input insulin plot. (c) Blood insulin plot

For the meal disturbance analysis based on the CHO intake, the bolus size of the CHO intake during the lunch has been reduced by 6000 mg/min. The simulation results of the blood glucose concentration, input insulin and blood insulin concentration plots before and after the reduction can be seen in Table 4. The results show that with higher CHO intake, each of the three plots has a higher increasing peak at the minutes of 400 to 600 min, and with a lesser CHO intake, each of the plots shows a lower peak in the same time frame. Based on these results, it could be understood that less CHO intake can prevent the diabetic patient from having higher blood glucose and the patient needs lesser input insulin administration. The result shows, when diabetic patient take less amount of CHO, glucose level can be control efficiently [10],[14].

Table 4: Results from the meal disturbance analysis based on the reduction in CHO intake during lunch.

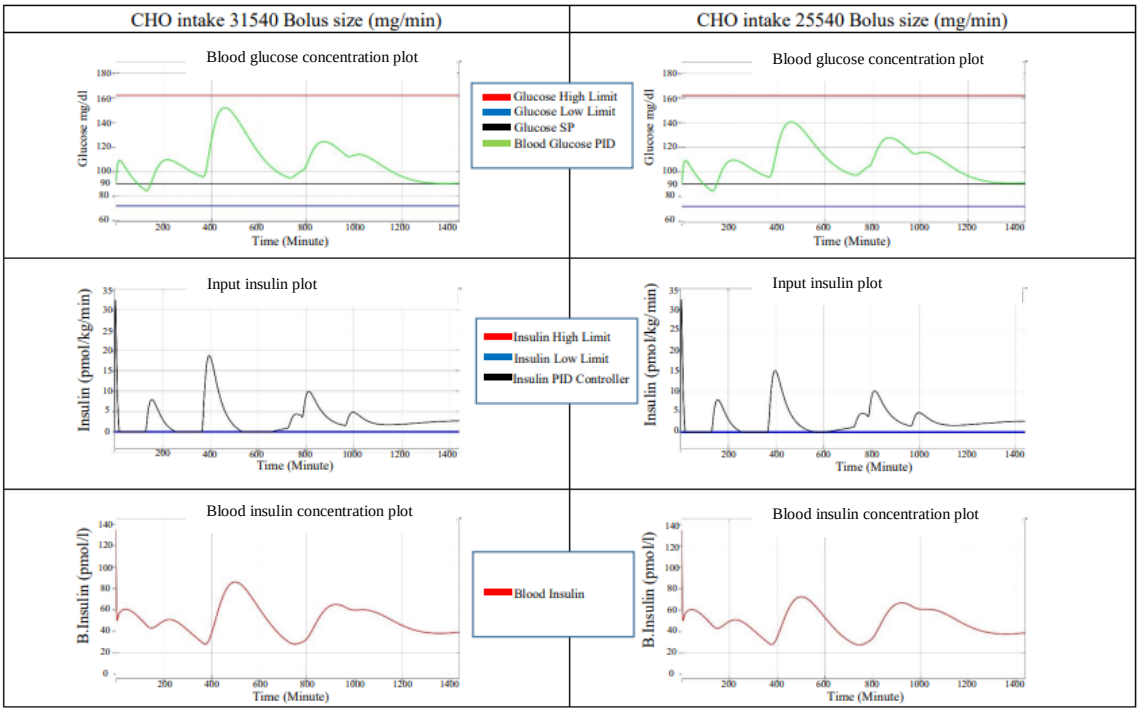
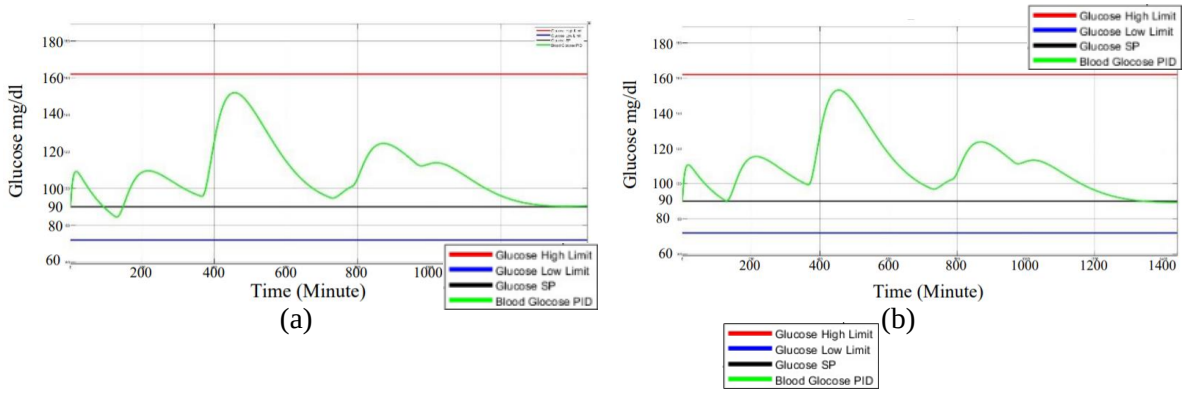
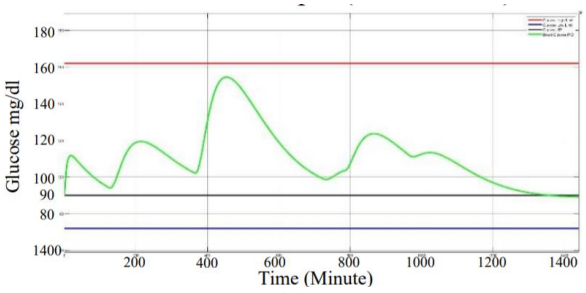


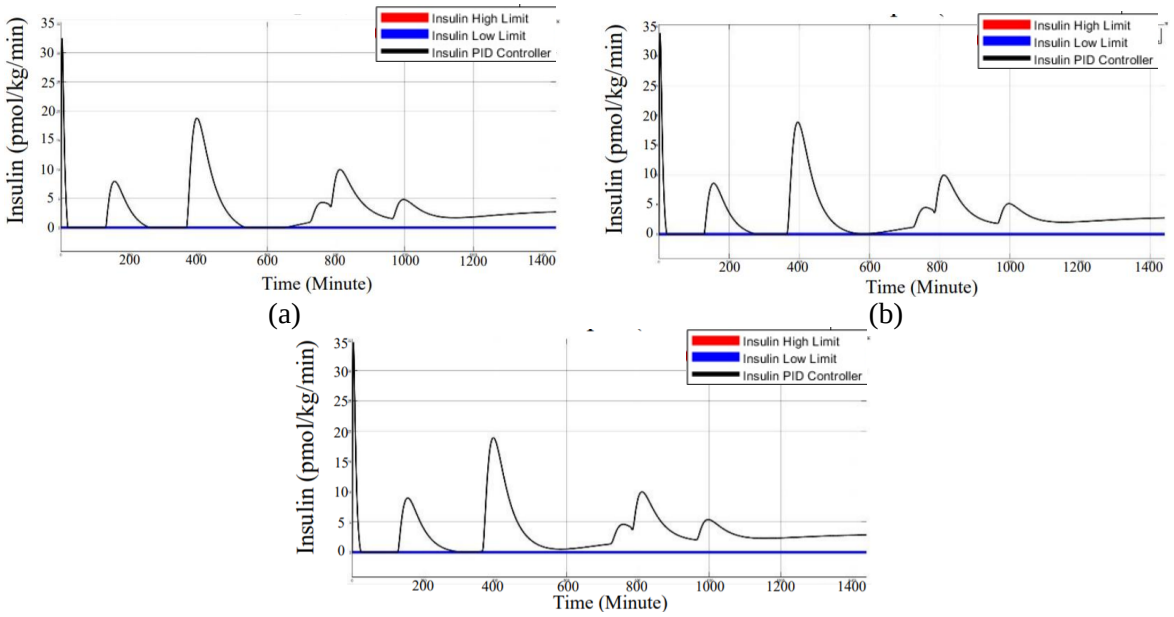
Figure 8 (a) to (c), Figure 9 (a) to (c) and Figure 10 (a) to (c) show the blood glucose concentration, input insulin and blood insulin concentration plots, respectively for 100%, 70%, and 50% of the insulin sensitivity analysis based on the PID controller system. Based on the results, the system demonstrated that as the insulin sensitivity decreases, the blood glucose concentration, the input insulin and the blood insulin concentration slightly increase. This is because when the sensitivity of the insulin is low, the glucose level affecting less efficient [3][7] [10].





(c)

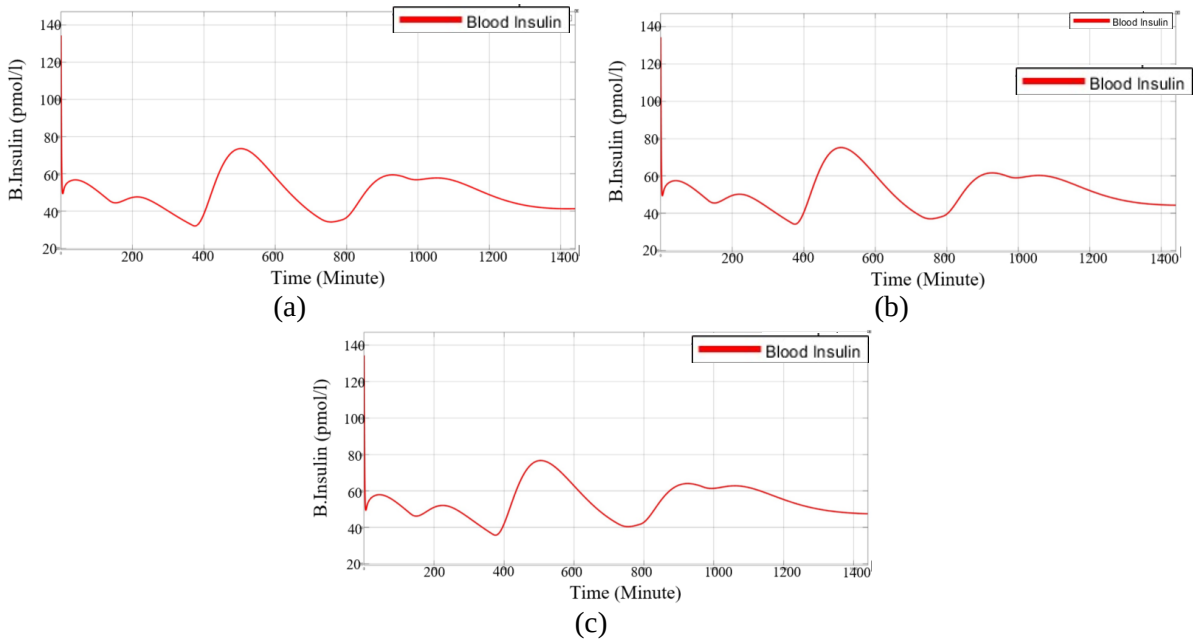
Figure 8: Simulation results of blood glucose concentration plots for the insulin sensitivity (a) 100%. (b) 70%. (c) 50%.



(a) (b)

(c)

Figure 9: Simulation results of input insulin plots for the insulin sensitivity (a) 100%. (b) 70%. (c) 50%



(a) (b)

(c)

Figure 10: Simulation results of blood insulin plots for the insulin sensitivity (a) 100%. (b) 70%. (c) 50%

4. Conclusion

This project resulted in a simulation of a PID controller-based glucose-insulin closed-loop regulation system using MATLAB Simulink based on the Cobelli model Type 1 diabetic. This project modelled a 24-hour simulation system with a meal disturbance to indicate a more realistic computational simulation of continuous glucose-insulin closed-loop regulations. Transfer function-based tuning technique from MATLAB PID Tuner application was used to optimize the PID controller and the optimum settings *Slow-Normal* and *Normal* Response Time, with *Robust* Transient Behavior to achieve appropriate blood glucose concentration plots which stay near the normoglycemic level. A simple analysis on meal disturbance also was done and showed that with lower CHO intake, the peak of blood glucose is lower and needs lower input insulin to control the blood glucose than with higher CHO intake. Lastly, an analysis of 100%, 70%, and 50% insulin sensitivity was done to evaluate the performance of the optimization graph plot and it has given relevant results of the blood glucose concentration, the input insulin and the blood insulin concentration plots.

Acknowledgement

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