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MEAL SIMULATION IN GLUCOSE-INSULIN REACTION ANALYSIS USING HOVORKA MODEL TOWARDS SYSTEM-ON-CHIP IMPLEMENTATION

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ABSTRACT

In this paper, a mathematical modeling concept is used to analyse the glucose-insulin interaction in managing Type 1 Diabetes Mellitus (T1DM). The Hovorka model has been chosen to design the glucose kinetics, so that the relationship between reaction of insulin to blood glucose concentration can be observed. This mathematical model implements a nonlinear ordinary differential equation where each parameter represents specific functions. The meal and exogenous insulin bolus are the two inputs in this mathematical model for prediction of glucose levels. The analysis of this model is done by using C++ programming language which is the first step towards system-on-chip (SoC) implementation for real time simulation based analysis of glucose-insulin dynamics.

Key words: Hovorka Model • Ordinary Differential Equation • Glucose-Insulin Recation • System-on-Chip •

INTRODUCTION

According to International Diabetes Federation (IDF), in 2014, there are 385 millions of people worldwide suffering from diabetes which most of the numbers come from Western Pacific region such as Malaysia, China and Cambodia (Aguiree et al. 2013). This figure is expected to increase to 592 millions on 2035. Statistic of diabetes in Malaysia shows that 24,049 people died due to diabetes on 2013 (Lum. 2015) and this make the diabetes prevalence in Malaysia is 15.2 % (Health 2011). The total money spent in this issue is almost RM 88.4 billion in 2013 (Lum. 2015). Diabetes can give effects to the economy, social and healthcare system since the population of the people suffering diabetes is high (Ajmera et al. 2013).

Diabetes is a term used to describe the level of blood glucose concentration in the bloodstream. It is normally refer to high blood glucose level or also known as hyperglycemia. The glucose level can be high in the blood because there is insufficient amount of insulin produced by the pancreas. A quick action must be taken as the condition will get worse with time (Lum. 2015). If the glucose level is not tightly control, it will lead whether to hyperglycemia or hypoglycemia (low blood glucose level).

There are four types of diabetes; Type 1 Diabetes Mellitus (T1DM), Type 2 Diabetes Mellitus (T2DM), Gestational Diabetes Mellitus (GDM) and other specific types (Gonzales and Adi, 2012). In this study, the focus is based on T1DM. Type 1 Diabetes Mellitus or known as insulin dependent is a condition where the pancreas unable to produce adequate amount of insulin to promote the uptake of glucose into the tissues. It may be due to destruction of β-cell in the pancreas. This type of diabetes normally experience by the children and young adult (Persatuan Diabetes Malaysia, 2006). People who is suffering TIDM must take insulin exogenously to prevent the level keep on increasing, so that the glucose concentration can be kept near to normaglycemic level (70 – 140 mg/dL) (Soru et al., 2012). If the diabetes is poorly controlled, it can lead to long term complications such as retinopathy, nephropathy and cardiovascular pathologies.

Metabolic disease such as diabetes is the result of imbalance in glucose homeostasis (McKnight et al. 2013). A research on managing diabetes has been carried out since 50 years ago especially towards using mathematical modeling (Bergman et al., 1981), (Chen and Tsai, 2010), (Cobelli et al., 2014), (Wilinska et al., 2005). The minimal model introduced by Bergmann (Bergman et al. 1979) has lead the advancement in managing diabetes and Hovorka (Hovorka et al., 2002) has improved the model by implementing compartmental model. Mathematical modeling is very useful because it can help the researcher to obtain knowledge on the glucose-insulin dynamic system, and to give a clear picture on how the glucose-insulin interaction works (Ajmera et al. 2013).

By doing the simulation based analysis of the glucose-insulin dynamics, an optimum theraphy can be suggested to the diabetes patient, so that the blood glucose level concentration can be kept under controlled since any inaccuracy prescription of insulin dosage will lead to more serious problem (Yusof et al, 2014). Moreover, using a model predictive control (MPC) with the Hovorka model, the glucose concentration can be predicted by controlling the insulin pump based on the output of the Hovorka model (Pedersen and Hansen, 2010). The advantages of using MPC is that it is able to control nonlinear system (Wang et al., 2010) and has the ability in dealing with time delays (Jiang and Wang, 2010), however faster and longer time interval of computations for the prediction are needed. There is a microchip within the insulin pump that to carry out the computation however with a small capacity

(Naerum, 2010). Recently, towards low power and a compact system, a System-on-Chip (SoC) implementation based on field-programmable gate array (FPGA) has gained much attention providing higher performance system when compared to microcontroller-based architecture. The interconnection between the processor and the FPGA logic enables the system performance to be improved due to high-bandwidth produced between them (Chen and Kung, 2008).

Therefore, the aim of the research is to conduct a simulation based analysis for glucose-insulin reaction in Type 1 Diabetes Mellitus Patient using the Hovorka model as the first step before System-on-Chip (SoC) implementation can be realized for a high performance real-time system. The information on the amount of meal taken and the insulin bolus is taken into consideration to examine the effect on the glucose concentration in the bloodstream. The proposed FPGA-based SoC implementation and design process are also described in this paper to highlight the final target of this research work.

This paper is organized into four sections; introduction, methodology, result and analysis and conclusion. Section methodology discusses the method used to study the glucose-insulin reaction. All the equations involved in the Hovorka model is discussed in the section. In result and discussion section, the simulation results regarding the virtual type 1 diabetes mellitus with respect to meal disturbances and insulin bolus are presented and analyzed. The overall finding in this paper is concluded in the conclusion section.

METHODOLOGY

Hovorka Model

The Hovorka model (Hovorka et al., 2004), (Naerum, 2010), (Lassen and Nielsen, 2008), (Andersen, 2014) has been introduced by Dr Roman Hovorka who is a researcher in University of Cambridge under the Department of Paediatrics. His research focus is to develop a medical device that is the artificial pancreas to acquire the blood glucose level overnight by implementing mathematical modeling approach (Juvenile Diabetes Research Foundation). The artificial pancreas can be described as a monitoring tool where it uses continuous glucose monitor to check the glucose level in every minute, so that the insulin pump can release adequate amount of insulin controlled by the control algorithm (Cambridge Immunology).

This model consists of three types of subsystems; glucose absorption subsystem, subcutaneous insulin absorption subsystem and insulin action subsystem. It includes eight nonlinear ordinary differential equations (ODE) that can be categorized as nonstiff equation (Boiroux et al., 2010).

Subcutaneous Insulin Absorption Subsystem

The insulin is injected into a patient's body through subcutaneous. This method is more practical because the insulin is given to the patient non-invasively compared to classical method injected directly to the bloodstream. The insulin absorption can be represented in equation as follows:

$$\frac{dS_1(t)}{dt} = u(t) - \frac{S_1(t)}{\tau_S} \quad (1)$$

$$\frac{dS_2(t)}{dt} = \frac{S_1(t)}{\tau_S} - \frac{S_2(t)}{\tau_S} \quad (2)$$

By knowing the amount of injected insulin, the rate of absorption of insulin into the bloodstream, $U_I(t)$ can be calculated as in equation (3). It is measured in mU/min.

$$U_I(t) = \frac{S_2(t)}{\tau_S} \quad (3)$$

As the insulin entered the bloodstream, it becomes the plasma insulin. The plasma insulin concentration, $I(t)$ [mU/L] can be calculated by using the following formula.

$$\frac{dI(t)}{dt} = \frac{U_I(t)}{V_I} - k_e I(t) \quad (4)$$

$S_1(t)$: Amount of insulin in compartment 1, stomach [mU]
$S_2(t)$: Amount of insulin in compartment 2, colon [mU]
$u(t)$: Insulin input [mU/min]
τ_S : Time constant of injected insulin absorption [min]
V_I : Insulin distribution volume [L/kg]
k_e : Insulin elimination rate from plasma [min^{-1}]

Insulin Action Subsystem

The relationship between insulin and glucose can be observed in insulin action subsystem. The input for this subsystem comes from the insulin absorption rate in the blood, $U_I(t)$. It involves three parameter insulin dependent state; transport and distribution, $x_1(t)$, glucose disposal, $x_2(t)$ and endogenous production of glucose, $x_3(t)$. The nonlinearity of this model is due to these interactions and can be calculated by using the following formulas equation (5-7).

$$\frac{dx_1(t)}{dt} = -k_{a1}x_1(t) + k_{b1}I(t) \quad (5)$$

$$\frac{dx_2(t)}{dt} = -k_{a2}x_2(t) + k_{b2}I(t) \quad (6)$$

$$\frac{dx_3(t)}{dt} = -k_{a3}x_3(t) + k_{b3}I(t) \quad (7)$$

The relations between the activation rates, k_{b1}, k_{b2} and k_{b3},the deactivation rates k_{a1}, k_{a2} and k_{a3} and the insulin sensitivities S_{IT}, S_{ID} and S_{IE} are shown in equation (8-10).

$$k_{b1} = k_{a1}S_{IT} \quad (8)$$

$$k_{b2} = k_{a2}S_{ID} \quad (9)$$

$$k_{b3} = k_{a3}S_{IE} \quad (10)$$

k_{a1}, k_{a2}, k_{a3} : deactivation rate [min^{-1}]
k_{b1}, k_{b2}, k_{b3} : activation rate [min^{-1}]
S_{IT} : insulin sensitivity of transport/ distribution [L/mU/min]
S_{ID} : insulin sensitivity of disposal [L/mU/min]
S_{IE} : insulin sensitivity of EGP [L/mU/min]

Carbohydrate (CHO) Absorption Subsystem

In order to observe the effect of meal on the blood glucose concentration, additional subsystem has been included into the Hovorka model calledcarbohydrate (CHO) subsystem. It acts as the input to the model where it describes any uptake of meal. The function of this compartment is to know the glucose absorption rate, $U_G(t)$ [mmol/min] in the bloodstream when certain amount of carbohydrate is consumed, $d(t)$ [g/min]. The equations involve in this subsystem are as follows:

$$\frac{dD_1(t)}{dt} = A_G D(t) - \frac{D_1(t)}{\tau_d} \quad (11)$$

$$\frac{dD_2(t)}{dt} = \frac{D_1(t)}{\tau_d} - \frac{D_2(t)}{\tau_d} \quad (12)$$

$$D(t) = \frac{1000 * d(t)}{M_G} \quad (13)$$

$$U_G(t) = \frac{D_2(t)}{\tau_d} \quad (14)$$

$D_1(t)$: Amount of glucose in compartment 1, stomach [mmol]
$D_2(t)$: Amount of glucose in compartment 2, colon [mmol]
$D(t)$: Ingested CHO input [mmol/min]
$A_G(t)$: CHO bioavailability
$M_G(t)$: Molecular weight of CHO [g/mol]
τ_d : Time constant for glucose absorption rate [min]

Glucose Subsystem

This subsystem represents the amount of glucose in the bloodstream, $Q_1(t)$ [mmol] and in the peripheral tissue $Q_2(t)$ [mmol] from equation (15) and (16), respectively. When meal is consumed, carbohydrate content breakdown into glucose as it goes down into the stomach, thus increasing the glucose concentration. An increase value in the glucose concentration will force the glucose to be distributed to nearby tissue that has low gradient of glucose concentration.

(15)

$$\frac{dQ_1(t)}{dt} = U_G(t) - F_{01,c} - F_R - x_1(t)Q_1(t) + k_{12}Q_2(t) + EGP_0[1 - x_3(t)]$$

$$\frac{dQ_2(t)}{dt} = x_1 Q_1(t) - [k_{12} + x_2(t)]Q_2(t) \quad (16)$$

$$F_{01,c} = \begin{cases} F_{01} & , \quad G(t) \geq 4.5\text{mmol/L} \\ \dfrac{F_{01}G(t)}{4.5} & , \quad \text{otherwise} \end{cases} \quad (17)$$

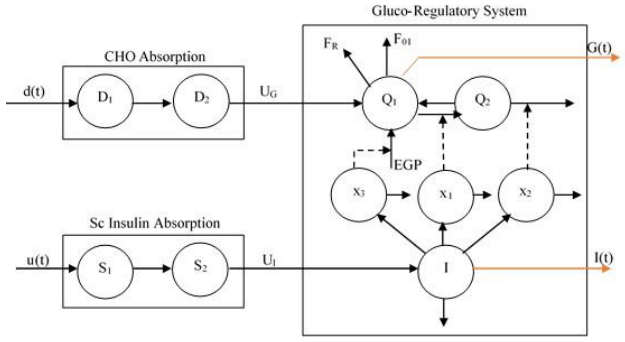
$$F_R = \begin{cases} 0.003(G(t) - 9)V_G & , \quad G(t) \geq 9\text{mmol/L} \\ 0 & , \quad \text{otherwise} \end{cases} \quad (18)$$

The blood glucose concentration measurement is an important parameter for people who is suffering diabetes. Therefore, it is important to know the blood glucose concentration, $G(t)$ [mmol/L] before and after meal that can be calculated from Eq. 19.

$$G(t) = \frac{Q_1(t)}{V_G} \quad (19)$$

$U_G(t)$: Glucose absorption rate [mmol/min]
$F_{01,c}$: Consumption of glucose by the central nervous system [mmol/min/kg]
F_R : Renal glucose excretion [mmol/min]
k_{12} : Glucose transfer rate from the blood to the tissue [min^{-1}]
EGP_0 : EGP extrapolated to zero insulin concentration [mmol/min/kg]
V_G : Glucose distribution volume [L/kg]
F_{01} : Non-insulin dependent glucose consumption [mmol/min/kg]

Figure 1 shows the flow of each compartment in the Hovorka model. The first compartment which is CHO absorption will produce $U_G(t)$ which later use as the input for the gluco-regulatory system compartment. The output for the second compartment which is the subcutaneous insulin absorption is $U_I(t)$. This become the input for the insulin action subsystem. The third compartment which is the gluco-regulatory system compartment represents the glucose kinetics which shows the glucose distribution inside the body system. The final output of this model is the glucose concentration, $G(t)$ and the plasma insulin concentration, $I(t)$. For the constant parameters refer



(Hovorka et al. 2004).

Figure 1: The Hovorka model representation (Andersen, 2014)

Simulation Setup

In order to get a realistic view of the Hovorka model a number of different simulations are performed to examine how the blood glucose concentration reacts to meal disturbances according to insulin inputs. The simulations have been done using C++ language The ordinary differential equations (ODEs) of the Hovorka model are solved using forward Euler's method with fixed step size of 0.001. The initial value for every variable present in the equations is and is summarized in Table 1. The overall simulation is based on patient's body weight (BW). In this simulation, the body weight is set constant to 70 kg because the body weight does not show significant changes when consumed certain amount of meal.

Table 1: Initial value of each variable

Variables	Initial value
$D_1(t)$	0
$D_2(t)$	0
$S_1(t)$	3.6734×10^2
$S_2(t)$	3.6734×10^2
$I(t)$	5.7616
$x_1(t)$	0.0295
$x_2(t)$	0.0047
$x_3(t)$	0.2996
$Q_2(t)$	23.3565
$Q_1(t)$	55.9971

The C++ codes of the simulation will then be used for SoC implementation on FPGA to become the analysis-based tool in more interactive way.

RESULT AND ANALYSIS

Meal Simulation in Glucose-Insulin Reaction

The amount of meal taken can affect the blood glucose concentration. For diabetic person, they need to know how much carbohydrate they consumed, so that the amount of insulin administered can be effectively controlled the blood glucose concentration. This is to avoid a major problem that is hypoglycemia.

By using the Hovorka model, simulations have been conducted to analyze the effect of meal disturbances and insulin inputs, $u(t)$ that come from a constant basal insulin infusion rate, $u_{ba}(t)$ as in equation (20) and insulin boluses, $u_{bo}(t)$ (Table 5) to the blood glucose concentration.

$$u_{ba}(t) = 0.0954119 * \mathrm{BW} \quad (20)$$

As shown in Table 2, a summary of daily meal intake has been constructed based on the amount of carbohydrate taken during breakfast, lunch, afternoon snack, dinner and evening snack.

Table 2: Daily meal intake

Meal	Item	Quantity	CHO Content	g CHO
Breakfast	Oatmeal	2 cup	15g CHO per ½ cup	60.00
	Milk	1 cup	15g CHO per 1 cup	15.00
	Dates	4 units	15g CHO per 3 units	20.00
	Dried fruit	1 1/2 tbsp	15 g CHO per 2 tbsp	11.25
Total				106.25
Lunch	Rice	2/3 cup	15g CHO per 1/3 cup	30.0
	Carrot (cooked)	1/2 cup	5g CHO per 1/2 cup	5.0
	Curry korma	1/2 serving	14g CHO per 1 serving	7.0
	Honeydrew	1 slice	15g CHO per 1 slice	15.0
Total				57.0
Afternoon snack	Sandwich crackers	5 units	15g CHO per 3 units	25.0
	Raisin	1 tbsp	15g CHO per 2 tbsp	7.5
Total				32.5
Dinner	Rice	1 cup	15g CHO per 1/3 cup	45.0
	Fish fingers	3 unit	11g CHO per 2 units	16.5
	Banana	1 unit	15g CHO per 1 unit	15.0
	Cabbage (cooked)	1 cup	5g CHO per 1/2 cup	10.0
Total				86.5
Evening snack	Sandwich crackers	5 units	15g CHO per 3 units	25.0
	Raisin	1 tbsp	15g CHO per 2 tbsp	7.5
Total				32.5

Table 3 shows the starting time for each meal taken. Each meal consumed at different duration of time. For breakfast and snack it is estimated to finish the meal within 10 minutes while for lunch and dinner it is approximately 20 minutes each. The timing of each meal is important to note because it helps to calculate the rate of carbohydrate taken for each meal at the interval of five minutes which is according to a duration for a single bolus. the reason for five minutes intervals is because at this interval the basal insulin infusion continuously supply to the virtual patient and blood glucose concentration is also measured every five minutes (Pejtersen and Jesen, 2010), (Skjaervold et al., 2012). The simulations are set to start at 6 o'clock in the morning.

Table 3: The time and duration of each meal

Meal	Starting time	Duration (min)
Breakfast	9:30	10
Lunch	12:30	20
Afternoon snack	16:00	10
Dinner	18:30	20
Evening Snack	21:00	10

Table 4 shows the summary of bolus-like carbohydrate of each meal which based on the duration in Table 3. The information for total size, rate and bolus size are dependent to each other. The bolus size is the size of the meal when gathered as a single bolus. The rate and the bolus size can be calculated by referring to the following formula.

$$\text{rate} = \frac{\text{total size}}{\text{duration}} \quad (21)$$

$$\text{bolus size} = \text{rate} * \text{number of time in 5 minute interval} \quad (22)$$

Table 4: Bolus size for each meal

Meal	Total size (g)	Rate (g/min)	Bolus size (g/min)
Breakfast	106.25	10.625	21.25
Lunch	57.00	2.850	11.40
Afternoon snack	32.5	3.250	6.50
Dinner	86.5	4.325	17.30
Evening snack	32.5	3.250	6.50

According to the meal times and bolus sizes in the Tables 3 and 4, respectively, the meal disturbances are represented in Figure 2. The timing of meal is measured in minutes.

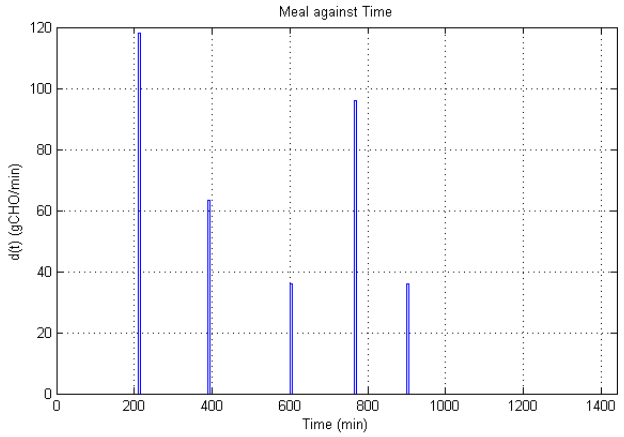


Figure 2: Meal disturbances with respect to time of meal.

Figure 3 shows the result of the glucose concentration against time in response to the meal disturbances by considering only the basal insulin input that is computed to be 6.68 mU/min. The area within the two horizontal lines in light blue colour indicate the normal level of blood glucose concentration which in the range of 3.89 mmol/L to 7.77 mmol/L (Soru et al., 2012). A person with glucose level concentration above or below this range will experience hypoglycemia or hyperglycemia, respectively. According to Figure 3, the blood glucose concentration seems very high when a meal is taken due to lack of amount of insulin produced by the pancreas to keep the blood glucose level within normal range.

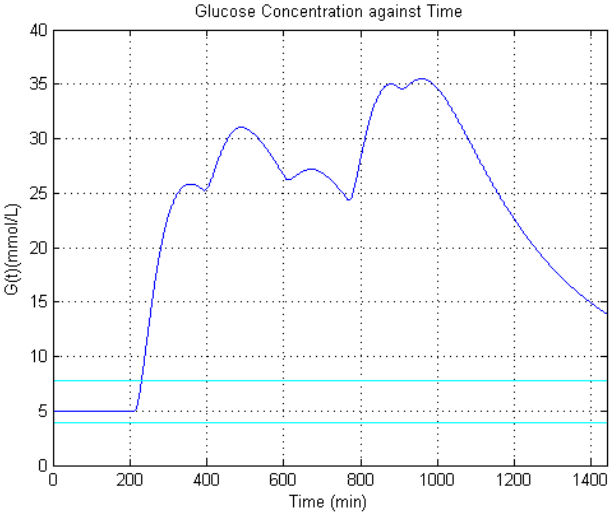


Figure 3: Glucose concentration against time by considering only the basal insulin.

In order to control the glucose concentration level down to normal level after every meal, exogenous insulin inputs are added which are came from insulin infusion boluses in the simulations. These insulin boluses are found using trial and error in order to get the possible minimum level of glucose concentration while staying above hypoglycemia at 3.89 mmol/L. Table 5 shows the rate of insulin boluses administration at five minute intervals which is also according to a duration for a single bolus. Here, the insulin bolus describes how one unit of insulin can affect on how much grams of carbohydrate.

Table 5: Insulin boluses for the meals during a typical day found by trial and error

Meal	Insulin bolus, $u_{bo}(t)$ (mU/min)
Breakfast	730
Lunch	450
Afternoon snack	250
Dinner	650
Evening snack	240

The simulation is done according to three conditions such that an insulin bolus is administered at 30 minutes before, during and 30 minutes after each meal to observe the effectiveness of the insulin administration relative to the time of the meals. The amount of insulin administered on the three different time are the same. The insulin boluses together with basal insulin are represented in Figure 4.

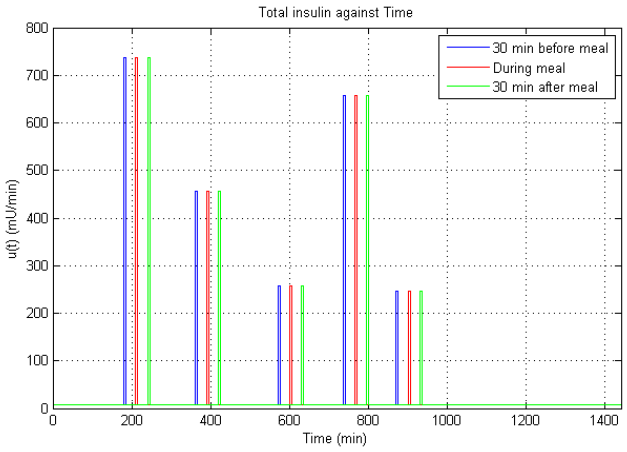


Figure 4: Total insulin at each meal time.

Figure 5 shows the simulation results of the glucose concentrations against time with bolus insulin administered according to the three simulation conditions. From the result, the level of blood glucose concentration keep on increasing and decreasing gradually for each meal time as the effect from the insulin boluses administration. Throughout the day, the blood glucose concentration is kept near to normal level but more stable and steady blood glucose levels are able to be controlled when the insulin bolus is given at 30 minutes before each of the meal time. Moreover, during the afternoon snack at time around 600 min and 1100min, the blood glucose level reached the hypoglycemic state when the insulin bolus is administered during and 30 minutes after the meals. Thus, it shows that it is preferred to give insulin injection 30 minutes before meal time as it gives more steady reading of the blood glucose concentration and able to regulate the level within the normoglycemic range.

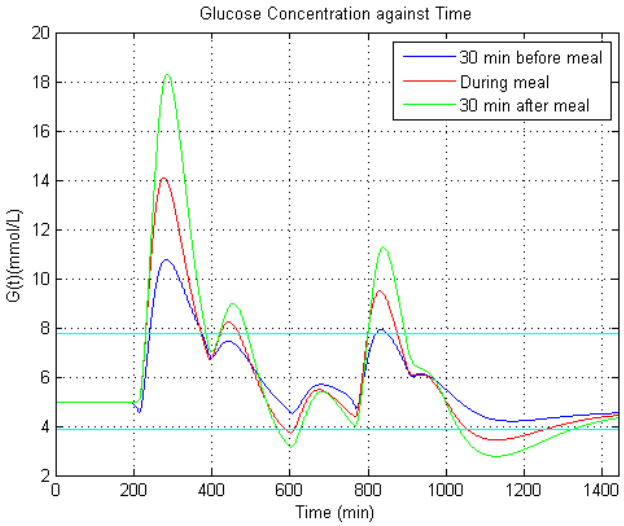


Figure 5: Glucose concentration against time by considering the basal insulin and the insulin boluses administered before, during and after each meal intake.

Glucose-Insulin Reaction Design Work for SoC implementation

Field programmable gate array (FPGA) is a platform enable the circuit designer to configure their own digital logic blocks. The advantages of using FPGA are it can be used to provide real time simulation and configurable according to desired design requirements.

SoC is an embedded system where the complete hardware system for a target application is integrated in a single chip (Hau et al. 2011) offering many benefits including lower hardware cost and power consumption. These benefits make SoC the best architecture for real time embedded systems having tight design constraints such as used in medical electronic devices.

Based on the C++ simulation program developed in this study, the project will focus on the hardware design in which the high-level synthesis (HLS) approach will be used before further step is taken towards SoC implementation. A software Vivado HLS 2014.1 will be used to convert the C++ code into hardware description language (HDL) to enable the code implement into the FPGA board. This is known as hardware accelerator.

Next, the design wll be furthered into designing the SoC platform using MicroBlaze soft processor core. The MicroBlaze intellectual property (IP) will be chosen. The synthesized IP package produced during the convertion into HDL code will be inserted into the SoC platform as one of the process required. Then, the process will undergo logic synthesis. The bitstream file will be generated to make possible the execution process into the FPGA board. Figure 6 shows the overall process.

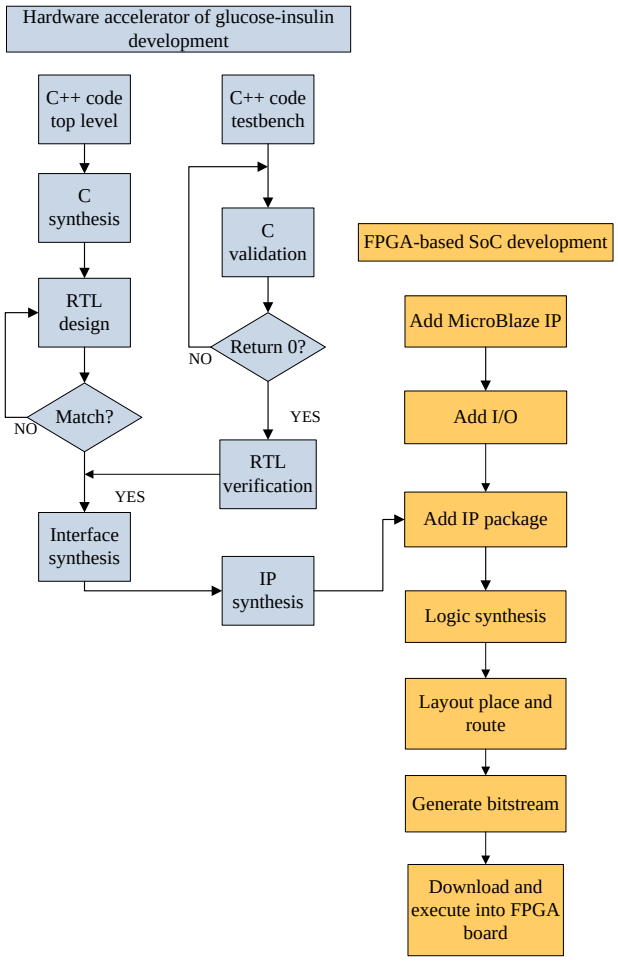


Figure 6: The flow for SoC implementation

The proposed block diagram of glucose-insulin reaction analysis for SoC implementation is shown in Figure 7. The SoC will act as the virtual diabetes patient where it contains the Hovorka model that later will be used to do further analysis to get appropriate therapy for the patient. The virtual patient depends on three inputs; body weight, meal in terms of weight of carbohydrate and insulin bolus. Then, these information will be processed in the SoC to obtain the glucose concentration level and eventually could suggest the amount of insulin accurately to be taken by the patient.

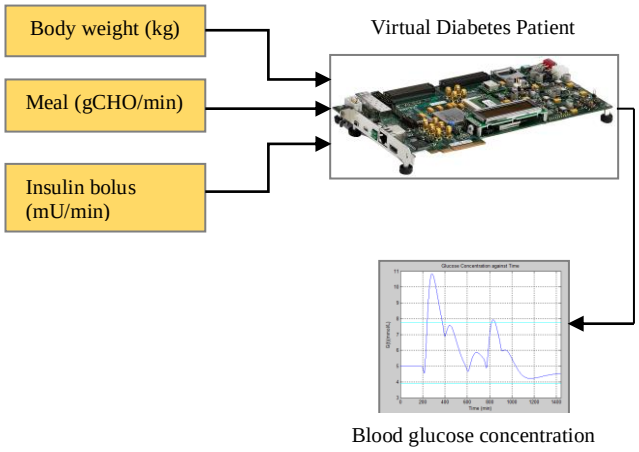


Figure 7: Proposed block diagram for SoC implementation of real time glucose-insulin reaction.

CONCLUSION

According to the C++ programming used in this study, the blood glucose concentration has been analyzed based on the Hovorka model related to the effect of meal disturbances and insulin bolus. Later, this simulation-based analysis will be used for the SoC implementation to target for real time analysis system of glucose-insulin reaction. In the future, this type of SoC design work may have a potential to be further designed into a model predictive control of glucose-insulin for artificial pancreas system that act as a control system in regulating the glucose homeostasis in the bloodstream.

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REFERENCES

Aguiree, F., Brown, A., Cho, N.H., et al. (2013). IDF Diabetes Atlas. Sixth edition.

Ajmera, I., Swat, M., Laibe, C., Nover, N.L and Chelilah, V. (2013). Review: The impact of mathematical modeling on the understanding of diabetes and related complications. *Pharmacology & Systems Pharmacology*, 2013(2), e54; doi: 10.1038/psp.2013.30.

Altera's User-Customizable ARM-based SoC (2014). Retrieve from https://www.altera.com/en_US/pdfs/literature/br/br-soc-fpga.pdf

Andersen, S. H. (2014). Software for in silico testing of an artificial pancreas. Master thesis. Technical University of Denmark.

Bergman, R.N., Ider, Y.Z., Bowden, C.R. and Cobelli, C. (1979). Quantitative estimation of insulin sensitivity. *American Journal of Physiology*, 236(6): E667-E677.

Bergman, R.N., Philips, L.S. and Cobelli, C. (1981). Physiological evaluation of factors controlling glucose tolerance in man. *Journal of Clinical Investigation,*. vol. 68. pp.1456-1467.

Boiroux, D., Finan, D.A., Jorgensen, J.B., Poulsen, N.K. and Madsen, H. (2010). Meal estimation in nonlinear model predictive control for type 1 diabetes. *8th IFAC Symposium on Nonlinear Control System*. pp.1052--1057.

Cambridge Immunology. Dr Roman Hovorka. University of Cambridge. Retrieved from http://www.immunology.cam.ac.uk/directory/rh347@cam.ac.uk

Chen, C.L. and Tsai, H.W. (2010). Modeling the physiological glucose-insulin system on normal and diabetic subjects. *Computer methods and programs in biomedicine* 97. pp. 130-140.

Chen, Y.K. and Kung, S.Y. (2008). Trend and challenge on system-on-chip designs. *Journal of VLSI Signal Processing System*, Vol 53(2), pp 217-229. Doi: 10.1007/s11265-007-0129-7.

Cobelli, C., Man, C.D., Pedersen, M.G., Bertoldo, A. and Toffolo, G. (2014). Advancing our understanding of the glucose system via modeling: a perspective. *IEEE. Doi: 10.1109/TBME.2014.2310514.*

Ghosh, P. (2006). Numerical methods with computer programs in C++. Prentice-Hall India.

Gonzales, A. G. and Adi, S. (2012). Chapter 1: An overview. Nutritional and therapeutic interventions for diabetes and metabolic syndrome. pp.3–13. Doi: 10.1016/B978-0-12-385083-6.15001-6

Hamblen, J.C., Hall, T.S. and Furman, M.D. (2008). Chapter 15: Introducing system-on-a-programmable chip. Rapid prototyping of digital system. Springer.

Hau, Y.W., Hani, M.K. and Marsano, M.N. (2011). SystemC-based hardware/software co-design of elliptic curve cryptographic system for network mutual authentication. *Malaysian Journal of Computer Science*, Vol 24(2), pp 111-130.

Health Public. Nationa Health and Morbidity Survey 20011. Fact Sheet.

Hovorka, R., Moradie, F.S., Carroll, P.V., Chassin, L.J., Gowrie, I.J., Jackson, N.C., Tudor, R.S., Umpleby, A.M and Jones, R.H. (2002). Partitioning glucose distribution/transport, disposal, and endogenous production during IVGTT. *Am.J Physiol Endocrinol Metab* 282: E992-E1007.

Hovorka, R., Canonico, V., Chassin, J.L., Haueter, U., Benedetti, M. M., Federici, M.O., Pieber, T. R., Schaller, H.C., Schaupp, L., Vering, T. and Willinska, M. (2004). Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. Physio. Meas. 25 (2004) 9050-0920.

IDF Diabetes Atlas Sixth Edition Update, International Diabetes Federation 2014. Retrieved from http://www.idf.org/diabetesatlas/update-2014.

Jiang, X. and Wang, Y. (2012). Closed-loop glycemic control for critically ill subjects based on data-driven model predictive control. *31st Chinese Control Conference.* pp.7061--7066.

Lassen, A. L. and Nielsen, T. S. S. (2008). Modeling and simulation of glucose-insulin dynamics. Bachelor thesis. Technical University of Denmark.

Lum, S. (2015, March 15). New Diabetes Drug Launched. *The Star.* Retrieved from http://www.thestar.com.my/Lifestyle/Health/2015/03/15/New-diabetes-drug-launched/.

Lum, M. (2015, March 15). Before it gets too sweet: testing for diabetes. *The Star.* Retrieved from http://www.thestar.com.my/Lifestyle/Health/2015/03/15/Testing-for-diabetes/.

McKnight, L.L., Lopez, S., Shoveller, A.K and France, J. (2013). Models for the study of whole-body glucose kinetics: a mathematical synthesis. *Hindawi Publishing Corporation. Doi: 10.1155/2013/120974*

Naerum, M. M. N. (2010). Model predictive control for insulin administration in people with Type 1 Diabetes. Bachelor thesis.Technical University of Denmark.

National Health and Morbidity Survey 2011. Fact Sheet.

Pedersen, S.N. and Hanse, L.B. (2010). System identification for prediction of glucose levels in people with type 1 diabetes. Bachelor thesis. Technical University of Denmark.

Pejtersen, M. and Jensen, K.S. (2010). Detection of events using continuous glucose monitors. Bachelor thesis. Technical University of Denmark.

Persatuan Diabetes Malaysia. (2006, December 28). What is diabetes. Retrieved from http://www.diabetes.org.my/article.php?aid=5.

Research in Cambridge. Jauvenile Diabetes Research Foundation Ltd. Retrieve from https://www.jdrf.org.uk/research/overview-of-research-programme/treat/artificial-pancreas/research-in-cambridge.

Skjaervold, N.K., Lyng, O., Spigset, O. and Aadahl, P. (2012). Pharmacology of intravenous insulin administration: implications for future closed-loop glycemic control by the intravenous/ intravenous route. *Diabetes Technology and Therapeutics. Vol. 14.* Doi: 10.1089/dia.2011.0118.

Soru, P., Nicolao, G.D., Man, C.D., Cobelli, C. and Magni, L. (2012). MPC based artificial pancreas: strategies for individualization and meal compensation. *Annual Reviews in Control, 36,* pp.118--128

Wang, Y., Dassau, E. and Doyle, F.J. (2010). Closed-loop control of artificial pancreatic β-cell in type 1 diabetes mellitus using model predictive iterative learning control. *IEEE Transaction on Biomedial Engineering, vol 57(2).*

Wilinska, M.E., Chassin, L.J., Schaller, H.C., Schaupp, L., Pieber, T.R. and Hovorka, R. (2005). Insulin kinetics in type 1 diabetes: continuous and bolus delivery of rapid acting insulin. *IEEE.* Doi: 10.1109/TBME.2004.839639.

Yusof, N.F.M., Som, A.M., Ibrehem, A.S. and Ali, S.A. (2012). Parameter addition in interaction of glucose and insulin for Type 1 Diabetes. 2012 IEEE EMBS International Conference on Biomedical Engineering and Sciences.