A STUDY OF INSULIN DELIVERY SYSTEMS

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Abstract: Insulin delivery to diabetic patient using manual methods is a tedious job and requires significant efforts clinically. It doesn't ensure optimal performance and causes noncompliance to the prescribed drug and results in several medical complications. The insulin delivery system, often called as artificial pancreas, is a portable insulin delivery pump used to control blood glucose concentrations. An insulin pump is design and developed to deliver insulin in precise and accurate amount to the diabetic patient, in order to regulate the blood glucose concentrations. In this paper, theoretical analysis has been performed to regulate the blood glucose-insulin concentration on the basis of some mathematical models. These models includes an open loop control of insulin delivery, based on mathematical model of insulin curve and closed loop control based on modified Stolwijk and Hardy's dynamic model. These models are implemented and analyzed using MATLAB. Moreover some experiments have been carried out and the results are analyzed based on medical parameters. This paper elaborates the insulin delivery mechanism and developments which are discussed will enhance the quality of life of the diabetic.

Keywords: Biological system modeling, artificial biological organs, artificial pancreas, drug delivery system, insulin, glucose control.

1. Introduction

Diabetic patient suffer with a metabolic disorder and loses the ability to produce insulin sufficiently or it can't perform its functions properly. Insulin is a hormone, produced by pancreas, regulates the metabolism of carbohydrate and fat. It is an incurable disease affecting approximately 177 million peoples throughout the world and expectedly it will increase to 300 million by 2025 [1]. On average one out of five individual is on the risk of developing diabetes [2]. Current research is focusing on developing new techniques and providing wearable solutions to improve the lifestyle of the patient. As the pancreas is not producing sufficient amount of insulin, the patient is dependent on external source of insulin to regulate the blood glucose level in body. The optimal blood glucose concentration ranges from 60-120 mg/dL [1].

Blood glucose concentrations are regulated by two hormones released by pancreas, insulin and glucagon, which affect the glucose levels inversely. Insulin suppresses the glucose concentration whereas glucagon boosts it. The absorption of glucose and carbohydrates through the gastrointestinal tract results in an increase of glucose concentration into the bloodstream. The increase in glucose results in release of insulin from pancreas to prevent substantial increase in glucose level. This is accomplished by utilization of glucose by muscles and storage into liver and muscles in the form of glycogen. In contrary, during sleep or longer gap between meals results in fall of glucose level which is prevented by the release of glucagon. Glucagon increases the glucose level through the breakdown of glycogen to prevent significant decrease in glucose in bloodstream. Hence the blood glucose is regulated and managed through careful balance between glucose and glucagon [1].

Most consequences of the disease are long term. The diabetic patient is at an increased risk of blindness, kidney dieses, and gangrene and heart dieses. Continuous exposure to higher glucose concentration causes ineffectiveness of immune system and nerve damage [4, 5]. The life expectancy of diabetic is three times less than a normal healthy individual [3]. Proper regulation of blood glucose concentration evidenced increased life span of a diabetic by 50%. Diabetic patient follow a strict schedule of routines activities, diet and insulin infusion in order to better manage the blood sugar level at and suitable level. Typically a diabetic has to take oral pills and infuse rapid acting insulin at each mealtime to reduce the sudden increase in glucose level [6, 7].

Diabetics are classified in two major groups, Type-I & Type-II, and both of these are observed in all age groups [8]. Type-I diabetics are totally dependent on external source of insulin as the

pancreas losses the ability to produce insulin, whereas Type-II diabetics are not completely dependent on insulin. Type-I diabetic patients needs tight control of glucose concentration because the body is completely dependent on external source of insulin. Diabetes therapy consists of infusion of insulin through injections or insulin pump in order to replace the role of natural pancreas. An insulin pump is usually an electromechanical device which delivers the insulin through long flexible tube into the peritoneum. This pump releases a continuous amount of basal insulin and infuses bolus insulin at meal time in order to maintain the glucose level in a safe range [1, 9].

The blood glucose level of a patient varies dynamically depending on his nutrition and physical activity resulting in varied amount of insulin from time to time. Failure to provide the right amount of insulin may result in a variety of life-threatening complications [8]. Hypoglycemia - a condition which occurs when the glucose concentrations in bloodstream falls too low - can cause uneasiness and seizures. It may result in brain damage or death in some exceptional cases. Hyperglycemia is the condition when the blood glucose concentration exceeds 120 mg/dL. Patients facing hyperglycemia over longer period of time may develop other health related complications such as neuropathy, retinopathy, and damage to other tissue and organs [10].

According to American Diabetes Association [11] enhanced glucose regulation can result in reduction of some long term complications. These findings were opposed by Siperstein et al. [12]. They believe the present findings don't justify the idea of reduced complications with enhanced control of glucose and the risk of hypoglycemia will increase with tight control of glucose level. Availability of better method of blood glucose regulation can justify this point [13]. Pancreatic transplant is available as an option to the problem but some short-term solutions to the insulin therapy may be available. Continuous Glucose Monitoring (CGM) and insulin pump has encouraged the research into closed-loop systems [14-18] for the delivery of insulin for better glucose control and management.

If the patient's blood glucose level falls below the normal range, they will take some carbohydrates to bring it to normal level. Sticking to a strict schedule with regular monitoring and insulin infusion is proved to be effective in improved glucose control [6]. It is practically infeasible for a patient to accurately estimate the required amount of insulin to maintain normal glucose level. Open-loop system is prescribed by some researchers to regulate the blood glucose level [19-23]. In such systems blood glucose level is measured and entered manually with the approximate amount of carbohydrates for a particular mealtime and then it deliver the essential amount of insulin to manage glucose concentrations.

Blood glucose concentrations are regulated and managed by a number of algorithms and most of these techniques deliver insulin based on measurement of glucose level at regular intervals. Closed-loop (autonomous) and open-loop (semi-controlled) systems are the two fronts for the development of insulin delivery systems [24].

2. Open Loop Method

Open-loop systems automatically deliver the basal insulin continuously and bolus insulin manually at meal time. Carbohydrates contents are estimated and pre-meal blood glucose is measured to calculate the amount of insulin necessary to cover the meal. The calculated insulin is injected through insulin pump in subcutaneous tissues and the glucose level is measured after a certain interval to test the glucose level which can be balanced by eating some more carbohydrates or injecting some more insulin. The design of an electronic insulin delivery system is the first step in simulating the behavior of pancreas. It can precisely deliver small amounts of insulin and its electronic control allows shaping of insulin curve over time to match the insulin profile required for a given scenario. Once a bolus has been delivered, the pump continuously delivers the basal insulin according to the predicted insulin requirements for that user. One such open-loop block diagram is shown in Figure 1.

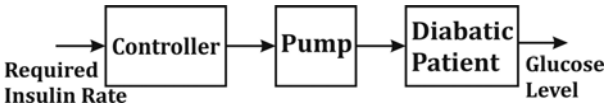

Figure 1. Open-Loop Control for Diabetic Patient

2.1 Design of a predictive open-loop insulin delivery system

To design an open-loop insulin delivery system a controller has to generate a derive signal for insulin pump in such a way that the insulin delivery rate i(t) approximates the desired delivery rate iD(t). Fig. 2 shows the glucose concentration and the required bolus insulin for one meal time.

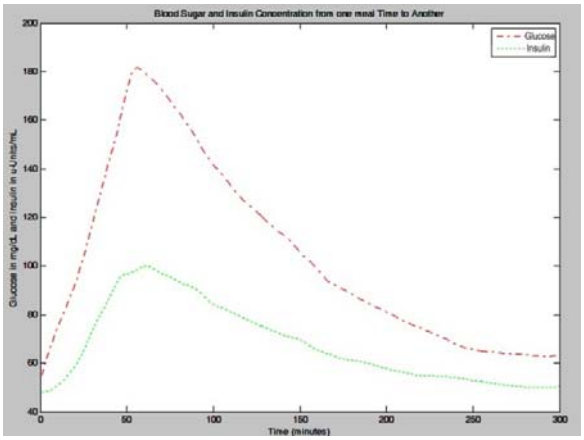

Figure 2. Glucose and required insulin concentration for one meal time.

Glucose concentrations are in mg/dL and Insulin concentrations are in µ-units/mL and time is taken in minutes and the insulin concentration will be maximum at t=60min or 3600s.

A function which can approximate this insulin concentration can be given by an exponential ramp function.

$$i(t) = Ate^{-at}u(t)$$

Laplace transform of this function gives us

$$I(s) = L[i(t)] = \frac{A}{(s+a)^2}$$

The function can be best approximated if A and a are selected such that $i(t)$ is maximum at $t = 3600s$ (i.e. after one hour) as is $iD(t)$ and so that the areas under the curve are equals the value $0.139\ cm^2$.

Taking derivative of the function

$$\frac{di}{dt} = -aAte^{-at} + Ae^{-at} = A(1-at)e^{-at}$$

By putting $t = 3600$ we get maximum $i(t)$

$$\left|\frac{di}{dt}\right| = A(1-3600a)e^{-3600a} = 0$$

$$a = \frac{1}{3600} = 2.78 \times 10^{-4}$$

The area under the $i(t)$ curve after $t = 0$ is

$$\int_0^{\infty} Ate^{(-at)}\,dt = A[-1/a\ te^{(-at)} - 1/a^2\ e^{(-at)}] = A/a^2$$

Equating to the desired area of $0.139\ cm^2$ gives

$$\frac{A}{a^2} = (3600)^2 A = 0.159$$

$$A = 1.23 \times 10^{-8}$$

If $i(t)$ is to be produced by the system input $r(t)$, then

$$I(s) = \frac{A}{(s+a)^2} = \frac{K}{\tau s + 1} R(s)$$

Giving the required programmed signal for each mealtime:

$$R(s) = \frac{\frac{A(\tau s + 1)}{K}}{(s+a)^2}$$

For a motor pump with transfer function

$$\tau = 3s \quad K = 2.3 \times 10^{-6} \frac{cm^3}{volt \times s}$$

And with the delivery rate for which

$$a = \frac{1}{3600} = 2.78 \times 10^{-4}, \qquad A = 1.23 \times 10^{-8}$$

Then

$$R(s) = \frac{0.0267s + 0.0083}{(s + 2.78 \times 10^{-4})^2}$$

$$= \frac{K_1}{(s + 0.000278)} + \frac{K_2}{(s + 0.000278)^2}$$

$$(0.0267s + 0.0083) = K_1(s + 0.000278) + K_2 \ldots\ldots (a)$$

Put $s = -0.000278$ in (a)

$$[0.00267(-0.000278) + 0.0083)] = K2$$

$$K2 = 8.29 \times 10 - 3, \qquad K1 = 2.67 \times 10 - 2$$

So,

$$R(s) = \frac{(2.67 \times 10^{-2})}{(s + 0.278 \times 10^{-3})} + \frac{8.29 \times 10^{-3}}{(s + 0.278 \times 10^{-3})^2}$$

By taking inverse Laplace,

$$r(t) = 1 \times 10^{-2} e^{(-0.7420)} + te^{(-0.1471t)}$$

This is sketched in figure 3. Reception, three times a day, of the motor drive signal will provide insulin delivery for periodic meals.

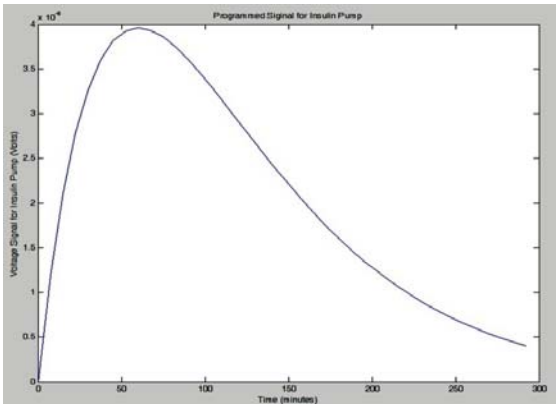

Figure 3. Response of Insulin Delivery System.

This voltage signal is applied to motor and resulting insulin output will have same shape as the applied voltage signal.

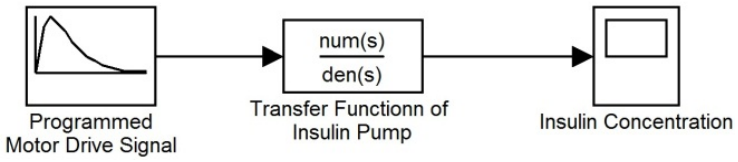

Figure 4. Simulink Model of Open-loop System.

This system is designed by calculating the transfer function of insulin pump and the programmed voltage signal is given as its input.

3. Close-Loop Method

Closed-loop insulin delivery system requires three components for insulin therapy, an implantable continuous glucose sensor (CGS), an effective control algorithm and a pump. A variety of continuous glucose sensors, including extracorporeal, needless and needle type sensors, were developed to be used in closed-loop insulin delivery systems. Well-developed insulin delivery pumps are available and their performance is also studied well. The development of a tentative closed-loop delivery algorithm is needed for proper glucose control. The closed-loop insulin delivery method closely mimics the natural pancreas and it is more reliable for glucose control [25,9].

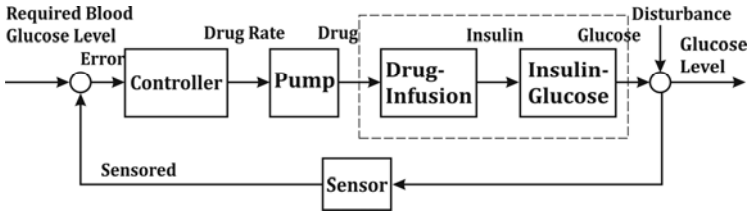

Figure 5. Control Model of Closed-loop System for Diabetics

Tight control of glucose is necessary in diabetic patients, especially in insulin dependent Type-I diabetes. These patients have deficiency of insulin production so glucose metabolism is not accomplished appropriately and glucose regulation by insulin infusion through external source is mandatory. The patients undergoing insulin therapy uses external devices such as insulin pump or syringes to deliver the insulin to mimics the pancreatic function. The insulin pump delivers the insulin when the glucose levels goes high and deliver insulin through flexible tube ending near abdomen preferably in peritoneum. The need to develop an artificial pancreas to deliver insulin in closed-loop by continuous measurement of blood glucose is in urgent. It will help greatly in insulin therapy and the patient will be free from a routine physical activity or diet. Furthermore the complications caused by miscalculation and accidental excess delivery of insulin will also be avoided [3].

3.1 Stolwijk and Hardy's Model Based Methods

The main function of pancreas is to manage and regulate the glucose concentration in bloodstream through the release of insulin and glucagon. A mathematical model is needed to replace the functionality of the pancreas. Khoo et al [26] has presented a dynamic model based on Stolwijk and Hardy's design to regulate the blood glucose concentration. The model was modified and used for critically ill patients by Nicolas et al [27] with the addition of exogenous insulin infusion. The same model has been used by Jameel et al [9] for blood glucose-insulin regulation. The glucose dynamics in this model are governed by the following equations [2].

$$CG\frac{dG}{dt} = UG + QG - \lambda G - \nu GI, G \geq 0 \quad (1)$$

$$C_G \frac{dG}{dt} = U_G + Q_G - \lambda G - \nu G I - \mu(G - \theta), \qquad G \geq \theta$$

Whereas the insulin dynamics are governed by

$$C_I \frac{dI}{dt} = U_I - \alpha I G \leq \varphi, \qquad (2)$$

$$C_I \frac{dI}{dt} = U_I - \alpha I + \beta(G - \varphi)G \geq \varphi$$

Where,

G = Instantaneous blood glucose level in $\frac{mg}{dL}$

U_G = Instantaneous blood insulin level in $\frac{mg}{h}$

U_I = Exogenous insulin infusion in $\frac{mU}{h}$

G = Instantaneous blood glucose level in $\frac{mg}{dL}$

C_G = Glucose capacitance in the extra cellular space

C_I = Insulin capacitance in the extra cellular space

Q_G = Glucose inflow into blood in $\frac{mg}{h}$

λ = Tissue usage rate of glucose that is independent of I (t)

N = Tissue usage rate of glucose that is dependent on I (t)

α = Insulin destruction rate

β = Insulin production rate by the pancreas

θ = Threshold for renal discharge of glucose

φ = Threshold for pancreatic production of insulin

μ = Constant proportionality factor (gain)

Glucose concentration in bloodstream is generated by continuous production from liver or through absorption from food. The model described by equation-1 and equation-2 includes a feedback loop and can be taken as a dynamic system with two inputs and two outputs as in Figure 6.

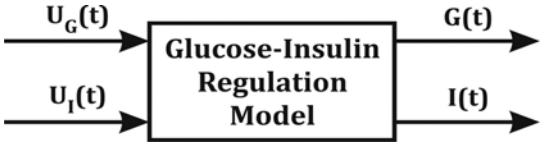

Figure 6. Two-Input Two-Output Pancreatic Model

3.2 Design Parameters

Parameters mentioned in Table 1 can be used to successfully implement the model described in equation-1 and equation-2. Therefore, interstitial fluid and plasma are represented in a single compartment ($12L + 3L$ in a normal adult). The concentration of blood glucose in this compartment is $\kappa \frac{mg}{dL}$. Glucose enters in the bloodstream through absorption from gastrointestinal tract or is produced by the liver at flow rate of $Q_G(t)$ in $\frac{mg}{h}$. Glucose enters the cells for metabolism or storage by leaving the extracellular space. The glucose utilization depends solely on extracellular to intracellular glucose gradient in case of insulin independent tissues. In insulin dependent tissues,

the intracellular concentration is ignored and glucose acceptance is facilitated by insulin concentration y . Consequently, the rate of insulin dependent glucose consumption is given as

$$UI(t) = \nu y$$

Rate of insulin production depends upon the plasma glucose level. Nevertheless, secretion of insulin stops if the glucose level x decreases below a threshold. The enzyme insulinase involve with the removal of insulin from plasma at a rate proportional to its concentration in bloodstream. The insulin concentration y in steady state is given as

$$Y = 0, X = \varphi$$

$$Y = \alpha(X - \varphi), X > \varphi$$

The simultaneous solution of these equations, under certain conditions, can give a prediction of steady state concentration of insulin and glucose in the bloodstream. Moreover, the parameter values given in Table 1 are used for pancreatic model [2]. Some of formulas used in the calculation of the parameters used in the model are given below:

$$\text{Glucose Capacitance (CG)} = \text{Extracellular}\frac{\text{Space}}{100}\text{dL}$$

$$\text{Insulin Capacitance (CI)} = \text{Extracellular}\frac{\text{Space}}{100}\text{dL}$$

$$\text{Extracellular Space} = 15000\text{mL}$$

$$\text{Serum Insulin Level} = \frac{\text{Extracellular Insulin}}{\text{Insulin Capacitance}}$$

$$\text{SerumGlucoseLevel} = \frac{\text{Extracellular Space}}{\text{Glucose Capacitance}} \times 1000$$

$$\text{Insulin Release Magnitude} = 0.\frac{092\text{g}}{\text{hr}}$$

$$\text{Insulin Release Rate} = (\text{Insulin Release Magnitude}) \times (\text{Extracellular Glucose} - \text{Pancreas Threshold})$$

$$\text{Pancreas Threshold} = 7.5\text{g}$$

Table 1: Parameters for Pancreatic Model

Parameters	Values
$G(t)$	2.5 mg/mL
μ	7200 mL/h
λ	2470 mL/h
ν	139000 l/(mUh)
φ	0.51mg/mL
β	1430mUmL/(mgh)
α	7600mL/h
Q_{DG}	8400mg/h
C_G	150 dL
C_I	150 dL

The pancreatic model of Figure 7 is designed, implemented and analyzed using Simulink based on the parameters of Table 1. The model is based on feedback system approach to show the function of pancreas.

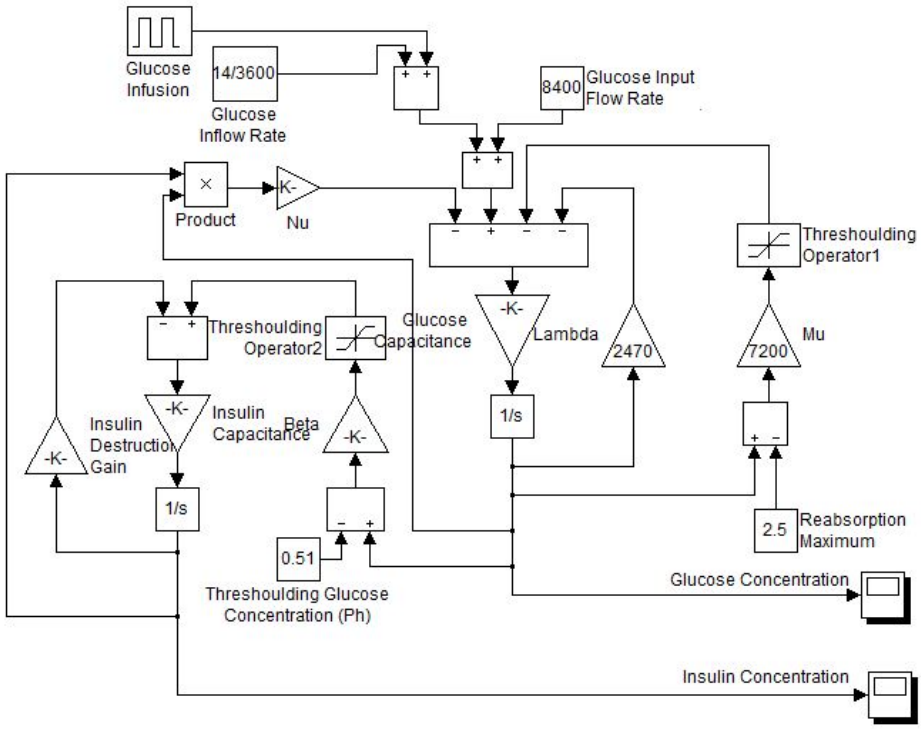

Figure 7. Simulink Model of glucose-insulin regulation control system.

4. Results

Conventional insulin therapy using manual dosing to regulate blood glucose depend on manual measurement of glucose and subsequent infusion of insulin into bloodstream. It is difficult to timely measure the glucose and correctly calculates the amount of insulin to be infused. The blood glucose level, amount of insulin in the reservoir and the battery charge is automatically read and transmitted wirelessly to a portable device. The programmed motor drive signal is generated on the basis of current blood glucose level and amount of carbohydrates to be eaten for the meal. The pump infuses the desired insulin in the bloodstream according to the programmed motor drive signal to control the blood glucose concentration. Figure 8 shows the infused insulin rate into the bloodstream.

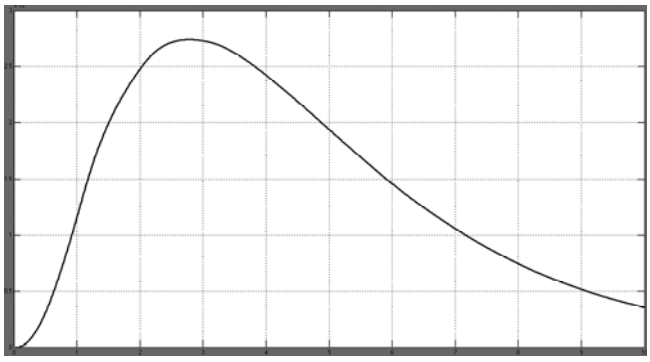

Figure 8. Insulin concentration produced by the insulin pump for open-loop system

The simulation result shows that the open-loop insulin delivery system can meritoriously manage the blood glucose concentration. It infuses the insulin into blood stream according to the patients need. The problem with such type of system is that it is not fully automatic and need patients input to work effectively. Every time the patient has to determine the total carbohydrates

contents in the meal and check the blood glucose level after the meal to confirm the blood glucose level adjustment. Such system can be effective if the patient can easily control the insulin delivery system and the problem of malfunctioning of glucose sensors and some other flaws in the closed loop systems can also be avoided. Such types of semi-automatic systems are in use and have provided effective glucose control especially in the presence of an expert to operate the system.

The closed loop model used by [9] and [27] has been utilized to model the pancreatic function for simulation according to the parameters stated in Table. 1. The model is implemented with a careful approach using Simulink. A variety of input signals are used to test the behavior of model in Figure 7.

Figure 9 shows the glucose concentrations in $\frac{mg}{dL}$ against the time scale taken in minutes. The graph clearly indicates the sharp increase in glucose concentration and then returning to stable state after certain time period. Figure 10, shows the amount of insulin, in $\frac{mU}{ml}$ infused into the blood stream against the time interval in minutes. Moreover, blood glucose control highly depends on the parameters defined in Table 1. The success of the model depends on careful selection of Simulink blocks.

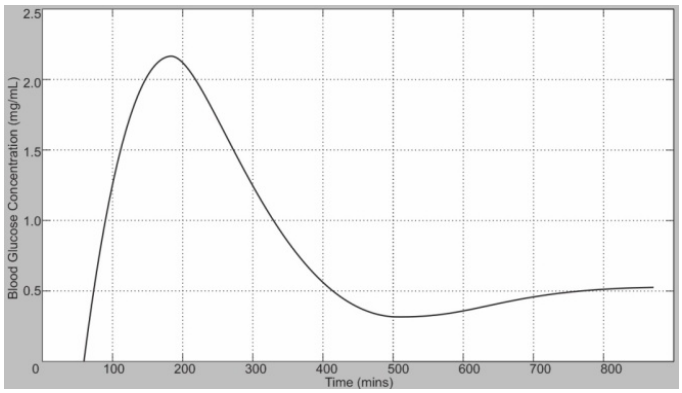

Figure 9. Blood Glucose Concentration

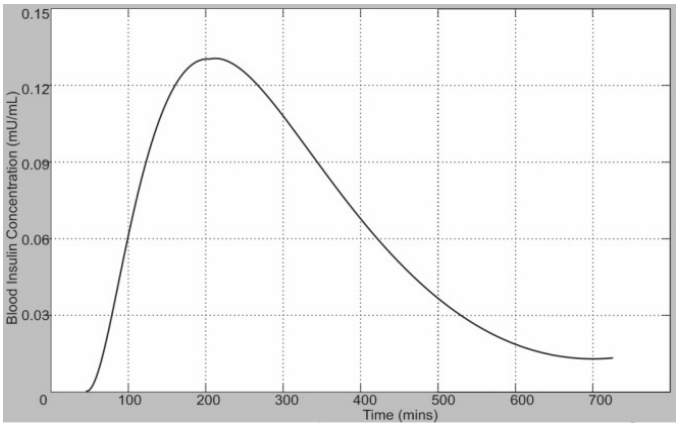

Figure 80. Blood Insulin concentration

The simulation results of the closed-loop model shows that it mimics the behavior of a pancreas. As the blood glucose level increases from steady state it infuses insulin into bloodstream to regulate the glucose concentration. It is evident from the Figure 9 & Figure 10 that the insulin levels increase as the glucose concentration approaches to peak which shows a proportional rate. As the level of glucose returns to stable state, insulin infusion rate slows down till it comes to steady state.

Parameters	Open-Loop System	Implantable Closed-Loop System
Control	Semi-automatic	Automatic
Clinical Trials	Successful	Under investigation
Complexity	Less complex	More complex
Expenses	Affordable	More expensive
Risk of Infection	Yes	Yes
Reliability	Conditionally Reliable	Reliability under investigation
Reprogramming	Need reprogramming	No Need to reprogram
Security	Risk of intruder	No issue of security

Table 2. Comparison of open-loop and implantable closed-loop systems

Table 2 compares the open-loop and implantable closed-loop systems on the basis of some evaluation parameters. The closed-loop system possesses the quality of better glucose regulation and management and can provide better reliability. It offers and expensive solution freeing the patient from all dietary regimen and worry free. Open-loop system needs to be reprogrammed through a wireless channel so need regular maintenance and there is also risk of intruder. The implantable closed-loop system offers a more reliable solution without all these restrictions but its reliability has not been completed through clinical trials. It is still under investigation and some studies suggest that tight control of glucose through close-loop system doesn't guarantee the stopover of complications. Tight glucose control prevents from earlier onset of complication but in the long run it unfavorably affects the neurological process and reasons the loss of consciousness.

However, the implantable closed-loop insulin delivery system tracks the insulin requirements of the patient by taking input from continuous blood glucose sensor so it frees the patients from some aspects of dietary regimen and provide a better solution from diabetes management then all the currently available insulin delivery systems.

5. Conclusion

Open-loop and closed-loop insulin delivery systems have been studied and two of them are implemented using Matlab/Simulink. Both the models are simulated and different experiments are performed to check the response of the system and its analysis has shown good results. Close-loop systems are best suitable in the presence of an expert or if the patient stick to a specific diet plan. There is very less possibility of malfunctioning as the system is semi-automatic and require user input to infuse bolus insulin. However the closed-loop system gets its feedback directly from the sensors and infuses insulin into the bloodstream. The closed-loop system provides a tighter control of glucose concentration and is more robust. The closed-loop algorithm presented by Kahoo [26] is an efficient algorithm to manage and regulate the blood glucose-insulin concentration.

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