SIMULATION OF BLOOD GLUCOSE LEVEL USING FUZZY CONTROLLER

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Approval

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ABSTARCT

Diabetes mellitus is an illness caused due to inefficiency of the pancreas. This illness caused can result in many side difficulties and even death. For effective control of diabetes mellitus fuzzy logic theory seems to be more viable technique. Control theory has emerged as one of the most active areas for research during past several years in application of fuzzy set theory. Fuzzy logic is incorporated into fuzzy controller. This is a logical system which is much more reliable than traditional logical systems. In this research, a closed loop algorithm using fuzzy logic controller of Mamdani type is developed for glucose regulation in blood of diabetic patients. The blood glucose level is desired to be maintained at normoglycemic average of 80mg/dl. Using a simple mathematical model developed by Stolwijk and Hardy's glucose-insulin regulation model is obtained. This model imitates artificial pancreas. Main function of pancreas is to regulate glucose concentration in body through release of enzyme insulin. Terms glucose and insulin are interrelated. The performance of controller is assessed by its ability to efficiently stabilize glucose level in optimal time as compared to other researches. This research proposed an optimal technique for regulation of blood glucose level of both type-I and type-II diabetic patients. The analysis of type-I and type-II diabetic person has been done by implementing model with closed loop feedback system in Matlab/Simulink. The development in this research proposed simple mechanism of insulin delivery in diabetic patients which enhances their quality of life by early stabilization of glucose level.

CERTIFICATE OF ORIGINALITY

I hereby declare that this submission is my own work and to the best of my knowledge. It contains no materials previously published or written by another person, nor material which to a substantial extent has been accepted for the award of any degree or diploma at SEECS-NUST or any other education institute, except where due acknowledgment, is made in the thesis. Any contribution made to the research by others, with whom I have worked at SEECS-NUST or elsewhere, is explicitly acknowledged in the thesis.

I also declare that the intellectual content of this thesis is the product of my own work, except for the assistance from others in the project's design and conception or in style, presentation and linguistic is acknowledged.

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Dedicated to my Parents and Siblings

For their love, kindness, sacrifices, and encouragement

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CHAPTER 1

1. INTRODUCTION

1.1 Diabetes

Glucose from food is converted into energy for proper working of our bodies. For this conversion of food into energy a special hormone called insulin is necessary. Insulin converts glucose in our body, obtained from food, into energy. In diabetic patients, insulin production is either stopped or is not produced in sufficient amount. The reasons could be either, pancreas fails to produce enough amount of insulin, uptake of insulin by body cells and muscles is not efficient or both.

This is a type of disease which is incurable and effecting many people around the world. Approximately 177 million people are currently suffering from this disease and this number is expected to double by the year 2025[1].Much of this increase will occur in developing countries because of population growth, aging, unhealthy diets, obesity and sedentary lifestyles. Focus is on developing solutions which are more feasible and improve the life of patients.

When people with diabetes eat glucose, which they get from food they eat such as fruit, bread, vegetables, legumes, milk and yogurt, it can't be converted into energy. Instead of conversion of glucose into energy it remains in blood. This is the reason that glucose level remains higher in people with diabetes. This blood glucose level is called as glycemia.

1.2 Types of Diabetes Mellitus

This disease can be categorized as follows

1.2.1 Type I Diabetes Mellitus

Type I Diabetes is formerly known as insulin-dependent. In this type the pancreatic beta cells responsible for producing insulin stop producing insulin which converts food into energy. This results in insulin deficiency. Previously it was known as "juvenile diabetes" because its majority cases were found in children. The patient is totally dependent on external source of insulin to maintain their blood glucose level in normal glycemic range.

1.2.2 Type II Diabetes Mellitus

Type II Diabetes is formerly known as non-insulin dependent. This is most common form of diabetes. In this type pancreatic alpha cells fail to use insulin properly and sometimes combine with absolute insulin deficiency. This condition arises due to insulin resistance. Previously it was known as adult onset diabetes. Type II diabetes is much more common and accounts for 90% of all cases of diabetes worldwide.

1.2.3 Gestational Diabetes

Mostly pregnant women when develops high blood glucose level without any kind of previous diagnosis suffers from gestational Diabetes. This may lead to Type II diabetes. Diabetes in pregnancy may give rise to severe conditions, like congenital malformations, elevated risk of perinatal mortality and increased birth weight. The risk can be reduced through strict metabolic control.

Other forms of Diabetes include congenital diabetes which is due to genetic defects of insulin secretion, steroid diabetes, cystic fibrosis- related diabetes and several form of monogenic diabetes.

1.3 Symptoms of Diabetes

Symptoms of Type I Diabetes include excessive secretion of urine known as polyuria, thirst known as polydipsia, weight loss and tiredness. In Type II Diabetes these symptoms are less noticeable. In this form, mostly symptoms appear years after its onset, when complications have already been increased.

1.4 Complications caused by untreated diabetes

Complications caused due to untreated may be categorized as follows

1.4.1 Acute Complications

Acute complications include diabetic ketoacidosis in which fatty acids metabolism is increased by liver into ketones and glucose via glycogenolysis in an attempt to supply energy to peripheral cells which are unable to transport glucose in absence of insulin and nonketotic hyperosmolar coma in which high blood sugar cause severe dehydration, increases in relative concentration of solute and a high risk of complications, coma and eventually death[2].

1.4.2 Long-term Complications

Diseases like cardiovascular, chronic renal failure and diabetic retinopathy (eye disease) comes under long term complications. Diabetic retinopathy is a leading cause of blindness and visual disability. It damages small blood vessels in retina which results in loss of vision. Metabolic control can delay the progression and onset of retinopathy. Kidney failure is also associated with diabetes. Control of high blood sugar level can slow down the progress of renal failure. Heart disease accounts for approximately 50% of all deaths among people with diabetes worldwide. One of the common complications of diabetes is diabetic neuropathy. Neuropathy can lead to sensory loss and damage to limbs. Foot disease caused by diabetes due to changes in blood vessels and nerves, often leads to ulceration and subsequent limb amputation. Diabetes is most common cause of non-traumatic amputation of lower limb. This condition could be prevented by regular inspection and good care of the foot.

1.5 Importance of insulin

Insulin is a hormone. It plays a major role in helping body to uptake glucose from the blood into most cells. Insulin regulates the body usage and storage needs of glucose and fat. Insulin helps in controlling blood glucose level by signaling liver and muscles and fat cells to take in glucose from the blood. If sufficient energy is present in the body, then the excessive amount of glucose is taken up by the liver and is stored as glycogen. In body some cells take glucose from blood without insulin, but most cells require insulin to be present.

1.6 Blood glucose levels Ranges

According to the measurement taken by means of glucose meter in mg/dl, a normal person glucose level is 70-110mg/dl, person suffering from hypoglycemia have the glucose level < 40mg/dl and the person suffering from hyperglycemia has the glucose level >150mg/dl [3].

The glucose-insulin system is a type of closed-loop physiological system. This system helps us to keep steady state. The description of the system is shown in figure 1.1.Most of the time the blood glucose level of healthy person remains in normal range. If the person ingests additional glucose via a meal, the person glucose level rises to higher blood glucose concentration. At this time pancreatic β cells are stimulated to secrete hormone insulin. This insulin increases glucose uptake by cells, muscles and liver, and brings person back to level of normal glucose concentration. If blood glucose falls below normal level, the person lies in low glucose concentration range. At this stage pancreatic α cells are stimulated to release glucagon. Glucagon signals liver cells to release glucose into the person blood until normal level is regained [4].This is simple description of glucose-insulin metabolism, which can easily be presented by different mathematical models.

Insulin dependent diabetic patients can be treated through exercise, healthy diet and most importantly through insulin injection. These injections are made with different devices, syringes and pumps. The major problem lies in using these injections is that they all have to be controlled by the patient, as a result these injections are sometimes used unnecessarily.

Solution to the problem could be creating treatment where patient need not to worry about having diabetes. This could be done by self-regulated system acting like artificial pancreas.

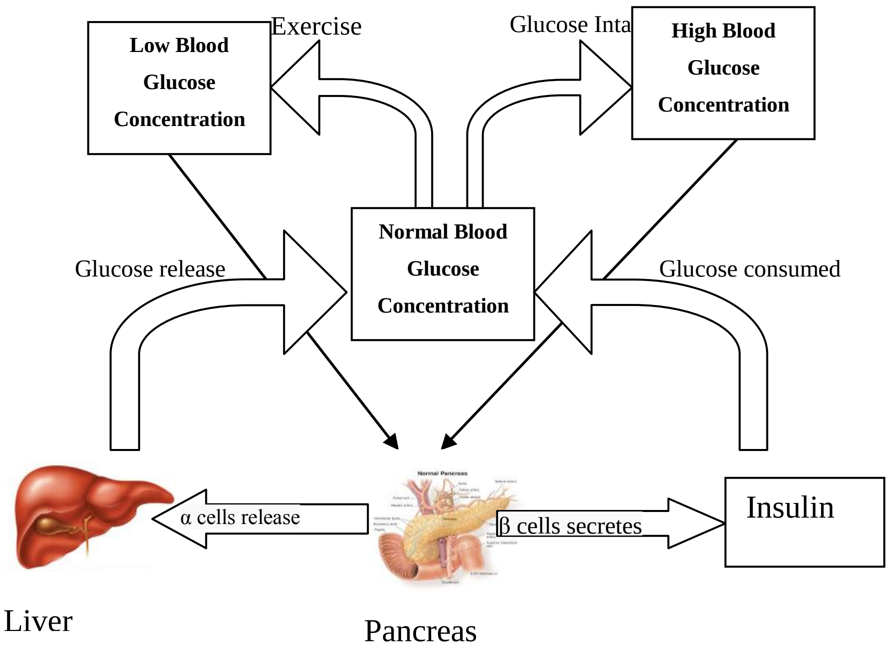


Figure 1.1: Closed-loop physiological system of Blood Glucose-insulin

To describe glucose-insulin metabolism many complicated models, with many parameters, could be designed. To make good analysis a simple model would be helpful in many cases. One of the simple models was introduced by Richard N. Bergman and is called Bergman minimal model [5].

1.7 Bergman Minimal Model for Glucose and Insulin Regulation

This is one compartment model with basal concentration of glucose and insulin. This model is based on two minimal models. One describes that how glucose concentration reacts with insulin concentration and the other describes mechanism of reaction. In these models input data consists of glucose and insulin. Meals and exogenous insulin infusion could be incorporated in this model by making small modifications [5]. Bergman minimal model illustrates the behavior of glucose in relation to insulin data. This is basically a one compartment model which is being divided into two parts. The one which describes glucose clearance and uptake is the main part. The other part marks out delay in the active insulin I_2 which results in change in the glucose uptake by tissues and the uptake and production by liver. Following differential equations 1.1 and 1.2 describe these two parts mathematically [8]

$$\frac{dG(t)}{dt} = -\left(p_1 + X(t)\right)G(t) + p_1G_b \qquad G(0) = Go \qquad (1.1)$$

$$\frac{dX(t)}{dt} = -p_2X(t) + p_3\left(I(t) - I_b\right) \qquad X(0) = 0 \qquad (1.2)$$

To explain the meaning of these equations the derivation of these equations is needed to understand. The derivations of these equations are based on model of Steil et al [6] and mass balance rule:

assembled = in – out + produced – utilized

In derivation the following parameters will be used:

Parameter	Unit	Description
t	min	Time
G(t)	[mg/dL]	Blood Glucose Concentration
G_b	[mg/dL]	Steady state blood glucose concentration (baseline)
$I_2(t)$	[mU/L]	Active insulin concentration
X(t)	1/min	Effect of Active insulin
I(t)	[mU/L]	Blood insulin concentration
I_b	[mU/L]	Steady state blood insulin concentration
V_G	[dL]	Volume of glucose
V_{I2}	L	Volume of remote pool
Q_{G1}	[dL/min]	Flow
Q_{G2}	[dL/min]	Flow
$Q_{I2}1$	[L/m]	Flow
Q_{I22}	[L/m]	Flow
W_1	[dl^2/min.mU]	Effect factor
W_2	[dl^2/min.mU]	Effect factor

Table 1.1: Parameters of Bergman minimal model

1.7.1 Model Derivation

In the model large compartment is represented by volume $V_{G.}$ Consider the figure given below.

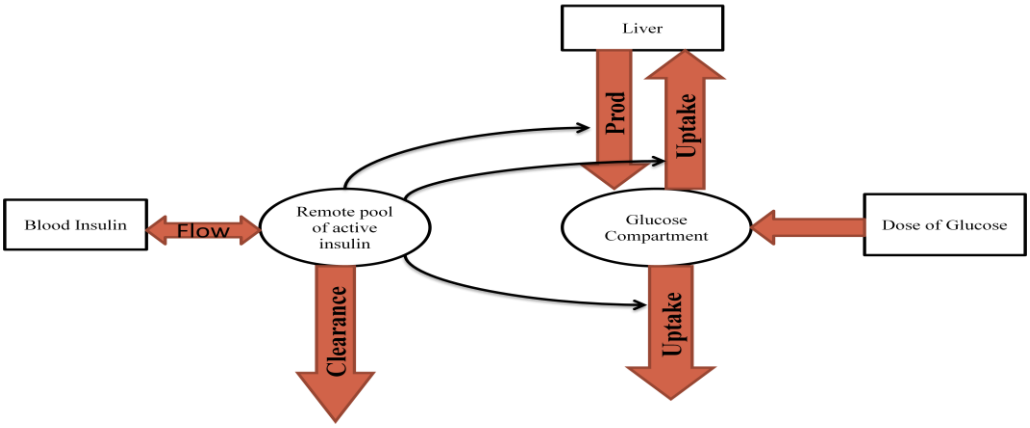


Figure 1.2: Graphical Representation of minimal model

The steady state of glucose in body is known as the basal concentration, and is denoted by G_b. when a bolus of glucose is injected in the body this steady state is disturbed. To describe this situation mathematically we use mass balance equation. The difference between initial and final mass is basically assembled part of glucose compartment.

$$assembled = V_G \,.\, G(t0 + \Delta t\ ) - V_G . G(t_0) \tag{1.3}$$

Glucose injection in body by the bolus is given by initial condition *G(0).* Outgoing mass can be categorized into two types. In one category comes the mass uptake by the liver and in the other comes mass uptake by the peripheral. In-take mass contains glucose produced by the liver. This whole mechanism is determined by the threshold level G_b also known as basal glucose concentration. This value is obtained by the difference between independent production and uptake of glucose and insulin. To maintain the level of glucose in the body in case when concentration of glucose rises above this basal concentration, glucose uptake by the liver (upt_l) and the peripheral tissues (upt_p) increase to take the level of glucose back to normal level. In other situation when level of glucose falls below the basal level then liver starts producing glucose until the required basal level is attained. This balance is referred as (Net Hepatic Glucose Balance) by steil et al [6].

By the use of insulin NHGB and peripheral tissues uptake of glucose can be enhanced. This is done by the active insulin present in remote pool rather then the insulin concentration present in the blood that gives this effect directly. The uptake and balance are described mathematically by following equations:

$$upt_p = (Q_{G1} \cdot G(t) \cdot \Delta t + G(t) \cdot k \cdot w_1 \cdot I_2(t) \cdot \Delta t) + upt_{gluinsind} \tag{1.4}$$

$$NHGB = prod_{gluinsind} - (Q_{G2} \cdot G(t) \cdot \Delta t + G(t) \cdot k \cdot w_2 \cdot I_2(t) \cdot \Delta t) \quad (1.5)$$

For changing L to dl a constant K is used and is set to 1. By inserting it in rule of mass balance equation we get,

$$assembled = in - out + produced - utilized \iff$$

$$assembled = NHGB - upt_p \iff$$

$$\begin{aligned} &V_G \cdot G(t_0 + \Delta t) - V_G \cdot G(t_0) = prod_{gluinsind} - ((Q_{G2} \cdot G(t) \cdot \Delta t \\ &+ w_1 \cdot I_2(t) \cdot G(t) \cdot \Delta t) + (Q_{G1} \cdot G(t) \cdot \Delta t + w_2 \cdot I_2(t) \cdot G(t) \cdot \Delta t)) \\ &- upt_{gluinsind} \end{aligned} \quad (1.6)$$

According to Steil et.al [6] insulin/glucose independent terms are formulated mathematically as follows

$$prod_{gluinsind} - upt_{gluinsind} = Q_{G1} \cdot G_b \cdot \Delta t + Q_{G2} \cdot G_b \cdot \Delta t$$

By inserting this term in the rule of mass balance, following equation is obtained

$$assembled = in - out + produced - utilized \iff$$

$$assembled = NHGB - upt_p \iff$$

$$\begin{aligned} &V_G \cdot G(t_0 + \Delta t) - V_G \cdot G(t_0) = (Q_{G1} \cdot G_b \cdot \Delta t + Q_{G2} \cdot G_b \cdot \Delta t) \\ &+ (Q_{G2} \cdot G(t) \cdot \Delta t + w_2 \cdot I_2(t) \cdot G(t) \cdot \Delta t) \\ &+ (Q_{G1} \cdot G(t) \cdot \Delta t + w_1 \cdot I_2(t) \cdot G(t) \cdot \Delta t) \end{aligned} \quad (1.7)$$

The following term is derived by dividing above equation with Δt and V_G:

$$\frac{G(t_0 + \Delta t)}{\Delta t} = \frac{Q_{G1}}{V_G} G_b + \frac{Q_{G2}}{V_G} G_b - \left(\frac{Q_{G1}}{V_G} G(t) + \frac{w_1}{V_G} G(t) I_2(t) + \frac{Q_{G2}}{V_G} G(t) + \frac{w_2}{V_G} G(t) I_2(t) \right) \quad (1.8)$$

By setting $\frac{Q_{G1}}{V_G} = k_1, \frac{w_1}{V_G} = k_4, \frac{Q_{G2}}{V_G} = k_5, \frac{w_2}{V_G} = k_6$ and going to the limit $\Delta t \rightarrow 0$, it gives the following differential equation:

$$\frac{dG(t)}{dt} = k_1 G_b + k_5 G_b - (k_1 G(t) + k_4 I_2(t) G(t)) - (k_5 G(t) + k_6 I_2(t) G(t) \quad (1.9)$$

A differential equation is derived which ignores the delay during the transport across the capillaries. The rule of mass balance is used to describe the inflow and outflow. The assembled part is given by:

$$assembled = V_{I_2} \cdot I_2(t_0 + \Delta t) - V_{I_2} \cdot I_2(t_0) \tag{1.10}$$

Insulin flows into the remote pool as a result of increase in insulin concentration above its basal value I_b. similarly if the concentration of insulin in blood falls below I_b then insulin flows out of the remote pool. This procedure is called as $balance_{ins}$. When active insulin level raises this clearance rate also rises. By using rule of mass balance we can formulate this procedure as follows:

$$assembled = in - out + produced - utilized \Leftrightarrow$$

$$assembled = balance_{ins} - a_{clearance} \Leftrightarrow$$

$$V_{I_2} \cdot I_2(t_0 + \Delta t) - V_{I_2} \cdot I_2(t_0) = (QI_{21} \cdot (I(t) - I_b)\Delta t) - (QI_{22} \cdot I_2(t)\Delta t) \tag{1.11}$$

By Taking limit $\Delta t \rightarrow 0$, and dividing above equation with Δt and V_{I2} following equation is obtained:

$$\frac{dI_2(t)}{dt} = -\frac{QI_{22}}{V_{I_2}} I_2 + \frac{QI_{21}}{VI_2}(I(t) - I_b) \tag{1.12}$$

by setting $\frac{Q_{I_21}}{V_{I_2}} = k_2$ and $\frac{Q_{I_22}}{V_{I_2}} = k_3$ we get:

$$\frac{dI_2(t)}{dt} = -k_3 I_2 + k_2(I(t) - I_b) \tag{1.13}$$

Instead of using $I_2(t)$, $X(t)$ is used which describes $X(t) = (k_4 + k_6) I_2(t) \hat{U}\ I_2(t) = \frac{X(t)}{k_4 + k_6}$. By inserting this we get:

$$\frac{dG(t)}{dt} = -(k_1 + k_5 + X)G(t) + (k_1 + k_5)G_b \tag{1.14}$$

$$\frac{dX(t)}{dt} = -k_3 X(t) + k_2(k_4 + k_6)(I(t) - I_b). \tag{1.15}$$

Now the model takes following form shown in figure 1.3.

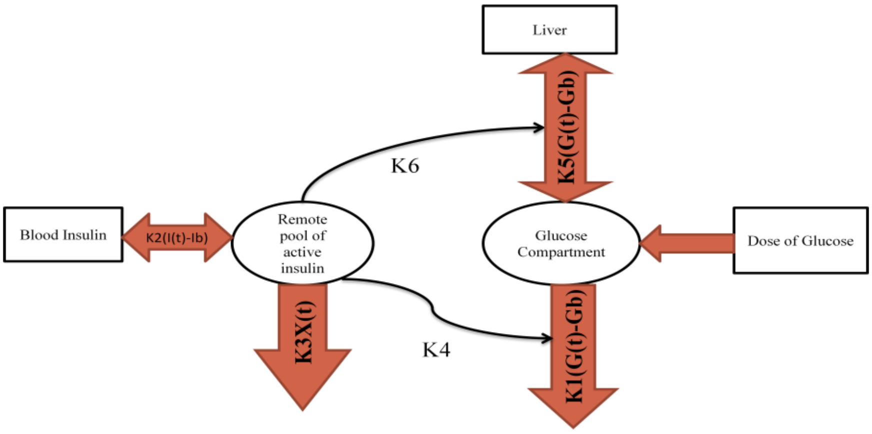


Figure 1.3: Model showing glucose balance in human body

By replacing $p1 = k1 + k5, p2 = k3$ and $p3 = k2(k4 + k6)$ equations 1.1 and 1.2 are obatined.

1.7.2 Short Comings of Bergman minimal model

This model is designed to show the concentration of glucose and insulin after glucose is infused in body artificially. This is a model which depends on time; it does not start in response to the glucose bolus. After glucose is infused into the system the human body responds with the release of an insulin bolus to compensate for the glucose. The BMM does not intend to model this response by the body. In that sense it is not an insulin release model, but models the glucose insulin dynamics in their return to basal values after the glucose injection.

The BMM does not have any mechanism to model the first phase peak of insulin release. As a result it ignores initial values for glucose concentration and insulin concentration, far from the measured values, are ignored along with the first minutes. It took 15 minutes to fit the data well.

Due to the short comings of Bergman minimal model we used Stolwjik and hardy's model as it is more efficient and covers all the important aspects related to the blood glucose and insulin regulation.

1.9 Stolwijk and Hardy's Dynamic Model for Glucose and Insulin Regulation

Stowijk and Hardy's proposed dynamic model for blood glucose and insulin interaction [7]. The glucose concentration and insulin concentration in body is obtained by differentiating equation of glucose insulin balance. Assume that glucose concentration in body is denoted by *G* and insulin concentration is denoted by *I*. Total Glucose concentration in the body is obtained by taking the derivative of *G* with respect to time *t*.

Hence,

$$\frac{C_G d(G)}{dt} = glucose\ production - glucose\ release \tag{1.16}$$

Similarly insulin concentration in the body is obtained by taking the differentiation of *I* with respect to *t*.

Hence,

$$\frac{C_I d(I)}{dt} = insulin\ production - insulin\ usage \tag{1.17}$$

Following assumptions are taken to calculate glucose and insulin concentration. Total volume of blood and interstitial fluid is assumed to be as single large compartment which is equal to 15L (1/15000ml) in a healthy adult. Glucose level in this compartment is considered to be *X* mg/ml which is constant. To maintain the constant level(*X*) the glucose coming inside the body must be equal to glucose leaving the body.

1.9.1 Glucose Production

Glucose enters the body through the absorption from gastrointestinal tract and production from liver by taking meal and is denoted by U_G in mg/hr. Input flow rate is assumed to be Q_G at time *t* in mg/hr. Q_G in normal adult is 8400 mg/h.

Hence,

$$\frac{C_G d(G)}{dt} = glucose\ production - glucose\ release$$, becomes

$$\frac{C_G d(G)}{dt} = U_G(mg/hr) + Q_G(mg/hr) - glucose\ release \tag{1.18}$$

1.9.2 Glucose Release

When glucose inside the body increases from its constant level and reaches at certain threshold level (Θ = 0.51mg/ml) kidneys start excreting glucose and the rate of excretion is proportional to gradient between Constant level of glucose which is *X* and threshold level which is Θ.

Renal loss rate is then equal to the difference between *X* and Θ, which can be written as

$$Renal\ loss\ rate = (X - Q) \tag{1.19}$$

This excretion happens only when *X* is greater than Θ, i.e.

$$X > \Theta$$

As the two values are proportional so we added a constant of proportionality μ in the equation, therefore the above equation becomes

$$Renal\ loss\ rate = m(X - \Theta) \tag{1.20}$$

Value of μ = 7200mL/h in normal adult

When *X* is less than or equal to Θ then

$$Renal\ loss\ rate = 0$$

Some tissues use glucose independent of insulin depending only on extracellular to intracellular difference in glucose concentration.

$$TissueUtilization\ rate\left(insulin\text{-}independent\right) = G$$

As the two values are proportional so we need to add a constant of proportionality λ in the equation, therefore the above equation becomes,

$$Tissue\ Utilization\ rate\left(insulin\text{-}independent\right) = \lambda\ G$$

(1.21)

Value of λ = 2470mL/h in normal adult. In cells like muscles uptake of glucose depends upon the insulin. The rate of glucose usage is proportional to glucose concentration *G*, as well as blood insulin Concentration *I*.

$$TissueUtilization\ rate\left(insulin\text{ - }dependent\right)=GI \qquad (1.22)$$

As the uptake is proportional to glucose and insulin Concentration, we need to add constant of proportionality. Hence, above equation becomes

$$Tissue\ Utilization\ rate\left(insulin\text{ - }dependent\right)=vGI$$

Value of ν = 139000 1/ (mUh)

By adding above equations we get:

$$C_G\, d\left(G\right)/\,dt=U_G\left(mg\,/\,hr\right)+Q_G\left(mg\,/\,hr\right)\ -\ \lambda\, G\text{ - }vGI \qquad when\ x\leq\ \Theta \qquad (1.23)$$

$$C_G\, d\left(G\right)/\,dt=U_G\left(mg\,/\,hr\right)+Q_G\left(mg\,/\,hr\right)-\ \lambda\, G\text{ - }vGI-\ \mu\,(X\text{ - }Q) \qquad when\ x>\Theta \qquad (1.24)$$

It shows that the difference between the rates at which glucose is added to the blood and the rate at which it is released equals the rate at which the glucose concentration *G* will increase or decrease.

For calculating insulin capacitance consider following assumptions

1.9.3 Insulin Production

Insulin is produced in the body by pancreatic beta cells but only when glucose concentration rises above threshold level

The constant level of insulin(y) in plasma is given by

$$Insulin\ Production=0 \qquad G\leq\ \varphi$$

In case when Glucose concentration is less than or equal to threshold level of pancreatic production of insulin i.e. φ

Value of φ = 0.51 mg/mL in normal adult

When glucose concentration in body is greater than φ then insulin production depends directly on the difference between glucose concentration and threshold level [7]

$$Insulin\ ProductionRate=(X\text{ - }\ \varphi) \qquad (1.25)$$

As these values changes with the proportional rate so we need to add constant of proportionality in equation.

$$Insulin\ Production\ Rate = \beta (X - \varphi) \tag{1.26}$$

Value of β = 1430mUmL/ (mgh) in a healthy adult

Insulin enters body also when we inject it by some external means. Exogenous insulin infusion is denoted by U_I.

Adding these parameters in insulin concentration equation we get:

$$\frac{C_I d\left(I\right)}{dt} = insulin\ production - insulin\ usage$$

$$\frac{C_I d\left(I\right)}{dt} = U_I + b\,(X - f) - insulin\ usage \tag{1.27}$$

1.9.4 Insulin usage

Insulin utilization totally depends on the level of glucose in the body. Therefore, insulin usage is directly proportional to the glucose concentration.

$$Insulin\ usage = insulin\ destruction\ rate * instantaneous\ blood\ insulin\ level$$

$$Insulin\ usage = \alpha I$$

By adding this in above equation, we get:

$$\frac{C_I d\left(I\right)}{dt} = U_I + \beta\,(X - \varphi) - \alpha I \tag{1.28}$$

This equation is used to calculate insulin concentration (C_I) in human body.

Figure 1.4 shows that total inflow of glucose in the body is equal to total glucose leaving body.

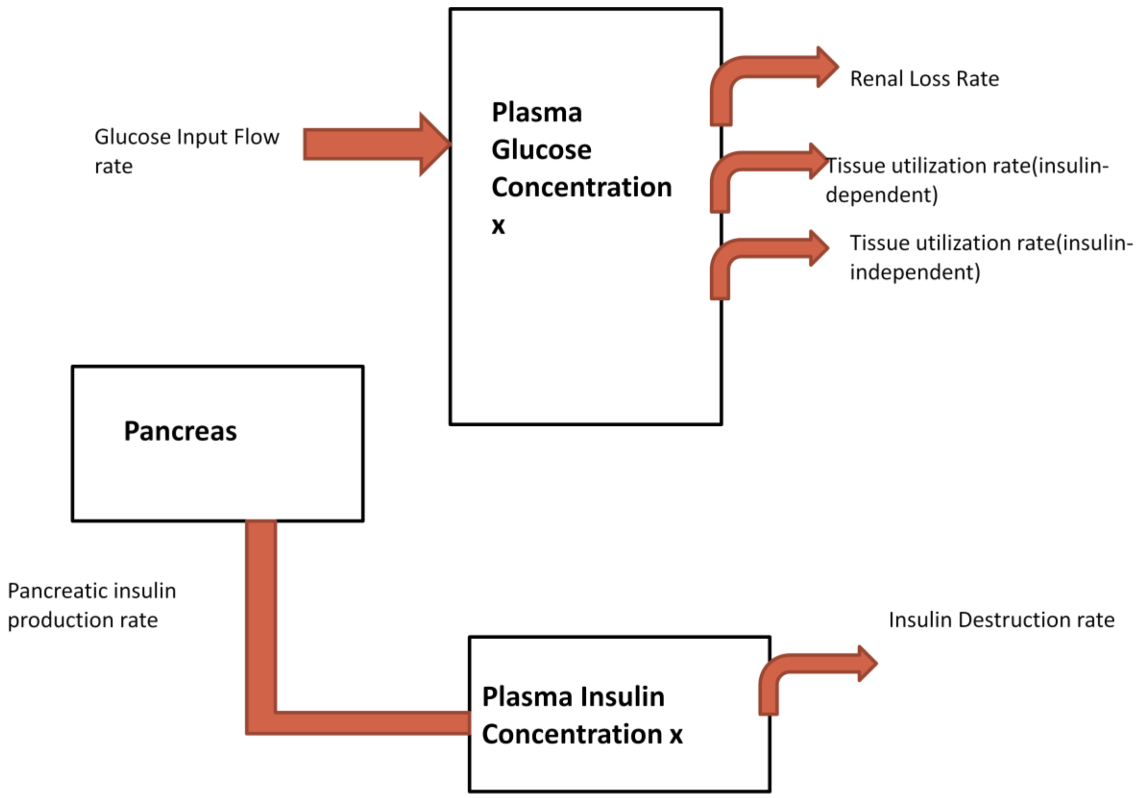


Figure 1.4: Glucose and Insulin Regulation Process

This chapter discusses that what diabetes is, what its major causes are and what life threatening risks are caused by it. Different mathematical model of glucose-insulin regulation are explained with their benefits and drawbacks. In next chapter usage of these models by different researchers are elaborated. The results obtained and their benefits and drawbacks are explained.

1.10 Thesis Organization

The aim of the thesis is to study the blood glucose-insulin regulation and assess the feasibility of using the model to control diabetic patient. A detailed model of glucose-insulin system is indispensable to achieve this. Chapter 2 provides the detailed view of different glucose-insulin regulatory models and the extent of ease they provide to diabetic patients. In chapter 3, a fuzzy controller design to control the diabetic patient blood glucose level, is explained. The use of the fuzzy controller in patient model to keep blood glucose level in safe range using different rules is described in detail in chapter 4. Chapter 5 discusses and compares the results obtained by the proposed technique with other techniques. The advantage of using the proposed technique over the other techniques is also being discussed in this chapter. Chapter 6 is on analysis of results obtained and future directions that can be pursued in this domain.

Further investigation for tight control of level of glucose in the blood of diabetic patient is becoming necessary with the growing understanding of diabetes.

CHAPTER 2

2. LITERATURE REVIEW

Literature review is a report for evaluation of information that helps in analyzing the research work relating to particular domain. Through it user knowledge about area of interest is being broaden. By considering strengths and weaknesses of different research, new ideas flourish. This chapter discusses the work in the field of medical cyber-physical systems. It effects on increasing patient care and different systems which comes and work under this domain. Medical cyber-physical systems are integration of computational elements with physical process that is able to interact with humans through different modalities. Rather than treating patients independently of each other now a day's patients are treated with system that is distributed and able to control different physiological parameters of patients at the same time[8].

MCPS is system of medical devices which works and provides functionality to patients in intelligent way. MCPS alters the traditional concept of treating the patients by helping caregivers to treat patients using computational entities. The conceptual overview of MCPS is given in Figure 2.1.Based on the functionality MCPS can be categorized in two groups. Group one consist of monitoring devices and treatment device comes under category of group two. Monitoring devices send collected data to decision support system. Decision support in MCPS process data and generate alarms on critical situations. Alarms inform clinician about the state of a patient. Treatment is then provided to patient according to state. Now a day's many health issues requires continuous gathering and management of data which includes dealing with aging population and people with chronic conditions such as diabetes and asthma.

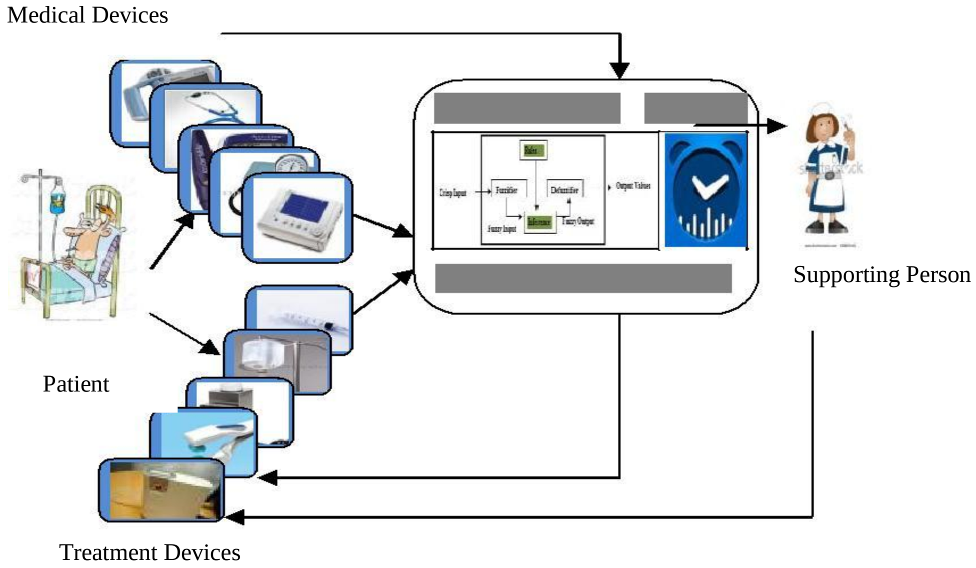


Figure 2.1: Conceptual over view of closed loop of MCPS

High confidence medical devices and systems come under the domain of CPS. MCPS is basically a distinct of CPS domain. Visualization of new capabilities like the process of power generation which is distributed in nature requires accuracy of time and operation at power grid. Embedded intelligence in automobiles helps in improving efficiency and safety related issues. Distributed real time control systems used in technologies like RFID to track goods, services and now-a-days location of person is also of great importance. These applications have great influence on economic aspect and their importance cannot be ignored. Technologies based on software components include design which is object-oriented and architecture which is service oriented. These are built on ideas that are more close to software than physical systems. Development of safe and effective MCPS (as shown in Figure 2.1) requires new design, composition, verification, and validation techniques due to increase in size and complexity[9]. MCPS require efficient regulatory procedure to treat patients. Traditional process which was used by Food and drug Administration in U.S is becoming massive and costly with the increased complexity of MCPS[8].

2.1 Need for MCPS Research

Reliability and predictability of embedded systems is higher than systems for computation of general purpose. Users of a system do not want their system to collide while they are using it. Use of computer controllers improved the reliability and efficiency of medical devices, cars and other systems. Introduction of CPS will increase the expectation of reliability. Accurate predictability of real world is not possible. Cyber physical systems may be working in an uncontrolled environment, and must be volatile and adaptable to handle different situations like unexpected conditions and subsystem failures. Research of CPS is still in its early stages[10]. Research is partitioned into disciplines that are isolated such as sensors, computer science, communications, and networking control theory. Different formalism techniques highlight some features and disregard others[11].

Formalism is used to represent either the physical or cyber process but not both at one time. Differential equations support physical processes, petri net and automata frameworks are used for representation of discrete behavior and control flows. This approach to modeling and formalism may be enough to support component based approach of divide and conquer to MCPS development[12]. Overall robustness, safety and security of system are being ensured by ambiguity in the physical world, attacks on security, and physical devices errors. Security related issues can be realized by exploring the physical nature of MCPS with the help of different mechanisms such as time-based, location based and tag based. Research needs of MCPS are described as follows.

2.1.1 Abstraction and Architectures

Real time and computational abstractions comes under this aspect. New scheme for resource allocation is needed to ensure fault tolerance and scalability. Methods for computing real time communication and distribution are needed. This will help in secure communication between distributed medical devices.

For rapid design and deployment of MCPS innovative approaches to abstraction and architecture must be developed. Technologically feasible components must be predicable and reliable at any level of abstraction. For infeasible technological components the next level of abstraction above these components must be vigorous. The overall design makes possible for heterogeneous design of systems as composed of plug and play fashion giving way to new trends in internet and technology development. Standardization is required to support integration and interoperability[12].

2.1.2 Distributed Computations and Network Control

Many systems related to network control impose challenges of time and event driven computing, reconfiguration, time delays and decision support. Design of protocols for real-time services assures adjustment between design and real time implementation. Caregivers sometime operate distributed medical devices plug-and-play system in incorrect way because of their complexity and massiveness. Complexity reduction and robustness of large systems are some of the needs of MCPS research.

2.1.3 Verification and Validation

Medical devices are becoming more interconnected and complex so it is now necessary that verification and validation must be done during the start of the project. Hardware and software components must be highly dependable, reconfigurable, and when required work efficiently as integrated systems. Complex systems in cyber infrastructure are lacking trustworthiness[10]. Over design is the only path for safe and successful system deployment and certification. This approach is also becoming useless in complex systems where interoperability is required. At control design new models are needed for software and system verification and validation.

2.1.4 Software Enabled Functionality

New functionality is needed when new possibilities emerge as a result of software based development of medical device systems. Example could be robotic surgery in which real-time processing of high resolution images and haptic feedback is required. Other example is proton therapy treatment. In which precise doses of radiations are given to cancer patients. The treatment requires precise guiding of proton beam from cyclotron to patients, requiring adaptation to even minor shifts in position.

2.1.5 Connectivity of Medical Devices

Rather than relying on software medical devices are mostly equipped with network interfaces. The networking capability of medical devices is limited and relies mostly on proprietary communication protocols offered by major vendors. Interoperability between medical devices will lead to increased patient safety and improved procedures of treating patients. Medical devices plug-and-play interoperability will help in improving the patient's safety and health care efficiency.

2.1.6 Physiologically Closed Loop Systems

Most clinical scenarios have caregivers for controlling the process. Such dependency on human in loop in medical community may compromise patient safety. Nurses or caregivers may miss critical alarm or get distracted. The use of automatic controller which continuously monitors patient state helps in handling situation which in turn will provide a big relief to nurses and also helps in improving patient's safety. Closed loop scenarios are practiced less in medical device systems. Patient controlled analgesia (PCA) pump are used to control pain of patients after patient has undergone operation. PCA pump delivers opioids for pain treatment mostly after surgery. In this scenario benefit could be obtained using closed loop.

But there are also many problems associated with it. More accurate processes for development are needed which improves the functioning and properties of PCA pump.

2.1.7 Continuous Monitoring and Care

There has been increasing interest in home care due to high cost of in-hospital care. Interest is increasing in use of options like care provided at home, living aid, telemedicine and sport activity monitoring. Health of a patient can be accessed remotely all the times by mobile monitoring and home monitoring of vital signs and physical activities. Sophisticated technologies are getting popularity such as body sensor networks to measure training effectiveness and athletic performance based on physiological data such as heart rate, breathing rate, blood sugar level, stress level, and skin temperature. Most of current systems operate in store and forward mode, with no real time diagnostic capability. Physiologically closed loop technology will allow evaluation of vital signs diagnostically in real time and as a result make constant care possible.

2.2 Challenges and Opportunities

CPMS research can be accelerated by the identification of needs, challenges and opportunities in different sectors of industry and increase multidisciplinary collaborative research between academia and industry. The aim is to develop new methods for building high confidence systems in which cyber and physical designs are compatible. Current and past research investments in the MCPS research mostly focus on short-term and quicker pay-off proprietary technology. Now mostly industries are focusing on longer-term precompetitive technologies[13].

In medicine and biomedical MCPS is revealing many challenges and opportunities. In this category come operating rooms and hospitals which are intelligent, surgery and therapy guided by image, development of neural prostheses and fluid flow control for medicines and biological content[14]. MCPS rely on medical devices and networked systems that are needed for patients with special circumstances. Medical devices and systems are needed that can be reconfigured dynamically and used in accordance with care takers and patients in complex environment. For example devices like ventilators, infusion pumps for sedation and variety of sensors used to monitor patient condition. These devices must be assembled in new system to match specific patient. The challenge is to develop system and control methodologies to handle these systems in secure way that can be trusted.

The organization in U.S named as National Information Technology Research and Development (NITRD) explained some of the major challenges faced by health care and medical technology[15]. One of the challenges for MCPS research is cognition and neuroscience for understanding the fundamental principles of human motor functions and exploiting this understanding in engineered system. Examples are brain-machine interfaces, prosthetics and exoskeleton. Given below are some of the challenges that are to be faced by MCPS in future with increased complexity

2.2.1Clinical workflows

The increased interconnectivity and interoperability of medical devices open the way for dynamic construction and deployment of MCPS in order to implement custom clinical scenarios based on the patient needs. To construct dynamic MCPS contains a challenge for ensuring patient safety. Clinical scenarios could be used to propose the possible solution based on rigorous modeling and their subsequent analysis. A scenario model can compile components at runtime that will provide information like decision support for caregivers, detect incompatibilities in device, and recovery from faults.

2.2.2 Model Based on Development

One of major challenge is to develop a model which simulates the working of interconnected devices before the whole system is built. To cope with it a model is introduced at level of clinical scenarios that would serve as top level system requirement. Analysis of this scenario model helps in assessing the patient safety in a scenario before the device is built and then generate requirements for the devices that are suitable for the particular scenario. These requirements could be checked during deployment to ensure system safety. The interface between static and dynamic check is also precisely specified by this challenge.

2.2.3 Closed Loop Physiological Control

Automatic controls raise the administrative control for the application of control theory in medical applications. Patient with complicated medical condition requires application of many treatments at once. This could affect many systems of body in complicated and less understandable ways. There is also a possibility that different treatments interfere with one another. Results of these treatments differ from patient to patient. Under this highly uncertain condition control theory such as supervisory adaptive control may help[16, 17].

2.2.4 Patient Modeling and Simulation

Closed loop control needs the patient security and scenarios safety analysis. For example in closed loop technique of patient controlled analgesia we need to model drug absorption by the body of patient and also the relation between dose and concentration of drug, on one hand, and vital signs of patients, on other hand. Literature provide us with a model to handle this situation known as Pharmacokinetic model, and also statistical data is available for checking effect of drug on vital signs[8, 18]. But these models are very complex and new reliable model is needed to address these challenges. Also highly reliable models and efficient simulators are needed for testing and validation of MCPS.

2.2.5 Patient Specificity

There are some medical devices which are specially designed for patient having similar medical conditions. The uncertain responses of patients to the same treatment and vital signs variations for the same condition make this approach generic and at the same time inefficient. For example there are medical devices which generate signals to alarm in critical situation. However, condition which initiates alarm are aimed at an average patient, which results in production of false alarm and divert attention of nurses to unimportant issues. As a result nurses experiences alarm fatigue and stop paying attention to alarm and potentially ignore critical situations. Adaptive algorithm and smart alarm technique could be developed to avoid these situations[8, 18].

2.2.6 Design is Doctor/User Centred

Errors that arise due to false operation of medical devices by caregivers are one of the major sources of adverse events[18, 19]. These errors may arise due to caregivers overload or poor user interface design. If a device has difficult interface, hard to operate, or respond to user input in an unusual way, errors are more likely to occur. Device design and validation must take user expectations into account. Caregivers behaviour needed to model in order to made interactive design of medical devices. To design such a model is a challenging problem.

2.2.7 Infrastructure for Integration and Interoperation of Medical Devices

At present MCPS are built by single manufacturer using proprietary protocol. This limit the benefits of inter device communication and medical professionals creativity [13]. Standards like ICE [20] for open interconnectivity of MCPS, lays groundwork for medical device interoperability. Current progress in this area is the release of MCDF toolset [21]. This proves to be useful in the development of MCPS but still there are some flaws in using this toolset. To make these standards effective, development and deployment standards should be implemented. Therefore, interconnectivity between medical devices is a big challenge in MCPS domain.

2.2.8 Compositionality

MCPS devices are mostly built dynamically and reasoning behind their composition is the only way through which the safety of these devices can be ensured. A big problem could be the kind of interaction between devices which is not expected in system. One of the design challenges is to identify and provide all interaction sources as clear input to system.

2.2.9 Privacy and Security related issues

MCPS network could be attacked by the person who enters into it. That person could get access to critical function of the device and may harm patient. One way the manufacturers used to avoid it is that they could limit functionality of the MCPS interconnected devices which could be accessed through network. Finding the right balance between flexibility and security is the major challenge for MCPS. Verification, validation and Certification of the dynamic system are also a big challenge. Modeling and model driven engineering have to take leading role in the development of MCPS systems.

2.3 Applications of MCPS

CPS includes assisted living, advanced automotive systems, energy conservation, intelligent robots, manufacturing, medical devices and medication systems. Operating room shown in Figure 2.2, National health information network, record initiatives of electronic patient, and home care comes under the domain of MCPS. Hardware and software component based systems mostly control these machines. Other applications of CPS are in the field of RFID, intelligent machines and electric power grid [10].

Figure 2.2: A case of MCPS (operating room)

2.3.1 Medication Systems

Medical and medication devices fall under category of real time systems and include timing and safety requirements. These devices include hard real-time, embedded pacemakers and soft real-time dispensers for medication. Devices are linked to remote computers to continuously monitor the medical conditions of the patient in operating rooms. Different formal methods are used to speed up the patient’s recovery with the help of medical ventilators. Systems based on computer with hardware and software components easily control medical and medication devices. For cyber-physical operations to accomplish fast technologies verification and validation must be applied to ensure safety and performance of these real time systems. Service quality of medical cyber physical systems lies between hard and soft real-time constraints [22]. Formal methods prove to be beneficial in safe operation of patients using cyber technology and speeding up their recovery.

2.3.2 Improved Patient Safety

One of the applications of Cyber-Physical System is to treat the patients having diabetes. Diabetes affect different vital signs of patient so all the vital signs are needed to monitor concurrently. MCPS helps in monitoring different signs of patients concurrently. Diabetes is the kind of metabolic disorder in which the internal failure in production of insulin requires the external injection of drug. Architecture of artificial pancreas is being proposed and simulation results are used to check its effectiveness. The basic aim is to keep the patients Glucose level in safe range suffering from diabetes and to avoid the occurrence of harmful state of Hypoglycemia. The criteria used for effective detection is careful monitoring of vital signs. The system consists of two pumps one for glucagon infusion and one for insulin injection. Both these perform their injections based on current glucose level. A controller is designed to keep the glucose level in safe range using neural network.

According to the report of WHO 177 million people are suffering from diabetes today and this amount will be double by 2025. It is all due to the failure of pancreas in producing insulin. Types in which the diabetes is categorized is mostly three, Type 1, Type 2, and gestational diabetes. The safe range of blood glucose level of normal person lies between 60-120mg/dl. The best observed value for Glucose level in blood is 80mg/dl [23]. When the Blood Glucose level increases from 120mg/dl the person suffers from Hyperglycemia and when it went below 60mg/dl the person is said to be in state of Hypoglycemia. Hypoglycemia is more fatal and may cause coma or even death. Continuous monitoring of glucose and infusion of insulin is available today. Subcutaneous route for external infusion is found to be very effective and secure. Insulin delivery system is mainly composed of three parts[22]. A device which continuously sense the blood glucose level, a pump for external infusion and a controller with embedded algorithm which calculates the drug amount to be delivered. This architecture have problem that release of glucagon hormone is very low in the patients with

Type 1 Diabetes which results in long Hypoglycemia state secondly insulin absorption via subcutaneous route is very slow which may results in overdose of insulin which again take patient to the Hypoglycemia state. Therefore Hypoglycemia state control is still a major issue. Writer of paper proposed an architecture which continuously monitors three vital signs and any irregularity sensed by MCPS in these signs invokes controller to infuse glucagon in body of patient [19].

Diabetes control is improved by using the closed loop glycemic treatment. A neural network predictive controller is useful in predicting the future behaviour of a system which is nonlinear and dynamic thus giving the opportunity to control the output of a system in desired manner. System identification is the first step involved in calculation neural network plant model which mainly involve the training to observe future behaviour of model. Prediction error between the real output and observed output helps in training neural network for signal generation. This neural network based controller is embedded inside the decision support of MCPS. This then triggers the treatment devices for action based on patient state illustrated by monitoring devices.

2.3.3 Cardiac Pacemaker

A cardiac pacemaker is a device as shown in Figure 2.3 which is electronic and embedded in the body used to compensate disturbance in the heat beat by the delivery of electrical stimuli which serves as a beat for heart. Heart activity which is natural may also be detected by the pacemaker. Timing cycles full fill the timing requirements of the pacemaker for operation. The applicable timing cycle relies on the mode of the pacemaker in which it is operating. Physician mostly keep operating mode on depending upon the condition of the patient before it is implanted. The mode describes correlation between sensing and pacing. For example mode based on ventricular inhibition is characterized by the ventricular sensing and pacing. The heart then beats on its own until the next pace is sensed [24].

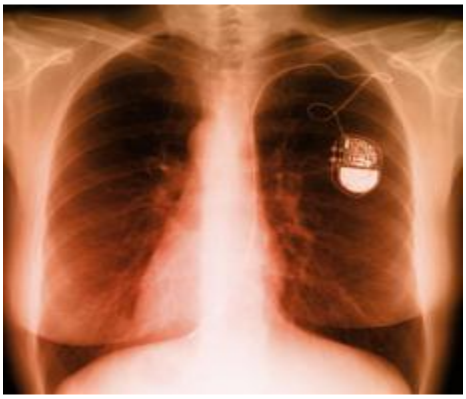


Figure 2.3: Cardiac pacemaker

Refractory period of ventricular and lower rate limit interval is used in timing cycles applicable in ventricular mode. Lower rate interval is the maximum interval of time between two beats. Sensing has to be turned off, during the ventricular refractory period, which begins after every pace to avoid false sensing. Pacemaker specifies the tolerances to be linked with cycles. The pacemaker controller is implemented using the described process [8]. Model of controller is created in the UPAAL tool using the timed automata, and then UPAAL model checker is used to verify temporal logic properties followed by code generation. Validation showed that tolerance levels were not aligned with timing constraints. Operations which contribute most to the property violation are identified by analyzing the timing traces of controller and their execution time is measured. Tightening of transition guards modified UPAAL model making the offending operation start earlier. By generation of code and re-verification controller implementation validation phase is being passed. To face this problem an effective MCPS with more accurate software functionality is needed so that delay in inducing paces or induction of excessive paces can be avoided. As both situations can be hazardous for the patient's health and may take patient to deterioration state.

2.4 Future Trends in MCPS

The use of MCPS is increasing day by day. The medical devices produced by the industry in the US are diverse[25]. These devices include digital measuring devices, prosthetics and implants. Over the past few decades technological revolution replaces the devices and systems based on information technologies with analog devices along digital counterparts performing better in diagnosis, monitoring and treatment. The advancement in microprocessors, networking and miniaturization of circuits opens new ways for digital device enhancement. With the progress of these new technologies large scale interconnected systems emerges. These systems contain sensors and actuators that control different processes. Technologies like sensing, computing, modeling and communication integrated inside physical components allow new cyber physical systems to achieve high level of performance.

Today there is lack of interoperability in architecture of medical devices. Devices which we typically use have proprietary system and rely on trained professionals to operate the device and interpret the output of system which frequently needs to be connected to a patient at one time. For example in operating room where doctor need to examine every device independently. This is an error producing process, stress, fatigue and other human factors can affect it. When we take medical devices into account hardware and software technologies need to be addressed. The hardware part consists of embedded systems and recently, systems on a chip. Hardware architecture for medical devices consists of either wired or wireless interfaces which facilitates networked communication of patient data. Different efforts made by practitioners and clinicians to combine data across devices that are designed for separate operation lead to accidental or unintended results. So there is a need to manage devices in to operate on network in an automatic and secure manner.

Advancement in the field of medical devices is driven by the growing interest in capabilities such as aging population, telemedicine, and online clinical lab analysis. Available methods for software development are not sufficient to handle interoperable medical devices.

From past 25 years the design of medical devices transform from analog to digital [25]. Analog designs were simple and the only method of controlling the risk was human intervention. Device was only used when the specialist was present to handle the device. Today technological innovations changed this field. Most devices in medical domain now contain embedded systems which are critical because they control functions of, and correspond with patient themselves. Some of the future trends related to cyber physical systems in medical domain are discussed below.

2.4.1 Sensor Fusion

Research in every field now-a-days is exploring sensors that can be fixed in person's body. These sensors are fixed inside the body through small surgery or attached to the clothes of patient. Sensors communicate with wired network woven in fabrics or wirelessly. They are used for detection of falling, gait analysis, and monitoring the abnormality in person's movements and activities. This sensor fusion technology seems to bring huge change in the medical world. As it can play important role in MCPS by remotely providing the information about person physiological parameters.

Rapidly growing research concentrate on environments where monitoring technologies are used to make more reliable and helpful assisted living and homecare. For example, in treatment of diabetes patient shifted from difficult test-based technology to device-based in-home measurement of glucose level in patients along with infusion pumps containing insulin dose [25]. Skin sensing technology based on closed loop is also progressing. In the same way different kinds of tests are taken and then send to laboratory for monitoring. This promotes dynamic online models obtained by continuous monitoring. It also opens door to closed loop control technology.

2.4.2 Artificial Body Parts

The increase in the demand for the devices by the people with disabilities to help them is key factor motivating novelty in prosthetics of various types. Prosthetic devices have their dependency on the control technology and the provided information. Improvement in biomedical expand with the emergence of new treatment targets, and new biomechanical technologies. Examples of these include deep brain and neural stimulation, and implantation of cochlear. Intelligent prosthetics in artificial hands, feet and limbs is beginning to be explored. Research is going in the area that one can control prosthetic with the help of different pattern of one's own brain movement. Artificial organs like smart skin, pancreas and engineered materials are becoming reality. There are varieties of challenges in making use of these devices practical. Prosthesis will play important role in treating patients in near future and its use will become common in people with disabilities.

2.4.4 Least invasive technologies

Currently there is a trend towards obtaining biometric data through less invasive methods and performing surgical interventions. This could give multiple benefits because by minimally invasive method different risks can be avoided. The data needed can be collected easily by least invasive monitoring devices in MCPS. This will also speed up patient recovery and lower care requirements because by using this method large surgical wounds could be avoided. This technology also benefits precision microsurgery, by providing micro- and nano- electromechanical systems.

Devices enter blood vessels like snake to approach the parts of heart that control contraction rhythm. Microsurgery is then performed by that device which induces scar to reduce conductivity and alter electrical signal to alleviate tachycardia, also called as tachyarrhythmia as illustrated in figure 2.4.

Figure 2.4: ECG showing tachycardia with rate of 100 beats per minute[26]

These devices also face some challenges which include avoidance from causing damage to surrounding tissues and to precisely control natural motion and events in the environment of human biology.

2.4.5 Control based on Feedback

Technologies like prosthesis and therapeutic clarify that system need to communicate with the user in an understandable and easy way. The systems must be designed in a way that the user is aware of multiple functions of device and can easily control the current operating mode. Mode confusion may result in erroneous action and harm could be induced potentially. Multiple devices operating simultaneously must interact in the way to avoid harmful situations, and must not interfere with other device and stop that to perform its function properly. Dangerous conditions can develop rapidly when patient and operator are in highly dynamic situations. To avoid these situations system must provide modes to deal with these changes in rapid manner and also the clear representation of the state and condition of patient to user. There are situations in which haptic feedback provides more information then visual feedback.

Biomarkers need significant technology support for providing detailed information about patient's health. Data fusion and synchronization may be needed. For example to achieve correlation between ECG, EEG, and muscular signals dynamically following areas need to be focused.

- Confusion between modes which results in wrong decision
- Feedback based on sense of touch
- The actual way in which you deal with prosthesis
- Intelligence
- Data fusion and synchronization
- Human inclusion
- Adaptive control

Future technologies will keep these issues under consideration before designing any medical device. So that chances of its failure can be reduced.

2.4.6 RFID Tags

Implantation of Radio- Frequency identification (RFID) tags in hands of a person is a new trend through which different benefits can be obtained. For example it reduces the need to keep the keys of every door with you. Now with the help of RFID tags one can open any door and start one's car or motorcycle without any key. RFID tag is basically a mini transmitter which sends a radio-frequency pulses sequence representing a unique number. That number is usually 10-16 digits long. The RFID locks are programmed with a list of numbers which are authorized, if tag of a person emit any one of those numbers available in the list, that person is then in. This RFID tag technology has huge potential to be a part of MCPS. Different information's related to person physiological parameters can now be taken with more ease.

Significant interest is continuously developing in the emerging domain of MCPS. In spite of rapid progress we still have to tackle with many difficulties and challenges associated with this field. We concisely reviewed different aspects of MCPS which include research needs, challenges and different opportunities. MCPS are expected to play a major role in the design and development of future engineering systems with new capabilities. MCPS domain challenges offer a unique set different from any other CPS domain. These challenges will provide major opportunities for MCPS domain to flourish in future. The research in this domain can also be accelerated by close collaboration between different disciplines.

The writer of the paper Active Insulin Infusion Using Fuzzy Based Closed Loop Control – 2008[27] proposed a model to control blood glucose level which uses closed loop control strategy. The level of blood glucose is decided to be maintained at normoglycemic level of 70mg/dl. Mamdani type fuzzy logic controller is used along with bergman mathematical model which shows glucose and insulin level in the body. Performance of controller is checked and measured by its ability of rejecting multiple disturbances caused as a result of meal intake and its robustness. In spite of presence of uncertainty and measurement noise model showed accuracy. Preference of the designed model over the other conventional techniques has shown by the writer by simulating results.

In 2009 a technique of for control of glucose level in diabetic patients by Agents was proposed by Sh. Yasini [3]. The control strategy of reinforcement learning based on Q-learning algorithm was used. The level of glucose is to be maintained at 80mg/dl. The approach used is based on trial and error and agent learn from its mistakes. Writer uses ε Greedy selection to train its agent for balance. Mathematical model used to show glucose and insulin concentration in body is Bergman minimal model. Performance evaluation of the technique is based on its ability to reject multiple meal disturbances, its ability to overcome variability from patient to patient and appropriate settling time of body glucose level.

In 2013 a technique based on A Fuzzy Controller for Blood Glucose-Insulin System was proposed by Ahmed Y. Ben Sasi[28]. Control strategy used is based on closed loop control.

Both fuzzy logic and PID controller is used and their performance is checked. Simulation results showed that Fuzzy Logic controller outperformed PID controller. The model used by the writer shows interaction between glucose, insulin and free fatty acids (FFA). Mixed meal and exercise serve as disturbance to proposed model. In delay of 5min PID controller failed to keep glucose level at basal level, whereas the response of FLC was stable. Writer concluded that FLC is more reliable, safer and has less consumption of insulin as compared to PID controller.

An Improved Fuzzy PI Controller for Type 1 Diabetes was designed in 2012[29]. The control strategy used is closed loop control as it mimics the behaviour of pancreas. Mathematical model used is Bergman minimal model to show the concentration of insulin and glucose in human body. The features of the technique used include design of fuzzy proportional integral controller based on Mamdani type structure. To decrease the complexity of controller less linguistic rules are used. Performance was tested under standard meal for 10h.Comparison with previous studies proves that the proposed controller reduces blood glucose level in less time.

In 2012 a research based on neural network and physiological parameters control of Artificial Pancreas for Improved Patient Safety was carried [19]. Control strategy used was based on closed loop control. In order to efficiently detect Hypoglycemia condition vital signs monitoring is introduced. These signs are then used to depict irregularity in blood glucose. Designed system consist of insulin and glucagon pump. To keep glucose level in safe range a neural network predictive controller is designed. Blood level is desired to maintain at 81md/dl. Subcutaneous route is used for insulin infusion because of its least invasive nature. Bergman minimal model is used to show the glucose and insulin level in body of the person with diabetes. Neural network model of plant is being generated by the controller and then predicts the future behaviour of the system.

In 2005 [30] Glycemic Control in Critically Ill Patients was administered and mathematical model of glucose-insulin regulation have formulated. Validation with patient data concluded that delay in implementation of insulin infusion rates result in longer time to control glycemia in all types of patients. Stolwijik and hardy’s model was used to obtain the insulin and glucose level in human body. Set point for glucose level is adjusted at 100mg/dl. Effects of delay in insulin infusion to patient have shown by the writer by simulation.

In this chapter, various medical cyber physical systems for increased patient care have been presented. This helps in comparing the designed model with various existing models. Already provided facilities and benefits are being highlighted. A detailed literature review of MCPS, artificial pancreas and other systems has been presented. This review has helped us in the identification of the key features as well as the short comings of existing approaches. This chapter also provides a foundation upon which the proposed model has been designed. In next chapter the implementation and the methodology used in designing the proposed model have been presented.

CHAPTER 3

3. METHODOLOGY

In this chapter the proposed model is described in detail. The proposed model will help diabetic patients to lead their life with ease. The methodology used to design the proposed model is also discussed in detail.

In application of fuzzy set theory, fuzzy control has manifested as one of the most active and fruitful areas for research. Its benefit goes to industrial processes because they lack quantitative data and conventional methods suppress their performance. Fuzzy control is based on fuzzy logic. This system resembles to human thinking and natural language than traditional logical systems. Strategy on which fuzzy logic controller works is that it converts linguistic control strategy based on expert knowledge into automatic control strategy.

Zadeh's seminal papers on the linguistic approach and system analysis based on theory of fuzzy sets motivated Mamdani and his colleagues' research on fuzzy control on the linguistic approach and system analysis based on theory of fuzzy sets. Use of fuzzy control in complex processes increases as a result of recent applications of fuzzy control in different areas. Approximate and inexact nature of real world can be captured using fuzzy control. Essential part of the fuzzy logic controller is the set of linguistic control rules related to fuzzy implication and compositional rules of inference. FLC provides an algorithm which covert the linguistic control strategy based on expert knowledge into an automatic control strategy. FLC is very useful in case when processes are too complex for analysis by conventional quantitative techniques or when the available sources of information are interpreted qualitatively, in exactly, or uncertainly. Three steps are involved in fuzzy control. Fuzzification, inference based on set of IF/THEN rules and defuzzification. Following is the block diagram of the fuzzy control.

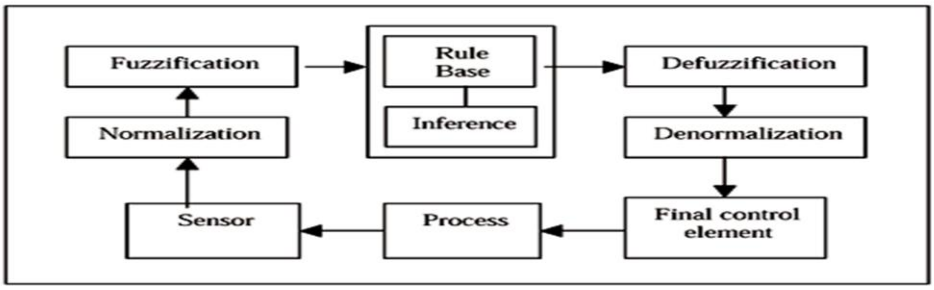


Figure 3.1: Block Diagram of Fuzzy Control

3.1 Control Systems

Control systems are based on control theory. Mostly dynamical systems with inputs are deal with inputs. Reference is basically external output of the system. When one or more output variables of system required following a certain reference over time then a controller manipulates the inputs to a system to obtain the desired effect on system output. Control theory basically calculate solution for the proper corrective action from the controller that result in system stability of the system as a result of which system will hold the set point and not oscillate around it. Control systems which are widely used are

— Open loop Control System
— Closed loop Control System

3.1.1 Open loop Control System

In this type only the input signal is needed by the control system to activate an output. For process adjustment no automatic feedback is needed. For adjustment manual procedure is followed.

3.1.2 Closed loop Control System

The output of system is monitored by sensor which feeds the obtained data to controller to adjust control. Closed loop control work as follows

Sensor measure the system output and feedback that measurement to reference value. The difference between the reference and the output is taken by the controller to change the inputs to the system under control. This kind of controller is also called feedback controller. Diagrammatic view of closed loop or feedback control system

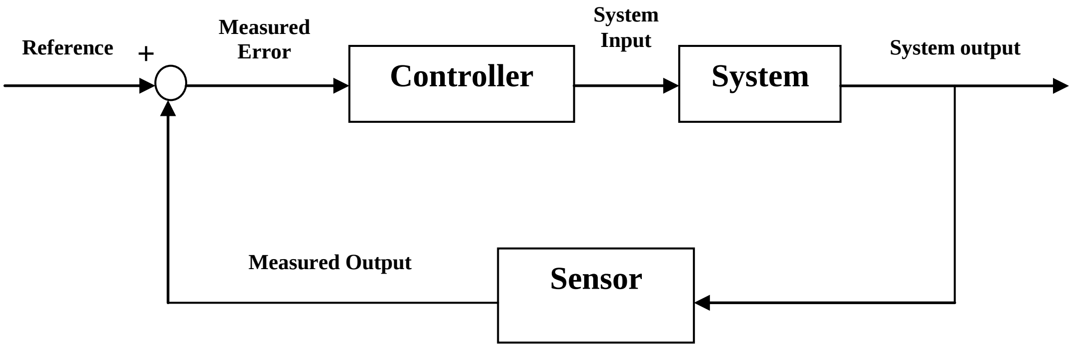


Figure 3.2: Closed Loop Feedback Control

3.2 Fuzzy sets and terminology

If U be the collection of objects then it is generically denoted by [31], this may be discrete or continuous. First represents universe of discourse and former represents the generic element of U. Universe of discourse U is characterized by membership function μ_F characterizes fuzzy set F. which values lies in interval [0, 1].

$$\mu_F : U \to [0,1] \tag{3.1}$$

The grade of membership function and ordered pair of generic element u represents fuzzy set F by:

$$F = \sum_{i=1}^{n} \mu_F(u_i) / u_i. \tag{3.2}$$

Set of all points u which are crisp in U is support of Fuzzy set denoted as follows

$$\mu_F(u) > 0$$

The point at which $\mu_F = 0.5$ is called the crossover point and a fuzzy set whose support is a single point in U is with $\mu_F = 1.0$ is referred to as fuzzy singleton.

Membership functions are used to define set operations of union, intersection and complement for fuzzy sets. Following principal components are needed to denote a fuzzy relation: a fuzzification interface, a knowledge base, decision-making logic and a defuzzification interface.

The work of fuzzification interface is to measure values of input variables, scale mapping that transfers input variable ranges into corresponding universe of discourse, function of fuzzification to convert input data into suitable linguistic values.

The knowledge of the application domain and attendant control goals are the parts of knowledge base. It consists of a database and linguistic control rule base. Necessary definitions used to explain linguistic control rules and fuzzy data manipulation are provided by database and the rule base characterizes the control goals and control policy of the domain experts by means of a set of linguistic control rules.

Core part of FLC is decision making as it has the capability of simulating human decision making based on fuzzy and of inferring fuzzy control actions employing fuzzy implication and rules of inference in fuzzy logic.

Scale mapping which converts range of values of output variables into corresponding universe of discourse is performed by defuzzification interface and defuzzification which yields nonfuzzy control action from an inferred fuzzy control action.

3.2.1 Conditional Statements and fuzzy Control Rules

The set of rules of linguistic description based on expert knowledge characterizes dynamic behavior of fuzzy system in FLC. The form in which the expert knowledge could be represented is as follows

IF (condition fulfilled) THEN (consequences are inferred)

These IF-THEN rules have antecedents and consequents which are associated with fuzzy concepts; they are often called fuzzy conditional statements. Fuzzy control rule is a conditional statement in which antecedent is a condition in its application domain and the consequent is a control action for the system under control. Control policy and domain knowledge are conveniently expressed by fuzzy control rules. When several linguistic variables are involved in antecedent and the conclusion of these rules, system is referred as MIMO fuzzy system. When there is two input and single output then system is referred as MISO fuzzy systems.

In order to interpret temperature as a linguistic variable, then its term set T (speed) could be

T (speed) = [30 very cold, more or less hot...]

Cold can be taken as a temperature below 10°C, normal as a temperature close to 35°C, and hot as a temperature above 55°C. Fuzzy sets characterizes these terms whose membership functions are shown in the figure below.

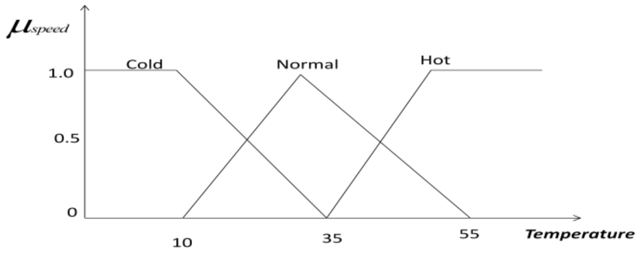


Figure 3.3: Diagrammatic representation of fuzzy temperature

3.2.2 Design parameters of the FLC

FLC design parameters are described below

- Fuzzification and interpretation of a fuzzification operator strategies.
- Database performs input and output spaces fuzzy partition, normalization, completeness and primary fuzzy set selection.
- Selection of Input and output variable of fuzzy control rules, source and derivation of fuzzy control rules, consistency, interactivity and completeness tasks are done in rule base
- Fuzzy implication, interpretation of sentence connective and, interpretation of sentence connective also, definitions of a compositional operator, inference mechanism are involved in decision making logic.
- Interpretation of a defuzzification operator and defuzzification strategies

Fuzzy logic configuration is shown in detail in following figure

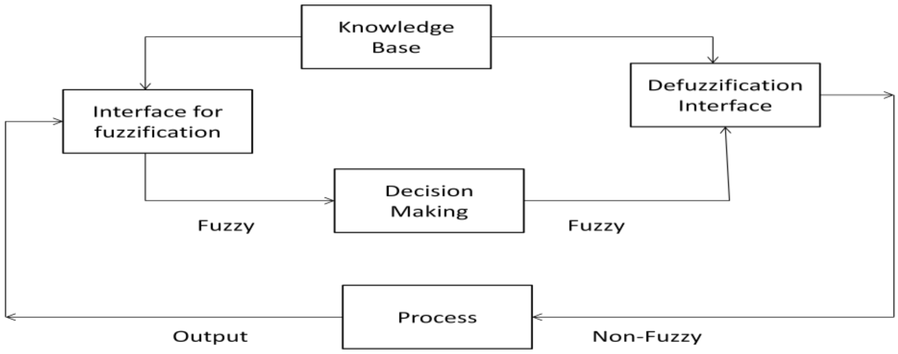


Figure 3.1: Basic Configuration of FLC

3.3 Fuzzification Techniques

Imprecise and vague nature of natural language is related to fuzzification. Uncertain information of any nature can be controlled by fuzzification.

Firstly, crisp value is converted into fuzzy singleton by fuzzification operator. Then probabilistic data has been converted into fuzzy numbers by fuzzification operator. This helps in enhancing computational efficiency.

Fuzzification strategy used the concept of “hybrid numbers”, which covers uncertainty as well as random nature of system. This strategy is used when some observations about behavior of large scale systems and applications are precise, while others are measured only in statistical sense.

3.3.1 Data Base

Fuzzy control rule base and database are two components of the knowledge base of Fuzzy Logic Controller. Database formation includes normalization of universe of discourse, fuzzy partition of input and output spaces, completeness and membership function of a primary Fuzzy set.

3.3.2 Rule Base

Linguistic statements based on expert knowledge comprises of fuzzy system. The expert knowledge is usually in the form of “if-then” rules, which are easily implemented by fuzzy conditional statements in fuzzy logic. Rule base or rule set is formed by the collection of these statements.

3.4 Types of fuzzy controller

Two types of fuzzy inference systems Takagi-Sugeno-kang and Mamdani fuzzy systems are known as universal approximators. The difference between these is based on the way they determine their outputs.

3.4.1 Mamdani type fuzzy inference system

This type is most commonly used. This is the first control system using fuzzy set theory. Ebrahim Mamdani proposed this system when he attempted to control a system engine and boiler combination by synthesizing a set of linguistic control rules obtained from experienced human operators.

Mamdani type inference expects the output membership functions to be fuzzy sets. After aggregation fuzzy set is obtained which needs defuzzification for each output. Using distributed fuzzy set proved to be more efficient in some cases instead of using single spike as output membership function. Efficiency of defuzzification process is enhanced because it greatly simplifies the computation required by the more general Mamdani method, which finds the centroid of two dimensional functions.

3.4.2 Takagi Sugeno Type Fuzzy Inference System

Weighted average of a few data points is taken in sugeno type fuzzy inference system. Inferences system in which the output membership functions are either linear or constant are usually modeled using Sugeno type systems.

Fuzzy inference system is very successful in fields such as automatic control, data classification, expert system and computer vision.

3.5 Difference between Mamdani type and takagi-sugeno type fuzzy inference system:

Fuzzifiaction of input data and application of fuzzy operator processes are same for both the inference systems. Difference between Mamdani and Sugeno type is based on the output membership functions. Sugeno output membership functions are either linear or constant. The form of rule used by sugeno fuzzy model is as follows:

If input 1 = a and input 2 = b, then output is

$$n = al + bm + c$$

The fuzzy inference system that we used here is of Mamdani type fuzzy inference system because it accepts multiple inputs and generates multiple outputs. In the glucose insulin control model we take glucose concentration and glucose deviation as two inputs which are then processed by the Mamdani type fuzzy inference system to generate two variables named glucose intake and insulin infusion as outputs. Defuzzification is done using centroid method.

3.6 Fuzzy controller implementation in Matlab

Fuzzy controller is implemented in Matlab using its tool fuzzy. It contains two inputs and two outputs and a type of (MIMO) fuzzy controller. The designed controller in FIS editor is shown in the figure below

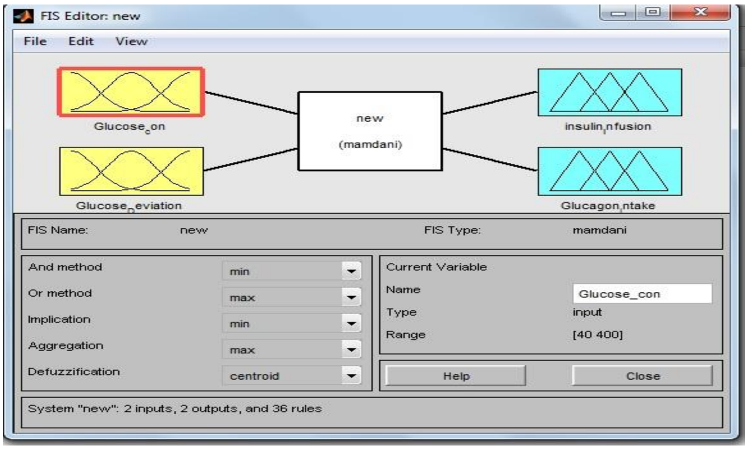


Figure 3.4: FIS Editor

3.6.1 Design of Fuzzy Controller

Input variables of glucose level and glucose deviation are described with interval and membership functions in the following table.

Input variables	Interval	Membership Functions				
Glucose Level	[40 400]mg/dl	Very low	low	normal	High	Very high
Glucose Deviation	[-20 20]mg/dl	negative	zero	positive		

Table 3.1: Membership Functions of Glucose Level and deviation

Output variables of insulin infusion and glucose intake are described with interval and membership functions in the table given below

Output Variables	Interval	Membership Functions				
Insulin Infusion	[-1 8] [μU/mg/min2]	Very low	low	Normal	High	Very high
Glucose Intake	[-1 8] [mmol/l]	Very low	low	Normal	High	Very high

Table 3.2: Membership Functions of Insulin Infusion and Glucose Intake

If then rules designed to keep glucose level in desired range are given in the table given below

		Rate of Change of Glucose		
		Negative	Zero	Positive
Glucose Level	Ext high	Extreme	Extreme	Extreme
	Very high	Very high	Very high	Extreme
	High	High	High	High
	Normal	Zero	Zero	Zero
	Low	Very Low	Low	Low
	Very Low	Very Low	Very Low	Very Low

Table 3.3: Insulin infusion

The results obtained after applying these rules to input are expressed by following figure

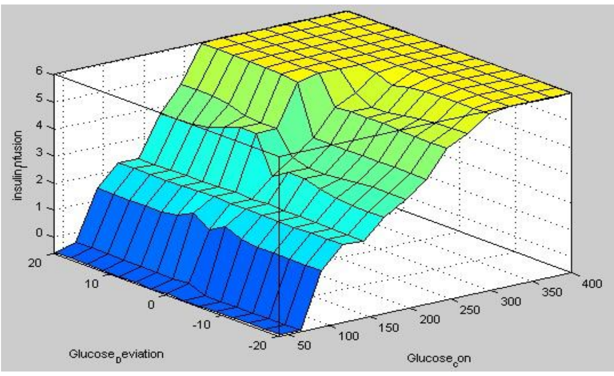


Figure 3.5: Surface

This graph is plotted with glucose deviation and glucose concentration as input and insulin infusion as output. The rules we set to control blood glucose concentration keeps the glucose concentration in save range with very slight fluctuation.

In the same way we set rules for glucose intake in the body in case when glucose level falls below certain value

		Rate of Change of Glucose		
		Negative	Zero	Positive
Glucose Level	Ext High	Very Low	Very Low	Very Low
	Very high	Very Low	Low	Very Low
	High	Low	Low	Low
	Normal	Normal	Normal	Normal
	Low	Very High	High	High
	Very Low	Very High	Very High	Very High

Table 3.4: Glucose Intake

The results obtained after applying these rules are expressed by following figure

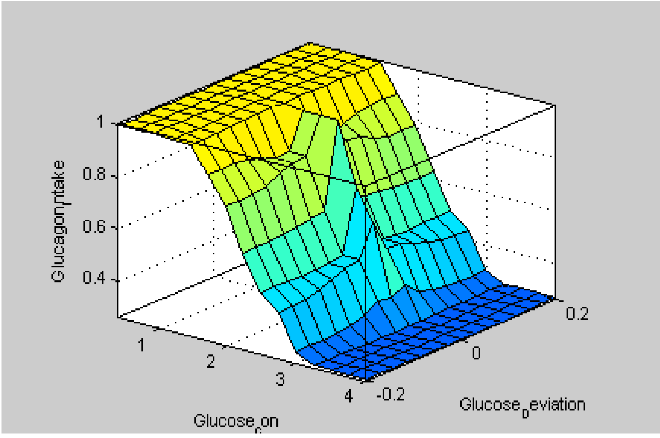


Figure 3.6: Surface

This graph is plotted without glucose deviation and glucose concentration as two input variables and glucose intake as output variable. It helps the patient of diabetes to keep their glucose level in safe range.

In this chapter the methodology used to design the proposed controller is described in detail and the results are obtained. The fuzzy controller is discussed in detailed in this chapter and its design for the proposed model is presented with the obtained results. The working and details of the fuzzy controller is also included in this chapter. In next chapter detailed implementation of fuzzy controller with patient model is explained with results obtained.

CHAPTER 4

4. IMPLEMENTATION

In this chapter implementation techniques and methods used are discussed. In order to get better results to maintain blood glucose level in normal range the model is developed in simulink. This model mimics the pancreatic function of normal human and control the blood glucose level to keep it in normoglycemic range.

4.1 Existing Model with properties

There are various implementations of the blood glucose level [3, 27, 32]. Some of them use Simulink® for the simulations and analysis. The model which we implemented is of type used by Soleh Yasini in his paper [32]. In this model a fuzzy based closed loop controller is applied to obtain a robust controller for blood glucose regulation in type 1 diabetes mellitus patients. The control technique incorporates expert knowledge about treatment of disease by using Mamdani- type fuzzy logic controller to robustly stabilize the blood glucose concentration in normoglycemic level. Performance of a controller is considered in terms of its ability to reject multiple meals, on an averaged nonlinear patient model.

In testing the performance of the control algorithm, a virtual patient needs to be implemented by using a suitable mathematical model. It has been assumed that glucose measurements are done subcutaneously, considering that accurate sensors are available for such measurements. To describe dynamics of glucose-insulin regulatory system many mathematical models have been derived. Many linear to nonlinear are present with different complexity levels. However, primary drawback of these mathematical models is identifying a nominal patient to implement the model parameters. It is evident that physical characteristics vary from person to person and so different patients have different responses to the same treatment, which in turn can cause parameter variations in the system. Thus, designed controller should be robust to uncertainty in model parameters and meal disturbances.

Many algorithms based on control theory have been developed to control the blood glucose level in people with diabetes by using these mathematical models. Most commonly used algorithms are proportional-integral-derivative and proportional-derivative. They use linearized model for the design, as well as H_∞ control technique. Some level of performance is obtained by using H_∞ algorithm but full robustness cannot be achieved by use of these algorithms. But in diabetic patients H_∞ control offers a promising result in maintaining blood glucose regulation. Sometimes optimal control algorithms are also applied for blood glucose regulation in semi closed-loop control system. However, mathematical models are used as crisp model in many of these researches and uncertainty in the model parameters has been ignored. Due to this reason these models may show good responses in simulations, but probably would fail when applying to the real patient data. Hardy's designed a fuzzy controller to keep the blood glucose concentration of diabetic patient in normoglycemic range. In his model uncertainty in patient model parameters has not been considered but the results were promising for nominal patient.

Fuzzy logic has emerged as powerful tool in control theory to employ expert knowledge about the systems for implementing an appropriate control. Specially, the ability of expert knowledge in the fuzzy logic field has increased a lot of attention in the biomedical engineering field.

The goal of this research is to achieve a high level of accuracy in predicting the safe range of blood glucose levels in diabetic patients. For this purpose a robust feedback controller is designed to stabilize the blood glucose concentration of type I diabetic patients around normal value. Mamdani-type of fuzzy controller is designed by using expert knowledge about diabetes mellitus treatment. Proposed algorithm main features are insensitivity to typical error in commercial device, multiple meal disturbances, accuracy, robustness to model parameter variations, and appropriate settling time.

As complex models require patient specific data and known glucose input they are not suitable for real-time control . However, simple models capture essential dynamic behaviours and provide a more suitable foundation for real-time control design.

The goal of our research is to develop a control technique based on a physiological model that capture the essential system dynamics, which do not require unavailable data, and are applicable to a wider variety of subjects. Simple models capture these essential dynamic behaviours, providing a more suitable model for real-time control design and analysis. Bergman's minimal model has been proposed as a powerful modeling approach to estimating the insulin sensitivity and the glucose effectiveness, which are very useful in the study of diabetes, and is the most popularly used model. But that model has some draw backs and shortcomings. That is why we used model of stolwijk and hardy's equations for modeling.

4.2 Proposed model

In this model I designed a controller whose architecture is based on Mamdani principles. The controller uses two input linguistic variable and two output variables. One of the two input variables shows plasma glucose level G (t) and the other shows its rate of change dG/dt, and the output variables are exogenous insulin infusion rate and glucose intake. Triangular membership functions are chosen for the simplicity. These membership functions depend on the fuzzy classification of input and output data. The shapes of input membership functions are presented in. The output membership function is then shown below. By the definition of the input and output membership functions, 21 IF-THEN rules were defined. These rules were of AND (minimum) type antecedent. The output (defuzzification method) is calculated by the CENTROID method.

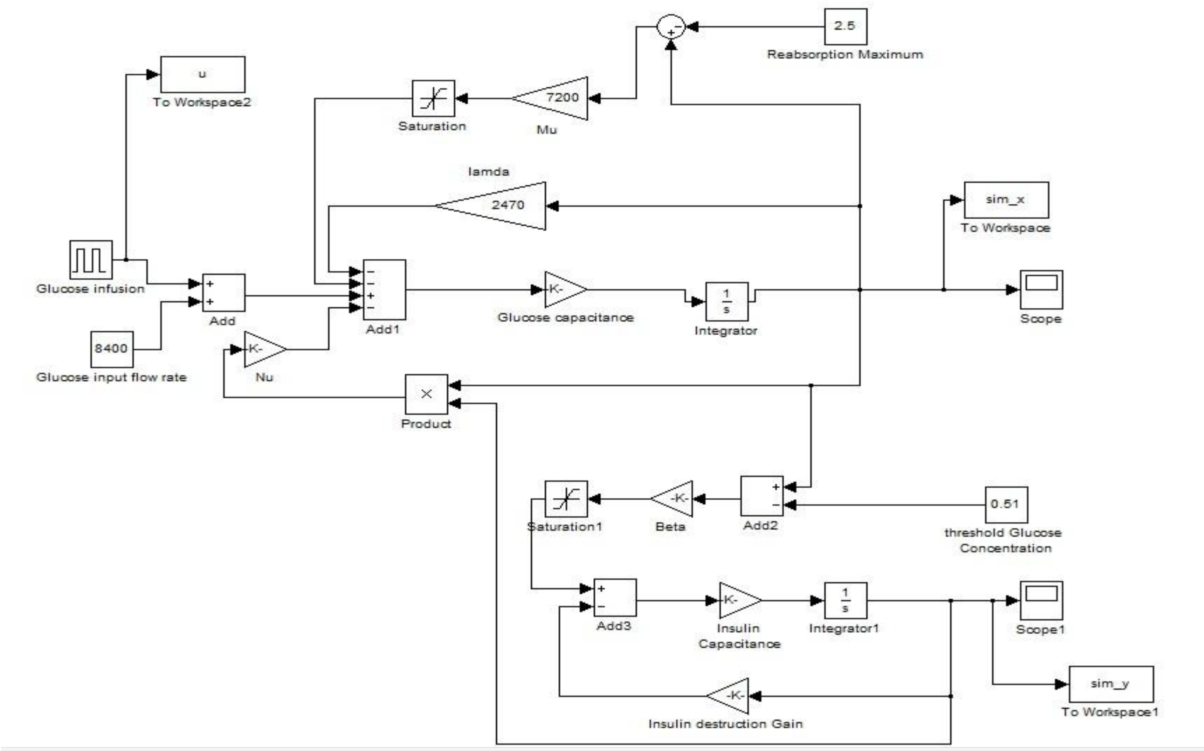


Figure 4.1: Simulink Model

In Matlab we use simulation loop to use the threshold operator and integrator block which are present in control design and simulation tool kit. In the front panel of LABVIEW we represent the food intake and glucose concentration and insulin concentration graphs where as in the back panel we implement the modeling equations obtained for a normal, type-1 and type-2 diabetic persons.

The glucose and insulin concentration levels for normal person, Type-1 and Type-2 diabetic persons are simulated and results are tabulated in the Table 2. The glucose infusion rate is considered as step input. When the food is taken the glucose concentration is increased, resulting in the release of insulin. After a period glucose concentration reaches to its steady state value. And there after the insulin concentration also reaches to its steady state.

The fuzzy logic controller has shown to have comparable performance. In relation to robustness to uncertainty, both controllers show good performance. The selection of a control algorithm is clearly a multi-objective problem where fuzzy .The automaton of insulin delivery in Type I diabetic patients is enhanced by using the suggested scheme.

Many simulink blocks are used while construction of the pancreatic model. Following are the some blocks which are used.

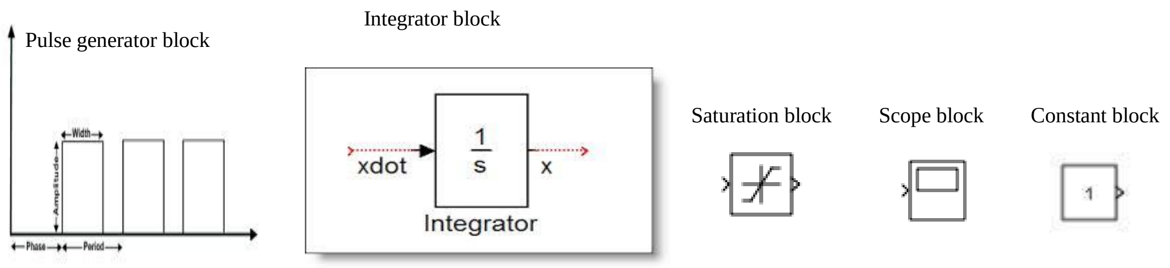
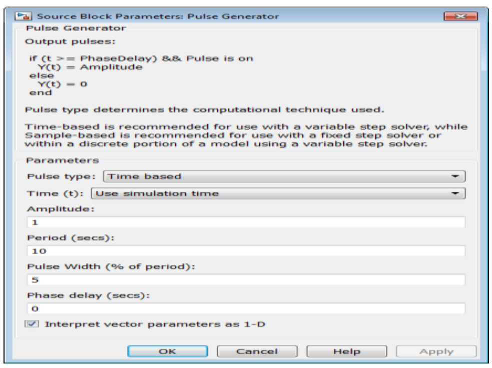


Figure 4.2: Simulink Blocks

The pulse generator block generates square wave pulses at regular intervals. The parameters which it uses are as follows


Source Block Parameters: Pulse Generator

Pulse Generator

Output pulses:

```
if (t >= PhaseDelay) && Pulse is on
  Y(t) = Amplitude
else
  Y(t) = 0
end
```

Pulse type determines the computational technique used.

Time-based is recommended for use with a variable step solver, while Sample-based is recommended for use with a fixed step solver or within a discrete portion of a model using a variable step solver.

Parameters

Pulse type: Time based

Time (t): Use simulation time

Amplitude:

1

Period (secs):

10

Pulse Width (% of period):

5

Phase delay (secs):

0

☑ Interpret vector parameters as 1-D

OK Cancel Help Apply

Figure 4.3: Source Block Parameters

Here in our model we changed the parameters as

Amplitude = 1000(which shows energy intake)

Period = 5

Pulse width = 5

Phase Delay = 0.5

A constant block shows real or constant value which we are giving 8400 to show the input flow rate.The parameters of constant block are as follows

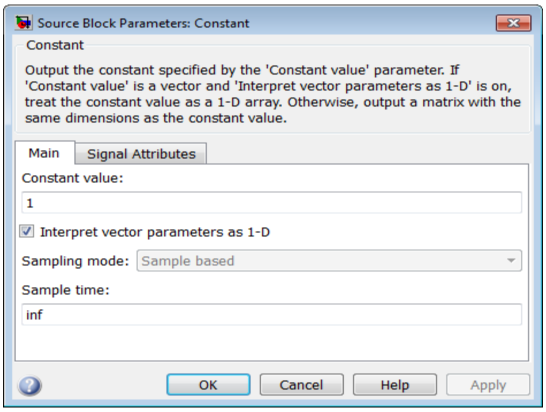


Figure 4.4: Constant Block Parameters

Then we use add block which adds the energy taken and input flow rate of glucose in blood to give one value. After that gain block is used. The Gain block generates its output by multiplying its input by a specified constant, variable, or expression. The value we used in gain block is of Nu (v) as a constant of proportionality. The value we used is 139000. The block parameters are as follows

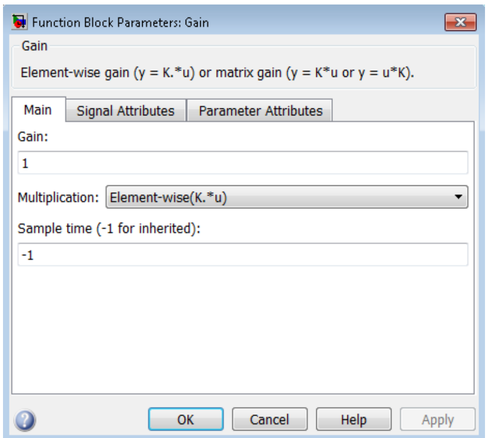


Figure 4.5: Gain Block Parameters

One integrator block is used in the model. The Integrator block outputs the value of the integral of its input signal with respect to time.

We also used saturation block in the model. Basically saturation block is used to impose upper and lower bounds on a signal. When the input signal is within the range specified by the Lower limit and Upper limit parameters, the input signal passes through it unchanged. When the input signal is outside these bounds, the signal is clipped to the upper and lower bound. When the parameters are set to the same value the block output that value. The saturation block accepts and outputs real signals of any data type

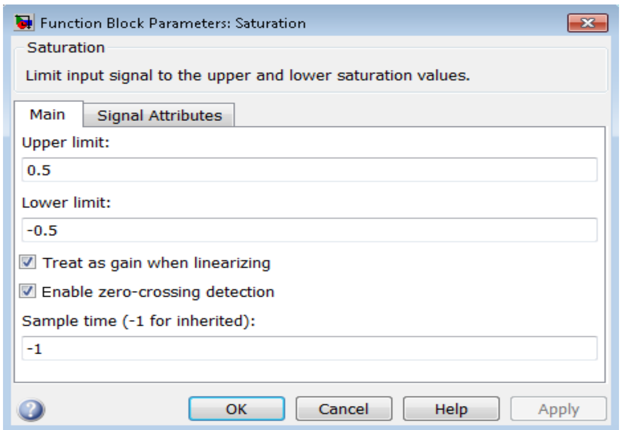


Figure 4.6: Saturation Block Parameters

In our model we set upper limit 100000 and lower limit 0.0. We also used scope block in our model. Signals generated during simulation are displayed by this block.

The Scope block displays its input with respect to simulation time. The Scope block can have multiple axes (one per port); all axes have a common time range with independent *y*-axes. The Scope allows you to adjust the amount of time and the range of input values displayed. You can move and resize the Scope window and you can modify the Scope's parameter values during the simulation.

When you start a simulation, Simulink does not open Scope windows, although it does write data to connected Scopes. As a result, if you open a Scope after a simulation, the Scope's input signal or signals will be displayed.

If the signal is continuous, the Scope produces a point-to-point plot. If the signal is discrete, the Scope produces a stair step plot.

The Scope provides toolbar buttons that enable you to zoom in on displayed data, display all the data input to the Scope, preserve axes settings from one simulation to the next, limit data displayed, and save data to the workspace. The toolbar buttons are labeled in this figure, which shows the Scope window as it appears when you open a Scope block. Scope properties could be set by changing its parameters.

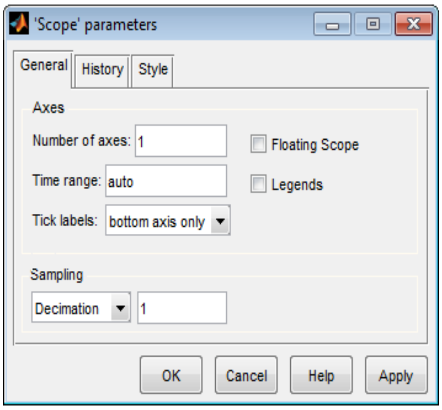


Figure 4.7: Scope Block Parameters

4.3 Results obtained

The results obtained by model are as follows. Consider the situation in which the normal person takes in food at 0.5 hrs.

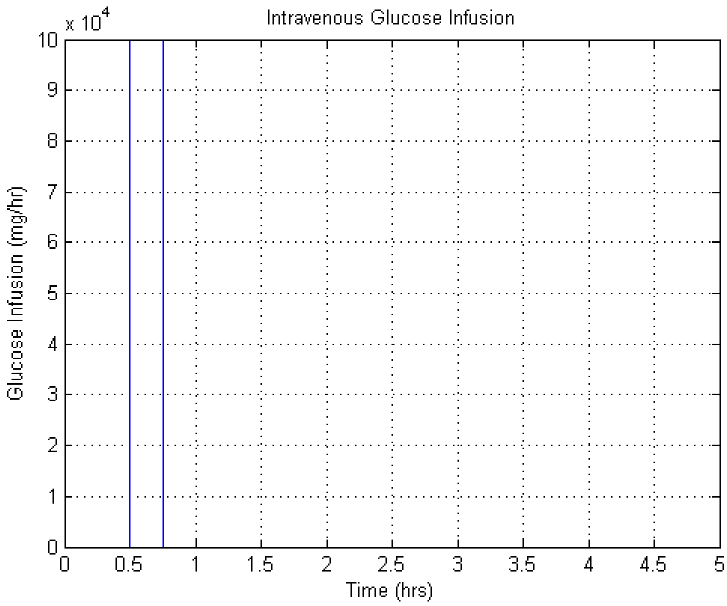


Figure 4.8: Glucose Intake

Now consider the responses of normal, type I, and type II diabetic patients. Following are the results of normal person. When normal person takes in food the blood sugar level rises in the body. This high blood glucose level triggers pancreatic beta cells to secrete insulin with the rate proportional to the rate at which glucose level rises. This insulin makes the body cells and tissues to use glucose with increased rate. As a results glucose level comes back to it normal range.

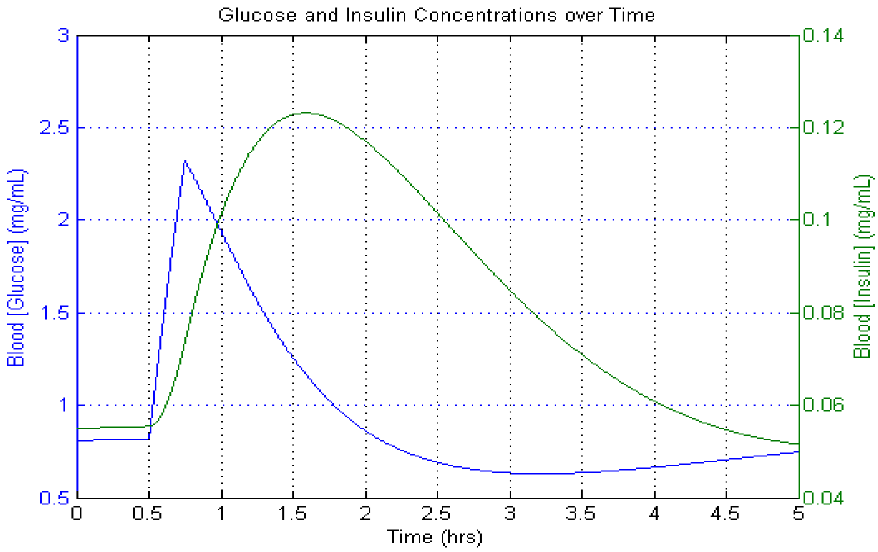


Figure 4.9: Normal Person

In order to get the results for Type I diabetic patients, beta cells are reduced by 20 percent. As a result less insulin is produced and blood glucose level is maintained at higher level than normal person.

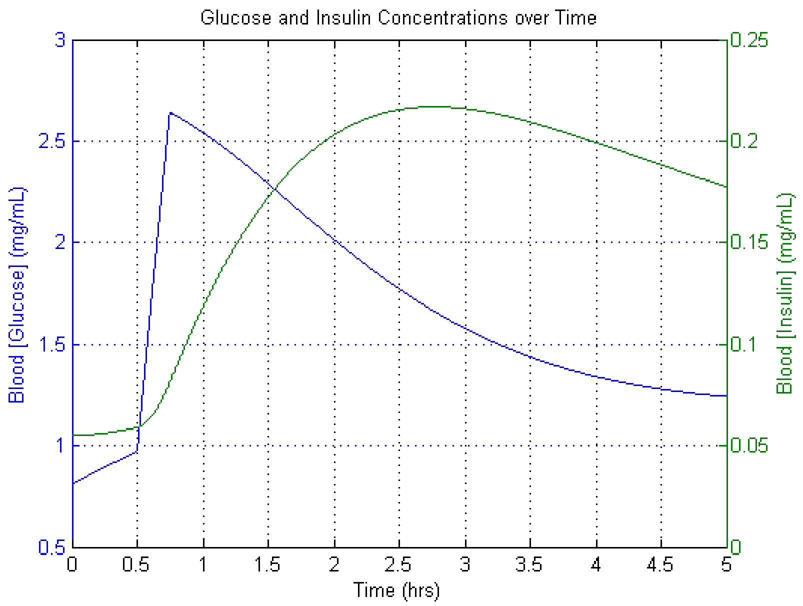


Figure 4.10:Type I Diabetic Patient

In the above figure as glucose level of the person after taking food raises from 0.9mg/ml to 2.7mg/ml the level of insulin need to rise in direct proportion. But beta cells of the diabetic person does not work properly because of which the insulin release is less in the blood streams which results in balancing blood glucose level at 1.3mg/ml instead of balancing it at 0.8mg/ml. In this condition the patient need assistance from other sources to provide the body with enough insulin as to maintain blood glucose level at desired range. Insulin pump provides the body with the external insulin. But to decide that what amount of insulin should be injected to patient body to meet his need is a tough task. To cope with this situation many controllers have been designed.

The body of type I diabetic person produces very less amount of insulin as compared to normal person. As a result excessive amount of glucose starts accumulating in the blood. Even though the blood has plenty of insulin, diabetic person cells are unable of getting their crucial energy and growth requirements.

Similarly in type II diabetic patients alpha cells are reduced. As a result insulin level in the body shows abrupt behaviour. Sometimes remains too high and sometimes remains too low. In this case patient need to be monitor for both situations of insulin injection, in case when insulin production is low and glucose level is high, and glucose injection in case when glucose level is high.

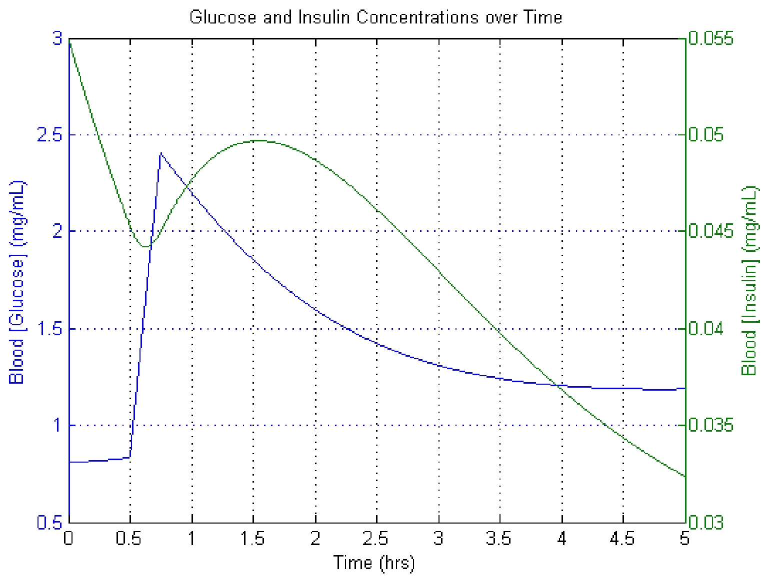


Figure 4.11: Type II Diabetic Patient

Based on these results we observed that type II diabetic patient produces insulin but works in abrupt manner. In above figure when the glucose level is normal at 0.2 hrs the insulin in the body should be low but it concentration at that time was very high. Later on, when food is taken by the patient the level of insulin comes down and then again rises. Insulin is produced by the body but its insulin sensitivity is undermined and does not work as it should do.

The chapter provides insight into the mathematical model used and fuzzy controller performance. The implementation has been based on mathematical model of stolwijk and hardy's. The description of blocks used in construction of model has also been included in this chapter. In next chapter obtained results are compared with the previous results and the efficiency of proposed model is being calculated to compare with other models.

Chapter 5

5. ANALYSIS

In this chapter results are obtained by applying proposed technique. The comparison of the proposed technique with the other techniques is being performed based on the results obtained. Also this chapter describes the contribution made by this work in treating diabetic patients.

5.1 Analyzing Results:

Research in the field of Bio-Medical instrumentation is expanding. Diabetes is included in one of the demanding areas for research. Glucose and Insulin are related terms. Glucose provides energy to the cells whereas insulin is a hormone which helps in absorption of glucose by body cells. The concentration of both glucose and insulin need to remain in a desired range in order to ensure balance. A steady state model for type-1 and type-2 diabetic person is being developed and dynamics is included to avoid non-linearities. Using this closed loop feedback system has been designed for regulation of glucose insulin for type-1 and type-2 diabetic persons. Two types of feedback mechanisms are widely used. One is open loop and the other is closed loop. In open loop control a predetermined amount of insulin is given to patient as suggested by physician. In this method 2-3 daily insulin injections are given to patients based on measurements. Drawback of this approach is lack of reliable continuous monitoring

In closed loop feedback is taken from body through sensor which senses human body glucose level. The sensor output is then given to the controller and based on the difference between value obtained by sensor and the desired value controller pumps the required amount of insulin or glucagon to body. The closed loop control is shown in the following figure

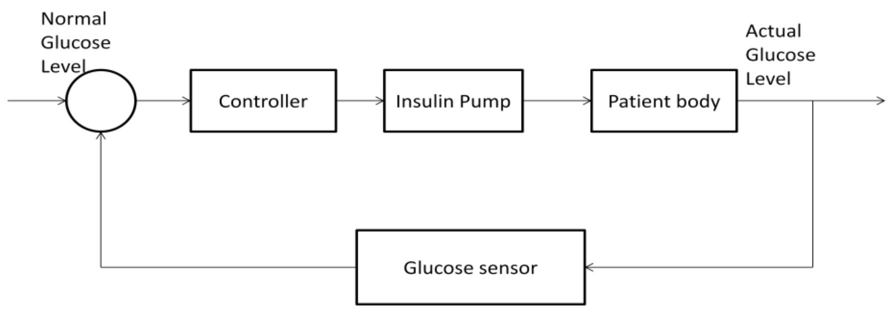


Figure 5.1: Controller Design

The proposed rule base fuzzy controller is trying to handle both the insulin and glucagon intake in human body. So the above figure is being changed as below

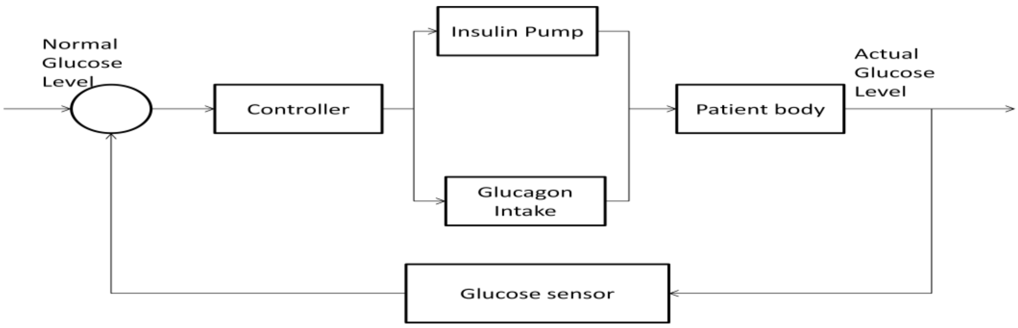


Figure 5.2: Enhanced Controller Design

The desired controller is implemented in Matlab using mathematical modeling. Mathematical model for pancreatic function is used to observe the effects of glucose and insulin regulation. Simulink is used for simulation of pancreas using different parameters.

The closed loop feedback system approach is used in model to attain pancreatic functionality. It mimics the control of blood glucose level inside the human body. Closed loop feedback system leads to improved control of diabetes. As the person takes some food his/her glucose level increases as a results pancreatic beta cells secretes insulin. By this mechanism insulin in plasma is increased and remote insulin in action raises the glucose uptake in muscles, liver and tissues. This way the glucose concentration in plasma falls back to basal value.

In normal person glucose and insulin concentartion remains at basal value until that person is subjected to glucose intake. When a normal person takes some food his/her glucose level increases from basal value and correspondingly insulin level also rises. Which forces body cells and tissues to uptake gluocse. As a result glucose level decreases and returns back to basal level.

Pancreatic beta cells are destroyed in type 1 diabetic person body by immune system which are the only cells in the body that are responsible for the production of insulin, which regulates blood gluocse. Patient reamins at risk for neuropathy, nephropathy, blindness and other vascular complications when glucose level is hugh for longer period of time. Intensive insulin therapy in isnulin dependent diabetic pateints helps in reducing the risk of developing complications.

We mimic the reduction of beta cells by reducing the concentration of beta cells by 20 percent. The results obatined showed that if insulin production is reduced plasma glucose concentration remains at high level. When this model containing the beta cells reduction is passed through the designed controller, the designed controller detects shortage of insulin and sends command to inject insulin in the body. So that glucose level comes to basal value.

In type II diabetic person body cell fails to use insulin properly and sometimes combine with absolute insulin deficiency. In this type we need to take care of both insulin infusion and glucagon intake.

5.2 Comparison

Making comparison of the designed controller with existing techniques proved that the designed controller outperformed the existing techniques in maintaining the blood glucose level of the diabetic patient.

The designed controller detect that either the patient requires insulin injection or glucagon intake. If insulin concentration is elevated in body of patient, glucose level decreases below the required range, in this case controller outputs the signal to take some glucagon and if insulin concentration decreases inside the body of patient, glucose level increases above the required range. Controller detects this increase and send signal to glucagon pump to inject glucose.

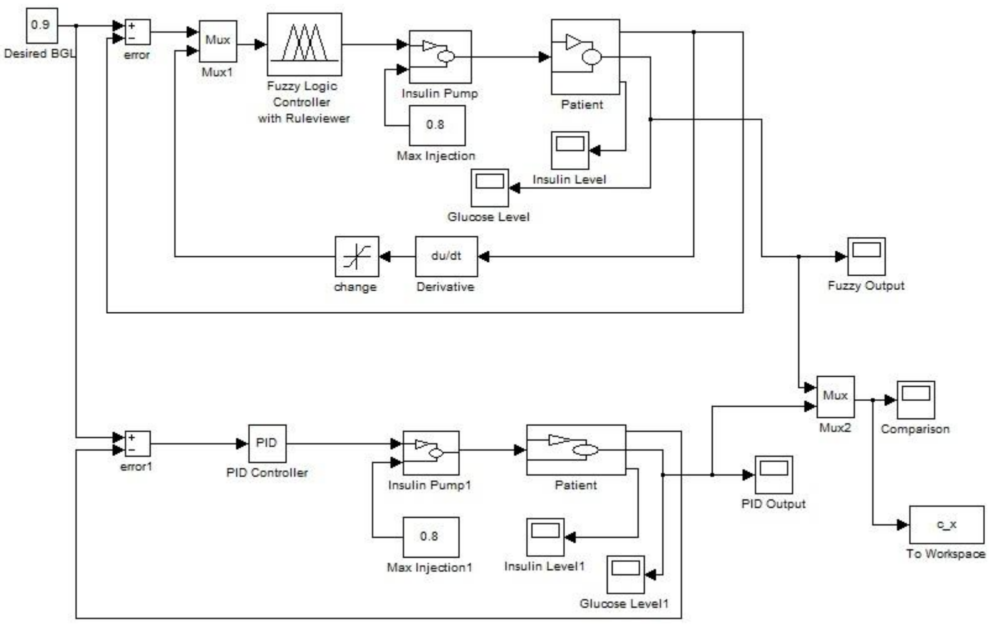


Figure 5.3: Model with fuzzy and PID controller

The model shown in figure 5.3 shows results of the designed controller and the PID controller when subjected to a Type I diabetic patient. The results obtained shows that the results obtained by using the fuzzy controller to control the blood glucose level of diabetic patients are more accurate and efficient then the results obtained by using the PID controller. The designed fuzzy controller maintains the blood glucose level of the diabetic patient at the ideal level of 90mg/ml, whereas the PID controller maintains level at much higher level of 130mg/ml. The obtained results are shown by following figure.

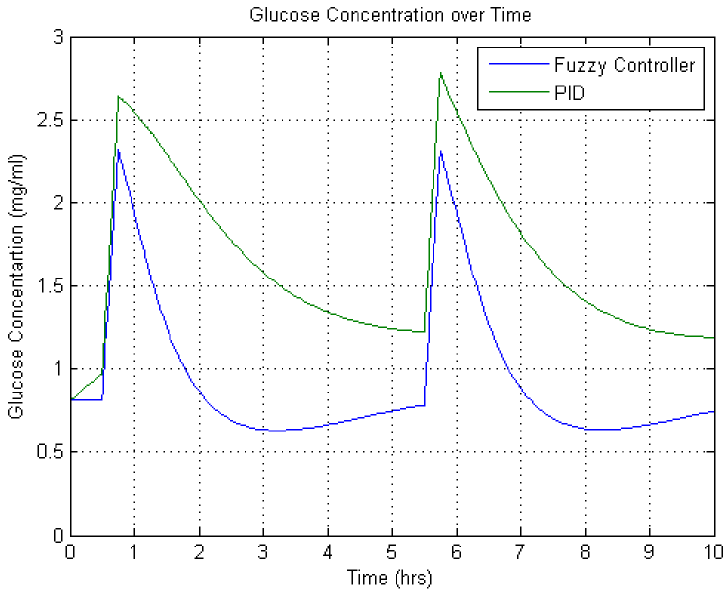


Figure 5.4: Fuzzy and PID curves

If the food taken provides less amount of glucose the results obtained are as follows.

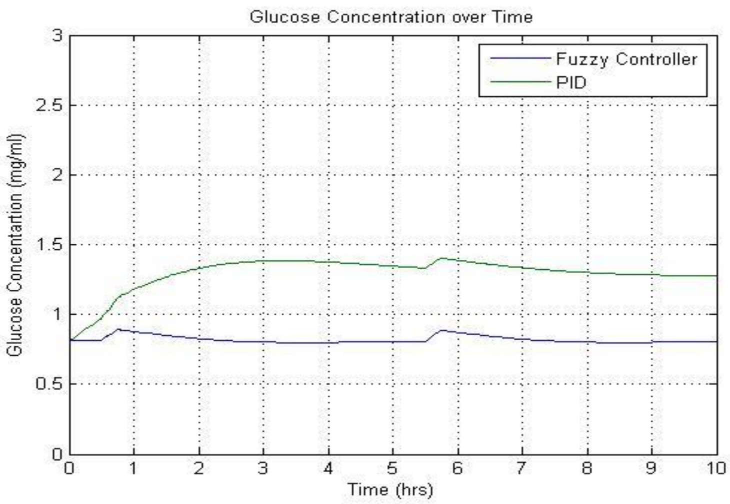


Figure 5.5: Fuzzy and PID curves

The PID controller shows abrupt behaviour and keeps the glucose level of a person at high level for longer period. Moreover, it also stabilizes the glucose level of the patient at high level of 1.4mg/ml. On the other hand, fuzzy controller maintains glucose level at desired range of 0.8mg/ml with very little fluctuations at the time when food is taken by the patient.

Now consider the situation when the patient take very little amount of glucose in the form of food. Following results are obtained. This result also shows that the fuzzy controller provides promising results in maintaining the blood glucose level as compared to PID controller.

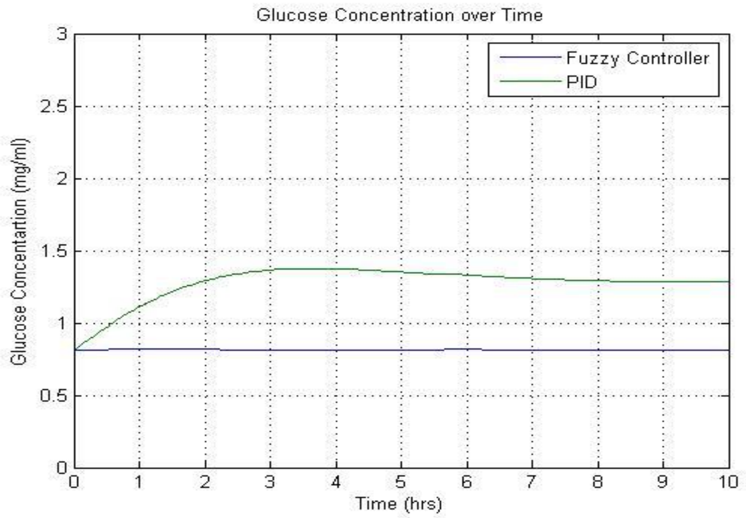


Figure 5.6: Fuzzy and PID curves

Now consider the situation when the food intakes provide too high glucose to the patient. The comparison between controllers showed following results.

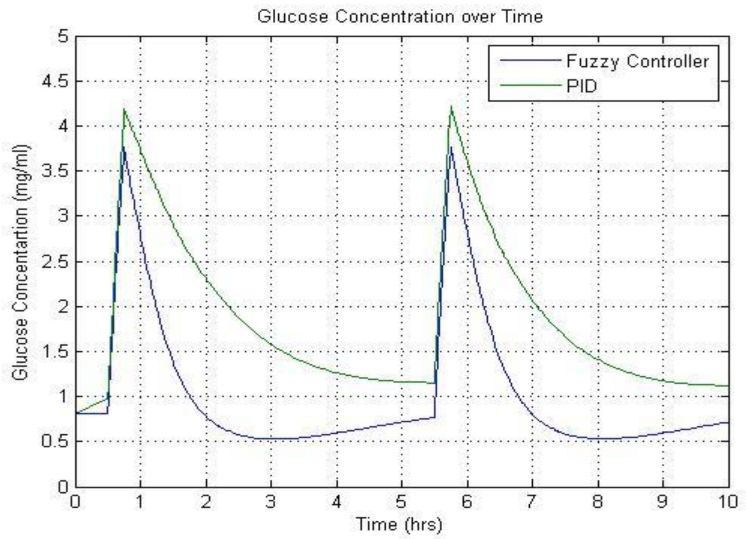


Figure 5.7: Fuzzy and PID curves

The PID controller takes the level of blood glucose to high level of 4.4mg/ml which could be very dangerous for the patient. Also the time taken to low the level is high as compared to fuzzy controller. From above results it is clear that the proposed controller showed better results in every case. Whether the food intake provides less amount of glucose or large amount, in both cases the performance of designed controller is better.

The result shows that the diabetic patients are controlled more accurately by proposed fuzzy controller as compared to the PID controller. As blood glucose level of diabetic person is maintained at 70mg/ml by fuzzy controller and 130mg/ml by PID controller.

From above simulated model we see that how a natural pancreas model can be imitated as artificial pancreatic model using simulink. We observe that when glucose concentration approaches to its peak value pancreas secretes insulin accordingly and when blood glucose level is at its peak the insulin concentration secreted by pancreas is also at its peak level which shows that insulin and glucose have proportional relation in body. As early as blood glucose level approaches to stable state pancreas secretion becomes slow till it comes to stable state in the body.

5.2.1 Transient Exclusion

The curve obtained by running the designed simulink model is steep in nature. Transient from the curve is excluded by the use of FLC controller in order to keep the patient away from painful continues injection. In transient curve first the level of the glucose is taken back to normal level by injecting insulin and the injected insulin takes the glucose level below normal and then again forcing the patient to take some food and again the curve goes above the normoglycemic level. This way after many fluctuations the normoglycemic level is achieved. Whereas, in designed controller by removing transient from the curve we provided the patient with relief from continues injection of insulin.

5.2.2 Comparison with SOTA Technique.

After making comparison with the PID controller I made comparison with the latest technique used by Yasini and Elmalki [28] in 2013. In their research they assumed that there are two different input of fuzzy logic controller one is the glucose concentration and the other is the rate of change in glucose concentration, and one output of the dose of insulin. The controller is proved to be reliable, safer and has less insulin consumption. By comparing with the designed FLC controller I proved that the insulin consumption in designed controller is even more less than the existing controller designed by Yasini and Elmalki.

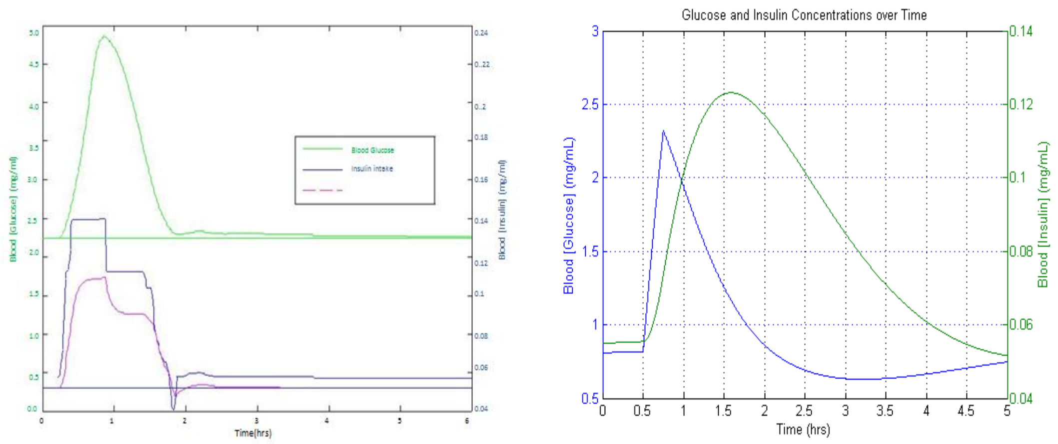


Figure 5.8: Comparison

The performance of the designed controller is more accurate in that it maintains the glucose level of the diabetic patient at 90mg/ml whereas the existing technique maintains level at 220mg/ml. Moreover, less insulin is used to put the level of the glucose to desired level.

Item	**Designed Controller**	**Existing Controller**
Maximum Glucose	270 mg/ml	420 mg/ml
Minimum Glucose	90 mg/ml	220 mg/ml
Total Infused Insulin	0.12 mg/ml	0.14 mg/ml

Table 5.1: Comparison Table

The following figure and table have shown that the designed FLC is more reliable, safer and has less insulin consumption than existing controller. Therefore, the designed FLC would be preferable and advisable when treating critical diabetes cases.

Chapter 6

6. CONCLUSION AND FUTURE WORK

In this chapter research contribution made by this work is described in detail. The problem of diabetic patient to maintain their blood glucose level in safe range is identified and analyzed. Objective of the research is elaborated and described with the proposed solution. The control strategy used to deal with the diabetic patients is also discussed with its benefits. The reason why we used this strategy is also described in detail. The results obtained by comparing the proposed controller with the already designed PID controller are also discussed to prove that the designed controller performs well as compared to the already existing techniques. The future directions which will be pursued are also discussed in this section in detail. In section 6.1 we summarize all the work done during this MS thesis whereas in section 6.2 the directions to continue this research in future are provided and discussed.

6.1 Conclusion

Diabetes management is one of the most important issues in the field of human regulatory systems, which is being addressed by the research done. Various research works are being done in this area which includes reinforcement learning, Q learning algorithm, fuzzy controller, and H_∞ technique. In this research, a system of closed loop control based on fuzzy logic control for type I diabetic patient has been proposed. The reason to use closed loop method is that it is a new direction, and it can control human blood glucose ideally. A controller is designed, which incorporate knowledge about the treatment of patient, using Mamdani-type fuzzy controller. Designed controller used the fuzzy if- then rules to keep the blood glucose of patient in normal range. The proposed controller can successfully tolerate dynamic uncertainty in patient model. This research shows that fuzzy logic framework has the potential to synthesize expert knowledge to treat diseases.

In order to demonstrate the proposed controller performance, it was tested under standard meal disturbances. Proposed controller simplicity provides a novel approach for implementing a controller with less time management in comparison with other researches. Simulation studies performed in this work show that the novel approach of using fuzzy controller is more reliable than previous techniques.

As part of this research we also made comparison of the proposed controller with PID controller. This Comparison of proposed controller with PID controller showed that, FLC is more reliable, safer and has less insulin consumption than the PID controller. It has also been proved that this method has preference over other conventional techniques in controlling the glucose level of diabetic patient. The proposed model is expected to enhance the automation of insulin delivery and increase quality of life, and life expectancy of type I diabetic patients.

6.2 Future Works

In this work, a fuzzy controller with enhanced functionality has been proposed. The devised controller has proven to effectively control the blood glucose level near to the control provided by the real pancreas. It can be extended to enhance its functionality to make it more robust.

As various aspects are catered of diabetic patients for implementation and subsequent exercise of results, nevertheless we understand that it is very absorbing area for research that the work could substantially be carried forward in following directions as a future work.

- Further improvement in mathematical model of insulin-curve
- Increase in efficiency and reliability of controller
- Biological compatibility of sensor, device and patient
- The model needs to be transformed on efficient and high speed hardware
- Inclusion of an exercise regime in the overall model of Type I diabetic patient in order to have more realistic simulation.

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