I.1.Introduction*:*

Diabetes mellitus is a widespread disease. According to the World Health Organization (WHO), in 2011 approximately 346 million people suffered from diabetes world-wide. India, China and the USA rank among the top three countries with the largest numbers of diabetic patients [1]. For 2030, an increase up to 552 millions patients is prognoses by the International Diabetes Federation , In the human body, the pancreas is responsible for blood glucose control. By producing and releasing the counteracting hormones insulin and glucagon, blood glucose concentration can be decreased or increased, respectively, and stabilized within the physiological range of 70−120 mg/dl.

Diabetes mellitus is characterized by a dysfunction of the pancreas, often in combination with reduced insulin sensitivity. Based on the underlying pathological mechanisms, the disease is classified into three types. Patients suffering from type 1 diabetes are insulin-dependent because the majority of insulin-producing cells in the pancreas is destroyed due to an autoimmune reaction.

 Patients with type 2 diabetes are initially independent of exogenous insulin administration, but will become insulin-dependent over time. These metabolic disturbances are generally caused by reduced insulin sensitivity of the glucose-consuming cells, or deteriorated glucose sensing of the pancreas. Initially, this results in increased insulin production and, finally, in a progressive loss of insulin secretion. Other forms of diabetes which are frequently nonpermanent are caused by metabolic stress in critically ill patients, drug-induced hypoglycemia or by pregnancy.

At the moment, insulin-dependent diabetic patients face the daily challenge of manually controlling their blood glucose concentration After measuring their blood glucose concentration.

 In this chapter brief physiological overview of the insulin production and the characteristics of the diabetes mellitus are provided. Furthermore, the artificial pancreas system is presented along with a description of its elements and we described a simple mathematical model of the dynamics of glucose and insulin interaction in the blood system developed by Bergman and The Glucose Minimal Model.

I.2.Physiology of the Pancreas

The Pancreas is an organ located in the abdomen with two different functions: exocrine and endocrine. The exocrine function is the production and secretion of digestive enzymes; the cells of the pancreas which have this purpose are known as pancreatic acini. The endocrine function is the production of several important hormones such as insulin and glucagon, and cells involved in this secretion are called isles of Langherans or pancreatic islets. Each distinct type of islet cell is involved in the production of a different hormone: the β-cells (or B cells) secrete insulin, whereas α-cells (or A cells) provide glucagon. Another molecule that is secreted by the islet cells is somatostatin which is produced by δ-cells (D cells). This hormone has the capability of inhibiting the secretion of both insulin and glucagon [2].

Insulin is a protein hormone composed of two chains: A and B, with 21 and 30 amino acids, respectively. Insulin's task is to control organic metabolism since it induces glucose to enter from the extracellular fluid into cells[2]. The insulin effect is felt by the target cells, which are insulin-dependent. These target cells are
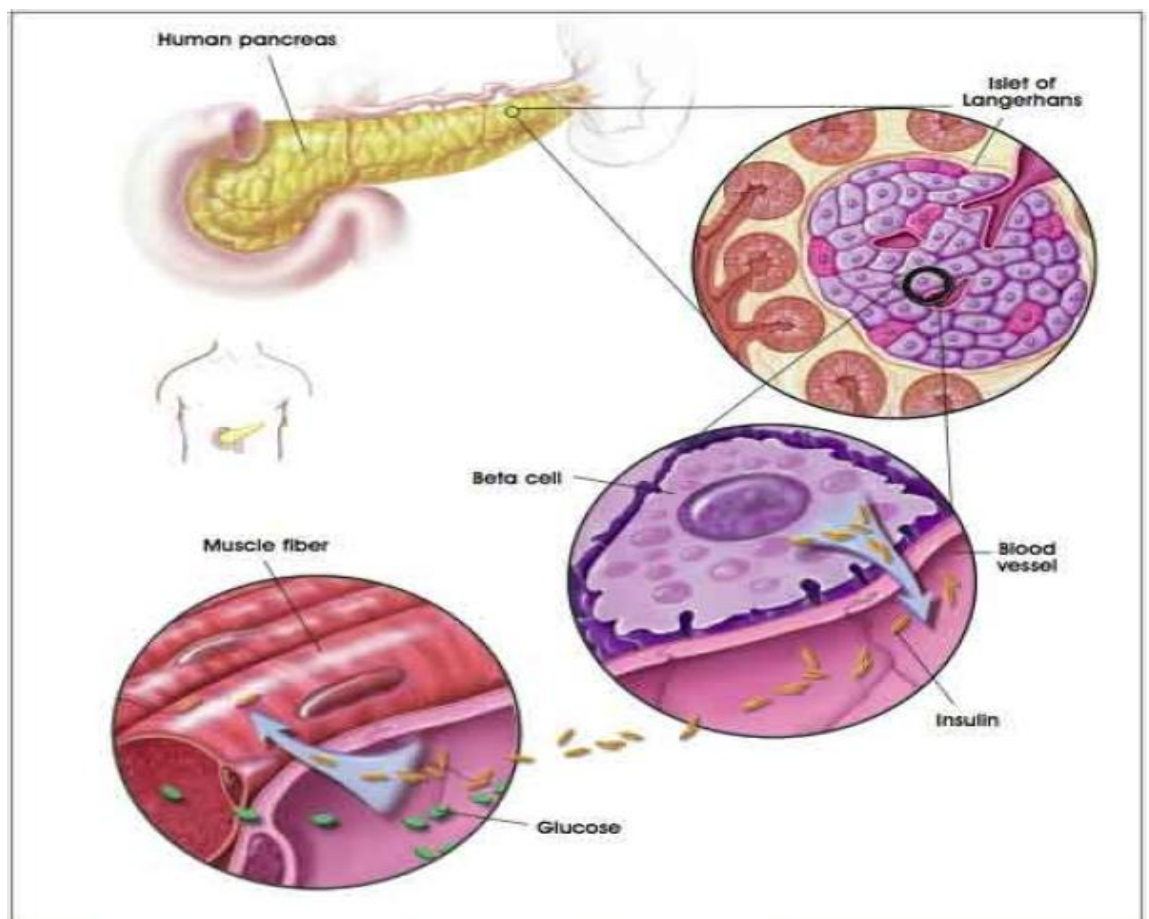

Figure I.1: Insulin secretion by pancreatic islets and insulin path throughout the blood before reaching the target cells [2].

mainly muscle cells (both cardiac and skeletal), adipose tissue cells and liver cells. When insulin is secreted, it circulates throughout the blood and reaches the insulin receptors of the cells as shown in **Figure I.1**. Once the insulin hormone binds to the cell receptors, they stimulate cytoplasmic vesicles containing the glucose transporter, inducing them to reach the plasma membrane and then merge with it. An increase in the number of glucose transporters in the plasma membrane facilitates the glucose movement from the extracellular fluid into the cells by facilitated diffusion. Plasma glucose concentration plays the most important role in controlling the insulin secretion. Stimulation and activation of pancreatic β-cells depends on changes in plasma glucose concentration. If plasma glucose concentration increases, e.g after a meal, the β-cells are activated and the secretion of insulin begins. On the other hand, a decrease in plasma glucose concentration leads to removal of the insulin secretion stimulus [2]. **FigureI.2** provides a schematic representation of the glucose-insulin mechanism. An increase in plasma glucose concentration causes a rapid stimulation of insulin secretion and consequently an increase in plasma insulin concentration. Afterwards, plasma insulin passes to the liver which degrades half of it, avoiding liver glucose output since insulin inhibits conversion of the glycogen into glucose. The other half of plasma insulin induces cells of the insulin-dependent tissues to uptake glucose. As a result of the two different actions of the insulin, one over the cells and the other over the liver, the plasma glucose concentration is returned to normal, around 80-140 mg/dl [2]. The antagonist of insulin is glucagon which has the function of reducing the insulin concentration in the plasma, and therefore stops the insulin action and in this way prevents hypoglycemia.
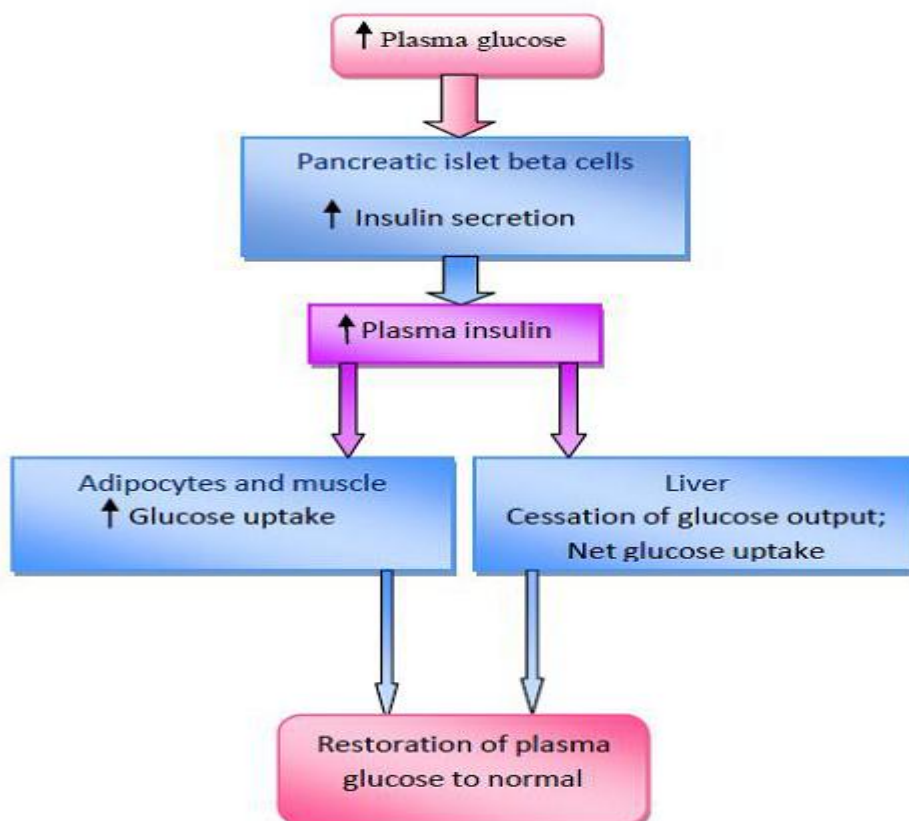

Figure I.2: Effect of plasma glucose concentration over insulin secretion

I.3.The Blood Glucose-Insulin System

The glucose-insulin system is an example of a closed-loop physiological system. A healthy person, normally has a blood glucose concentration at about $70 - 110 mg/dL$. The glucose-insulin system helps us to keep this steady state. In **Figure I.3** a simple description of the system is shown. Most of the time a healthy person is in the green area, having normal blood glucose concentration.[3]
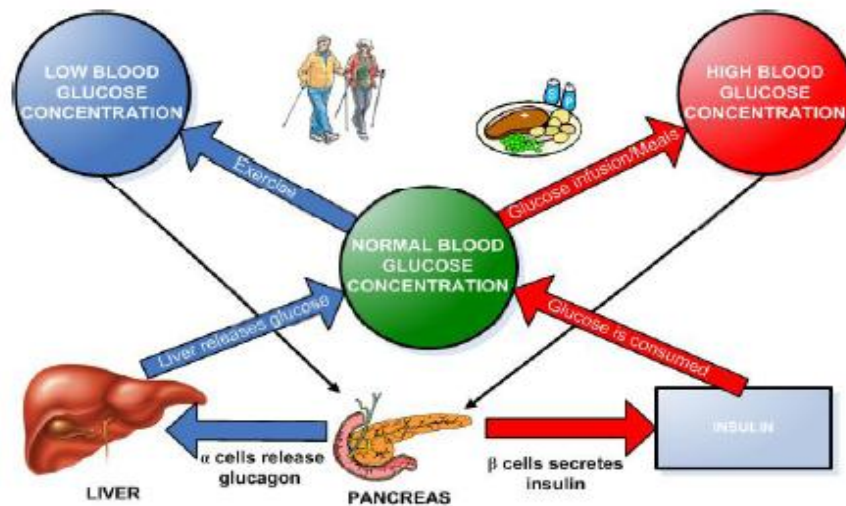

Figure I.3: The blood glucose-insulin system

If the person then ingest additional glucose to the system e.g via a meal, the person moves to the red area, with a higher blood glucose concentration. When this happens a signal is sent to the pancreas, which _ cells react by secreting the hormone insulin. This insulin increase the uptake of glucose by the cells, liver etc. and brings the person back in the green area. If the blood glucose concentration goes below the normal level, the person is in the blue area. This could happen as a response to exercise, which increase the glucose uptake. When the person is in the blue area with low blood glucose concentration a signal is also send to the pancreas. The pancreas _ cells react by releasing glucagon.

This glucagon affects the liver cells to release glucose in to the blood until the person is back in the green area again [3]. This is a very simple description of a more complicated system. But it is this simplistic way of explaining the metabolism, which will be presented in a mathematical model in this chapter.

I.4.Diabetes

Diabetes is a large problem today. According to the Diabetes Atlas 2003, 194 million people suffer from the disease. Diabetes is not a single disease, but actually many. The connection between the deceases is that they are caused by a disfunction in the blood glucose-insulin system. If not treated,

diabetes can lead to heart diseases, blindness and other malfunctions. The two most frequently seen diabetes types are diabetes type 1 and diabetes type 2[3].

I.5.Type 1 Diabetes Mellitus(T1DM)

T1DM is an autoimmune disorder characterized by destruction of insulin-producing β-cells in the pancreas. The consequence of this damage is the loss of endogenous secretion of insulin that is essential to maintain euglycemia, causing life threatening hyperglycemia and keto-acidosys. As written above, the lack of insulin secretion causes a loss in the ability to regulate glycemic levels in people affected by T1DM, thus making them suffer from long periods of hyperglycemia without proper insulin management [3]. This process usually develops in a few years, and hyperglycemia rises when 10% of the beta cells are still working. At that point, functional β-cells still exist, but they are not able to supply a minimum level of insulin needed to maintain euglycemia. Nevertheless, during this phase, glycemic control can be reached with modest insulin administration. Unfortunately, this is a temporary phase and it[2].

I.6 .Diabetes Type 2

Diabetes type 2 is the most common type of diabetes. When you have this type of diabetes the pancreas is able to produce some insulin, and in some cases it can produce insulin as for a healthy person. The problem is that the insulin is not able to affect the cells, of the body to increase their uptake of glucose. Thus people suffering from type 2 diabetes are insulin resistant. Over time the number of _ cells start to decrease, and then the type 2 diabetics should be treated with insulin injections like a type 1 diabetic. Type 2 almost also have the same symptoms as type 1 diabetes.[3].

I.7. Hyperglycemia

A person has hyperglycemia, when the blood glucose level is above 270mg/dL . This can arise e.g. when a diabetic eats a large meal or has a low level of insulin in the blood. Hyperglycemia is extremely dangerous if not treated.

I.8. Hypoglycemia

A person has hypoglycemia when the blood glucose level is below 60mg/dL . This can happen ex. after too much exercise, a too large insulin dosage, small amount of carbohydrates in the food or if the diabetic skips meals. Hypoglycemia can result in loosing of the conscience. Avoiding hypoglycemia is an important issue when you are using insulin as treatment.[3].

I.9. The Insulin Pump

Insulin pumps allow continuous subcutaneous infusion of insulin 24 hours a day at present levels, and the ability to program bolus doses of insulin as needed at meal times. Subcutaneous injection is

considered the safest way to infuse insulin to the body, because it is relatively simple and the risk of infection at the injection site is smaller than with an intravenous route . Intravenous injection would, however, have been more optimal from a control technical point of view, because the time delays are smaller here. The study of [4] found the lag from subcutaneous injection to insulin concentrations in blood plasma to vary between 8- 24 minutes.

Figure I.4: The MiniMed insulin pump from Medtronic.

Insulin is injected through the syringe. A basal insulin infusion amount can be preprogrammed by the user, in addition to bolus doses before meal.

There are several insulin pumps on the market today. Most of them are powered by batteries and consist of a small processing module with a display, a dispos-able insulin reservoir and an insulin syringe. In a closed-loop control scheme, the amount of insulin supplied from the pump would be set automatically, depending on blood glucose measurements and the control algorithm.

I.10. The Model

I.10.1. Bergman's minimal model

Bergman's minimal model is a one compartment model, meaning that the body is described as a compartment/tank with a basal concentration of glucose and insulin. The minimal model actually contains two minimal models. One describing glucose kinetics, how blood glucose concentration reacts to blood insulin concentration and one describing the insulin kinetics, how blood insulin concentration reacts to blood glucose concentration. The two models respectively take insulin and glucose data as an input. The two models have mostly been used to interpret the kinetics during the test, and in their original form they cannot be used to much else [3] ,but with small additions or modifications they can also be used to describe meals and exogenous insulin infusion [3] .

In this section a description of the two kinetics are done and finally two couplings are proposed, which could be used as simulators of the entire blood glucose-insulin.

I.10.2. The Glucose Minimal Model

The original glucose minimal model describes how the glucose level behaves according to measured insulin data during a test. The model is a one compartment model divided into two parts. The first part is the main part describing the glucose clearance and uptake. The second part describes the delay in the active insulin I_2 which is a remote interactor which level affects the uptake of glucose by the tissues and the uptake and production by the liver. These two parts are described mathematically by two differential equations namely.

$$\frac{dG(t)}{dt} = -[P_1 + x(t)]G(t) + P_1 G_b \text{ .... G(0)=}G_0 \text{.........EqI.1.}$$

$$\frac{dx(t)}{dt} = -P_2 x(t) + P_3[I(t) - I_b] \text{ .... x(0)=0.........EqI.2.}$$

The best way to describe the meaning of these equations is to show how they are derived. A description of the parameters and the terms of the equations is then easier understood. The derivation is based on the description of the model by Steil et al. [3]and the rule of mass balances:

accumulated = in − out + generated − consumed Such a derivation will be done in the next subsection. In the derivation the following parameters will be used:

Table I.1: parameters of the Model

Parameter	Unit	Description
T	[min]	Time
G(t)	[mg/dL]	Blood glucose Concentration
Gb	[mg/dL]	Steady state blood glucose concentration (baseline)
I2(t)	[mU/L]	Active insulin concentration
X(t)	[1/min]	The effect of Active insulin.
I(t)	[mU/L]	Blood insulin concentration

Ib	[mU/L]	Steady state blood insulin concentration (baseline)
VG	[dL]	Volume of the glucose compartment
$VI2$	[L]	Volume of the remote pool
$QG1$	[dL/min]	Flow
$QG2$	[dL/min]	Flow
$QI21$	[L/min]	Flow
$QI22$	[L/min]	Flow
$w1$	$[dl2 \triangleleft (min \leq mU]$	effect factor
$w2$	$[dl2 \triangleleft (min \leq mU]$	effect factor

I.10.3.Model Structures

The minimal model of the glucose and insulin is perhaps the simplest model that is physiologically based and represents well for the observed glucose/insulin dynamics of a diabetic patient. The insulin enters or exits the interstitial insulin compartment at a rate that is proportional to the difference $(I(t) - I_b)$ of plasma insulin *I(t)* and the basal insulin level I_b. If the level of insulin in the plasma is below the insulin basal level, insulin exits the interstitial insulin compartment; and if the level of insulin in the plasma is above the insulin basal level, insulin enters the interstitial insulin compartment. Insulin also can flee the interstitial insulin compartment through another route at a rate that is proportional to the insulin amount inside the interstitial insulin compartment. On the other hand, glucose enters or exits the plasma compartment at a rate that is proportional to the differenc $(G(t) - G_b)$ of the plasma glucose level *G(t)* and the basal glucose level G_b . If the level of glucose in the plasma is below the glucose basal level, the glucose exits the plasma compartment; and if the level I of glucose in the plasma is above the glucose basal level, glucose enters the glucose

compartment. Glucose also can flee the plasma compartment through another route at a rate that is proportional to the glucose amount inside the interstitial insulin compartment.

Currently, the most widely used model in physiological research on the metabolism of glucose is the Minimal Model. This model structure describes experimental data well with the smallest set of identifiable and meaningful parameters. The Minimal Model consists of two parts: the minimal model of glucose disappearance and the minimal model of insulin kinetics.[5].

$$\frac{dG(t)}{dt} = -[P_1 + x(t)]G(t) + P_1 G_b \dots\dots\dots\dots\dots\dots\text{EqI.3.}$$

$$\frac{dx(t)}{dt} = -P_2 x(t) + P_3[I(t) - I_b] \dots\dots\dots\dots\dots\dots\text{EqI.4.}$$

$$dI(t)/dt = -nI(t) + \gamma[G(t) - h]t \dots\dots\dots\dots\dots\text{EqI.5.}$$

where $G(t)$ (mg/dL) is the blood glucose level in plasma, $I(t)$ (µU/mL) is the insulin concentration level in plasma, $x(t)(min^{-1})$ is the variable which is proportional to insulin in the remote compartment, G_b (mg/dL) is the basal blood glucose level in plasma, I_b (µU/mL) is the basal insulin level in plasma, t (min) is the time interval from the glucose injection. **Eqs.I.3** and **I.4** represent the glucose disappearance and **Eq.I.5** represents the insulin kinetics. The initial conditions of the above three differential equations are as the following:

G(0)=G_0, x(0)=0, I(0)=I_0

The model parameters carry some physiological meanings that can be summarized as follows. $P_1 min^{-1}$ describes the "glucose effectiveness" which represents the ability of blood glucose to enhance its own disposal at the basal insulin level. $P_2 min^{-1}$ describes the decreasing level of insulin action with time. $P_3(min^{-2}.(\frac{uU}{ml}))$ describes the rate in which insulin action is increased as the level on insulin deviates from the corresponding baseline. γ ((µU/mL) ·(mg/dL)

denotes the rate at which insulin is produced as the level of glucose rises above a "target glycemia" level. n (min^{-1}) represents fractional insulin clearance. h (mg/dL) is the pancreatic "target glycemia" level. G_0(mg/dL) is the theoretical glucose concentration in plasma extrapolated to the time of glucose injection $t = 0$. I_0 (µU/mL) is the theoretical plasma insulin concentration at $t = 0$. µU/mL is the conventional unit to measure the insulin level and has the following conversion formula: 1 micro-unit/ milliliter = 6 picomole/liter (1µU/mL = 6 pmol/L) [6]. $P_1, P_2, P_3, n, \gamma, h, G_0$ and I_0 are the parameters to be estimated. A fourth differential equation will be added to the set of the Minimal Model equations to represent a first-order pump dynamics:

$$\frac{dU_1(t)}{dt} = \frac{1}{a(-U_1(t)+u(t))} \quad \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\text{EqI.6.}$$

Where: $U_1(t)$ is the infusion rate, u(t) is the input command, and a is the time constant of the pump.

I.10.4.Model Linearization

Now let us recall the four differential **Eqs.I.6** that define the proposed mathematical model and denote them as $f_1(G), f_2(x), f_3(I) and f_4(U_1)$. The result is

$$f_1(G) = \frac{dG(t)}{dt} = -[P_1 + x(t)]G(t) + P_1 G_b \quad \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\text{EqI.7.}$$

$$f_2(x) = \frac{dx(t)}{dt} = -P_2 x(t) + P_3[I(t) - I_b] \quad \dots\dots\dots\dots\dots\dots\dots\dots\dots\text{EqI.8.}$$

$$f_3(I) = \frac{dI(t)}{dt} = -nI(t) + \gamma[G(t) - h]t + U_1(t) \dots\dots\dots\dots\dots\dots\dots\dots\dots\text{EqI.9.}$$

$$f_4(U_1) = \frac{dU_1(t)}{dt} = \frac{1}{a}(-U_1(t) + u(t)) \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\text{EqI.10.}$$

The above equations can be written and arranged as follows and can be further simplified as

$$f_1(G) = \frac{dG(t)}{dt} = -[P_1 G(t) + x(t)G(t)] + P_1 G_b \quad \dots\dots\dots\dots\dots\dots\dots\text{EqI.11.}$$

$$f_2(x) = \frac{dx(t)}{dt} = -P_2 x(t) + [P_3 I(t) - P_3 I_b] \quad \dots\dots\dots\dots\dots\dots\dots\dots\text{EqI.12.}$$

$$f_3(I) = \frac{dI(t)}{dt} = -nI(t) + [\gamma tG(t) - \gamma ht] + U_1(t) \quad \dots\dots\dots\dots\dots\dots\text{EqI.13.}$$

$$f_4(U_1) = \frac{dU_1(t)}{dt} = \left(-\frac{1}{a}U_1(t) + \frac{1}{a}u(t)\right) \quad \dots\dots\dots\dots\dots\dots\dots\dots\text{EqI.14.}$$

The above system is a nonlinear system due to the presence of the nonlinear term that appears in **EqI.11.** The nonlinear term is $x(t)G(t)$. Now let us make the following definitions

$$x_1(t) = G(t), x_2(t) = x(t), x_3(t)=I(t), x_4(t) = U_1(t)$$

$$f_1(G) = \frac{dx_1(t)}{dt} = -[P_1 x_1(t) + x_2(t)x_1(t)] + P_1 G_b \quad \dots\dots\dots\dots\dots\dots\text{EqI.15.}$$

$$f_2(x) = \frac{dx_2(t)}{dt} = -P_2 x_2(t) + [P_3 x_3(t) - P_3 I_b] \quad \dots\dots\dots\dots\dots\dots\dots\text{EqI.16.}$$

$$f_3(I) = \frac{dx_3(t)}{dt} = -nx_3(t) + [\gamma tx_1(t) - \gamma ht] + x_4(t) \quad \dots\dots\dots\dots\dots\text{EqI.17.}$$

$$f_4(U_1) = \frac{dx_4(t)}{dt} = \left(-\frac{1}{a}x_4(t) + \frac{1}{a}u(t) \right) \dots\dots\dots\text{EqI.18.}$$

The Jacobian matrices (J_x and J_u) of the model can be derived as

$$J_x = \begin{bmatrix} -p_1 - x_2 & -x_1 & 0 & 0 \\ 0 & -p_2 & p_3 & 0 \\ \gamma t & 0 & -n & 1 \\ 0 & 0 & 0 & -\frac{1}{a} \end{bmatrix}_{x=x_0, u=u_0}$$

And
$$J_u = \begin{bmatrix} 0 \\ 0 \\ 0 \\ \frac{1}{a} \end{bmatrix}_{x=x_0, u=u_0} \dots\dots\dots\dots\dots\dots\text{EqI.19.}$$

Where the point x_0, u_0 is equilibrium point .the equilibrium point can be calculated by setting the state equation to zero and solving:

$$-p_1 x_{10} - x_{10} x_{20} + p_1 G_b = 0 \dots\dots\dots\text{EqI.20.}$$
$$-p_2 x_{20} + p_3 x_{30} - p_3 I_b = 0 \dots\dots\dots\text{EqI.21.}$$
$$\gamma t x_{10} - n x_{30} + x_{40} - \gamma ht = 0 \dots\dots\dots\text{EqI.22.}$$
$$-\frac{1}{a} x_{40} + \frac{1}{a} u_0 = 0 \dots\dots\dots\dots\text{EqI.23.}$$

Where: $x_{10}, x_{20}, x_{30}, x_{40}$ *and* u_0 are the values of the state variables and the input at the

operating point (i.e the equilibrium point).at the equilibrium point $u_0 = 0$

The last equation becomes $-\frac{1}{a} x_{40} = 0$ that gives $x_{40} = 0 \dots\dots$EqI.24.

Substituting the value of x_{40} in **EqI.20** results in

$$\gamma t x_{10} - n x_{30} - \gamma ht = 0$$
$$And$$
$$x_{30} = \frac{(x_{10} - h)\gamma t}{n} \dots\dots\dots\dots\text{EqI.25.}$$

The value of x_{30} can be substituted in **EqI.21**

$$-p_2 x_{20} + p_3 \frac{(x_{10} - h)\gamma t}{n} - p_3 I_b = 0$$

To obtain

$$x_{20} = -\frac{p_3 \gamma t}{p_2 n}(x_{10}) - \frac{p_3 \gamma t h}{p_2 n} + \frac{p_3 I_b}{p_2} \quad\ldots\ldots\ldots\ldots\text{EqI.26.}$$

Now by substituting the value of x_{10} in **EqI.12** we have

$$-\frac{p_3 \gamma t}{p_2 n}(x_{10})^2 + (-p_1 + \frac{p_3 \gamma t h}{p_2 n} + \frac{p_3 I_b}{p_2})x_{10} + p_1 G_b = 0 \quad\ldots\ldots\text{EqI.27.}$$

There are two possible values of x_{10} since x_0, u_0 and are expressed in term x_{10}

$$x_{10} = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a} \quad\ldots\ldots\ldots\ldots\ldots\ldots\text{EqI.28.}$$

Where:

$$a = -\frac{p_3 \gamma t}{p_2 n}, b = -p_1 + \frac{p_3 \gamma t h}{p_2 n} + \frac{p_3 I_b}{p_2}, c = p_1 G_b$$

There are 2 possible values of x_{10}, since x_{20} and x_{30} are expressed in term of x_{10}

I.11conclusion:

The diabetes management as one of the challenging control problems in human regulatory systems.

In this chapter we discussed about Diabetes (caused, types and the insulin pump). And some theoretical analysis of the control of blood glucose levels in diabetic individuals is undertaken using a simple mathematical model of the dynamics of glucose and insulin interaction in the blood system developed by Bergman.

Sommaire

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