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Control of blood glucose levels in type 1 diabetics using electrodynamic transducer and piezoelectric actuator to activate the insulin tank

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Nous, Professeur **NANA NBENDJO Blaise Romeo** et Professeur **ESSIMBI ZOBO Bernard**, respectivement Examinateur et Président du jury de la Thèse de Doctorat/PhD de Madame **ESSAMBA MAH Ursule**, Matricule **10W1000**, préparée sous la direction du Professeur **WOAFO Paul** (Université de Yaoundé 1), intitulée : « **Control of blood glucose levels in type 1 Diabetics using Electrodynamic Transducer and Piezoelectric Actuator to activate the insulin tank** », soutenue le **Mercredi, 19 Avril 2023**, en vue de l'obtention du grade de Docteur/PhD en Physique, Spécialité **Mécanique, Matériaux et Structures,** option **Mécanique Fondamentale et Systèmes Complexes** attestons que toutes les corrections demandées par le jury de soutenance ont été effectuées.

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Fait à Yaoundé, le 11 MAI 2023

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Dedication

I dedicate this work:

To my lovely parents **Mr and Mrs Mah Kinda** who have always believed in me and have encouraged me to go far.

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List of abbreviations

ADC: Analog to Digital Converter

AP: Artificial pancreas

CERITD: Centre d'Etudes et de Recherches pour l'Intensification du Traitement du Diabète

CGM: Continuous glucose monitoring

CPU: Central processing unit

DAC: Digital to analog converter

DC: Direct current

Fortran: Formula Translator

HGP: Hepatic Glucose Production

IDGU: Insulin-dependent glucose utilization

IIDGU: Insulin-independent glucose utilization

I/O: Input/output

Matlab: Matrix laboratory

MPC: Model predictive control

ODE: Ordinary differential equations

PD: Proportional-Derivative

PI: Proportional-Integral

PP: Pancreatic polypeptide

RK: Runge − Kutta

TAH: Total artificial heart

VADs: Ventricular Assist Devices

Abstract

This thesis deals with the control of the glucose level of diabetic patients using an electrodynamic transducer and piezoelectric actuator. Two mathematical models describing the dynamics of the couple glucose-insulin are used : the Bergman's minimal and the Cheng's models. Firstly, the adaptive control is applied on the dynamics of a reservoir opener by an electrodynamic transducer. Then it is applied on the two models of the glucose-insulin dynamics. It is found that the control of the reservoir opener and that of the glycemia of a diabetic patient are efficient for some values of the control parameters. Afterwards the restoration based on an adaptive and proportional-integral controls monitored by the deviation of the glucose level of a diabetic relative to that of a healthy person is done. Particular attention is paid to the effect of time delay and the interval between the insulin injections. Using numerical simulations, the ranges of values for the control parameters leading to a good regulation of the blood glucose level are obtained. It is found that the PI control is the most efficient. An automation device made of a piezoelectric actuator directly monitored by the glucose deviation is also proposed in order to command the artificial insulin flow rate from a reservoir. Finally the results obtained numerically have been confirmed using microcontroller and a good agreement is observed.

Keywords: Diabetics, Glucose-insulin models, Bergman minimal model, glucose control, artificial insulin, proportional-integral control, adaptive control, electrodynamic control, piezoelectric actuator, artificial pancreas.

Résumé

Cette thèse traite du contrôle de la glycémie des patients diabétiques en se servant d'un transducteur électrodynamique et d'un actionneur piézoélectrique. Deux modèles mathématiques décrivant la dynamique du couple glucose-insuline sont utilisés : le modèle minimal de Bergman et le modèle de Cheng. Tout d'abord, la commande adaptative est appliquée sur la dynamique d'un bouchon d'ouverture de réservoir par un transducteur électrodynamique. Elle est ensuite appliquée sur les deux modèles de la dynamique glucose-insuline. On observe que le contrôle de l'ouvre-réservoir et celui de la glycémie d'un patient diabétique sont efficaces pour certaines valeurs des paramètres de contrôle. Ensuite, la restauration basée sur les contrôles adaptatifs et proportionnel-intégral surveillés par la différence entre la glycémie d'un diabétique et celle d'une personne saine est analysée. Une attention particulière est portée à l'effet du délai et de l'intervalle entre les injections d'insuline. A l'aide de simulations numériques, les plages de valeurs des paramètres de contrôle conduisant à une bonne régulation de la glycémie sont obtenues. On trouve que le contrôle proportionnel-intégral est le plus efficace. Un dispositif d'automatisation constitué d'un actionneur piézoélectrique directement asservi sur la déviation du glucose est également proposé afin de commander le débit d'insuline artificielle à partir d'un réservoir. Enfin les résultats obtenus numériquement ont été confirmés à l'aide d'un microcontrôleur et un bon accord est observé.

Mots-clés: Diabétiques, modèles Glucose-insuline, modèle minimal de Bergman, contrôle de la glycémie, insuline artificielle, contrôle proportionnel-intégral, contrôle adaptatif, contrôle électrodynamique, actionneur piézoélectrique, pancréas artificiel.

General introduction

The development of computer science, electrical and mechanical engineering, has contributed to the advancement of bioengineering. This science uses the principles of biology and those of engineering to solve problems in biology, medicine, and other fields. Bioengineering is made up of several branches such as agriculture engineering, bionics, bioenvironmental engineering and genetic engineering [1], and we also have medical engineering. Medical engineering refers to the application of engineering principles to medical problems, including the replacement of damaged organs, instrumentation, and the health care systems, comprising diagnosis applications by computers [1]. Diabetes is an example of a disease that might require organ replacement.

Diabetes is a metabolic disease characterized by hyperglycemia resulting from defect in insulin secretion, insulin action or both. The World Health Organization estimated that, in 2012, diabetes was the direct cause of 1.5 million deaths worldwide [2] .There are two main forms of diabetes: type 1 diabetes and type 2 diabetes. Type 1 diabetes occurs when the beta-cells are self-destroyed by the immune system leading to a total or partial absence of insulin secretion by the pancreas. Concerning the type 2 diabetes, it is due to reduced secretion of insulin or resistance to the action of this hormone. The chronic hyperglycemia of diabetes leads to failure of various organs such as the eyes, kidney, nerves heart and blood vessels [3].

With the increase of the number of diabetics, several researchers have been interested in modelling of the glucose-insulin couple in order to better understand the endocrine mechanisms responsible for diabetes. Among the proposed models, some of them were focused on the dynamics of beta cells [4–9]. It is the case of the model presented by Mosekilde et al. [6]. This model based on the Hodgkin-Huxley approach, describes the electrical activity of beta cells. Other models explain both the mechanisms responsible for the insulin secretion and the dynamics of glucose in the body [10–20]. Besides the

modeling goal, one important aspect is the development of theoretical and practical control strategies which can appropriately restore the glucose concentration to the normal level. To take care of diabetic patients, an external source of insulin is required (biological solutions are also in development and use) with appropriate control strategies. Thus, many controllers have been derived to optimize the insulin therapy of people with diabetes [21–31]. Among them one can cite PID control [21–25], PD control [26], fuzzy logic based control [27, 28], H_∞ control [29–31], adaptive control [32] and backstepping sliding mode [33]. Some of these controllers are open-loop, such as the fuzzy logic controller. This method is unreliable due to the approximation involved in the amount of insulin delivered. The other controllers are closed-loop insulin delivery systems also called artificial pancreas. The artificial pancreas is a system made of a glucose sensor, a control algorithm, and an insulin infusion device. The main challenge in designing an artificial pancreas is the control algorithm which will allows to imitate the dynamics of physiologic pancreas [34].

The use of electromechanical systems have gained popularity in biomedicine field over the last few years. Indeed, they are usually used in diagnosis for helping in precise and early detection of medical conditions. They are also used in the surgical field to achieve a less invasive surgery and thus reduce the recovery time or in therapeutic field to increase efficiency [35]. There are many kinds of electromechanical systems used in medicine such as piezoelectric actuators and electrodynamic transducer. Piezoelectric actuators are usually used for designing valveless micropump for drug delivery [36–38]. Concerning electrodynamic transducers, they can be used to design microfluid devices such as micro-pumps and micro-needles for biomedical applications [39]. **The aim of this work is to regulate the blood glucose levels of diabetics by using many control strategies, with the effects of time delay and time interval between insulin injections taken into account. The particularity of this work lies in the**

use of an electrodynamic transducer and a piezoelectric actuator to control the opening of an insulin reservoir. To achieve this work three main physical systems have been used.

- The first one is the mathematical model proposed by Bergman.
- The second one is the mathematical model of Cheng.
- The last one is an electromechanical system whose the electrical part reproduces the dynamic of the difference between healthy and diabetic person. This system is placed in a zone where magnetic field is present.

This thesis is divided in three chapters. In chapter one, we briefly present some generalities on artificial organs. After that, glucose control techniques are presented. We conclude this chapter by highlighting the problem to be solved in this thesis. In chapter two, we describe the methodology used. We describe diabetes and present some mathematical models of glucose-insulin system. Thereafter, the control schemes and numerical methods used are explained. Finally, methods based on microcontrollers are presented. In chapter three, the results are presented and we end with a general conclusion.

Chapter I

Litterature review

1.1 Introduction

The human body is made up of a set of organs in relation to each other in a coordinated manner and, the dysfunction of one organ can therefore disrupt the whole system. Thus in recent years, many scientists have been interested in the design of artificial organs and, thanks to technological advances, tissue engineering and regenerative medicine, many organs have benefited from an artificial equivalent [40]. The aim of this chapter is firstly to give general information on artificial organs especially on artificial pancreas. Then, the control strategies and techniques will be presented. We first describe mathematically diabetes models in section 1.4.Finally, the problems to be solved in the thesis will be given at the end of the chapter.

1.2 Generalities on artificial organs

An artificial organ is a mechanical device designed to replace the biological function of the natural organ. The replaced function is not necessarily vital but most often it is the case.

1.2.1 Motivation of artificial organs

The artificial organs are designed to :

- Cope with the shortage of organ donation.
- Assist the patients who do not meet transplant criteria.
- Repair a body organ by plastic surgery after a cancer or an accident.
- To deal with pathologies linked to aging.
- Improve the patient's ability to take care of himself.

1.2.2 Artificial organs

Artificial organs are integrated medical devices that have active mechanical or biochemical functions such as the heart, lungs, kidneys, liver, neurosensory organs or the pancreas [41].

a)Artificial heart

The heart is the most important vital organ in the human body, his role is to pump blood towards different organs through blood vessels. The heart diseases is the main cause of death worldwide [42]. The design of an artificial heart therefore appears as an ultimate solution to solve this problem. There exist two kinds of artificial heart.

– The first kind is the total artificial heart (TAH) which is a pump surgically installed to insure circulation and replace diseased or damaged heart ventricles [43].Carmat and synCardia total heart are examples of and their configurations are presented in Figures 1.1 and 1.2 respectively.

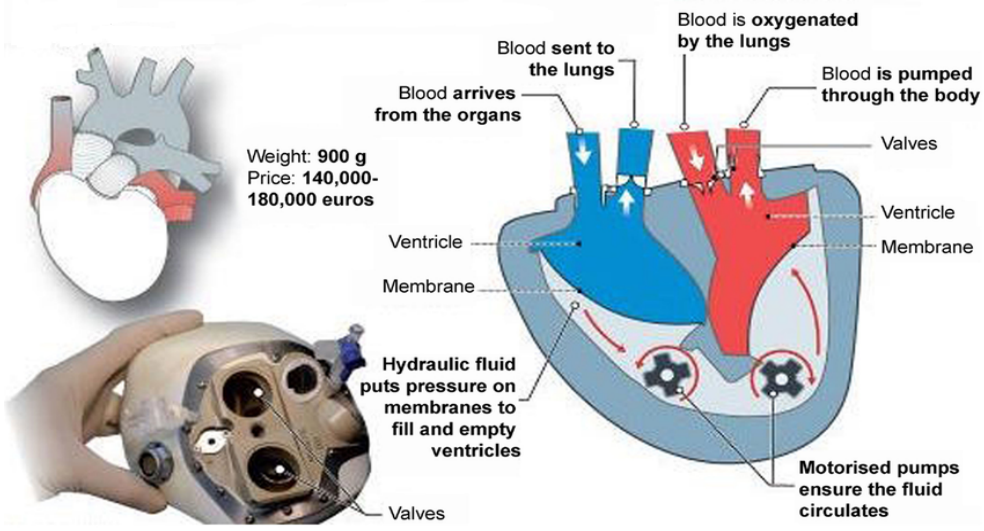

Figure 1.1: Carmat total artificial heart [44].

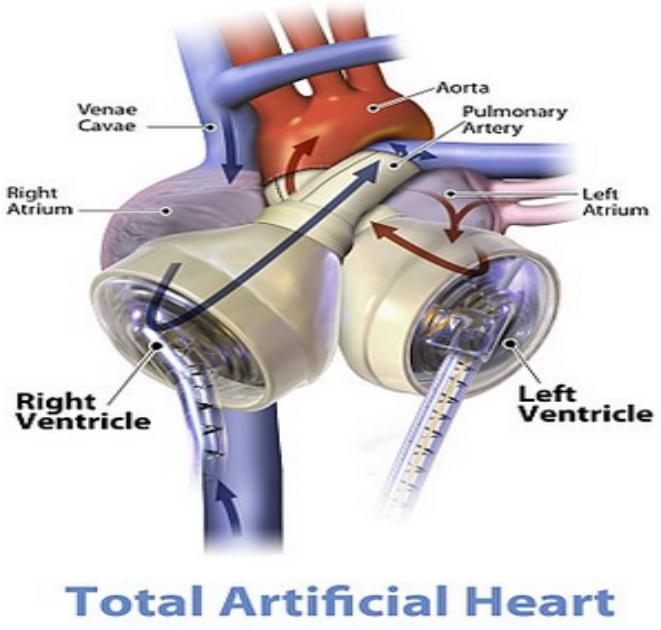

Figure 1.2: SynCardia total artificial heart [45].

– The second kind is the ventricular assist devices (VADs). Also known as a mechanical circulatory support device, VADs are implantable mechanical pumps that help to pump blood from the ventricles to the rest of body. They are usually used for people who have weakened hearts or heart failure [46].

b)Artificial lung

An artificial lung is a device designed to provide the blood oxygenation and the elimination of carbon dioxide. Also called blood oxygenator, artificial lungs are constituted of hollow fibers allowing gas exchanges [47]. Practically, they are used in cardiothoracic surgery and are part of the extracorporeal circulation circuit.

c)Artificial kidneys

Artificial kidney or hemodialysis is a purification technique based on the principle of exchanges between the blood and the purification fluid. An artificial kidney is made up of [48]:

– a blood circuit with its pump and control systems, connected to the patient;

– a dialysis bath circuit, with its own controls and heating system;

– a dialysis module, which is the main component of the kidney which includes the membrane where the blood and bath circuits are integrated together.

d)Artificial eye

According to the World Health Organization, approximately at least 2.2 billion people have a near or distance vision impairment [49]. Research laboratories are therefore trying to find technologies to restore the vision of the visually impaired. Retinal implants are designed for patients with functional loss of photo-receptors leading to blindness or near-blindness with preservation of a healthy optic nerve [50]. Visual prostheses consist of a camera located in the glasses worn by the patient which captures the images and transmits them to a microprocessor which processes them and transmits them to the implant via a wireless connection.

In the literature, there are two main areas of implantation of this prosthesis:

– Epi-retinal implantation where the implant is surgically fixed on the inner surface of the retina.

– Subretinal implantation. In this case the implant is fixed inside the eye.

1.2.3 Artificial Pancreas

a)Anatomy and physiology of pancreas

The pancreas is a long, slender organ located behind the lower half of the stomach (Fig.1.3). It is both an exocrine (it secretes a variety of digestive enzymes) and an endocrine gland. Endocrine function is ensured by the islets of Langerhans which secrete the following hormones: glucagon, insulin, somatostatin, and pancreatic polypeptide (PP).

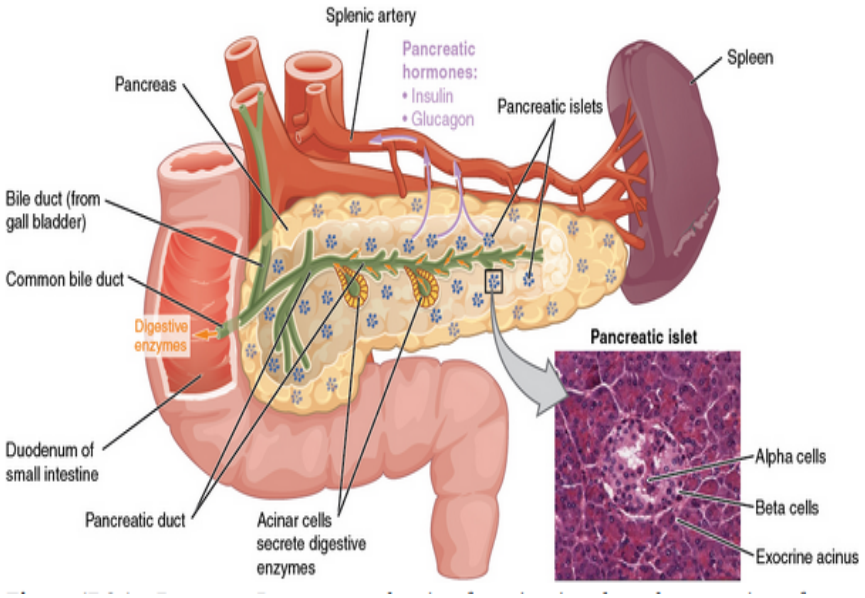

Figure 1.3: location of the pancreas [51]

Each pancreatic islets contains five varieties of cells:

– The alpha cell produces the hormone glucagon and represents approximately 20 percent of each islet [51]. Low blood glucose levels stimulate the release of glucagon.

– The beta cells produce the hormone insulin and makes up approximately 75 percent of each islet. Elevated blood glucose levels stimulate the release of insulin [51].

– The delta cells produce somatostatin, and make up 5-10 percent of the total islet cells [52].

– The pancreatic polypeptide cells produce pancreatic polypeptide, and make up 3-

5 percent of the total islet cells. The pancreatic polypeptide regulates both the endocrine and exocrine pancreatic secretions [52].

– Epsilon cells that produce ghrelin which stimulate hunger. It make up less than 1 percent of the total islet cells [52].

Glucagon and insulin are hormones secreted by the pancreas that play a key role in maintaining a stable blood glucose level. Indeed, the glucose is used in cellular respiration as a fuel for cells of the body. The body derives glucose from the breakdown of the foods containing carbohydrate and drinks we consume. Glucose that is not immediately uptakes by cells as fuel can be stored by the liver and muscles as glycogen, or converted to triglycerides and stored in the adipose tissue. These two hormones regulate both the storage and use of glucose as required. Receptors located in the pancreas sense blood glucose levels and, subsequently, the pancreatic cells secrete glucagon or insulin to maintain normal blood glucose levels [52].

b)Historical view of research on artificial pancreas

Also known as closed-loop control of blood glucose level in diabetic, the artificial pancreas (AP) is a system combining a glucose sensor, a control algorithm, and an insulin infusion device. During the last six decades, the design of artificial pancreas has undergone a gradual improvement. Indeed de first artificial pancreas was proposed by Kadish in 1964 [53]. This device about the size of a large backpack measured blood glucose levels and delivered insulin intravenously was not suitable for free daily use.

Inspired by this first work, five research teams simultaneously tried to improve the system between 1974 and 1978 [54–58]. In 1977 one of these realizations [55] resulted in the first commercial device.

In 1979 the studies of Pickup and al and that of Tamborlane and al showed that the subcutaneous route was feasible for continuous insulin delivery [59]. Three years later, a prototype of a wearable AP was tested by Shichiri et al. [60], which was further developed in subsequent studies [61, 62].

In the late 1980s, Leblanc et al introduced an implantable system using intravenous glucose detection and intraperitoneal insulin infusion. [63]. This technology was further developed, through long-term clinical trials [64, 65]. However, its clinical application remained limited due to surgical interventions that it required for sensor and pump implantation.

In September 2006, the Juvenile Diabetes Research Foundation International initiated a project on AP and, many centers reported interesting results. One of these accomplishments was the substitution of animal trials by type 1 diabetes simulator in the preclinical testing of closed-loop control strategies by the Food and Drug Administration of the University of Virginia and the University of Padova. The other achievement was the design by a team from the University of California Santa Barbara and the Sansum Diabetes Research Institute of a communication platform allowing the automated transfer of data between continuous glucose monitoring (CGM), control algorithm, and insulin pump [59].

Recently in 2011, Diabeloop project was initiated by the Centre d'Etudes et de Recherches pour l'Intensification du Traitement du Diabète (CERITD). Diabeloop is an artificial pancreas which safely automates and personalizes the treatment of Type 1 diabetes. It is made up of three separate devices communicating by Bluetooth. These three devices aim to reproduce the normal functioning of beta cells in pancreas. This device includes: a continuous blood glucose sensor, the connected insulin pump and a smartphone containing the Diabeloop application. The blood glucose sensor continually measures the

level of glucose in the interstitial fluid and sends this information to the Diabeloop application. This one, using computer algorithms, calculates the suitable dose of insulin to be injected. To perform this task, the application takes into account various parameters, such as: the person's weight, the speed of action of the insulin, the glycemic background, physical activities, etc. The amount of insulin thus determined by Diabeloop's algorithms is then transmitted to the connected insulin pump which will inject it. The application also allows the user to monitor their blood glucose values in real time on graphs [66]. The marketing of this device in Europe according to forecasts was suppose to start in 2021 [67].

1.3 Generalities on glucose control techniques and strategies

After taking a meal, the blood glucose of diabetics increases and is not regulated. Control of it therefore appears as a solution to solve this problem. To overcome this problem, scientists focused on the development of techniques and control strategies.

1.3.1 Control techniques

a)Opened- loop control

The opened-loop control is a method commonly used in blood glucose levels control in diabetic patients. This method consists of injecting a predetermined dose of insulin subcutaneously based on three or four time daily glucose measurements, usually by an invasive method of finger prick [68]. This method is not only painful and inconvenient but

also unreliable because of approximation of the amount of insulin to be injected.

b)Semi closed-loop control

The semi closed-loop control consists to adjust the insulin infusion rate according to intermittent blood glucose readings. The semi closed-loop control refers to a fully automatic insulin perfusion glucose-controlled. Usually, these insulin infusions are done between meals, overnight and sometimes during part of the meal. This insulin perfusion is combined with an open-loop insulin delivery patient-activated without automatic feedback from glucose sensor at other times (classically, insulin increases at the start of meal ingestion so as to reduce postprandial hyperglycemia) [69].

c) closed-loop control

The closed-loop control of blood glucose levels or artificial pancreas is a method which enables a diabetic patient to maintain normal their glycemia by providing the right amount of insulin at the right time, just as the pancreas does in normal subject. This method is therefore the most effective way to treat diabetes and could then improve the quality and life expectancy of people with diabetes [70]. As shown in figure 1.4, the artificial pancreas is made up of the glucose sensor which measures each time blood glucose level; the control algorithm that calculate de amount of insulin which need to be injected and the mechanical pump to deliver the desired amount of insulin.

1.3.2 Control strategies

Control strategies refers to the different algorithms used to solve the problem. Many control strategies are used to control the blood glucose levels of diabetics in the literature. They are presented hereafter.

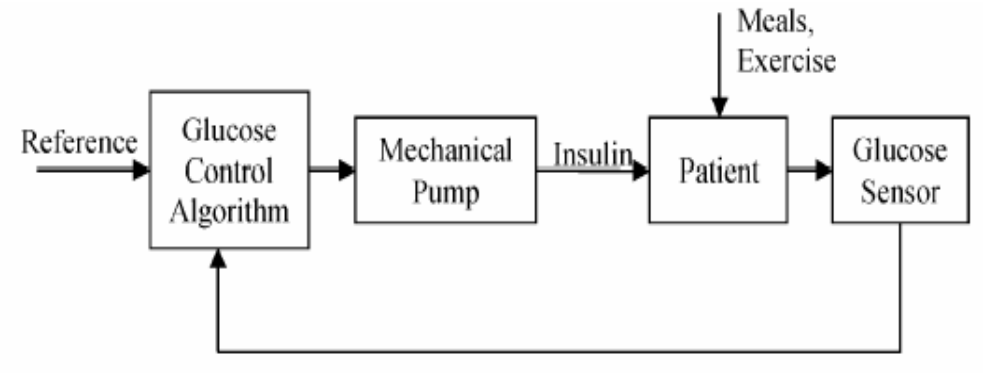

Figure 1.4: Closed-loop control of diabetic patient

a) PID strategy

PID control for diabetes requires high proportional and derivative action compared to integral action. However, this integral action is necessary because it is responsible for eliminating the steady state error when insulin sensitivity changes [71].

b) Adaptive control

An adaptive controller is a controller that can modify itself in response to changes in the characteristics and dynamics of the controlled system [72]. These controllers must adapt to a controlled system with varying parameters which are initially uncertain [73].

c) Model predictive control (MPC)

Usually, the work done in the MPC is for the glucose control in type 1 diabetics. MPC uses a model to predict and increase future processes behavior. In each time step, an optimization problem is solved to obtain an ideal control sequence that reduces a cost function and accomplishes constraints as the system progresses [73].

d) Fuzzy logic control

With the developments of computer systems and rapid searching methods, many systems using fuzzy logic and fuzzy set theory are being developed. Fuzzy logic control is an advanced process control, which imitates the logic of human thought, and much less rigid than the calculations computers generally perform [74, 75].

1.4 Modelling glucose-insulin dynamics in diabetics

1.4.1 Description of diabetes

Diabetes is a disease that occurs when blood glucose is too high. Indeed, glucose is the main source of energy of the body and it comes from food. When it increases in blood, a hormone called insulin is secreted by the pancreas to decrease its level. However, there are some people, whose body doesn't produce enough or any insulin or doesn't use it well. Blood glucose levels therefore remain high after taking a meal and those persons are thus considered to be diabetic. There are two main forms of diabetes :

– Type 1 diabetes: this form of diabetes is caused by the self-destruction of the beta cells by the immune system. Type 1 diabetes is usually diagnosed in children and young adults, although it can appear at any age. People with type 1 diabetes need to take insulin every day to stay alive.

– Type 2 diabetes: it results from a reduction of insulin secretion or a resistance to the action of this hormone. This kind of diabetes occurs most often in middle-aged and older people.

When the glucose level remains high for long periods of time, the patient is at risk for neuropathy, nephropathy, blindness, and other long-term vascular complications [68, 70].

Thus, in order to fight against diabetes and its opportunistic diseases, several researchers have proposed mathematical models.

In this work we are interested in type 1 diabetes because it attacks the juvenile population as well as the elderly.

1.4.2 Mathematical models of glucose-insulin in diabetics

With the increase of the number of diabetics, many researchers have been interested in the modeling of the glucose-insulin regulatory system in order to understand the endocrine system and thus develop a device for controlling the blood glucose in diabetics. In some of these models, the effects of the disease were taken into account. In this part we will review some of these mathematical models.

a) Bergman's minimal model

The Bergman's model is a nonlinear three compartment model. This model is commonly used in the literature because it presents the following advantages : It is based on physiological experiments, has parameters that can be estimated with a reasonable precision, has parameters with values that are reasonable, has physiological interpretation and the dynamics of the system is easy to simulate due to the reduced number of parameters.

Practically, the Bergman's minimal model includes three compartments: one compartment assigned to the blood glucose level, another to the plasma insulin level and a third compartment for remote insulin as shown in Figure 1.5.

Within this model, the kinetics of blood glucose and insulin is described by a set of three differential equations as follows (without $D(t)$)

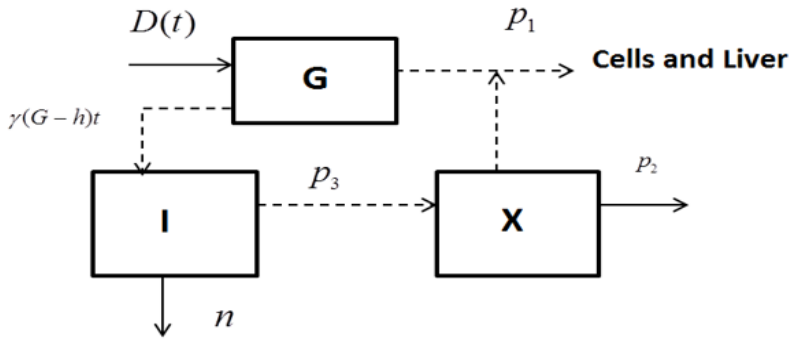

Figure 1.5: Block diagram of the Bergman's minimal model. The notations are explained in the text [68].

$$\begin{cases} \frac{dG}{dt} = -p_1 \left[G\left(t\right) - G_b\right] - X\left(t\right) G\left(t\right) + D(t) \\ \frac{dX}{dt} = -p_2 X\left(t\right) + p_3 \left[I\left(t\right) - I_b\right] \\ \frac{dI}{dt} = \gamma [G\left(t\right) - h]^{+} t - n\left[I\left(t\right) - I_b\right] \end{cases} \tag{1.1}$$

G(t) is the plasma glucose concentration in mg/dL, X(t) is the remote-compartment insulin in mU/L and I(t) is the plasma insulin concentration in mU/L. G_b is the basal glucose level in mg/dL, I_b is the basal insulin level in mU/L (U is equivalent to $6 \times 10^{-12}\, mol$). p_1 represents the rate of disappearance of glucose , p_2 the rate of disappearance of remote-compartment insulin, p_3 the rate with which insulin increases the uptake of glucose $(\min^{-1})$. β-cells release insulin at rate$(mU/L)\min^{-2}(\mathrm{m}g/dL)^{-1}$ with glucose level above h (mg/dL) and insulin disappears at a rate n $(\min^{-1})$. The term $\gamma[G(t) - h]^{+}$ in the third equation of the model acts as an internal regulatory function that formulates the insulin secretion in the body and this term does not exist in diabetic patients [68, 70, 76]. The description and values of the model parameters for a healthy and a diabetic person are given in Table 1.1.

The glucose absorption rate $D(t)$, considered as a disturbance for the system dy-

Table 1.1: Model Parameters for a healthy person and diabetic patient [68].

Parameters	**Healthy person**	**Diabetic patient**	**Description**
$p_1(\min^{-1})$	0.0317	0	Rate of disappearance of glucose
$p_2(\min^{-1})$	0.0123	0.0072	Rate of disappearance of remote−compartment insulin
$p_3(\min^{-1})$	4.92×10^{-6}	2.16×10^{-6}	Rate with which insulin increases the uptake of glucose
n $(\min^{-1})$	0.2659	0.2465	Rate of disappearance of insulin
$\gamma(mU/L)\min^{-2}(mg/dL)^{-1}$	0.0039		Rate of insulin release by β-cells
h (mg/dL)	79.0353		Value of blood glucose above which insulin is released
$D_0(mg/dL/\min)$	1.157	1.157	Initial value of the glucose absorbed during the meal
$K(\min^{-1})$	0.05	0.05	Absorption rate of the glucose by the body
$G_b(mg/dL)$	70	70	Basal glucose level
$I_b(mU/L)$	7	7	Basal insulin level

namics presented in Eq.(1.1), can be modelled by a decaying exponential function of the following form [77] :

$$D(t) = D_0 \exp(-Kt) \tag{1.2}$$

b) Sturis's model

The mathematical model of sturis contains two negative feedback loops for describing glucose utilization and insulin release in the pancreas [78]. The Sturis model is based on six ordinary differential equations (ODE) of the first order:

$$\begin{cases} \frac{dG}{dt} = G_{in} - f_2(G) - f_3(G) \times f_4(I_1) + f_5(x_3); \\ \frac{dI_p}{dt} = f_1(G) - E\left[\frac{I_p}{v_p} - \frac{I_i}{v_i}\right] - \frac{I_p}{t_p}; \\ \frac{dI_i}{dt} = E\left[\frac{I_p}{v_p} - \frac{I_i}{v_i}\right] - \frac{I_i}{t_i}; \\ \frac{dx_1}{dt} = \frac{3}{t_d}\left[I_p - x_1\right]; \\ \frac{dx_2}{dt} = \frac{3}{t_d}\left[x_1 - x_2\right]; \\ \frac{dx_3}{dt} = \frac{3}{t_d}\left[x_2 - x_3\right] \end{cases} \tag{1.3}$$

where $G(t)$ is blood glucose mass; I_p, I_i are blood insulin mass and intercellular space mass, respectively; v_p, v_i are rates of insulin diffusion in plasma and intercellular space, respectively; e is parameter of diffusion rate; t_p, t_i are time constants characterizing decrease in insulin concentration in blood and in intercellular space, respectively; x_1, x_2, x_3 are parameters of insulin propagation decay; $f_1(G)$ is insulin release in pancreas; f_2, f_3, f_2 are glucose uptake values in different segments of patient body (f_2- neurons and brain cells, f_3- muscular cells, f_4 fat cells); f_5 is glucose decay in liver cells; t_d is time of glucose decay.

c) Hovorka's model

Hovorka et al proposed a non-linear model to develop the Model predictive controller (MPC) in type 1 diabetic subjects [79]. The model consist of glucose subsystem, insulin subsystem and insulin action. The model is designed based on experimental and modeling work that used glucose tracers to determine the structure and parameter values of glucose kinetics in normal subjects during basal conditions and during glucose tolerance testing [79].

The equations of this model are as follows:

$$\begin{cases} \frac{dQ_1(t)}{dt} = -\left[\frac{F_{01}^c(t)}{V_G G(t)} + x_1(t)\right] + k_{12}Q_2(t) - F_R(t) + U_G(t) + EGP_0\left[1 - x_3(t)\right]; \\ \frac{dQ_2(t)}{dt} = x_1(t)Q_1(t) - \left[k_{12} + x_2(t)\right]Q_2(t) y(t)\, G(t) = Q_1(t)/V_G; \\ \frac{dS_1(t)}{dt} = u(t) - \frac{S_1(t)}{t_{\max,I}}; \\ \frac{dS_2(t)}{dt} = \frac{[S_1(t) - S_2(t)]}{t_{\max,I}}; \\ \frac{dI(t)}{dt} = \frac{U_I(t)}{V_I} - k_e I(t); \\ \frac{dx_1(t)}{dt} = -k_{a1}x_1(t) + k_{b1}I(t); \\ \frac{dx_2(t)}{dt} = -k_{a2}x_2(t) + k_{b2}I(t); \\ \frac{dx_3(t)}{dt} = -k_{a3}x_3(t) + k_{b3}I(t) \end{cases} \tag{1.4}$$

with :

$$U_I = \frac{s_2(t)}{t_{\max,I}} \tag{1.5}$$

The expressions of metabolic functions are:

$$F_{01}^c(t) = \begin{cases} F_{01}\,, & G \geq 4.5 mmol/L \\ F_{01}G(t)/4.5, & OTHERWHISE \end{cases}$$

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

$$U_G(t) = D_G A_G t e^{-t/t\max}/t_{\max,G}^2.$$

The definition and value of the parameters of this model are given in table 3.1 and 3.2 of the **Appendix**

d) Li's model

In order to better understand the glucose-insulin endocrine metabolic system, Li et al proposed a mathematical model with two explicit time delays by applying the mass

conservative law. The mathematical equations of this model are [80]:

$$\begin{cases} \frac{dG}{dt} = [G_{\text{int}}(t) + f_5(I(t-\tau_2))] - [f_2(G_s(t)) + f_3(G(t)) \times f_4(I(t))] \\ \\ \frac{dI}{dt} = f_1(G(t-\tau_1)) - d_i I(t) \end{cases} \tag{1.6}$$

$G(t)$ and $i(t)$ in mg and mU respectively denote the glucose and insulin concentrations. $G_m(t)$ is the mth exogenous food uptake. τ_1 is the delays of insulin secreted by beta cells and τ_2 the HGP delay. The expressions of the functions of the system of equations (1.6), their description and the values of the model parameters are given in table 3.3 and 3.4 of the **Appendix**

e) Cheng's model

The mathematical model of Cheng is a modified model from the one proposed by Li in 2006 [80]. Indeed, in his model, Li did not take into account the effects of the disease. To consider the effects of the disease, Cheng et al. added some parameters and functions. The equations describing the dynamics of this model are the following [19]:

$$\begin{cases} \frac{dG}{dt} = [G_{\text{int}}(t) + f_5(I(t-\tau_2)) \times f_6(G(t)] - \\ [f_2(G_s(t)) + f_7(G((t)-330) + \beta \times f_3(G(t)) \times f_4(I(t))] \\ \frac{dI}{dt} = \alpha \times f_1(G(t-\tau_1)) - d_i I(t) \end{cases} \tag{1.7}$$

where $G(t)$ and $I(t)$ in mg and mU respectively denote the glucose and insulin concentrations. is the mth exogenous food uptake. τ_1 is the delays of insulin secreted by beta cells and τ_1 the HGP delay. The parameters α and β respectively reveal insufficient insulin release from pancreas and the increasing severity of insulin resistance. Therefore, in type 1 diabetics, α is small while in type 2 diabetics β parameter takes the small value.

For a normal subject $\alpha \in [0.7;\ 1]$ and $\beta \in [0.5;\ 1]$.

The expressions and the description of the functions added by Cheng et *al* to describe the disease are given in table 1.2

Table 1.2: Functions and Description of the Cheng's model [19]

Functions	**Description**
$f_6(G(t)) = \frac{1}{1+e^{\gamma(\ (G(t)/c_3 v_g)-c_6)}}$	For evaluating hyperglycemia effect.
$f_7(G(t) - 330) = S_b + \frac{S_c - S_b}{1+e^{\delta(\ (\ (G(t)-330)/c_3 v_g)-c_7)}}$	For evaluating hyperglycemia effect.

The parameters describing the disease and the initial conditions are given in Table 1.3.

Table 1.3: Parameters for a diseased person of the Cheng model [19]

Parameters	**Healthy person**	**Diabetic person**
α	0.896	0.221
β	0.818	0.894
τ_1(min)	5.02	16.2
τ_2(min)	15.2	35.1
$d_i(\text{min}^{-1})$	0.107	0.26
$G_0(mg/dL)$	90	100
$I_0(mU/L)$	10	12

Table 1.3 shows the parameters which describe the disease. One observes that, for a type 1 diabetic patient, α and d_i are too small while the delays τ_1 and τ_2 are large. In this thesis the Bergman's model and the Cheng's model have been used because of the simplicity of their physiological interpretations.

1.5 Problem statement

The diabetic subject suffer from metabolic disorders in which insulin cannot perform its role properly. Scientists are therefore focusing their efforts on developing devices able to improve the life conditions of diabetic patients. The treatment of diabetes therefore usually requires most of time the provision of an external source of insulin to maintain in the normal range the blood glucose level. Several studies in the literature have been done on the control of the glycemia of a diabetic person with basal state as a reference [21–32].

With advancements in technology, the infusion pump has been designed to improve quality of patient care. These medical devices deliver fluids, such as nutrients and medications. In comparison to manual administration, they allow to control the dose of fluid delivery and have the ability to deliver fluids in small volumes or at precisely programmed rates or intervals [82]. So some infusion subcutaneous pumps have been proposed for the treatment of liver tumors, [83–85]. In these works, the authors showed that hepatic artery infusion chemotherapy improve overall survival in selecting patients with colorectal liver metastasis. In ref [86], Silvia et al showed that the use of smart pumps improved patient safety by enabling the interception of infusion programming errors that posed the potential for severe injury to pediatric patients. In addition, in recent years, insulin pump therapy has increased dramatically in people with type 1 diabetes [87–90]. All of these works have been done to improve blood level control by more closely mimicking what the body does naturally. Thus, these pumps allow diabetics to have a more flexible lifestyle.

As we indicated before, in the quest of understanding the glucose-insulin couple in healthy and sick people, several mathematical models have been developed and studied. It has come that with appropriate parameters these models deliver time variations of the insulin and glucose concentrations simi-

lar to the one obtained from measurements. Consequently, one can think that those models can be used in connection with controllers to regulate the glucose level in diabetics by managing the opening of an insulin tank. This is the main aim of this thesis: modelling and studying the diabetic glucose-insulin couple dynamics with a regulation through electrodynamic and piezoelectric actuators. On the first part we consider an electrodynamic transducer that we couple to the control law for the regulation of an orifice through which insulin moves from a container to the body when necessary. Afterwards, four control schemes are used, and we extend the work by introducing the time delay and the time interval between insulin injections. Finally, we propose and simulate a model of an opener of the artificial insulin reservoir. This opener is constituted of a piezoelectric plate whose extension is monitored by a voltage proportional to the glucose deviation.

1.6 Conclusion

In this chapter, we have provided a background on artificial organs especially on artificial pancreas. The control techniques have been also presented. Thereafter, diabetes and some mathematical models of glucose-insulin system have been described. Finally, the problem to be solved in the thesis has been stated. In the next chapter we will focus on the methodology used in this work.

Chapter II

METHODOLOGY

2.1 Introduction

This chapter deals with the modelling, the control methods and numerical simulations used to solve the problems of this thesis. We first present the different control schemes used in section 2.2. Thereafter in section 2.3, the microcontroller-based controllers are investigated. Then, the numerical methods will be developed in section 2.4 and the last section will be devoted to the conclusion.

2.2 Modelling the control schemes

2.2.1 Physical description of the control schemes

The problem of blood glucose regulation encountered in diabetic patients is due to the insufficient or even inadequate production of insulin. It is a complex technological problem since the response depends on each individual.

In this work, the control is based on a reference differential equation of a healthy person. Indeed, the normal subject considered shall be a reference person whose the dynamical behaviors of the glucose-insulin is supposed to be on average similar to what the patient should have to be in good state.

The control of the diabetic patient glucose referring to the basal level is used for more control schemes available in the literature. However, despite the simplicity of control strategy, this option might appear biologically delicate since the cells will not have time to consume the glucose as biologically required.

So the aim of this part is to model the regulation of the blood glucose of a patient by synchronizing it with the one of a healthy person. Four control methods are used: adaptive, proportional, integral and PI control. The proportional control consists to administer to

the patient an amount of insulin proportional to the difference between his glucose level G_m and that of the normal subject G_s (the index m for the patient and s for the healthy person). However, the integral control approach is based on the adding of artificial insulin to the diabetic patient proportionally to the integral of the difference between the glycemia of the diabetic subject and that of the healthy subject. In the case of PI control, the artificial insulin injected to the diabetic patient is the sum of both controllers.

The analysis of blood glucose dynamics for a healthy person showed that its glycemia is naturally regulated just after three hours.

Setting:

$$e(t) = G_m - G_s \tag{2.1}$$

The difference between the glucose level of the patient and that of a healthy person, one can thus assume that the control is good after three hours if $e(t)$ is close to zero at a given precision. This means that one sets the following condition :

$$|e(t)_{\max}| \leq \varepsilon \quad for \quad t \geq 3h \tag{2.2}$$

where $e(t)_{\max}$ represents the maximum value of $e(t)$. For this aim, we fix $\varepsilon = 10^{-1}$. Indeed, biologically an error of 0.1 of the diabetic patient with respect to the healthy person can be tolerated.

Using equation (2.1), the problem to solve is described by the following set of differential equations:

$$\begin{cases} \frac{dG_s}{dt} = -p_{1s}\left[G_s\left(t\right) - G_b\right] - X_s\left(t\right)G_s\left(t\right) + D\left(t\right) \\ \frac{dX_s}{dt} = -p_{2s}X_s\left(t\right) + p_{3s}\left[I_s\left(t\right) - I_b\right] \\ \frac{dI_s}{dt} = \gamma_s[G_s\left(t\right) - h_s]^{+}t - n_s\left[I_s\left(t\right) - I_b\right] \\ \frac{dG_m}{dt} = -p_{1m}\left[G_m\left(t\right) - G_b\right] - X_m\left(t\right)G_m\left(t\right) + D\left(t\right) \\ \frac{dX_m}{dt} = -p_{2m}X_m\left(t\right) + p_{3m}\left[I_m\left(t\right) - I_b + I_{art}\right] \\ \frac{dI_m}{dt} = -n_m\left[I_m\left(t\right) - I_b + I_{art}\right] \end{cases} \tag{2.3}$$

2.2.2 Modelling control based on electrodynamic actuator

a) Construction of the controller

Before commanding the electrodynamic transducer by the blood glucose deviation of the patient, we first use an electrical circuit delivering signal varying in the same manner as that of the blood glucose deviation. This is presented in Fig. 2.1. It is an RL circuit whose voltage taken at the terminals of a resistor is controlled using an electrodynamic transducer. Indeed, the RL circuit has been used to reproduce the difference between the blood glucose deviation level of diabetic subject and the one of a healthy person obtained from the Bergman's minimal model. The electromechanical system contains in its mechanical part a rigid rod in which flows an electric current I and linked its one end to the lid of an insulin tank. This rod is placed in a zone where a magnetic field B is present. The electrical part is made of a RL circuit, PD control loop and analog circuit of the controller. Indeed, the voltage taken at the terminals of the resistor is introduced into the PD control loop and the output signal of this one is used to actuate the displacement of the rod from M to N and thus that of the lid to allow the exit of insulin from the tank. Then, proportionally to that rod displacement, the analog controller will act on voltage to reduce it.The governing equation of the electrical part of the system can be written as

follows :

$$\frac{du}{dt} = -\alpha u + \beta + f(h, x) \tag{2.4}$$

where $f(x, h)$ denotes the action of rod on voltage u and is defined by:

$$f(x, h) = hx \tag{2.5}$$

Here, h is an estimated feedback gain updated according to the following adaptation algorithm:

$$\frac{dh}{dt} = \eta x \tag{2.6}$$

where η is a constant factor.

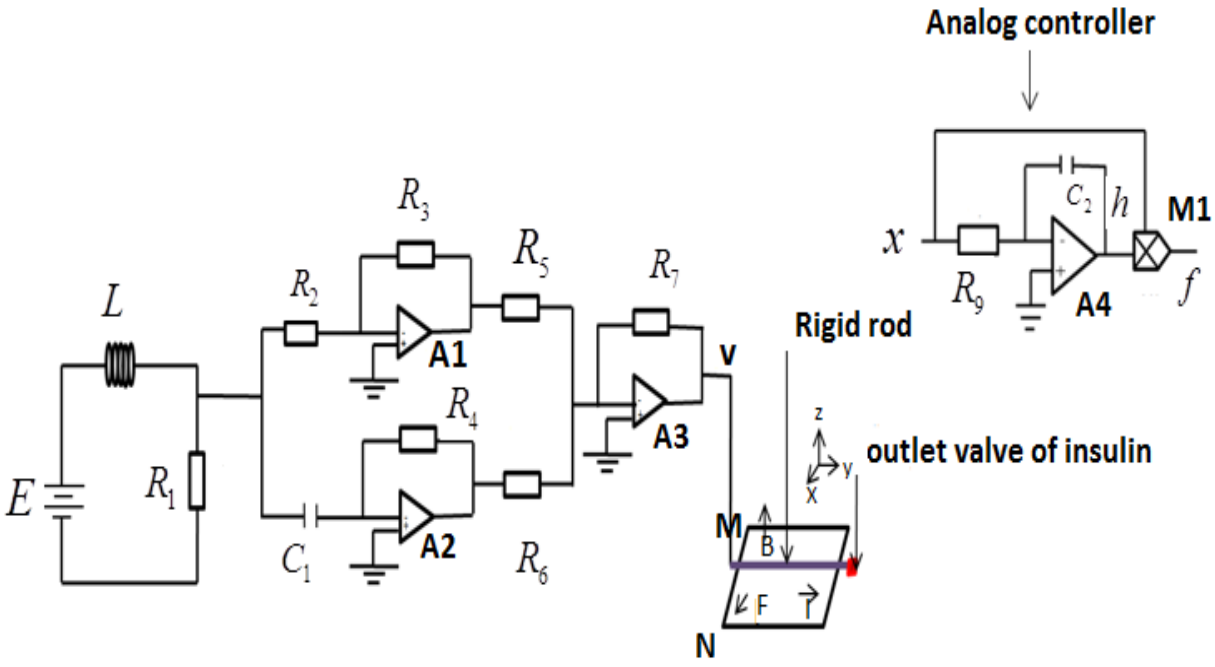

Figure 2.1: Electromechanical system used to actuate the opening of insulin tank

The dimensionless parameters in Eqs. (2.4), (2.5) and (2.6) are given by the following expressions:

$\alpha = \frac{R_1}{L}; \quad \beta = \frac{R_1}{L}E; \quad \eta = -\frac{1}{R_9 C_2}$

The dynamics of the rigid rod is described by:

$$m\ddot{x} + \lambda\dot{x} = F \tag{2.7}$$

where λ is the damping coefficient and F the Laplace force and is defined by:

$$F = IBL_0 \tag{2.8}$$

where L_0 is the rod length.

Assuming that the rod is electrically equivalent to a resistor R_8, the equation of the electrical part of the rod is :

$$R_8 I - e = \ V(t) \tag{2.9}$$

where e and $V(t)$ denotes respectively the electromotive force generated by the rod displacement and output voltage of the control loop PD. They are respectively defined by:

$$e = -BL_0\dot{x} \ ; \quad V = K_P u + K_d \frac{du}{dt} \tag{2.10}$$

with:

$K_p = \frac{R_7 R_3}{R_5 R_2}; \ K_d = \frac{R_7}{R_6} R_4 C_2$

By substituting Eqs.(2.8), (2.9) and (2.10) into Eq.(2.7), the final equation governing the mechanical part is given as follows :

$$\ddot{x} + \lambda_m \dot{x} - \gamma_m (K_P u + K_d \dot{u}) = 0 \tag{2.11}$$

with :

$\lambda_m = \frac{1}{m}(\lambda + \frac{B^2 {L_0}^2}{R_8})$; $\gamma_m = \frac{BL_0}{mR_8}$

The following dimensionless time is used:

$\tau = \omega t$

The new form of the equations of the device is thus:

$$\begin{cases} \frac{du}{d\tau} = -\alpha_1 u + \beta_1 + (hx)/\omega \\ \frac{dh}{d\tau} = \eta_1 x \\ \ddot{x}(\tau) + \lambda_{m1} \dot{x} - \gamma_m (K_{p1} u + K_{d1} \dot{u}) = 0 \end{cases} \tag{2.12}$$

with :

$\alpha_1 = \frac{\alpha}{\omega}$; $\beta_1 = \frac{\beta}{\omega}$; $K_{p1} = \frac{K_p}{\omega^2}$; $K_{d1} = \frac{K_d}{\omega}$

$\lambda_{m1} = \frac{\lambda_m}{\omega}$; $\eta_1 = \frac{\eta}{\omega}$

The values of the parameters used are as follows :

$\omega = 10^3 s$; $R_1 = 2\Omega$; $L = 1\ mH$; $\lambda = 0.7\, kg/s$

$B = 30 \times 10^{-3}\ T$; $L_0 = 2\ cm$; $\rho_{cu} = 8960\ kg/m^3$; $d_{cu} = 4\ mm$; $E = 0.01\, V$ ·

$R_8 = 200\Omega$

These component values have been taken by referring to those available on the market.

From these values, the dimensionless coefficients are:

$\alpha_1 = 2$; $\beta_1 = 0.02$; $\lambda_{m1} = 0.31$; $\gamma_m = 0.0013$

The initial conditions used are the following:

$u_0 = 0$; $x_0 = 0$; $\dot{x}_0 = 0$; $h_0 = 0$

b) Control of insulin provision based on Bergman's model

The problem of blood glucose regulation that diabetic patients have as presented previously is due to insufficient production of insulin. So the aim of this part is to model the regulation of the patient's blood glucose so that it has the same dynamics as that of the healthy person. The control approach is based on an adaptive control which consists to administer to the patient an amount of insulin proportionally to the rod displacement which opens the insulin tank. Furthermore, it is important to mention that, this rod displacement depends on the deviation between the glycemia of the diabetic and that of healthy person. To link the electrodynamic transducer to the glucose deviation, a sensor measures the blood glucose deviation, converts into an electrical voltage which replaces the voltage taken across the resistor R of the RL circuit of Fig. 2.1 (this RL circuit with the DC voltage E is not more present). When the voltage proportional to the deviation enters at the R level, it is converted into different format for each type of control scheme (proportional-derivative or active scheme) and then used to control the opening of the insulin tank through the electrodynamic transducer. Thus, the artificial insulin rate I_{art} can be expressed as follows:

$$\begin{aligned} I_{art} &= hx \\ with \qquad \frac{dh}{dt} &= \eta x \end{aligned} \tag{2.13}$$

Using eq.(2.13), the equations describing the dynamics of the system under control are the following:

$$\begin{cases} \frac{dG_s}{dt} = -p_{1s}\left[G_s\left(t\right) - G_b\right] - X_s\left(t\right)G_s\left(t\right) + D\left(t\right) \\ \frac{dX_s}{dt} = -p_{2s}X_s\left(t\right) + p_{3s}\left[I_s\left(t\right) - I_b\right] \\ \frac{dI_s}{dt} = \gamma_s[G_s\left(t\right) - h_s]^{+}t - n_s\left[I_s\left(t\right) - I_b\right] \\ \frac{dG_m}{dt} = -p_{1m}\left[G_m\left(t\right) - G_b\right] - X_m\left(t\right)G_m\left(t\right) + D\left(t\right) \\ \frac{dX_m}{dt} = -p_{2m}X_m\left(t\right) + p_{3m}\left[I_m\left(t\right) - I_b + I_{art}\right] \\ \frac{dI_m}{dt} = -n_m\left[I_m\left(t\right) - I_b + I_{art}\right] \\ \ddot{x}(t) + \lambda_m\dot{x} - \gamma_m K_p(G - G_s) \ - \gamma_m K_d(\frac{dG_m}{dt} - \frac{dG_s}{dt}) = 0 \\ \frac{dh}{dt} = \eta x \end{cases} \tag{2.14}$$

The first three equations are those of the healthy person. The next three equations are those of the diabetic person in which we have inserted the artificial provision of the insulin. The last two equations describes the dynamics of the rod governing the opening of the insulin tank (the adaptive controller appears in the last equation).

The following dimensionless variables are used :

$$\tau = wt;\ G_{s1} = \frac{G_s}{G_{01}}; X_{s1} = \frac{X_s}{X_{01}}; I_{s1} = \frac{I_s}{I_{01}}; G_{m1} = \frac{G_m}{G_{01}}; X_{m1} = \frac{X_m}{X_{01}}$$

$$I_{m1} = \frac{I_m}{I_{01}};\ x_1 = \frac{x}{a};\ h_1 = \frac{h}{h_{01}}$$

Thus, Eq.(2.14) takes the following dimensionless form :

$$\begin{cases} \frac{dG_{s1}}{d\tau} = -(\frac{p_{1s}}{\omega G_{01}})\left[G_{01}G_{s1}\left(\tau\right) - G_b\right] - (\frac{X_{01}}{\omega})X_{s1}\left(\tau\right)G_{s1}\left(\tau\right) + (\frac{D_0}{\omega G_{01}})\exp(-k\tau/\omega) \\ \frac{dX_{s1}}{d\tau} = -(\frac{p_{2s}}{\omega})X_{s1}\left(\tau\right) + (\frac{p_{3s}}{\omega X_{01}})\left[I_{01}I_{s1}\left(\tau\right) - I_b\right] \\ \frac{dI_{s1}}{d\tau} = (\frac{\gamma_s}{\omega I_{01}})[G_{01}G_{s1}\left(\tau\right) - h_s]^+\frac{\tau}{\omega} - (\frac{n_s}{\omega I_{01}})\left[I_{01}I_{s1}\left(\tau\right) - I_b\right] \\ \frac{dG_{m1}}{d\tau} = -(\frac{p_{1m}}{\omega G_{01}})\left[G_{01}G_{m1}\left(\tau\right) - G_b\right] - (\frac{X_{01}}{\omega})X_{m1}\left(\tau\right)G_{m1}\left(\tau\right) + (\frac{D_0}{\omega G_{01}})\exp(-k\tau/\omega) \\ \frac{dX_{m1}}{d\tau} = -(\frac{p_{2m}}{\omega})X_{m1}\left(\tau\right) + (\frac{p_{3m}}{\omega X_{01}})\left[I_{01}I_{m1}\left(\tau\right) - I_b + ah_{01}h_1x_1\right] \\ \frac{dI_{m1}}{d\tau} = -(\frac{n_m}{\omega I_{01}})\left[I_{01}I_{m1}\left(\tau\right) - I_b + ah_{01}h_1x_1\right] \\ \ddot{x}_1(\tau) + (\frac{\lambda_m}{\omega})\dot{x}_1 - (\frac{K_{p1}\gamma_m G_{01}}{a\omega^2})(G_{m1} - G_{s1}) - (\frac{K_{d1}\gamma_m G_{01}}{a\omega})(\frac{dG_{m1}}{d\tau} - \frac{dG_{s1}}{d\tau}) = 0 \\ \frac{dh_1}{d\tau} = (\frac{\eta a}{\omega h_{01}})x_1 \end{cases} \tag{2.15}$$

The parameter values and the initial conditions used are as follows:

$$G_{01} = 2.;\mathrm{X}_{01} = 1;\mathrm{I}_{01} = 2;a = 2;\ h_{01} = 2;$$

$$G_{0s1} = 35.;\mathrm{X}_{0s1} = 0;\mathrm{I}_{0s1} = 3.5;G_{0m1} = 35;\mathrm{X}_{0m1} = 0;\mathrm{I}_{0m1} = 3.5;\ x_0 = 0;\ \ h_0 = 0$$

c)Control of insulin provision based on the Cheng's model

The two first equations of the system (2.16) are similar to Eq.(1.7) for a healthy person. The next two are those of a diabetic in which we have added the artificial insulin coming, as before, from an insulin tank whose openings are monitored by the rod displacement of the rod which is adaptively controlled.

$$\begin{cases} \frac{dG_s}{dt} = [G_{\text{int}}(t) + f_5(I_s(t-\tau_2))] - [f_2(G_s(t)) + f_3(G_s(t)) \times f_4(I_s(t))] \\ \frac{dI_s}{dt} = f_1(G_s(t-\tau_1)) - d_{is} I_s(t) \\ \frac{dG_m}{dt} = [G_{\text{int}}(t) + f_5(I_m(t-\tau_2) + I_{art})] - [f_2(G_m(t)) + f_3(G_m(t)) \times f_4(I_m(t) + I_{art})] \\ \frac{dI_m}{dt} = f_1(G_s(t-\tau_1)) - d_{im}(I_m(t) + I_{art}) \\ \ddot{x}(t) + \lambda_m \dot{x} - \gamma_m K_p (G_m - G_s) - \gamma_m K_d (\frac{dG_m}{dt} - \frac{dG_s}{dt}) = 0 \\ \frac{dh}{dt} = \eta x \end{cases} \tag{2.16}$$

with :

$I_{art} = hx\,; \quad \frac{dh}{dt} = \eta x$

The dimensionless variables used are as follows :

$\tau = wt;\ G_{s1} = \frac{G_s}{G_{01}};\ I_{s1} = \frac{I_s}{I_{01}}; G_{m1} = \frac{G_m}{G_{01}};$

$I_{m1} = \frac{I_m}{I_{01}};\ x_1 = \frac{x}{a};\ h_1 = \frac{h}{h_{01}}$

So we obtain :

$$\begin{cases} \frac{dG_{s1}}{d\tau} = (1/\omega G_0)\ [G_{\text{int}}(\tau) + f_5(I_{s1}(\tau-\tau_2))] - (1/\omega G_0)\,[f_2(G_{s1}(\tau)) + f_3(G_{s1}(\tau)) \times f_4(I_s(\tau))] \\ \frac{dI_s}{d\tau} = (1/\omega I_0)(f_1(G_{s1}(\tau-\tau_1)) - d_{is} I_{s1}(\tau)) \\ \frac{dG_{m1}}{d\tau} = (1/\omega G_0)\ [G_{\text{int}}(\tau) + f_5(I_m(\tau-\tau_2) + a h_{01} h_1 x_1)] - \\ (1/\omega G_0)\,[f_2(G_{m1}(\tau)) + f_3(G_m(\tau)) \times f_4(I_{m1}(\tau) + a h_{01} h_1 x_1)] \\ \frac{dI_{m1}}{d\tau} = (1/\omega I_0)(\ f_1(G_s(\tau-\tau_1)) - d_{im}(I_{m1}(\tau) + a h_{01} h_1 x_1) \\ \ddot{x}_1(\tau) + (\frac{\lambda_m}{\omega})\dot{x}_1 - (\frac{K_{p1}\gamma_m G_{01}}{a\omega^2})(G_{m1} - G_{s1}) - (\frac{K_{d1}\gamma_m G_{01}}{a\omega})(\frac{dG_{m1}}{d\tau} - \frac{dG_{s1}}{d\tau}) = 0 \\ \frac{dh_1}{d\tau} = (\frac{\eta a}{\omega h_{01}}) x_1 \end{cases} \tag{2.17}$$

The values of dimensionless variables and the initial conditions are as follows :

$G_{01} = 2;\ \mathrm{I}_{01} = 2;\quad a = 1;\quad h_{01} = 2$

$G_{s1} = 126.9/2; \mathrm{I}_{s1} = 0.25; G_{m1} = 126.9/2; \mathrm{I}_{s1} = 0.25; \dot{x}_1 = 0;\ x_1 = 0;\ \ h_1 = 0$

2.2.3 Modelling control based on piezoelectric actuator

In this subsection .The design of a blood glucose control device based on a piezoelectric actuation is proposed. Before that, four control methods were used in order to choose the best one to use to operate the control device.

The first control scheme used is adaptive control. In this case considered, the artificial insulin to be injected is defined by :

$$I_{art} = \omega\ (G_m - G_s) \tag{2.18}$$

ω is an estimated feedback gain updated according to the following adaptation algorithm :

$$\frac{d\omega}{dt} = \alpha(G_m - G_s) \tag{2.19}$$

where α is a constant factor.

After that we have considered the case where ω is constant ie the proportional control in this case the expression of artificial insulin is define as follows :

$$I_{art} = K_p(G_m - G_s)\ \ with\ G_m \succ G_s \tag{2.20}$$

where K_p is a proportional control gain parameter.

The case of integral control has been also considered and in this case the artificial insulin to be injected to the diabetic patient is given by :

$$I_{art} = K_i \int (G_m - G_s)dt \quad with\ G_m \succ G_s \tag{2.21}$$

where K_i is the integral control gain parameter.

In order to make control more efficient proportional and integral control have associated and in this case artificial insulin is given by :

$$I_{art} = K_p \left(G_m\left(t\right) - G_s\left(t\right)\right) \quad + K_i \int \left(G_m\left(t\right) - G_s\left(t\right)\right) dt \ \ with \ \ G_m \succ G_s \tag{2.22}$$

In reality, the controller acts after the sensing of the glucose deviation and its treatment by the control process. This introduces a delay which should be taken into consideration. We only consider PI control thus, the artificial insulin expression is given by the following expression :

$$I_{art} = K_p(G_m(t-\tau) - G_s) + K_i \int (G_m(t-\tau) - G_s)dt \tag{2.23}$$

where τ is the time delay.

A continuous control consumes energy and also poses a technological problem in its implementation. One can think of a controller which could act repeatedly at given times and goes back to rest; e.g:, an intermittent action of the controller. This is a control method which is applied to some dynamical systems. More recently, Zhang et al [81] explored the

effects of intermittent control on the stability and synchronization of memristor-based neural networks. In Ref. [91], the authors examined the relationship between predictive control of a time delay and intermittent control and showed that a simplified predictor can be used in the latter case. In the system considered in this study, the injection of insulin takes place after each period. Artificial insulin in this case can be written by :

$$\begin{aligned} &I_{art} = K_p \left(G_m \left(t-\tau\right) - G_s \left(t\right)\right) \delta \left(t - t_i\right) + K_i (\int \left(G_m \left(t-\tau\right) - G_s \left(t\right)\right) dt) \delta \left(t - t_i\right) \\ &with \qquad G_m \succ G_s \end{aligned} \tag{2.24}$$

with $t_i = it_0$, t_0 is the period of insulin injection (the time at which the controller acts to regulate the blood glucose), i represents the number of periods.

a) Automation design of the artificial insulin injection

In this part, the automation device associated to a sensor and a microcontroller is mainly constituted of a piezoelectric actuator which monitored the opening of an artificial insulin compartment. Practically, the principle could be as follows. A sensor measures the blood glucose level and a comparison with the normal level or basal level is made in a microcontroller. The microcontroller then calculates the amount of insulin to be injected into the patient. When this amount of insulin is determined, an electrical signal $E(t)$ whose voltage is proportional to the insulin quantity is sent to the piezoelectric actuator which extends to open the insulin pump. The electrical voltage applied to the piezoelectric actuator is thus given as :

$$E(t) = \eta I_{art} \tag{2.25}$$

where I_{art} is artificial insulin and η in $(V/mU/L)$ is the conversion coefficient. The insulin pump actuator that we model is presented in Figure 2.2. It has a rectangular cross section and it is constituted of a reservoir containing insulin, a syringe inserted under the skin to drain the insulin from the reservoir to the body. At the outlet of the syringe, there is a valve connected to the piezoelectric actuator by a rigid rod.

Two situations can be observed. In the absence of a voltage ($E(t) = 0$), the valve remains closed (see Figure 2.2a) which means the blood glucose level is normal and no insulin is required. In the second situation, when a voltage $(E(t) \neq 0)$ is applied to the piezoelectric element, it elongates and pushes the rod which displaces the valve and therefore allows the exit of insulin from the tank as shown in Figure 2.2b.

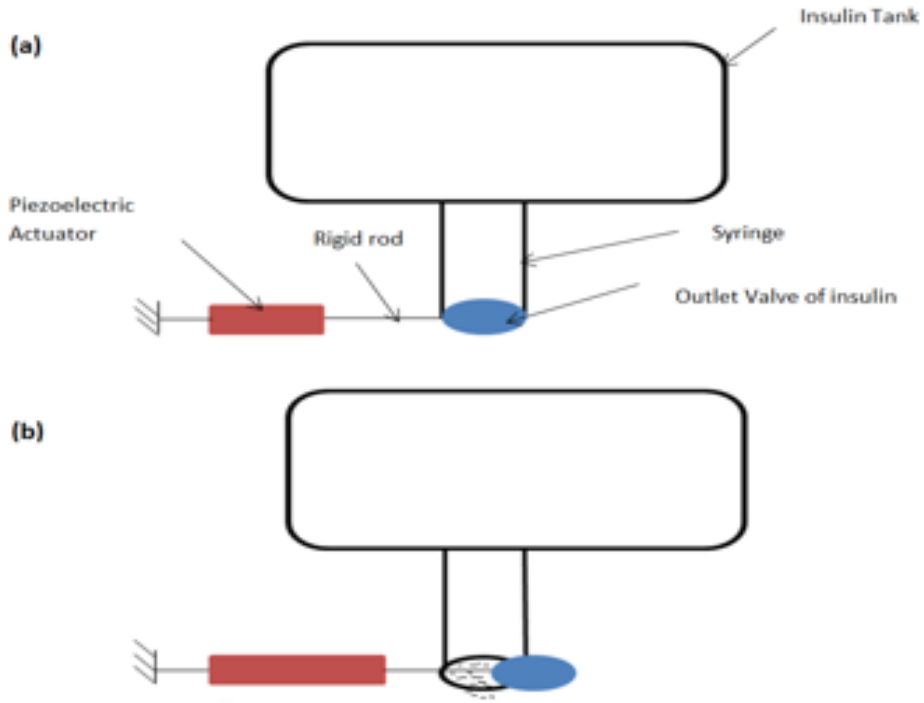

Figure 2.2: Insulin pump driven by a piezoelectric actuator: (a) closed in absence of a voltage; (b) open in the presence of a voltage

b) Modeling of the piezoelectric actuator

In this part we investigate the effect of the voltage $E(t)$ on the displacement of the piezoelectric actuator and thus on the opening of the insulin valve. In [92], Taffoti and Woafo considered a piezoelectric transducer connected to a sinusoidal voltage source in series with a RLC circuit where the capacitor is nonlinear. In this work we consider a linear capacitor (which is that of the piezoelectric plate). Assuming that the viscous damping of the structure is included in the analysis, the electromechanical behavior of the piezoelectric actuator can be represented by the electrical circuit shown in Figure 2.3.

The piezoelectric actuator is constituted of a stack of j disks of thickness e and the cross section S . We assume that all the electrical and mechanical quantities are uniformly distributed in the actuator.

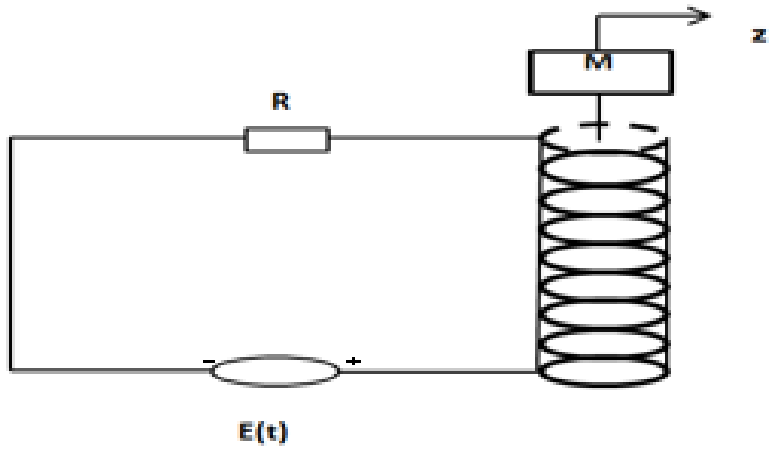

Figure 2.3: Piezoelectric actuator

The total stored electromechanical energy can be written as:

$$W_e(\Delta, q) = \frac{q^2}{2C_0(1-k^2)} - \frac{nd_{33}K_\alpha}{C_0(1-k^2)}q\Delta + \frac{K_\alpha}{1-k^2}\frac{\Delta^2}{2} \tag{2.26}$$

The details of the calculations of the total stored electromechanical energy are shown in [93]. q is the total electric charge on the electrodes of the piezoelectric actuator; C_0 is the capacitance of the piezoelectric actuator with no external load; K_α is the stiffness with short circuited electrodes, k The electromechanical coupling factor defined as $k^2 = \frac{d_{33}^2}{S^E \varepsilon^T} = \frac{j^2 d_{33}^2 K_\alpha}{C_0}$. $k^2 = \frac{d_{33}^2}{S^E \varepsilon^T} = \frac{j^2 d_{33}^2 K_\alpha}{C_0}$. ε^T is the dielectric constant (permittivity) under constant stress, d_{33} is the piezoelectric constant and S^E is the compliance, the inverse of the Young modulus under the field equal to 0. Δ represents the total displacement of the structure of mass M and is given by $\Delta = bz$, where b relates the end displacements of the actuator to the global coordinate system z.

The Lagrangian of the system is defined as :

$$\Gamma = T^* - V_s - W_e \tag{2.27}$$

The different energy of the Lagrangian is defined as :

−The kinetic co-energy of the structure

$$T = \frac{1}{2} M \dot{z}^2 \tag{2.28}$$

−The strain energy in the structure V_s is :

$$V_s = \frac{1}{2} K_0 z^2 \tag{2.29}$$

where K_0 represents the stiffness for stretching, supposed to be constant

−The electromechanical energy W_e of the piezoelectric actuator is presented in eq. (2.26).

We can rewrite the Lagrangian as:

$$\Gamma = \frac{1}{2} M \dot{z} - \frac{1}{2} K_0 z^2 - \frac{q^2}{2C_0(1-k^2)} + \frac{n d_{33} K_\alpha}{C_0(1-k^2)} qbz - \frac{K_\alpha}{1-k^2} \frac{b^2 z^2}{2} \tag{2.30}$$

The virtual work of the non-conservative forces is :

$$\delta W_{nc} = E(t)\delta q + F(t)\delta z \tag{2.31}$$

where $F(t)$ is the mechanical force.

The total dissipation function, which is the sum of dissipation function (viscous damping) of the piezo device and dissipation function of the resistor R is :

$$\Lambda = \frac{1}{2}\lambda_{m0}\dot{z}^2 + \frac{1}{2}R\dot{q}^2 \tag{2.32}$$

where λ_{m0} is the mechanical loss resulting from internal friction.

The Lagrange equations relative to the generalized coordinates q and z can be written as :

$$\begin{cases} \frac{d}{dt}\left(\frac{\partial \Gamma}{\partial \dot{z}}\right) - \frac{\partial \Gamma}{\partial q} = \frac{\partial \Lambda}{\partial \dot{q}} + E(t) \\ \frac{d}{dt}\left(\frac{\partial \Gamma}{\partial \dot{z}}\right) - \frac{\partial \Gamma}{\partial z} = \frac{\partial \Lambda}{\partial \dot{z}} + F(t) \end{cases} \tag{2.33}$$

One thus obtains

$$\begin{cases} R\dot{q} + \frac{1}{C_0(1-k^2)}q \ - \frac{nd_{33}K_\alpha b}{C_0(1-k^2)}z = E(t) \\ M\ddot{z} + \lambda_{m0}\dot{z} + \left(K_0 + \frac{K_\alpha b^2}{1-k^2}\right)z - \frac{nd_{33}K_\alpha b}{C_0(1-k^2)}q = F(t) \end{cases} \tag{2.34}$$

But only the voltage source intensity is taken into account $F(t) = 0$. Finally the dynamics of the glucose-insulin dynamics coupled to a piezoelectric actuator monitoring the quantity of artificial insulin is described by the following set of equations :

$$\begin{cases} \frac{dG_s}{dt} = -p_{1s}\left[G_s\left(t\right) - G_b\right] - X_s\left(t\right)G_s\left(t\right) + D\left(t\right) \\ \frac{dX_s}{dt} = -p_{2s}X_s\left(t\right) + p_{3s}\left[I_s\left(t\right) - I_b\right] \\ \frac{dI_s}{dt} = \gamma_s[G_s\left(t\right) - h_s]^{+}t - n_s\left[I_s\left(t\right) - I_b\right] \\ \frac{dG_m}{dt} = -p_{1m}\left[G_m\left(t\right) - G_b\right] - X_m\left(t\right)G_m\left(t\right) + D\left(t\right) \\ \frac{dX_m}{dt} = -p_{2m}X_m\left(t\right) + p_{3m}\left[I_m\left(t\right) - I_b + I_{art}\right] \\ \frac{dI_m}{dt} = -n_m\left[I_m\left(t\right) - I_b + I_{art}\right] \\ \dot{q} + \frac{1}{R}\left(\frac{1}{C_0(1-k^2)}\right)q - \frac{jd_{33}K_\alpha b}{RC_0(1-k^2)}z = \eta\frac{K_p}{R}(G - G_s) \\ \ddot{z} + \frac{\lambda_{m0}}{M}\dot{z} + \frac{1}{M}\left(K_0 + \frac{K_\alpha b^2}{1-k^2}\right)z - \frac{jd_{33}K_\alpha b}{MC_0(1-k^2)}q = 0 \end{cases} \tag{2.35}$$

Let us define the following terms :

−The natural frequency for the electrical part

$\omega_e{}^2 = \frac{1}{R}\left(\frac{1}{C_0(1-k^2)}\right)$

− The electrical coupling coefficient

$\beta_e = \frac{jd_{33}K_\alpha b}{RC_0(1-k^2)}$

− The mechanical damping

$\lambda_m = \frac{\lambda_{m0}}{M}$

− The frequency of the mechanical part

$\omega_m{}^2 = \frac{1}{M}\left(K_0 + \frac{K_\alpha b^2}{1-k^2}\right)$

− The mechanical coupling coefficient

$\beta_m = \frac{jd_{33}K_\alpha b}{MC_0(1-k^2)}$

Equation (2.35) becomes:

$$\begin{cases} \frac{dG_s}{dt} = -p_{1s}\left[G_s\left(t\right) - G_b\right] - X_s\left(t\right)G_s\left(t\right) + D\left(t\right) \\ \frac{dX_s}{dt} = -p_{2s}X_s\left(t\right) + p_{3s}\left[I_s\left(t\right) - I_b\right] \\ \frac{dI_s}{dt} = \gamma_s[G_s\left(t\right) - h_s]^+ t - n_s\left[I_s\left(t\right) - I_b\right] \\ \frac{dG_m}{dt} = -p_{1m}\left[G_m\left(t\right) - G_b\right] - X_m\left(t\right)G_m\left(t\right) + D\left(t\right) \\ \frac{dX_m}{dt} = -p_{2m}X_m\left(t\right) + p_{3m}\left[I_m\left(t\right) - I_b + I_{art}\right] \\ \frac{dI_m}{dt} = -n_m\left[I_m\left(t\right) - I_b + I_{art}\right] \\ \dot{q} + {\omega_e}^2 q - \beta_e z = \eta\frac{K_p}{R}(G - G_s) \\ \ddot{z} + \lambda_m\dot{z} + {\omega_m}^2 z - \beta_m q = 0 \end{cases} \tag{2.36}$$

Let us operate a time scaling relative to ω_e ie $t = \frac{t_1}{\omega_e}$

Equations (2.36) can be rewritten as :

$$\begin{cases} \frac{dG_s}{dt_1} = -p_{1s1}\left[G_s\left(t\right) - G_b\right] - \omega_{e1}X_s\left(t\right)G_s\left(t\right) + \omega_{e1}D\left(t_1\right) \\ \frac{dX_s}{dt_1} = -p_{2s1}X_s\left(t\right) + p_{3s1}\left[I_s\left(t\right) - I_b\right] \\ \frac{dI_s}{dt_1} = \gamma_{s1}[G_s\left(t\right) - h_s]^+ t - n_{s1}\left[I_s\left(t\right) - I_b\right] \\ \frac{dG_m}{dt_1} = -p_{1m1}\left[G_m\left(t\right) - G_b\right] - \omega_{e1}X_m\left(t\right)G_m\left(t\right) + \omega_{e1}D\left(t_1\right) \\ \frac{dX_m}{dt_1} = -p_{2m1}X_m\left(t\right) + p_{3m1}\left[I_m\left(t\right) - I_b + I_{art}\right] \\ \frac{dI_m}{dt_1} = -n_{m1}\left[I_m\left(t\right) - I_b + I_{art}\right] \\ \dot{q} + \omega_e q - \beta_{e1} z = \eta\frac{K_p}{R}\omega_{e1}(G - G_s) \\ \ddot{z} + \lambda_{m1}\dot{z} + {\omega_{m1}}^2 z - \beta_{m1} q = 0 \end{cases} \tag{2.37}$$

with :

$p_{1s1} = \frac{p_{1s}}{\omega_e};\ p_{2s1} = \frac{p_{1s}}{\omega_e};\ p_{3s1} = \frac{p_{3s}}{\omega_e};\ \gamma_{s1} = \frac{\gamma_s}{\omega_e};\ n_{s1} = \frac{n_s}{\omega_e};\ \omega_{e1} = \frac{1}{\omega_e}$

$p_{1m1} = \frac{p_{1m}}{\omega_e};\ p_{2m1} = \frac{p_{1m}}{\omega_e};\ p_{3m1} = \frac{p_{3m}}{\omega_e};\ \ n_{m1} = \frac{n_m}{\omega_e}$

$\beta_{e1} = \frac{\beta_e}{\omega_e};\ \ \lambda_{m1} = \frac{\lambda_m}{\omega_e};\ \beta_{m1} = \frac{\beta_m}{{\omega_e}^2};\ \omega_{m1} = \frac{\omega_m}{\omega_e}$

The values of the parameters used are [92] :

$R = 0.17\,\Omega;\ \ j = 100;\ d_{33} = 300 \times 10^{-12}\mu m\,;\ d = 80mm;\ e = 3.00\mu m;$

$\lambda_{m0} = 0.9\ SI\ units;\ \ K_0 = 6.67\,N/m\,;\ \rho = 7600;\ \ k = 0.4;\ \ b = 3 \times 10^{-6};\ \ M = 11.45g$

Thus we have :

$\omega_e = 51.23 rad/\min\,;\ p_{1s1} = \frac{p_{1s}}{\omega_e} = 6.18 \times 10^{-4};\ p_{2s1} = \frac{p_{1s}}{\omega_e} = 2.4 \times 10^{-4};\ p_{3s1} = \frac{p_{3s}}{\omega_e} = 9.6 \times 10^{-8};$

$n_{s1} = \frac{n_s}{\omega_e} = 5.19 \times 10^{-3};\ \omega_{e1} = \frac{1}{\omega_e} = 0.02;\ p_{1m1} = \frac{p_{1m}}{\omega_e} = 0;\ p_{2m1} = \frac{p_{2m}}{\omega_e} = 1.4 \times 10^{-4}$

$p_{3m1} = \frac{p_{3m}}{\omega_e} = 4.22 \times 10^{-8};\ \ n_{m1} = \frac{n_m}{\omega_e} = 4.81 \times 10^{-3};\ \ \beta_{e1} = \frac{\beta_e}{{\omega_e}^2} = 3.86;\ \gamma_{s1} = \frac{\gamma_s}{\omega_e} = 7.6 \times 10^{-5}$

$\lambda_{m1} = \frac{\lambda_m}{\omega_e} = 1.53;\ \beta_{m1} = \frac{\beta_m}{{\omega_e}^2} = 1.19;\ \omega_{m1} = \frac{\omega_m}{\omega_e} = 0.72$

The initial conditions used are the following :

$q = 0;\ \ \dot{q} = 0;\ z = 0;\ \dot{z} = 0$

2.3 Microcontroller-based controllers

A microcontroller is an integrated circuit that can be programmed to perform a set of functions to control a collection of electronics devices. Also known as embedded controller, the basic structure of a microcontroller includes [94]: CPU (the brain of the microcontroller); Memory (that stores all programs and data); Serial Ports (give serial interfaces amid microcontroller and various other peripherals such as parallel port); timers (control all timing and counting operations within a microcontroller) ; ADC (for converting analog signals to digital ones); DAC (executes opposite functions that ADC perform); Interpret (for giving delayed control for a work program) and special Functioning Block generally integrated in certain microcontrollers for special devices such as space systems, robots; etc. Microcontrollers are classified according to their memory (External Memory Microcontroller and Embedded Memory Microcontroller), architecture (Harvard Memory Architecture Microcontroller and Princeton Memory Architecture Microcontroller) and bits (8 bits microcontroller, 16 bits microcontroller and 32 bits microcontroller).

2.3.1 Presentation of microcontrollers technology

The principle consists of programming the differential equations describing the dynamics of our system using a microcontroller and then making sure that the electrical signal obtained is similar to the one numerically obtained. To do this, we discretize the equations describing the dynamics of our system through the fourth-order Runge Kutta method. Afterwards, one write a computer program using the software Arduino compiler and the digital signal of the microcontroller is converted into an analog signal via a resistors network (R-2R). The designation R-2R come to the fact that they are coupled in pairs with

a fixed resistance on the one hand and a double resistance on the other hand. For the realization of our microcontroller generator, we used resistors of resistance R =4.7 k and 2R =10 k. the electrical signal will be visualized using a Proteus oscilloscope.

We note that, Arduino Uno module is a board based on the ATmega328 microcontroller with the following specifications: operating voltage 5V, Input Voltage (7-12V), 14 Digital I/O Pins which can be set as input or output, 6 analog inputs and 6 digital pins. The Arduino software used the "C/Arduino" programming language which is very closed and compatible with the "C" programming language.

2.3.2 Microcontroller implementation of control laws with sensors and actuators

The blood glucose control device of a diabetic patient consists of a sensor, a microcontroller and a reservoir containing insulin. Indeed, the sensor measures each time the blood glucose level of the diabetic subject and subsequently compares it to that of a healthy subject and a signal is sent to a microcontroller which calculates the amount of insulin injected into the patient. When the amount of insulin has been determined, the microcontroller sends a voltage $E(t)$ to actuate the opening of a reservoir containing insulin. The purpose of this part is to generate the voltage $E(t)$ which serves to actuate the opening of an insulin reservoir. To do this, the equations of the dynamics of a diabetic subject under control will be simulated using Arduino Uno and the generated electrical signal will be observed through Proteus oscilloscope.

2.4 Numerical methods

2.4.1 Fourth-order Runge-Kutta method for ordinary differential equations

Runge−Kutta methods are numerical approximation analysis methods of solutions. They are widely used for solving the initial-value problems of differential equations. These techniques were developed by the mathematicians Carl Runge and Martin Wilhelm Kutta in 1901. These methods are based on the iteration principle. Runge−Kutta methods can be used to construct high order accurate numerical method by functions' self without needing the high order derivatives of functions. [95].

Let us consider a vectorial variable $X(t) = (x_1(t), x_2(t), ...x_n(t))$ with n-dimensional vectorial flow $F = (F_1, F_2, ...F_n)$ the ODE which reads

$$\frac{dX(t)}{dt} = F(t, X(t)) \text{ with} X(t_0) = X_0 \tag{2.38}$$

The $RK4$ scheme for this problem is given as follows :

$$x_{i+1,j} = x_{i,j} + \frac{h(L_{1,j}+2L_{2,j}+2L_{3,j}+L_{4,j})}{6}$$

$$x_{i+1,j} = x_{i,j} + \frac{h(L_{1,j}+2L_{2,j}+2L_{3,j}+L_{4,j})}{6}$$

where

$$L_{1,j} = F_j\left(t_i, x_{i,j}\right),$$
$$L_{2,j} = F_j\left(t_i + \frac{h}{2}, x_{i,j} + \frac{hL_{1,j}}{2}\right)$$
$$L_{3,j} = F_j\left(t_i + \frac{h}{2}, x_{i,j} + \frac{hL_{2,j}}{2}\right)$$
$$L_{4,j} = F_j\left(t_i + h, x_{i,j} + hL_{3,j}\right)$$

Where i runs for time incrementation and j labels the variables related to x_j. $L_{1,j}, L_{2,j}, L_{3,j}, L_{4,j}$ are intermediate coefficients and is the time step. This numerical method has been used to numerical solve the equations of our systems. When the time delay is considered, it is rather preferable to use RK method for delay. Its algorithm is presented in the next sub-section.

2.4.2 Second-order Runge-Kutta method for delay ordinary differential equations

Any system involving a feedback control will almost certainly involve time delay. Indeed, it takes a time for the system to detect information and react to it [96]. In the case of delayed differential equations, the dynamics at each t depends on the value involve time delays [96].In the case of delayed differential equations, the dynamics at each t depends on the value of the vector X at the same instant t and at $t-\tau$, $\tau > 0$ with $X\left(t-\tau\right)$ is the delayed parameter [96]. If one introduces the delayed variable , the ODEs becomes :

$\frac{dX(t)}{dt} = F\left(X\left(t\right), X\left(t-\tau\right), t\right) \text{for} t \in \left[0, \tau\right].$

where, $F = \left(f_1, f_2, ..., f_n\right)$ is a vectorial function with the unknown vectorial variables $X\left(t\right) = \left(x_1\left(t\right), x_2\left(t\right), ..., x_n\left(t\right)\right)$ and $X\left(t-\tau\right) = \left(x_1\left(t-\tau\right), x_2\left(t-\tau\right), ..., x_n\left(t-\tau\right)\right)$ with the initial condition $x\left(0\right) = y\left(t=0\right)$, when $t \in [-T, 0[$, T is the temporal amplitude

of delay. The initial condition is a constant function in the finite interval. Let consider $N_T = \frac{T}{\Delta t}$, $t = i\Delta t$ where i in an integer and Δt is the time step. The solution of this equation is given by the RK2 scheme for ODEs [96] as follows :

$$\begin{aligned} x_{i+1} &= x_i + \tfrac{1}{2}\left(L_1 + L_2\right), \\ t &= t + \Delta t \end{aligned} \tag{2.39}$$

where

$$\begin{aligned} L_1 &= \Delta t \cdot f\left(x_i, x_{\tau - N_T}, i\Delta t\right), \\ L_2 &= \Delta t \cdot f\left(x_i + L_1, x_{\tau - N_T + 1}, (i + 0.5) \times \Delta t\right) \end{aligned} \tag{2.40}$$

where i runs for time incrementation and the variables related to x_i, L_1 and L_2 are intermediate coefficients.

2.5 Conclusion

In this chapter, the control schemes and the models for opening an insulin reservoir have been presented in order to control the dynamics of diabetic patients. Two kinds of models have been distinguished: control based on piezoelectric actuator and control based on electrodynamic actuator. Afterwards, microcontroller-based controllers have been presented. Finally we have defined fourth order Runge Kutta, second order Runge Kutta with delay. In the next chapter the results and discussions on control of blood glucose of diabetic patients using all these methods will be presented.

Chapter III

RESULTS AND DISCUSSION

3.1 Introduction

In this chapter, the main results obtained in this thesis are presented. These results follow those of Chapter 2 where the modelling of glucose-insulin and the control methods were designed. The control of the blood glucose level by the use of a piezoelectric actuator to command the opening of insulin tank is considered in section 3.2. In section 3.3 we analyse the effect of controller on blood glucose level by using an electrodynamic transducer and analog electronics. Then, section 3.4 handles the control of glucose in diabetics based on microcontroller. The last section 3.5 concludes the chapter.

3.2 Control of blood glucose level by use of an electrodynamic transducer and analog electronics

3.2.1 Verification of the controller functioning

In this subsection, the effect of some parameters which characterizes the control is investigated. We present here results obtained from Eq. (2.12) of chapter 2.

a) Effect of the constant factor η

In this part, we study the effects of η on the system. The following fixed parameters are used : $K_d = 10^5$; $K_p = 5$. According to the figure 3.1, we observe that, when $\eta = 0$ the voltage increases and stabilizes at the high value of about $0.01V$, this shows the absence of control (first line of Fig. 3.1). The rod will be thus carried out of the zone where the magnetic field is present and eventually be blocked by locking plates of the device.

However, for the two other values of $\eta \neq 0$ the voltage oscillate between negative and positive values and then return to 0 after a certain time. Moreover, with the decrease of the values of η parameter, a lowering of voltage amplitude is observed. The control is thus more efficient when η takes high negative values (see 2 and 3 panels of Fig. 3.1). Regarding the rod displacement, the same dynamics have been observed and we see that, η acts on the closing of the tank. When $\eta = 0$ the tank remains open while for $\eta \neq 0$, the more it becomes small the more rod and thus the cap will return rapidly to their initial position 0 after the opening of the tank.

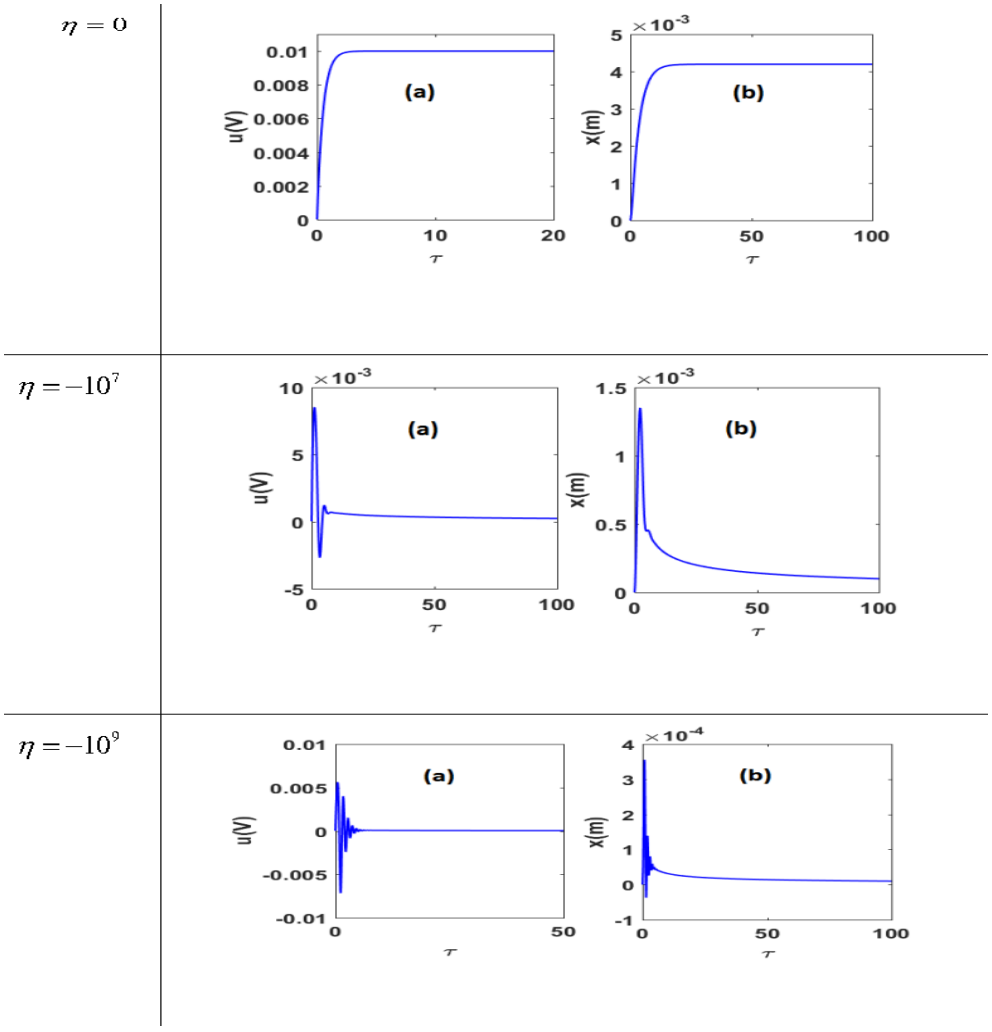

Figure 3.1: Time series of voltage and rod displacement for three values of η : (a) voltage (b) rod displacement.

b) Effect of K_d and K_p

One of the interesting parameters is the gain K_d of the derivative controller. Figure 3.2 shows the time evolution of the voltage u and the rod displacement x for 3 values of K_d when : $\eta = -10^9$; $K_p = 5$. We observed that, when $K_d = 0$ (first line of Fig. 3.2), the voltage u grows and stabilizes at the maximal value. However, for the two other values of $K_d \neq 0$ (two other value of Fig.3.2), the voltage oscillate between the negative and positive values and then return to 0 after a certain time. Furthermore, when K_d is large, a reduction of the voltage amplitude is noticed.

Concerning the rod displacement, we remark that, for the value of $K_d = 0$, it increases infinitely. This result shows that in spite of the controller presence, the signal sent to the rod is not enough to control its motion and thus allows the control of the voltage. Nevertheless, for the values of $K_d \neq 0$ the rod displacement oscillate between negative and positive values and then return to 0 after a certain time.

Now concerning the effects of the gain K_p of the proportional control, we have fixed $\eta = -10^9$ and $K_d = 10^7$ and also analyzed the time series for the voltage and rod displacement when K_p varies. We notice that the voltage and the rod displacement present the same dynamics and, for these three values of K_p , they oscillate and then decrease afterwards to return to 0 as above. With the increase of the values of K_p, the voltage amplitude and that of the rod displacement remains almost the same. The obtained results demonstrate that K_p does not really affect the dynamics of the system.

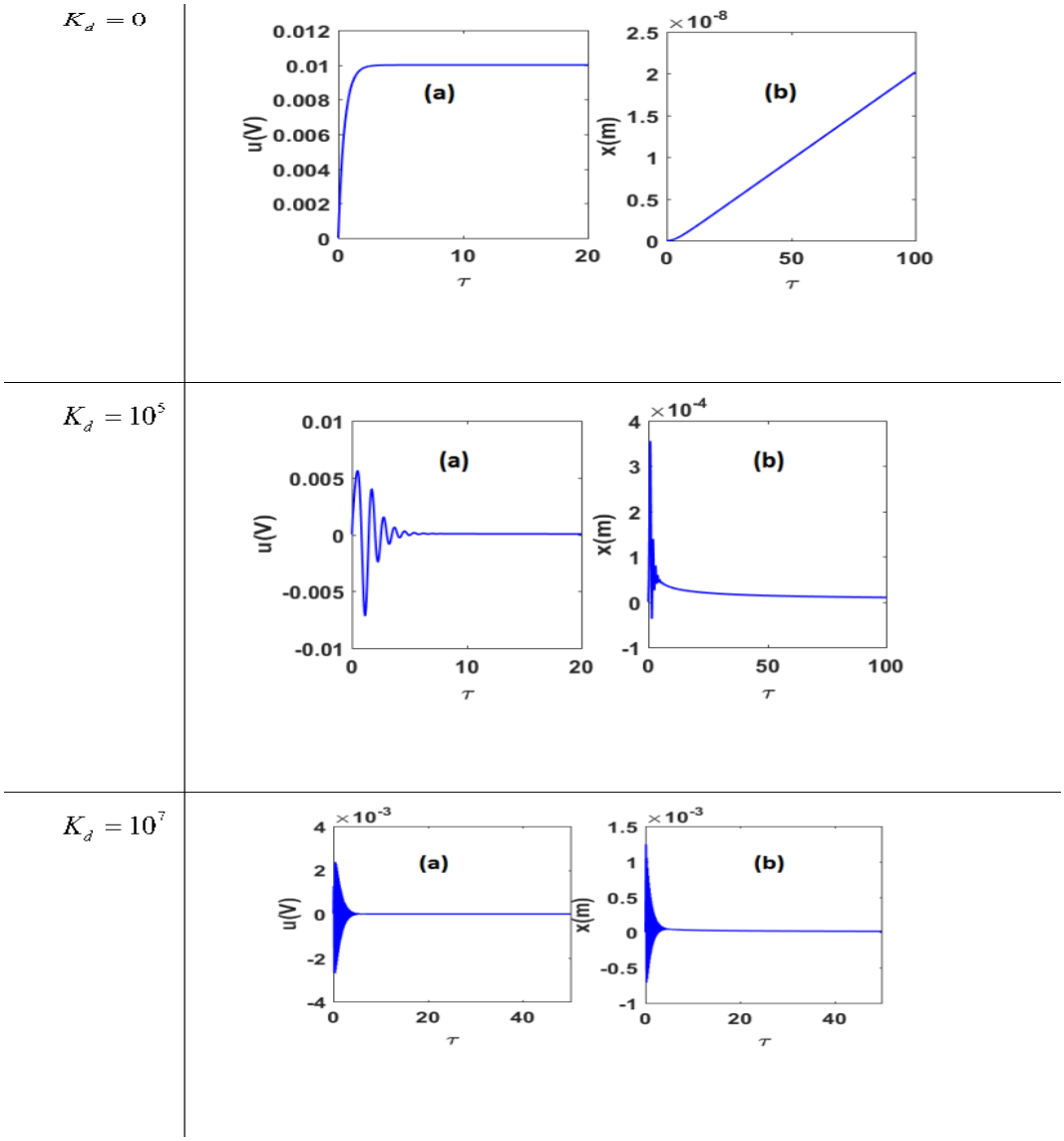

Figure 3.2: Time series of voltage and rod displacement for three values of : K_d (a) voltage (b) rod displacement.

The study of the effect of the parameters η, K_d and K_p on the electromechanical system dynamics has shown that for some values of these parameters, the voltage u which reproduces electrically the deviation between the diabetic and normal subject is controlled. It would be interesting to see how the electrodynamics transducer acts on the model describing the glucose−insulin dynamics of a diabetic person.

3.2.2 Control of insulin provision based on Bergman's model

a) Blood glucose dynamics in healthy subject and diabetic subject

Using the parameters presented in the previous chapter, after numerical simulations of Eq.(1.1) the time evolutions of the blood glucose level of the healthy subject, the diabetic subject and their deviation have been represented.

Figure 3.3 presents the dynamics of the system after a meal has been taken. We notice that the blood glucose level of the healthy person increases and then decreases and stabilizes at the basal value (70 mg/dL) after about 3 hours, whereas that of the diabetic subject grows and saturates at a maximal value around 93 mg/dL. In the same manner the deviation between the glycemia of the diabetic subject and the one of the healthy subject in this situation increases and stabilizes at a high value of about 23.14 mg/dL as shown in figure 3.3b.

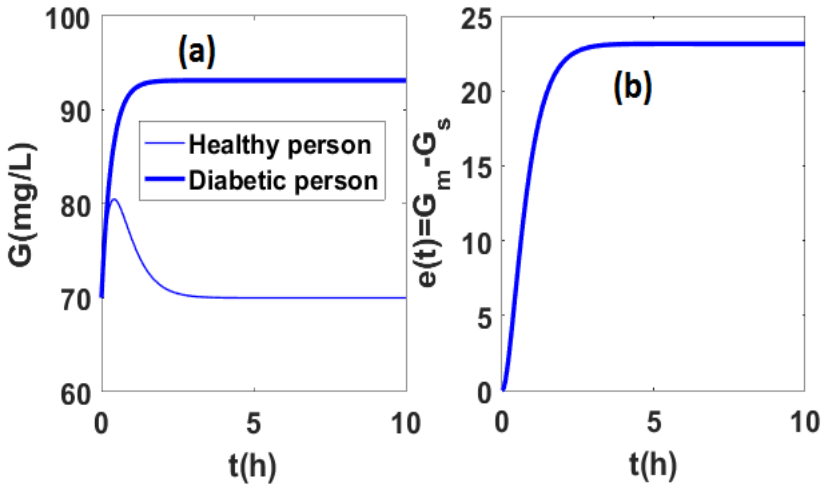

Figure 3.3: Time series of blood glucose and deviation in the case of the Bergman's model: (a) Blood glucose after a meal; (b) Deviation of glycemia between the diabetic and healthy person.

In order to overcome to this problem that has the diabetic subject to regulate his blood glucose level, a solution can be a controller design as we have indicated in the introduction. Below, we will consider the same problem by using an adaptive controller monitoring the opening of an insulin tank. Accordingly Eq.(2.15) is considered.

b) Effects of the automatic provision of insulin on the glycemia deviation

In this part, the effect of the coefficients η, K_d and K_p which act on the system will be studied.

- Effect of η

The study of the impact of η parameter on the behavior of the deviation $e(t)$ has been done by varying this parameter η. We set $K_d = 10^4$ and $K_p = 1$. Figure 3.4 presents the time evolution of the glucose deviation and the rod displacement for three values of η.We notice that $e(t)$ exhibits damped oscillations during a time and then returns to 0 after a certain period. As η increases, the damped oscillations continue to take place, but the values of $e(t)$ at the corresponding time diminishes. This is a strong indication of the efficiency of the control. According to the control conditions, control is thus efficient for these three values of η.

The same dynamics has been also observed for the rod displacement and the results obtained show that the rod displacement is further reduced with the increase of η. But the control remains efficient despite this decrease of the rod displacement.

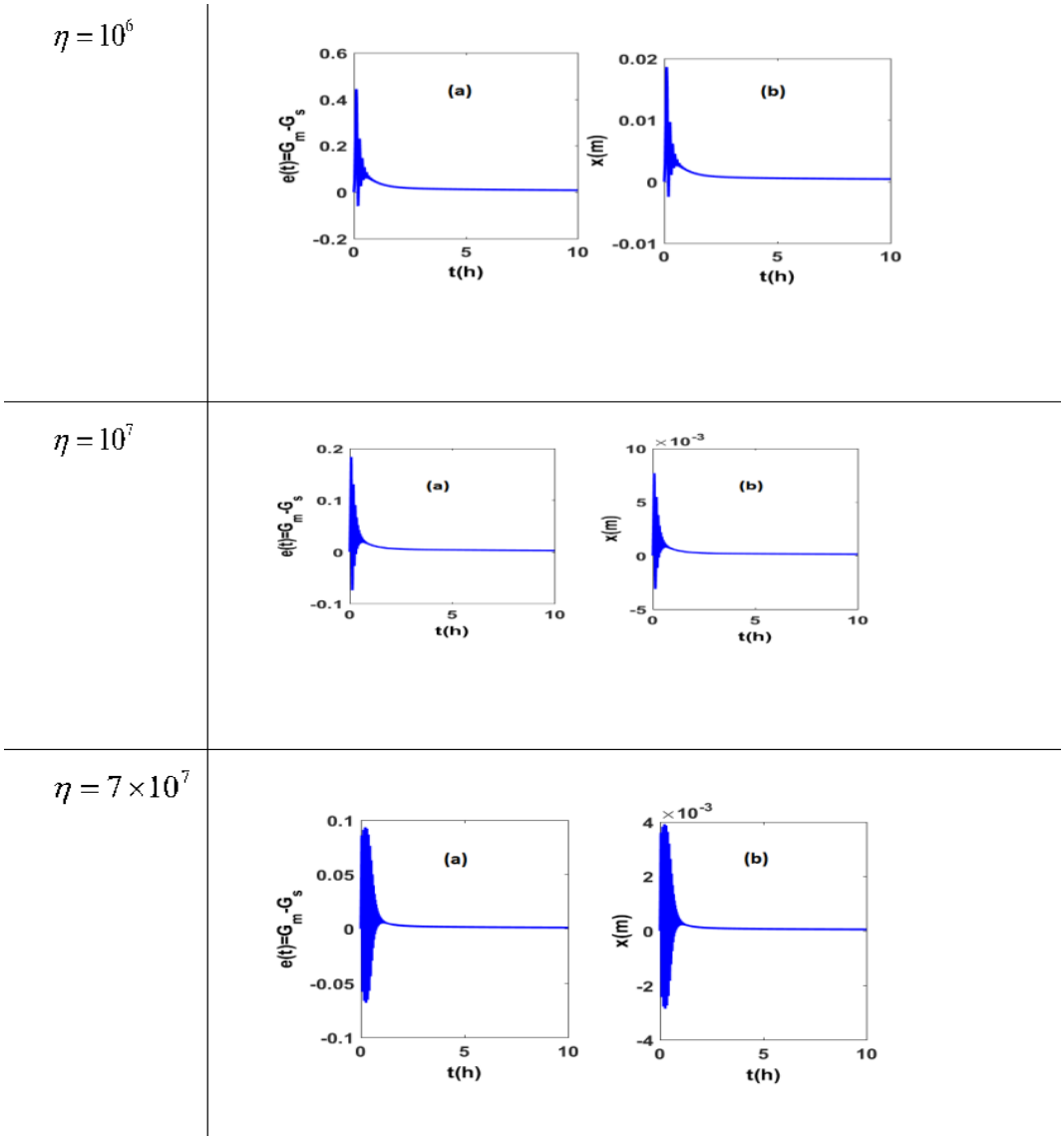

Figure 3.4: Time series of deviation and rod displacement for three values of η : (a) glucose deviation; (b) rod displacement.

- Effect of K_d and K_p

In this part of the work, the influence of K_d on the system dynamics is explored by varying it we fix $\eta = 7 \times 10^7$ and $K_p = 1$. The results appear in Fig. 3.5. For $K_d = 0$, one notices that $e(t)$ first increases then decreases and finally attains a value close to 0. For the rod displacement, it saturates at a given value which is not equal to 0. This means that the insulin flows out continuously when $K_d = 0$.When one increases K_d, one observes

that the control is efficient since $e(t)$ and $x(t)$ both tend to 0. As in previous section, it has been found here that K_p has little effects on the control.

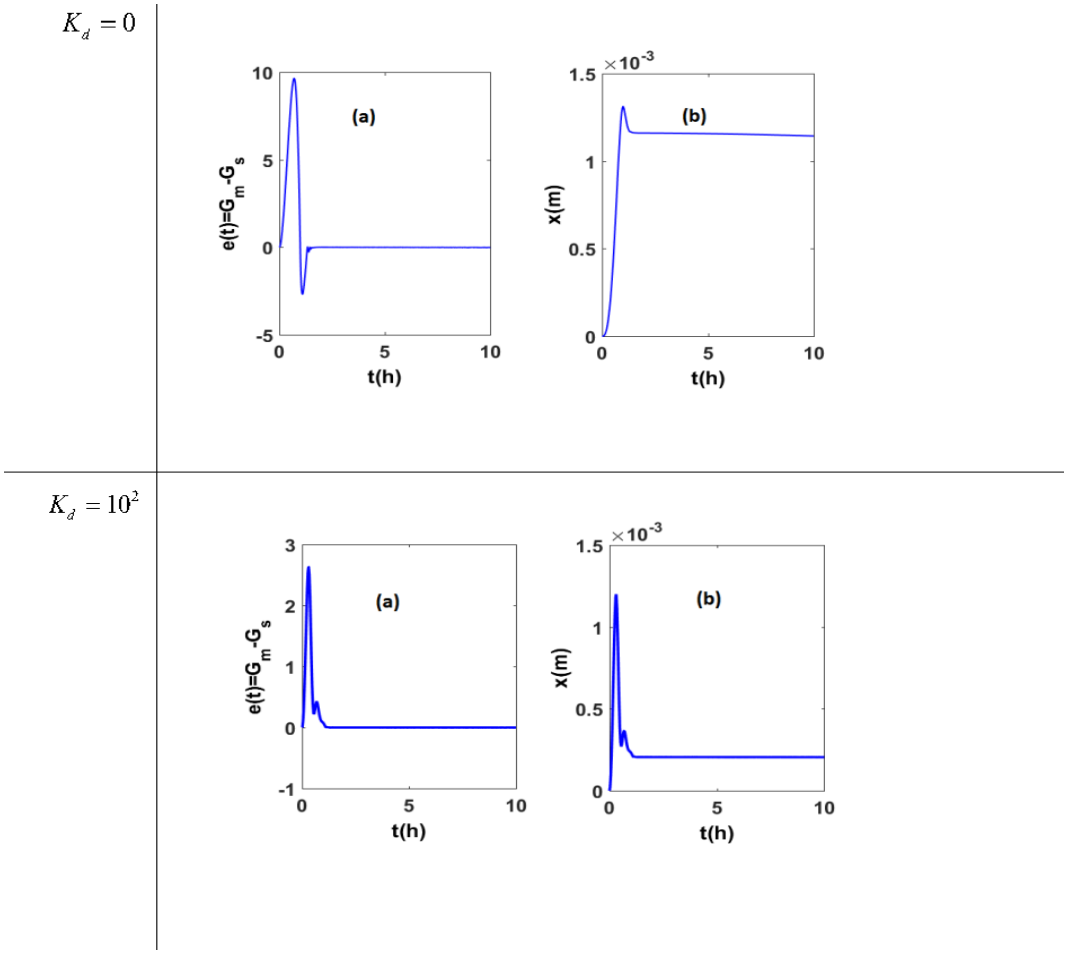

Figure 3.5: Time series of glucose deviation and rod displacement for three values of K_d : (a) glucose deviation; (b) rod displacement.

3.2.3 Control of insulin provision based on Cheng's model

a) Blood glucose dynamics in healthy subject and diabetic subject

Using the parameters of the Cheng's model presented above, the natural dynamics of the healthy subject and that of the diabetic subject have been represented by considering

Eq.(1.7). Figure 3.6 shows the behavior of healthy and diabetic person after a meal. In the both cases, a growth followed by a decrease and stabilization of blood glucose concentration is observed. However, the amplitude of the diabetic person is higher than that of the healthy person. Likewise, the value at which blood glucose concentration of diabetic stabilize is larger than the one of a healthy person (about 103 mg/dL for diabetic person and about 90 mg/dL for healthy subject). The deviation between the glucose concentrations for healthy and diseased subjects is presented in Figure 3.6 b. One observes that its high value is 250 mg and the deviation stabilizes at 13 mg.

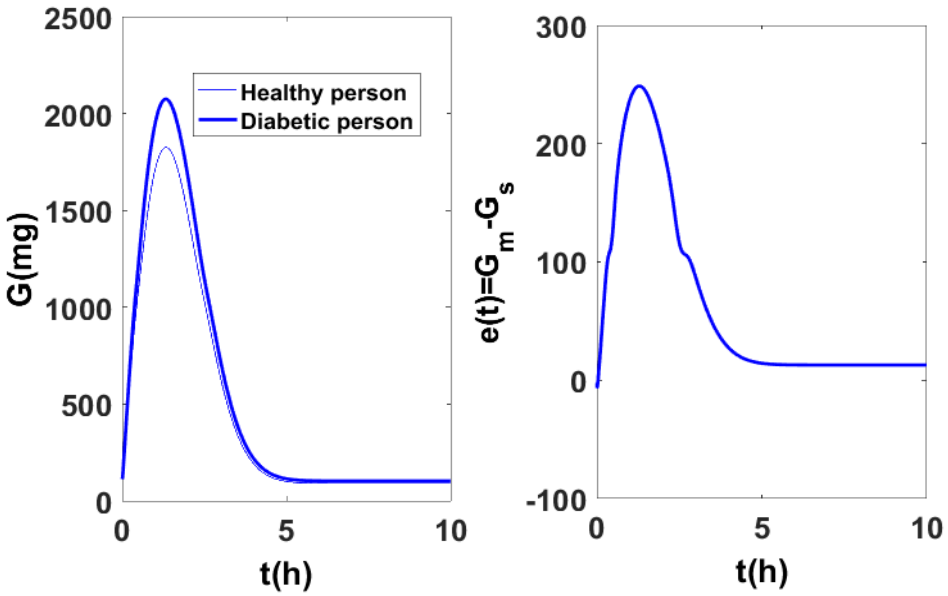

Figure 3.6: Time series of blood glucose and glucose deviation taken a meal in the case of the Cheng's model : (a) blood glucose level; (b) glucose deviation.

In order to reduce the deviation $e(t)$ at any time so that the glucose concentration of the diseased person is approximately equal to that of the healthy person, a controller has also been used here.

b) Effects of the automatic provision of insulin on the glycemia deviation

As in the case of the Bergman's minimal model, the influence of the parameters η and K_d acting on the control of blood glucose is analyzed. The main results are presented in Figs. 3.7−3.9. Figures 3.7 and 3.8 display the effect of η parameter on the deviation and rod displacement when $K_d = 10^{-3}$. We notice that, for the value of $\eta = 0$, which means that h is constant, the amplitude of the deviation increases, attains about 123 mg, then decreases and finally saturates at 6 mg. However, for the values of $\eta \neq 0$, the increase of η leads to the lowering of the amplitude of deviation. A reduction of the value at which the saturation occurs is also observed. Furthermore, the more the value of η is large, the longer the system will take to stabilize. Compared to the case where the control was not present in the system, we note a reduction of the amplitude of the deviation. The same behavior has been also observed for the rod displacement where we remark that, the more the value of η is large, the more the value at which it stabilizes becomes smaller and further closer to 0. Considering now K_d as the control parameter when $\eta = 10^8$, as shown in Fig. 3.9, the growth of K_d leads to the lowering of the deviation amplitude and the value at which stabilization occurs. Concerning the rod displacement, we see that, amplitude raises when K_d becomes larger.

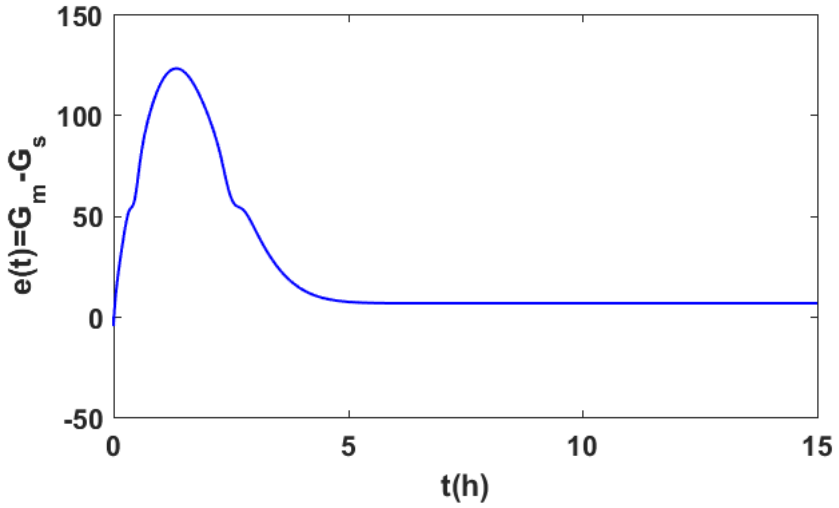

Figure 3.7: Time series of the glucose deviation for $\eta = 0$

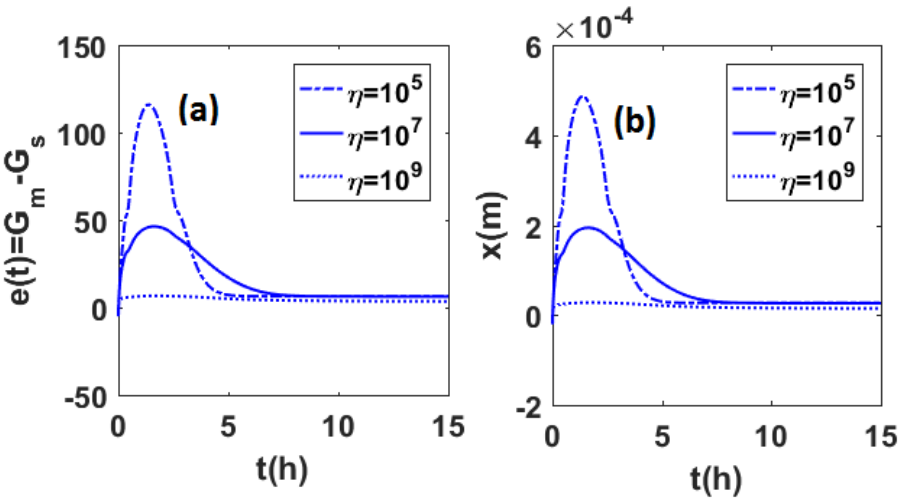

Figure 3.8: Time series of glucose deviation and rod displacement for three values of η : (a) glucose deviation (b) rod displacement.

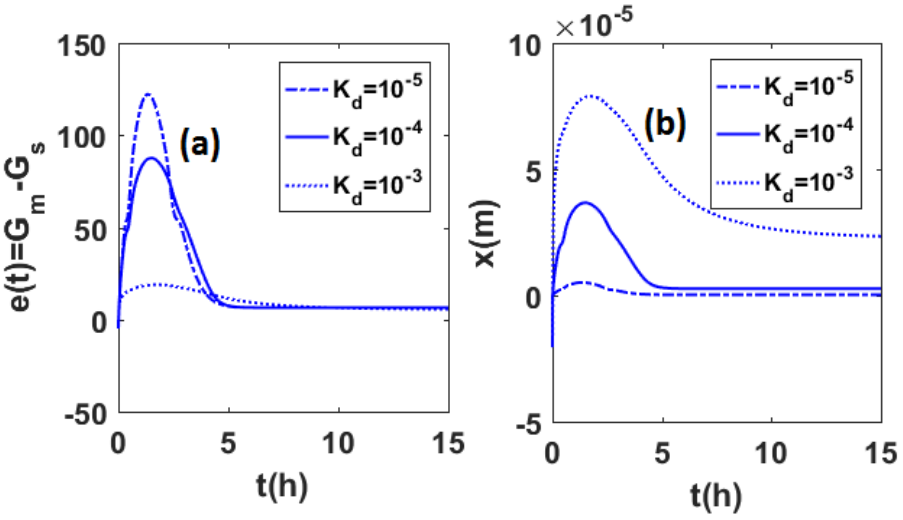

Figure 3.9: Time series of the glucose deviation and rod displacement for three values of K_d : (a) glucose deviation; (b) rod displacement.

The use of an electrodynamic transducer to command the opening of an insulin valve has shown interesting results. Another option could be to use a piezoelectric actuator to control the opening of an insulin valve this will be done in the next section.

3.3 Control of blood glucose level by use of a piezoelectric actuator to command the opening of insulin tank

3.3.1 Control of blood glucose level using adaptive, proportional, integral and PI Control with analog electronics

In this part, four main control techniques are used to control the blood glucose level of a type 1 diabetic. The set of Eq.2.35 is considered.

a) Control using an adaptive control scheme

For studying the control condition of this of system, the effect of α has been investigated by saving $e_{\max}$ as a function of α . Carrying out the numerical simulations, the values of α for which the control condition (2.2) is satisfied have been looked for. By varying α from 0 to 150, It is found that the control is efficient for $\alpha \in [49; 150]$ as shown in Figure 3.10. Figure 3.11 shows the time traces of e(t) for two selected values of α . One notes that, for $\alpha = 10$, the highest value of the error after 3 hours is equal to 0.14 (see figure 3.11 a). This does not satisfy the control condition. Taking $\alpha = 60$, Figure 3.11 b shows that the maximal value of the error is 0.05 corresponding to a good control.

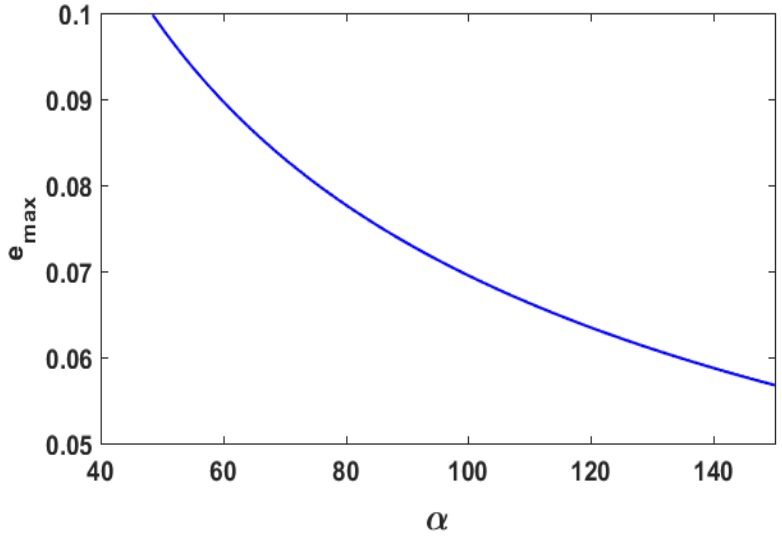

Figure 3.10: maximum value of $e(t)$ plotted as a function of parameter α.

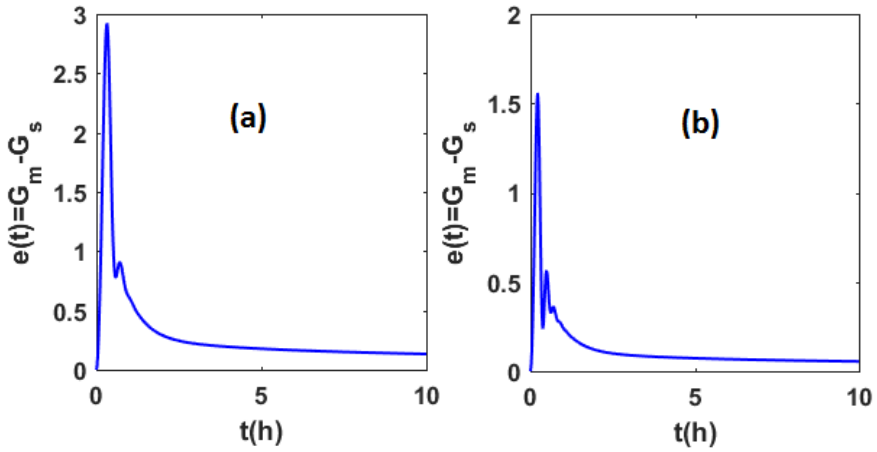

Figure 3.11: Time traces of $e(t)$ for two value of α : (a) $\alpha = 10$ and (b) $\alpha = 60$.

b) Control using a proportional control scheme

Carrying out numerical simulations, we look for the values of coefficient K_p for which the control condition is satisfied. By varying K_p from 0 to 50000, it is found that the control is efficient for $K_p \in [2524; 50000]$ as depicted in Figure 3.12 in which $e_{\max}$ is

plotted versus K_p. Indeed, Figure 3.13 shows the time traces of $e(t)$ for some selected values of K_p. One notes that the quality of the control is obtained for large values of K_p. The time traces of $e(t)$ are plotted in Figure 3.13 for two values of K_p. For $K_p = 1000$, the highest value of the error after 3 hours is equal to 0.25 (see figure 3.13 a). This does not satisfy the control condition. Taking $K_p = 10000$, Figure 3.13b shows that the maximal value of the error is smaller than ε ; corresponding to a good control. Let us mention that taking smaller values of ε would make control more efficient and will reduce de range of K_p for which control is efficient. An important fact to note here is that whatever the value of the control parameter K_p, the deviation $e(t)$ does not give 0; meaning that despite the control, the diabetic patient glucose level does not go back to that of the healthy person. It only saturates to values close to those of the healthy person. This constitutes a limit of the classical proportional feedback control scheme for the process analysed here. As it is seen in the following, the integral and PI schemes are more efficient.

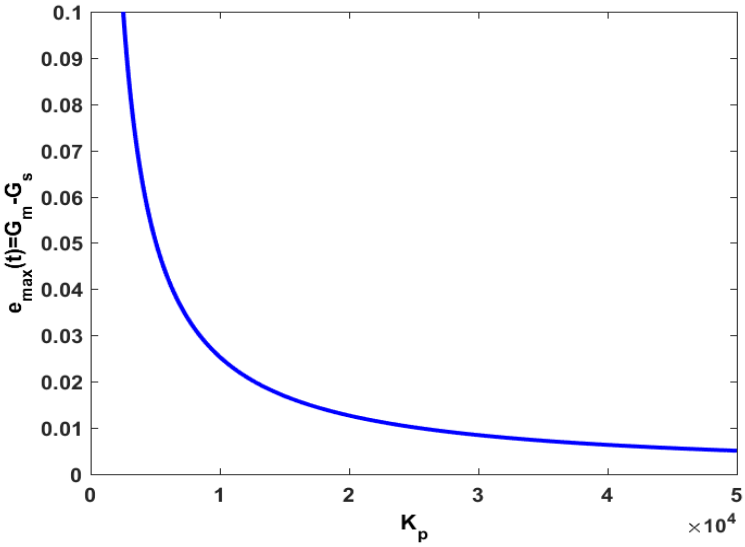

Figure 3.12: Maximum value of $e(t)$ plotted as a function of proportional control gain parameter K_p

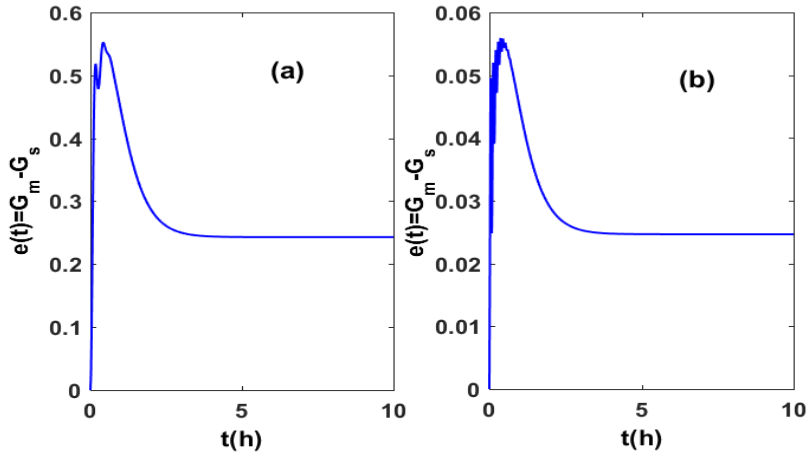

Figure 3.13: Time traces of error for two values of K_p : (a) $K_p = 1000$; (b) $K_p = 10000$

c) Control using an integral control scheme

Carrying out the numerical simulations, the values of the coefficient K_i satisfying the control condition have been looked for. By varying K_i from 0 to 10, it is found that the control is efficient for $K_i \in [0.4\,;10]$ as presented in Figure 3.14 in which $e_{\max}$ is plotted versus K_i. Moreover, we notice that the maximum value of the error is very close to 0 for values of $K_i \geq 0.7$. The time traces of $e(t)$ are plotted in Figure 3.15 for two values of K_i. For $K_i = 0.2$, the highest value of the error after 3 hours is equal to 6 (see figure 3.15 a). This does not satisfy the control condition. However, when $K_i = 7$, as shown in Figure 3.15 b, the maximal value of the error is equal to 3.64×10^{-6} corresponding to a good control. But we notice that even if $e(t)$ does not go close to zero after 3 hours, this happens after some time whatever is the value $K_i \geq 0$. For instance, in Figure 3.15b, the deviation $e(t)$ goes to 1.63×10^{-4} after about 4 hours.

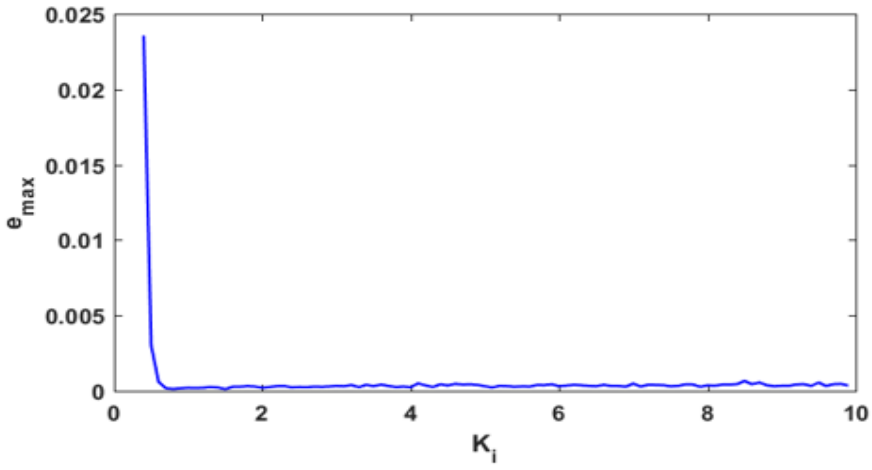

Figure 3.14: Maximum value of $e(t)$ plotted as a function of integral control gain parameter K_i

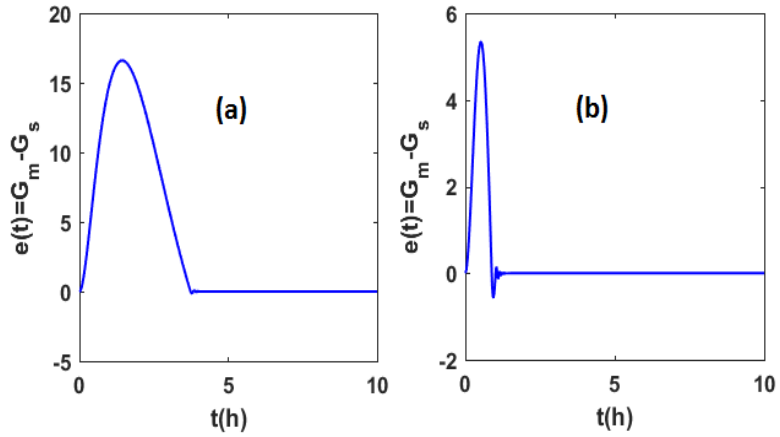

Figure 3.15: Time traces of error for two values of K_i : (a) $K_i = 0.2$; (b) $K_i = 7$

Despite the success of the integral control scheme, an interesting fact appears when one compares Figure 3.13 and Figure 3.15. The time evolution of the deviation in Figure 3.15 corresponding to the integral control scheme presents high values in the transient period while in the proportional control the deviation remains small although it does not completely go to zero. Consequently one can think of the association of both schemes

and find the range of K_p and K_i leading to good control. This is conducted in the next subsection.

d) Control using a proportional-integral control scheme

The purpose of this part is to see if the presence of proportional and integral controller makes control of the blood glucose level of diabetic subject optimal. For this, the stability boundaries of system have been plotted in Figure 3.16 by varying K_p from 0 to 1000 and K_i from 0 to 10. The blue area indicates the region where the control is efficient. We observe that the control is efficient for $K_p \geq 0$ and for $K_i \geq 0.5$. Furthermore with the increase of the values of K_p, a reduction of the range of K_i for which the control is efficient is observed.

In order to better see the influence of K_p in the control system, the time evolution of the error for three values of K_p has been plotted in Figure 3.17 for a fixed value of K_i. It is found that with the increase of the values of K_p, a reduction of the error amplitude is observed.

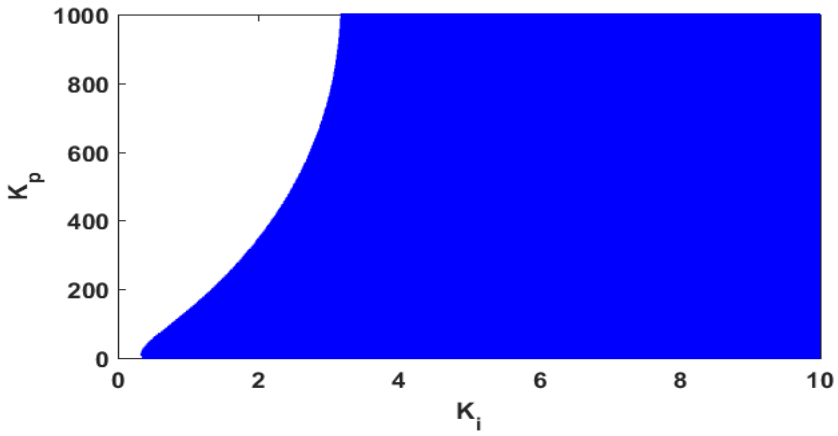

Figure 3.16: Stability boundaries of proportional control gain parameter K_p plotted as a function of integral control gain parameter K_i

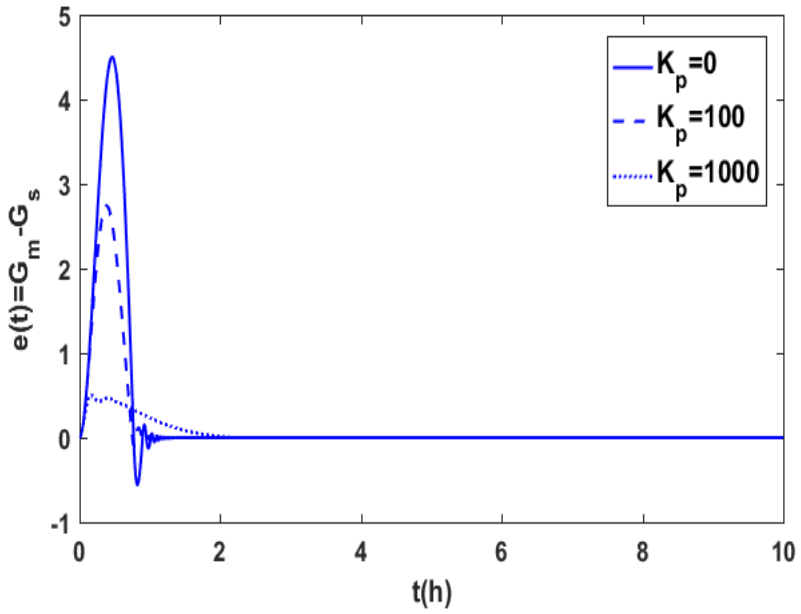

Figure 3.17: Time traces of error for three values of K_p when $K_i = 10$: (a) $K_i = 0.2$; (b) $K_i = 7$

Comparing the obtained results in the case of PI control with those obtained in the case of the adaptive, the proportional control and the integral control, it turns out that PI control is more efficient than the three others.

Other important parameters to be taken into account in this work may be the time delay and the time between insulin injection.

3.3.2 Effects of delay and insulin injection period

a) Effects of delay

The controller in the real case acts after the sensing of the glucose deviation and its treatment by the control process. This introduces a delay which should be taken into consideration.

In order to study the effect of the time delay on the system, the values of the

proportional gain as a function of the delay for a value of $K_i = 10$ has been represented. Figure 3.18 is obtained by varying K_p from 0 to 2000 and τ from 0 to 0.45. The blue area represents the region where the control is efficient. In this region, the control is efficient for $K_p \geq 0$ and $\tau \in [0\,;\, 0.45]$. Moreover, when τ increases, the range of value of K_p for which control is good also decreases.

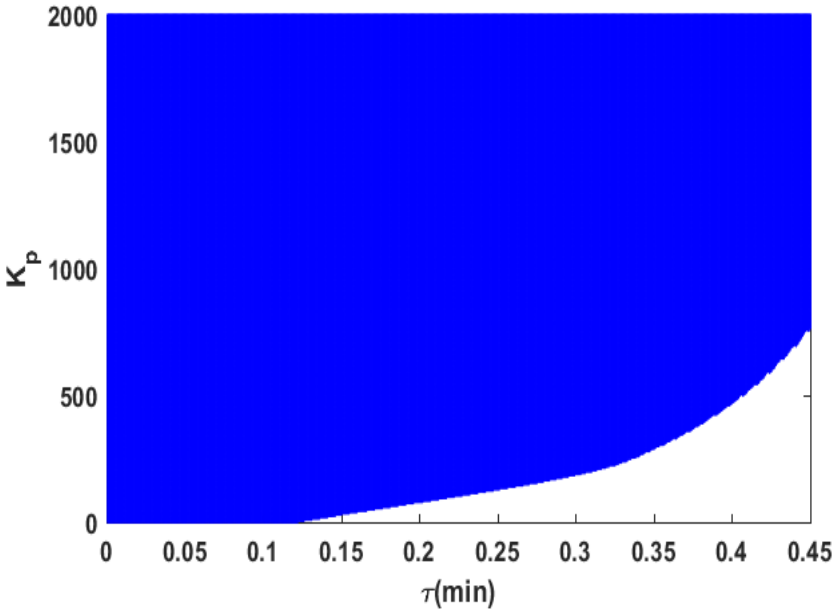

Figure 3.18: Proportional control gain parameter K_p plotted as a function of the delay τ for $K_i = 10$

b) Effect of insulin injection period

It is important to reiterate here that the controller acts only if the blood glucose level of the diabetic patient is larger than the one of the normal person and after each period. By varying K_p from 0 to 2000 and t_0 from 0 to 5 and setting the delay τ to 0.01 and K_i to 10, we get Figure 3.19. We notice that the control is efficient when $K_p \in [0, 2000]$ and $t_0 \in [0\ ;\ 4.55]$. The region where the control is efficient is divided into two parts. In the first part, corresponding to the values of $K_p \in [0, 255]$, there is a regular value range

of $t_0 \in [0\ ;\ 1.37]$ where the control is efficient while for $K_p \geq 255$ when K_p increase, the range of t_0 corresponding to a good control decreases from $[0\,;\,4.55]$ to $[0\,;\,1.79]$.

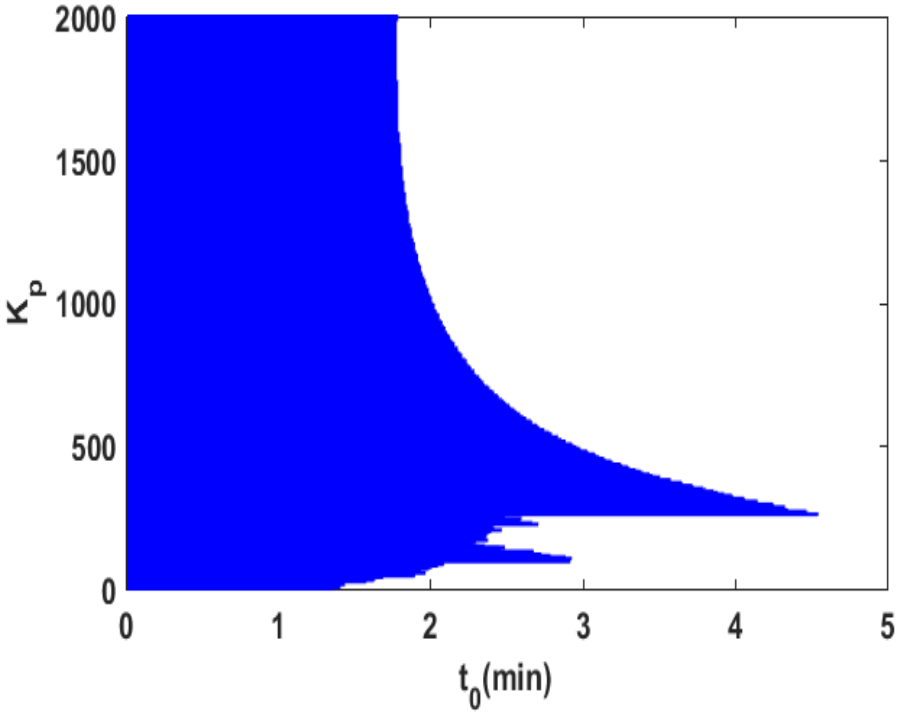

Figure 3.19: Proportional control gain parameter K_p as a function of the time between insulin injections t_0 for $\tau = 0.01$

To conclude this section, let us mention that we have also carried out simulation when the control is made with respect to the basal level as indicated above. Qualitatively, the results are the same as those presented in the above figures.

Having found the right parameters for the controller to be effective, it is also important to focus on the dynamics of a device which will deliver automatically the required amount of artificial insulin into the organism. This is done in the next section considering a piezoelectric actuator whose motion is monitored by an electrical signal proportional to I_{art} or to the deviation of the glucose level.

3.3.3 Automation of the artificial insulin injection

As the electrodynamic transducer, the piezoelectric actuator may be also use to command the opening of the insulin valve. Thus, in order to well analyze the behavior of piezoelectric actuator the deviation of the glucose and that of artificial insulin are presented in Figure 3.20 for $K_p = 2000$ (proportional control parameter) and $K_i = 10$ (integral control parameter).

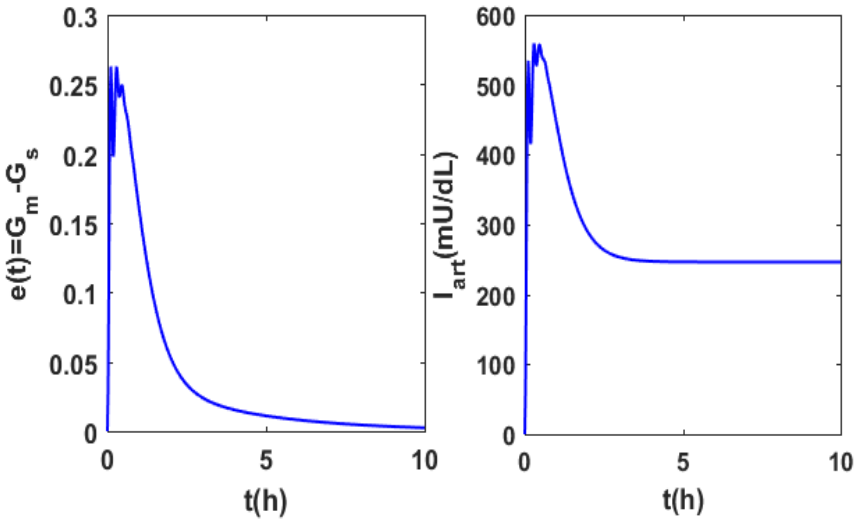

Figure 3.20: Time evolution of the glucose deviation for $K_p = 2000$, $K_i = 10$ and $\tau = 0.01$ min ; (b) Time evolution of the artificial insulin for $K_p = 2000$, $K_i = 10$ and $\tau = 0.01$ min

In Figure 3.21, the time evolution of the piezoelectric actuator displacement z is plotted for five values of η. It is found that the displacement of the piezoelectric actuator has the same dynamics as the artificial insulin. Moreover, by varying the values of η, an increase in the mechanical displacement is observed. This increase corresponds to the opening level of the valve. A particular fact observed in Figure 3.21 is that the actuator displacement does not go back to zero after the regulation. This is in accordance with

what we observe in the evolution of the deviation of glucose level $e(t)$ which does not attain 0 whatever the value of the control coefficients. Consequently, with the level of disease considered here, a permanent injection of tiny quantity of insulin is necessary. This might be understood since in the analysis conducted here, it has been considered that the natural rate of the consumption of glucose is equal to zero and that there is no internal regulation for the insulin secretion. The artificial insulin will thus be continued to be provided at a constant rate for the basal equilibrium of the biological state. If instead on considers a patient for whom there is just a reduction of the rate of disappearance of glucose and a reduction of the rate of internal regulation for the insulin secretion, then final deviation of the blood glucose will go to zero when the control is applied and consequently the piezoelectric displacement will also return to zero after the control has been achieved.

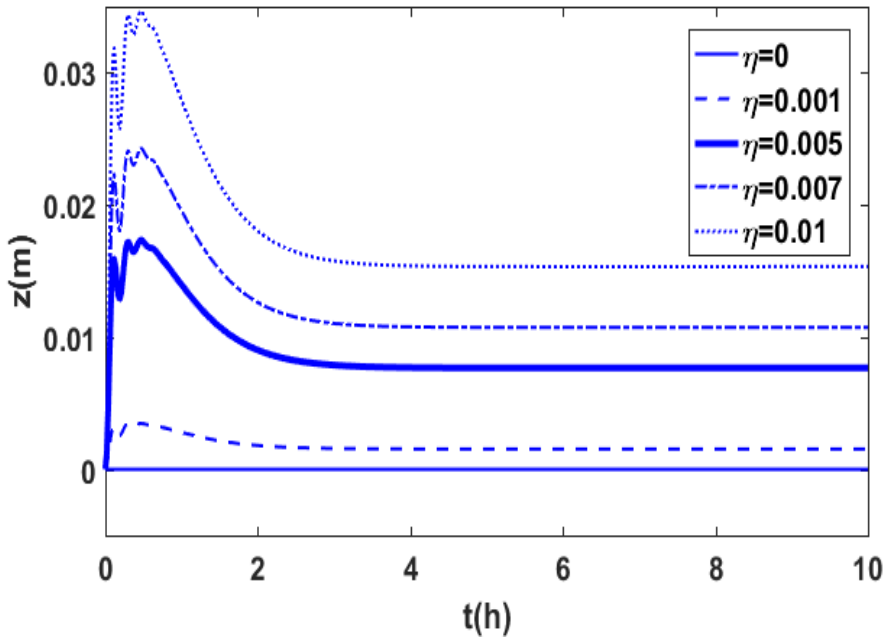

Figure 3.21: Time Evolution of displacement of the piezoelectric Actuator for five values of η for $K_p = 2000$, $K_i = 10$ and $\tau = 0.01$ min

3.4 Microcontroller based control of glucose level in diabetics

3.4.1 The structure of the controller

In this part of the work, microcontroller programming is presented. For this, we need a computer in which we install the Arduino interface. Subsequently, using the fourth-order Runge Kutta method, we program the dynamics of a diabetic subject under control and the digital calculations performed by the microcontroller are sent to the Port D of the microcontroller. The programs implemented in the microcontroller in the case of the four control schemes, are done using the control condition presented in eq.2.2 and the program proposed in ref [97]. With the network of resistors, the digital signal of the microcontroller is visualized through a Proteus oscilloscope. The four control schemes (adaptive, proportional, integral and PI schemes) used in the case of piezoelectric actuation are used in this part.

3.4.2 Results of the control schemes using different types of controls

In this subsection the voltages generated by the microcontroller to actuate the opening of the insulin tank are presented using the fourth control schemes used in section 3.3.

– Control using an adaptive, proportional, integral and proportional-integral scheme

For studying the control of our system using Arduino Uno, we have chosen the same parameters taken in the cases of adaptive, proportional, integral and PI control in section

3.3. The time traces of the voltage produced by Arduino microcontroller in the cases of adaptive, proportional, integral and PI control have been plotted in figures 3.22, 3.23, 3.24 and 3.25 respectively. We observe that, they present respectively the same dynamics as that obtained in figure in figures 3.11, 3.13, 3.15 and 3.17. These four control schemes show that the voltage delivered by the microcontroller present the same dynamics as that of a diabetic subject under control. This means that the voltage increases to promote the opening of the insulin reservoir and once regulation is complete, it gradually decreases to tender towards 0 and thus allow the reservoir to close.

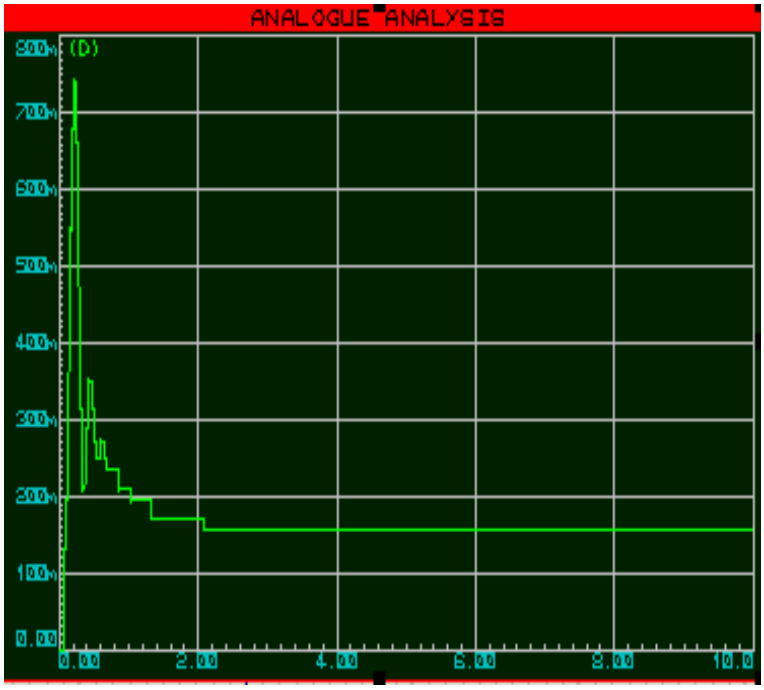

Figure 3.22: Time trace of the voltage in the case of adaptive control

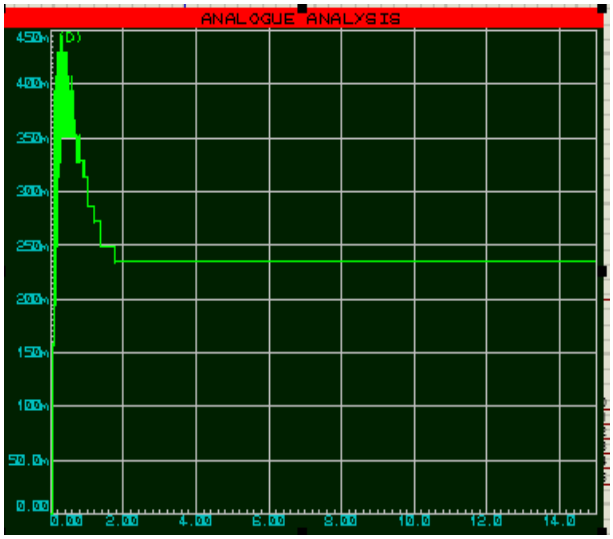

Figure 3.23: Time trace of the voltage in the case proportional control

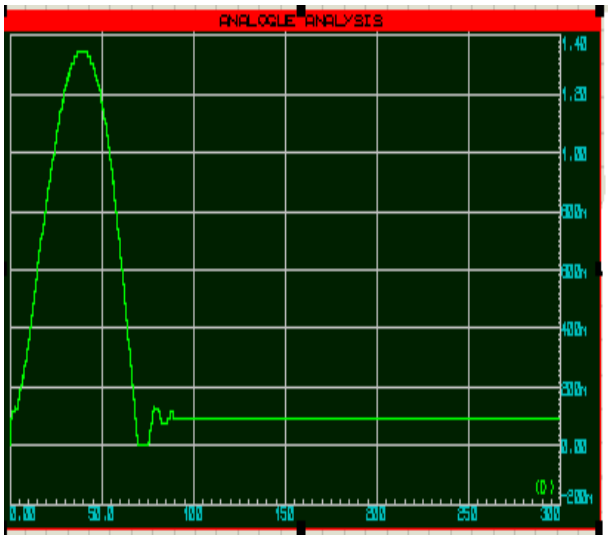

Figure 3.24: Time trace of the voltage in the case integral control

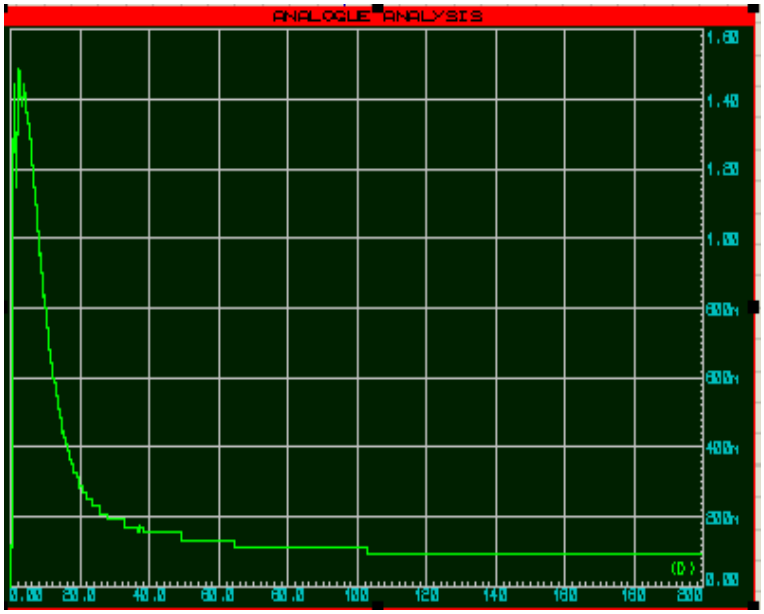

Figure 3.25: Time trace of the voltage in the case PI control

3.5 Conclusion

In this chapter we have presented and discussed the results obtained in the thesis. Starting by the construction of the controller in the case of electrodynamic actuation, we have first studied numerically the effect of the parameters which condition the control of the system. We found out that for some values of these parameters control is efficient. Afterwards, this control has been applied to two mathematical models of the glucose insulin couple where we observed that for some values of the control parameters the blood glucose levels of type 1 diabetic is controlled. In the case of piezoelectric actuation, the case of adaptive, proportional, integral and PI control has been investigated .It is found that control is more efficient for the large values of control coefficient. Moreover the effect of time and the curve have indicated that the range of appropriate control coefficient increases with the time delay. We have also considered the situation where instead of continuously controlling the glucose level, the control takes place at different times in a

periodic manner in the case of PI control. It has been found that this control procedure leads to the reduction of the range of the appropriate control coefficient. Finally we have presented the microcontroller simulations in the case of piezoelectric actuation and the results were in agreement with the numerical simulations.

General conclusion

1-Main results of the thesis

In this thesis, the study on the control of blood glucose levels in type 1 diabetics using electrodynamic transducer and piezoelectric actuator for activating an insulin tank has been done. We focussed on three main points to achieve these objectives: the control of blood glucose level by the use of an electrodynamic transducer and analog electronics, the control of blood glucose level by use of a piezoelectric actuator to command the opening of insulin tank and the control of blood glucose level based on microcontroller.

In chapter 1 we have presented a review of literature on artificial organs and some generalities on glucose control techniques and strategies. In addition the problems of this thesis have been presented.

Chapter 2 has emphasized on the methodology of the work. We have first presented some models of the glucose-insulin systems in diabetics. Afterwards, the different control schemes used in the work have been modeled. The case of the control based on the electrodynamic actuator and that of the control based on piezoelectric actuator have been presented. Furthermore an extension of the modelling of microcontroller-based controllers has been made. Finally, Numerical methods used to solve the differential equations which model the dynamics of glucose-insulin dynamic have been presented.

The third chapter has been devoted to the results and discussion of this thesis. We have mainly focused on the effects of the controllers on blood glucose levels of diabetic patients. We first studied numerically an adaptive control of blood glucose level based on mathematical models of diabetic patients. The adaptive controller converts the deviation between the glucose concentrations of a diabetic person and that of a healthy person (considered as a reference to be followed) into an electrical signal, which is used to command a rod monitoring the opening of an insulin tank. Two mathematical models have

been considered: the Bergman's minimal model and the Cheng's model. The effect of the constant for the adaptive control parameter which characterizes the adaptive control of the derivative gain and that of proportional gain on the glucose deviation and rod displacement have been investigated. It is seen that, with large values of the constant for the adaptive control, the amplitude of glucose deviation and that of the rod displacement are reduced. However, with the increase of the value of the derivative gain, the amplitude of the glucose deviation decreases while the amplitude of rod displacement increases. Regarding the proportional gain parameter it has been found that it does not really affect the dynamics of the system. An extension of this work has been done by studying the effect of this transducer on an analog circuit which mimics the behavior of the deviation between glycemia of diabetic person and that of healthy subject obtained from the Bergman's minimal model. The results have shown that, with the lowering of the values of the constant for the adaptive control, a reduction of the voltage amplitude and that of the rod displacement amplitude is observed. However by varying the derivative gain, it appears that when the derivative gain, takes large values, the amplitude of the deviation decreases while that of the rod displacement increases.

In addition, one have applied an adaptive, proportional, integral and PI control strategies on the Bergman model of glucose-insulin dynamics in order to regulate the blood glucose level of a type 1 diabetic patient. The reference system was the Bergman model for a healthy person and the goal of the control was to drive the patient glucose level to that of the healthy person. Taking the case of the adaptive control, the effect of the constant factor which characterizes the adaptive control, have been also investigated. It is found that, the control is more efficient when this coefficient is large. In the case of proportional control, the range of the proportional control coefficient to good results has been plotted. It has been observed that the control is more efficient when the proportional

control coefficient is large. The case of the integral control has also been considered it turns out that the control is also good for large values of the integral control coefficient. The both proportional and integral control have been thereafter combined and by varying the proportional control parameter when the integral control parameter is set it is seen that the control is more effective for large values of the proportional control parameter.

Since the detection of the glucose level before the action of the controller takes place, the effects of time delay in the case of PI control has been considered and a curve presenting the limit of, proportional coefficient versus the time delay has been obtained for a fixed value of integral coefficient. This curve have indicated that the range of appropriate control coefficient increases. The situation where instead of continuously controlling the glucose level, the control takes place at different times in a periodic manner in the case of PI control has also considered. It has been noticed that this control procedure leads to the reduction of the range of the appropriate control coefficient. In all the cases, whatever is the value of the proportional control coefficient, the diabetic glucose concentration tends to a value close to that of the healthy person without being equal to that the healthy person. The study has been complemented by the analysis of a model of actuator which will inject the required insulin in the body. The actuator of the piezoelectric type is monitored by a voltage proportional to the value of the artificial insulin. It has been found for type 1 diabetic patient, there is a need for a permanent injection of small quantities of insulin if one uses the PI controller.

Finally, the problem of microcontroller based control of glucose level in diabetics was considered. Four control schemes was used: adaptive, proportional, integral and PI control. The results obtained were dynamically similar to those obtained numerically.

2- Future works

Despite the results obtained in this thesis, other points of interest will be investigated in the future to complement results of this work.

For instance, the same work can be undertaken using other glucose-insulin models. But more important is the experimental investigation first by using chemical systems mimicking biological systems for instance sugar detection process.

Appendix

Table 3.1: Definition and value of Hovorka's model parameters [79]

Variable	**Definition**	**Units**
G	Plasma glucose concentration	$mmol/L$
Q_1	The masses of glucose in the accessible (where measurements are made)	$mmol$
Q_2	The masses of glucose in the non accessible compartments	$mmol$
S_1	Absorption of subcutaneously administered short-acting insulin	$(\min^{-1}(mU)^{-1}L)$
S_2	Absorption of subcutaneously administered short-acting insulin	$(\min^{-1}(mU)^{-1}L)$
F_{01}^c	The total non-insulin-dependent glucose flux corrected for the ambient glucose. Concentration	$mmol/(L\min)$
F_R	Renal glucose clearance above the glucose threshold of $9mmol.L^{-1}$	$mmol/(L\min)$
U_G	Gut absorption rate	$mmol/(L\min)$
I	Plasma insulin concentration	mU/L
x_1	Effects of insulin on glucose transport	$\min^{-1}$
x_2	Effects of insulin on glucose disposal	$\min^{-1}$
x_3	Effects of insulin on endogenous glucose production	$\min^{-1}$
U_I	Insulin absorption rate	$(\min^{-2}(mU)^{-1}L)$

Table 3.2: Definition and value of Hovorka's model parameters [79]

Parameter	**Definition**	**Value**
k_{12}	Transfer rate	$0.066\,\mathrm{min}^{-1}$
k_{a1}	Deactivation rate	$0.066\,\mathrm{min}^{-1}$
k_{a2}	Deactivation rate	$0.06\,\mathrm{min}^{-1}$
k_{a3}	Deactivation rate	$0.03\,\mathrm{min}^{-1}$
k_{b1}	Activation rate	$3.07 \times \exp(-5)\,\mathrm{min}^{-1}$
k_{b2}	Activation rate	$4.92 \times \exp(-5)\,\mathrm{min}^{-1}$
k_{b3}	Activation rate	$1.56 \times \exp(-4)\,\mathrm{min}^{-1}$
k_e	Insulin elimination from plasma	$0.138\,\mathrm{min}^{-1}$
V_I	Insulin distribution volume	$0.12L/Kg$
V_G	Glucose distribution volume	$0.16L/Kg$
D_G	Amount of carbohydrates digested	0.8
$t_{\max,G}$	Time-to-maximum of carbohydrate absorption	$40min$
EGPO	Endogenous production of glucose extrapolated to 0 insulin concentration	$0.0161\,mmol(L)^{-1}(\mathrm{min})^{-1}$
F_{01}	Non-insulin-dependent glucose flux	$0.0097\,mmol(L)^{-1}(\mathrm{min})^{-1}$
$t_{\max,I}$	Time-to-maximum of absorption of subcutaneously injected short-acting insulin	$55min$

Table 3.3: Description of functions for the Li's model [81]

Functions	**Description**
$G_{\mathrm{int}} = \sum_m G_m(t-t_m)\delta(t-t_m)$, $With\ G_m(t) = \frac{k_1 t}{b^2} e^{-t^2/2b^2}$	Overall effective exogenous food uptake
$f_1(G(t-\tau_1)) = \frac{R_c}{1+e^{(\ c_1-(G(t-\tau_1)/v_g)\ )(1/e1)}}$	Insulin released from beta-cells stimulated by the elevated glucose level with a physiological delay τ_1
$f_2(G(t)) = U_b(1 - e^{-(\ (G(t)/c_2 v_g)})$	Insulin-independent glucose utilization (IIDGU) occurred in brain and nerve cells.
$f_3(I(t)) \times f_4(I(t)) = \frac{G(t)}{c_3 v_g}(U_0 + \frac{U_c - U_0}{1+e^{-K\log(\ (I/c_4)(1/v_c)+(1/E\times tc)\ )}})$	Insulin-dependent glucose utilization (IDGU) by fat and other cells
$f_5(I(t-\tau_2)) = \frac{R_g}{1+e^{e_{11}(\ (I(t-\tau_2)/vp)-c_5)}}$	Hepatic glucose production with a reaction delay with delay τ_2

Table 3.4: Parameters and associated values of Li's model [81]

Parameters	**Values**	**Parameters**	**Values**
V_g	$10L$	E	$0.2L/min$
V_p	$3L$	e_1	$30mg/dL$
V_c	$11L$	e_{11}	$0.29L/mU$
U_b	$72mg/min$	c_1	$2000mg/dL$
U_c	$940mg/min$	c_2	$144mg/dL$
U_0	$40mg/min$	c_3	$1000mg/dL$
k	1.77	c_4	$80mU/L$
t_c	$100min$	c_5	$26mU/L$
R_c	$210mU/min$	c_6	$2mg/L$
γ	5	c_7	$2mU/L$
S_b	$20mg/min$	R_g	$180mg/min$
S_b	-2.4	S_c	$140mg/min$
k_1	$4300mg/dL$	b	80

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List of publications

1- **U. Essamba Mah** and P. Woafo, Numerical Simulation of an Electrodynamic transducer Control of Insulin provision in the Bergman's and the Cheng's models for the Dynamics of the couple Glucose-Insulin in Diabetics.*Journal of Mechanics in Medicine and Biology* ,vol 20, no. 08, 2050055, 2020, [1-23].