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M. Sc. Program in Mechatronics Engineering

**Improving Tuning Techniques of Digital Proportional
Integral Derivative Controller for Blood Glucose Level
of Diabetic Patient**

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السكر في الدم لمريض السكر

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

الرَّحْمَنُ ﴿١﴾ عَلَّمَ الْقُرْآنَ ﴿٢﴾ خَلَقَ الْإِنْسَانَ ﴿٣﴾ عَلَّمَهُ
الْبَيَانَ ﴿٤﴾ الشَّمْسُ وَالْقَمَرُ بِحُسْبَانٍ ﴿٥﴾ وَالنَّجْمُ وَالشَّجَرُ
يَسْجُدَانِ ﴿٦﴾ وَالسَّمَاءَ رَفَعَهَا وَوَضَعَ الْمِيزَانَ ﴿٧﴾ أَلَّا تَطْغَوْا
فِي الْمِيزَانِ ﴿٨﴾ وَأَقِيمُوا الْوَزْنَ بِالْقِسْطِ وَلَا تُخْسِرُوا الْمِيزَانَ
﴿٩﴾ وَالْأَرْضَ وَضَعَهَا لِلْأَنَامِ ﴿١٠﴾ فِيهَا فَكِهَةٌ وَالنَّخْلُ ذَاتُ
الْأَكْمَامِ ﴿١١﴾ وَالْحَبُّ ذُو الْعَصْفِ وَالرَّيْحَانُ ﴿١٢﴾ فَبِأَيِّ آيَاءِ
رَبِّكُمَا تُكذِّبَانِ ﴿١٣﴾ خَلَقَ الْإِنْسَانَ مِنْ صَلْصَلٍ كَالْفَخَّارِ ﴿١٤﴾

سورة الرحمن الآيات ١ - ١٣

DEDICATION

To my parents, to my family, to all greater who worked hard providing knowledge for me, to all persons whom did their best to made happiness and to plant smiles on people faces around them.

ACKNOWLEDGMENT

First of all, I would like to express my gratitude to my supervisor Prof. Dr. Rashid A. Saeed who has supervised the overall project, gave support and sharing some of his knowledge, and for his guidance and valuable experience. Without his invaluable support, insightful suggestions, and continual encouragement to now I would have never written this thesis.

ABSTRACT

The closed-loop control algorithm for regulating the blood glucose concentration in diabetic patients is used. The digital Proportional-integral derivative (PID) controller is designed based on different tuning methods, Ziegler–Nichols method, Cohen-Coon method, and Chien-Hrones-Reswick (CHR) method, to control the blood glucose level for diabetic patient.

The blood glucose level of the patient is considered as input variable & injected insulin level is considered as output variable which is to be manipulated. A dynamic model is constructed and transfer function is defined for this system. The tuning responses are studied and the parameters were compared. During the process the step responses given by the PID is converted into digital PID controller.

The results show that Ziegler-Nichols method yields a very high overshoot where as Cohen-Coon method exhibits a low overshoot with a low settling time, Chien-Hrones-Reswick yields high settling time.

المستخلص

تم استخدام نظرية نظام التحكم المغلق لتنظيم تركيز الجلوكوز في الدم لمريض السكر. تم تصميم المتحكم الرقمي (التناسبي، التكاملي، التفاضلي) اعتماداً على عدد من طرق الضبط المختلفة طريقة زيقلر-نيكولس، طريقة كوهن-كون و طريقة شين-هرونس-ريسوك. للتحكم في مستوى السكر في الدم لمريض السكر. تم إعتبار مستوى السكر في الدم كمتغير دخل و مستوى الإنسولين المراد حقنه كمتغير خرج ، و الذي يراد معالجته. تم استخدام النموذج الديناميكي للنظام و كذلك تم تعريف دالة التحويل للنظام.

تمت دراسة الإستجابات المضبوطة و مقارنة المعاملات. أثناء المعالجة تم تحويل الإستجابات الناتجة من المتحكم (التناسبي، التكاملي، التفاضلي) التقليدي إلى المتحكم (التناسبي، التكاملي، التفاضلي) الرقمي. النتائج أوضحت أن طريقة زيقلر-نيكولس حصلت على قيمة عالية لتجاوز الزمن الأقصى و بالمقابل حصلت طريقة كوهن-كون على قيمة أقل لتجاوز الزمن الأقصى و زمن استقرار أقل، و حصلت طريقة شين-هرونس-ريسوك على قيمة زمن استقرار أعلى.

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ABBREVIATIONS

BG	Blood Glucose
FOA	Fruit Fly Optimization Algorithm
FPGA	Field Programmable Gate Array
GI	Gastro Intestinal
ICU	Intensive Care Unit
IDDM	Insulin-Dependent Diabetes Mellitus
IV	Intravenous
IVGTT	Intravenous Glucose Tolerance Test
NIDDM	Non-Insulin-Dependent Diabetes Mellitus
PID	Proportional Integral Derivative
TPN	Total Parenteral Nutrition
WHO	World Health Organization

CHAPTER I
INTRODUCTION

Chapter 1

Introduction

1.1 Preface

According to WHO (World Health Organization) report, 9% of adult and older age people suffered from diabetes in 2014 and in 2012 1.5 million people died due to diabetes and day by day the numeric figure is increasing. Diabetes is a chronic disease (or lifelong disease) which occurs either when the pancreas doesn't produce insulin or body does not respond to insulin appropriately.

Due to diabetes many problems occur such as coronary heart disease, weakness, kidney problem, non-traumatic amputations, blindness, secondary infection and so on. There are three main types of diabetes such as Type-1 diabetes, Type-2 diabetes and Gestational diabetes [1].

Type-1 diabetes occurs due to absence of beta cells in the pancreas and pancreas does not produce insulin in appropriate amount i.e. as per body requirement (healthy blood glucose level is between 60 mg/dl to 120 mg/dl). It is also referred as insulin-dependent or childhood diabetes.

Hence we can easily diagnose by applying insulin injection and the amount of insulin provided for type-1 diabetes patient is automatically controlled by using Digital PID (Proportional integral derivative) controller [3].

Type-2 diabetes is commonly taking place in the person who has over weight or above the age of 40. It happens when insulin secretion is not enough

because person has developed resistance to insulin. It also referred as non-insulin dependent or adult onset [1].

Gestational diabetes usually occurs in pregnant woman. During pregnancy hyperglycemia increases and it affects the offspring (babies).

Due to high blood glucose level (above 180 mg/dl) it is referred as Hyperglycemia. Conversely Hypoglycemia occurs due to low blood glucose level (less than 60 mg/dl) [2].

1.2 Related Works

Different contributions and studies have already been done about the control of blood glucose level of diabetic patients:

For instance, authors in [4] undertaken a theoretical analysis of the control of plasma glucose levels in diabetic individuals using a simple mathematical model of the dynamics of glucose and insulin interaction in the blood system.

Authors in [5] developed a model-based predictive algorithms for insulin infusion pump control. This algorithm is sufficient for controlling blood glucose, but results in glucose concentrations near the output lower bound.

Authors in [6] demonstrate the subcutaneous route to insulin dependent diabetes therapy system by using different schemes, these schemes is concentrated on one type of diabetic patients.

Authors in [7] presented two Control methodologies for regulating multiple variables in critical care patients, they were focused on critical care patients such as those in intensive care or undergoing surgery, require close monitoring of all their vital signs.

Authors in [8] focused to envisage the regulation and management of the concentration of glucose and insulin in the blood of a diabetic, implemented and analyzed using Matlab/Simulink.

Authors in [9] present a novel method for determining the PID controller parameters based on Fruit Fly Optimization Algorithm (FOA), namely FOAPID.

Authors in [10] designed a digital PID controller based on Field Programmable Gate Array (FPGA) device for regulating blood glucose level of diabetic patients.

Authors in [11] studied the performances of three types of closed loop controllers to control blood glucose level of a type 1 diabetes patient as a nonlinear model, which was simulated in MATLAB Simulink environment. In this thesis we use various tuning algorithms in PID controller to control blood glucose level of diabetic patient, we also convert the conventional PID into the digital PID controller.

1.3 Problem Statement

Diabetes mellitus is a syndrome of impaired carbohydrate, fat, and protein metabolism caused by either lack of insulin secretion or decreased sensitivity of the tissues to insulin. The problem of blood glucose system is the lack of the stability of the system that affect the life of the patient, so care must take to make a life of a patient safe.

If someone's glucose concentration level is constantly out of range, this person is considered to have blood glucose problem.

1.4 Proposed Solution

Using digital Proportional integral derivative (PID) controller which control automatically blood glucose level of diabetic patient by externally applied insulin dosage.

Using digital PID controller with the plant can enhance the value of the parameters of the step response of the diabetic patient.

1.5 Objectives

The objectives of this thesis are to:

1. Compare between different PID tuning methods.
2. Convert the conventional PID to digital PID controller.

1.6 Methodology

In order to implement digital PID controller parameters, equations and relations to get results we use MATLAB environment as a simulation tool.

The system model equations are applied in the MATLAB environment as a differential equation by setting the values of parameters, then the solution was converted to Laplace transform as a transfer function, this called the plant.

Then the PID controller is applied to the plant by using different tuning methods, then the conventional PID controller in s-domain is converted to digital PID controller in z-domain.

1.7 Thesis Outlines

The rest of this thesis is organized as follows: Chapter 2 gives background of diabetes and blood glucose control systems. Chapter 3 gives a description of the system model and explanation of its parameters. Chapter 4 provides results from a system model of blood glucose patient and discussion about the results, and the final chapter presents the conclusion and also gives a brief discription on how this work can be extended for further enhancement.

CHAPTER II
LITERATURE REVIEW

Chapter 2

Literature Review

2.1 Introduction to diabetes

Diabetes mellitus is a condition of chronically elevated blood glucose concentrations which give rise to its main symptom of passing large quantities of sweet tasting urine (*diabetes* from the Greek word meaning “a siphon”, as the body acts as a conduit for the excess fluid, and *mellitus* from the Greek and Latin for honey). The fundamental underlying abnormality is a net (relative or absent) deficiency of the hormone insulin. Insulin is essentially the only hormone that can lower blood glucose.

There are two categories of diabetes: type 1 is caused by an autoimmune destruction of the insulin producing β cell of the islets of Langerhans in the pancreas (absolute deficiency); and type 2 is a result of both impaired insulin secretion and resistance to its action often secondary to obesity (relative deficiency).

Diabetes is common and is becoming more common. Age adjusted prevalence is set to rise from 5.9% to 7.1% (246 – 380 million) worldwide in the 20 – 79 year age group, a 55% increase (Figure 2.1). The relative proportions of type 1 to type 2 vary from 15 : 85 for Western populations to 5 : 95 in developing countries [12]. Estimated comparative prevalence (age adjusted) of diabetes and impaired glucose tolerance (IGT) together with numbers affected for the global population age 20 – 79 years for 2007 (red) and 2025 (blue) is shown in Figure 2.1.

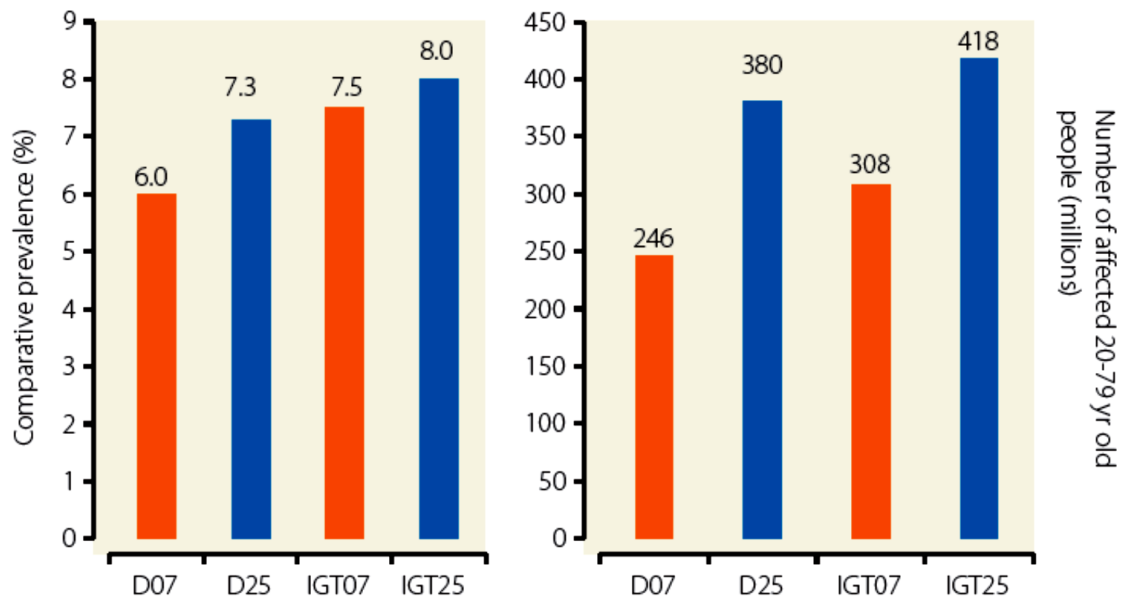


Figure 2.1 Estimated comparative prevalence (age adjusted) of diabetes and impaired glucose tolerance (IGT) together with numbers affected for the global population [12]

2.2 Hyperglycemia

Hyperglycemia refers to an elevated glucose concentration in the circulating blood. While blood glucose level (BG) is often elevated after a meal, it usually normalizes to a range of 3.5–5.6 mmol/l within 3 hours of a meal in a healthy individual. During fasting, BGs are also usually maintained within the normal range of 3.5–5.6 mmol/l [13]. Patients with diabetes mellitus, however, exhibit impaired regulatory responses.

BG remains elevated postprandially, and during the fasting state. Patients under surgical or medical stress may also exhibit a diabetogenic response, even though they are not diabetics [14]. This is due to an elevated catecholamine and other “counter-regulatory” hormones in their circulation.

2.3 Causes of Hyperglycemia

2.3.1 Physiological Background

Blood glucose level is usually regulated by two hormones insulin and glucagon secreted by the endocrine pancreas. Insulin is anabolic, and causes rapid uptake and use of glucose by most tissues in the body.

It also causes the storage of excess glucose as glycogen, mainly in the liver and skeletal muscles. Excess glucose, that cannot be stored as glycogen, is converted to fatty acids and stored in adipose tissues. Insulin also promotes protein synthesis and storage.

Conversely, glucagon is catabolic, mobilizing glucose, fatty acids and amino acids from stores to the circulation, primarily through a breakdown of liver glycogen (glycogenolysis) and the generation of glucose from amino acids (gluconeogenesis).

The two hormones (insulin and glucagon) are reciprocal in their overall action and are secreted appropriately in most circumstances to keep the blood glucose concentration within the normal range [15]. When the glucose concentration rises too high, insulin is secreted, which then lowers the blood glucose concentration toward normal. Conversely, a decrease in blood glucose stimulates glucagon secretion; glucagon then functions in the opposite manner to increase the glucose concentration towards normal [16].

2.3.2 Historical Background

Before insulin was discovered, patients with diabetes suffered from polyuria and a catabolic state, which depleted them of strength, weight and fluid. As described by Aretaeus of Cappadocia in the 2nd century, “Diabetes is a dreadful affliction, not very frequent among men, being a melting down of the flesh and limbs into urine. The patients never stop making water and the flow is incessant, like the opening of aqueducts.

Life is short, unpleasant and painful, thirst unquenchable, drinking excessive, and disproportionate to the large quantity of urine, for yet more urine is passed. One cannot stop them either from drinking or making water. If for a while they abstain from drinking, their mouth becomes parched and their body dry; the viscera seem scorched up, the patients are affected by nausea, restlessness and a burning thirst and within a short time, they expire.

For centuries, the only available treatment for patient with diabetes was starvation. If the diabetes worsened, then more starvation was prescribed.

The discovery of insulin at the University of Toronto in 1921–1922 was one of the most important milestones in the history of medicine [18]. The team that discovered insulin was quickly awarded a Nobel Prize in 1923.

2.3.3 Diabetic Patients

In patients with diabetes mellitus, the correlation between insulin delivery and blood glucose concentration is impaired. Both Type I and Type II diabetics have a dysfunctional endocrine pancreas, which produces little (as in Type II) or no insulin (as in Type I). Apart from this, the insulin receptor on the tissue cells in Type II diabetics also respond abnormally to the circulating insulin (“insulin resistance”). Type I diabetes is also known as Insulin-Dependent Diabetes Mellitus (IDDM), while Type II is also known as Non-Insulin-Dependent Diabetes Mellitus (NIDDM).

2.3.4 Surgical Patients

Surgical patients commonly enter a hypermetabolic stress state, induced by the area of infection or injury, and promoted by organs involved in the immunologic response to stress. In this stressed state, insulin secretion is suppressed, and the normal carbohydrate metabolism is altered. This results in increased glucose production, depressed glycogenesis (i.e. reduced conversion of glucose into the storable form of glycogen), glucose intolerance, and insulin resistance [19].

2.4 Importance of Tighter BG Level Control

BG level should be kept within the normal range, because:

1. A high glucose concentration exerts an osmotic pressure in the extracellular fluid, and can cause cellular dehydration.
2. Too low a BG level carries the risk of hypoglycaemic coma. Glucose is the only source of energy that can be used by the brain. Prolonged and profound

hypoglycaemia can produce severe brain damage.

3. Too high a glucose concentration (>11.1 mmol/l) can affect wound healing and interfere with human neutrophil function [20].

4. Therapy that maintains BG level at below 11.9 mmol/l has been shown to improve the long-term outcome of diabetic patients with acute myocardial infarction [21].

Researchers in the last few decades have found that the mere use of insulin alone is not enough to guarantee the well-being of the patient ([17, 21]), as diabetic microvascular complications have emerged. These microvascular complications include retinopathy (visual impairment), nephropathy (kidney disease) and neuropathy (nerve damage).

2.5 Achieving Tighter Control

In an effort to achieve tighter control, attempts have been made to sample the patients' BG level regularly, and adjust the insulin infusion rate automatically, so as to steer the BG towards a given target value. In such early experiments, whole blood was sampled continuously for glucose measurement, using the invasive method.

On the other hand, clinical routines have progressed with manual BG level control, which uses intermittent (and not continuous) BG level sampling. BG samples are taken from finger pricks or in-dwelling cannula, hourly, 2 hourly or 4 hourly, depending on severity. Various algorithms for perioperative control of BG level have been proposed, using hourly and three-hourly whole blood BG level sampling. Closed-loop (automatic) systems were not practical for use in routine treatment, due to the cost and preparation associated with their operation. Furthermore, long term use of the system posed safety concerns, due to the invasive nature of the measuring technique.

2.6 Glucose Control: Input and Output

Automatic regulation of a patient's blood glucose (BG) level requires a minimum of three components, namely, a continuous BG sensor, a controller that matches BG level with an appropriate insulin delivery rate, and an infusion pump to deliver the insulin to the subject.

Shown here is a simple model of the control loop:

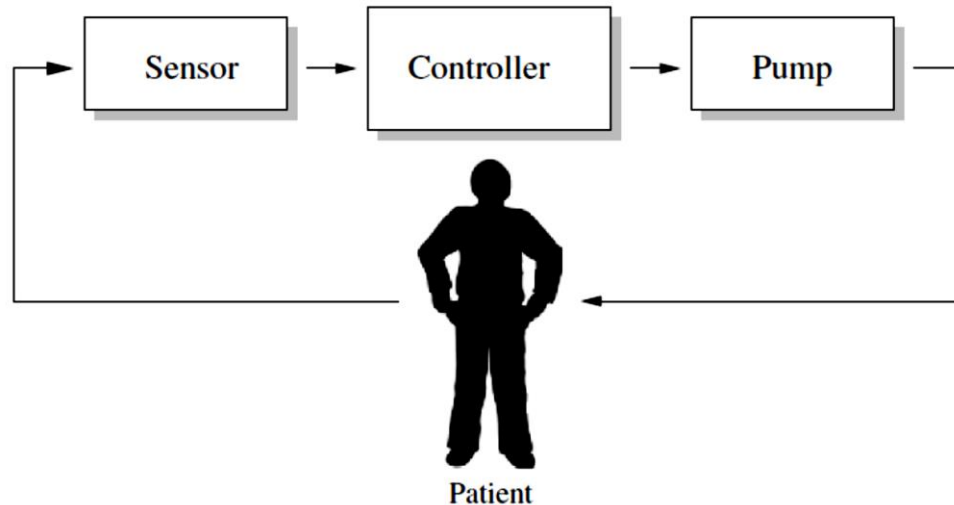


Figure 2.2 Simple model of the control loop

As the variable to be controlled is a patient's BG level, a knowledge of the BG is required. This is provided by a glucose sensor, and represents the input to the control system. Since insulin is used to lower a high BG level, the rate of insulin delivery represents the output of the control system. The patient is the "plant" to be controlled in control system terminology.

The controller is the component of the system that regulates the blood glucose levels in the patient. The formulation of the control rule depends on the knowledge we have about the sensor, the pump and the patient and specifically, the BG measurement methods, the type (or preparation) of insulin used, the route of infusion, and the patient's characteristics. Various BG measurement techniques exist, and each has its unique characteristics.

As for insulin, each type of insulin has different kinetics, and different infusion routes exhibit different characteristics.

2.7 Glucose Control: Patient Dynamics

The role of the control algorithm in a closed-loop insulin delivery system is to regulate the patient's BG level, replacing the intrinsic glucose regulatory function, which is abnormal in diabetics. To develop an effective algorithm, a knowledge of how glucose is intrinsically regulated in a healthy person is essential.

The human pancreas has between 1 and 2 million islets of Langerhans. These islets contain three major cell types: alpha, beta and delta. The beta cells constitute about 60% of the cells, and secrete insulin.

The alpha cells, about 25% of the total, secrete glucagon. The delta cells, about 10% of the total, secrete somatostatin. The remaining 5% of cells are made up of other cell types which secrete hormones of uncertain function [22]. Insulin and glucagon play the most important roles in the glucose-regulatory system.

The glucose-regulatory mechanism is not an isolated system, but has connections with many other metabolic pathways in the body.

2.8 Intrinsic Blood Glucose Regulation

In a normal healthy person, blood glucose concentration is controlled to within a narrow band, usually between 3.5 mmol/l and 5.6 mmol/l in the fasting state.

During fasting, insulin secretion is reduced to a basal level, and glucagon is released to allow the liver to:

- mobilize glucose from its glycogen stores (glycogenolysis) and
- synthesize glucose from amino acid (gluconeogenesis).

In addition, when insulin levels are low, the uptake of glucose by muscle is minimized, and there is lipolysis of stored fats to release free fatty acids. When fasting persists longer than 12 to 18 hours, these free fatty acids then become the main energy substrate, used by essentially all tissues of the body,

except the brain. Gluconeogenesis still supplies glucose for obligatory glycolytic tissues, notably the brain.

This mechanism effects a stable fasting blood glucose concentration so that the brain, which has no energy stores, has a sufficient supply of nutrients for normal activity. Glucose is an essential nutrient for the brain, retina, and germinal epithelium of the gonads.

Insulin is always present, and a low level of circulating insulin regulates the rate of lipolysis, glucose transport and gluconeogenesis at all times [23]. When a person prepares to eat a meal, two phases of insulin secretion occur: an anticipatory phase (first phase) and a glucose-sensitive phase (second phase).

In the anticipatory phase, the sight of food and the first bite of a meal cause the brain to send signals to the pancreas. These signals cause the pancreas to release insulin into the hepatic circulation (Figure 2.3). Once the insulin is in the hepatic circulation, the liver stops breaking down glycogen into glucose. As the food enters the stomach, the release of insulin is further facilitated by gastrointestinal hormones. These hormones increase the sensitivity of the islet cells to glucose [24].

As nutrients are absorbed into the circulation, the glucose sensitive phase begins, and there is continuous secretion of insulin. These two phases are sometimes termed the biphasic response of insulin secretion.

After absorption of all the carbohydrates, the feedback system for control of blood glucose returns the glucose concentration rapidly back to the control level, usually within 2 hours.

Although glucose is an important physiological stimulant of insulin secretion, nutrients other than glucose, particularly amino acids, are also capable of stimulating insulin release.

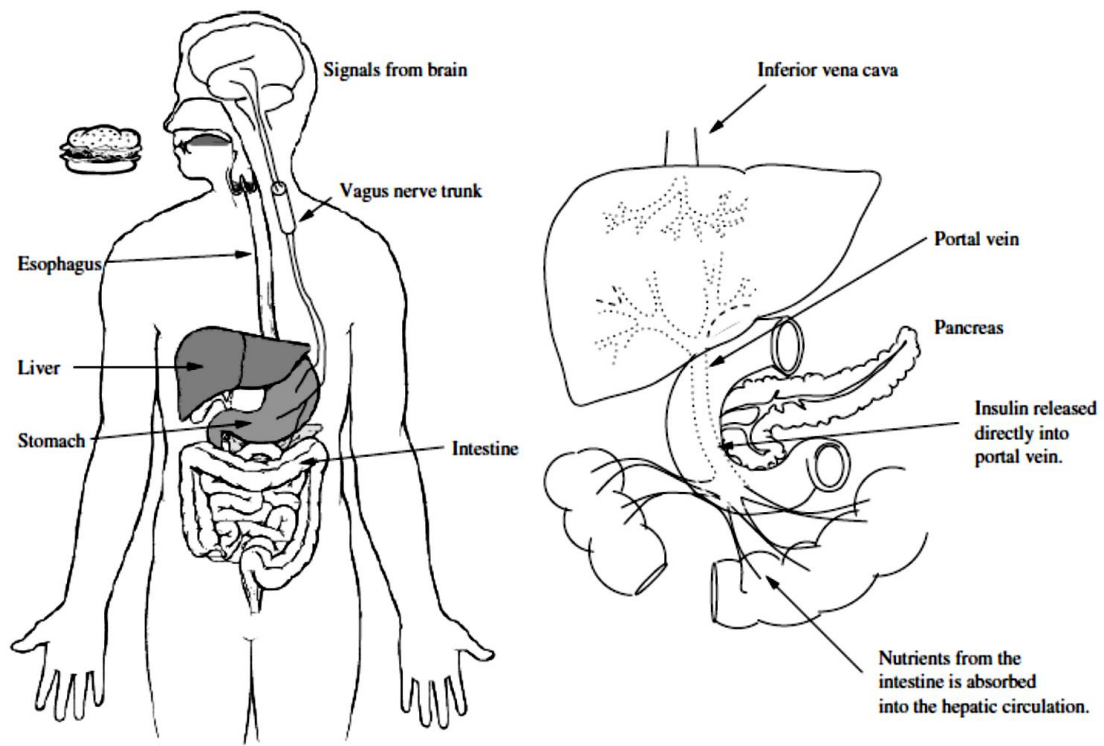


Figure 2.3 Anatomy of the intrinsic blood glucose regulation mechanism

Nevertheless, amino acids stimulate a much greater insulin response when accompanied by hyperglycaemia, than the modest degree expressed in the presence of normal plasma glucose level.

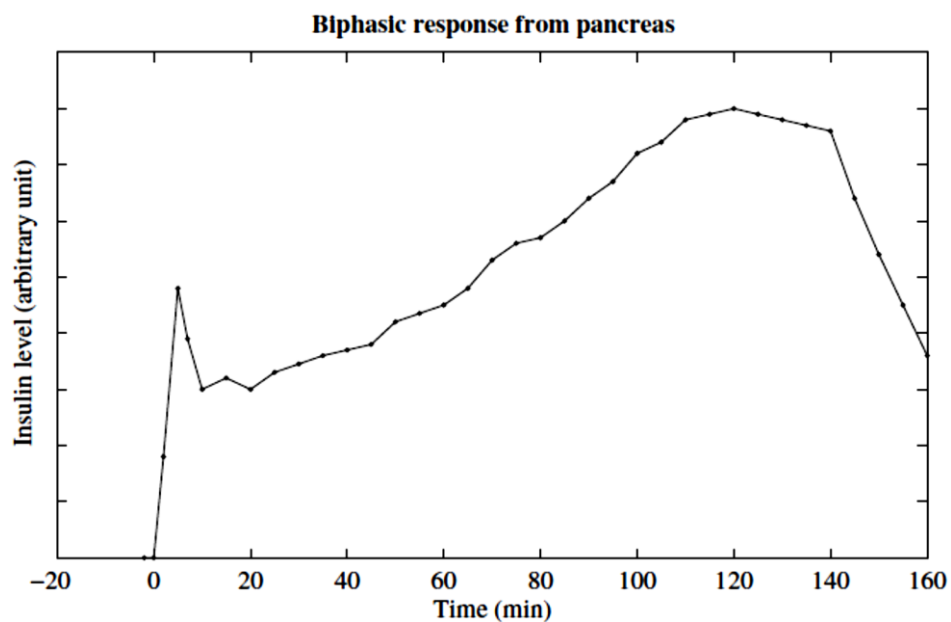


Figure 2.4 Biphasic insulin response (illustration)

The biphasic response (Figure 2.4) is also observed in the plasma compartment during glucose clamp studies, where a square wave of hyperglycaemia is introduced intravenously under normal conditions in a normal individual. The first phase of the insulin response consists of a rapid rise in the insulin level during the first 10 min, with a peak response at 4 min; the plasma insulin level then falls and reaches a nadir at 10 min [25]. After 10 min, the plasma insulin level is then observed to increase gradually according to the degree of hyperglycaemia and persists for the duration of the stimulus [26].

2.9 Diabetic Patients

In patients with Type I and Type II diabetes mellitus, beta cells have either been partially (as in Type II) or completely (as in Type I) destroyed. The destruction of beta cells results in reduced or no insulin secretion, and also the disappearance of the first phase (anticipatory phase).

With no anticipatory phase, the liver does not receive the message to stop breaking down glycogen into glucose, resulting in continued hepatic glucose production.

Added the glucose absorbed from the meal, and a lack of insulin release, hyperglycaemia ensued [27]. The major difference between Type I and Type II diabetes mellitus is that Type I diabetic patients cannot survive without exogenous insulin, contrary to Type II patients who suffer from either a reduced (but present) insulin secretion, or abnormal insulin response (increased peripheral insulin resistance) or both. Hence, Type I diabetes is also known as insulin-dependent diabetes mellitus (IDDM), whereas Type II is also known as non-insulin-dependent diabetes mellitus.

A solution to “artificially” achieve the first phase insulin release using a closed loop system would be to use sensors that have a very fast response time (e.g. 1 min at least), and to immediately deliver insulin when BG level

starts rising (with the assumption that the rise of BG level signifies the start of a meal).

As for the second phase insulin release, the matching of the insulin dose to the blood sugar intake depends on:

- A knowledge of how much glucose is ingested. In a healthy pancreas, beta cells also function as “fuel-sensors” and are capable of adapting the rate of insulin secretion to variations in plasma glucose level.
- The responsiveness of the insulin receptors on target cells to enable glucose to enter and be utilized by the cells.

2.10 Importance of BG Control

It is important for BG level to be kept within the normal range, because:

1. A high glucose concentration exerts an osmotic pressure in the extracellular fluid, and causes cellular dehydration. This excessive BG level causes loss of glucose through urination (glycosuria), leading to osmotic diuresis that depletes the body further of fluids and electrolytes.
2. Too low a BG level carries the risk of hypoglycaemic coma. The BG level should not drop below a certain level because glucose is the only nutrient that can be used for energy by the brain, retina, and germinal epithelium of the gonads.
3. Too high a glucose concentration (>11.1 mmol/l) can affect wound healing and interfere with human neutrophil function [20].
4. Therapy that maintains BG level at below 11.9 mmol/l improves the long term outcome in diabetic patients with acute myocardial infarction [21].
5. Pre-prandial blood glucose concentrations between 3.9 mmol/l and 6.7mmol/l, and postprandial concentration of less than 10 mmol/l was found to delay the onset of diabetic microvascular complications. These microvascular complications included retinopathy (visual impairment),

vision-threatening lesions, nephropathy (kidney disease) and neuropathy (nerve damage).

Complications not only occurred in diabetic patients, but also has an impact on critically ill patient population:

1. A recent finding ([21]) has shown that the use of intensive insulin therapy to maintain BG at a level that did not exceed 110 mg/dl (6.1 mmol/l) substantially reduced mortality and morbidity in critically-ill patients in the ICU (8.0% with conventional treatment to 4.6% with intensive insulin therapy).
2. The finding also reported that a pronounced hyperglycaemia in critically ill patients, even those who have not previously had diabetes, may lead to complications in such patients [21].
3. Patients with mean glucose concentrations >11.1 mmol/l within 36 h following surgery were more likely to develop infectious complications than their counterparts who were under better glycaemic control.

2.11 Glucose Control in Critically Ill Patients

Critically ill patients are different from non-critically ill patients in many respects. Major surgery and critical illness are physiologically stressful events that provoke complex metabolic responses in the patient. In general, the greater the degree of surgical trauma, the greater the endocrine upset.

Critical care medicine uses the term “stress” to describe the systemic response to severe injury or infection.

Some of the responses to stress include alterations in carbohydrate metabolism, and a state of hypermetabolism. The hypermetabolic state is induced by sepsis or injury, as well as by organs involved in the immunologic response to stress [19].

It is manifested as an increase in glucose production that appears to be directed toward maintaining glucose delivery to wound and immune tissues.

These alterations make the control of plasma glucose more difficult than in ordinary diabetic patients.

Factors that affect glucose regulation in critically ill patients include:

- Loss of the inhibitory effects of elevated glucose levels.
- Stress-induced release of counter-regulatory hormones
- Increased Insulin resistance
- Medication that induces hyperglycaemia
- Effects of Feeding
- Gastro-intestinal (GI) tract functionality
- Stress in liver

2.11.1 Loss of the Inhibitory Effects of Elevated Glucose Levels

In the non-stressed state, elevated serum glucose levels exert an inhibitory effect on gluconeogenesis. In critically ill patients, this important feedback mechanism is blunted, often resulting in continued endogenous hepatic glucose production and hyperglycaemia. Although there may be an increase in glucose production and turnover, the reliance on glucose as an energy source is reduced.

2.11.2 Stress-Induced Release of Counter Regulatory Hormones

In response to stress, the counter-regulatory or anti-insulin hormones are secreted. These hormones include epinephrine, norepinephrine, cortisol, growth hormone, and glucagon.

- Both norepinephrine and epinephrine cause constriction of essentially all blood vessels of the body (vasopressor activity), and an increased activity of the heart (inotropic activity). The constriction of the vessels increases the total peripheral resistance and elevates arterial pressure. Epinephrine (also known as adrenaline) also mobilizes glucose from glycogen and raises blood glucose level.

- Cortisol (a gluco-corticoid) stimulates hepatic glycogen and glucose production, and inhibits insulin action on peripheral tissues. It stimulates protein synthesis, providing substrate for gluconeogenesis. Gluco-corticoids also suppress the inflammatory and immune response [16].
- Growth hormone increases the rate of protein synthesis in all cells of the body, and increases mobilization of fatty acid from adipose tissues into the blood.

There is also increased use of the fatty acid for energy, with a decreased rate of glucose utilization throughout the body [16].

2.11.3 Increased Insulin Resistance

Patients with Type II diabetes (also known as NIDDM) are usually insulin resistant.

Surgical stress potentiates this insulin resistance, mainly due to the release of the counter-regulatory hormones. Enhanced gluconeogenesis during stress is also resistant to inhibition by insulin and glucose. Although skeletal muscle has traditionally been implicated as the major site of peripheral insulin resistance, stress may also induce insulin resistance in adipose tissue, liver, and heart [19].

2.11.4 Medication that Induces Hyperglycemia

Concurrent administration of exogenous vasopressors and gluco-corticoids can further amplify the effects of stress-induced counter-regulatory hormones in ICU patients as described above. Drugs with vasopressor and/or inotropic activity (such as epinephrine and norepinephrine) are useful for resuscitation of critically ill patients, and are administered when fluid resuscitation alone fails to reverse hypotension.

2.11.5 Effects of Feeding

Patient in Intensive Care are usually sedated. During this period, nutrition is delivered either enterally or parentally.

- Enteral nutrition delivery is always the preferred route whenever the GI tract is functional. Nutrition is delivered proximal or distal to the pylorus through a naso-enteric tube. Since gastric emptying is often impaired in critically ill patients, feeding distal to the pylorus maybe preferable [28].
- Total parenteral nutrition (TPN) is given in situations where the patient has contra-indications to enteral feeding (such as bowel obstruction, overwhelming intra-abdominal sepsis, or necrotizing pancreatitis), or when the patient is unable to absorb nutrients via the GI tract. TPN in the ICU setting is delivered through a central venous catheter, since most critically ill patients already have central venous monitoring in place.

2.11.6 GI Tract Functionality

In terms of meal intake, perhaps the difference between an outpatient and a critically ill patient is in “how” and “when” they receive their daily nutrition. The direct intubation to the pylorus implies that food ingestion does not go through any peristaltic action of the esophagus, nor the normal stomach stimulation by the presence of food, as would occur in a normal individual. There is the effect of no chewing, no visual stimulation by food, and no activity of the stomach which pre-empts insulin release in sedated patients. Food absorption in critically ill patients remains dependent on gut motility and other functions of the GI tract. The meal pattern is also abnormal in that nutrient is given continuously over hours rather than as discrete meals.

2.11.7 Stress in Liver

The liver functions as an important blood glucose buffer system. During the blood glucose rise after a meal, the liver stores as much as two thirds of the glucose absorbed from the gut in the form of glycogen.

The stored glycogen is later released back into the circulation as glucose when required. This action of the liver decreases the fluctuations in blood

glucose level. However, in patients with severe liver disease, it becomes difficult to maintain a narrow range of blood glucose level [16].

2.12 BG Management in the ICU

Critically ill patients are treated by the method of continuous administration of intravenous insulin by infusion pump, although intermittent subcutaneous injections may also be given in certain cases. Continuous intravenous infusion obviates concerns over the patient's state of perfusion (which influences subcutaneously injected insulin), and permits fine-tuning of BG level within a chosen range:

- 8.3–13.8 mmol/l (150–250 mg/dl) [23]
- 6.7–10 mmol/l (120–180 mg/dl) [29]
- 6–10 mmol/l (108–180 mg/dl) [30].

In the current clinical setting, BG level less than 6 mmol/l (108 mg/dl) carries the potential risk of hypoglycaemia, while BG level in excess of 13.8 mmol/l (250 mg/dl) would also require intervention.

Continuous infusion of insulin may increase the risk of hypoglycaemia, but the continuous monitoring of patients in an ICU minimizes this risk and enables BG to be controlled safely.

2.12.1 BG Measurement

Current clinical practices examine BG two- to four-hourly, with hourly checks during critical cases. BG determination is by conventional glucometer with the blood sample obtained from arterial or venous cannula.

2.12.2 Insulin Infusion Adjustment

Insulin infusions are administered in saline or colloid solution, and mixed such that 1ml/hr of delivery equates to 1U/hr of insulin. A rate of 0.5 to 1 unit of insulin per hour is the recommended starting dose.

This dose is usually for patients who are not severely stressed. Higher rates may be needed for adequate BG control.

Adjustments to insulin rate are made hourly, two-hourly or four hourly based on arterial blood (from arterial cannula) or finger stick glucose determinations. The adjustment frequency depends on the stability (or severity) of the BG elevation.

Patients may vary greatly in their sensitivity to insulin and some, especially long-term type 1 diabetic patients are quite sensitive to small changes in insulin dose.

2.13 Mathematics of Glucose Control

Recall that the beta cells (which being the fuel sensor as well as the insulin production source) were destroyed in a diabetic patient, causing an impairment of the ability to self-regulate glucose level. Glucose level regulation must then be restored by means of carefully calculated external insulin infusion. The goal of a closed-loop control system is thus to mimic the functionality of the pancreas in providing automatic regulation of blood glucose level in patients.

To be precise, the closed-loop control systems (with its algorithm) should really answer the question: “How much insulin should be given such that the person blood glucose is restored, as closely as possible, to that of a healthy individual?”

2.14 Model-Less (Empirical) Control Algorithms

In the model-less (empirical) approach to control algorithm design, the relationship between the input (insulin) and output (desired glucose level) are determined based on experimental data, not on a theory. A control rule is then formulated using the experimental data as the basis.

2.14.1 Control Algorithm Based on Curve-Fitting

In this method, the relationship between the inputs and outputs are obtained by fitting simple curve equations to the experimental data. As an example, experiments could be conducted to observe the glucose level measured from

a patient when different amounts of insulin injections were given over a period of time. A curve would then be fitted to arrive at a simple glucose-insulin response curve, which would then be used as the control rule.

The control equation formulated by Albisser et al consists of a sigmoidal dose response curve, with an incorporated predictive equation.

The predictive portion of Albisser et al's algorithm takes into account:

- The trend of BG (i.e. rise, fall)
- The delay between blood extraction and the ultimate measurement

The control equation is likened to a Proportional-Derivative controller. The derivative action is based upon the rise or fall of BG, while the dose-response curve provides the Proportional action.

Unlike other methods that relied on variables that correlated with the whole blood glucose, invasive BG measurement has the advantage of being more accurate, because it measured glucose content in the whole blood itself.

2.14.2 Glucose-Insulin Response Curve (Sigmoidal Dose-Response Curve)

The glucose-insulin response curve came from the discovery that insulin secretion did not respond as a linear function of glucose concentration. The relationship between the extracellular glucose concentration and the rate of insulin secretion in vitro is sigmoidal, with a threshold corresponding to the glucose level normally seen under fasting conditions, and with the steep portion of the dose-response curve corresponding to the range of glucose levels normally achieved postprandially.

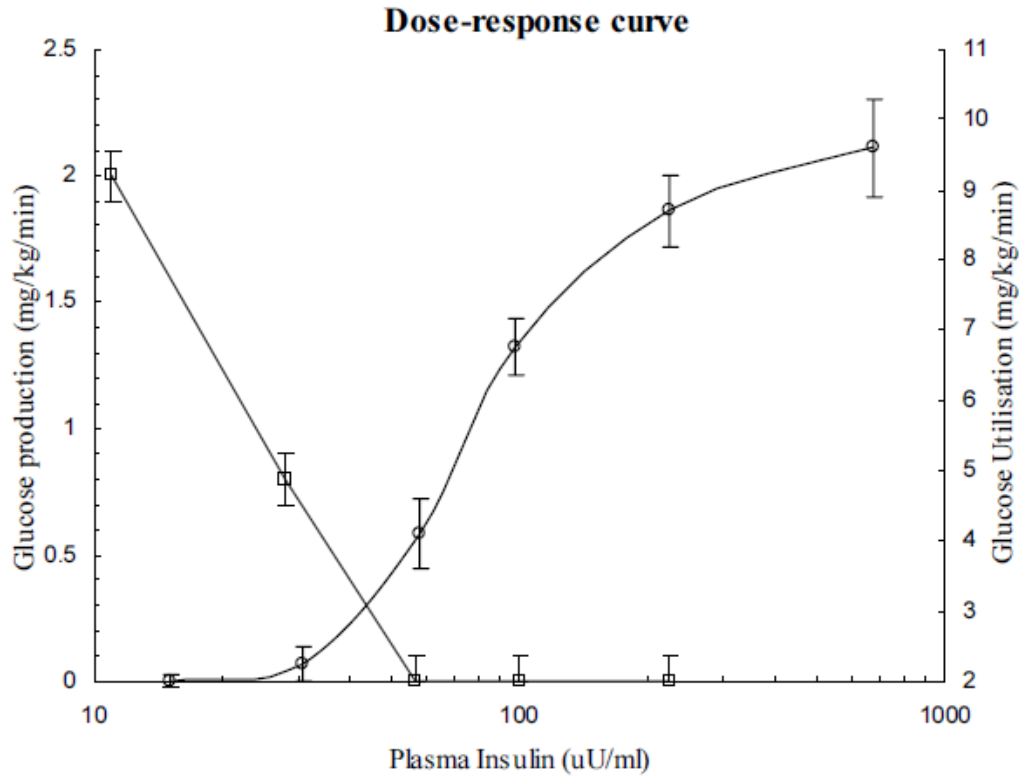


Figure 2.5 Sigmoidal Glucose-Insulin Response Curve

This sigmoidal nature of the dose-response curve could be attributed to a Gaussian distribution of threshold for stimulation in beta-cells. This also means that linear model is not adequate to describe the glucose-insulin interaction in human.

Albisser et al's Infusion Algorithm

- Glucose infusion rate, $R_d = \frac{1}{2} M_d [1 - \tanh S_d (G - B_d)]$
- Insulin infusion rate, $R_i = \frac{1}{2} M_i [1 - \tanh S_i (G_p - B_i)]$
- Projected BG, $G_p = G + K_1 [\exp (A/K_2) - 1]$

where M = maximum infusion rate; S = slope; B = BG level at which half maximum infusion rate is chosen to occur; subscript d, i = for glucose/dextrose and insulin respectively; A = rate of change of BG, which is minute to-minute changes of BG averaged over the preceding four minutes; K_1 is chosen to adjust the magnitude of the difference factor, and K_2 selected to establish its sensitivity to changes in A .

2.14.3 Control Algorithm Based on Lookup Table

In this method, the relationship between the inputs and outputs is obtained by mapping the inputs and outputs in the form of a lookup table. In the day-to-day care of patients in the hospital settings, blood glucose control is commonly achieved using model-less approach in an open loop manner.

BG samples are taken intermittently (at defined intervals), and insulin delivery rate is adjusted manually using:

- Lookup table control, such as a sliding scale table. The table has a continuous BG “partitioned” into ranges, with an insulin rate assigned to each range.

Insulin is given in accordance with the range in which the BG sample resides (Table 2.1). The insulin delivery can either be intravenous or subcutaneous, and different tables are prescribed for different routes of delivery. Tables that used 1-hourly [32], and 3-hourly BG sampling [31] for subsequent adjustment of intravenous insulin delivery rate have been reported to achieve good normalization of high BG.

- Linearized lookup table, where the “step-wise” insulin increase is replaced by a “slope”. Furler et al [33] used such an algorithm, where insulin rates are 0.5 U/hr for $BG < 4$ mmol/l and 2.5 U/hr for $BG > 8$ mmol/l, with a linear transition between these rates over the range of BG of 4–8 mmol/l.

Table 2.1 Example sliding scale table

BG range (mmol/l)	Insulin infusion rate (U/hr)
> 20.0	4
15.1 – 20.0	3
10.1 – 15.0	2
6.1 – 10.0	1
0 – 6.0	0

2.14.4 Control Algorithm Based on Rule-Based Control

Model-less approach to blood glucose control could also use expert rules (rules that are based on experience) as the control rules. They can be seen in clinical techniques, which include:

- Titration control, where the intravenous (IV) insulin infusion rate is started at an empirical level, and progressively tuned to an appropriate rate which lowered and maintained the BG in the target range;
- Variable-rate IV insulin infusion algorithm, where insulin rates are increased/decreased by 0.5 U/hr (or remain unchanged) every 2 hours, based on the BG measurement. This method is similar to a sliding table, except that the insulin rates are given in terms of increment or decrement to the previous rate, instead of a fixed insulin rate for each BG ranges. Proposed by Watts et al [20] to maintain BG in patients within a certain range, this method was reported to be safe and efficacious [14];
- Experience, where control is achieved by means of accumulated experiences in controlling glucose level;
- Neuro-fuzzy method, where insulin rates are increased/decreased every 4 hours, based on a simple nomogram (similar to a look-up table). The nomogram details the insulin infusion rate variation to be added or subtracted from the current rate based on “preceding” and “present” BG values. The nomogram is obtained by training a Back Error Propagation Neural Network using 1000 paired BG–insulin values, and then providing the neural network with 400 pairs of BG values that represents every possible combination of glycaemic values between 3.3 and 13.9 mmol/l to obtain 400 corresponding variations of the insulin infusion rates [29].

2.14.5 Control Algorithm Based on PID Control

Proportional-Integral-Derivative control (or any combination of P, I or D) is an easy-to-use feedback control system. It does not require advanced

mathematics to design and can be easily “tuned”. The controller takes a measurement from a plant process and compares it with a set point (reference) value. The difference (or “error” signal) is then used to adjust the input to the plant in order to bring the measured value back to its desired set point (Figure 2.6). PID controller can adjust process outputs based on the history and rate of change of the error signal.

However, PID controller are sensitive to dead-time in the measurement (i.e. delay in measurement could upset the control action, bringing the control loop into possible oscillations).

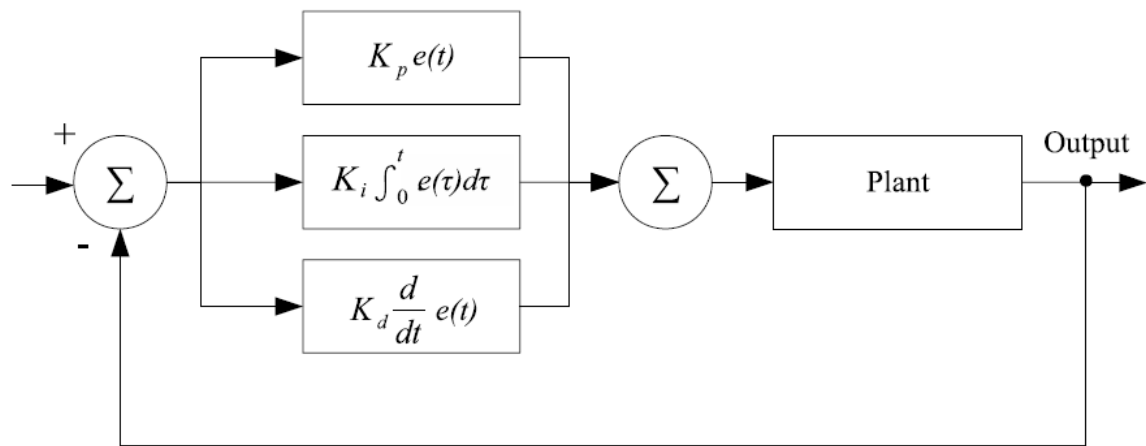


Figure 2.6 PID controller

- Proportional (P): The error signal is multiplied by a constant K_p for immediate correction.
- Integral (I): To learn from the past, the error signal is integrated (added up) over a period of time, and then multiplied by a constant K_i . The result is then added to the controller output signal.
- Derivative (D): The slope of the error signal (i.e. the change of the error signal over a pre-defined interval) is calculated, and multiplied by a constant K_d , and the result is added to the controller output signal.

2.15 Model-Based Control Algorithms

As the name implies, the model-based approach involves the use of a model in the control of blood glucose level. This model is the human glucose-insulin interaction.

If this complex interaction can be captured and described in terms of mathematics, then the glucose control problem becomes a mathematical problem, and mathematical problem can be solved using various mathematical techniques.

Other advantages of using a model:

- It offers useful description and insight into the underlying process. For example, the observations obtained from accessible variables (e.g. glucose at tissue) can be used to measure those system quantities that are of interest, but were inaccessible to direct measurement (e.g. glucose at hepatic artery).
- It can help in predicting overall system behavior under a variety of perturbations [34]. In another word, it can serve to determine how a system would respond to a stimulus or changes in the system.
- It allows the testing or simulation of the control algorithm to be performed without involving real patients.
- It allows the study into the effect of insulin therapy regime to be undertaken without risking patient safety.

The mathematical model used in BG regulation can be divided into two groups:

2.15.1 Theoretical

Theoretical modelling attempts to model the underlying process by means of a theory. The theory is derived using the knowledge about the function or structure of the underlying system, chemical process, physical laws, and quantitative data (from observable measurements).

The extent to which a pure theoretical model can be derived depends on current understanding of the system or process. It may not always be possible to fully model the underlying process, either due to a lack of measurable variables, or simply lack of detailed knowledge about the system.

2.15.2 Empirical + Theoretical

In metabolic system, it is rare to have adequate detailed knowledge of the underlying system to allow full derivation of the theoretical models.

Hence, a combination of theoretical and empirical knowledge is used.

Certain parts of the system are modelled empirically, whereas others are modelled theoretically. We could postulate about the internal structure of a system based on empirical observation, and fit the hypothesis to the observation.

When deriving the glucose-insulin model, one could conceptualize the model based on

- Physiological knowledge of the system,
- Functional description of the relevant processes
- The interconnection between the processes, and
- Relationship between the processes to the observable glucose (or insulin) measurements in practical situation.

2.16 Mathematical Models of Gluco-regulatory System

The attempts to capture the glucose-insulin mechanism have resulted in the formulation of various glucose-insulin kinetic models. These models range from simple expressions that relate glucose and insulin, to very complete mathematical models. The three general groupings of mathematical models are:

1. Linear
2. Non linear
3. Comprehensive

2.16.1 Linear Models

Linear models are adequate when the intrinsic dynamics of the metabolic system are essentially linear. In linear modelling of glucose-insulin kinetics, the models are described by linear time-invariant equations:

$$\dot{\mathbf{x}}(t) = A\mathbf{x}(t) + B\mathbf{u}(t) \quad (2.1)$$

$$y(t) = C\mathbf{x}(t) + D\mathbf{u}(t); \quad t_0 < t < T \quad (2.2)$$

where the state variable $\mathbf{x}(t)$ and its derivative appear in linear combination only, and $\mathbf{u}(t)$ represents the input (or disturbances) into the system.

Models of glucose-insulin kinetics can be derived using technique like “compartmental analysis”.

Compartmental Analysis

Compartmental analysis is the simplest method in biomathematics to describe the transfer of materials in biological systems, and it can quickly lead to mathematical relationships.

A compartment is fundamentally an idealized store of a substance. Compartmental analysis consists of studying the exchanges of matter between the stores (i.e. compartments) as a function of time, t . The material exchange between compartments takes place either by physical transport from one location to another, or by chemical reactions (Figure 2.7). The mathematical model then consists of the mass balance equations for each compartments and relations describing the rate of material transfer between compartment:

$$\frac{dQ_{ij}}{dt} = \sum R_{ij} - \sum R_{ji} \quad (2.3)$$

where Q_{ij} = quantity of substance in compartment i that interchanges matter with other compartments; $\sum R_{ij}$ = summation of the rates of mass transfer into compartment i from all relevant compartments; $\sum R_{ji}$ = summation of

the rates of mass transfer from compartment i to other compartments of the system.

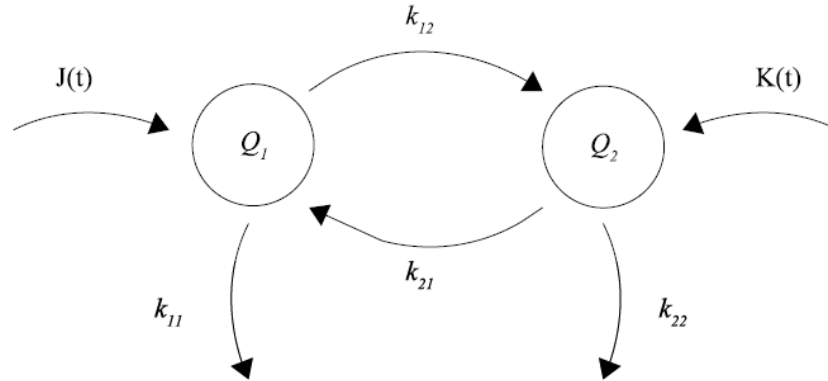


Figure 2.7 Compartmental analysis

For example, consider two compartments 1 and 2. Figure 3.3 shows the flow of material between the two compartments. K_{ij} indicates the rates at which the materials in i is transferred to compartment j and vice versa.

Let $Q_1, Q_2 =$ quantity of materials in compartment 1 and 2 respectively, and $J(t), K(t) =$ flow of material from exogenous sources, the mass balance equations can be written as follows:

$$\frac{dQ_1}{dt} = -k_{11}Q_1 - k_{12}Q_1 + k_{21}Q_2 + J(t) \quad (2.4)$$

$$\frac{dQ_2}{dt} = k_{12}Q_1 - k_{21}Q_2 - k_{22}Q_2 + K(t) \quad (2.5)$$

which can be simplified to:

$$\frac{dQ_1}{dt} = -m_1Q_1 + k_{21}Q_2 + J(t) \quad (2.6)$$

$$\frac{dQ_2}{dt} = k_{12}Q_1 - m_3Q_2 + K(t) \quad (2.7)$$

where $m_1 = k_{11} + k_{12}$ and $m_3 = k_{21} + k_{22}$

2.16.2 Ackerman's Linear Model

There are many linear models proposed in the literature to-date. Among them, Ackerman's model has been by far the most commonly cited linear model. Ackerman's model consists of a system of equations in which the

parameters have been lumped into two dependent variables, G and H , and four rate constants [3]:

$$\frac{dg}{dt} = -m_1g - m_2h + J \quad (2.8)$$

$$\frac{dh}{dt} = -m_3h + m_4g + K \quad (2.9)$$

where G = glucose concentration; G_0 = fasting glucose concentration; $g \equiv G - G_0$; H = blood hormone concentration (including insulin).

This is the effective hormone concentration which included consideration of the role of epinephrine and other hormone; H_0 = fasting blood hormone concentration (including insulin); $h \equiv H - H_0$

The rate constants are:

- m_1 = rate constant for the removal of glucose above the initial fasting level due to its own excess above the initial level. Also known as glucose effectiveness, this term normally has a value of 0.01–0.02/min but it is likely that its true value is reduced at chronic hyperglycemia due to glucose toxicity;
- m_2 = rate constant for the removal of glucose above the initial level due to blood hormone concentration above the initial level has a value of 0.0031/min;
- m_3 = rate constant for the removal of hormone above the initial fasting level due to its own excess above the initial level (duration of insulin action) has a value of 0.0415/min;
- m_4 = rate constant for the removal of hormone above the initial level due to blood glucose concentration above the initial level equal to zero.

2.16.3 Non-linear and Comprehensive Models

The linear model has the disadvantage that it is a gross oversimplification of the underlying glucose-insulin interaction in actual human (which is far more complex than the linear model). Biological system dynamics are often non-

linear in nature, and low-order models may not adequately describe the real process and therefore could contain both unacceptable levels of modelling error and significant process-model mismatch [35].

2.16.4 Minimal Model

Also known as Bergman's model, the minimal model was proposed by Bergman et al [36] in the early 1980's for the interpretation of glucose and insulin plasma concentrations following the intravenous glucose tolerance test (IVGTT). This model has been popular among past physiological researches on the metabolism of glucose.

It is composed of two parts:

1. Minimal model for glucose disappearance: Two differential equations which describe the glucose plasma concentration time-course, accounting for the dynamics of glucose uptake dependent on, and independent of circulating insulin. It treated insulin plasma concentration as a known forcing function [201].

$$\frac{dG(t)}{dt} = -(p_1 + X(t)) G(t) + p_1 G_B \quad (2.10)$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3 [I(t) - I_B] \quad (2.11)$$

where the term $p_1 G_B$ accounts for the body's natural tendency to move towards basal glucose levels [37].

2. Minimal model for insulin kinetic: Single equation which describes the time-course of plasma insulin concentration, accounting for the dynamics of pancreatic insulin release in response to the glucose stimulus. The glucose plasma concentration is to be regarded as a known forcing function.

$$\frac{dI(t)}{dt} = \begin{cases} \gamma[G(t) - h]t - n[I(t) - I_B] & \text{for } G(t) - h > 0 \\ -n[I(t) - I_B] & \text{for } G(t) - h \leq 0 \end{cases} \quad (2.12)$$

where the state variables:

- $G(t)$ [mg/dl] = the blood glucose concentration at time t [min];
- $I(t)$ [μ U/ml] = blood insulin concentration at time t [min];
- $X(t)$ [min^{-1}] = a function representing insulin-excitabile tissue glucose uptake activity, proportional to insulin concentration in a “distant” compartment;
- G_B [mg/dl] = the subject’s basal glucose level (or pre-injection value of glucose concentration);
- I_B [μ U/ml] = the subject’s basal insulin level (or pre-injection value of insulin concentration);
- G_o [mg/dl] = the theoretical glucose level at time 0 after the instantaneous glucose bolus, i.e. glucose concentration that would be obtained immediately after glucose injection if there were instantaneous mixing of glucose in the extracellular fluid compartment [38].

The parameters are:

- γ [$(\mu\text{U/ml})/(\text{mg/dl})^{-1}\text{min}^{-1}$] = the rate of pancreatic release of insulin after the bolus, per minute and per mg/dl of glucose concentration above the “target” glycaemia;
- h [mg/dl] = the pancreatic “target glycaemia” [39]. It is a threshold value such that only glucose level above h will effect a secretion of insulin [41]. It represents the critical value of plasma glucose at which glucose begins to have a marked influence on the magnitude of the second phase;
- n [min^{-1}] = the time constant for insulin disappearance [36], or fractional disappearance rate constant for endogenous insulin [40];
- I_o [μ U/ml] = the theoretical plasma insulin concentration at time 0, above basal insulinemia, immediately after the glucose bolus.

The two parts are to be separately estimated on the available data. That is, the model parameter fitting has to be done in two steps:

1. Using the recorded insulin concentration as input data, in order to derive the parameters in the first two equations.
2. Then, using the recorded glucose as input data to derive the parameters in the third equation.

The glucose and insulin recordings are obtained by first injecting a bolus of glucose into the bloodstream of the experimental subject, to induce an (impulsive) increase in the plasma glucose concentration $G(t)$ and a corresponding increase of the plasma insulin concentration $I(t)$, secreted by pancreas. These concentrations are measured during a three-hour time interval beginning at injection, until $G(t)$ and $I(t)$ have returned to normal [39].

To represent a person in a diabetic state, the original model has taken the general form:

$$\frac{dG(t)}{dt} = -(p_1 + X(t)) G(t) + p_1 G_B + p(t) \quad (2.13)$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3 [I(t) - I_B] \quad (2.14)$$

$$\frac{dI(t)}{dt} = -n[I(t) - I_B] + u(t) \quad (2.15)$$

where endogenous insulin secretion (i.e. the term $\gamma[G(t) - h]t$) in equation 2.12 was removed, and a term of exogenous infusion of glucose $p(t)$ and insulin $u(t)$ was added.

2.16.5 Cobelli's Model

Cobelli et al's model consists of a metabolic plant (glucose), and two-hormone controller (insulin and glucagon) [42]. The glucose subsystem is described by a one-compartment model of distribution and metabolism (extracellular fluids), involving net hepatic glucose balance (i.e. the difference between liver glucose production and liver uptake), renal excretion of glucose, insulin-dependent glucose utilization (mainly by muscle and

adipose tissue), insulin-independent glucose utilization (mainly by the central nervous system and the red blood cell).

Glucose Subsystem

$$\begin{aligned} \dot{x}(t) &= \text{NHGB}(x_1, u_{12}, u_2) - F_3(x_1) - F_4(x_1, u_{13}) - F_5 I_x(t), \\ x_1(0) &= x_{10} \end{aligned} \quad (2.16)$$

$$\dot{u}_{1p}(t) = -k_{21}u_{1p} + k_{12}u_{2p} + W(x_1), \quad u_{1p}(0) = u_{1p0} \quad (2.17)$$

$$\dot{u}_{2p}(t) = k_{21}u_{1p} - (k_{12} + k_{02}(x_1))u_{2p}, \quad u_{2p}(0) = u_{2p0} \quad (2.18)$$

where

$\text{NHGB} = F_1(x_1, u_{12}, u_2) - F_2(x_1, u_{12})$ is the net hepatic glucose balance;

F_1 = the liver glucose production;

F_2 = the liver glucose uptake;

F_3 = the renal excretion;

F_4 = the peripheral insulin-dependent glucose utilization;

F_5 = the peripheral insulin-independent glucose utilization;

$I_x(t)$ is the rate of exogenous glucose given intravenously;

$W(x_1)$ = insulin synthesis controlled by BG concentration;

x_1 = quantity of glucose in plasma and extracellular fluids [mg];

u_{1p} = quantity of pancreatic stored insulin [μU];

u_{2p} = quantity of pancreatic, promptly releasable insulin [μU].

The constants are $k_{12}=0.01$, $k_{21}=4.34 \times 10^{-3}$ (values for a normal state).

Liver glucose production

$$F_1(x_1, u_{12}, u_2) = a_{11}G_1(u_2)H_1(u_{12})M_1(x_1) \quad (2.19)$$

where

$$G_1(u_2) = 0.5 \{1 + \tanh[b_{11}(e_{21} + c_{11})]\} \quad (2.20)$$

$$H_1(u_{12}) = 0.5 \{1 - \tanh[b_{12}(e_{12} + c_{12})]\} \quad (2.21)$$

$$M_1(x_1) = 0.5 \{1 - \tanh[b_{13}(e_x + c_{13})]\} \quad (2.22)$$

Baseline parameter values for a normal state: $a_{11} = 1.51$; $b_{11} = 2.14$; $b_{12} = 0.0728$; $b_{13} = 0.0275$; $c_{11} = -0.85$; $c_{12} = 7$; $c_{13} = 20$.

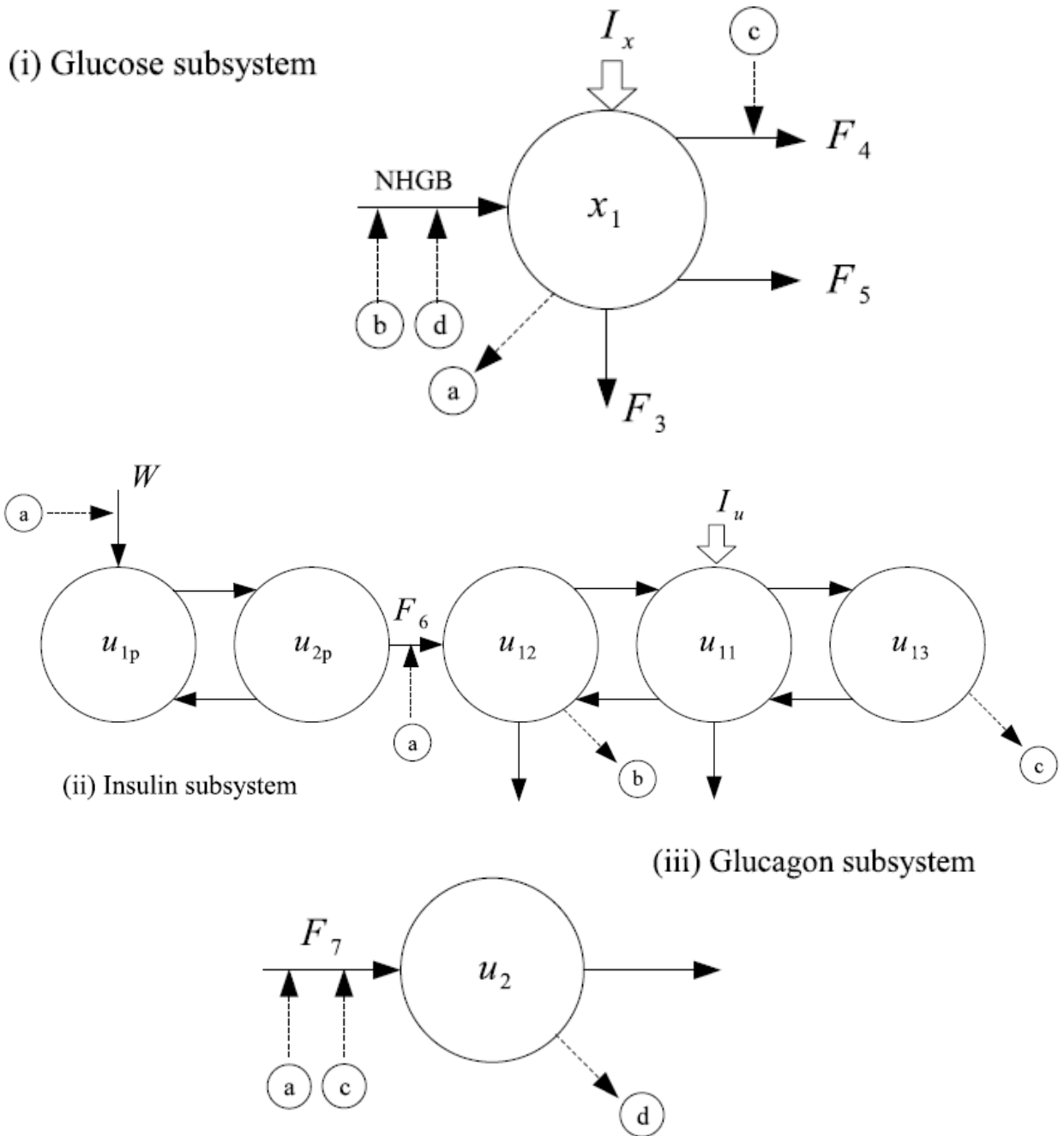


Figure 2.8 Cobelli et al's compartmental model. Solid line represents material flow; Dashed line represents control signal

- Liver glucose uptake

$$F_2(x_1, u_{12}) = H_2(u_{12})M_2(x_1)$$

$$H_2(u_{12}) = 0.5\{1 - \tanh[b_{21}(e_{12} + c_{12})]\}$$

$$M_2(x_1) = a_{221} + a_{222} 0.5 \{1 + \tanh[b_{22}(e_x + c_{22})]\}$$

Baseline parameter values for a normal state: $a_{221}=0.00195$; $a_{222}=0.00521$;
 $b_{21}=0.0111$; $b_{22}=0.0145$; $c_{12}=51.3$; $c_{22}=-108.5$.

- Renal excretion of glucose

$$F_3(x_1) = M_{31}(x_1)M_{32}(x_1)$$

where

$$M_{31}(x_1) = 0.5 \{1 + \tanh[b_{31}(y_1 + c_{31})]\}$$

$$M_{32}(x_1) = a_{321}y_1 + a_{322}$$

Baseline parameter values for a normal state: $a_{321}=1.43 \times 10^{-5}$; $a_{322}=-1.31 \times 10^{-5}$;
 $b_{31}=20$; $c_{31}=-180$.

- Insulin-dependent peripheral glucose utilization

$$F_4(x_1, u_{13}) = a_{41}H_4(u_{13})M_4(x_1)$$

where

$$M_4(u_{13}) = 0.5 \{1 + \tanh[b_{41}(e_{13} + c_{41})]\}$$

$$M_4(x_1) = 0.5 \{1 + \tanh[b_{42}(e_x + c_{42})]\}$$

Baseline parameter values for a normal state: $a_{41}=0.0287$; $b_{41}=0.031$;
 $b_{42}=0.0144$; $c_{41}=-50.9$; $c_{42}=-20.2$.

- Insulin-independent glucose uptake

$$F_5(x_1) = M_{51}(x_1)M_{52}(x_1)$$

where

$$M_{51}(x_1) = a_{51} \tanh[b_{51}(e_x + c_{51})]$$

$$M_{52}(x_1) = a_{52}e_x + b_{52}$$

Baseline parameter values for a normal state: $a_{51}=1.01 \times 10^{-3}$; $a_{52}=4.6 \times 10^{-6}$;
 $b_{51}=0.0278$; $b_{52}=4.13 \times 10^{-4}$.

Insulin Subsystem

The insulin subsystem is described by a five-compartment model, involving pancreatic insulin storage, liver and portal plasma insulin, plasma insulin and insulin in the interstitial fluid.

$$\begin{aligned}\dot{u}_{11}(t) &= -(m_{01} + m_{21} + m_{31})u_{11} + m_{12}u_{12} + m_{13}u_{13} + I_u(t), & u_{11}(0) &= u_{110} \\ \dot{u}_{12}(t) &= -(m_{02} + m_{12})u_{12} + m_{21}u_{11} + k_{02}(x_1)u_{2p}, & u_{12}(0) &= u_{120} \\ \dot{u}_{13}(t) &= -m_{13}u_{13} + m_{31}u_{11} & u_{13}(0) &= u_{130}\end{aligned}$$

where u_{11} = the quantity of insulin in plasma [μU]; u_{12} = the quantity of insulin in the liver [μU]; u_{13} = the quantity of insulin in the interstitial fluid [μU]; $I_u(t)$ = the insulin test input. The constants are $m_{01}=0.125$, $m_{02}=0.185$, $m_{12}=0.209$, $m_{13}=0.02$, $m_{21}=0.268$, $m_{31}=0.042$ (values for a normal state). The term $k_{02}(x_1)u_{2p} = F_6(u_{2p}, x_1)$ represents the insulin secretion rate.

- Insulin synthesis

$$W(x_1) = 0.5a_w \{ 1 + \tanh[b_w(e_x + c_w)] \}$$

Baseline parameter values for a normal state: $a_w=0.287$; $b_w=0.0151$; $c_w=-92.3$.

- Insulin secretion

$$F_6(u_{2p}, x_1) = 0.5a_6 \{ 1 + \tanh[b_6(e_x + c_6)] \} u_{2p}$$

Baseline parameter values for a normal state: $a_6=1.3$; $b_6=0.0923$; $c_6=-19.68$.

Glucagon Subsystem

The glucagon subsystem is described by a one-compartment model:

$$\dot{u}_2(t) = -h_{02}u_2 + F_7(x_1, u_{13}), \quad u_2(0) = u_{20}$$

where u_2 = the quantity of glucagon in the plasma and interstitial fluid [ng]; F_7 = the endogenous release of glucagon, dependent on BG and interstitial fluid insulin; $h_{02}=0.086$.

- Glucagon secretion

$$F_7(x_1, u_{13}) = a_{71}H_7(u_{13})M_7(x_1)$$

where

$$H_7(u_{13}) = 0.5 \{ 1 - \tanh[b_{71}(e_{13} + c_{71})] \}$$

$$M_7(x_1) = 0.5 \{ 1 - \tanh[b_{72}(e_x + c_{72})] \}$$

Baseline parameter values for a normal state: $a_{71}=2.35$; $b_{71}=6.86 \times 10^{-3}$; $b_{72}=0.03$; $c_{71}=99.2$; $c_{72}=40$.

W and $F_1 - F_7$ are nonlinear functions, m_{ij} , h_{ij} , and k_{ij} are constant rate parameters [min^{-1}] with the exception of k_{02} which is a function of x_1 .

CHAPTER III
SYSTEM MODEL

Chapter 3

System Model

This chapter concentrate about parameters used in this thesis, simulation, the operation of evaluation and modeling the project simulation tool.

3.1 Normal Subject

The model describing the glucose–insulin control system during a meal is shown in Figure 3.1. This section provides a brief overview of the model.

Continuous lines denote fluxes of material and dashed lines control signals. In addition to plasma glucose and insulin concentration measurements, glucose fluxes (i.e., meal rate of appearance, production, utilization, and renal extraction) and insulin fluxes (i.e., secretion and degradation)

The model is made up of a glucose and insulin subsystem linked by the control of glucose on insulin secretion and by insulin on glucose utilization and endogenous production.

The glucose subsystem consists of a two-compartment model of glucose kinetics: insulin-independent utilization occurs in the first compartment, representing plasma and fast equilibrating tissue, while insulin-dependent utilization occurs in a remote compartment, representing peripheral tissues.

The insulin subsystem also consists of two compartments, the first representing the liver and the second the plasma. The most important model unit processes are endogenous glucose production, glucose rate of appearance, glucose utilization, and insulin secretion.

Suppression of endogenous glucose production is assumed to be linearly dependent on plasma glucose concentration, portal insulin concentration, and a delayed insulin signal.

Key parameters are hepatic glucose effectiveness (glucose control on endogenous glucose production suppression) and hepatic insulin sensitivity (insulin control on endogenous glucose production suppression).

Glucose intestinal absorption describes the glucose transit through the stomach and intestine by assuming that the stomach is represented by two compartments (one for solid and one for triturated phases), while a single compartment is used to describe the gut; the rate constant of gastric emptying is a nonlinear function of the amount of glucose in the stomach.

Glucose utilization during a meal (both insulin independent and dependent) is made up of two components.

Insulin-independent utilization in the brain and erythrocytes takes place in the first compartment and is constant, whereas insulin-dependent utilization in muscle and adipose tissue takes place in the remote compartment and depends nonlinearly from glucose in the tissues.

Beta-cell insulin secretion is described by dynamic and static components. The dynamic component likely represents the release of promptly releasable insulin and is proportional to the rate of increase of glucose concentration through a parameter called dynamic beta-cell responsiveness.

The static component describes the provision of new insulin to the releasable pool and is proportional to a delayed glucose signal through a parameter called static beta-cell responsiveness [45].

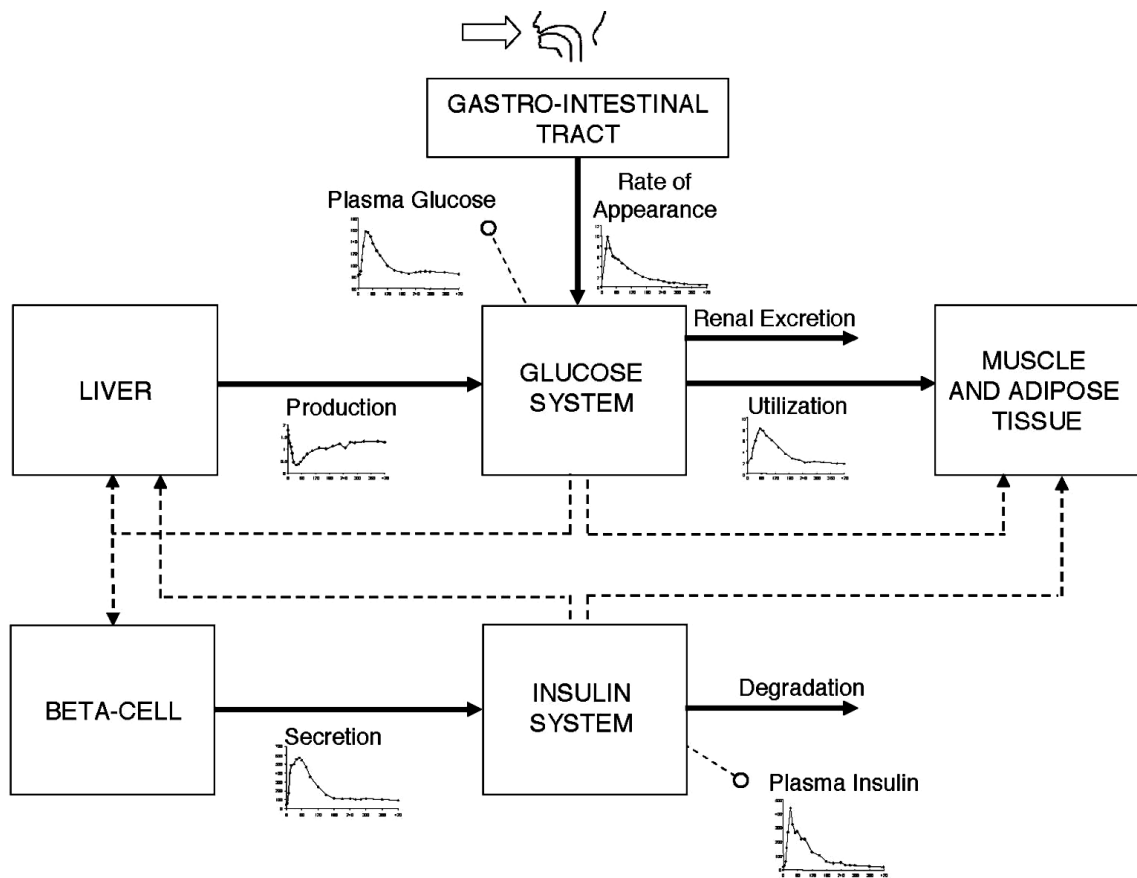


Figure 3.1 Scheme of the glucose–insulin control system

3.2 Tuning of PID Controllers

If a mathematical model of the plant can be derived, then it is possible to apply various design techniques for determining parameters of the controller that will meet the transient and steady-state specifications of the closed-loop system.

However, if the plant is so complicated that its mathematical model cannot be easily obtained, then an analytical or computational approach to the design of a PID controller is not possible. Then we must resort to experimental approaches to the tuning of PID controllers.

The process of selecting the controller parameters to meet given performance specifications is known as controller tuning.

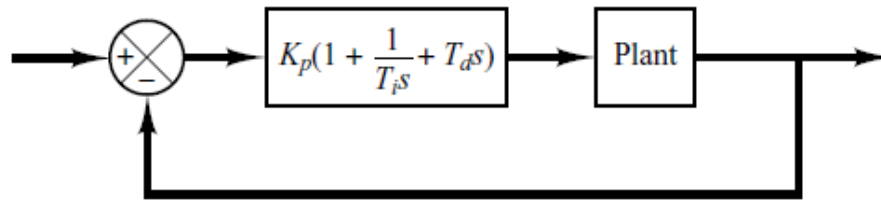


Figure 3.2 PID control of a plant

Ziegler and Nichols [5] suggested rules for tuning PID controllers (meaning to set values k_p , T_i and T_d) based on experimental step responses or based on the value of k_p that results in marginal stability when only proportional control action is used [43].

3.2.1 Ziegler–Nichols Rules for Tuning PID Controllers

Ziegler and Nichols proposed rules for determining values of the proportional gain k_p integral time T_i and derivative time T_d based on the transient response characteristics of a given plant. There are two methods called Ziegler–Nichols tuning rules: the first method and the second method.

First Method. In the first method, we obtain experimentally the response of the plant to a unit-step input. If the plant involves neither integrator(s) nor dominant complex-conjugate poles, then such a unit-step response curve may look S-shaped. This method applies if the response to a step input exhibits an S-shaped curve [43].

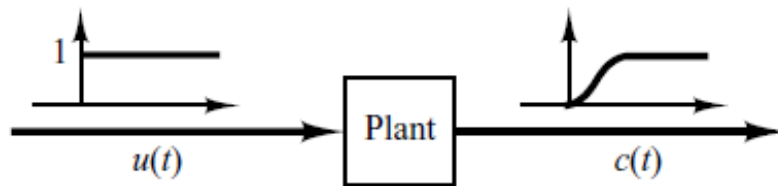


Figure 3.3 Unit-step response of a plant

The S-shaped curve may be characterized by two constants, delay time L and time constant T . The delay time and time constant are determined by drawing a tangent line at the inflection point of the S-shaped curve and

determining the intersections of the tangent line with the time axis and line $c(t) = K$.

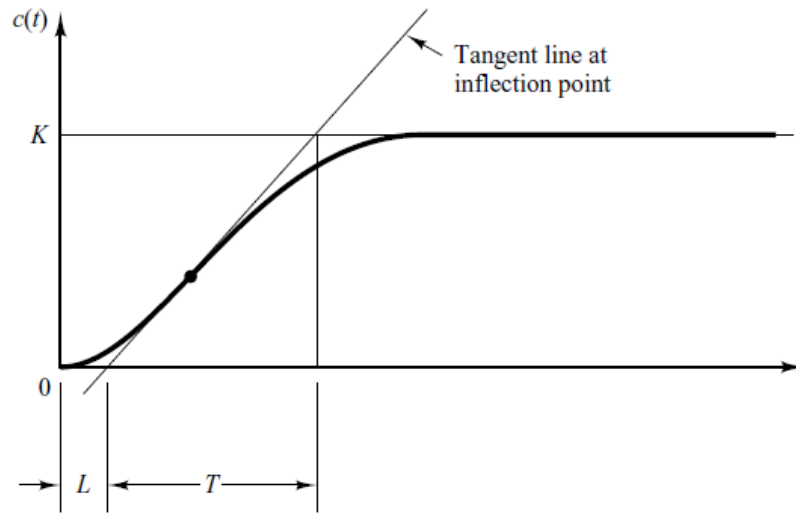


Figure 3.4 S-shaped response curve

Ziegler and Nichols suggested to set the values of k_p , T_i , and T_d according to the formula shown in Table 3.1.

Table 3.1 Ziegler–Nichols Tuning Rule Based on Step Response of Plant (First Method)

Type of Controller	k_p	T_i	T_d
P	$\frac{T}{L}$	∞	0
PI	$0.9 \frac{T}{L}$	$\frac{L}{0.3}$	0
PID	$1.2 \frac{T}{L}$	$2L$	$0.5L$

3.2.2 Cohen–Coon Tuning Method

Cohen-coon method is another tuning method of PID controller where using this tuning method the steady state response is minimum as given according to Ziegler Nichols method. The Cohen-Coon method is a more complex version of the Ziegler-Nichols method. The method is similar to the Ziegler-

Nichols method but the difference comes with the fact that Cohen-Coon provides the faster rise time [44].

Based on time constant and time delay the output response can be determined.

Table 3.2 Cohen–Coon Tuning method

Type of Controller	k_p	T_i	T_d
P	$\frac{1}{K} \frac{T}{\tau} \left(1 + \frac{\tau}{3T}\right)$		
PI	$\frac{1}{K} \frac{T}{\tau} \left(0.9 + \frac{\tau}{12T}\right)$	$\tau \frac{(30 + 3\tau/T)}{(9 + 20\tau/T)}$	
PID	$\frac{1}{K} \frac{T}{\tau} \left(\frac{4}{3} + \frac{\tau}{4T}\right)$	$\tau \frac{(32 + 6\tau/T)}{(13 + 8\tau/T)}$	$\tau \frac{4}{(11 + 2\tau/T)}$

3.2.3 Chien-Hrones-Reswick tuning method

This method was developed by Chien-Hrones-Reswick which gives a better way to select a compensator for control applications. There are basically two forms of CHR which are Chien- Hrone-Reswick (set point regulation) also known as CHR-1 and the Chien-Hrone-Reswick (disturbance rejection). According to Chien-Hrones-Reswick suggestion controller parameters are tuned in industry process. These controller parameters has 0% and 20% overshoot which is summarized in Table 3.3.

Table 3.3 Chien-Hrones-Reswick Tuning method set point regulation

Overshoot	0 %			20 %		
Type of Controller	k_p	k_i	k_d	k_p	k_i	k_d
P	$0.3a$			$0.7/a$		
PI	$0.35/a$	$1.2T$		$0.6/a$	T	
PID	$0.6/a$	T	$0.5L$	$0.95/a$	$1.4T$	$0.47L$

3.3 Mathematical Model of Blood Glucose Level

By considering the blood glucose equation of Ackerman's Linear Model, in order to obtain the differential equation, we use the MATLAB simulation to solve the differential equations.

We use the function `dsolve` to solve the differential equations because it gives the solution as a function in time domain, the solution of the equations has many terms, so we use another function `simplify` to simplify the solution and also in time domain.

Now we convert this equation into Laplace domain by using the function `laplace` transform, and also we use the function `simplify` to simplify the solution in a simple form.

The open loop transfer function of blood glucose level obtained is

$$G(s) = \frac{20s + 8}{100s^3 + 52s^2 + 3s} \quad (3.1)$$

The closed loop transfer function of blood glucose level obtained is

$$G(s) = \frac{20s + 8}{100s^3 + 52s^2 + 23s + 8} \quad (3.2)$$

The step response of blood glucose level of diabetic patient is shown in figure 3.5.

3.3 Step response of blood glucose of diabetic patient

Figure 3.2 shows the step response of blood glucose level of diabetic patient. This figure shows the blood glucose insulin system has taken more settling time to settle down to steady state, it means that system takes more time to reach steady state of the system, so we can use digital PID controller to overcome the steady state error and we can also get accurate step response with less rise time.

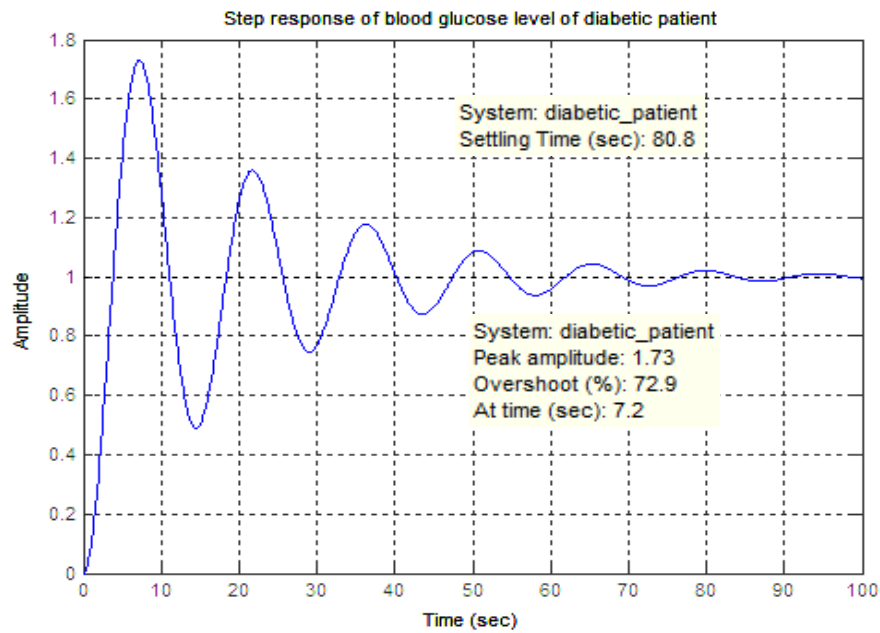


Figure 3.5 Step response of blood glucose of diabetic patient

The figure shows that the settling time is 80.8 sec and the overshoot value is 72.9 % so the performance of the system cannot be a good system for us.

The transfer function of blood glucose level in time domain is

$$G_c(s) = \frac{3.155 s^3 + 3.973 s^2 + 1.462 s + 0.1511}{s^4 + 3.675 s^3 + 4.003 s^2 + 1.462 s + 0.1511} \quad (3.3)$$

The discrete transfer function in z-domain with sampling time 0.5 sec is

$$G(z) = \frac{0.0082 z^3 - 0.0256 z^2 - 0.185 z - 0.0065}{z^3 - 2.764 z^2 + 2.536 z - 0.7711} \quad (3.4)$$

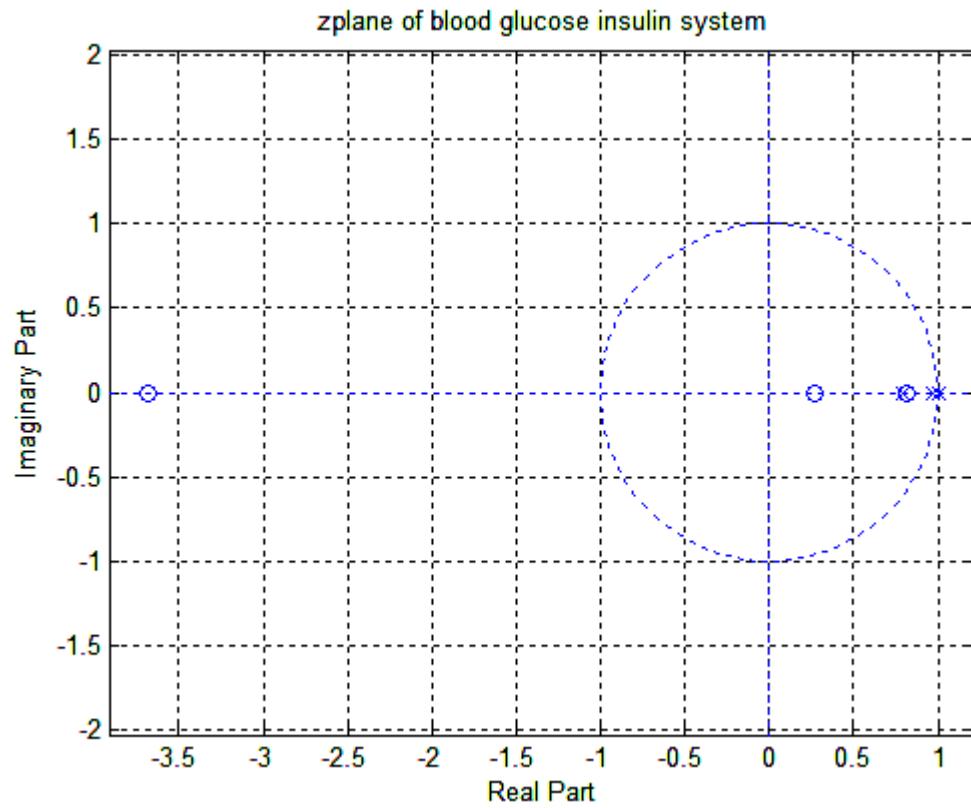


Figure 3.6 z-plane of blood glucose of diabetic patient

In which the zeros and poles are:

Zeros: $-3.678, 0.8187, 0.2639$.

Poles: $1, 0.9675, 0.797$.

Gain: 0.0082

CHAPTER IV
RESULTS AND DISCUSSIONS

Chapter 4

Results and Discussions

This chapter illustrates the results of the simulation after executing the program which is described in the previous chapter. Also, analysis and comment on these results has been described.

4.1 Tuning of PID controller by using Ziegler-Nichols

By applying the PID controllers on the blood glucose equation, we obtain the unit step response as in figure 4.1.

The value of PID parameters can be determined by using table 3.1.

$$k_p = 4.8, T_i = 3, T_d = 0.75.$$

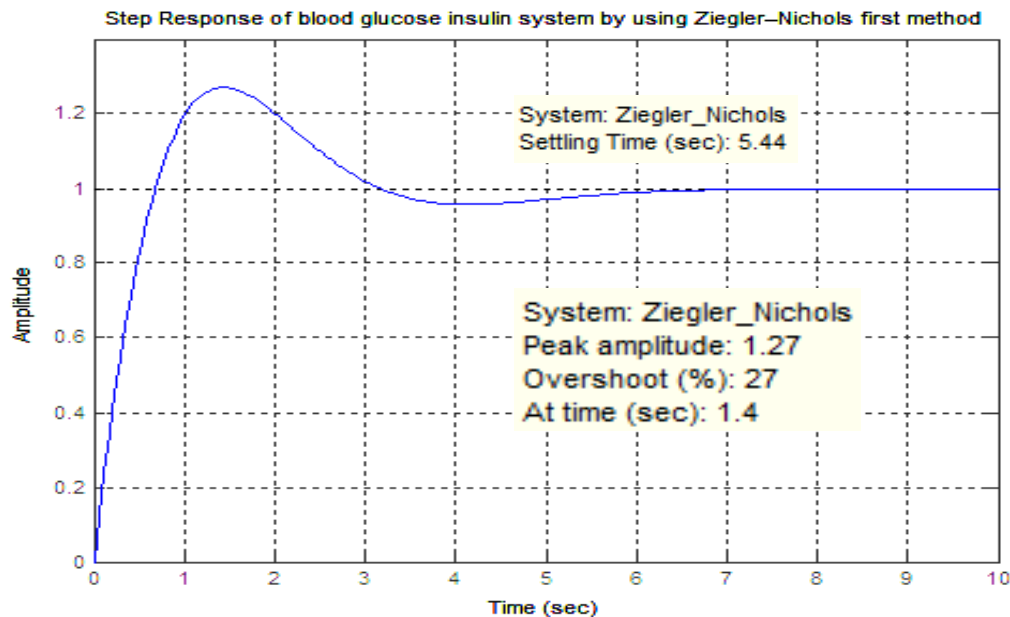


Figure 4.1 Step response of blood glucose insulin system by using Ziegler-Nichols

The figure shows that the settling time is 5.44 sec and the overshoot value is 27 % so the performance of the system is not say a good system for us.

The transfer function of Ziegler-Nichols method in time domain is

$$G_c(s) = \frac{2.16 s^3 + 3.744 s^2 + 2.112 s + 0.384}{s^4 + 2.68 s^3 + 3.774 s^2 + 2.112 s + 0.384} \quad (4.1)$$

The discrete transfer function in z-domain with sampling time 0.5 sec is

$$G_c(z) = \frac{0.8894 z^3 - 2.111 z^2 + 1.669 z - 0.4399}{z^4 - 2.664 z^3 + 2.624 z^2 - 1.135 z + 0.1827} \quad (4.2)$$

In which the zeros and poles are:

Zeros: 0.8189, 0.7329, 0.693.

Poles: 0.8265, 0.7764, 0.5465 + 0.3308*i*, and 0.5465 - 0.3308*i*.

Gain: 0.8239

Figure 4.2 shows z-plane of the system.

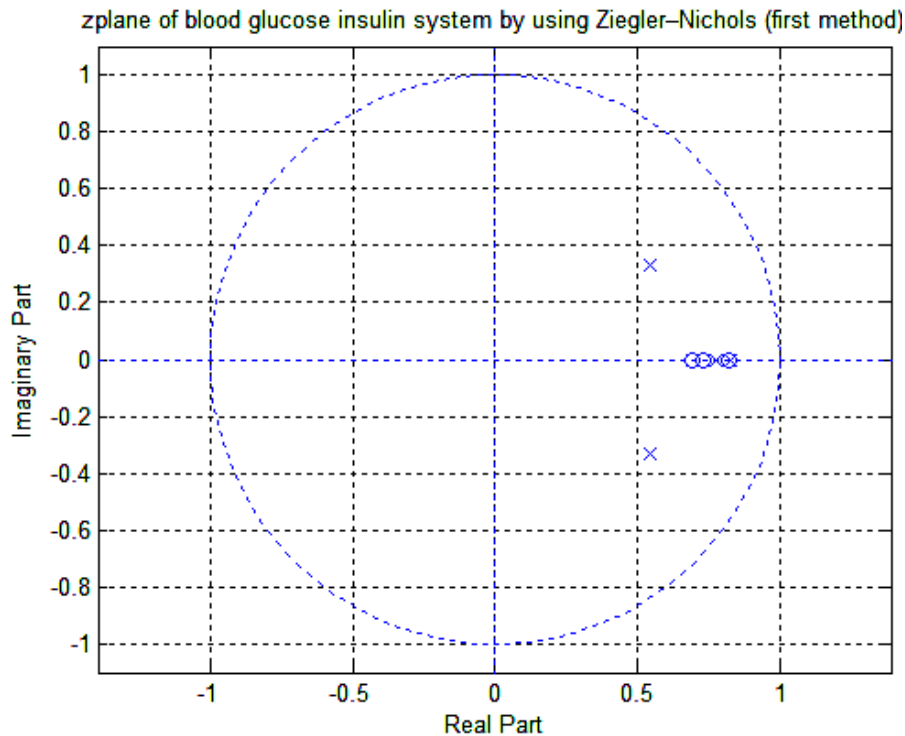


Figure 4.2 z-plane of blood glucose insulin system by using Ziegler-Nichols method

4.2 Tuning of PID controller by using Cohen-Coon method

By applying the PID controllers on blood glucose equation we obtain the unit step response as in figure 4.3.

The value of PID parameters can be determined by using table 3.2.

$$k_p = 1.8893, T_i = 7.1744, T_d = 1.1638.$$

The figure shows that the settling time is 3.72 sec and the overshoot value is 13.7 % so the performance of the system can be say a good system for us.

The transfer function of Cohen-Coon method in time domain is

$$G_c(s) = \frac{3.155 s^3 + 3.973 s^2 + 1.462 s + 0.1511}{s^4 + 3.675 s^3 + 4.003 s^2 + 1.462 s + 0.1511} \quad (4.3)$$

The discrete transfer function in z-domain with sampling time 0.5 sec is

$$G_c(z) = \frac{0.8989 z^3 - 2.196 z^2 + 1.778 z - 0.4773}{z^4 - 2.685 z^3 + 2.611 z^2 - 1.081 z + 0.1592} \quad (4.4)$$

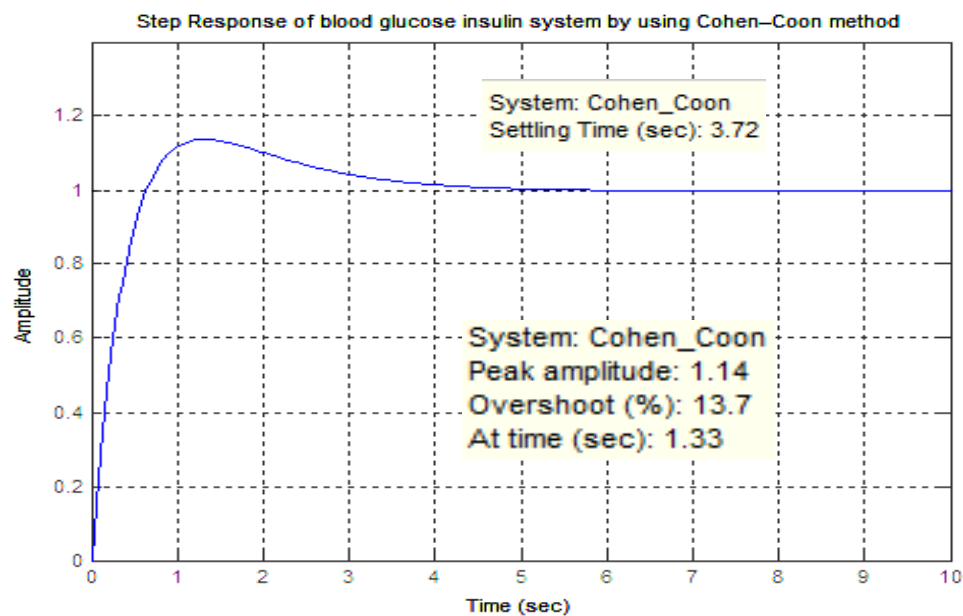


Figure 4.3 Step response of blood glucose insulin system by using Cohen-Coon method

In which the zeros and poles are:

Zeros: 0.708, 0.8168, 0.9162.

Poles: 0.3574, 0.5967, 0.8138, and 0.9173.

Gain: 0.8989

Figure 4.4 shows z-plane of the system.

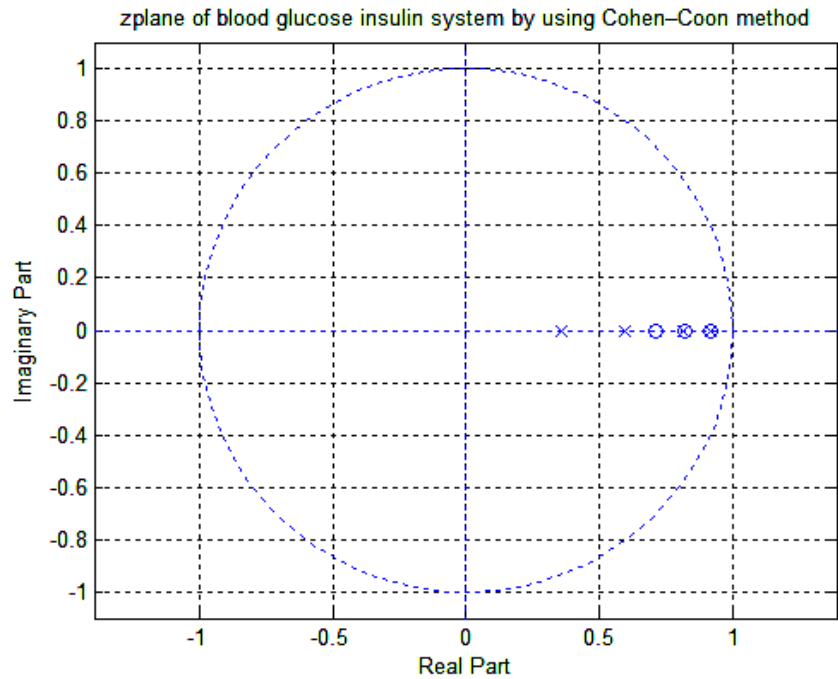


Figure 4.4 z-plane of blood glucose insulin system by using Cohen-Coon method

4.3 Tuning of PID controller by using Chien-Hrones-Reswick method

By applying the PID controllers on blood glucose equation we obtain the unit step response as in figure 4.5.

The value of PID parameters can be determined by using table 3.3.

$$k_p = 1.2, k_i = 7, k_d = 1.$$

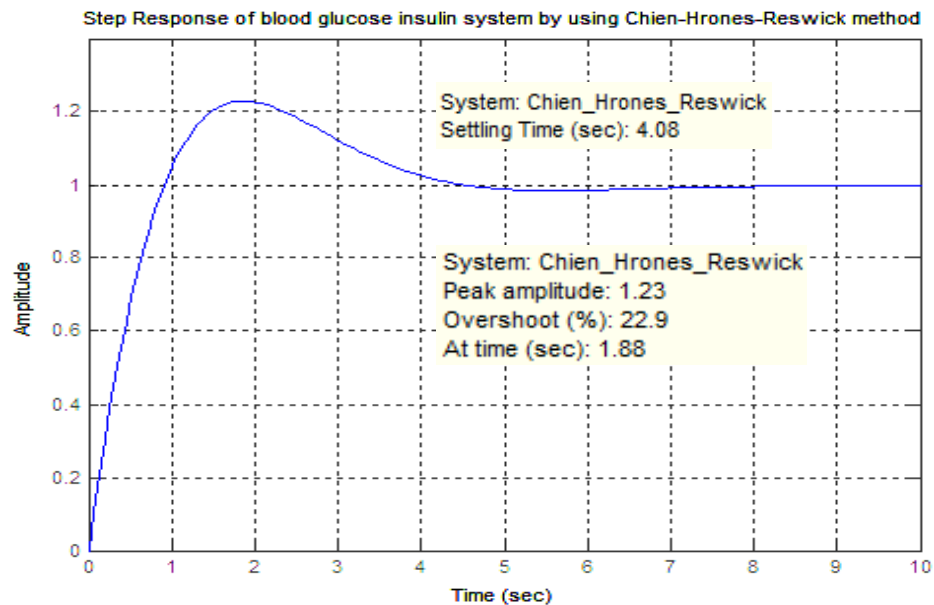


Figure 4.5 Step response of blood glucose insulin system by using Chien-Hrones-Reswick method

The figure shows that the settling time is 4.08 sec and the overshoot value is 22.4 % so the performance of the system is not good for us.

The transfer function of Chien-Hrones-Reswick method in time domain is

$$G_c(s) = \frac{1.68 s^3 + 2.352 s^2 + 0.912 s + 0.096}{s^4 + 2.20 s^3 + 2.382 s^2 + 0.912 s + 0.096} \quad (4.5)$$

The discrete transfer function in z-domain is by using Zero-Order hold with sampling time 0.5 sec is

$$G_c(z) = \frac{0.6738 z^3 - 1.613 z^2 + 1.275 z - 0.3325}{z^4 - 2.949 z^3 + 3.301 z^2 - 1.681 z + 0.3329} \quad (4.6)$$

In which the zeros and poles are:

Zeros: 0.6572, 0.8186, and 0.9173.

Poles: 0.9188, 0.813, $0.609 + 0.2733i$, and $0.609 - 0.2733i$.

Gain: 0.6738

Figure 4.6 shows z-plane of the system.

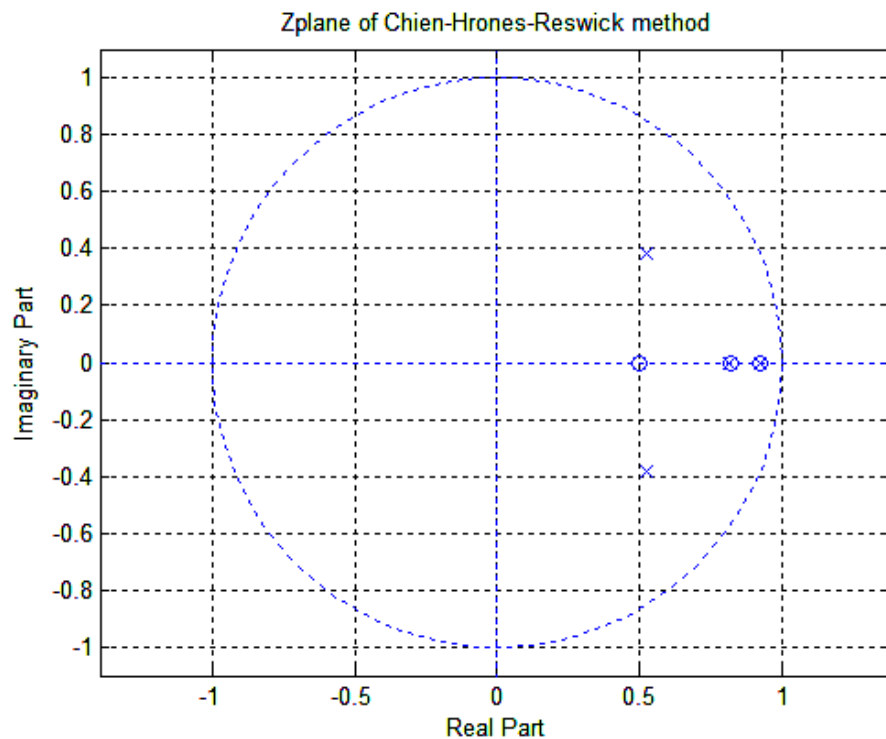


Figure 4.6 z-plane of blood glucose insulin system by using Chien-Hrones-Reswick method

CHAPTER V
CONCLUSION AND RECOMMENDATIONS

Chapter 5

Conclusion and Recommendations

The main ideas presented in the thesis are collected and summarized in this chapter and recommendation for future work.

5.1 Conclusion

In this thesis we designed the Digital PID controllers for blood glucose level of diabetic patient using various tuning algorithm.

The plots of time response characteristics of blood glucose level gave a very awful response without using tuning methods.

From the results it is obvious that Ziegler-Nichols method yields a very high overshoot where as Cohen-Coon method exhibits a low overshoot with a low settling time. The overshoot in blood glucose level controller may create sudden high insulin level and endanger the life of patient.

Similarly due to high settling time in Chien-Hrones-Reswick method the blood glucose level takes a very long time to maintain the steady state hence resulting in chances of life danger.

Finally these PIDs are converted into digital PIDs using various conversion methods. After tuning the PID it is essential to convert the analog PID to digital PID.

5.2 Recommendations

The work presented in this thesis can be extended and enhanced in some specific areas. There are different models of blood glucose level of diabetic patients, Linear Models, Bolie's Model, Minimal Model (Bergman's) and Cobelli's Model.

Further tuning of PID after implementation also become very easy and the system also becomes very accurate.

It is essential to convert the analog PID to digital PID as we known hardware implementation of digital PID is very easy in minimized area.

References:

- [1] Dan L. Longo, Anthony S. Fauci, Dennis L. Kasper, Stephen L. Hauser, J. Larry Jamenson, Joseph Loscalzo, Eugene Braunwald “Harrison’s principle of Internal Medicine”, 17th Edition textbook, 2008.
- [2] Kaveh, Parisa and Shtessel, Yuri, “Higher Order Sliding Mode Control for Blood Glucose Regulation”, IEEE International Workshop on Variable Structure Systems, pp. 11-16, June 2006.
- [3] Pinky Dua, Francis J. Doyle, and Efstratios N. Pistikopoulos, “Model-Based Blood Glucose Control for Type 1 Diabetes via Parametric Programming”, IEEE Transactions on Biomedical Engineering, vol. 53, pp. 1478-1491, August 2006.
- [4] Michael E. Fisher “A Semiclosed-Loop Algorithm for the Control of Blood Glucose Levels in Diabetics”, IEEE Transactions on Biomedical Engineering, vol. 38, pp. 57-61, January 1991.
- [5] Robert S. Parker, Francis J. Doyle, and Nicholas A. Peppas, “A Model-Based Algorithm for Blood Glucose Control in Type I Diabetic Patients”, IEEE Transactions on Biomedical Engineering, vol. 46, pp. 148-157 , February 1999.
- [6] R. Bellazi, G. Nucci, and C. Cobelli, “The subcutaneous route to insulin-dependent diabetes therapy”, IEEE Engineering in Medicine and Biology, vol. 20, pp. 54-64, Jan-Feb 2001.
- [7] R. Rao, C. Palerm, B. Aufderheide, and B. W. Bequette, “Automated regulation of hemodynamic variables”, IEEE Engineering in Medicine and Biology, vol. 20, pp. 24-38, Jan-Feb 2001.
- [8] Jameel Ahmed, Bilal A. Alvi, Zeeshan and Ali khan “Blood Glucose-Insulin Regulation and Management System Using MATLAB/SIMULINK”, IEEE International Conference on Emerging Technologies (ICET), pp. 304-308, October 2008.

- [9] Jiuqi Han, Peng Wang, and Xin Yang “Tuning of PID Controller Based on Fruit Fly Optimization Algorithm”, IEEE International Conference on Mechatronics and Automation, pp. 409-413, August 2012.
- [10] Anil kumar, Rekha Phadke, “Design of digital PID controller for Blood Glucose monitoring system”, International Journal of Engineering Research & Technology (IJERT), vol. 3, pp. 307-311, December-2014.
- [11] Sanaul Haque, Piplu Sony Paul, Md. Shaikh Ahmed, Md. Asif Uz Zaman, and Md. Abdul Mannan, “Performance Studies of Different Closed Loop Glucose Controllers for Treating Type 1 Diabetes Mellitus”, IEEE International Conference on Advances in Electrical Engineering (ICAEE), pp. 145-148, December 2015.
- [12] Rudy Bilous and Richard Donnelly, “Handbook of Diabetes”, John Wiley & Sons Ltd, 4th edition 2010.
- [13] J. Desemore, J.P. Mordes, and A.A. Rossini. “Hypoglycemia. In J.M. Rippe, R.S. Irwin, J.S. Alpert, and M.P. Fink, editors, Intensive Care Medicine 2nd Ed., chapter 99, pp. 1000-1009. Little, Brown and Company, 1991.
- [14] I.B. Hirsch and J.B. McGill, “Role of insulin in management of surgical patients with diabetes mellitus”, Diabetes Care, pp. 980-991, September 1990.
- [15] W.F. Ganong “Review of Medical Physiology”, Appleton & Lange, Stanford, Connecticut, 1997.
- [16] A.C. Guyton and J.E. Hall “Textbook of Medical Physiology”, W.B. Saunders Company, 9 edition, 1996.
- [17]. I.A. Macfarlane “The Millenia Before Insulin”, vol. 1, pp. 3-9. Blackwell Scientific Publications, 1991.
- [18] M. Bliss “The Discovery of Insulin”, vol. 1, pp. 10-14. Blackwell Scientific Publications, 1991.

- [19] B.A. Mizock “Alterations in carbohydrate metabolism during stress: A review of the literature”, *The American Journal of Medicine*, pp. 75-84, January 1995.
- [20] N.B. Watts, S.S.P. Gebhart, R.V. Clark, and L.S. Phillips. Postoperative management of diabetes mellitus: Steady-state glucose control with bedside algorithm for insulin adjustment. *Diabetes Care*, pp. 722-728, Nov-Dec 1987.
- [21] G. Van den Berghe, P. Wouters, F. Weekers, C. Verwaest, F. Bruyninckx, M. Schetz, D. Vlasselaers, P. Ferdinande, P. Lauwers, and R. Bouillon. “Intensive insulin therapy in critically ill patients”, *N Engl JMed*, pp. 1359-1367, 2001.
- [22] A.H. Clemens, P.H. Chang, and R.W. Myers, “The development of Biostator, a glucose-controlled insulin infusion systems (GCIIS)”, *Horm Metab Res Suppl*, pp. 23-33, March 1977.
- [23] J.P. Mordes and A.A. Rossini, “Management of diabetes in the critically ill patient”, In J.M. Rippe, R.S. Irwin, J.S. Alpert, and M.P. Fink, editors, “Intensive Care Medicine,” 2nd Ed., chapter 92, pages 955-962. Little, Brown and Company, 1991.
- [24] N.M. O’Meara and K.S. Polonsky. Insulin secretion in vivo. In C.R. Kahn and G.C. Weir, editors, *Joslin’s “Diabetes Mellitus”*, 13th Ed, chapter 5, pp. 81-96, Lea & Febiger, Malvern, Pennsylvania, 1994.
- [25] D. Elahi, “In praise of the hyperglycemic clamp”, *Diabetes Care*, pp. 278-286, 1996.
- [26] L.C. Ramirez and P. Raskin. “Pancreatic Abnormalities in Non-Insulin-Dependent Diabetes Mellitus”, volume 1, chapter 22, pp. 198-204, Blackwell Scientific Publications, 1991.
- [27] D.S. Bell, “Importance of postprandial glucose control”, *South Med. J.*, pp. 804-809, 2001.

- [28] B.C. Borlase, T.J. Babineau, R.A. Forse, S.J. Bell, and G.L. Blackburn. Enteral nutritional support, In J.M. Rippe, R.S. Irwin, J.S. Alpert, and M.P. Fink, editors, "Intensive Care Medicine", 2nd Edition, chapter 174, pp. 1669-1674, 1991.
- [29] D. Dazzi, F. Taddei, A. Gavarini, E. Uggeri, R. Negro, and A. Pezzarossa, "The control of blood glucose in the critical diabetic patient: A neuro-fuzzy method", *Journal of Diabetes and Complications*, pp. 80-87, 2001.
- [30] F. Chee, T. Fernando, and P.V. van Heerden, "Closed-loop glucose control in critically-ill patients using continuous glucose monitoring system (CGMS) in real time", *IEEE Trans. Inf. Tech. Biomed*, pp. 43-53, March 2003.
- [31] D.J. Chisolm, E.W. Kraegen, D.J. Bell, and D.R. Chipps, "A semi-closed loop computer-assisted insulin infusion system: Hospital use for control of diabetes in patients", *Med J Aust*, pp. 784-788, 1984.
- [32] N.H. White, D. Skor, and J.V. Santiago, "Practical closed-loop insulin delivery: A system for the maintenance of overnight euglycemia and the calculation of basal insulin requirements in insulin-dependent diabetes", *Ann Intern Med*, pp. 210-213, 1982.
- [33] S.M. Furler, E.W. Kraegen, R.H. Smallwood, and D.J. Chisolm, "Blood glucose control by intermittent loop closure in the basal mode: Computer simulation studies with a diabetic model. *Diabetes Care*", pp. 553-561, 1985.
- [34] E. R. Carson, C. Cobelli, and L. Finkelstein, "The Mathematical Modelling of Metabolic and Endocrine Systems - Model Formulation, Identification", and Validation, volume 2 of *Biomedical Engineering and Health Systems*. John-Wiley and Sons, 1983.
- [35] F.J. Doyle III, C. Dorski, J. Harting, and N.A. Peppas, "Control and modelling of drug delivery devices for the treatment of diabetes", *American*

Conference, volume 1, pp. 776-780, Seattle, Washington, USA, 21-23 June 1995, IEEE.

[36] R. N. Bergman, L. S. Phillips, and C. Cobelli, "Physiological evaluation of factors controlling glucose tolerance in man", *Journal of Clinical Investigation*, pp. 1456-1467, December 1981.

[37] R.L. Ollerton, "Application of optimal control theory to diabetes mellitus", *Int. J. Control*, pp. 2503-2522, 1989.

[38] M. Ader, G. Pacini, Y.J. Yang, and R. Bergman, "Importance of glucose per se to intravenous glucose tolerance", *Diabetes*, pp. 1093-1103, 1985.

[39] A. De Gaetano and O. Arino, "Mathematical modeling of the intravenous glucose tolerance test", *Journal of Mathematical Biology*, pp. 136-168, 2000.

[40] G. Toffolo, R. N. Bergman, D. T. Finegood, C. R. Bowden, and C. Cobelli, "Quantitative estimation of beta cell sensitivity to glucose in the intact organism a minimal model of insulin kinetics in the dog. *Diabetes*", pp. 979-990, December 1980.

[41] F. J. Vega-Catalan, "A program to estimate insulin sensitivity and pancreatic responsivity from an IVGTT using the minimal modeling technique," *Computers and Biomedical Research*, pp. 1-9, 1990.

[42] C. Cobelli and A. Mari, "Control of diabetes with artificial systems for insulin delivery algorithm independent limitations revealed by a modeling study", *IEEE Transaction on Biomedical Engineering*, pp. 840-845, 1985.

[43] Katsuhiko Ogata, "Modern Control Engineering", Prentice Hall, Fifth Edition, 2010.

[44] Amit kumar, K.K Garg, "Comparison of Ziegler-Nichols, Cohen-Coon and Fuzzy Logic Controllers for Heat Exchanger Model", *International Journal of Science, Engineering and Technology Research (IJSETR)*, Volume 4, Issue 6, June 2015.

[45] Chiara Dalla Man, Davide M. Raimondo, Robert A. Rizza, and Claudio Cobelli, “GIM, Simulation Software of Meal Glucose–Insulin Model”, *Journal of Diabetes Science and Technology*, Vol. 1, Issue 3, May 2007.