A Thesis

entitled

Modeling and Design of Suboptimal LQR Controller For Response of Parathyroid Hormone to Change in Calcium

by

Pramod Sapkota

Submitted to the Graduate Faculty as partial fulfillment of the requirements for the Master of Science Degree in Electrical Engineering

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An Abstract of

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Modeling and design of complex systems such as physiological and biological systems are challenging work. Calcium homeostasis is one of the complex biological systems which is pivotal for maintaining normal human physiology. It is an interconnected network of several sub-systems that involves interactions between numerous cells, tissues, organs, and hormones that operate on different time scales in the range of minutes to days. This work is centralized on developing a nonlinear mathematical model of a particular subsystem that relates change of concentration of parathyroid hormone (PTH) to change in calcium in human blood plasma, and designing an optimal linear controller to regulate this sub-system. The dynamics of the Calcium-Parathyroid sub-system is modeled as a set of nonlinear differential equations. Linearization of the model is around a nominal steady-state operating point is performed using Pearson's method.

In this thesis, a linear quadratic regulator (LQR) control method modified with a proportional non zero setpoint controller is applied to the linearized model. The internal stability of the system is checked using Routh-Hurwitz stability criteria. The mathematical model and controller are simulated using MATLAB and Simulink. The simulation results indicated that a modified LQR controller with a non-zero set-point controller was the appropriate controller for the model. Parameters for two different pathological conditions: healthy conditions and unhealthy IDDM (Insulin-Dependent Diabetes Mellitus) conditions,

were implemented. Simulation results reflected the effectiveness of the optimized control system.

Starting with unit values, the elements of the performance index weighting matrices were tuned. The use of the tuning method was effective to obtain a state and control response within the design characteristics of rise time, fall time, and steady-state values. The implementation of the optimal controller technique in the system performance demonstrated that the required control energy was minimized.

For my parents hard work and dedication

Acknowledgments

First and foremost I would like to express my most sincere gratitude to my advisor, Professor Dr. Richard Molyet, for his continuous encouragement, guidance, and support throughout my research and thesis. His depth knowledge, valuable mentorship and constructive feedback with all the freedom and necessary resources help me to accomplish this thesis on time.

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Contents

List of Tables

List of Figures

List of Abbreviations

CaSR	Calcium Sensing Receptors
CTL	Calcitriol
IDDM	Insulin- Dependent Diabetes Mellitus
LQR	Linear Quadratic Regulator
LTI	Linear Time Invariant
mmol	mili mole
NZSP	Non-Zero Set Point
PI	Proportional Integral
PID	Proportional Integral Derivative
PTH	Parathyroid Hormone
SISO	Single Input Single Output

List of Symbols

x_1	Concentration of Parathyroid hormone (PTH) in the gland/cell
x_{1s}	Steady State Concentration of Parathyroid hormone (PTH) in the cell
x_2	Concentration of Parathyroid hormone (PTH) in the blood plasma
x_{2s}	Steady State Concentration of Parathyroid hormone (PTH) in the blood plasma
k_p	Constant self-production rate of PTH in the parathyroid gland
k_s	Secretion rate of PTH that depends on plasma calcium concentration
l_1	Decay or loss of PTH in the parathyroid cells
l_2	Loss of PTH in the blood plasma
A	System matrix
B	Input Matrix
C	Output Matrix
D	Feed-forward matrix
PTH	Parathyroid Hormone
PTG	Parathyroid Gland
Ca	Calcium Concentration
Ca^{++}	Ionized Calcium
Q	State Weighting Matrix
R	Controller Weighting Matrix
K_p	Proportional Gain
k_i	Integral Gain
K_d	Derivative Gain
k_{ss}	Steady State Concentration of Secretion of PTH

J_x . . . . . Jacobian Matrix of State Matrix
J_u . . . . . Jacobian Matrix of Input Matrix

u . . . . . Control Vector
x . . . . . State Vector

Chapter 1

Introduction

1.1 Background and Motivation

Calcium homeostasis is defined as a complex biological mechanism that maintains a constant concentration of plasma calcium (Ca++) in the extracellular fluid. The stable concentration of plasma calcium is regulated within a required normal physiologic range with control of fluxes of calcium between different organs involved in calcium homeostasis. In the human body, maintenance of stable plasma calcium is important as it plays a crucial role in many biological activities such as transmission and conduction of nerves, the formation of blood, cell growth, regulation of cardiac activity, formation and remodeling of bone, and secretion of hormones [3][26]. Abnormalities and disorders of calcium homeostasis give rise to several pathological implications in the human body such as hypocalcemia, hypercalcemia, and several bone diseases such as osteoporosis. When the serum level of calcium is below the normal physiological range, the parathyroid gland releases the PTH hormone which then binds with the receptors of the intestine, bone, and kidney. This process stimulates the level of calcium to the required normal range. Similarly, the opposite phenomenon occurs when the serum level of calcium rises above the normal range, the inhibition of PTH hormone takes place [4][26]. As a result, serum calcium decreases to the normal range.

Calcium homeostasis system consists of several numbers of smaller sub-systems where

interactivity and reactions of those sub-systems occur frequently. These interactions of the subsystems of the calcium homeostasis take place at different scales of time from seconds to weeks. [26]. As a result, it becomes impractical to keep track of all the interactions and disturbances of these subsystems using traditional biological approaches. For this reason the focus was on a particular subsystem of calcium homeostasis as the Calcium-Parathyroid hormone subsystem as parathyroid hormone (PTH) is the most important regulating hormone to maintain the level of calcium in the human body within the required range. A nonlinear system that defines the relationship between calcium and PTH has been used.

Due to the limitations and irregularities of the nonlinear mathematical system, a closed-loop control system is required to control the system more efficiently. Different kinds of controllers are implemented by the researchers for different design requirements in [8][9][15]. Almost all of these works are focused on designing the controller for physical systems such as voltage regulation, inverted pendulum, quadrotor, aircraft pitch control, solar system. Although, over the past decades with the advancement in technology, research works in the field of the mathematical modeling of the complex biological systems have increased to a greater extent, only a few of them have focused on designing the optimal linear control of non-linear systems. The main reason being the biological systems are interconnections of various smaller subsystems with perturbations in one subsystem affecting the functioning of other subsystems and organs. There is a probability of losing certain responses while deriving the nonlinear system into an optimal linear system using the linearization technique. Due to the lack of pioneering work and literature in support of this research, the focus was on designing an LQR controller for a smaller but more important subsystem of the calcium homeostasis model, and analyzed the design characteristics to see the efficacy of the model. Some of the important properties that illustrate the robustness, stability, and performance of the controllers are transient characteristics such as rise time, settling time, overshoot, peak time, and steady-state error [5]. With the advent in the optimal control theory in the last few decades, the use of optimal state feedback controller

called Linear Quadratic Regulator (LQR) has increased to a greater extent to linearize the nonlinear system as this controller focused on maintaining the cost of the controller at a minimum as compared to other traditional controllers such as Proportional Integral Derivative (PID) controller.

This research work focuses on modeling and deriving an optimal controller for the response of PTH to the change in calcium concentration in the human body using the LQR controller. An optimal linear system is derived from the nonlinear system around its nominal point. Steady-state points have been used as the nominal points for modeling and designing. For validating the results, a control system has been developed and simulated in MATLAB and Simulink. The main design criteria for the model is the rise time and settling time of the response of the concentration of the PTH in the blood plasma. It is desired to keep the control effort at a minimum value so that the optimal LQR controller maintains the concentration of PTH in the plasma at a steady-state value. Tuning of weighting elements (which is explained in chapter 4) was performed to obtain better and acceptable results.

1.2 Thesis Objectives

The objectives of this research work are summarized below:

1. Review the literature related to human physiological systems (specifically calcium system), their subsystems, working mechanism, and importance in the human body.

2. Develop nonlinear mathematical modeling of a subsystem of calcium homeostasis system relating to calcium and parathyroid hormone (PTH).

3. Apply the optimal linearization technique to derive the optimal linear form of the nonlinear system using the Pearson method around the steady-state point.

4. Develop and simulate the model in MATLAB and Simulink using the Linear Quadratic Regulator Controller.

5. Examine and analyze the results in terms of various design characteristics for different pathological conditions.

1.3 Organization of the Thesis

Chapter 1 - Introduction

This chapter introduces the brief description of the calcium homeostasis, the importance of mathematical modeling in complex biological systems, problem statement, objectives of the research, and the contribution of the thesis in the field of nonlinear modeling.

Chapter 2 - Literature Review on Calcium Homeostasis Models

This chapter discusses the overview of calcium and PTH and their fluxes, previously developed mathematical models of calcium homeostasis, and their importance in the human physiological system. Also, it explains about vitamin D and parathyroid hormones.

Chapter 3 - Calcium-PTH Sub-system Models

Chapter 3 presents the review of the Ca-PTH sub-model. In addition, the history of calcium homeostasis models is explained.

Chapter 4 - Design of the Controller

A top-level description of the various kind of controllers in the control system and their importance are described in this chapter. The design of the LQR controller with a proportional non-zero set-point controller and the methods to perform the stability analysis of the control system is explained in this chapter.

Chapter 5 - Development of the PTH Response System Mathematical Model

In chapter 5, the development of the mathematical model for the thesis work is documented. Besides, the techniques to derive the linearized system around the nominal operating points(steady-state points) is also explained.

Chapter 6 - Simulink Control System Design

The design of the optimal linear system of the Ca-PTH model in MATLAB Simulink

is discussed in this chapter. The implementation of the proposed P-NZ-SP LQR controller around the several design characteristics of the model is discussed in this chapter.

Chapter 7 - **Observation and Simulation Results**

The observed simulation results for different pathological conditions are presented in this chapter. In addition, the tuning approach for the weighting elements of the LQR controller and its significance are also discussed.

Chapter 8 - **Conclusion and Future Work**

Finally, this chapter provides a summary of the thesis research along with the problems and efficacy of the work. Also, suggestions for possible future work are presented.

Chapter 2

Calcium Homeostasis System

2.1 Overview of calcium homeostasis and its fluxes

The intestine, bone, kidney, and plasma play a vital role in the exchange of flux of calcium which are four major pools of calcium in the human body. Normally, about 1000 to 1200 g. of calcium is present in the healthy human body as depicted in the above figure, most of which(99 %) is found in the skeleton whereas the remaining 1 % is present in the intracellular and extracellular spaces [26][1].

Approximately, 48 % of total serum calcium consists of ionized calcium, 46 % of total serum calcium is protein-bound and about 7 % is of complexed fractions with phosphate and citrate.

The average plasma calcium concentration in the human body ranges from 2.1-2.6 mmol/L [22][27][25]. At normal healthy condition, there is about 1.1-1.3 mmol/L of ionized calcium, 0.9-1.1 mmol/L of protein-bound calcium, and 0.18 mmol/L of calcium in complexed form. Among all forms of plasma calcium, the calcium homeostatic process strongly regulates ionized calcium (1.1-1.3 mmol/L) as this form of calcium is metabolically active. As shown in figure 2-1, overall plasma calcium balance is regulated by the joint coordinated action of bone, intestine, kidney, and plasma. The fluxes of calcium are maintained by the absorption of calcium in the small intestine, exchange of fluxes from

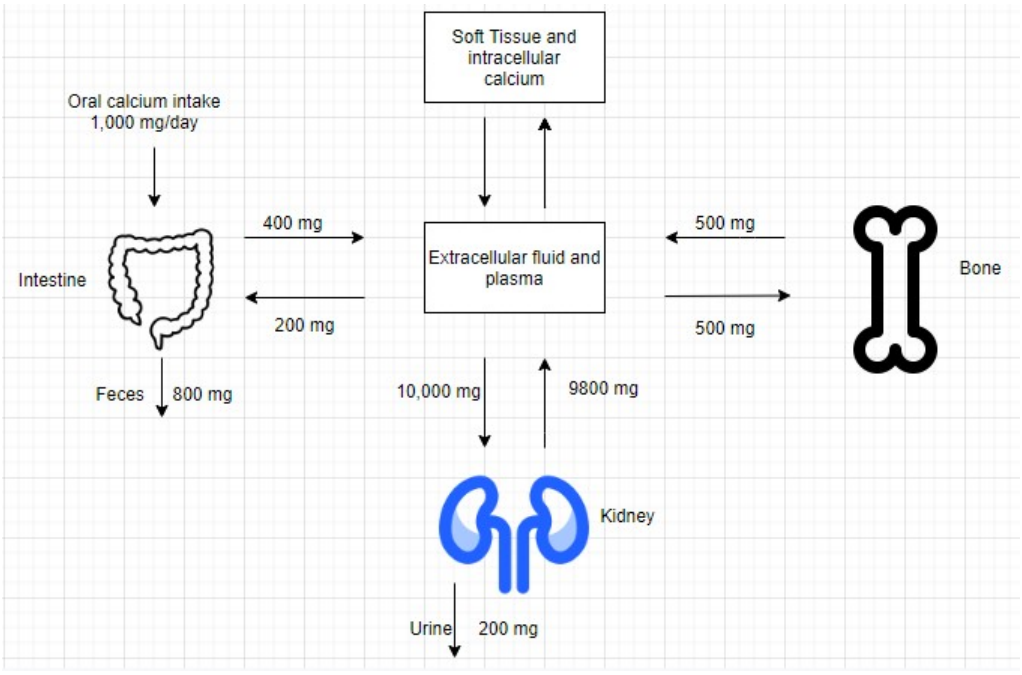

Figure 2-1: Daily calcium balance and flux between body compartments in a healthy human [1]

bone, and reabsorption of calcium from the tubular fluid in the kidney.

In healthy adults, about 1000 mg of calcium is ingested daily through a normal diet. During the digestion process, approximately 400 mg of ingested calcium is absorbed by the intestine whereas about 200 mg effluxes back into the intestine from plasma. So, the net absorption of calcium is roughly 200 mg per day. About 800 mg of calcium is excreted from the body in the form of feces. Similarly, 10,000 mg of calcium is filtrated out of the plasma into the kidney and 9000 mg of calcium is reabsorbed by the proximal distal tubules after the filtration by nephrons while about 200 mg of calcium is excreted out from the kidney as urine. On a daily basis, approximately there is an exchange of 500 mg of calcium between the plasma and bone [1].

Overall calcium homeostasis is controlled mainly by three hormones: parathyroid hormone, calcitonin and active form of vitamin D which are collectively referred as calciotropic hormones [26][21]. The effect of calcitonin hormone is neglected as this hormone doesn't play an effective role in the regulation of plasma calcium as compared to

parathyroid and Vitamin D (CTL) hormones [6]. The next sections present the secretion and regulation of two chief hormones responsible for the Calcium homeostasis process; PTH and Vitamin D hormones in brief.

2.1.1 Vitamin D

The metabolically active form of Vitamin D is derived from the conversion of 7-dehydro cholesterol in the skin by exposure to ultraviolet radiation light. This natural form of vitamin D called cholecalciferol is also known as vitamin D_3. The circulating form of vitamin D_3undergoes a loosely regulated process in the liver called 25-hydroxylation which results in 25-hydroxyvitamin D_3[6]. Then, the conversion of 25- hydroxyvitamin D_3 by the tight regulation of renal α hydroxylase enzyme occurs in the kidneys, forming a metabolically active form of vitamin D3 called 1, 25-dihydroxyvitamin D_3.

2.1.2 Parathyroid Hormone (PTH)

There are four parathyroid glands in the human body that are located in the neck adjacent to the thyroid glands as a pair in each half of the thyroid glands [26][22][24]. Figure 2-2 depicts the anatomy of the parathyroid gland in the human body. The parathyroid gland mainly constitutes of oxyphile cells and chief cells. The chief cells of the parathyroid glands synthesized PTH and are stored in vesicles that are ready to be transported out of the parathyroid gland (PTG)cells. Hence, PTH acts on the short time scales of minutes. Usually, the secretion of PTH actively occurs only in 20% of the cells [26]. This whole phenomenon is described clearly in [24][25] which give us a clear picture of PTH bio-synthesis and regulation.

The concentration of PTH in plasma is always inferred in relation to ionized plasma calcium concentrations and phosphatemia [10][24]. Plasma calcium strictly controls the secretion of PTH as given by the reverse sigmoidal function. PTH stimulates the reabsorp-

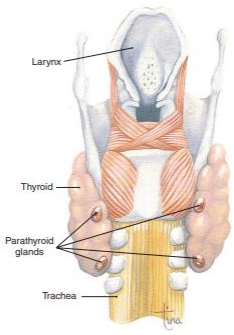

Figure 2-2: Anatomy of Parathyroid glands (Rajiv P Shrestha, 2008)

tion of calcium from bones to the blood which increases the concentration of calcium in plasma. This resorption process occurs at the osteoblasts surface in bones by the increment in the maturation of osteoclasts via osteoblasts [12]. Also, it increases calcium reabsorption from nephrons of the kidneys and stimulates the activation of vitamin D (calcitriol) in the kidneys. This process increases the reabsorption of calcium in the plasma. Overall, PTH aids in the increment of calcium level in the blood plasma and lower the level of phosphate in the blood plasma. In contrast, whenever the concentration of plasma calcium rises above the normal range, the secretion of PTH is inhibited which results in the decrement of reabsorption of Ca^{++} and increment in the excretion of calcium in urine form. This process ultimately balances the equilibrium process [7][12].

A decrease in the normal level of plasma calcium concentration increases the secretion of PTH. Conversely, an increase in the normal level of plasma calcium concentration results in a decrease in the secretion of PTH. The response of parathyroid glands to change in plasma calcium concentrations occurs in a time-scale range of seconds to minutes. A decrease in the normal level of blood calcium concentration, known as hypocalcemia acutely stimulates the secretion of PTH from the PTG gland by the process of exocytosis which is a negative feedback mechanism. In general terms, exocytosis can be defined as the transportation of materials such as hormones, enzymes out of the cells to the plasma membrane through vesicles. On the other hand, an increase in the normal blood level plasma, known as

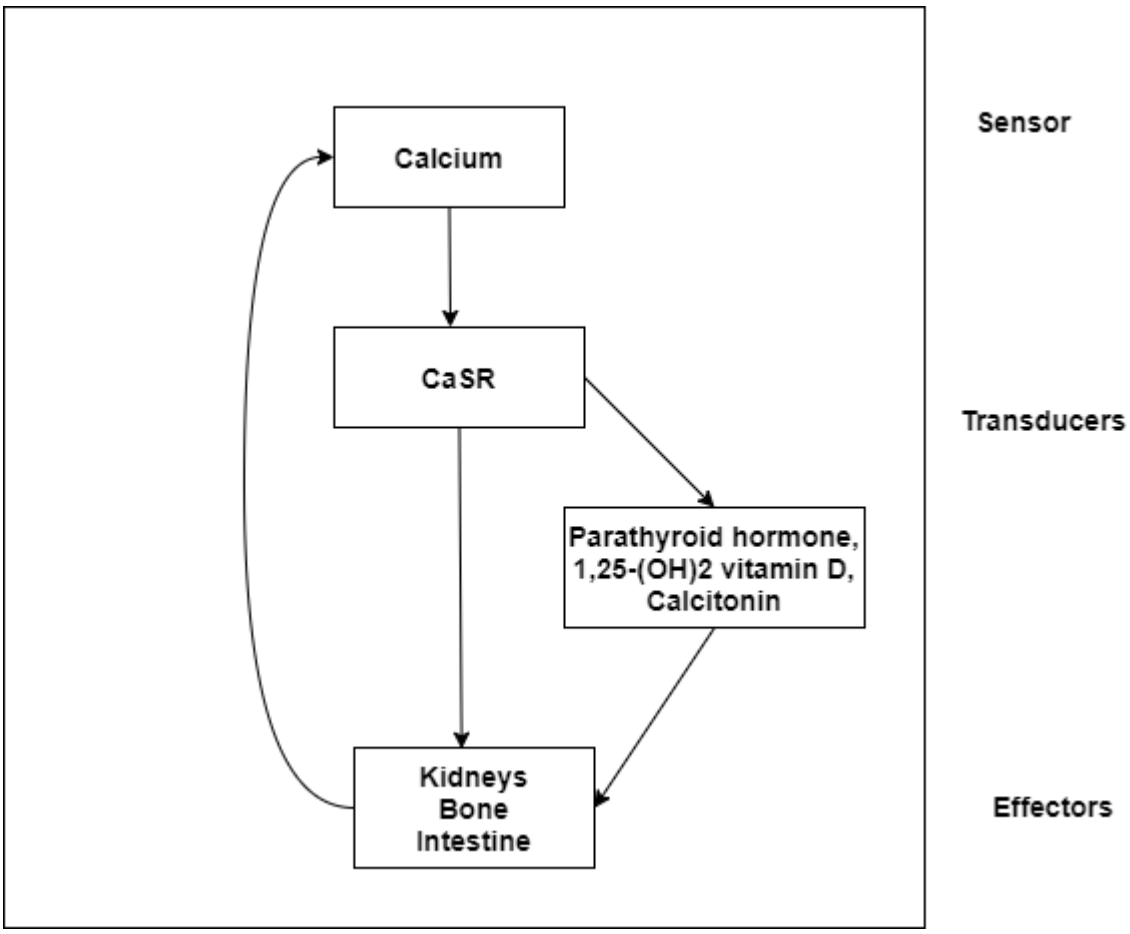

Figure 2-3: Calcium Homeostasis system

hypercalcemia acutely inhibits the PTH secretion from the gland. This exocytosis process occurs on a time scale of minutes. Like, the engineering control system, Ca^{++} homeostatic system can be represented as a biological control system as shown in figure 2-3 [12]. The system is composed of plasma calcium pool as a controlled process, calcium-sensing receptors (CaSR) as the sensors, and parathyroid glands as the controller. Besides, hormones like PTH, calcitonin, and vitamin D3 act as the transducers whereas the target organs kidneys, intestine, and bone act as the effectors.

The regulation of calcium starts with the detection of a change in Ca^{++} ions via the signaling pathways of the calcium-sensing receptors (CaSR). The CaSR which is found on the cell membrane of the chief cells of the PTG can detect very small perturbations in

the concentration of calcium. Though CaSR is primarily expressed at the PTG's surface, it is also located in bones, kidneys, and intestine. The increment of the level of plasma calcium concentration results in a decrement of PTH secretion by the process of regulation of exocytosis. On the contrary, a reduction in the concentration of plasma calcium increases the secretion of PTH.

Since the response of the PTH to an acute change in the concentration of plasma calcium occurs in a small-time range of seconds to minutes as compared to other processes involved in calcium homeostasis, it is reasonable to study the response of plasma PTH to changes in plasma calcium independently [27]. The next chapter presents the mathematical model of plasma Ca-PTH axis models which is the focal point of study for this thesis.

Chapter 3

Calcium-Parathyroid Hormone Sub-System Models

3.1 History of Calcium Homeostasis models

The earlier research works of calcium homeostasis were focused on the experiments performed on animals and birds [12][13]. Later, with the discovery of various calcium signaling receptors and advancement in science and technology, recent works focused on utilizing data from humans. In the past couple of decades, investigations and research on calcium homeostasis in humans have progressed substantially with a detailed understanding of calcium mechanisms and signaling pathways.

One of the earliest works relevant to the mathematical modeling of calcium homeostasis was developed in early 1974 [21]. A theoretical complex mathematical model of calcium homeostasis was developed based on the data of several animals. This model considered parathyroid and calcitonin as the principal hormones which were based on data from different animals. The model considered the opposite effects of parathyroid and calcitonin hormones and took into account the linear relationships between both plasma PTH and calcitonin with blood plasma calcium. Eventually, the author stated that he was unable to validate the model due to a lack of data available for the model because of the unavailabil-

ity of the techniques to regulate the concentrations of parathyroid and calcitonin hormones. He, however, suggested some possible experiments to determine data for his model in the future.

A mathematical model of calcium homeostasis in birds was suggested in [13]. This model took into account the vitamin D and PTH as the main regulating hormones and considered the flow of calcium fluxes between different calcium pools such as bone, intestine, kidney, and plasma. Calcitonin was neglected in this model as the role of calcitonin was unclear in the calcium homeostasis process. Overall, in this model, simulations were performed to study the effects of deficiency of vitamin D hormone, calcium infusion, and regulation of hydroxylase enzyme by parathyroid hormone. The extended version of this model appears in [14]. This extended model accounts for the effects of the intake of energy and growth of the body in chicks which were not considered in previously developed models.

The latest models of calcium homeostasis were presented in [22] which can be considered as the most complete model of calcium homeostasis as it was the improvement of previously developed models. This model composed of distinct pools of phosphate and calcium and depicted the exchange of flux of calcium and phosphate between the bone and plasma. In addition, the effect of vitamin D3 on bone resorption is also presented in the model. The inhibition of the secretion of PTH by vitamin D3 and blood plasma calcium is considered in this model. Overall, in comparison to previous models, all the important effects and aspects of calcium homeostasis are incorporated in this model, and simulation outcomes were compared with the clinical data of renal failure conditions.

3.2 Review of Ca-PTH models

In this section, the models that incorporated PTH synthesis as the main regulating hormone for calcium homeostasis are presented. In 1983, for the first time, EM Brown pre-

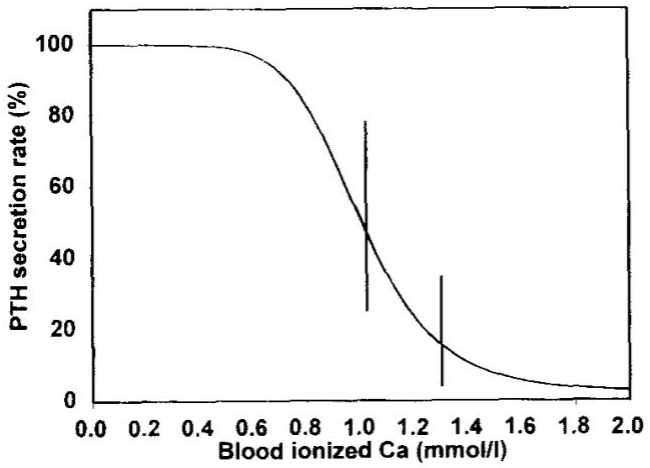

Figure 3-1: Sigmoidal curve showing relation between PTH secretion and calcium concentration (G Momsen, 1997)

sented the decisive study that determined the nonlinear relationship between the secretion of parathyroid hormone and the concentration of plasma calcium [2]. In this model, the relationship between the blood plasma calcium concentration and secretion of parathyroid hormone in a normal and pathological human in vitro was demonstrated as the reverse sigmoidal curve. This relationship was proposed using the four-parameter mathematical model related to various aspects of the PTH secretion given by the following equation

$$k_{ca} = \frac{A-B}{1+(\frac{C}{D})^m} + B \tag{3.1}$$

where A denotes the maximal PTH secretion rate from cells to plasma, B is the minimal PTH secretion rate, C denotes the ionized calcium concentration, D is the setpoint value of C at which $k_{ca} = \frac{(A+B)}{2}$, and m is the slope of the curve. The figure 3-1 depicts a reverse sigmoid curve relationship between Ca++ and PTH release rate.

In [23], a two-pool, time-invariant (LTI) mathematical model of parathyroid hormone was assumed to study the features of Ca-PTH relationship. This model studies the pulsatile secretion of parathyroid hormone using the hyper-calcemic and hypo-calcemic clamp test

data in humans.

Similarly in [19], for the first time, Schwarz and Momsen developed a mathematical model using the biochemical and biological processes in the parathyroid glands responsible for the secretion of parathyroid hormone that occurs from the reduction of extracellular calcium. Their model was based on the work of Brown [2]. The dynamics of Ca-PTH were considered for a short time duration of minutes. A two-pool model of PTH-Calcium dynamics was derived, considering one pool in the blood plasma and the other in the parathyroid gland cells (PTG). Their model used the experimental data obtained from healthy subjects and patients to study the response of parathyroid hormone to lowering of the plasma calcium for a short time duration (in minutes). The experiment was performed by the injection of citrate and the impacts of the calcium-sensing receptors (CaSR) on the response of parathyroid were studied for 120 minutes. The authors parameterized the model using the experimental data for hypocalcemia conditions and simulations were run for short spans (minutes) to match the results. However, the impact of the hypercalemic clamp test by increasing the concentration of calcium on the secretion of the parathyroid hormone was not explored in the model.

A two-pool, linear and time-varying Ca-PTH mathematical model which is a subsystem of a calcium homeostasis process was developed in [26] that incorporates the effect of change in plasma calcium to the PTH concentration in the human body. The model development was based on the secretion and regulation of PTH and clinical observations of induced calcemic clamp test. In this model, the author parametrized the model using the clinical data for both the induced hypocalcemia (low calcium level) and hypercalcemia (more calcium level). Simulations were performed for healthy humans and compared with the clinical data of the literature. Also, the author proposed a new protocol to develop a reverse sigmoidal curve to show the relationship between plasma calcium and PTH concentrations based on his mathematical model.

Chapter 4

Controller Design

4.1 PID Controller

Different kinds of process control methods are used by the researchers for various control systems and automation. One of the most commonly used controllers is Proportional-Integral-Derivative (PID) controller. In today's world, most of the low-level controllers used are PID types as they offer the low-level computational demand but most efficient solutions to numerous problems of real-world applications. The PID controller is based on the error between the desired setpoint value and the measured value. The commonly used block diagram of a PID controller is shown in figure 4-1 below.

A PID controller's output (u) is based on the error signal which is the difference between the desired set point and measured processed value. The output of PID controller has the following general form :

$$u_t = K_p e(t) + K_i \int_0^t d(\tau) + K_d \frac{de}{dt} \tag{4.1}$$

K_p denotes the proportional gain, K_i corresponds to the integral gain, and K_d is the derivative gain of the controller. The proportional gain determines the current values of the error, the integral gain accounts for the reaction based upon the sum of past values of

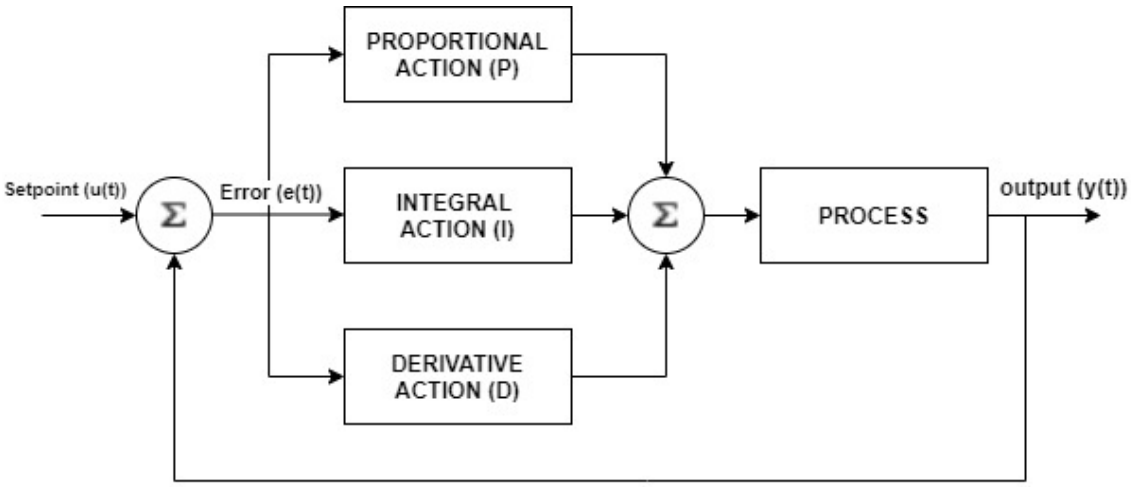

Figure 4-1: Block diagram of a PID Controller

the errors and the derivative gain determines the future values which account for the rate of change of the errors. Tuning can be performed based on different methods such as error and trial method to obtain the better performance of the controller. However, one of the main drawbacks of the PID controller is for the given certain set of conditions with multiple states, it doesn't converge on an optimal control response. Also, another major setback of using the PID controller is that PID controllers are already linear in nature themselves so when used for the highly nonlinear systems such as calcium modeling biological complex systems, they express the unpredictable and undesired outputs and results.

4.2 LQR Controller

4.2.1 Overview of a LQR Controller

On the other hand, linear quadratic regulator (LQR) is a modern type of controller technique that accounts for the optimization of the control responses by finding the state feedback gain for the closed-loop system. LQR controller is also known as a predictive control method that aims to operate the control system at the minimum cost over a given

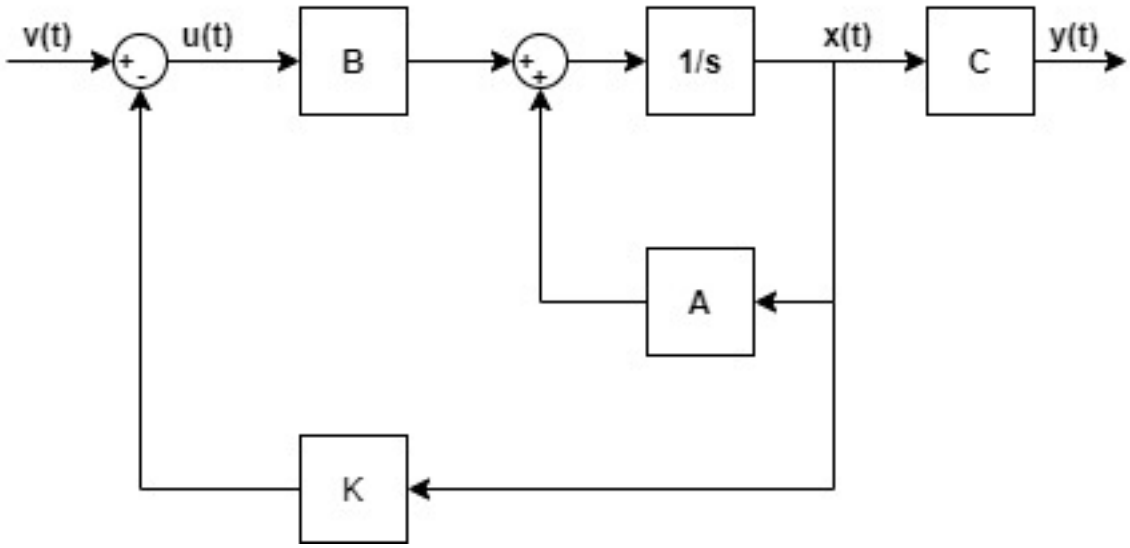

Figure 4-2: Block diagram of LQR Controller

certain reference trajectory. In the LQR design method, the optimal control method is formulated where the dynamics of the systems are commonly represented as a set of linear differential equations, and the cost function in the control process is described as a quadratic function.

The output of the LQR controller helps to formulate the optimal control law that maintains the robustness of the controller while guaranteeing the closed-loop stability. A linear quadratic regulator can be designed for both discrete and continuous-time systems.

The main advantage of using the LQR controller over the other available controllers is it helps to minimize the overall energy associated with the cost function of the system and delivers optimally controlled feedback gains to enable the high-level performance design and closed-loop stable of the system [8][16]. In this thesis, a continuous linear model of calcium dynamics have been used for the design of the LQR controller A block diagram of a schematic representation of a LQR controller is depicted in figure 4-2.

The state space equations of a continuous-time linear system with m states and n inputs can be described by the following equations (4.2) and (4.3) below [5]:

$$System : \dot{x} = Ax + Bu \tag{4.2}$$

$$Output : y = Cx + Du \tag{4.3}$$

The performance index also called the cost function of the LQR controller is given as

$$Cost function : J(x,u) = \frac{1}{2}\int_0^\infty (x^T Q(x)x + u^T R(x)u dt \tag{4.4}$$

where, x(t) is the state of the system and u(t) is the input of the system, y denotes the output of the system. It is assumed that each of the states of the system is available for control in LQR control. Using this technique, a control u(t) which minimizes the above cost function is sought. Since, LQR control method is a type of optimal control method, J must be minimal subjected to the constraints presented in equation (4.4).

Here, Q and R matrices are the weighting matrices associated with the states and inputs of the system. They are square matrices where dimension of Q is *m*m* whereas R matrix has dimension *n*n*. They can also be defined as the penalties associated with the states and inputs of the system. Since selecting a large Q means the states should be kept smaller to keep minimal cost function (J). On the contrary, choosing a larger value of R means the control input (u) should be smaller so that less control effort is required to minimize the performance index.

4.2.2 Restrictions on Q and R matrices

In the design of an LQR controller, the choice of Q and R matrices is a vital factor. Q and R matrices are selected by the design engineer. However, there is no common technique to tune the parameters of these weighting matrices. One of the methods to define these controller matrices is to define each of these matrices as diagonal matrices. While choosing these matrices, the following limitations should be placed so that the performance index is

minimized:

1. Q matrix should be a positive definite or positive semi-definite matrix, which means Q should be symmetric and its eigenvalues must be either zero or positive.

2. R matrix should be positive definite which means R is a symmetric matrix and its eigenvalues must be strictly positive.

4.2.3 Solving K and P

The optimal controller (u) that minimizes the cost function is given as:

$$Optimalcontroller : u = -Kx \tag{4.5}$$

And the optimal state forward gain associated with each of the states of the system for minimizing cost function is defined as :

$$Optimalgain : K = R^{-1}B^{T}P \tag{4.6}$$

The matrix P is positive and semi-definite which should satisfy the following algebraic Riccati equation (ARE) also called as continuous Algebraic Riccati (CARE) equation at the steady state defined as :

$$\dot{P} = A^{T}(x)P(x) + P(x)A(x) - P(x)B(x)R^{-1}(x)B^{T}(x)P(x) + Q(x) = 0 \tag{4.7}$$

The minimal value of the performance measure (J) using the optimal gain is expressed as

$$J = \frac{1}{2}.X(0).P.X(0) \tag{4.8}$$

From the above equation, it is clear that the minimal value of the performance criterion depends on the initial condition of the states X_0 which means the cost of using the LQR

controller can be calculated from the initial conditions of the states before its application to the system.

The flowchart in figure 4-3 summarizes the overall steps used in solving the simplest kind of a LQR problem.

4.3 Observability and Controllability

For the control system design, it is essential to have a controllable state if it is desired to consider the energy of any state in the performance index. A given system is called a controllable if there always exists a control input (u) which derives any states of the system to any other state in a finite time. In order to determine if a given system is controllable, one can evaluate using the controllability matrix below. This controllability matrix is for a n*n system and is represented as :

$$C_o = \begin{bmatrix} B & AB & A^2B & \dots & A^{n-1}B \end{bmatrix} \tag{4.9}$$

If the rank of the controllability matrix C_o is equal to the size (n) of the system then the given system is controllable. But if the rank of the system is less than n, the difference between n and a rank of C_o is the number of states which are not controllable.

After determining the controllability of the system, it is essential to find the observability of the control system. Over the finite amount of time, if we can determine the initial state using the control input (u) and the output of the system (y), then the system is termed as an observable.

The observability of the system can be determined using the observability matrix shown below for a given n*n matrix.

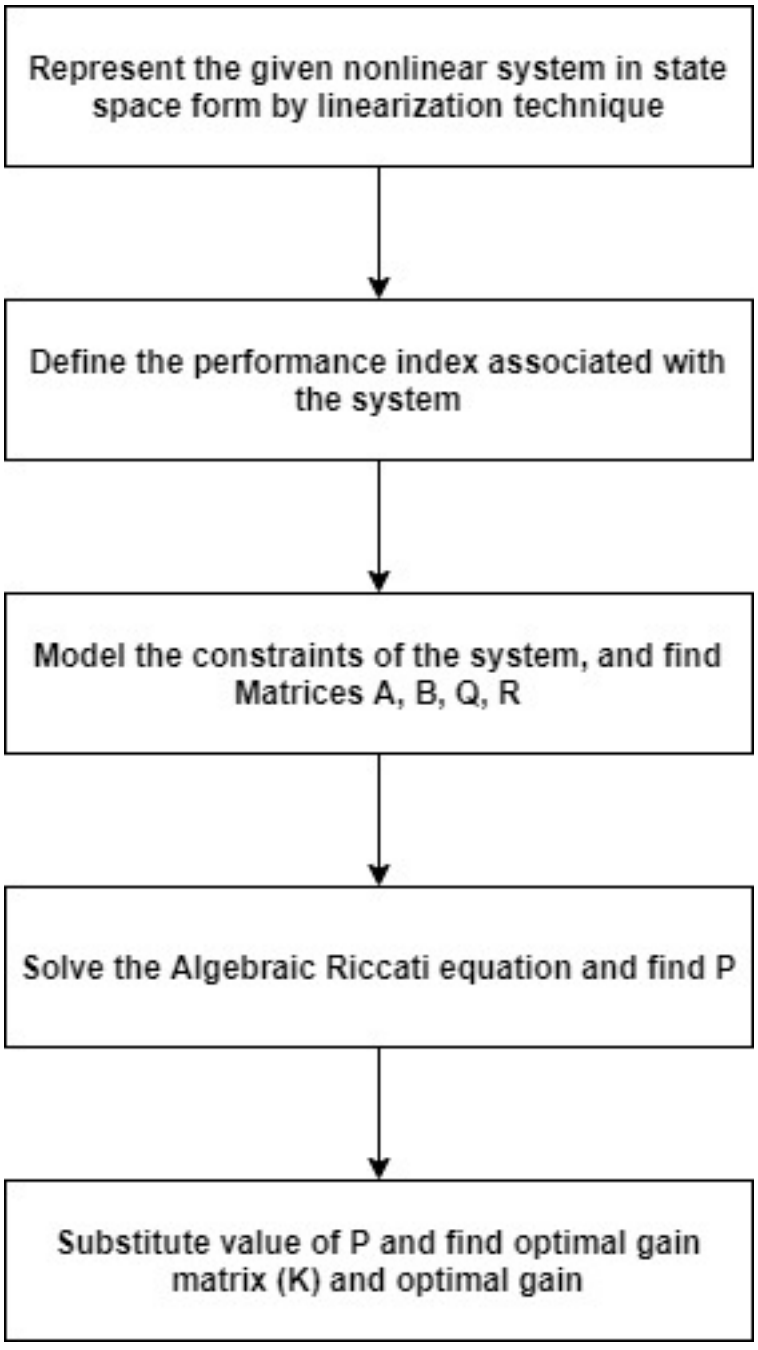

Figure 4-3: Flowchart of a LQR Control Method

$$O_b = \begin{bmatrix} C \\ CA \\ \dots \\ CA^{n-1} \end{bmatrix} \tag{4.10}$$

The system is said to be observable if the rank of O_b is equal to the size (n) of the system. If the rank is less than n, then the difference between n and rank of O_b is the number of states which are not observable.

The stability of the system using the LQR controller can be determined using the Ruth-Hurwitz criterion which is described in the next section.

4.4 Stability of the system

Before moving further and design the controller it's utmost important to check the internal stability of the system and thus we have applied the Routh Hurwitz criterion to our system. Moreover, another renowned method to check the stability of the system is by finding the eigenvalues of the state matrix. If all the eigenvalues of the system matrix are negative, the system is said to be a stable system. Otherwise, it is called an unstable system.

Let us consider our system matrix A of the form :

$$A = \begin{bmatrix} a & b \\ c & d \end{bmatrix} \tag{4.11}$$

The second degree polynomial for A is calculated as:

$$Poly(A) = \lambda^2 + (-a-d)\lambda + (ad-bc) \tag{4.12}$$

Let's formulate the Routh's table as below:

$$\begin{array}{lcll} s^2 & : & 1 & (ad-bc) \\ s^1 & : & (-a-d) & 0 \\ s^0 & : & (ad-bc) & \end{array}$$

According to Routh's criteria, if the given system is stable then there should be no changes in sign in the first column of the formulated Routh's table. Otherwise, it is an unstable system. The use of the Routh Hurwitz method to determine the stability of the control system design is performed in chapter 5.

4.5 LQR with PID and non-zero setpoint controller

LQR controllers can be combined with PID architecture controllers using the proportional, integral, and derivative gains. The advantage of combining LQR with the PID controller is it helps to improve the response of the desired system and controller. Moreover, for the system with multiple states, using the modified LQR controller with a PID controller is advantageous.

Moreover, LQR control can be used as an optimal controller by designing it as a nonzero setpoint controller with a slight modification on the regular LQR controller. The nonzero setpoint controller (NZSP) differs from the regular LQR controller in a way that it has nonzero command [17][11]. It operates with the nonzero setpoint command as a new reference value. The use of NZSP helps in retaining the optimality of the LQR controller. Once the identification of the new trim values and controls is done, a quad partition matrix (QPM) is used that connects the new controls and states to the state-space model and desired output. This algebraic relationship is shown in the below equation

$$\begin{bmatrix} A & B \\ C & D \end{bmatrix} \begin{bmatrix} x^* \\ u^* \end{bmatrix} = \begin{bmatrix} 0 \\ I \end{bmatrix} \tag{4.13}$$

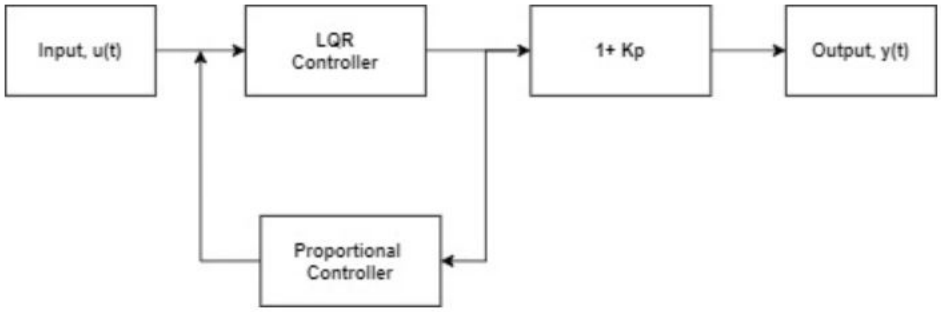

Figure 4-4: Block diagram of LQR with Proportional Controller

The solution of the above equation exists only when the QPM is a non-singular and square matrix. It means the number of states which are being driven to the new setpoint using a nonzero set-point controller must be equal or less than the number of controls used in the system. In this model, the proportional type nonzero set-point controller is used to control the response of the system. It takes the input as a state-space model and returns the sub-matrices of the partition matrix. And, the unique solution using the quad partition matrix for the optimal control is given in equation below

$$Optimal control(P-NZ-SP): u=-kx=u^{*}-K(x-x^{*})=(X_{22}+KX_{12})Y_{m}-Kx \quad (4.14)$$

The purpose of using NZSP architecture is it helps to drive the states of the system to some desired nonzero values. The block diagram of LQR modified with the proportional controller is shown in figure 4-4.

In this study, a linear quadratic regulator controller has been designed that utilizes the proportional nonzero set point technique to control the change in response of parathyroid hormone for the lowering of calcium in the body. The linear model of a nonlinear system is designed by performing linearization around its nominal point (or steady-state point). LQR controllers are advantageous for linearized systems. For each condition, analysis is performed by studying the steady and transient response characteristics of each control

system design.

The response of concentration of PTH with time for the healthy and pathological conditions is determined by evaluating different design characteristics such as rise time, settling time, and percentage overshoot. From the literature [19], the settling time for the response of PTH concentration for the healthy condition needs to be less than 50 minutes. Besides, unhealthy IDDM subjects must have a rise time of around 5 minutes and should be approaching the steady-state slower as compared to the healthy model.

Chapter 5

Development of a Mathematical Model of Ca-PTH Subsystem

5.1 Parathyroid Hormone Response to the Change in Calcium

Several research and literature works have been done for developing the mathematical model of the calcium homeostasis sub-system relating to the Ca-PTH. [27][19][23].

In this section, based on the understanding of parathyroid hormone secretion and transportation, the development of a model for the parathyroid hormone response to a change in calcium in the human body relating to the constant secretion of PTH by the PTH gland is presented [19]. This model is a two-pool model where one pool of PTH in plasma and another pool of PTH in the PTH cell gland as shown in Figure 5-1 is considered. With the severe decrease in the concentration of plasma calcium, calcium-sensing receptors (CaSR) located on the membrane of chief cells of parathyroid glands stimulate the exocytosis process of parathyroid hormones which are stored in the vesicles. This phenomenon occurs in a short time, typically on the scale of minutes. In this model, the focus is on the response of PTH to the change in calcium concentration for a short time scale. As a result, as mentioned in [26], the bio-synthesis process of PTH as it occurs in time scales of hours to days

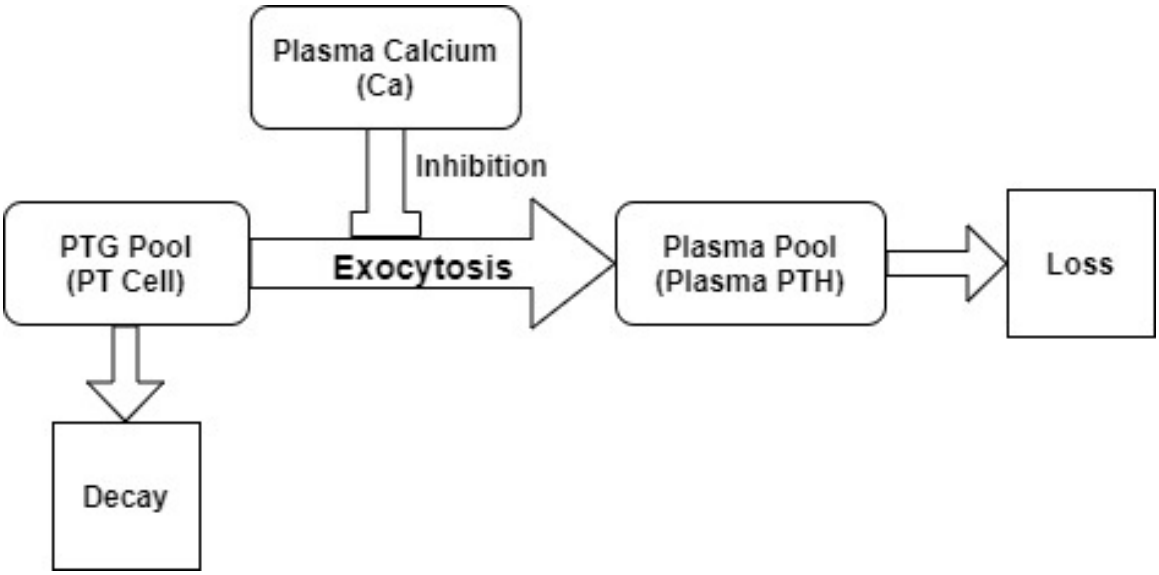

Figure 5-1: Ca-PTH subsystem isolated from Calcium homeostasis model, [26]

is not considered.

After the understanding of Ca-PTH phenomenon and making the required assumptions, the governing differential equations and variables for the development of the model are given in equations (5.1)-(5.2)

$$\frac{dx_1}{dt} = k_p - k_s x_1 - l_1 x_1 \tag{5.1}$$

$$\frac{dx_2}{dt} = k_s x_1 - l_2 x_2 \tag{5.2}$$

Based on the assumptions in the literature, the four parameter reverse sigmoidal relationship model of Brown is used to relate the plasma calcium concentration to the secretion rate constant of PTH as shown below :

$$k_s = \frac{A-B}{1+(\frac{C}{D})^s} + B \tag{5.3}$$

where C is Ca, the plasma calcium concentration, A is the maximal value of the secre-

tion rate, B denotes the minimal value of the secretion rate, D is the set point given when $K_s = (A+B)/2$ and s is the slope of the curve.

Since the model is developed based on the dynamics of mass balance, the concentrations of plasma calcium and parathyroid hormone have been multiplied by the average plasma volume which is about 2.75 L [19][26]. Also, for the simplification of model development, a step-change in plasma calcium is assumed [26].

In order to further develop a mathematical model of calcium-PTH axis for controller design, a steady-state solution of the given system is assumed for the governing equations of PTH concentrations in plasma and cell. At the steady-state region, the solution of each mass balance equation is zero where two concentrations reach steady-state value denoted as X1s and X2s. At the steady-state conditions, assuming the constant calcium concentration, we have the following relations

$$\Delta x_1 = 0, \Delta x_2 = 0, k_s = k_{sss}, \Delta Ca_s = 0 \tag{5.4}$$

After specifying the steady-state parameters for the governing differential equations of the Ca-PTH model, the steady-state assumptions are derived to derive the corresponding steady-state solutions for PTH concentrations in the plasma and PTG pool. After that, the state-space model of the system is developed by the process of linearization around its steady-state point (equilibrium point).

5.2 Control of a nonlinear system via linearization and state space model

The mathematical model that was developed in the above section is a nonlinear system, so there is a need to linearize the given system around its nominal operating point. The steady-state point is the nominal operating point for the system.

Analysis and development of the model in real-time for the given calcium-PTH concentrations can be challenging as explained in the above sections. The reasons being the strong nonlinearity nature, disturbances, and impulsive responses that occur for the biological systems. Time dynamics can also vary for the biological system depending on the duration of the injection time for calcium citrate (increases calcium concentration) or for sodium gluconate (decreases calcium concentration). Overall, the change in PTH concentration with the change in calcium can be considered for a time span of minutes to hours and even days. It's a challenging, and time-consuming task to obtain data required to design a model for each of the conditions. Therefore, a simple state-space model as being developed, which assumes that a steady-state level of basal calcium concentration can be achieved within a period of minutes.

In this study, the linearized system model is obtained through an application of Pearson Method[20][18]. The technique is described as follows:

For a given nonlinear system,

$$\dot{x} = f(x,u), x(0) = x_0 \tag{5.5}$$

$$y = g(x,u) \tag{5.6}$$

Here, x denotes the state variables of the system and u is the control input, y is the desired output of the system, and f and g are nonlinear functions. The above system is first transformed into a linear time-varying system by the application of the Taylor series expansion technique. The expansion introduces a perturbation about the equilibrium (operating) point, often the steady-state point, known as

$x_{ss}, u_{ss}, y_{ss} = y_{desired}$.

The system is assumed to be operating around the periphery of its steady state point expressed as

$$x(t) = x_{ss} + \Delta x(t) \tag{5.7}$$

$$u(t) = u_{ss} + \Delta u(t) \tag{5.8}$$

$$y(t) = y_{ss} + \Delta y(t) \tag{5.9}$$

Here, $\Delta x(t), \Delta u(t)$ and $\Delta y(t)$ are small quantities which are zero at the steady state point.

So, around the nominal point the equation becomes:

$$\dot{x}_{ss}(t) + \Delta\dot{x}(t) = f[x_{ss}(t), u_{ss}(t), t] + J_x[x_{ss}(t), u_{ss}(t), t]\Delta x(t) + J_u[x_{ss}(t), u_{ss}(t), t]\Delta u(t) + h(t) \tag{5.10}$$

Here, J_x and J_u are the Jacobian matrices of the first-order partial derivatives of f with respect to x and u respectively.

The steady state(equilibrium) point is given by

$$\dot{x}_{ss}(t) = f[x_{ss}(t), u_{ss}(t), t] \tag{5.11}$$

Utilizing equation (5.11) in equation (5.10), and noting that h(t) is negligible in the vicinity of the equilibrium point, equation (5.10) reduces to

$$\Delta\dot{x}(t) = J_x[x_{ss}(t), u_{ss}(t), t]\Delta x(t) + J_u[x_{ss}(t), u_{ss}(t), t]\Delta u(t) \tag{5.12}$$

or,

$$\Delta\dot{x}(t) = A[x_{ss}(t), u_{ss}(t), t]\Delta x(t) + B[x_{ss}(t), u_{ss}(t), t]\Delta u(t) \tag{5.13}$$

where A and B are the Jacobian matrices J_x and J_u respectively. This technique of obtaining Jacobian matrices was first utilized by Pearson [20]. Hence, the linearized system around its nominal points leads to a linear system in Δ x(t) , Δ u(t) and Δ y(t), and is represented as:

$$\Delta\dot{x}(t) = A\Delta x(t) + B\Delta u(t) \tag{5.14}$$

And, the linearized output of the system is given as:

$$\Delta y(t) = C\Delta x(t) + D\Delta u(t) \tag{5.15}$$

where,

$$A = \frac{\delta f}{\delta x}_{|xss,uss} \quad B = \frac{\delta f}{\delta u}_{|xss,uss} \tag{5.16}$$

$$C = \frac{\delta g}{\delta x}_{|xss,uss} \quad D = \frac{\delta g}{\delta u}_{|xss,uss} \tag{5.17}$$

Here, Δx(t), Δ u(t) and Δy(t) are small quantities. Since the equations of the above system are linear in nature, we can use any LQR controller design technique to control Δx(t) via Δu(t).

5.3 Linearization of the Mathematical Model

Following the method proposed in the above section, the steady state assumptions are applied to the governing equations (5.1)-(5.3) of the Ca-PTH model and the linearized system is obtained. The system is linearized at the steady state as:

$$0 = k_{pss} - k_s x_{1ss} - l_1 x_{1ss} = f_1(x_{1ss}, x_{2ss}) \tag{5.18}$$

$$0 = k_{ca} x_{1ss} - l_2 x_{2ss} = f_2(x_{1ss}, x_{2ss}) \tag{5.19}$$

$$y_{ss} = y_{desired} = x_{2ss} \tag{5.20}$$

So, the steady state points for the system are obtained as

$$x_{1ss} = \frac{k_{pss}}{k_{sss} + l_1} \tag{5.21}$$

$$x_{2ss} = \frac{k_{sss}}{(x_{1ss} + l_2)} \tag{5.22}$$

It is assumed that plasma calcium can reach a steady-state such as $k_s = k_{sss}$. Also, the states and control input for the linearized state space model are identified. The state vector (x) contains the PTH concentration in the PTG cell and blood plasma. The controller vector (u) includes the PTH secretion rate which depends on the plasma calcium concentration. But the output of interest is X_2 (PTH concentration in plasma) as the focus is on analyzing the response of PTH in blood plasma. Hence, the system can be considered a single input single output (SISO) with a single controller and single output. Calculating the Jacobian matrices as given below, the matrices of the linearized system are obtained.

$$A_{11} = \frac{\delta f_1}{\delta x_1} = -(k_{sss} + l_{1ss}) \tag{5.23}$$

$$A_{12} = \frac{\delta f_1}{\delta x_2} = 0 \tag{5.24}$$

$$A_{21} = \frac{\delta f_2}{\delta x_1} = k_{sss} \tag{5.25}$$

$$A_{22} = \frac{\delta f_2}{\delta x_2} = -l_{2ss} \tag{5.26}$$

$$B_{11} = \frac{\delta f_1}{\delta u_1} = -x_{1ss} \tag{5.27}$$

$$B_{21} = \frac{\delta f_2}{\delta u_1} = x_{1ss} \tag{5.28}$$

$$C_{11} = \frac{\delta g_1}{\delta x_1} = 0 \tag{5.29}$$

$$C_{12} = \frac{\delta g_1}{\delta x_2} = 1 \tag{5.30}$$

$$D = \frac{\delta g_1}{\delta u_1} = 0 \tag{5.31}$$

So, the system state space matrices are as follows:

$$A = \begin{bmatrix} -(k_{sss} + l_{1ss}) & 0 \\ k_{sss} & -l_{2ss} \end{bmatrix} \tag{5.32}$$

$$B = \begin{bmatrix} -x_{1ss} \\ x_{1ss} \end{bmatrix} \tag{5.33}$$

$$C = \begin{bmatrix} 0 & 1 \end{bmatrix} \tag{5.34}$$

$$D = [0] \tag{5.35}$$

It is assumed that basal plasma calcium concentration is constant for this model. The model emulates the system response to the change in plasma PTH concentration which occurs during a two hours period following the lowering of calcium concentration in the human body by the injection of citrate, and was developed using a hypocalcemic model taken from the literature [19]. The parametrization of the model was done for two different conditions presented in the literature study.

Values were assigned to the steady-state parameters of the model based on a steady-state PTH secretion by PTG gland of 0.278 and 0.476 for healthy and IDDM subjects, respectively, as presented in the literature [19]. The nominal parameters for the Ca-PTH model using the steady-state solutions are given in table 5.1.

As the application of steady-state values is performed,it is observed that the nonlinear system has two operating points each for the PTH in cell and plasma. Before moving further in designing the controller, each condition needs to be analyzed for the system stability. This is one of the crucial steps for control system design as the goal is to stabilize the nonlinear system using the LQR controller. There are different methods to check the

Table 5.1: Nominal Parameters for our Ca-PTH Model Design

Parameters	Parameters Description	Healthy subjects	IDDM subjects	Units
k_p	Self production of PTH	2.75	2.32	pmol/min
k_s	Secretion of PTH by Ca	0.278	0.476	min
l_1	Loss of PTH in cell	0.0169	0.0150	min^{-1}
l_2	Loss of PTH in plasma	0.1098	0.0953	min^{-1}
k_{s_0}	Steady state initial value	0.0110	0.0096	min^{-1}

internal stability of the system. For example, the Eigenvalues of the system matrix A can be analyzed to determine if they have negative real parts as required for the stable system.

Once the nominal parameter values of the system and steady-state operating points for the PTH concentration in the cell and the plasma were determined, the values were applied to the formulated state-space model. The first representation of the state-space model is for the healthy condition. The equations (5.36)-(5.37) represent the initial and final steady-state values for the first condition (healthy condition). Similarly, the values for the system and output matrices are shown in the equations (5.38) - (5.41). As mentioned in the literature, the initial values of the healthy condition are the steady-state value of the healthy condition before the lowering of calcium in the subjects, whereas the final steady-state values are the values after two hours (120 minutes) of the experiment. This is important as the optimal control system is being designed, to see the response of the PTH to the change in calcium in the body. Also, an analysis could be done to study the stability of the system.

$$\textit{Initial value} : x(t \to 0) = \begin{bmatrix} 17.48 \\ 148.45 \end{bmatrix} \tag{5.36}$$

$$\textit{Steady state value} : x(t \to \infty) = \begin{bmatrix} 44.88 \\ 6.63 \end{bmatrix} \tag{5.37}$$

$$A = \begin{bmatrix} -0.073 & 0 \\ 0.494 & -0.05081 \end{bmatrix} \tag{5.38}$$

$$B = \begin{bmatrix} -6.63 \\ 6.63 \end{bmatrix} \tag{5.39}$$

$$C = \begin{bmatrix} 0 & 1 \end{bmatrix} \tag{5.40}$$

$$D = [0] \tag{5.41}$$

The next field of interest is the IDDM condition where the results for the IDDM condition is analyzed to see the response of PTH. In a similar approach to the healthy condition, the steady-state and nominal parameters were applied to obtain the state-space model for the IDDM condition. For this system, the values for the initial and final steady-state conditions are represented in the equations (5.46) and (5.47). Also, the system and output matrices are given in the equations (5.42) - (5.45). The initial and final values are obtained assuming the similar conditions of the healthy condition.

$$A = \begin{bmatrix} -0.491 & 0 \\ 0.476 & -0.0953 \end{bmatrix} \tag{5.42}$$

$$B = \begin{bmatrix} -4.72 \\ 4.72 \end{bmatrix} \tag{5.43}$$

$$C = \begin{bmatrix} 0 & 1 \end{bmatrix} \tag{5.44}$$

$$D = [0] \tag{5.45}$$

$$\textit{Initial value} : x(t \to 0) = \begin{bmatrix} 94.30 \\ 9.50 \end{bmatrix} \tag{5.46}$$

$$\textit{Steady state value} : x(t \to \infty) = \begin{bmatrix} 4.72 \\ 23.60 \end{bmatrix} \tag{5.47}$$

In conjunction with the calculation of the system and output matrices for both of the conditions, it is necessary to perform the stability analysis of the system to be sure whether the operating regions are stable or unstable. The calculated eigenvalues for the stability matrix A for the healthy and IDDM conditions are given in the equations (5.48) and (5.49 respectively. The negative real values mean the response is stable for both the system models.

$$Eigen(A_H) = \begin{bmatrix} -0.0643 \\ -0.5199 \end{bmatrix} \tag{5.48}$$

$$Eigen(A_I) = \begin{bmatrix} -0.7901 \\ -0.0825 \end{bmatrix} \tag{5.49}$$

Also, in this thesis, the Routh Hurwitz criterion, has been applied to perform stability analysis. Consider the system matrix A in equation (5.32) in the generalized form below:

$$A = \begin{bmatrix} a & b \\ c & d \end{bmatrix} \tag{5.50}$$

The second degree polynomial for A is calculated as:

$$Poly(A) = \lambda^2 + (-a-d)\lambda + (ad-bc) \tag{5.51}$$

The Routh's table is formulated as:

s^2 : 1 $(ad-bc)$

s^1 : $(-a-d)$ 0

s^0 : $(ad-bc)$

According to Routh's criteria, if the given system is stable, there should be no changes in sign in the first column of the formulated Routh's table.

Thus, it is necessary that:

$$1)(-a-d) > 0 \Longrightarrow a+d < 0 \tag{5.52}$$

$$2)(ad-bc) > 0 \Longrightarrow ad > bc \tag{5.53}$$

As, b is 0 in the system matrix A, this leads to :

$$ad > 0 \tag{5.54}$$

Since

$$a = -(k_{pss} + l_{1ss}) \text{and d} = -l_{2ss} \Longrightarrow ad > 0 \tag{5.55}$$

Also,

$$a+d < 0 \tag{5.56}$$

In other words, the a and d terms in the system matrix must be negative, which is true for the model. Hence, the formulated system is asymptotically stable. In the next chapter, the MATLAB and Simulink control system design for the modified LQR controller is presented.

Chapter 6

Simulink Control System Design

The state-space models developed in the previous chapter are implemented in MATLAB and Simulink to design a controller for the system. The advantage of modeling the control system using Simulink is that it averages out the responses of the states of the system, consequently eliminating the disturbances and noise in the system response [8]. The system has two states and single input with the concentration of PTH in plasma (x_2) being the interest of output. Besides, the setpoint is defined as the new trim value which is not regulating to zero. As a result, the LQR nonzero (NZ) set-point is used for the design of the controller.

For each condition, the steady-state value of x is the commanded output which is given in the table (5.1). While designing the optimal system controller, the focus must be on the optimization of the design characteristics. The design criterion such as overshoot, settling time, rise time, and steady-state performance for the change in concentrations of PTH affect the performance of the system. In control system theory, the step response helps to analyze various transient parameters as mentioned above. The application of the step response to the control system aids in analyzing the behavior of the system with the change in input to the system.

At first weighing matrices can be defined as given in equations (6.1) and (6.2). The Q11 and Q22 terms of the state weighting matrix correspond to the weighting elements for

each of the states of the system. Similarly, the R1 element is the weighting element for the controller input of the system. As described in a chapter (4), one of the most popular approaches for assigning the weighting matrices Q and R is Bryson's rule. Bryson's rule for finding diagonal elements of Q and R matrices is given as below. Select Q and R diagonal with

$$Q_{ii} = \frac{1}{\text{maximum acceptable value of } {x_i}^2}, i = 1, ..., l \tag{6.1}$$

$$R_{jj} = \frac{1}{\text{maximum acceptable value of } {u_j}^2}, j = 1, ..., k \tag{6.2}$$

Since the system of interest is a single input single output system, Bryson's rule can be used to compute the weighting element for the most important state of the system which is the PTH concentration in plasma denoted as x_2 and leaving another weighting element as unity. In defining the weighting elements using the LQR controller, the focus is on normalizing the state feedback variables of the control system by figuring out the maximum permissible values. Therefore, one should be aware that standardization of the system's state feedback variables over a permissible range does not necessarily reflect all the variations in the behaviors of the system. Hence, the selection of weighting matrices Q and R using Bryson's rule cannot always gives the exact optimal operating value for the design of our LQR controller. Nevertheless, the use of Bryson's rule provides a good starting point for designing the LQR controller using the defined set of constraints. However, it was decided to start the simulation with the selection of unity values for both the system and control weighting matrices as given in equations (6.3) and (6.4). Then, the values of the parameters of the Q and R matrices can be further tuned to obtain the desired characteristics of the controller.

Although the model has two states as x_1 and x_2 in the system, there is the only single controller as k_t that regulates the control system. Using the multiple outputs with the single

input is troublesome for the design of the control system using a nonzero set-point LQR controller. Also, only analyzing the response of x_2 with the application of the controller is of interest. So, the x_1 scope block in the Simulink control system model is terminated using the terminator block. The quad partition matrix was implemented by finding the inverse of the partition matrix. The scopes block in the Simulink assists in observing the responses of the system output and the controller input. Additionally, the characteristics of the design from the Simulink model is sent to MATLAB using the workspace command which makes the analysis of the results easier.

$$\textit{Initial state weighting matrix} : Q = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} \tag{6.3}$$

$$\textit{Initial control weighting matrix} : R = [1] \tag{6.4}$$

In this parathyroid-calcium system design, the data for the maximum value of the secretion of parathyroid hormone in response to Ca concentration in the plasma was unavailable. Also, data for the change in parathyroid hormone concentration in plasma and the parathyroid gland is unavailable. So, approximating the initial weighting elements as unity values for the controller design was a good approach.

The model for the control system was designed using the Simulink block diagram that implements proportional and LQR Controller. The matrices involved in the system design can be imported from the MATLAB workspace into Simulink. Also, the design characteristics acquired from Simulink can be sent to MATLAB workspace to analyze the design results. Using the MATLAB function 'LQR', the algebraic Riccati equation of the controller which can be applied to find the optimal gain (K) of the control system can be solved. The Simulink block diagram used for modeling the system using the nonzero setpoint controller architecture is shown below in figure (6-1).

At first, designing of the classical Proportional-Integral-Derivative (PID) controller was

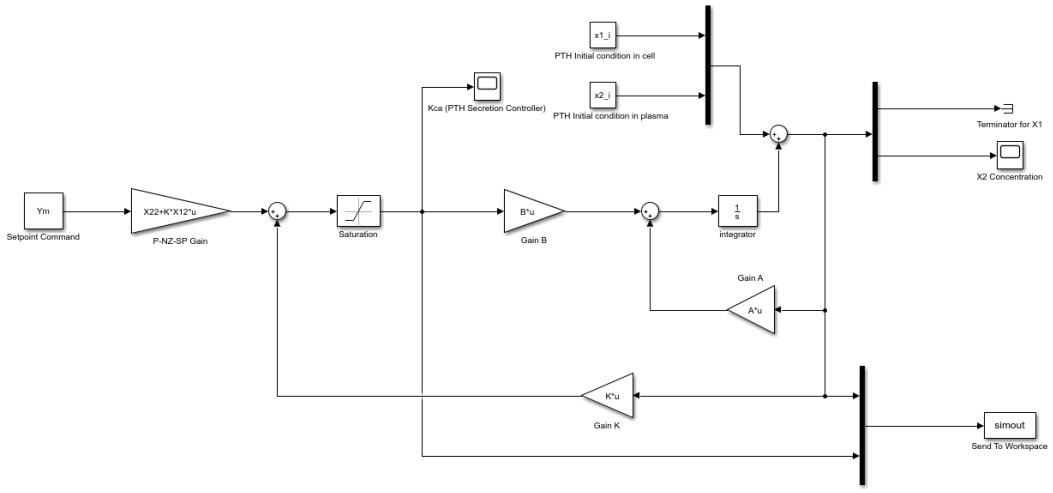

Figure 6-1: P-NZ-SP LQR Controller Simulink Model for the Ca-PTH Control System

done, and the system matrices and weighting elements were applied. The results weren't convincing and the responses were not smooth either. Normally, the traditional PID controllers are used when the system involves a single state and single controller. As a result, the Linear Quadratic Regulator (LQR) controller was implemented which is advantageous over the use of the PID controller as mentioned in the literature. Also, the developed control system model has two states as X1 and X2 which makes the application of the LQR controller more relevant and practical. Moreover, for tuning the weighting elements and improving the performance of the control and system, a PID controller with proportional gain is added to the LQR controller. Also, as the setpoint values which is not regulating to zero are defined, a nonzero set point design architecture is also applied with the controller.

As discussed in section (5), the priority of the Ca-PTH model is to maintain the concentration of PTH in plasma around its steady value. The nonzero set point LQR controller design is mainly concerned with the response of PTH concentration. In the next section, the results observed in the design of the control system for the state and controller response are analyzed.

Chapter 7

Observations And Simulation Results

In this thesis, the MATLAB programming engineering environment is used to perform all the simulations. At first, the results and plots for the healthy conditions model were obtained by performing the simulations . Initial conditions for both the states were defined before the injection of citrate which lowers the concentration of calcium. And, the command output or the set-point values for the controller are the final steady-state values of healthy conditions obtained from the literature [19]. These state values along with the controller input are applied to the Simulink model for simulation. The final Simulink model for the healthy condition using the proportional-nonzero-set-point LQR controller is shown below in figure (7-1).

As shown in the block diagram, 'send to workspace' Simulink block is used to send the design characteristics of the controller and system response to MATLAB workspace where analysis is made for each of the responses. Moreover, using the 'step info' function in MATLAB, the design criterion of our control system to compare with the required characteristics are obtained.

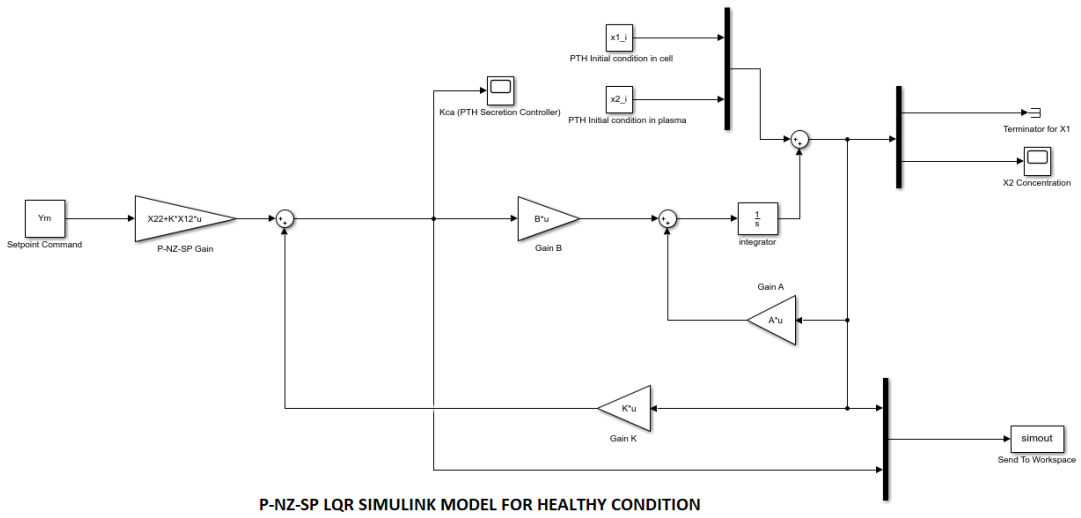

Figure 7-1: Simulink Block Diagram for Healthy Condition

7.1 Healthy condition

At first, the results for the healthy conditions model for the lowering of Ca concentration was obtained using MATLAB and Simulink simulations. The initial conditions used for the states of the system are the steady-state values that were obtained at time t=0 before the injection of citrate in the body. The set-points of the system are the values for the final steady state solutions of the hypocalcemia conditions. The weighting states and the initial and set-point values were applied to MATLAB. Using the LQR command in MATLAB, the gain (K) of the control system was obtained. The model was run for the simulation time of 120, the units are minutes for our model.

The initial response obtained from MATLAB for the desired state(X2) and the controller are depicted in figures (7-2) and (7-3) respectively. From the plots and step info data in MATLAB, it is seen that the rise time of the state is less than 5 minutes which is within the required time restrictions for the model. Although the response of the curve is smooth, it has a greater peak value which is not the required criteria of the design. Moreover, as seen in the figure (7-2), the X2 state has a slight settling time error as it goes to the stead-

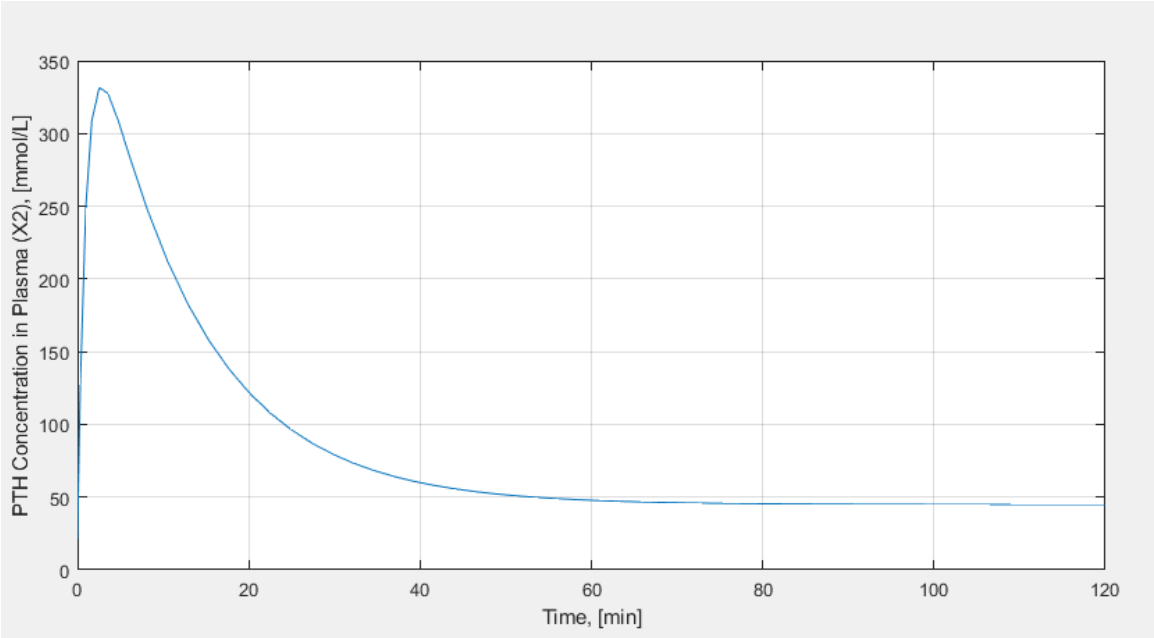

Figure 7-2: System response for initial condition

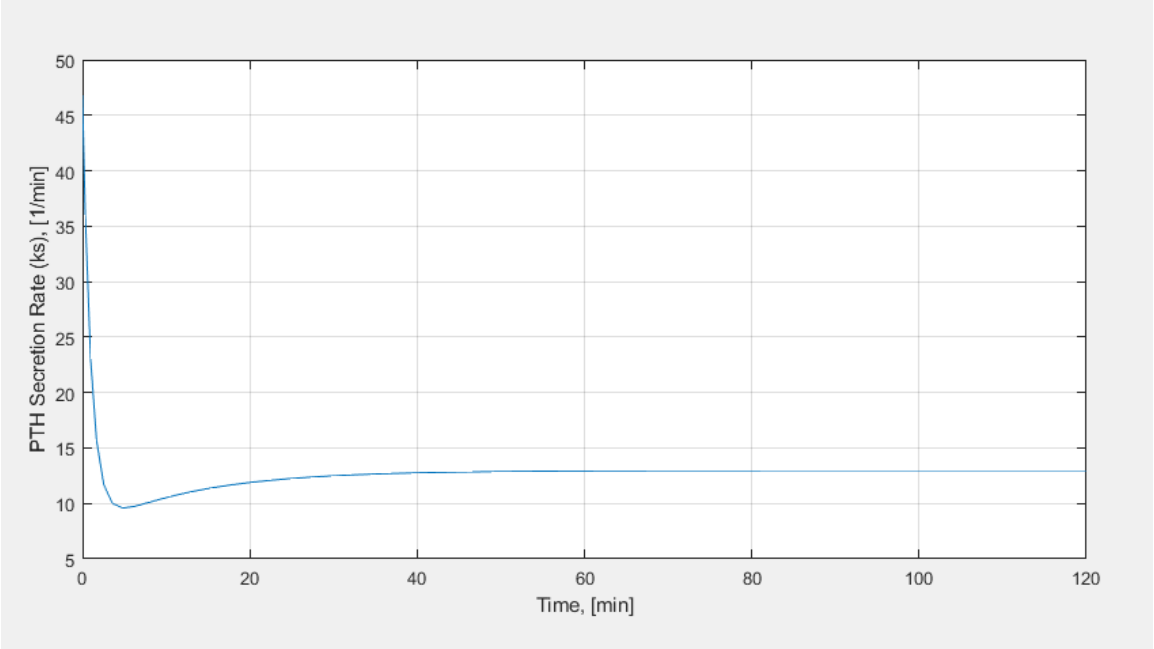

Figure 7-3: Controller response for initial condition

state condition late.

Since the design parameters such as peak time and selling time were not satisfied with the initial weighting values of the control system, weighting matrices elements can be tuned to obtain better results that optimize the design characteristics such as rise time and settling time of the model. From the study presented in the literature, the settling time of the concentration of PTH is specified around 50 minutes which must be less than the time taken by the X2 concentration to settle for the IDDM condition. So, in order to decrease the peak time, the value of R is increased further by a factor of 10. Moreover, the value of Q11 and Q22 are decreased to smaller values to have better responses. The design criteria for the state for different values of the weighting matrices are presented in the tabular form in the table (7.1). The second row of the table presents the simulations design results with these tuned values whereas the figures (7-4) and (7-5) show the response of the system and the controller for these weighting values.

Table 7.1: Tuning Values and Design Parameters For Healthy Operating Condition

Q11	Q22	R	Rise Time (Minutes)	Settling time (Minutes)
1	1	1	2.0512	55.836
0.01	0.1	10	3.142	83.3114
0.001	0.01	10	3.261	50.502

From the state response curve, it is observed that the peak time of the curve decreases but the settling time of X2 concentration increases further beyond the design requirements that is not ideal for the model. In both cases, the controller has smooth and better responses as per the concentration of the states.As there was not any data to compare the controller's response, the value of the controller was kept constant to 10 in other simulations. The reason for keeping the value of R constant without additional increment is to have the cost of the controller cheaper as increasing the weighting element for R makes the controller expensive. Decreasing the value of R enables to operate the controller within the larger range as it penalizes the control input of the control system given in performance index.

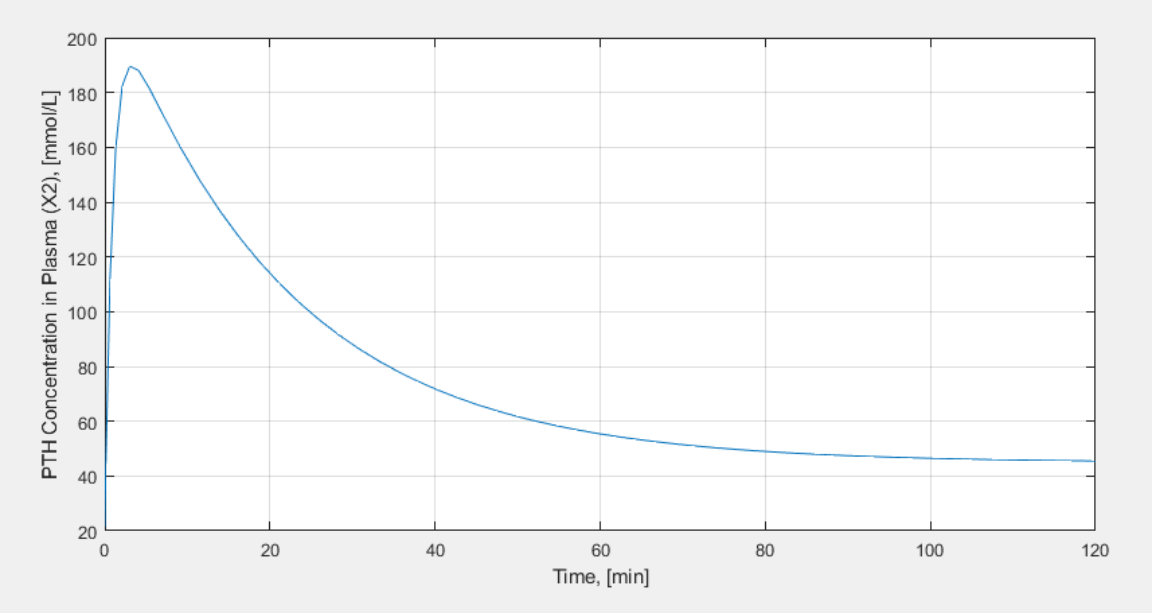

Figure 7-4: System response for Q11 as 0.01 and Q22 as 0.1

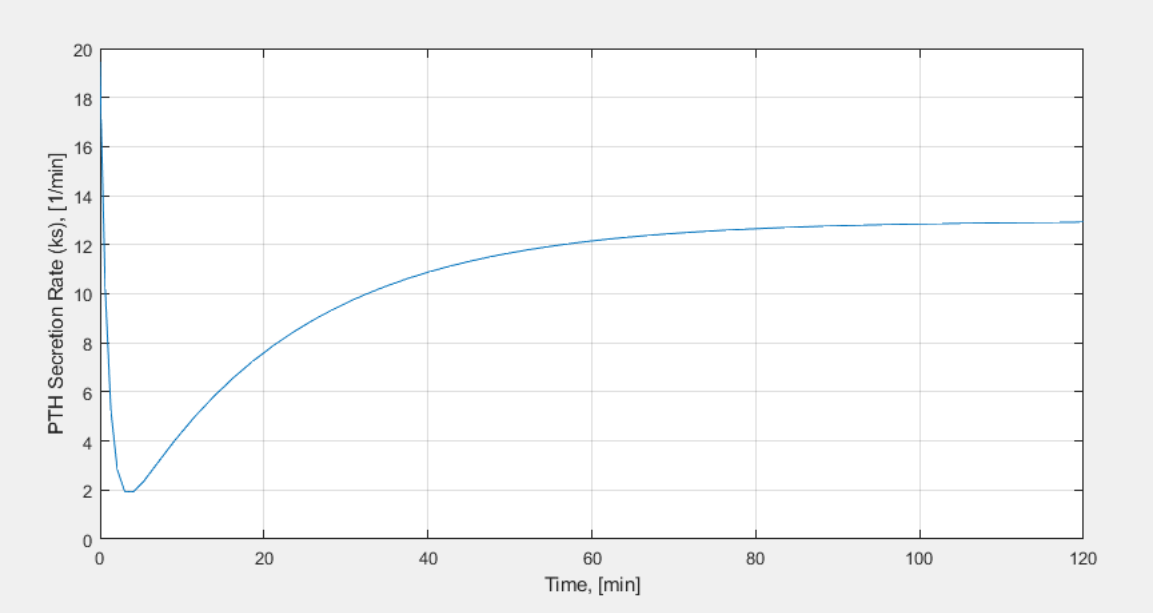

Figure 7-5: Controller response for Q11 as 0.01 and Q22 as 0.1

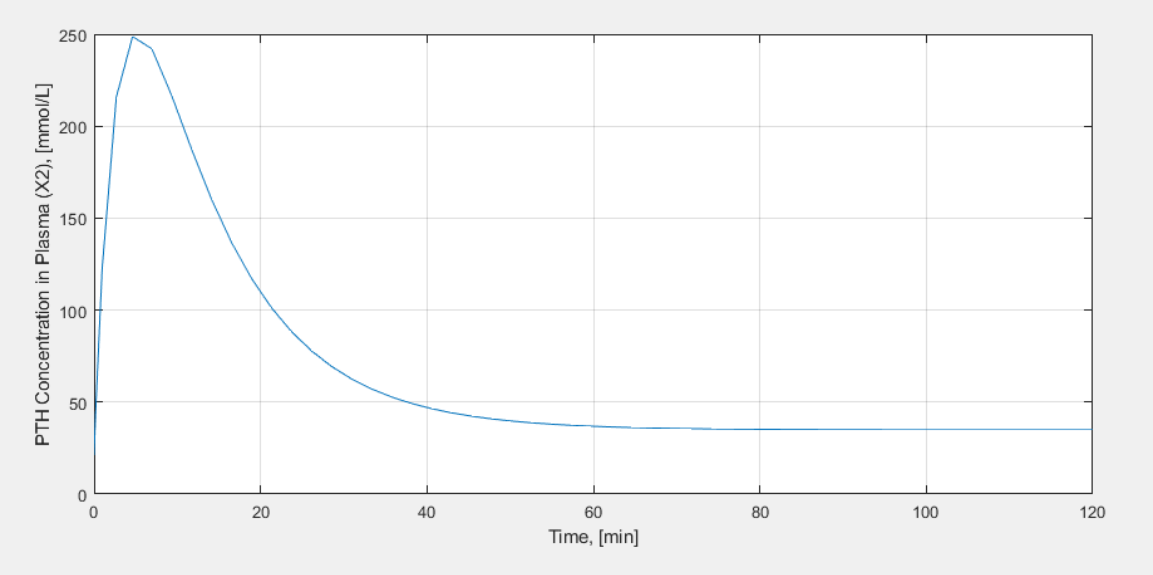

Figure 7-6: System response for Q11 as 0.001 and Q22 as 0.01

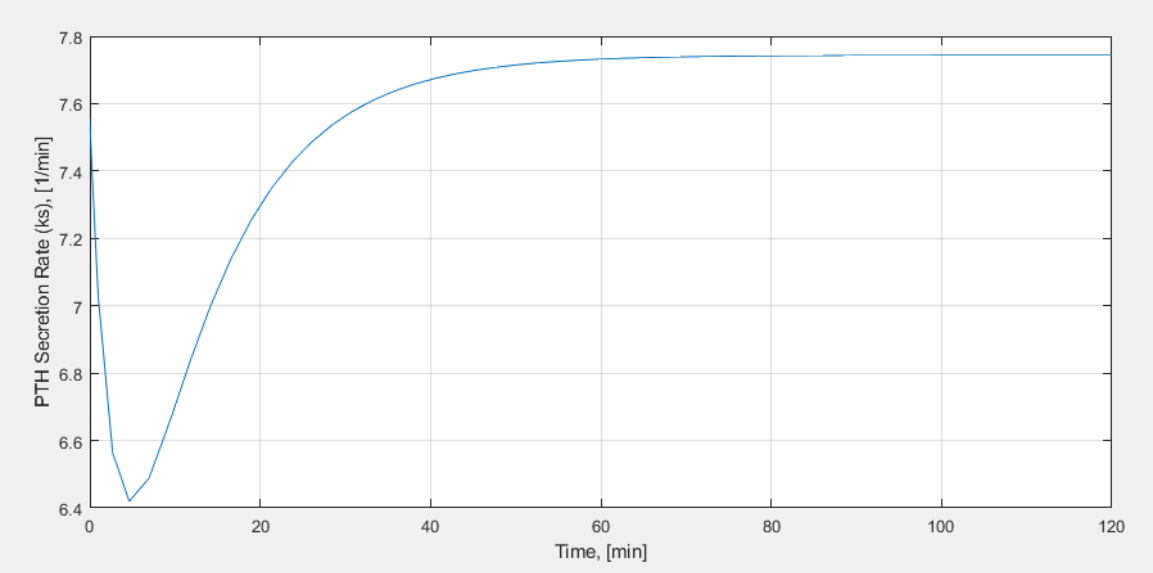

Figure 7-7: Controller response for Q11 as 0.01 and Q22 as 0.01

From table (7.1), it is seen that the rise time of the X2 concentration is around 3 minutes and the settling time is around 80 minutes which is more than we desired. Having the X2 concentration within the time restrictions of 50 minutes is essential for the healthy conditions to have better performance of the control system. Now, to decrease the settling time of the X2 concentration, the weighting element for Q11 and Q22 were varied keeping the weighting element for R constant. Finally, using the weighting values of the Q11 and Q22, as given in the third row of the table, the response of the system and the controller for the control system are shown in the figures (7-6) and (7-7) respectively. The design criteria were observed for both the responses. The settling time and rise time for the controller obtained were within the limit of the design requirements. The response of the controller was responsive to the change in the weighting elements, and showed a smooth response to the change in the x2 concentrations. Overall utilizing the tuning approach by changing the values of the weighting elements proved to be effective for controlling the healthy conditions of the model by keeping the cost of the controller cheaper.

After the completion of the simulations and analyzing the design results, it's equally important to analyze the stability of the system. The use of any controller should stabilize the control system in order to be eligible for the implementation and to obtain better design performance. As a result, an analysis of the stability of a healthy operating condition for the LQR controller was performed. The stability of the closed-loop system controlled by the setpoint LQR controller can be analyzed with the approach of eigenvalues. If the system matrix has all the elements of the eigenvalues negative, then it is said that the controller has succeeded in stabilizing the system. But if any of the elements of the eigenvalue is positive, the system is considered an unstable system.

The eigenvalues of the closed-loop system of the model for the healthy operating condition are given in equation (7.1) which is obtained by the use of MATLAB. From the negative signs of eigenvalues, it is concluded that the setpoint LQR controller stabilizes the healthy operating condition of Ca-PTH model. Moreover, the second eigenvalue is more

negative which means it is the most stable eigenvalue or pole placement. Additionally, equation (7.2) details about the eigenvectors corresponding the eigenvalues of the system. The most negative eigen vector which is the second column in equation (7.2) corresponds to the concentration of X2. This means the response of the X2 concentration of the system should have a better control response to stabilize the control system.

$$Eigen(Ac) = \begin{bmatrix} -0.0748 \\ -0.4666 \end{bmatrix} \tag{7.1}$$

$$Eigenvector(Av) = \begin{bmatrix} -0.6215 & -0.5180 \\ 0.7384 & -0.8554 \end{bmatrix} \tag{7.2}$$

7.2 IDDM condition

Using a similar approach applied to the healthy conditions, the model was run for the unhealthy conditions in Simulink, and results were obtained from MATLAB. Here, the initial values of the states were obtained before the citrate was infused in the body. Also, the final steady-state conditions were obtained assuming the steady-state conditions of parathyroid hormones in plasma and gland. For the IDDM condition, the initial conditions implemented for the states of the system are the steady-state values which were obtained at time t=0 whereas the final setpoint values of the system are the values for the final steady-state solutions of the hypocalcemia conditions. A similar procedure to the healthy condition was followed and the values and the weighting elements were applied to the Simulink model with the same architecture. After that, the LQR command was used to determine the gain of the control system and response of the controller in MATLAB. The Simulink block diagram with P-NZ-SP linear quadratic regulator architecture for the implementation of the model is shown in the figure (7-8).

For the analysis of the control of this IDDM condition, a different architecture with

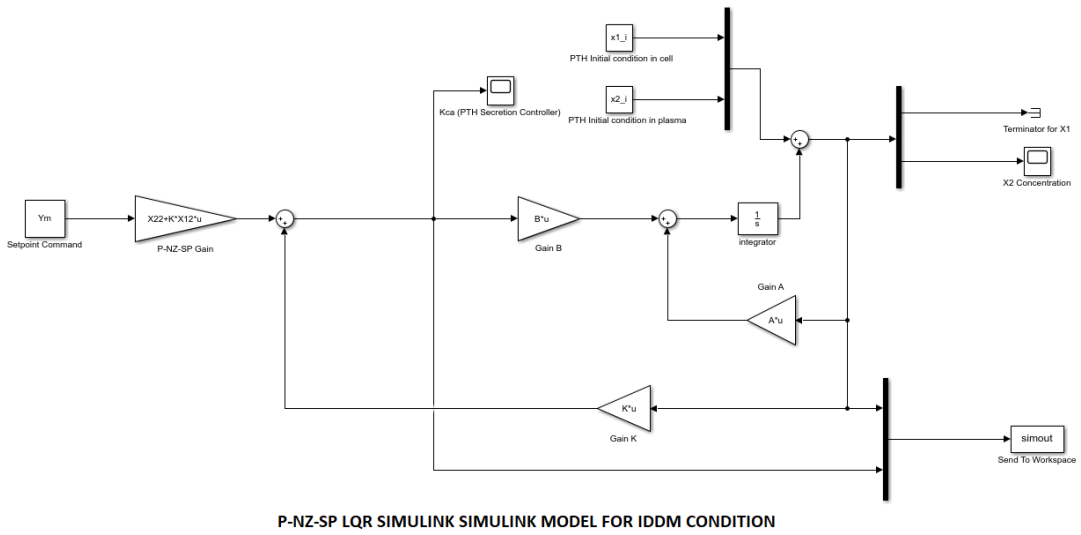

Figure 7-8: Simulink Block Diagram for IDDM Condition

different control systems could be used. But the use of a similar control architecture proves to be cost-efficient and practically feasible for the implementation of the controller. The other advantage for the use of the same P-NZ-SP LQR controller for this condition eases us to obtain the desired design parameters just with the tuning of the weighing elements of the controller.

The initial response of the states and the controller of the system after the implementation of the LQR controller are shown in figure (7-9) and (7-10) respectively. The simulation time of 120 minutes similar to the first condition was used for this condition as well. The observation of the minimal steady-state errors consents to consider the same control architecture for this condition.

From the literature, it is known that the rise time of the x2 state should be under 10 minutes whereas the concentration of the state should decrease gradually after it reaches the peak. Now, from the design characteristics obtained in MATLAB, it is seen that the rise time is only around 1 minute whereas the settling time is about 57 minutes. The concentration of the state decreases gradually after it reaches its peak value as mentioned in the

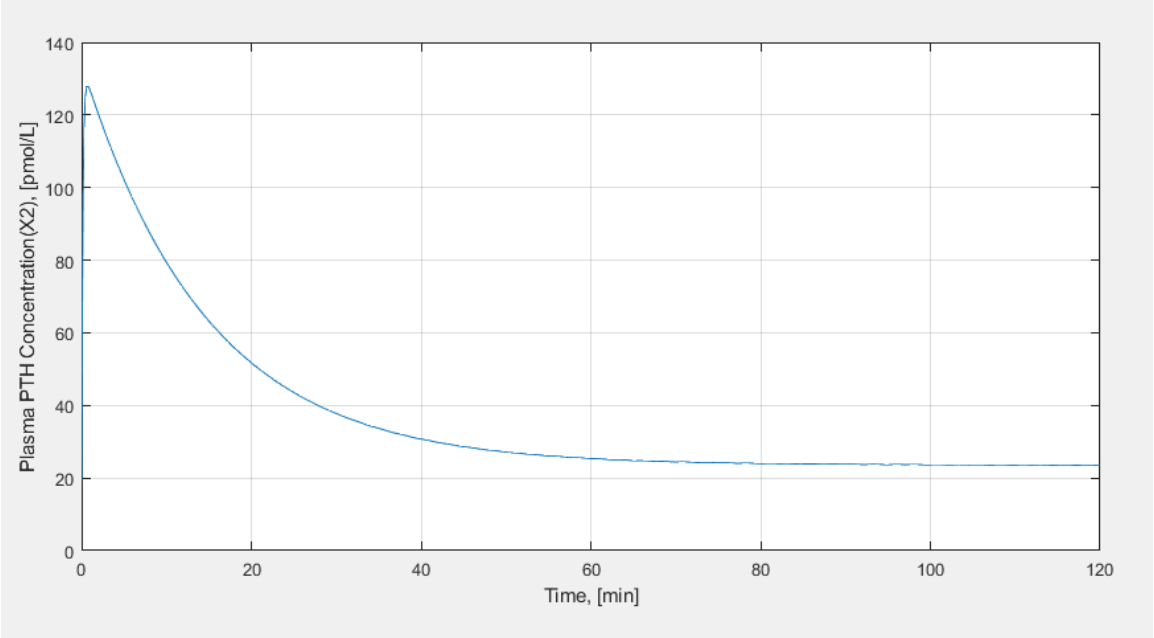

Figure 7-9: System response for initial condition

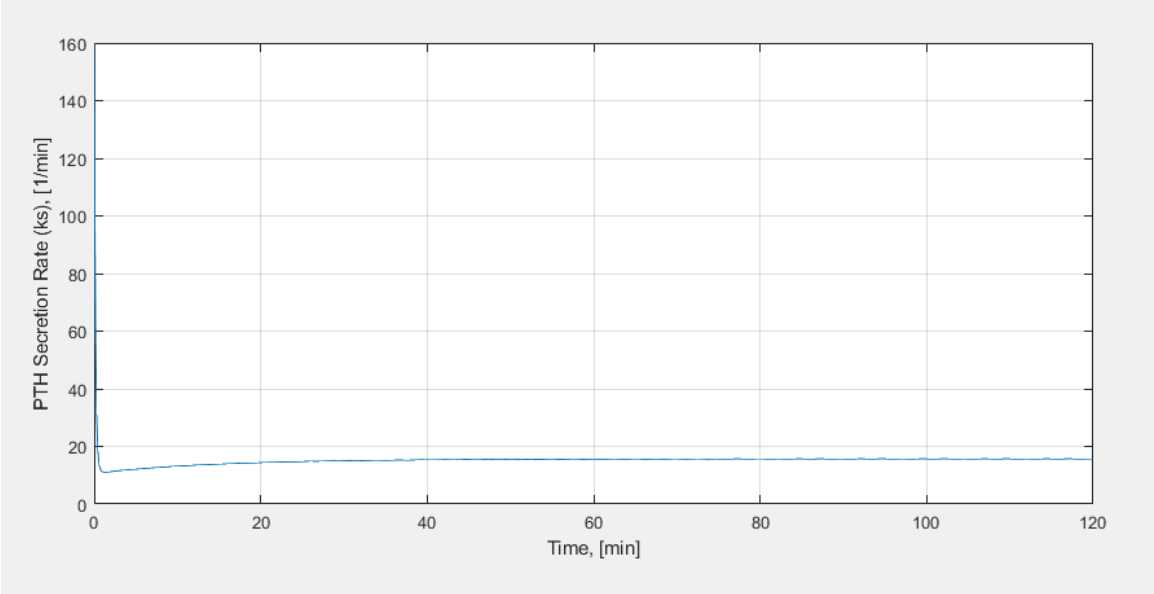

Figure 7-10: Controller response for initial condition

control study. Similarly, the response of the controller which is the response of the PTH secretion rate has ambiguity in the response. The response of the controller for the PTH secretion as seen in figure (7-10) has a downward aggressive trend towards the origin which is not ideal for the control system. From the initial simulations, it can be concluded that although the responses were not accurate, the results obtained were following the desired path. As a result, the simulations using the additional control architecture were not performed for this condition. Now, to obtain better responses for the controller and the state, the optimization of the design characteristics was performed by tuning the elements of the weighting matrices. The simulation was started using the unity values for the state weighing elements and controller weighting element. Then,the value of Q2 and Q1 were tuned as these elements penalize the states x1 and x2 respectively. Similarly, to minimize the undershoot and for the smooth response, the value of R was tuned by the factor of 5. The table below (**??**) displays the design characteristics of the state concentrations for various tuned values of the weighting elements obtained from MATLAB for this IDDM operating condition. As seen in the figure (7-9), although the rise time was within the desired time restriction, the settling time was not desired for the initial condition. The next simulation was performed using the weighting elements of the second row of the table (7.2).

Table 7.2: Tuning Values and Design Parameters for Unhealthy Conditions

Q11	Q22	R	Rise Time (Minutes)	Settling time (Minutes)
1	1	1	1.058	57.474
0.01	0.01	5	4.0	88.053
0.01	0.5	5	0.0150	95.600

The main design criteria for the IDDM unhealthy condition is it should have more settling time than that of the healthy operating condition. This was mentioned in section 5 of the literature. The response of the system and controller after the optimization was improved which are shown in figures (7-11) and (7-12) respectively. The responses were similar to that of initial weighting conditions but with better performance.

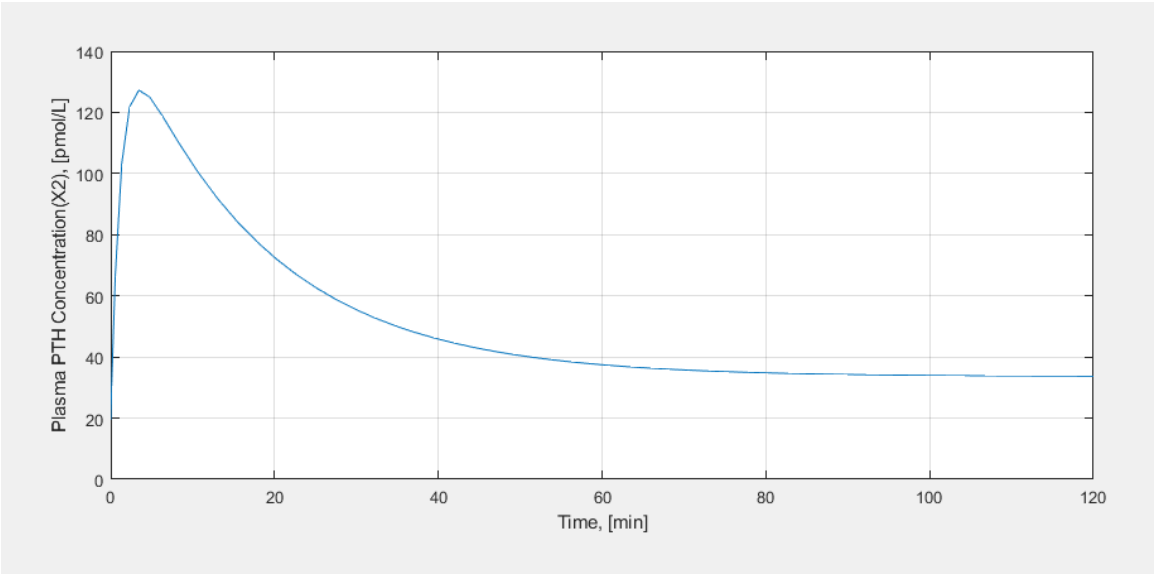

Figure 7-11: System response for Q11 as 0.01 and Q22 as 0.01

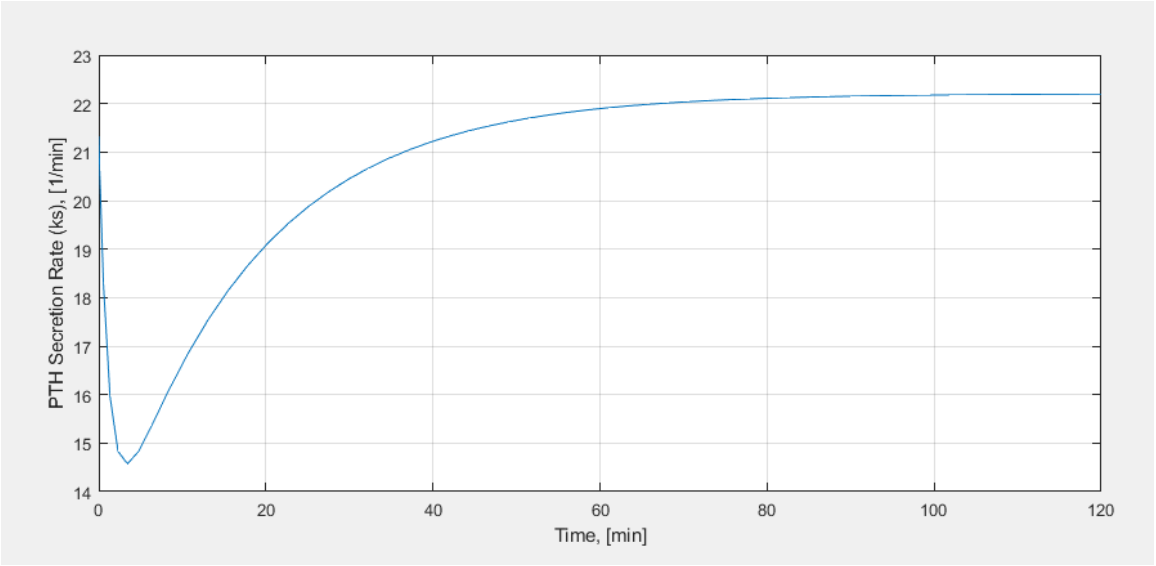

Figure 7-12: Controller response for Q11 as 0.01 and Q22 as 0.01

The response of X2 concentration in the figure (7-11) shows that there is need to have still more settling time for the system. As a result, manipulation of the Q1 and Q2 elements for different values were carried out and the simulations were performed. The Q2 element has an effect on the X2 concentration which is the interest of output for our control system. Also, as mentioned earlier, keeping the low value of R means the control used in the system is less expensive and the system responds less aggressively. The value of R can aslso be increased further, but it would result in a more expensive controller. The goal of the design of the control system is to keep the cost of the controller as cheap as possible. So, keep the value of R constant to 5 for our other simulations. Final simulations were performed keeping Q11 and R constant by tuning only the value of weighting element Q22. The third row of the table with Q22 as 0.5 gives us the better performance for the concentration of the state as clearly seen in the figures (7-13) and (7-14). From the figure (7-13), it is observed that the concentration of X2 reached the peak value which has the rise time within the time restrictions as mentioned in the control study. Besides, it has a better response as it moves towards its steady-state value. As a result, the method of tuning of the weighting elements for the proportional nonzero set-point LQR controller proved to be effective and practical.

Similarly, the stability analysis was carried out for the IDDM condition using a similar methodology used for the healthy condition. The optimal control law of the LQR controller was formulated and implemented in the system. MATLAB was used to obtain the simulation results which is detailed in Appendix (A). The eigenvalues for both the open-loop (without controller) and the close loop system (with controller) were determined. The closed loop eigenvalues obtained for the IDDM condition are given in equation (7.3). From the results, it is clear that the use of the LQR controller in the model stabilizes the system as both the values are negative. Moreover, the second eigenvalue is more negative which means it is the most stable eigenvalue or pole placement. This is also one of the important characteristics in the design of the control system. Additionally, equation (7.4) details about the eigenvectors corresponding the eigenvalues of the system. The most negative

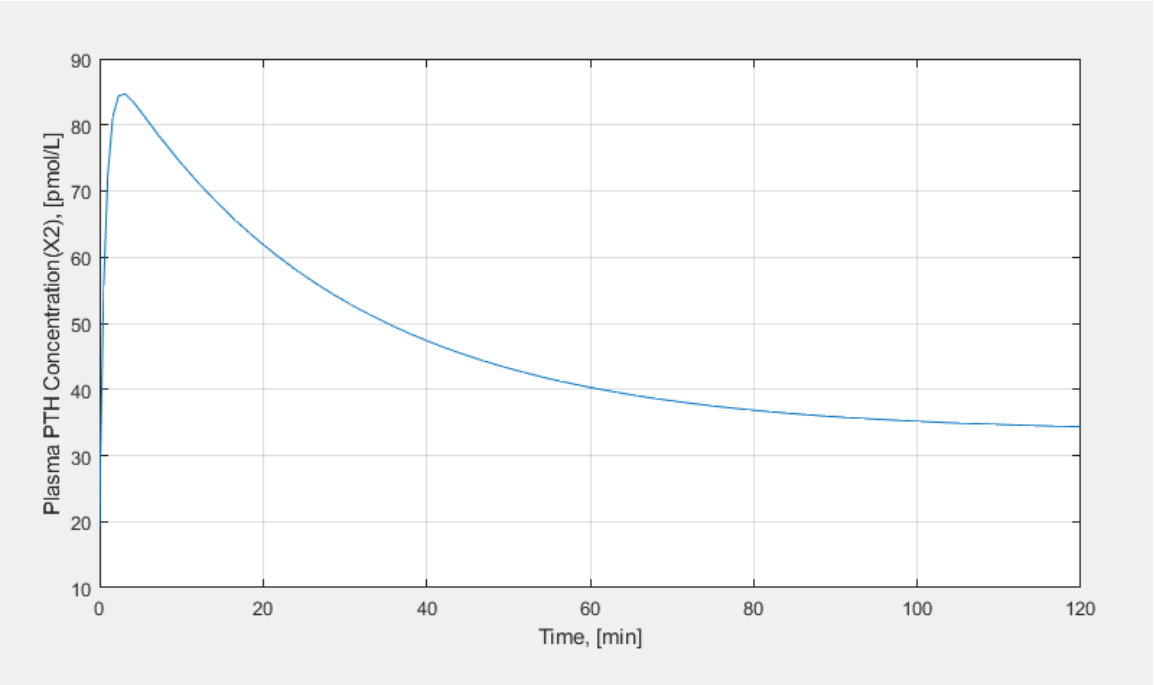

Figure 7-13: System response for Q11 as 0.01 and Q22 as 0.5

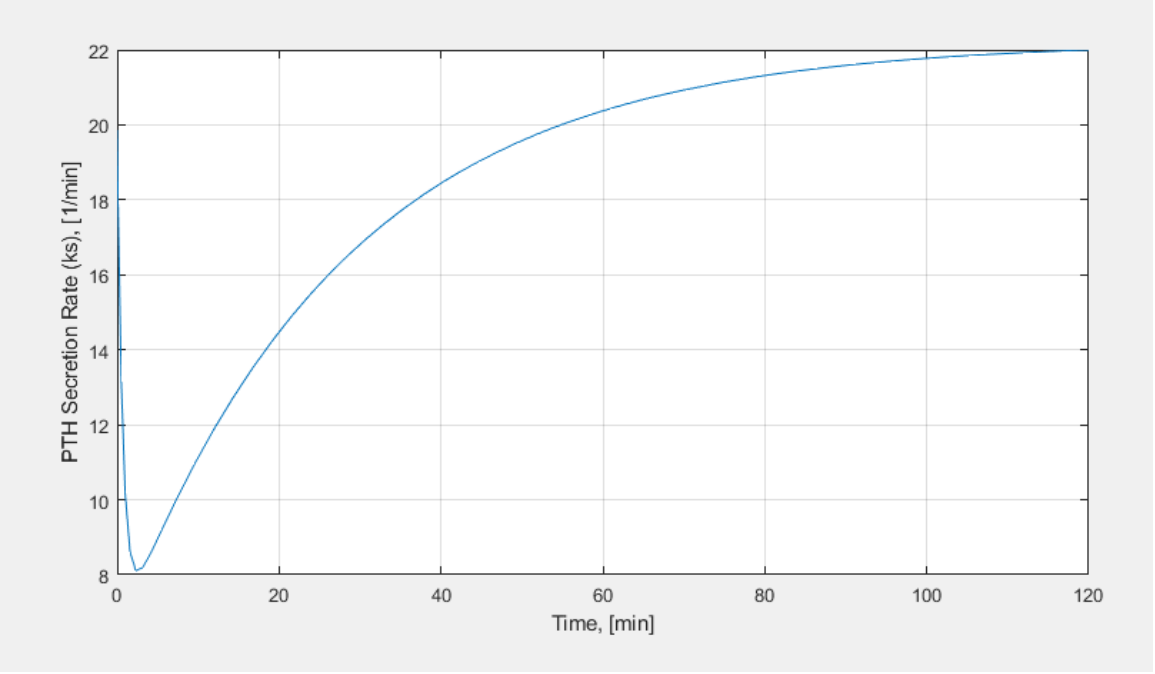

Figure 7-14: Controller response for Q11 as 0.01 and Q22 as 0.5

eigenvector which is the second column in equation (7.4) corresponds to the concentration of X2. Therefore, a rapid and aggressive control response of X2 is needed to obtain a more stable performance of the system.

$$Eigen(Ac) = \begin{bmatrix} -0.0350 \\ -1.5879 \end{bmatrix} \tag{7.3}$$

$$Eigenvector(Av) = \begin{bmatrix} 0.9489 & -0.6883 \\ 0.3155 & 0.7254 \end{bmatrix} \tag{7.4}$$

7.3 Comparison of Results of different conditions of the model

In this work, a Simulink model was developed incorporating the proportional non zero set point linear quadratic regulator architecture. Then the simulations for both the healthy and IDDM (patients) conditions were performed. The healthy operating condition has a normal balance of calcium and parathyroid hormones whereas the IDDM operating condition has less concentration of parathyroid (PTH) hormones as compared to the healthy condition. Section (7) demonstrated the results and analysis of the design performances for both the conditions respectively. The values of the model parameters such as the loss of PTH concentration in the cell and plasma, self secretion of PTH in the cell, PTH secretion due to the change in calcium concentration were kept constant taking their steady-state values for both the conditions. At first, initial conditions for the system and the input control before the lowering of the calcium occurs was followed as given in the literature . The final steady-state values for the model parameters were obtained using the steady-state condition. It is seen from the analysis that the use of the LQR controller in the model proved to be effective in controlling the control system. Further, due to the lack of a complete set of data, it was difficult to compare the results for the response of the input controller of

our system. But from the response curves, it can be assumed the response shown by the controller was responsive to the change in the concentration of the system as the response of the system rises towards its peak, the controller responses fall downwards and achieve the steady-state value.

The comparison of the weighting elements and the design results along with their stability analysis was performed in the previous section. The tuning of the weightings elements provided to be effective in obtaining better performance results. In each of the conditions, the LQR design provides better design criteria such as rise time. settling time and stable steady-state response for the output system. The control system design requirement of rise time less than 5 minutes for the x2 concentration of the system in both the condition was achieved. Also, the concentration of x2 in IDDM condition needs to have more settling time as it needs to go to the stable steady-state slower than that of healthy condition. This time restriction was also successfully achieved with the use of the LQR controller for the system. Also, if there is need to have any other design specifications, tuning of the weighting elements can be done further.

Chapter 8

Conclusion and Future work

In this thesis, a mathematical model of calcium homeostasis sub-model that relates the Ca-PTH relationship was designed. The objective of this research was to implement the SISO optimal control design using the Linear Quadratic Regulator for different health conditions. Besides, it was required to have the settling time of the system concentration in healthy conditions faster than the IDMM (unhealthy) conditions as the design requirements for the research work.

Biological systems such as calcium homeostasis systems are highly nonlinear in nature. It is a challenging job to linearize the system as obtaining clinical data for every point is difficult. As a result, most of the biological systems, modeling and, analysis of the results for the models are difficult. In this model, the linearization of the calcium-parathyroid nonlinear relationship at a nominal point is performed. The steady-state operating condition was considered as nominal points for the model, and a state space representation of the system was developed after the linearization. The Jacobian matrices of the system were obtained using the linearization method developed by Pearson. Then, the nominal values given in the literature were utilized and applied to the state space linear model of the system. The steady state values for the states and controller were obtained.

Generally, for the control of the biological system, the objective is set to minimize the control effort by deriving the control process to the desired final state. Hence, to reduce

the control effort required for the system, the optimal controller design as a non-zero set point linear quadratic regulator was used that helps to minimize the control energy of the system. Moreover, it is necessary keep the value of the weighting element of R minimum as possible. The weighting element of R penalizes the controller values of the system. So, the greater the value of R, the more expensive the controller. As a result, most of the simulations involve the tuning of weighing elements of the Q matrix.

A novel method of LQR controller with proportional nonzero set point architecture was proposed in the study for each of the pathological conditions. The use of the PID controller was considered at the initial phase, but due to the unwanted controller and system response, the LQR controller with slight modification as a set-point controller was implemented.

To start the simulation of the controller, the weighting matrices of the LQR controller were chosen as a unity matrix initially. Since the state for PTH concentration in plasma is the only desired state, the weighting elements of Q11 and Q22 were varied that penalize the states of the system. Initially, the saturation limit controller block on the Simulink model was incorporated. But due to the unavailability of the data set for the range of the controller input, the saturation limit block from the control system design was removed. Overall, due to the unavailability of the complete set of data, comparison of all the design criteria of the system and controller responses for each condition was not possible. Moreover, there was not any previous work related to the work performed in this thesis which makes it difficult to analyze the obtained design performances. Most of the work in the field of designing the optimal controller has been performed to see the system and controller response in the physical systems such as heating system, bioreactor system, mass-spring system, and solar system spaces. The biological and physiological systems are complex and highly nonlinear as they incorporate different hormones, enzymes, organs, and sub-systems. Additionally, the response of one organ or hormone affects the other organ's performance which is difficult and time-consuming to incorporate into the single system. Also, the modeling of the nonlinear physiological system into linear form causes loss of certain parameters depen-

dence onto other parameters that impact the desired results. Nevertheless, studying and analyzing the physiological and biological systems related to calcium or any other hormones are equally important which would help for a better analysis of such systems' performance in the medical field. In the future, with the availability of the complete set of data for the nominal parameters, work or research could be done to study how the application of other hormones such as Vitamin D and calcitonin affect the calcium subsystem model. Further, people can perform the research to see the effect on the PTH and calcium concentration with the increase in the calcium level (hypercalcemia) in the human body. The future research works can also incorporate additional and multiple controllers which would aid in understanding how the biological system functions and analyze their performances.

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Appendix A

MATLAB Code for Simple LQR Controller

clear all;

close all;

clc;

Define the parameters values

ks= 2.32

kp =0.278;

l1= 0.0169;

l2= 0.1098;

Define the simulation time in minutes

Stime = 120;

Define the initial conditions for the states of the system

$x1_i = 98.56$;

$x2_i = 9.87$;

Define Steady State Conditions for State(x) of the system

$x1_s = 44.88$

$x2_s = 6.63$;

Calculate state space matrices of healthy condition

A = [-(ks+l1) 0; ks -l2]

B = [-x1$_s$;$x1_s$];

C = [0 1];

D= [0];

Define the weighting matrices of Q and R

Q = diag[1 1];

R =[1];

Find the open loop system

System open loop = ss(A, B, C, D);

Solve the value of P matrix

P = care(A,B,Q)];

Find the value of gain matrix K

K= lqr(A, B, Q, R);

Find the closed loop matrix

Ac= [(A-BK)];

Find the close loop system

System close loop = ss(Ac, B, C, D)

Find the eigen values of the system

Eigen values Ac = eig(Ac);