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Modelling and control of calcium levels from hormonal regulation in mammals for physiological Functions

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Abstract

Almost all cells employ calcium signals to transmit information and control a variety of metabolic activities. Without calcium ions, it would be unable to beat the heart, contract the skeletal muscles, activate the immune system to fight off invaders, or trigger the release of neurotransmitters to mediate cognitive functions. The cell nucleus can be reached by calcium signals, which can also function locally around the point of calcium entrance into the cytoplasm. The body attempts to maintain a constant level of calcium in the blood and tissues so that it can carry out essential everyday processes. The bones will release calcium into the circulation when blood calcium levels get dangerously low, according to parathyroid hormone. In order to enhance calcium absorption in the intestines, this hormone may also activate vitamin D. PTH instructs the kidneys to release less calcium into the urine at the same time. When the body has enough calcium, a separate hormone called calcitonin works to accomplish the opposite: it lowers the blood calcium levels by preventing the release of calcium from bones and telling the kidneys to excrete more calcium in urine. Our aim is to study the role of calcium in our body and how its homeostasis can affect organisms on both land and sea the work will enable mankind to understand organism better. Understand the diseases in organisms much better and to develop medicine for such diseases. This is only possible when mankind has sufficient knowledge. Our approach in this research paper will be to gain snippets of knowledge already gained by people all around the world.

Keywords: Calcium, Homeostasis, Mitochondria, medical system, Calcium Receptors.

1. INTRODUCTION

Calcium (Ca2+) is a vital element in biological systems, essential for numerous physiological processes such as muscle contraction, neurotransmission, and enzyme activity. The regulation of calcium levels within cells and tissues, known as calcium homeostasis, is crucial for maintaining cellular function and overall health. Disturbances in calcium homeostasis can lead to various disorders, including cardiovascular diseases, osteoporosis, and metabolic imbalances. Research in this field has highlighted the importance of proteins and receptors that regulate calcium levels, such as the calcium-sensing receptor (CaSR) and the mitochondrial calcium uniporter (MCU). Despite significant advances, the precise mechanisms by which these components contribute to calcium regulation and their dysfunction's implications remain inadequately understood. [1]

Calcium ions are involved in virtually all aspects of cellular physiology, acting as a key second messenger in signal transduction pathways. This universal messenger role of calcium is due to its unique properties, such as its ability to bind to proteins and influence their function, its versatility in various cellular compartments, and its rapid mobilization and sequestration by cellular organelles. Calcium's pivotal role in these processes underscores the importance of tightly regulating its concentration both inside and outside of cells. [2]

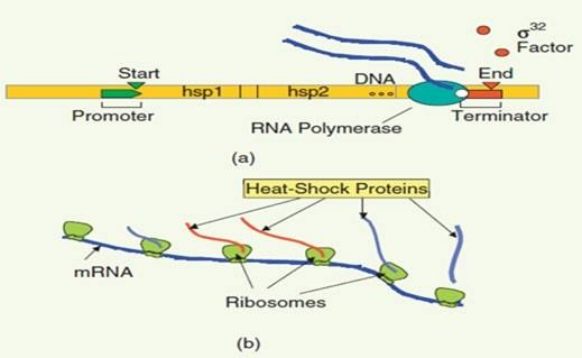


Figure 1: (a) Transcription of DNA gene sequence into messenger RNA (b) Translation process of mRNA into linear sequence of amino acids [13]

The importance of calcium in biological systems extends beyond human health. Calcium signaling is crucial in many different organisms, from simple unicellular organisms like yeast to complex multicellular organisms like plants and animals. For instance, in plants, calcium signaling is essential for responses to environmental stimuli, such as light, gravity, and pathogens. In animals, calcium signaling regulates processes as diverse as muscle contraction, hormone secretion, and neural activity. This widespread significance makes calcium homeostasis a fundamental topic of study across various fields of biology and medicine. [3]

Calcium homeostasis involves the intricate regulation of calcium levels in the body to ensure optimal cellular function. This process includes calcium absorption in the intestines, reabsorption in the kidneys, and storage in bones. Parathyroid hormone (PTH) and vitamin D are key hormones that regulate these processes, ensuring that calcium levels remain within a narrow physiological range. The balance of calcium is critical for various bodily functions, including muscle contraction, nerve transmission, blood clotting, and bone health. [4]

Calcium is absorbed from the diet through the small intestine. This process is regulated by vitamin D, which increases the expression of calcium-binding proteins in the intestinal cells, facilitating the transport of calcium from the gut into the bloodstream. There are two primary pathways for calcium absorption in the intestines: the transcellular pathway, which involves active transport through enterocytes, and the paracellular pathway, which involves passive diffusion between cells. The efficiency of calcium absorption can be influenced by several factors, including age, dietary components, and hormonal status. [5]

The kidneys filter calcium from the blood and reabsorb most of it back into the bloodstream, preventing excessive loss in the urine. This reabsorption process is regulated by PTH, which increases calcium reabsorption in the distal convoluted tubules of the kidneys. The renal handling of calcium is also influenced by other factors such as dietary calcium intake, acid-base balance, and the presence of certain hormones and medications. [6]

Bones serve as a major reservoir for calcium, storing approximately 99% of the body's total calcium. Bone remodeling is a dynamic process involving the coordinated actions of osteoclasts (cells that break down bone tissue) and osteoblasts (cells that form new bone tissue). PTH and vitamin D play crucial roles in regulating bone remodeling. PTH stimulates osteoclast activity, leading to bone resorption and the release of calcium into the bloodstream, while vitamin D enhances the absorption of calcium from the gut and its incorporation into the bone. [7]

Other factors, including mechanical stress, cytokines, and growth factors, also influence bone remodeling. Mechanical stress, such as weight-bearing exercise, promotes bone formation, while cytokines and growth factors can either stimulate or inhibit the activities of osteoclasts and osteoblasts depending on the physiological context. [8]

The mitochondrial calcium uniporter (MCU) is a significant channel that facilitates the uptake of calcium ions into the mitochondria. This process is vital for regulating mitochondrial function and energy production. Mitochondria, often referred to as the powerhouses of the cell, rely on calcium to generate ATP, the primary energy currency of the cell. Dysfunctions in the MCU can lead to altered cellular metabolism, contributing to various diseases, including neurodegenerative disorders and cardiac diseases. [9]

The MCU is part of a larger protein complex that spans the inner mitochondrial membrane. This complex includes regulatory proteins such as MICU1, MICU2, and EMRE, which modulate the activity of the MCU channel in response to changes in cytosolic calcium levels. The coordinated function of these proteins ensures that calcium uptake is tightly regulated and occurs only when necessary. Within the mitochondrial matrix, calcium ions activate several enzymes of the tricarboxylic acid (TCA) cycle, including pyruvate dehydrogenase, isocitrate dehydrogenase, and alpha-ketoglutarate

dehydrogenase. These enzymes increase the production of NADH and FADH2, which are essential for driving the electron transport chain and ATP synthesis. Therefore, MCU-mediated calcium uptake is crucial for maintaining cellular energy balance. [10]

While calcium is essential for mitochondrial function, excessive uptake can lead to mitochondrial dysfunction and cell death. High levels of mitochondrial calcium can trigger the opening of the mitochondrial permeability transition pore (mPTP), leading to loss of membrane potential, release of pro-apoptotic factors, and initiation of apoptosis. This dual role of mitochondrial calcium in supporting cell survival and promoting cell death underscores the importance of tightly regulating MCU activity. Dysfunctions in the MCU have been linked to various diseases, including neurodegenerative disorders such as Alzheimer's and Parkinson's diseases, as well as cardiac conditions like ischemia-reperfusion injury. Understanding the molecular mechanisms underlying MCU regulation and function can provide insights into potential therapeutic strategies for these conditions. [11]

G proteins and beta arrestin are responsible for the The calcium-sensing receptor (CaSR) is a G-protein-coupled receptor that plays a pivotal role in maintaining systemic calcium homeostasis. It is primarily expressed in the parathyroid glands and kidneys, where it detects changes in extracellular calcium levels and modulates PTH secretion accordingly. When extracellular calcium levels rise, CaSR activation leads to a decrease in PTH secretion, reducing calcium release from bones, reabsorption in the kidneys, and absorption in the intestines. The CaSR is a dimeric receptor with an extracellular domain that binds calcium ions, a seven-transmembrane domain typical of G-protein-coupled receptors, and an intracellular domain that interacts with G-proteins to initiate downstream signaling pathways. [12]

The receptor can bind not only calcium but also other divalent cations and polyamines, making it a versatile sensor of extracellular ionic changes. Upon binding calcium, the CaSR activates several signaling pathways, including the phospholipase C (PLC) pathway, which generates inositol trisphosphate (IP3) and diacylglycerol (DAG), leading to the release of intracellular calcium stores and activation of protein kinase C (PKC). These signaling events ultimately result in the regulation of PTH secretion and other cellular responses. [13]

Mutations in the CaSR gene can lead to disorders characterized by abnormal calcium levels. For instance, inactivating mutations in CaSR cause familial hypocalciuric hypercalcemia (FHH), a condition characterized by elevated blood calcium levels and reduced urinary calcium excretion. Conversely, activating mutations in CaSR lead to autosomal dominant hypocalcemia (ADH), characterized by low blood calcium levels and increased urinary calcium excretion. These conditions highlight the critical role of CaSR in maintaining calcium balance. Understanding the function and regulation of CaSR has therapeutic implications for various calcium-related disorders. For example, calcimimetics, which are CaSR agonists, are used to treat secondary hyperparathyroidism in patients with chronic kidney disease. Conversely, calcilytics, which are CaSR antagonists, have potential applications in treating conditions like osteoporosis by stimulating PTH secretion and increasing bone formation. [14]

Calcium ions serve as versatile signaling molecules in various cellular processes. The transient increase in intracellular calcium levels, known as calcium signaling, is a common response to external stimuli. This signaling mechanism is essential for processes such as muscle contraction, neurotransmitter release, cell proliferation, and apoptosis. [15]

In skeletal muscle cells, calcium signaling is crucial for contraction. The release of calcium from the sarcoplasmic reticulum into the cytoplasm triggers the interaction between actin and myosin, the proteins responsible for muscle contraction. This process is regulated by the troponin-tropomyosin complex, which undergoes a conformational change in response to calcium binding, allowing myosin to bind to actin and generate force. [16]

In cardiac muscle, calcium-induced calcium release (CICR) is a key mechanism. The entry of calcium through voltage-gated L-type calcium channels during the cardiac action potential triggers the release of additional calcium from the sarcoplasmic reticulum. This amplifies the calcium signal and ensures a robust contraction necessary for effective heart function. [17]

The calcium-sensing receptor (CaSR) mediates pluripotent effects by connecting to multiple heterotrimeric G-proteins and downstream signaling pathways in a ligand- and cell-type-specific manner. Calcium mobilization and activation of Gi/o through CaSR-induced Gq/11 activations, Calcium-dependent inhibition of adenylyl cyclase, or Calcium-dependent

activation of PDE-1 all reduce camp levels. CaSR-induced G12/13 activation regulates the activity of the small G-protein Rho-A and several other signalling checkpoints that contribute to gene expression regulation, cytoskeleton modulation, and shape change. Classical CaSR agonists such as calcium, magnesium, and potentially polyamine spermine are physiologically relevant CaSR activators. Endogenous positive allosteric modulators include L-amino acids and perhaps glutathione analogs. pH and ionic strength also influence CaSR, with protons and high ionic strength acting as negative modulators. For the treatment of hyperparathyroidism, synthetic positive modulators of CaSR function (calcimimetics) such as cinacalcet have entered clinical use. Synthetic negative modulators of CaSR function are still being researched. The CaSR is resistant to desensitization and elicits agonist-driven insertional signalling (ADIS) to maintain receptor density at the plasma membrane to sustain its systemic role in Ca2 o monitoring. Finally, CaSR agonists and positive modulators cause significant stimulus-biased signalling, which may be used to better understand a variety of ligand-dependent physiological processes such as L- amino acid-induced gut hormone release and Calcium o-induced modulation of calcium homeostasis. These discoveries may also pave the path for the creation of novel medications with tissue-specificity and therapeutic results. [18]

Calcium-Dependent Transcription Factors: Calcium signaling is involved in regulating gene expression by activating calcium-dependent transcription factors. For example, nuclear factor of activated T-cells (NFAT) and cyclic AMP response element-binding protein (CREB) are transcription factors that are activated by calcium-calmodulin-dependent kinase (CaMK) pathways. These factors regulate the expression of genes involved in cell proliferation, differentiation, and survival.[19]

Calcium signaling can also play a role in programmed cell death (apoptosis). Elevated intracellular calcium levels can activate apoptotic pathways by triggering the release of cytochrome c from mitochondria, leading to the activation of caspases, the enzymes responsible for executing apoptosis. Additionally, calcium can activate calcium-dependent proteases such as calpains, which contribute to the apoptotic process by cleaving cellular substrates. Dysregulation of calcium signaling can contribute to various diseases and pathological conditions. For example, abnormal calcium handling in cardiac cells can lead to arrhythmias and heart failure. In neurons, disrupted calcium homeostasis is implicated in neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Understanding the mechanisms of calcium signaling and its dysregulation provides insights into potential therapeutic targets for these conditions. Research on calcium signaling has been greatly facilitated by advances in calcium imaging techniques. These techniques allow real-time visualization of calcium dynamics within cells and tissues. Fluorescent calcium indicators, such as Fura-2 and Fluo-4, are commonly used to monitor intracellular calcium levels. Genetically encoded calcium indicators (GECIs), such as GCaMP, have also been developed to enable cell-specific and subcellular resolution of calcium signals. These tools have provided valuable insights into the spatiotemporal dynamics of calcium signaling and its role in various physiological and pathological processes. [20]

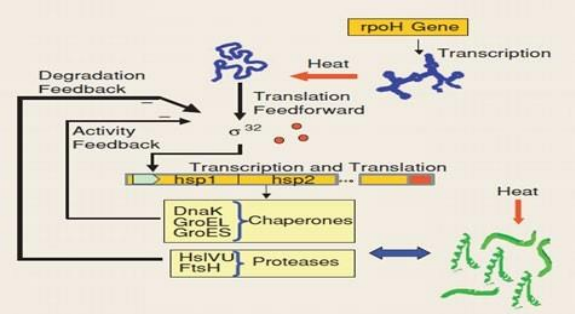


Figure 1: Block diagram of HS response [5]

Ref No	Paper Title	Approach	Outcomes
1	The physiological role of mitochondrial calcium revealed by mice lacking the mitochondrial calcium uniporter	Bioenergetic cell death have been postulated from mitochondrial calcium	The swelling of mitochondria was measured as a decrease in absorbance
2	Renal Control of Calcium, Phosphate, and Magnesium Homeostasis	Renal excretion is used to balance Gastrointestinal absorption	Renal Failure can be used to determine the importance of normal calcium
3	Role of Calcium Ions in the Regulation of Mammalian	Active system is possessed by mitochondria for specific transfer of calcium	Kinetics of mitochondria are damped down as matrix changes
4	Extracellular Ca2+ Sensing, Regulation of Parathyroid Cell Function, and Role of Ca2+ and	Calcium regulates muscle contraction hormonal	The sensitivity of calcium is important as it play important role in

	Other Ions as Extracellular (First) Messengers	secretion and cell metabolism	extracellular homeostasis
5	Regulation of sarcoplasmic reticulum Ca21 ATPase pump expression and its relevance to cardiac muscle physiology and pathology	The main role of the sarcoplasmic reticulum is to regulate cardiac function which has received great attention	For calcium removal and contraction SERCA2 is important because of its vital role
6	Extracellular Calcium Sensing and Extracellular Calcium Signaling	An actual molecular mechanism is provided by G protein for known effects of calcium on the cells and tissues	The sensors are versatile for calcium regulation and have great potential
7	Calcium Absorption Across Epithelia	Epithelia is important as calcium absorption take place there. The pathway into extracellular calcium is constituted by small intestine and kidney	Complex array is used for calcium transportation to regulate hormonal development and physiological functions
8	Calcium Dynamics: A Model System Approach	Calcium metabolism in growing chicks is simulated with the help of a computerized model and developing differential equations	The structural contribution of calcium to bone is emphasized by classical nutrition because of its importance in regulation purpose
9	Understanding calcium homeostasis in postnatal gonadotropin-releasing hormone neurons using cell-specific Pericam transgenics	Fertility in mammals is controlled using complex neuronal network which are the outputs of the gonadotropin hormone	Variable Pericam fluorescence hampered the simultaneous measurement of calcium In different neurons
10	Regulation of Calcium and Magnesium	Extrusion of calcium from the cell by ATP-dependent energy-driven calcium pumps is one of the mechanisms to	Calcium is the main regulator of PTH. The secretion of PTH is governed by a steep curve which is characterized
		prevent calcium-induced cell death	by the maximum rate
11	The calcium-sensing receptor in physiology and in calciotropic and noncalligraphic diseases	Parathyroid glands and kidneys are calciotropic tissues which is form in which calcium sensing receptor is expressed	CaSR influences many physiological processes as it is expressed in noncalcitropic tissues such as nutrient sensing and the secretion of insulin
12	Intracellular Calcium Dysregulation: Implications for Alzheimer's Disease	Mitochondria and endoplasmic reticulum are the subcellular components that are emerging in the pathogenesis and dysregulation of calcium	The proximal cause of cell dysfunction during AD is a mechanism of calcium imbalance mainly related to sub cellular organs
13	Ca2 homeostasis and endoplasmic reticulum (ER) stress: An integrated view of calcium signaling	Calcium sensors and buffers are used to maintain cellular calcium homeostasis through integrated and coordinated function	The in and out movement of calcium is maintained by the cell membrane containing many calcium transport and binding molecules
14	Nuclear calcium signaling in the regulation of brain function	Biochemical processes are initiated by synaptic activities leading to various outcomes like memory formation	Organism needs adaptation to cope with constantly changing environment
15	MICU1 regulation of mitochondrial Ca2 þ uptake dictates survival and tissue regeneration	Mitochondrial matrix receives signals from cytoplasmic for controlling ATP production but excessive can lead to death of cell.	The calcium transport measurement did not interfere with embryonic development and MICU1 deletion was validated
16	Calcium-sensing receptor (CaSR): Pharmacological properties and	the calcium-sensing receptor (CaSR) induces its	The calcium-sensing receptor (CaSR) mediates

	signaling pathways	cellular responses via the control of the signaling pathway	pluripotent effects by coupling in a ligand- and celltype-specific manner
17	Mitochondrial calcium and the regulation of metabolism in the heart	Mitochondria is important as it makes pathway for ATP production using calcium	Calcium is involved in regulating components involved in mitochondrial ATP production. In heart they are interconnected and are very abundant
18	Intracellular Calcium Homeostasis and Signaling	Calcium is released inside the cell with the interaction of first messenger as calcium is the second messenger with plasma membrane receptor. It can also deliver information without intermediation	Calcium is not only the signal that regulates cell life but also accesses the negative and death cells so that they could not cause damage to mammals
19	Calcium trafficking integrates endoplasmic reticulum function with mitochondrial bioenergetics	The divalent cation has an inherent ability to bind multiple target biological molecules reversibly for generating a versatile signaling system	There are numerous cell functions that extend beyond bioenergetics metabolism for which the communication between mitochondria and ER for coordination of cellular homeostasis is especially important
20	Calcium/calmodulin-mediated regulation of plant immunity	Diverse Calcium-binding proteins translate signatures to proper cell responses. Calmodulin protein is a primary calcium sensor that controls various functions by	CML are quite diverse in plants so defining the biological role will be difficult, However, the gene expression analysis and targeted isolations can to accessed to get more than enough
		simply targeting them	information about their behavior

2. METHODOLGY

A crucial physiological cation is calcium which plays a very important role in human functions. The integrity of the skeleton is maintained by calcium salts, and calcium ions in intracellular and extracellular fluids play a key role in the regulation of several metabolic processes. Extracellular calcium ions are required for many different processes, including hormone secretion, blood clotting, and neuro-muscular excitability, whereas intracellular calcium ions are important for the activity of many different enzymes and are also involved in transmitting information from the cell's surface to its interior. Extracellular and intracellular calcium concentrations must be kept within a certain range in order to carry out these crucial metabolic functions. In a publication, Ramberg et al (1984) attempted to describe the calcium homeostatic system in the dairy cow in terms of regulated, controlling, and disturbed signals. The plasma calcium concentration and bone calcium content are considered controlled signals, whereas intestinal calcium absorption, bone calcium resorption, and renal calcium reabsorption are considered controlling signals. The disturbing signals are those that cause loss of calcium from the blood plasma. Hurwitz et al. (1983) presented a model for the plasma calcium. The calcium plasma concentration is regulated sing a feedback control system to follow a setpoint, Calcium supply depends on the difference between the setpoint and the actual concentration. The proportional feedback model used by Ramberg et al. is based on the topic of overall calcium homeostasis mechanism. Proportional feedback cannot be used to achieve calcium homeostasis. Our approach is based on the dynamics formed from proportional feedback. In this case, proportionality constant is only the control block. It is very simple to design a minimal system. One approach uses the translational machinery for HS genes which are sensitive to temperature. Denatured proteins are refolded by chaperones produced during gene expression. This technique can be implemented using simple components used as open loop and do not require the complex HS system. Cells also have the ability to reduce the effect of undesirable noise. The model for basic calcium homeostasis is obtained

during lactation in dairy cows. This data is similar when obtained at the point of calving. Just before calving, the large increase in the lactational requirement for calcium is used as a step disturbance in Vcl ranging from 20 to 70 g/day. This is calculated as a proportionality constant between Vt and the tracking error e(t); that is given as,

$$V_T = K_P\, e(t) = 1770e(t) \left[\frac{g}{day}\right] \quad (1)$$

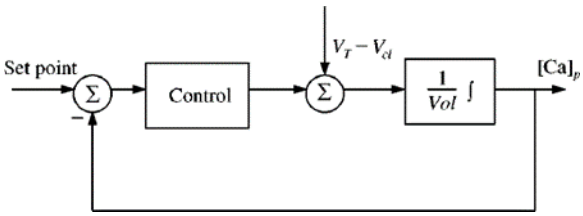


Figure 3: Block diagram for the controller system along with disturbances [16]

The characteristics of the feedback control system are characterized by the differential equation

$$\frac{d[Ca]_P}{dt} + \frac{K_P[Ca]_P}{vol} = -\frac{V_{cl}}{vol} + \frac{K_P(r)}{vol} \quad (2)$$

where r is calcium concentration setpoint.

A feedback model for Vt is proposed which has a proportional as well as an integral part. This is what is referred to as a PI controller. The expression for Vt at a given time instance is

$$V_T = K_P e + K_I \int e \quad (3)$$

where Kp and Ki are constants and e is the error in regulation which consists of a setpoint r and [Ca]p. the differential equation of the second order feedback system is given as,

$$\frac{d^2[Ca]_p}{dt^2} + \frac{K_P d[Ca]_p}{(vol)(dt)} + \frac{K_I[Ca]_P}{vol} \quad (4)$$

Step changes of any given magnitude results in zero steady-state error that too after a very short transient period. The transient response characteristics of the second order system are also desirable.

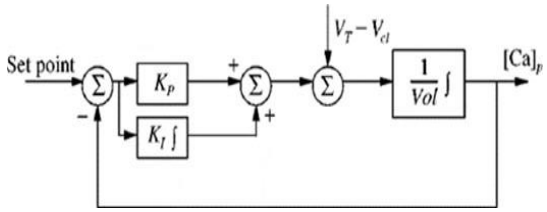


Figure 4: Block diagram of closed loop transfer function [16]

The Approach discussed is referred by Calcium Homeostasis and Parturient Hypocalcaemia by M. KHAMMASH

3. IMPLEMENTATION

For observing the system response and for improving it by the required characteristics we had options, we went for MATLAB as it is more compatible and user-friendly. MATLAB and Simulink used the main software for checking and implementing responses and results. MATLAB mostly was used for finding out transfer functions and for observing system transient characteristics whereas Simulink was used for plotting responses against various inputs and for making block diagrams of the system.

3.1 Time response of our system

Solving by partial fraction

$$s = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

$$s = \frac{-69 \pm \sqrt{69^2 - 4(1)(70.85)}}{2(1)}$$

$$s = \frac{-69 \pm 33.4574}{2}$$

$$s = -1.0426\,;\, -67.9574$$

$$\mathrm{T}(s) = \frac{1361}{(s+1.0426)(s+67.9574)}$$

$$\frac{1361}{(s+1.0426)(s+67.9574)} = \frac{A}{s+1.0426} + \frac{B}{s+67.9574}$$

A = 20.33; B = -20.33

So, our time response becomes

$$T(S) = \frac{1361}{(s+1.0426)(s+67.9574)} = \frac{A}{s+1.0426} + \frac{B}{s+67.9574}$$

$$\frac{1361}{(s+1.0426)(s+67.9574)} = \frac{20.33}{s+1.0426} - \frac{20.33}{s+67.9574}$$

And for time domain, we take inverse Laplace

$$f^{-1}\, T(s) = f^{-1}\left\{\frac{20.33}{s+1.0426} - \frac{20.33}{s+67.9574}\right\}$$

$$T(t) = -20.33e^{-67.95t} + 20.33e^{-1.04t} \text{ (Natural Response)}$$

3.2 System Characteristics

To find Natural Frequency ω_n and Damping Ratio ζ characteristics of a 2nd order system, we transform the transfer function into following form

$$G(s) = \frac{\omega^2 n}{s^2 + 2\,\zeta\omega n + \omega^2 n}$$

By comparing, we get

$$\omega^2 n = 70.85$$

which gives $\omega_n = 8.4172$

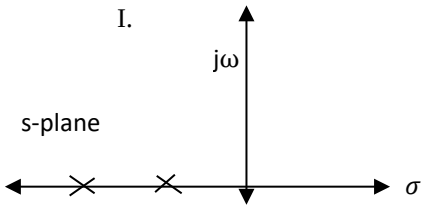
And from $2\,\zeta\omega n = 69$

We get $\zeta = 4.0988$ which is > 1

System is over damped because it has two real poles; and zeta is greater than 1

Hence Response is of form

$$c(t) = K_1 e^{-\sigma 1 t} + K_2 e^{-\sigma 2 t}$$



$$T_s = \frac{4}{\zeta\Omega N} = \frac{4}{(4.0988)(8.4172)} = 0.1159\ sec$$

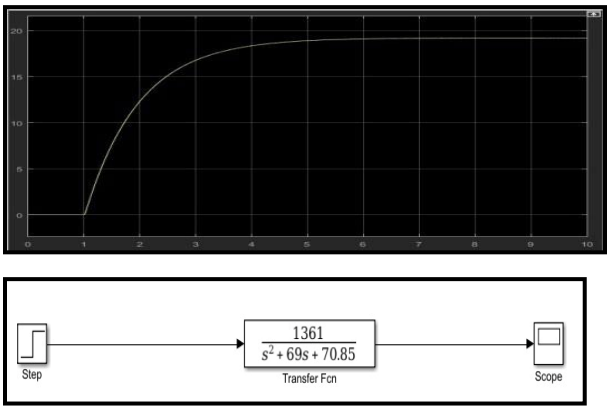


Figure 5: Step response of the system

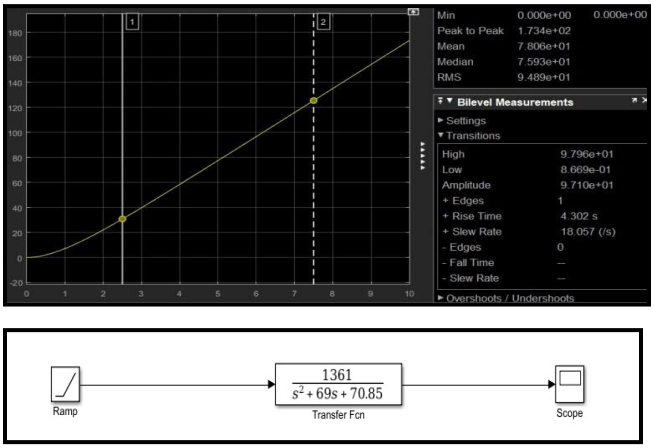


Figure 6: Ramp response of the system

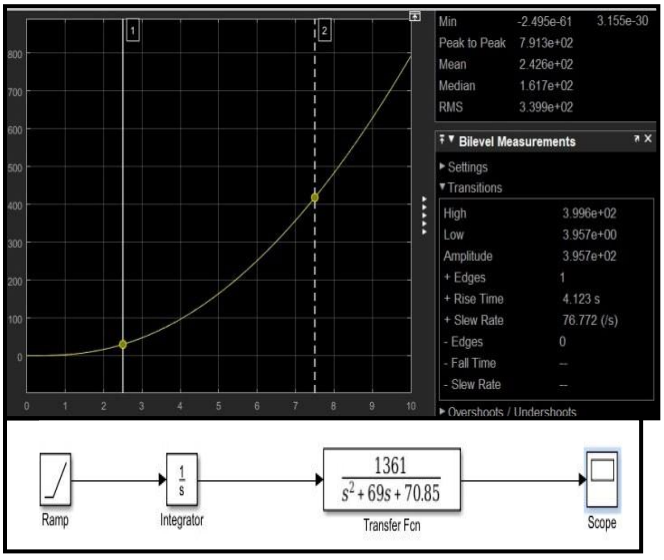


Figure 7: Parabolic response of the system

3.3 Stability of the system

Since both the closed loop poles lie in the left-half plane therefore, our system is stable.

3.4 Gain Limits of a P-Controller

Now for the gain limits of P-controller the transfer function of interest is as follows.

$$T(s) = \frac{1361k}{s^2 + 69s + (70.85 + 1361k)s^0}$$

Making Routh table with initial assumption that K>0.

s^0	1	70.85+1361k
s^1	69	0
s^0	$-\frac{\begin{vmatrix} 1 & 70.85+1361k \\ 69 & 0 \end{vmatrix}}{69} = 70.85 + 1361k$	0

For the system to be stable:

$$70.85 + 1361k > 0$$

$$k > -\frac{70.85}{1361}$$

$$k > -0.05$$

For the system to be marginally stable:

$$k = -0.05$$

For the system to be unstable:

Begin a sub-section on the same line but bold title.

$$k < -0.05$$

Since in the beginning we made assumption that K>0 therefore our P-controller gain K varies from 0 to $+\infty$ or $k > 0$.

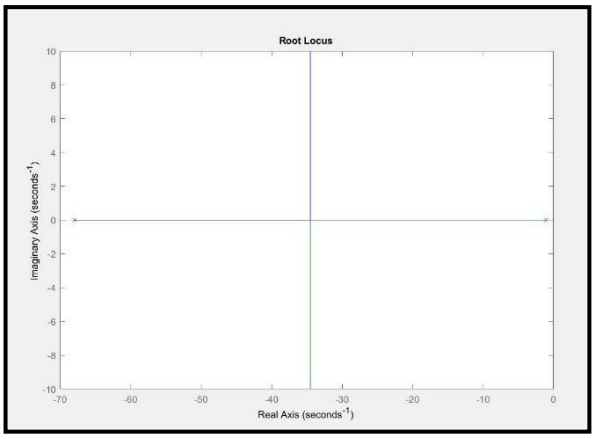


Figure 8: Root locus of the system

3.5 Steady State Error

The Open Loop Transfer Function is:

$$G(s) = \frac{1361}{s^2 + 69s + 70.85}$$

It is a type 0 system,

We compute steady-state error for step input

$$e_{step}(\infty) = \frac{1}{1 + K_p} = \frac{1}{1 + \lim_{s \to 0} G(s)}$$

$$= \frac{1}{1 + \frac{1361}{0 + 0 + 70.85}}$$

$$= \frac{1}{20.2095}$$

$$e_{step}(\infty) = 0.04948$$

$$e_{ramp}(\infty) = \frac{1}{K_v} = \frac{1}{\lim_{s \to 0} sG(s)}$$

$$= \frac{1}{0}$$

$$= \infty$$

$$e_{parabolic}(\infty) = \frac{1}{K_a} = \frac{1}{\lim_{s \to 0} s^2 G(s)}$$

$$= \frac{1}{0}$$

3.6 Root Locus

```
clc
clear all
num=[1361]
den=[1 69 70.85]
G=tf(num,den)
rlocus(G)
ylim([-10 10])
```

Figure 9: MATLAB coding for root locus

4 RESULTS

By plotting the response of the system against step input, it is observed that an error of 0.04948 is appearing and for ramp and parabolic inputs the errors appear to be infinity because the system is type 0 system and, in that case, $kkvv$ and $kkaa$ are 0 making the errors infinity. Moreover, a settling time of 0.1159 sec is observed, both these characteristics were not desirable under the situation and were meant to be improved. Less settling time and faster response along with least possible steady-state error was the requirement of the situation. Since the system response is ''Over-damped'' corresponding to ζ = 4.0988 (which is > 1). Because of it, peak time and percentage overshoot are not kept in regard. So, the only issue with the system appears to be steady state-error along with settling time. Both these characteristics were tried to be improved by usage of only P-controller but the results were not satisfying as steady-state error still sustained. The best approach to the solution was design of PI-controller to cater both settling time and steady-state error at the same time. The usage of PI-controller proved to be useful and gave the response that was required. Mat lab PID-Tuner was used to find the required values for gains of P and I controllers and then the values of $kkpp$ and kk were altered until the required response was achieved. The improved system response is as follows:

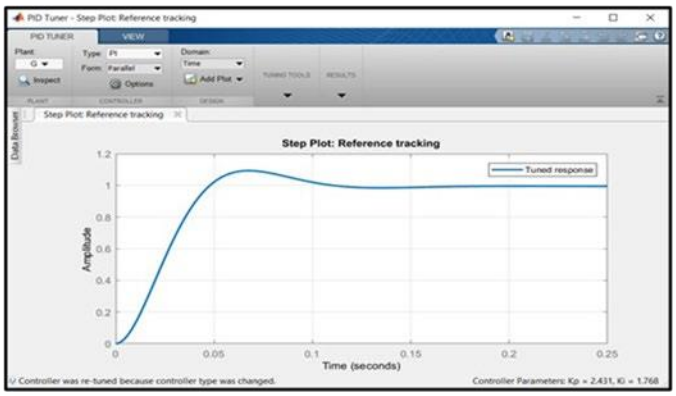


Figure 10: PID Tuner

4.1 MATLAB Code

```
clc
clear all
s=tf('s')
num=[201 252 50.4]
den=[1 10.93 109.26 193.4 126 25.2]
G=tf(num,den)
pidTuner(G,'p')
```

Figure 11: MATLAB Code for system parameters using PID Tuner

4.2 Improved Parameters

Controller Parameters

	Tuned
Kp	2.4314
Ki	1.7677
Kd	n/a
Tf	n/a

Performance and Robustness

	Tuned
Rise time	0.0321 seconds
Settling time	0.0999 seconds
Overshoot	9.29 %
Peak	1.09
Gain margin	Inf dB @ Inf rad/s
Phase margin	59 deg @ 41.5 rad/s
Closed-loop stability	Stable

Figure 12: Improved Parameters

4.3 Improved and unimproved system responses

	Un-improved	Improved
Steady-state error	0.04948	0
Settling time	0.1159 seconds	0.0999 seconds
Overshoot	0.0937 %	9.29 % (desired)
Rise time	0.0776 seconds	0.0321 seconds

4.4 Response

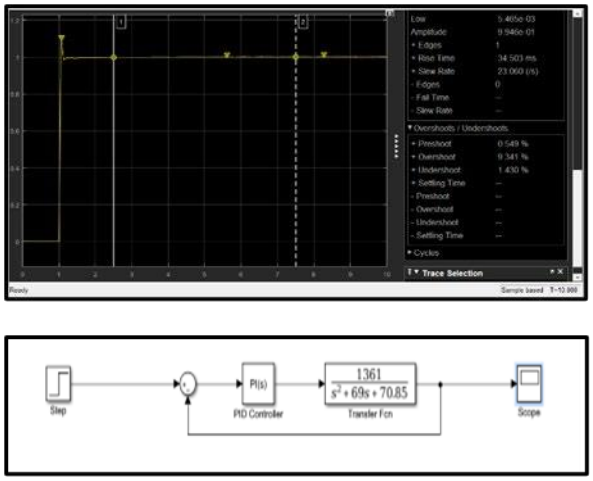


Figure 13: Final Response

5 CONCLUSION

We modelled a control system for hormonal regulation in mammals. We also analyzed responses that were generated from the transfer function Created Routh Table to check the stability and also calculated Steady State error and plotted Root Locus. We used PID controller to improve our system. The science of biology has undergone a revolution due to the discovery of DNA and its crucial involvement in cellular activity. Rapid advancements in biology have produced intriguing new findings that promise to reveal the fundamental principles of life. The importance of mathematics increases as biology gets more quantitative. Furthermore, an integrated systems approach is necessary due to the complexity of biological systems. Systems techniques have been heavily utilized in the technical sciences, notably engineering, to evaluate and create man-made systems. The idea of feedback serves as a major unifying principle. Very little work has been done to comprehend these complex mechanisms using concepts from control systems theory, despite the fact that feedback controllers are very common in biological systems and account for most of their complexity. For control scientists, studying and comprehending biological regulating processes offers a rare opportunity. One illustration may be taken from the significant discipline of endocrinology. Although several hormones have been shown to have a part in regulation, dynamical systems are rarely used as a setting for research on feedback mechanisms. statistical techniques involving the measurement of variables and their correlation with observed behavior. The vast disparities in these professions' methodologies, cultures, and instruments are one factor in the relative lack of engineering techniques in the biological sciences. However, the moment is right for a collaborative research project because of recent advances at the cellular level, new techniques for data collection, fast computers, and new theories for simulating and evaluating models. The important connection between what is understood at the system level and what is empirically seen may then be made as a result of this effort.

6 RECOMMENDATIONS

For the future generation, the changes of concentration of the intramitochondrial Ca2+ will prove to be a challenge, also in the respiratory chain components. When cytosolic concentrations rise, intramitochondrial Ca2+ plays a very important role. Cells of mammals when stimulated allow mitochondrial ATP production. The energy status is also maintained. It is to be noted that this will not always be the case. The effect of dehydrogenases activation may be less impactful in hearts perfused with medium contained glucose. When pyruvate is present, respiration is affected by an increased ADP concentration. Nevertheless, intramitochondrial Ca2+ acts as a catalyst for hormonal processes having an effect on the energy metabolism.

NOMENCLATURE

PTH: Parathyroid hormone

ATP: Adenosine triphosphate

MCU: Micturating Cystography

MICU: Medical Intensive Care Unit

Ca2+: Calcium Ion

SERCA: sarco/endoplasmic reticulum Ca^{2+}

V_t: Total calcium rate in plasma

V_{cl}: Total calcium clearance in plasma

vol: volume of plasma

CaSR: calcium-sensing receptor

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