Calcitonin Hormone Regulation of Calcium in Bones

Megan Wu, Armando Ramil, Mason Faust, Millicent Salvino, Jacob Orozco

***Abstract* - Calcium is an important mineral in numerous physiological processes, including bone formation, nerve function, and muscle contraction. Parathyroid hormone (PTH) and calcitonin are the primary regulators of blood calcium levels. This report focuses on the effect of calcitonin in response to an elevated level of blood calcium. This report aims to enhance understanding of the balance required for maintaining optimal calcium levels and the implications of its disruption in human health, by presenting a comprehensive overview of calcitonin's function and its critical importance in calcium regulation. A set of ODEs and parameters were designed to model this system in Simulink. Instability was found in the open loop system, in which a PD control was added to present a stable closed loop system. The omission of an integral control contributed to the stability of the system, as it displayed no signs of improvements to system response. Furthermore, manipulations of the closed-loop system's sensitivity aided in choosing the right "k" value. The contributions of PTH would further stabilize the system but is not a primary focus of this paper.**

***Clinical Relevance* - Understanding the role of calcitonin in calcium regulation is crucial for the diagnosis and treatment of calcium-related disorders. Abnormalities in parathyroid hormone and calcitonin levels can lead to conditions like hyperparathyroidism and hypoparathyroidism, affecting bone health, renal function, and neuromuscular activity. Accurate assessment and management of these conditions are essential for preventing long-term complications and ensuring patient well-being.**

I. INTRODUCTION

Calcium plays an integral role in several physiological processes, some of which include bone health, nerve transmission, and muscle function. By understanding the regulation of these calcium levels, we can better comprehend how our bodies regulate and maintain these processes. The goal of this paper is to explore the intricacies of calcium regulation with a particular focus on the role of calcitonin. This lesser-discussed yet important player in calcium regulation often gets overshadowed by the parathyroid hormone (PTH). This delicate dance between the hormones combined with cellular responses helps maintain homeostasis in the body [1]. When this balance is disrupted it can lead to serious health issues, highlighting the importance and severity of each mechanism. The response of calcitonin to elevated blood calcium levels is the mechanism we will explore. By incorporating PID control with our ODE we hope to see calcitonin's response will be enough to regulate calcium levels back to normal.This model will not only shed light on the existing knowledge but should help pave the way for new insights into how these complex regulatory systems can be controlled and influenced.

II. BACKGROUND

A. Parathyroid hormone and calcitonin physiology

Calcitonin is not an extensively studied hormone. However, it is known to play a key role in the regulation of blood calcium levels. The endocrine system responds to elevated levels of blood calcium by increasing the release of calcitonin which attempts to return the calcium concentration to homeostatic levels by increasing bone deposition (i.e. decreasing osteoclast activity), decreasing calcium absorption in the small intestine, and decreasing reabsorption in the kidneys. Calcitonin release is stimulated by calcium-sensing receptors (CaSR) in the parathyroid gland and kidney [2,5,6]. It is released from the thyroid gland in response to an elevated level of blood calcium concentration. Interestingly, there is little evidence of bone abnormalities or other effects associated with calcitonin deficiency [3,4]. This suggests that calcium blood regulation is more complex than the simplified model we have proposed, which

primarily looks at the effect of calcitonin on elevated blood calcium.

Parathyroid hormone (PTH) has the opposite effect of calcitonin and causes the blood calcium concentration to increase, as shown in Figure 1. This model specifically looks at the return of calcium blood levels to homeostasis from an elevated initial concentration and does not focus on the dynamic response of PTH in calcium regulation.

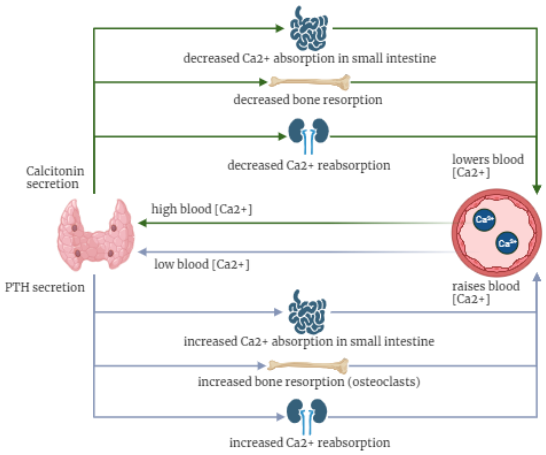

Figure 1: Diagram of parathyroid hormone and calcitonin calcium regulatory pathways.

III. MATHEMATICAL MODEL

A. Assumptions

This mathematical model for calcitonin regulation of calcium is based on the following simplifying assumptions:

1. The scope of the biosystem is limited to calcitonin and the parathyroid hormone.
2. This model only considers calcium interactions in the blood.
3. The effect of PTH is constant and does not change as a function of the calcium concentration since we are modeling the response to elevated calcium where calcitonin is assumed to have a more significant effect.
4. The initial concentrations of calcitonin and calcium are the concentrations at time zero.
5. Calcitonin is modeled as a PD control system.

IV. Parameters and equations

The behavior of the calcitonin response has been simplified into the following nonlinear ordinary differential equations.

$$\frac{dC}{dt} = -kC(t)N(t) + \frac{1}{\tau_1}C(t) \quad (1)$$

$$\frac{dN}{dt} = \alpha I(t) - \frac{1}{\tau_2}N(t) \quad (2)$$

$$I(t) = K\,e(t) + K_i \int_{-\infty}^{t} e(t)dt + K_d \frac{d}{dt}e(t) \quad (3)$$

$$e(t) = C_{meas}(t) - T(t) \quad (4)$$

C(t) and N(t) are the calcium concentration and calcitonin concentration respectively in mmol/L. I(t) represents the feedback control of the calcitonin in the system. Eqn.1 is the change in the calcium concentration with respect to time as a function of the calcitonin and calcium levels assuming a constant PTH level. As the calcitonin concentration, N(t), increases, the change in the calcium concentration becomes more negative, which translates physiologically to a more rapidly decreasing calcium blood level. The opposing effect of PTH is modeled as a constant $\frac{1}{\tau_1}$ that is a function of the calcium concentration. Eqn.2 is the change in the calcitonin concentration with respect to time as a function of the calcitonin concentration and calcitonin feedback controller, I(t). e(t) is the error between the measured calcium concentration and the target concentration which influences the response of the feedback controller.

The equations listed above (Eqns. 5-7), are the linearized version of the model. They were converted to a linearized version

V. RESULTS

A. Simulink Model

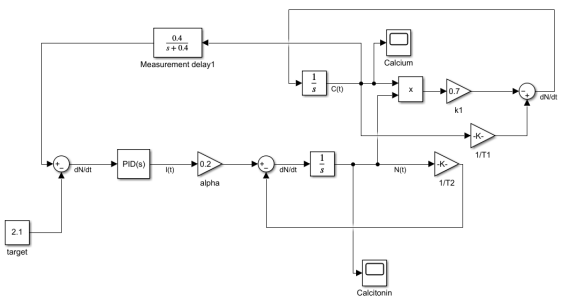

Figure 2: Simulink Model

The Simulink model (Figure 2) was designed from the system of nonlinear ordinary differential equations (Eqns. 1 - 4). The PD controller with tuned Kp and Kd parameters was used to model the continuously regulated calcitonin level. A measurement delay was considered in the calcium concentration and was modeled as a first-order lowpass response with a time constant of $\tau_{meas} = 2.5$ min (Eqn. 5).

$$\frac{dC_{meas}}{dt} = \frac{1}{\tau_{meas}}(C(t) - C_{meas}(t)) \qquad (5)$$

The parameters shown in Table 1 are representative of constants and concentrations in the calcitonin-calcium system.

- k: the sensitivity of the change in calcium concentration to the calcitonin concentration (L/min*mmol)
- τ_1: time constant derived from the assumed constant level of PTH
- τ_2: time constant derived for calcitonin secretion
- α: blood volume
- T: target blood calcium concentration
- N_0: initial blood calcitonin concentration
- C_0: initial blood calcium concentration

Variable	Value	Units
k	0.3	L/min*mmol
τ_1	276	min
τ_2	1642	min
α	0.2	1/L
T	2.1	mmol/L
N_0	2.0482e-9	mmol/L
C_0	4	mmol/L
K_p	0.3	L/min
K_d	0.9	L

Table 1. Simulink parameters of calcium and calcitonin model. T is from [5], τ_1,τ_2, and N_0 are from [7].

Sensitivity analysis of the closed-loop system was performed to obtain the k value of 0.3 L/min*mmol. As the sensitivity decreased, it took the calcitonin-calcium system longer to stabilize at the target calcium concentration, T, of 2.1 mmol/L. This makes physiological sense, as the sensitivity in the change in blood calcium concentration to the calcitonin concentration is directly related, as shown in Eqn.1. With the chosen sensitivity, the blood calcium concentration reaches the target value, T, in approximately 60 minutes.

The calcitonin controller, represented by Eqn.3, only utilized proportional and derivative control. After tuning the controller to appropriate physiological values, we determined that integral control did not improve the system response. With an integral control of $K_i = 0.01 \frac{L}{min^2}$, the output response had greater oscillatory effects. When the integral control was increased to $K_i = 0.05 \frac{L}{min^2}$, it led to overshooting of the target calcium value shown in Figure 3. Therefore, we chose to omit the integral term and used a PD controller.

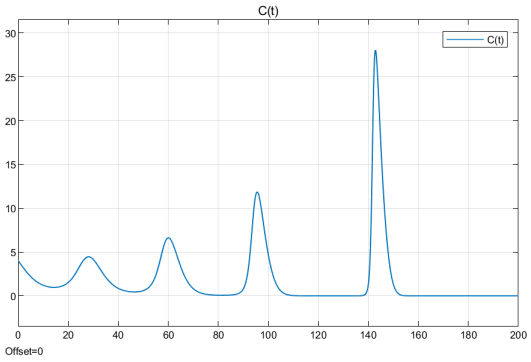

Figure 3: Calcium concentration response with PID control of calcitonin.

B. Open Loop Transfer Function

Eqn. 1 best represents the inverse dependency of the rate of change in calcium on the blood calcitonin and calcium concentration but is a challenge to model. After linearization, the system of nonlinear ordinary differential equations (Eqns. 1-4) resulted in the following equations:

$$C(s) = \frac{2kN_0C_0 - kC_0N(s) + C_0(1-\frac{1}{\tau_1})}{s + kN_0 - \frac{1}{\tau_1}} \quad (6)$$

$$N(s) = \frac{\alpha I(s) + N_0}{s + \frac{1}{\tau_2}} \quad (7)$$

Utilizing the linearized versions of the ordinary differential equations (Eqn. 6-7), the following open-loop transfer function was obtained:

$$H(s) = \frac{C(s)}{I(s)} = \frac{-kC_o\alpha}{s^2 + s(kN_o - \frac{1}{\tau_1} + \frac{1}{\tau_2}) + (\frac{kN_o}{\tau_2} - \frac{1}{\tau_2\tau_1})} \quad (8)$$

C. *Closed Loop Transfer Function*

Using the open-loop transfer function (Eqn. 8), the measurement delay (Eqn. 9), and controller response (Eqn. 10), the closed-loop transfer function was calculated using the following equation:

$$G(s) = \frac{0.4}{s+0.4} \quad (9)$$

$$F(s) = K_p + K_d s \quad (10)$$

$$CL(s) = \frac{F(s)H(s)}{1 + G(s)F(s)H(s)}$$

$$CL(s) = \frac{-0.045s^2 - 0.153s - 0.054}{s^3 - 0.403s^2 - 0.0528s - 0.0172} \quad (11)$$

D. *Open-Loop Bode Plots*

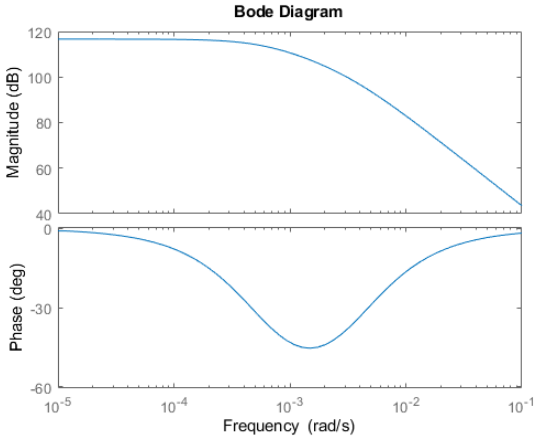

Figure 4: Bode diagram of the open-loop system.

As shown in the Bode diagram (Figure 4), the system response is stable until a frequency of approximately 10^{-4} rad/sec. The downward slope of the magnitude graph indicates the attenuation of the system at higher frequencies. Finally, a phase shift is observed when the system becomes unstable. Based on the transfer function given in Eqn.6, the poles of the open-loop system are at s = 0.00362 and s = -0.000609. Since one of the poles is positive, the system is unstable.

E. *Closed-Loop System Behavior*

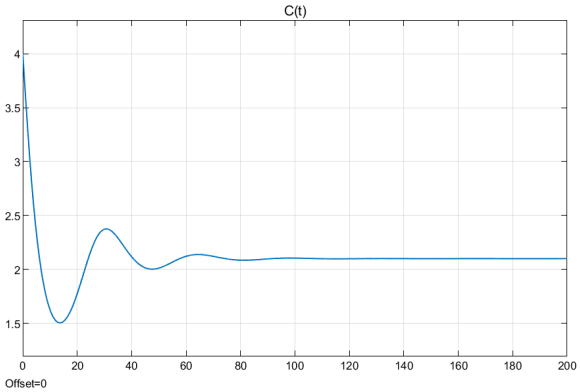

Figure 5: Blood calcium concentration (mmol/L) closed-loop response to input calcitonin as a function of time (min).

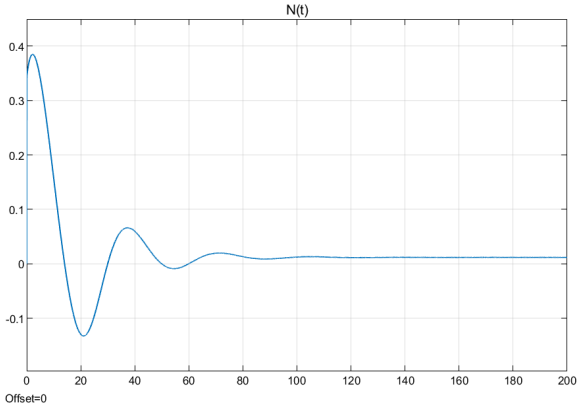

Figure 6: Blood calcitonin concentration (mmol/L) closed-loop response as a function of time (min).

Figure 5 and Figure 6 show the system response in the closed-loop Simulink model using the parameters listed in Table 1 for the blood calcium and calcitonin concentrations, respectively. The closed-loop system shows convergence toward the target calcium concentration, T, of 2.1 mmol/L and the initial calcitonin concentration. This suggests that the system response is stable after integrating a

proportional and derivative controller of the calcitonin feedback.

VII. ERROR/LIMITATIONS

The open loop system is unstable, which we attribute to a limitation of the cited initial calcitonin concentration. It should be noted that an increased initial calcitonin concentration would produce two negative poles and a stable system. Similarly, significantly increasing the sensitivity, k, produces a more stable system. Physiologically, this makes sense as calcitonin is the primary regulatory response to an elevated blood calcium level. Therefore, the error in the model could be reduced by manipulating the constants that were inputs of the transfer function (i.e. k, N_0, C_0) which would produce a more realistic response.

Our system is only focused on the changes of calcitonin levels in the blood. In the future, we would also be interested in modeling the parathyroid hormone mechanisms which would increase the calcium concentration in the blood in response to the undershoots that were modeled in the current system.

VIII. CONCLUSION

In the event of elevated calcium levels, calcitonin plays its role in regulating calcium and returning it to homeostatic levels. As previously mentioned, our open-loop system of calcium concentration response to changes in calcitonin levels is unstable. This was concluded from the positive poles of the transfer function and further displayed in the bode plots. This is attributed to the constant values plugged into the transfer function, which can be altered to create negative poles resulting in instability. In addition, playing around with the sensitivity, which is a measure of how much the output changes in response to changes in the input, can also help stabilize the system. That being said, the closed loop function tends to converge to a target value which indicates that it is stable. The addition of a PD control is responsible for this change in stability between the open-loop and closed-loop systems. For the simplicity of the ODEs modeled in this paper, the effects of parathyroid hormone on calcium were not studied but in future experiments, the role of PTH plays a significant part in counteracting any undershoots of calcium. The joint effort between calcitonin and PTH plays an integral part in maintaining blood calcium levels, which when disrupted, can lead to conditions such as hypo and hyper-parathyroidism.

IX. ACKNOWLEDGEMENT

We would like to thank Dr. Cauwenberghs for his instruction and guidance during the course this quarter. We would also like to thank Benjamin for his key assistance in both discussions and office hours. The willingness to meet with us outside of class was essential to our ability to work on this project.

X. REFERENCES

[1] “Lesson Explainer: The Thyroid and Parathyroid Glands | Nagwa.” Nagwa.com, Nagwa, 2023, www.nagwa.com/en/explainers/523154762780/.
[2] Felsenfeld AJ, Levine BS. Calcitonin, the forgotten hormone: does it deserve to be forgotten? Clin Kidney J. 2015 Apr;8(2):180-7. doi: 10.1093/ckj/sfv011. Epub 2015 Mar 20. PMID: 25815174; PMCID: PMC4370311.
[3] “Fractures & Osteoporosis | SSM Health.” Ssmhealth.com, 2023, www.ssmhealth.com/services/orthopedics/fractures-osteoporosis.
[4] Dr Gayatri Sabinkar. “Hypercalcemia: Causes, Symptoms, Treatment, Risks.” Best Hospitals in India | Medicover Hospitals, Medicover Hospitals, 20 May 2022, www.medicoverhospitals.in/diseases/hypercalcemia/.
[5] Goyal, Abhinav, et al. “Hypocalcemia.” Nih.gov, StatPearls Publishing, 15 Oct. 2023, www.ncbi.nlm.nih.gov/books/NBK430912/#:~:text=Most%20laboratories%20report%20total%20serum,are%20considered%20to%20be%20hypocalcemic. Accessed 4 Dec. 2023.
[6] Lakshmi Kantham, et al. “The Calcium-Sensing Receptor (CaSR) Defends against Hypercalcemia Independently of Its Regulation of Parathyroid Hormone Secretion.” American Journal of Physiology-Endocrinology and Metabolism, vol. 297, no. 4, American

Physiological Society, Oct. 2009, pp. E915–23, https://doi.org/10.1152/ajpendo.00315.2009. Accessed 4 Dec. 2023.
[7] Toledo, A., et al. “Hypercalcitoninemia Is Not Pathognomonic of Medullary Thyroid Carcinoma.” Clinics, vol. 64, no. 7, Elsevier España S.L.U., July 2009, pp. 699–706, https://doi.org/10.1590/s1807-59322009000700015. Accessed 14 Dec. 2023.