Modeling Hypocalcemia due to Parathyroid Regulation of Plasma Calcium Concentration

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Abstract— **Hypocalcemia, or low blood calcium levels, accounted for 27.72% of patients in hospitals between 2011 and 2014 [1]. The wide impact of this affliction makes understanding its causes and mechanisms of vital significance. Since hypocalcemia is the result of an abnormality in the regulation of calcium, modeling a control system that includes the major regulatory factors of calcium in the human body, such as parathyroid hormone and calcitriol (a vitamin D derivative), can help enhance our understanding of hypocalcemia. Additionally, this report utilizes a Simulink model to represent the hypocalcemic system in the body at various abnormal blood calcium concentrations. The vitamin D concentration was found to directly and linearly affect the blood calcium concentration, as increasing vitamin D concentrations led to an increase in calcium levels until both reached a steady-state value. On the other hand, decreasing parathyroid hormone concentrations led to an increase in blood calcium levels, revealing an inverse relationship between the two. The transfer function and bode plot from this model suggests that the system is stable and heads towards a steady-state value. Modeling this biosystem provides an insight into the regulation of calcium concentrations for hypocalcemia in the human body, as this model can be used to account for different patients by changing the model's parameters and inputs, allowing doctors to understand the regulation system and any abnormalities for each individual patient.**

Introduction

Calcium is an essential mineral involved in the regulation of multiple physiological systems. As one of the most common second messengers, calcium ions play a key role in cell signaling. For example, calcium ions enable the muscular contraction of skeletal and cardiac muscle. Calcium is also present in other forms, such as calcium salts, which are responsible for maintaining the structural integrity of bones. When in its ionized form, calcium is typically bound to proteins in blood plasma. The body regulates the concentration of blood calcium through the use of two main hormones: parathyroid hormone (PTH) and calcitriol (1,25-dihydroxy vitamin D). When the parathyroid glands' calcium-sensing receptors (CaSRs) detect low calcium levels, they secrete PTH. PTH stimulates the resorption of bone, where calcium ions are released from the bone, and the secretion of calcitriol, which promotes calcium absorption through the gastrointestinal system. This feedback system increases blood calcium concentration until the CaSRs detect normal levels of blood calcium [2].

Hypocalcemia is a condition where blood calcium levels are abnormally low. This can occur when the parathyroid glands are damaged or removed, if there is a genetic mutation in the CaSRs, when vitamin D levels are too low, or in response to prolonged use of some medications [3]. If left untreated, hypocalcemia can lead to itchiness, tiredness, changes in fingernails and toenails, anxiety and depression, and seizures [4].

The goal of this project is to model the regulation of blood calcium concentration in the human body. A system involving calcium, PTH, and vitamin D concentrations will be modeled in Simulink. The stability of this system will be tested by examining the concentration vs. time plots and Bode plots in response to hypocalcemic conditions. The plots revealed that calcium and vitamin D concentrations increase until they stabilize at a steady state value after approximately 5 minutes, while PTH concentration decreases and stabilizes at a steady state value after approximately 5 minutes. The transfer function and Bode plot of the system also indicate a stable system.

A model of the blood calcium regulatory system could provide valuable insights for patients suffering from hypocalcemia, as the system parameters could be adjusted to reflect a more accurate regulatory system for each patient and system inputs could be adjusted to account for varying degrees of hypocalcemia. As a result, doctors could use these models to determine the most effective treatment plan for each patient. Moreover, the equations behind this model could be slightly modified to model the system response to hypercalcemia, where blood calcium levels are abnormally high. Future improvements to the model should take potential lag between the measurement system and biosystem into account, which introduces a need for a PID controller to improve the stability of the system.

Method and Results

The control system models the regulation of blood calcium concentration through the interactions between calcium, vitamin D (calcitriol), and PTH. The input of the system is the initial concentration of blood calcium. To simulate hypocalcemic conditions, the values inputted into the system were less than 8.5 mg/dL [5]. The blood calcium concentration is measured by the sensor, the calcium-sensing receptors (CaSRs) in the parathyroid glands. The CaSRs compare the measured value to the nominal calcium concentration values of 8.5 to 10.2 mg/dL to determine a response method [6]. The system then attempts to return to the threshold values by increasing production of PTH, which acts as a proportional controller. The release of PTH in the system triggers the activation of vitamin D in the kidneys, which increases the blood calcium concentration. This system is illustrated in Figure 1.

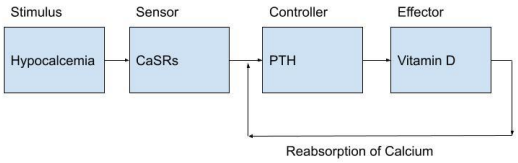

Figure 1: Block diagram of blood calcium regulatory control system in response to hypocalcemia.

A. Assumptions

The hypocalcemic model used in the analysis is in a post absorptive state, making the production of calcium dependent on its release from within the system. To simplify the model, it is assumed that the production of PTH is directly proportional to the increase in blood calcium concentration. It is assumed that the subject is in a resting state of minimal physical activity such that the rate of production and consumption of calcium within the system remains constant. First order kinetics is assumed for the release of calcium from bones, kidneys and gastrointestinal tract. The kinetic constants are assumed to remain constant at resting state. Effectively, the system contains the kidneys, gastrointestinal tract, bones, and parathyroid glands. It is assumed that there is no significant lag between the measurement and the physical system such that any changes are immediately responded to by the controller. The main quantities considered are the concentrations of calcium, PTH, and vitamin D. The system is analyzed over the the time it takes for the body to run out of stored calcium or the time it takes for calcium levels to reach equilibrium.

B. Mathematical Models and Equations

The rate of vitamin D secretion into the bloodstream can be modeled as:

$$M(t) = K_1(T - C(t)),$$

in which K_1 is the rate of secretion of vitamin D, T is the target calcium level, and C(t) is the total blood calcium concentration. Vitamin D levels are directly proportional to calcium levels, creating a feedback loop for total blood calcium concentration in the model.

The rate of vitamin D secretion M(t) is directly proportional to vitamin D concentration dN(t)/dt, as it is assumed that there is no other external source of vitamin D in the defined system:

$$\frac{dN(t)}{dt} = aM(t)$$

The constant a represents the rate of production of vitamin D in the blood. There is no constant for the inhibition of vitamin D production or consumption of vitamin D, as the natural decay of vitamin D is considered negligible.

The rate of parathyroid hormone (PTH) secretion is also proportional to calcium levels controlled by vitamin D secretion M(t):

$$\frac{dPTH(t)}{dt} = -bM(t),$$

where b is the rate of secretion of PTH and the negative sign shows how PTH secretion scales inversely to calcium levels as the system reaches its target concentration.

Finally, total blood calcium concentration can be modeled with:

$$\frac{dC(t)}{dt} = k_2 PTH(t)N(t) + M(t),$$

where k_2 is the rate of production of PTH(t) stimulated by vitamin D and calcium concentrations, and M(t) is the feedback loop for target calcium levels.

C. Analysis

I. Transfer Function

$$M(s) = \frac{kT}{s} - kC(s) \quad (1)$$

$$sN(s) - N(0) = aM(s) \quad (2)$$

$$\frac{sN(s) - N(0)}{a} = M(s) \quad (3)$$

$$sPTH(s) - PTH(0) = -bM(s) \quad (4)$$

$$sC(s) - C(0) = kPTH(s)N(s) + M(s) \quad (5)$$

$$C(s) = \frac{-kbN(s)}{sa} + \frac{N(s)}{a} \quad (6)$$

$$H(s) = a\left(\frac{s}{s-kb}\right) \quad (7)$$

The transfer function represents the mathematical function of a system's output for any input, which can be used to simplify block diagrams and, if applicable, calculate PID values. Transfer functions can only be derived from linearized models, which means the nonlinear 1st order differential for total calcium concentration must be linearized. However, due to PTH(t) and N(t) scaling on the same linear value, Eq. 5 can have its Laplace taken to calculate the transfer function.

Eq. 1-4 are simplified to be linear and the Laplace transform is taken to calculate the transfer function. Through algebraic manipulations and simplifications due to prior assumptions, the equations simplify to Eq. 7, where the transfer function H(s) is equal to vitamin D concentration N(s) divided by the total calcium concentration in the blood C(s).

The values of the parameters used in Eq. 1-7 can be found in Table 1. A healthy patient will have blood calcium concentration ranging from 8.5 to 10.2 mg/dL. A blood calcium concentration under 8.5 mg/dL indicates a lack of calcium and thus, hypocalcemia. Therefore, 9 mg/dL is

chosen as the target calcium level as it fits within this range and is a realistic change of setpoint for calcium in the body [2].

Table 1: System parameters used to model blood calcium regulatory system in response to hypocalcemia.

Parameter	Value	Units
T	9	mg/dL
K_1	0.0001	dL/min
K_2	0.0001	dL/min
a	0.000001	1/min
b	-0.000001	1/min

II. Simulink Model

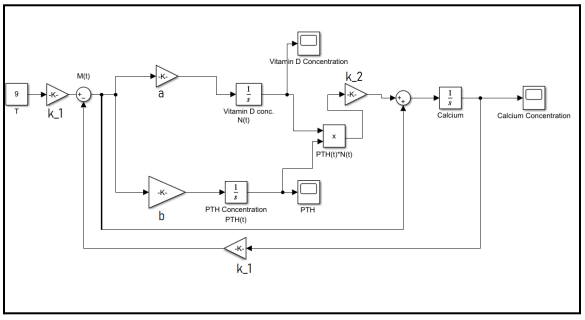

Figure 2: Simulink model of blood calcium regulatory control system in response to hypocalcemia.

The inputs for the calcium concentration C(t) include the concentration of vitamin D N(t) and parathyroid hormone PTH(t), the two integrator blocks in the middle, and a summation block that represents the feedback loop of the target calcium levels. The feedback loop has two gains that represent the distributive multiplication of K_1 in the equation for secretion of vitamin D M(t). A summation block is placed before the total calcium level integrator block to add the previous signal along with the previous target calcium feedback loop. A product block is placed after the integrator blocks for vitamin D and PTH to multiply them to gain constant K_2, the rate of PTH secretion stimulated by the vitamin D and calcium concentrations.

III. Concentration vs. Time & Bode Plots

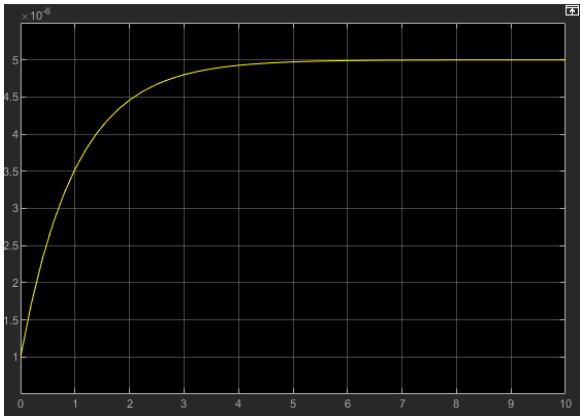

Figure 3: Vitamin D concentration (mg/dL) vs. time (min).

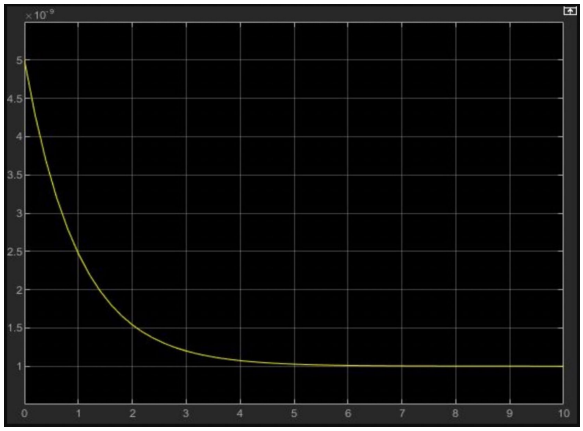

Figure 4: PTH concentration (mg/dL) vs. time (min).

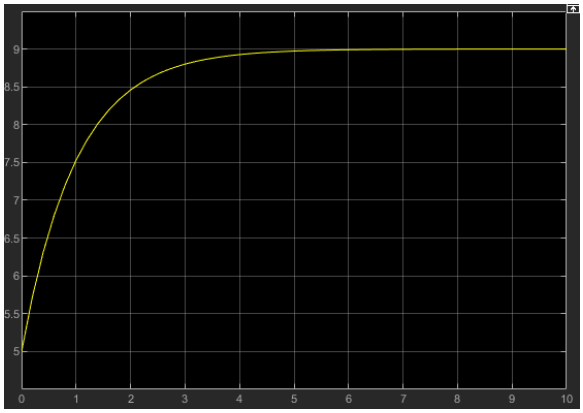

Figure 5: Blood calcium concentration (mg/dL) vs. time (min).

The plots in Figures 3-5 were generated by the Simulink model displayed in Figure 2 over a time span of 10 minutes. Figure 3 shows that the concentration of vitamin D started at the initial value of 10-6 mg/dL then grew to a steady state value of $5x10^{-6}$ mg/dL. Figure 4 shows that the concentration of PTH started at the initial value of $5x10^{-9}$ mg/dL then dropped to a steady state value of 10^{-9} mg/dL. Figure 5 shows that the concentration of calcium started at the initial value of 5 mg/dL then grew to a steady state value

of 9 mg/dL. All three concentrations reached a steady state after approximately 5 minutes.

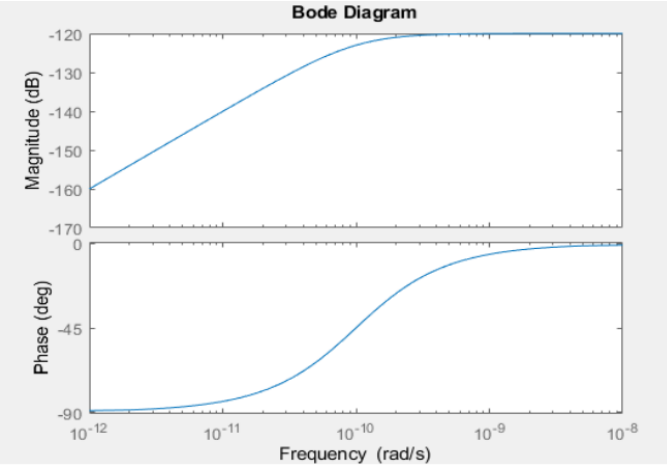

Figure 6: Bode plot of the blood calcium regulatory model.

The top plot shows the angular frequency in rad/s versus the gain magnitude, where each line represents a decade 10^1. The bottom plot shows angular frequency vs. phase (degree), where the system can be stable or unstable at different frequencies. The phase margin is a calculation of phase lag and can indicate overshoots or undershoots in a system, where a positive phase margin is an indicator of a stable system.

In the model, the Bode Diagram shows the increasing gain until 10^{-10} rad/s where it levels off, this represents how the system reaches its steady state and doesn't have to increase anymore. Moreover, in the phase diagram, the phase never reaches -180, and thus will always have a positive phase margin, which indicates that the system is stable throughout the decades.

Discussion

A. Interpretation of Graphs

The initial calcium concentration was less than 8.5 mg/dL, indicating hypocalcemia. In response to hypocalcemic conditions, the parathyroid glands secreted PTH into the bloodstream, leading to a large initial concentration of PTH. At this time, PTH had not stimulated the secretion of vitamin D, meaning the initial vitamin D concentration is close to 0 mg/dL. After t = 0, the effect of PTH on the secretion of vitamin D can be seen as the concentration of vitamin D quickly increases. Since both PTH and vitamin D contribute to the release of stored calcium in the body, the concentration of calcium also quickly increases. In contrast, the concentration of PTH decreases as the CaSRs detect an increase in calcium concentration, signaling a reduced need for releasing stored calcium. After t = 5 minutes, the calcium concentration stabilized at a steady state value of 9 mg/dL, which was the target value displayed in Table 1. This target value is greater than 8.5 mg/dL, indicating a return to normal blood calcium levels from hypocalcemic conditions. The concentrations of vitamin D and PTH also stabilized after t = 5 minutes. The steady state value of PTH concentration is close to 1 mg/dL, which is expected due to the body's normal calcium levels.

B. Error Analysis and Drawbacks

The calcium regulation model created in this project can be used to provide tailored treatment for hypocalcemia, however there are a few advantages and drawbacks that one must keep in mind. All governing equations, transfer functions, and data from literature applies to physiological conditions of normal people. However, in real world conditions, these parameters could vary among different individuals based on their age, height, weight, gender, etc. One of the advantages of this model is that system parameters could be changed in order to take patient variance into account. The other advantages of this model is that the model allows for a range of hypocalcemic system inputs at varying simulated concentrations.

The drawbacks of this model stem from the many simplifying assumptions made at the beginning of the experiment. While this model's scope is confined to blood calcium regulation by PTH and calcitriol (vitamin D) concentrations, there are more complex interactions between these hormones and other biosystems involved in calcium regulation. For example, the steady state concentration of vitamin D is unrealistically high for calcium levels to be stable, as vitamin D increases calcium levels. Additionally, the assumption that there is no lag between the measurement system (CaSRs) and other elements of the biosystem is unrealistic. Finally, this model is linear while the actual biosystem is nonlinear, which means that this model may not be able to provide accurate simulations of the regulation of calcium when adjusting system inputs and parameters to extreme values.

To further refine and develop the model, the other factors that influence the calcium regulation and hypocalcemia, such as vitamin D intake and the consumption or inhibition of calcitriol, should be added to this model. Moreover, the lag between the measurement system and other elements of the biosystem, as well as the lag between the secretion of PTH and secretion of calcitriol, should be added to the model. This would introduce additional noise and potential instability to the system, thus introducing a need for a PID controller.

C. Advantages and Disadvantages

The main advantage of our system is that it allows for testing to occur without the physical presence of a hypocalcemic patient, as long as the initial conditions are recorded. The system parameters can then be modified to fit each individual patient and conduct testing. The system dynamics in response to a variety of hypocalcemic calcium concentrations can be recorded. The main limitation of our system is that it does not take into account the interactions of each hormone with systems outside of this pool. This could influence the concentrations of each hormone by increasing or decreasing the expected values. Additionally, our system runs under the assumption that there is no time delay between inception and detection of hypocalcemia. In real data, such as those presented in Figure 7, a time delay is

present. Finally, as biological systems are often nonlinear, it is difficult to predict their behavior using linear models alone.

I. Comparison to Actual Data

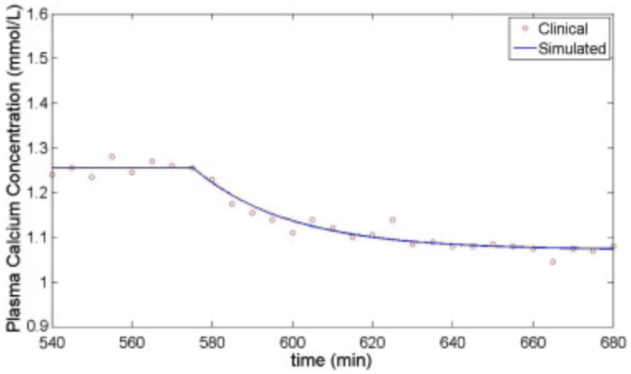

Figure 7: Calcium concentration (mmol/L) vs time (min) during induced hypocalcemia.

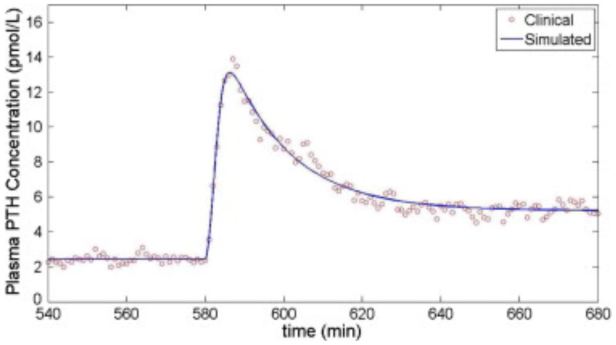

Figure 8: Calcium concentration (pmol/L) vs time (min) during induced hypocalcemia

Based on the research conducted by Rajiv Shrestha on "A mathematical model of parathyroid hormone response to acute changes in plasma ionized calcium concentration in humans," it is evident that a decrease in calcium concentration caused an increase followed by a decrease in PTH concentration [7]. The calcium concentration graph shows a sharp then gradual decrease following the introduction of PTH. Our graph in Figure 5 shows that calcium production increases over time after hypocalcemia is detected, which is similar to how the calcium decrease is slowed following hypocalcemia detection in Figure 7. The PTH concentration in Figure 8 after the initial peak is very similar to our own plot in Figure 4. The difference can be attributed to our graph starting at the detection of hypocalcemia while the experiment by Shrestha induces it after a set amount of time. After that point, both PTH curves decrease logarithmically.

II. Modified Clinical Syndrome

The clinical syndrome that a modified version of this model corresponds to is hypercalcemia. Hypercalcemia occurs when calcium concentration in the blood exceeds 10.5 mg/L and is caused by excessive absorption of calcium and vitamin D [6]. The system's differential equations are modified as such:

$$M(t) = K(C(t) - T) \tag{8}$$

$$\frac{dN(t)}{dt} = -aM(t) \tag{9}$$

$$\frac{dPTH(t)}{dt} = bM(t) \tag{10}$$

$$\frac{dC(t)}{dt} = K \cdot PTH(t) \cdot N(t) - M(t) \tag{11}$$

The Simulink model for hypercalcemia would invert the feedback loop to as shown:

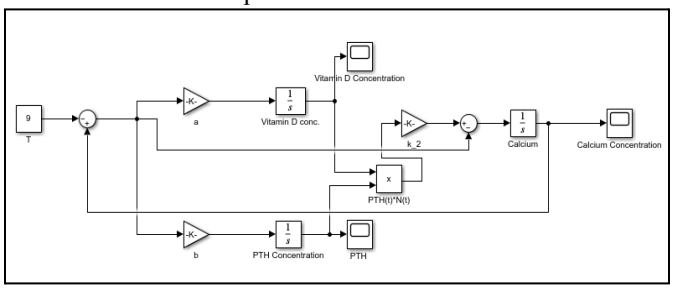

Figure 9: Hypercalcemia Simulink model.

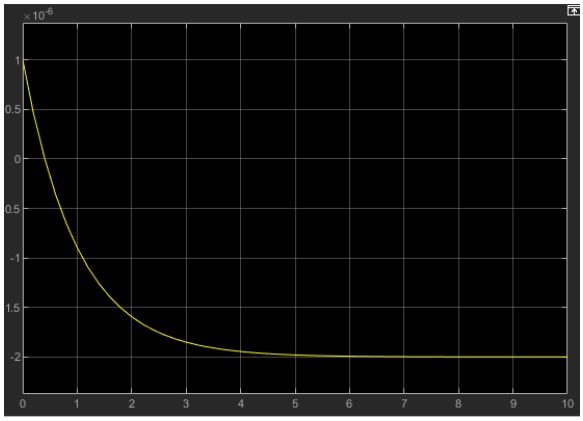

Figure 8: Vitamin D concentration (mg/dL) vs. time (min).

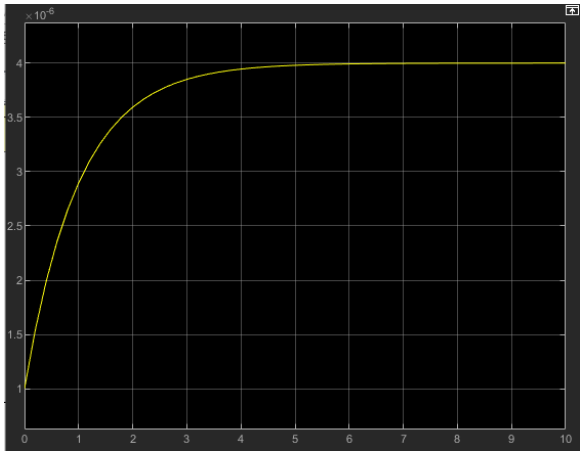

Figure 9: PTH concentration (mg/dL) vs. time (min).

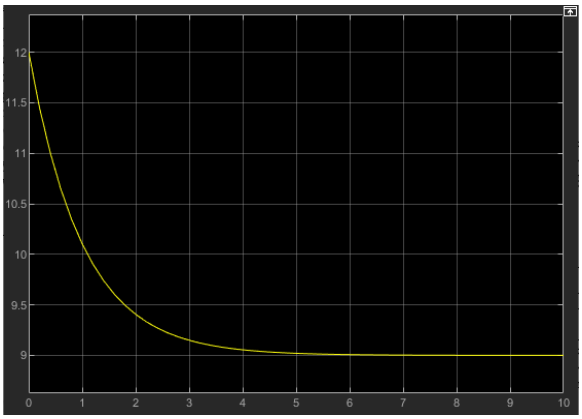

Figure 10: Blood calcium concentration (mg/dL) vs. time

Figures 8-10 are the graphs generated in the modified Simulink hypercalcemia model. Vitamin D concentration on Figure 8 drops from initial value 1.2 x 10^{-5} mg/dL to steady state value of 0.9 x 10^{-5} mg/dL. PTH concentration increases from its initial value at 1 x 10^{-6} mg/dL to its steady state value of 4 x 10^{-6} mg/dL. Blood calcium concentration drops from 12 mg/dL to its steady state value of 9 mg/dL, which is our target value. All three concentrations reach their steady state value at around 5 minutes.

Conclusion

As hypocalcemia causes the hospitalization of many people in the United States, it is important to understand how the body reacts to the condition and how to treat it effectively using a model of the parathyroid hormone, calcitroid, and calcium concentration interaction. Using systems control, the behavior of the body for the regulation of calcium was defined in terms of differential equations in Simulink. As the calcium concentration was assumed to only be affected by calcitriol and the parathyroid hormone, the model was able to reach normal values for each variable within a couple of minutes, where the concentration of calcium and vitamin D followed the same trend and the parathyroid hormone was inversely proportional to the two signals. In a real life situation, the equation would have to take into account more variables in the body that use and produce calcium to make it more accurate, such as the life decay of hormones, diffusion rate of calcium, and agonist/antagonist relationships to the variables present in the study.

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