A Mathematical Model of Bone-Calcium Regulation

Abstract

Human plasma calcium regulation is a biologically complex issue that consists of many variables. Plasma calcium is integral to body functions varying from hormone signaling to bone management. Systemic calcium regulation is an important field of research because dysregulation can lead to developmental and physiological issues. Hypocalcemia, or low calcium levels, can hinder bone growth and damage the parathyroid gland. Increased calcium levels, hypercalcemia, may hint at osteoporosis or kidney failure. Therefore, it is imperative to understand the system. Here, we propose a mathematical model to analyze the stability and fluctuations in the plasma calcium regulatory network.

Introduction

Plasma calcium levels are controlled by multiple organs. It is primarily regulated by the kidneys, bone, and gut. The kidney controls the rate of calcium excretion. The intestinal system controls the rate of calcium absorption. The bones control calcium deposit and resorption. Out of the three systems, the bone is the biggest variable. 99% of the calcium in the human body is located in bone. Bones control the majority of calcium released and absorbed from the plasma and plays a big role in maintaining plasma calcium homeostasis. Subsequently, issues in homeostasis also largely affect bone. To analyze the system, we chose to focus on how the skeletal system interacts with plasma calcium levels.

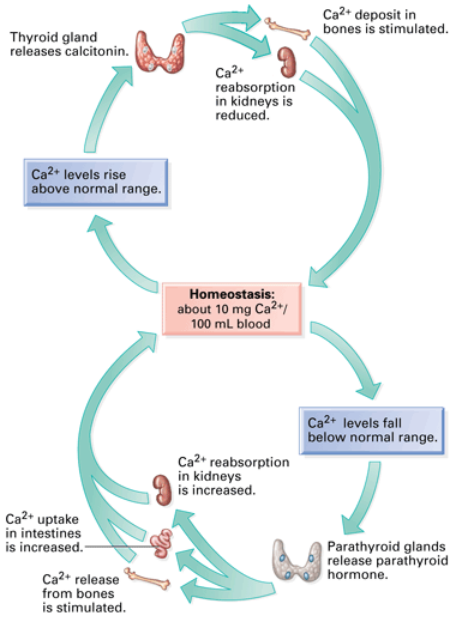


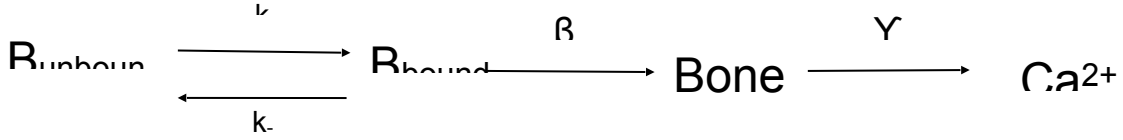
Figure 1: plasma calcium regulation network

Bone tissue consists of two major cell types: osteoblasts and osteoclasts. Osteoblasts focus on creating bone through secreting minerals for a bone matrix. These cells translate calcium and other minerals from the circulatory system to bone. Osteoclasts resorb bone back into the circulatory system. Essentially, it recycles the minerals from bone back into the body. These two cells are regulated by the competing hormones in the endocrine system. Osteoblasts can be regulated by calcitonin, a hormone secreted from the thyroid. Calcitonin signals osteoblasts to increase bone formation, lowering plasma calcium levels and transferring the excess calcium into

bones. Osteoclasts are stimulated by parathyroid hormone (PTH) and vitamin D which signal for the cells to increase bone resorption. These hormones are markedly activated when calcium levels dip below homeostatic levels, prompting the body to use stored calcium in increasing plasma calcium levels.

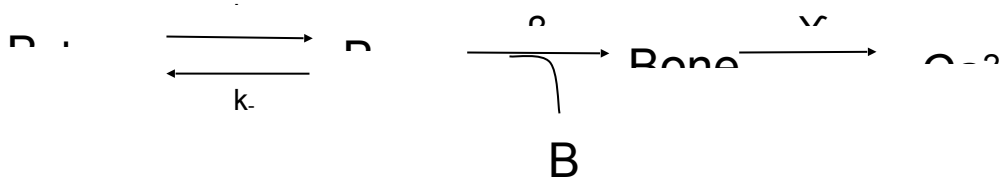
Methods

Before building our model, we want to define some key terminology and abbreviations. A picture of the model is shown below for reference.



Osteoblasts are abbreviated as B. Calcium is abbreviated as Ca^{2+}. Since the amount of calcium ions far exceed the number of osteoblasts, we will assume that osteoblasts are the limiting concentration in this system. Osteoblasts come in two states: bound and unbound. Calcium and osteoblasts can bind at a rate k_+ and unbind at a rate k_-. These rates remain constant and do not vary much from external forces. Bound osteoblast-calcium complexes, B_{bound}, can become bone at a rate β. This rate can be modulated by calcitonin, which increases β when plasma calcium is too high. Bone can then degrade and release calcium through osteoclasts at a rate γ. This rate can be regulated by PTH and vitamin D, which increase osteoclast function when plasma calcium is too low.

However, this model does not place the focus on calcium. While it may be a more accurate representation of bone regulation, we are more focused on calcium regulation. Therefore, we propose another model revolving around the human calcium levels. In this case, we use calcium levels as the rate limiting step. In addition, we add the premise that when the osteoblast-calcium complex creates the bone matrix at rate β, it also frees unbound osteoblasts.



Results

We begin analyzing this model by defining the rates of each variable.

$$d[B]/dt = k_-[B\text{-}Ca^{2+}] - k_+[B][Ca^{2+}] + \beta[B\text{-}Ca^{2+}]$$

$$d[B\text{-}Ca^{2+}]/dt = - k_-[B\text{-}Ca^{2+}] + k_+[B][Ca^{2+}] - \beta[B\text{-}Ca^{2+}]$$

$$d[Bone]/dt = \beta[B\text{-}Ca^{2+}] - \gamma[Bone]$$

$$d[Ca^{2+}]/dt = \gamma[Bone] + k_-[B\text{-}Ca^{2+}] - k_+[B][Ca^{2+}]$$

Since we are mainly focused on the interplay between calcium and bone, we will get [B] and [B-Ca^{2+}] into the other two equations. We will use the conservation law of $B_T = [B\text{-}Ca^{2+}] + [B]$ to replace [B] in our equations.

$$[B\text{-}Ca^{2+}]_{ss} = (B_T k_+ [Ca^{2+}])/(k_- + k_+ [Ca^{2+}] + \beta)$$

Thus, we get our final rates:

$$d[Bone]/dt = \beta(B_T k_+ [Ca^{2+}])/(k_- + k_+ [Ca^{2+}] + \beta) - \gamma[Bone]$$

$$d[Ca^{2+}]/dt = \gamma[Bone] + k_-(B_T k_+ [Ca^{2+}])/(k_- + k_+ [Ca^{2+}] + \beta)$$

$$- k_+ B_T(k_- + \beta)/(k_- + k_+ [Ca^{2+}] + \beta))[Ca^{2+}]$$

$$= \gamma[Bone] - k_+ B_T \beta [Ca^{2+}]/(k_- + k_+ [Ca^{2+}] + \beta)$$

The steady states are derived below.

$$[Bone]_{ss} = (\beta/\gamma)[B\text{-}Ca^{2+}] = (\beta/\gamma)(B_T k_+ [Ca^{2+}])/(k_- + k_+ [Ca^{2+}] + \beta)$$

$$[Ca^{2+}]_{ss} = (\gamma[Bone] + k_-[B\text{-}Ca^{2+}])/k_+[B] = -\beta/k_+$$

Biologically, this makes sense. First, analyze the bone steady state. When β increases, osteoblasts are essentially being signalled by calcitonin to synthesize plasma calcium into bone. Thus, the level of Bone increases. When γ increases, osteoclasts are signalled by PTH and vitamin D to break down bone for increasing plasma calcium levels. This would decrease the level of Bone. Next, we look at the calcium steady state. When β increases, plasma calcium levels decreases. Again, this makes some biological sense because increased calcitonin signalling would lower plasma calcium levels.

Before we continue, we want to address some limitations in our model. For one, it only takes into account one aspect of a regulatory system. Without including other factors like kidney and gut calcium regulation, we cannot use data to accurately assess the viability of our model. In addition, we assume a rate γ for the resorption of bone to calcium. However, this is neither a dimensionally accurate method nor conservationally possible because some calcium must be lost in steps like creating new cells or mineral degradation. Still, given the methods and topics we have learned in class, this is the best possible representation of the system.

To compute the stability of this system, we calculated the Jacobian and computed its eigenvalues. These eigenvalues were 0 and

$$-(B_T k_- k_+ \beta + B_T k_+ \beta^2 + k_-^2 \gamma + 2k_- k_+ [Ca^{2+}]\gamma + k_+^2 [Ca^{2+}]\gamma + 2k_- \beta\gamma + 2k_+ [Ca^{2+}]\beta\gamma + \beta^2\gamma)/(k_- + k_+ [Ca^{2+}] + \beta)^2.$$

Since none of our parameters can be negative, the second eigenvalue will always be negative. Therefore, the steady state solutions for bone and blood plasma calcium concentrations form a saddle point, which is always unstable.

Conclusion

With our model, we hoped to show that we could find a stable steady state solution for bone and blood plasma calcium concentrations, but we were unable to do so. We were able to find a saddle point for the system, but ultimately this is still not stable. To find a stable critical point for our bone and blood plasma calcium concentrations, we would likely need a more complex model that accounts for calcium in more areas of the body, like the kidney and gut. However, we could

also more closely model the osteoclast and osteoblast interactions, instead of treating them as “black boxes” like we did in our model. Additionally, we could use the Hill Approximation to vary the amount of calcium needed to create bone and the amount of calcium released in bone degradation, instead of assuming a 1:1 ratio of calcium ions and osteoblasts in bone formation and a 1:1 ratio of calcium ions and bone in bone degradation. The Hill Approximation would help us further the research and look at cases such as osteoporosis or osteopenia when the rates constants vary.