Mathematical Model of Blood Calcium Ion Regulation

MBI Problem Solving Workshop, 16–20 July, 2012

Report: September 2012

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Contents

1 Introduction 2
  1.1 The presented problem .................................................. 2
  1.2 Biological background .................................................. 2

2 Mathematical model 4
  2.1 Parameter values .......................................................... 6

3 Numerical Results 6
  3.1 Healthy State ............................................................. 9
  3.2 Cancer ..................................................................... 9
  3.3 Renal Disease ............................................................ 10

4 Discussion and future work 10
1 Introduction

1.1 The presented problem

Dr. Thomas Rosol came to the Mathematical Biosciences Institute (MBI) Problem Solving Workshop hoping to learn more about plasma calcium regulation. In particular, he proposed that we develop a mathematical model that captures the tightly and rapidly regulated nature of plasma calcium levels in healthy individuals, and how homeostasis is disturbed over the longer timescale of months in patients with renal disease or cancer. If it were possible to develop a model consistent with known calcium levels in health and disease, Dr. Rosol was interested in using the model to predict patient response to various therapeutic targets, and to determine how dosing and timing of drug delivery influences this response.

1.2 Biological background

Calcium homeostasis is the way in which the body maintains a relatively fixed level of calcium (Ca) in the plasma. Figure 1 shows that in the adult body, 99% of calcium is found in the bone, 0.9% is found in cell organelles, and 0.1% is found in in extracellular fluid/plasma. The organs that are involved in regulating blood calcium are the parathyroid gland (PTG), C-cells of the thyroid gland, gastrointestinal tract, kidney, and the bone.

![Diagram of calcium distribution](image.png)

Figure 1: Illustration of the amount of calcium in the human body, and the forms in which it is found. Whilst there are vast reserves in bone, regulating the precise concentration in circulating plasma is crucial for health.

Calcium regulates many important processes in the body. It acts as a second messenger in many cellular pathways, has a role in neuron firing, and is necessary for muscle contraction and bone development.

Parathyroid hormone (PTH) is the main regulator of calcium levels in the plasma. If the plasma calcium level is high, then there is little production of PTH. However, if the plasma calcium level
is low, there is an increase in the PTH production by the PTG, as shown in Figure 2.

Figure 2: Illustration of PTH production as a function of plasma calcium. Note that the healthy range corresponds to a low production of PTH.

In the gastrointestinal tract, about 20-40% of calcium is absorbed into the body (or plasma). The passive absorption depends on Ca while the active absorption depends on calcitriol which is the active form of vitamin D. The parathyroid hormone (PTH) controls the production of calcitriol made in the kidney via \(1\alpha\)-hydroxylase. Typically, in the kidney, calcium is filtered out and then 98% of calcium is reabsorbed into the body. The kidney can also excrete calcium through urine.

The bone serves as a large store of calcium. At around the age of 30, the bone density reaches a peak. After the age of 30, the rate of resorption (or loss) is greater than the rate of formation. If the calcium level in the plasma is low, PTH causes the resorption (or loss) of calcium in the bone to increase the calcium level in the plasma. In addition, PTH causes production of calcitriol in the kidney which then aids in the absorption of calcium into the plasma. Calcitriol decreases release of calcium from the bone but this is short-acting.

Diseases such as cancer and renal disease can disrupt the system. Certain tumor types have shown to increase the level of PTH which causes resorption of calcium from the bone. Renal disease causes a decrease in the production of calcitriol which causes a decreases in the amount of calcium in the plasma.

A review of calcium control, including calcitonin and the role of the kidney in the process, has been written by Hurwitz [4]. Figure 5 of [4] shows the evolution of plasma calcium over time following a perturbation, from experiments on chickens, together with results of simulations of their model, which splits the fluxes into that due to the bone and kidney. Figure 2 of Hurwitz et al. [5] shows how the rate of PTH production varies with changes in Calcium, this figure is similar to Figure 2 discussed above. Hurwitz et al. [6] also proposes a compartmental model of calcium homeostasis using ODEs to simulate the evolving concentrations and fluxes of calcium and PTH around the body. Equation (12) of Hurwitz et al. [6] supports our assumed form for the dependence of PTH production on calcium concentration, in particular our exponent of six sits in their determined ranges of 5.71 ± 0.37.
A detailed description of the functioning of the parathyroid gland and associated hormone is given by Shrestha in his thesis [10]. The significant parts of this are summarized in the published work of Shrestha et al. [11], where they focus on their mathematical model of the regulation of the calcium system over the timescale of hours.

Although Raposo et al. [9] describe their model as ‘minimal’, it is far from simple, since it covers phosphate as well as calcium, and PTH, but not calcitonin or calcitriol. They model inhibition and activating effects using tanh functions to model the sigmoidal dependencies, each of which requires four parameters to fit. Their model thus ends up requiring approximately forty parameters to yield any predictions. Whilst it provides sensible predictions we believe it is possible to find a simpler model of the processes. An even more detailed model of calcium and phosphorus metabolism is provided by Raposo et al. in [8]. Thus, in what follows we aim to use significantly fewer parameters to address calcium regulation over both shorter and longer timescales.

Our goal is to develop a mathematical model based on plasma calcium regulation. In Section 2 we present the multi-scale model we developed of the processes involved in calcium regulation. In particular, the concentrations of three main regulators, calcium, PTH, and calcitriol, evolve on the time scale of minutes, whereas the size of the parathyroid gland and physiological response to changes in the three regulators operate on the time scale of months. In Section 3 we illustrate the results of numerical simulations of the system of equations over the relevant time scales in both healthy and diseased states, and compare the simulation results to experimental expectations. Finally, we draw conclusions and summarize the potential for future work in Section 4.

2 Mathematical model

This model seeks to describe calcium homeostasis. The components in the blood plasma are the calcium concentration $Ca$, parathyroid hormone $P$, and calcitriol $C$. The size of the parathyroid gland can change and we denote its size by $G$. A schematic describing the interactions between these components is found in Figure 3. We develop a system of nonlinear ordinary differential equations to model the interactions between the main components involved in plasma calcium regulation in Equations (1)–(4)

\[
\frac{dCa}{dt} = \frac{\lambda_1}{IC - \frac{Ca(1 + 10(Ca - X_c)H(Ca - X_c))}{1 + \gamma_1C + \gamma_7P}} + \frac{\lambda_5}{1 + \gamma_11Ca}(1 + \gamma_12P), \quad (1)
\]

\[
\frac{dP}{dt} = \frac{\lambda_2}{AG \left[ \frac{1 + (\gamma_2C)^6 + \gamma_3Ca^6}{(1 + \gamma_2C)^6 + \gamma_3Ca^6} - P + T_p \right]}, \quad (2)
\]

\[
\frac{dC}{dt} = \frac{\lambda_3}{KP \left[ \frac{(1 + \gamma_4Ca)(1 + \gamma_6C)}{(1 + \gamma_4Ca)(1 + \gamma_6C)} - C \right]}, \quad (3)
\]

\[
\frac{dG}{dt} = \frac{\lambda_4}{L \left[ \frac{1 + \gamma_10C + \gamma_9Ca}{(1 + \gamma_10C)(1 + \gamma_9Ca)} + G \right]} \quad (4)
\]

The rate of change of plasma calcium with respect to time is described by Equation (1). Calcitriol, $C$, aids in the absorption of calcium in the intestine with a rate $I$. Higher levels of Calcitriol $C$ will cause an increase in the calcium level in the plasma, $Ca$, while low levels will have little effect on $Ca$. The limiting effect on the loss of calcium in the plasma depends on how much calcium is present as well as calcitriol, $C$, and PTH, $P$. If the amount of PTH is high, then there is a small
decrease in calcium, $Ca$, since PTH causes a decrease in loss of calcium in urine which is denoted by $\gamma_7 P$. If the amount of calcitriol $C$ is high, then the decrease of calcium $Ca$ is low since calcitriol aids in the absorption of $Ca$.

Figure 3: Flowchart illustrating the activation and inhibition of the various chemical species in our model: ionic calcium in the plasma, PTH, calcitriol, and the size of the PTG. Note that PTH is produced in the PTG and calcitriol in the kidney.

We assume an inexhaustible supply of calcium in the bone. The term $\frac{\lambda_5}{1+\gamma_{11}Ca}(1 + \gamma_{12}P)$ in Equation (1) describes the amount of calcium being resorbed from the bone. If plasma calcium is high, then no calcium needs to be resorbed from the bone. However, under low levels of calcium in the plasma, PTH causes the calcium from the bone to be resorbed so that the level of calcium in the plasma can be maintained. We note that if there is no PTH and if the person is older than 30, the rate of resorption will be greater than the formation of bone. Thus, there will always be an influx of calcium from the bone to the plasma.

The key component in this model is the amount of parathyroid hormone, $P$. As shown in Equation (2), the size of the parathyroid gland, $G$, affects the amount of $P$ produced. It has been shown that the gland can grow or shrink in response to calcium levels in the plasma. If the gland grows, more PTH, $P$, is produced. This growth is limited to the amount of $C$ and $Ca$. Calcitriol, $C$, limits the gene expression of PTH, $P$ [12]. If there is a sufficient amount of plasma calcium, there is no need for PTH and hence, little production. The half-life of PTH, $P$, is about 2-4 hours and degrades at the rate proportional to the size of $P$. With certain cancers such as breast and lung cancers, there can be an increase in the amount of parathyroid hormone-related protein (PTHrP), which acts similar to PTH, and the presence of such cancer is denoted by $T_p$ [1].

The rate of change of calcitriol, $C$, with respect to time is shown in Equation (3). Even though there is a small amount of calcitriol made by other mechanisms, the main effect of its production is by the parathyroid hormone, $P$. However, this production is limited by the amount of plasma calcium and calcitriol [9]. We note that 1α-hydroxylase produces calcitriol but is inhibited by high levels of $Ca$. The rate of degradation of calcitriol is proportional to the amount present, namely $C$.

The rate of change of the size of the parathyroid gland (PTG) is described in Equation (4). If
there are low levels of calcium in the plasma, the PTG will grow so that it can produce more PTH. It has been shown that calcitriol can limit the growth of PTG [9]. The rate of decrease in the size of the PTG as a result of apoptosis is proportional to the current size of PTG.

2.1 Parameter values

Many of the parameters in the model represent “lumped” parameters in that they capture the impact that several biological factors have on the production/decay of the specified chemical species. Therefore, we did not have easy access to experimentally-measured parameter values.

As a result, we developed an ad hoc parameter estimation method. We started with data on the steady-state values of calcium, PTH and calcitriol in the plasma, see Table 1. Seeking to find the parameter values of a healthy human, we solved for the steady-states of our system in Equations (1)–(4), and equated the steady-state value of each component with the known homeostatic level of that component.

These three data points are not sufficient to uniquely determine the parameters in our system of differential equations because there were more than three unknown parameters to estimate. To handle this issue, we focused in on the timescale parameters in our model, indicated by \( \lambda_i \) and the inhibition/activation parameters indicated by \( \gamma_i \). Dr. Rosol provided us with data on the relative timescale of the different interactions taking place in Figure 3, as well as the relative strength of each activation and inhibition term. Using these order-of-magnitude estimates on the values of \( \lambda_i \) and \( \gamma_i \), we were able to determine parameter values that, for our model, give rise to steady-state levels of calcium, PTH and calcitriol consistent with biologically-measured values. The parameter values we use to simulate a healthy individual are shown in Table 2.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Steady-State Value</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca</td>
<td>1.5 mmol/L</td>
<td>Plasma calcium concentration</td>
</tr>
<tr>
<td>P</td>
<td>(3 \times 10^{-9}) mmol/L</td>
<td>PTH concentration</td>
</tr>
<tr>
<td>C</td>
<td>(10^{-7}) mmol/L</td>
<td>Calcitriol concentration</td>
</tr>
<tr>
<td>G</td>
<td>1 (dimensionless)</td>
<td>Normalized “size” of PTG</td>
</tr>
</tbody>
</table>

Table 1: List of variables in the model and their steady-state values in healthy humans. All steady-state values except \( G \) are obtained from experimental measurements.

3 Numerical Results

Equations (1)–(4) were solved using the MATLAB routine ode23s, which solves stiff systems of ODEs using a modified Rosenbrock formula of order two. We found it necessary to use this solver, as the standard ode45 algorithm (an explicit Runge-Kutta method) could not handle our system. Simulations were run for three parameter sets, corresponding to the healthy, cancerous, and renal disease states. For each simulation, we present temporal changes in the concentrations of calcium (\( Ca \)), PTH (\( P \)), and calcitriol (\( C \)), along with the size of the parathyroid gland (\( G \)), see Figure 4(a). We also present plots of the fluxes of calcium into the blood plasma from the bone and intestine and from the blood plasma into the urine as a function of time see Figure 4(b). Simulations were
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$X_c$</td>
<td>1.7 mmol/L</td>
<td>Critical calcium concentration in plasma at which secretion of calcium from the bone is upregulated</td>
</tr>
<tr>
<td>$A$</td>
<td>$6 \times 10^{-8}$ mmol/L</td>
<td>Activity of the PTG in production of PTH</td>
</tr>
<tr>
<td>$K$</td>
<td>72 (dimensionless)</td>
<td>Activity of the kidney in converting vit D to calcitriol</td>
</tr>
<tr>
<td>$I$</td>
<td>$7 \times 10^5$ (dimensionless)</td>
<td>Source of calcium in the diet</td>
</tr>
<tr>
<td>$L$</td>
<td>4 (dimensionless)</td>
<td>Natural growth of PTH</td>
</tr>
<tr>
<td>$\lambda_1$</td>
<td>1 min$^{-1}$</td>
<td>Rate of absorption of dietary calcium, $O$(min$^{-1}$)</td>
</tr>
<tr>
<td>$\lambda_2$</td>
<td>1 min$^{-1}$</td>
<td>Timescale for PTH equilibration from PTG, $O$(min$^{-1}$)</td>
</tr>
<tr>
<td>$\lambda_3$</td>
<td>$10^{-2}$ min$^{-1}$</td>
<td>Timescale of calcitriol turnover $O$(hour$^{-1}$)</td>
</tr>
<tr>
<td>$\lambda_4$</td>
<td>$10^{-5}$ min$^{-1}$</td>
<td>Timescale for PTG growth/reduction $O$(week$^{-1}$)</td>
</tr>
<tr>
<td>$\lambda_5$</td>
<td>$10^{-5}$ min$^{-1}$</td>
<td>Timescale for bone reabsorption $O$(week$^{-1}$)</td>
</tr>
<tr>
<td>$\gamma_1$</td>
<td>$10^8$ L/mmol</td>
<td>Inhibition of calcium secretion by calcitriol</td>
</tr>
<tr>
<td>$\gamma_2$</td>
<td>$10^{14}$ L$^2$/mmol$^2$</td>
<td>Inhibition of PTH production by calcitriol</td>
</tr>
<tr>
<td>$\gamma_3$</td>
<td>$1.6$ L$^6$/mmol$^6$</td>
<td>Inhibition of PTH production by calcium</td>
</tr>
<tr>
<td>$\gamma_4$</td>
<td>0.07 L/mmol</td>
<td>Inhibition of calcitriol production by calcium</td>
</tr>
<tr>
<td>$\gamma_6$</td>
<td>$10^7$ L/mm L</td>
<td>Inhibition of calcitriol production by calcitriol</td>
</tr>
<tr>
<td>$\gamma_7$</td>
<td>$3.3 \times 10^9$ L/mmol</td>
<td>Inhibition of calcium secretion by PTH</td>
</tr>
<tr>
<td>$\gamma_9$</td>
<td>0.667 L/mm L</td>
<td>Inhibition of PTG growth by calcium</td>
</tr>
<tr>
<td>$\gamma_{10}$</td>
<td>$10^7$ L/mm L</td>
<td>Inhibition of PTG growth by calcitriol</td>
</tr>
<tr>
<td>$\gamma_{11}$</td>
<td>0.333 L/mm L</td>
<td>Inhibition of bone reabsorption by plasma calcium</td>
</tr>
<tr>
<td>$\gamma_{12}$</td>
<td>$0.669 \times 10^9$ L/mm L</td>
<td>Activation of bone reabsorption by PTH</td>
</tr>
</tbody>
</table>

Table 2: List of model parameters, values used in proceeding simulations, and an explanation of each term ($\gamma_5$ and $\gamma_8$ are intentionally absent).

run for times $t = 0$ min to $t = 10^6$ min (just over 2 years) to allow long-term physiological changes associated with disease to be revealed.

As initial conditions for the healthy individual simulation, we assumed the system was close to steady state: $Ca(0) = 1.5$ mmol/L, $P(0) = 3 \times 10^{-9}$ mmol/L, $C(0) = 10^{-7}$ mmol/L, and $G(0) = 1$. Note that $G$ represents a dimensionless size of the parathyroid gland, and $G = 1$ is taken to be the steady-state size without disease. The steady-state values of the healthy case simulation were used as the initial conditions for the disease simulations: that is, the disease simulations all start with the body at equilibrium so only the presence of the disease causes homeostatic disruption.
(a) Dynamics of calcium, PTH and calcitriol concentrations, along with PTG size.

(b) Fluxes of calcium into the blood plasma from the bone and intestine and from the blood plasma into the urine.

Figure 4: Graphs show the behavior of the system under healthy, cancerous and renal disease states. The $x$-axis uses a log$_{10}$ scale, whereas the $y$-axis uses a linear scale. The model is in good qualitative agreement with experimental results. Equations (1)–(4) were solved using ode23s for times $t = 0$ min to $t = 10^6$ min $\approx 2$ years, with initial conditions that represented near-healthy steady-state conditions.
3.1 Healthy State

In the absence of more extensive experimental data, model parameters were chosen such that a biologically realistic steady-state was achieved. In the healthy state we set $T_p = 0$ (no cancer) and $K = 72$ (normal renal function). Initial conditions close to the healthy steady-state were chosen and, as can be seen from Figure 4, the system reaches its steady-state practically instantaneously (on long time scales). The shorter time scale can be seen in Figure 5. From this figure we observe that it takes around two hours for the system to restore steady-state levels in a healthy individual whose calcium plasma levels are perturbed from homeostatic levels. This is consistent with the robust behavior of the calcium regulatory system: a healthy system maintains tightly-regulated calcium plasma levels. Small deviations from homeostasis are quickly normalized by the body.

![Figure 5: The short-time dynamics of a healthy individual’s response to small perturbations from homeostatic levels of Ca, P and C. The levels normalize to steady-state values in approximately two hours.](image)

3.2 Cancer

Many tumors produce parathyroid hormone related protein (PTHrP). PTHrP acts upon the body in the same way as PTH, but its production is unregulated. This is expressed in our model by setting $T_p > 0$. The simulations presented here used $T_p = 2 \times 10^{-8}$. Figure 4(a) shows the changes in chemical concentration, as well as PTG size. As a result of cancer, plasma calcium levels can at most double. In our simulations, we find that there is a 1.4 fold increase in calcium levels due to the presence of the tumor, as the steady-state calcium concentration without cancer is 1.49 mmol/L and cancer increases the steady-state level to 2.15 mmol/L. The next clinical expectation is that cancer causes a 5–50 fold increase in PTH levels. Our simulations revealed a 6.5 fold increase, as
cancer increased steady-state levels of PTH from $3.1 \times 10^{-9}$ mmol/L to $2.0 \times 10^{-8}$ mmol/L. This is within the expected range of values, though it is quite close to the minimum increase expected.

In addition, we should expect to have a twofold maximum increase in calcitriol concentration due to the presence of a tumor. Our simulations were not as consistent with this expectation. Instead, we observed a 3.1-fold increase in calcitriol concentration, with cancer increasing steady-state calcitriol levels from $10^{-7}$ mmol/L to $3.1 \times 10^{-7}$ mmol/L. As another comparison, in cancer patients who produce PTHrP, the parathyroid gland shrinks over a period of years. This is the body’s way of compensating for the additional source of PTH provided by the tumor cells. As the size of the PTG decreases, so too does it’s production of PTH, helping to reduce the blood plasma concentration of PTH. In our simulations, over a period of approximately two years, the gland shrunk to approximately 40% its healthy size. Finally, there should be a threefold increase in calcium bone flux due to PTHrP. Again, the model slightly over-predicted the impact of cancer, demonstrating a fourfold increase in calcium bone flux. Overall, the model produced satisfactory agreement with the quantitative data provided to us by Dr. Rosol, though further refinement of parameters will be required to ensure this is true for all variables.

3.3 Renal Disease

In renal disease state the function of the kidney is impaired. As a result its rate of production of calcitriol is reduced. We can capture this effect in our model by reducing the value of $K$ in Equation (3) by a factor of four. As with the healthy state we set $T_p = 0$. Figure 4(b) shows the changes in chemical concentration, as well as PTG size. Dr. Rosol informed us that renal disease leads to: no changes in plasma calcium concentration, a tenfold increase in PTH levels, and a 60% decrease in calcitriol levels. Our model produced fairly consistent results: calcium concentration did decrease by 9%, there is a twofold increase in PTH levels, and calcitriol levels decreased by 35%. Further, the PTG was anticipated to undergo fivefold growth, and in our simulations, the gland grew by only 20%.

During renal disease, a twofold increase in calcium flux from the bone is typically observed. Our model predicted a fourfold increase in this flux term. Only subtle changes should occur in the calcium flux to the urine, and our simulations revealed a decrease in this term. Finally, decreased absorption from the GI is expected in patients with renal disease, and our simulations produced a 35% decrease in GI absorption. Taken together, the model did not describe renal disease as well as it described cancer. Presumably, further refinement of the model parameters is required to ensure close quantitative agreement with renal disease data.

4 Discussion and future work

The primary focus during this workshop was to develop a mathematical model which describes calcium homeostasis in both health and disease. To keep model complexity to a minimum, the model incorporates the main regulatory feedback loops between plasma calcium, parathyroid hormone, calcitriol and the parathyroid glands. Additional important effects regulated via the intestine, kidney and bone are also taken into account, while calcitonin (which acts as short-lived emergency responder at high calcium) and phosphorous (which co-regulates some of the modeled effects) are not included at this stage.
By considering known steady-state values and inherent time scales, model parameters were fitted to yield numerical solutions which are qualitatively consistent with known data. Over short times (minutes) the model is able to regulate perturbations in PTH and calcitriol accurately. Furthermore, the model correctly predicts that over a period of months the parathyroid gland will grow in patients with renal disease, stimulated by depressed levels of calcitriol and calcium [3]. The model also shows that the gland will decrease in size in patients with a PTHrP-producing tumor (due to high levels of calcitriol and calcium). Compared to the healthy state, the high PTH levels observed in these two diseases lead to excessive release of calcium from the bone, which over time may cause osteoporosis.

We remark that in order to accurately describe bone loss due to dysregulation of calcium, the model might need to be extended. Our model does not explicitly account for the evolution of both calcium repositories in the bone. Rather, it only includes a phenomenological term in the calcium Equation (1) representing resorption of calcium from bone. We note that we have neglected the small, rapidly exchangeable pool of calcium stored in bone, and only considered the larger reserve pool. Both pools are regulated via bone-building and bone-destroying osteoblast-osteoclast pathways which we have only considered at a superficial level.

In its current form, the model could be used as a starting point for investigating the response of various therapeutic treatments. For renal disease, the first treatment option is the administration of vitamin D (or any of its analogs) [7]. In that context, we believe that the use of mathematical modeling could help answer currently open questions, as discussed by Joy et al. [7], regarding the best time to initiate treatment and what the optimal dose is. An excessive vitamin D intake could cause insufficient PTH levels, which in turn could lead to bone disease as a result of decreased bone remodeling (i.e., lower rates of bone absorption and resorption) [7]. The treatment protocol should also seek to avoid episodes of hypercalcemia, which promotes vascular calcification and which is linked to cardiovascular mortality in patients with chronic kidney disease [7]. In the case of PTHrP-producing tumors, the model could be used to study the effects of surgical tumor removal (by setting $T_p = 0$ at some point $t_s$ in time, $t_s > 0$). We anticipate that, if the cancer has caused the parathyroid gland to shrink considerably, surgery could induce an acute PTH deficiency which may require administration of calcium to avoid hypocalcemia. A similar situation sometimes occurs in renal patients who fail to respond to vitamin D treatment and must undergo parathyroidectomy. If too much of the gland is removed during surgery, then daily calcium supplementation becomes necessary [7].

Finally, we would like to mention that during the workshop the group spent some time discussing whether the model could feature hysteresis in the relationship between PTH and calcium, as has been reported from experiments that study induction of and recovery from hypocalcemia [2]. While the model’s potential for reproducing such data could be investigated further, it seems far from certain that true hysteresis has actually been observed experimentally since many of the studies may have reported transient/dynamic PTH and calcium values as opposed to equilibrium values [10]. Nevertheless, future model analysis should include a thorough determination of possible steady states, their linear stability, and the asymptotic behavior of the system.

References


