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# Calcium Homeostasis: a Feedback Control Point of View

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**Abstract**

In the biological sciences, the mathematical approach to studying feedback mechanisms has not been common despite the abundance of such mechanisms in those systems. In this paper, we will try to analyze the calcium homoeostatic mechanism in this context. In addition to a general modeling of this mechanism, the paper will also focus on *parturient paresis*, a common disease associated with the onset of parturition in dairy cows, due to a large increased demand for calcium.

## 1 Introduction and Background

The use of feedback for the purpose of regulation is prevalent in biological systems [1, 2, 3]. Although ideas concerning such regulation have been present for a long time, their implementation in the study of biological systems started to raise interest only recently. The major areas of interest in this context were the modeling and analysis of cardiovascular and respiratory systems in addition to some studies of thermoregulation, endocrine regulation, gastrointestinal secretions, blood flow, renal plasma regulation, muscle dynamics and eye accommodation models among many others. [1, 2, 3, 4]. The calcium homeostatic mechanism is addressed in this paper. A model for this mechanism from a control theory point of view is obtained. This model is then used to study a disease which affects dairy cows and is generally referred to as parturient paresis, or simply milk fever. Since milk fever is ultimately a failure of the feedback regulatory mechanism to cope with large calcium demands, it is a good candidate for study using ideas from feedback control theory. By viewing the calcium feedback regulation system as a dynamical system, this study aims to provide a better explanation for the calcium regulation mechanisms during normal operation and during failure.

Calcium has a particularly important physiological role. While calcium salts maintain the integrity of the skeleton structure, intracellular calcium ions play an important role in the activity of a large number of enzymes and are also involved in conveying information from the surface to the interior of the cell. Extracellular calcium ions are also necessary for neuro-muscular excitability, blood clotting and hormonal secretions among many other functions [6]. For this important biochemical role to be accomplished, extracellular and intracellular concentrations of calcium should be maintained within a very narrow range, typically between 8 and 10 mg/dl in dairy cows [7]. The three major compartments involved with calcium regulation of the equilibrium (homeostasis) are: the bone, the kidney and the intestine. It is agreed that calcium homeostasis is achieved by the constant influx and outflow of calcium from and to the blood plasma under a tight hormonal control that will be discussed in this paper. This entire homeostatic mechanism works on increasing the calcium influx into the extracellular fluid whenever its calcium ion concentration drops below normal due to some kind of calcium demand. Although dairy cows have a very effective mechanism for regulating the calcium concentration in the blood plasma, this mechanism may fail. On the day of calving, dairy cows produce around 10 liters of colostrum containing 23g or more of calcium, approximately 6 times as much calcium as the extracellular calcium pool contains. Most animals adapt to the onset of lactation. However, some become severely hypocalcemic, which disrupts nerve and muscle function, resulting in recumbency and the clinical syndrome referred to as parturient paresis [12]. Usually, milk fever cows are treated with intravenous calcium injection that keep them alive until the intestinal and bone mechanisms adapt to the large calcium clearance.

## 2 Derivation of the Model

In [13], Ramberg et.al describe calcium homeostasis in terms of controlled, controlling and disturbing signals. Controlled signals are defined to be the *plasma calcium concentration* $[Ca]_p$ and *bone calcium* $M_b$, while the controlling signals are taken to be the intestinal calcium absorption, the bone calcium resorption and the renal calcium reabsorption. The disturbing signals are those that cause loss of calcium from plasma and take the form of endogenous fecal calcium, clearance via glomerular filtration, placental calcium transport to the fetus during pregnancy, calcium deposition into the bone, and

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milk calcium secretion during lactation. In [13], it is also stated that for short term calcium regulation(hours to weeks), only control of $[\mathrm{Ca}]_p$ may be considered since it has higher priority than $M_b$ in that time period. Let us define $V_T = V_{bone} + V_{intestine}$, where $V_{bone}$ and $V_{intestine}$ are the rates (g/day) at which calcium is transported from bone and through intestinal absorption respectively into the plasma. Based on the conservation of mass, we can express the plasma calcium concentration as follows:

$$[\mathrm{Ca}]_p = \frac{1}{vol}\int_0^t (V_T - V_{cl})d\tau.$$

Where $vol$ is the total plasma volume (l), and $V_{cl}$ is the total calcium clearance through the various avenues mentioned above. Since the plasma calcium concentration are regulated quite accurately to follow a setpoint, the overall closed-loop system can be described in Figure 1. It should be pointed out that a physiological mechanism exists for generating this setpoint in the parathyroid gland. This will be elaborated on later in this paper. At this point the feedback control law shown in the figure is not specified and will be explored in the next section.

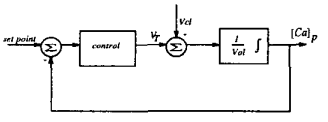


**Figure 1:** Overall closed-loop system for calcium homeostasis

### 2.1 Shortcomings of Existing Model and Necessity of Integral Control

The work in [13] suggests that the control in the system is proportional to the error. Indeed the expression for $V_T$ in [13] is given by:

$$V_T = 1770(0.104 - [\mathrm{Ca}]_p)$$

If one were to analyze this feedback law, it becomes quickly apparent that it cannot account for the observation since it could be easily seen that the steady-state error to a step change of $\overline{V_{cl}}$ in $V_{cl}$ is $e_{ss} = -\frac{\overline{V_{cl}}}{1770} \neq 0$. This implies that a sudden and large change in $V_{cl}$ – as would be the case due to the demands of lactation prior to parturition– will not allow the plasma calcium concentration to recover to its setpoint and a steady-state error will persist. This, however, is contrary to observation. Experimental data on normal animals suggests that after a period of transition, $[\mathrm{Ca}]_p$ will always return to its setpoint value which was present prior to the sudden increase in Calcium demand.In order to obtain this zero steady-state error, our modification to the model would start by the introduction of an integral term multiplying the error, resulting in a PI controller.

The transfer function from $V_{cl}$ to $[\mathrm{Ca}]_p$ then becomes:

$$\frac{[\mathrm{Ca}]_p}{V_{cl}} = -\frac{s/vol}{s^2 + (K_p/vol)s + (K_I/vol)}$$

which obviously yields a zero steady-state error to a step change in $V_{cl}$. Not only is this model consistent with the zero steady state error observation, the transient response characteristics of the resulting second order system agree quite well with the transient response characteristics seen in real data. This can seen from Figure 2 where actual response data is plotted at the same figure with the simulated response of our second order system. We can see that the system has an overdamped response to a step disturbance. The single points in the plot correspond to the ensemble average of Calcium plasma concentrations for 18 calving cows over a 10 day period around the day of parturition.The solid plot corresponds to the simulated response for the second order model when $V_{cl}$ is increased from 20 g/day to 70 g/day on the day of parturition. The values for $K_p$ and $K_I$ were selected to minimize the sum of the squared errors between the actual data and the model. The closeness of the fit underscores the fact that actual response can be approximated quite well by second order dynamics.

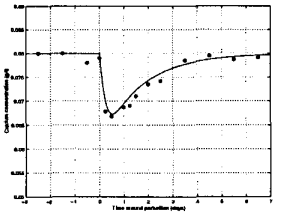

**Figure 2:** Plot of actual data and simulation result for second order system

## 3 Physiological Basis

The plausibility of this model cannot be advocated until it is physiologically validated, i.e. a physiological counterpart for the PI block is found. In this quest, we will seek the simplest possible setup that will yield a convincing explanation of this mechanism.

### 3.1 Realizing Integration by Means of Hormones

We start by considering a single hormone explanation. Suppose the total calcium into the plasma $V_T$ is proportional to the concentration of one hormone, say hormone A whose concentration is denoted by [Hormone A]. Then, PI feedback could only be explained in this

case when

$$\frac{d}{dt}[HormoneA] \propto (error + K\frac{d}{dt}error)$$

However, this relation is not very satisfying for at least two reasons. First, it suggests that there should exist two mechanisms for the production of Hormone A. Secondly, the above relation indicates that the mechanism for producing Hormone A must somehow rely on measurements of the *derivative* of the error which is likely to be a difficult and noise prone task. Alternatively, if one considers two hormones to realize the PI control for calcium regulation, an elegant and quite plausible solution emerges. Suppose we have two hormones A and B. If:

$$[HormoneA] \propto error$$

$$\frac{d}{dt}[HormoneB] \propto [HormoneA]$$

$$V_T = V_A + V_B$$

where

$$V_A \propto [HormoneA]$$

$$V_B \propto [HormoneB]$$

Then, the proportional component of our PI control is given by $V_A$, while the integral component is given by $V_B$. Furthermore, the concentration of Hormone A provides a measure of the error while the concentration of Hormone B provides a measure of the integral of the error. Without further information, it is hard to say more about the feedback control realization based on control theory alone. In the next section we will see that based on what is known in the physiology literature on calcium homeostasis, the above postulates are indeed very good representations of reality.

### 3.2 The Endocrinology of Calcium Homeostasis

It is agreed upon that when calcium demand from the plasma is increased, calcium homeostasis is achieved by the influx of calcium from and to the blood through bone, kidney, and intestine under the tight control of two major hormones: Parathyroid Hormone (PTH), and the most important metabolite of Vitamin D: 1-25 Dihydroxycholecalciferol (1,25-DHCC) [6, 7]. The parathyroid hormone is produced in the parathyroid glands in response to a decrease in the calcium plasma concentration from the desired setpoint. Experiments have shown that the production is very much a linear function of the deviation from the setpoint.Thus, PTH is an accurate measure of the error at a given time, which would be in agreement with our first postulate in the previous subsection if PTH is taken to correspond to Hormone A. Now PTH interacts mainly with the bone and kidney. In the bone, PTH has a marked effect on bone: upon the increase in PTH concentration a fast process known as osteocytic osteolysis that causes removal of bone salts takes place. If high concentrations of PTH persist, a delayed response (hours to days) takes place due to the activation of the bone osteoclasts. This process is known as the osteoclastic bone resorption. It allows the response to PTH continue even beyond what can be handled by osteocytic osteolysis. However, in most cases short term needs are met by osteocytic osteolysis. The effect of PTH on the kidney is to increase tubular reabsorption of calcium thus reducing calcium loss through urine. Thus the impact of PTH is to increase immediate calcium transfer into the blood plasma. On the other hand, the main role of 1,25-DHCC is to stimulate intestinal absorption through increasing formation of a calcium-binding protein in the intestinal epithelial cell [9]. Thus the plasma calcium influx is due to the impact of PTH and that of 1,25-DHCC. This would seem to coincide with our third postulate in the previous subsection, if we associate 1,25-DHCC hormone with Hormone B.
How then does the rate of production of Hormone B (1,25-DHCC) be proportional to the concentration of Hormone A (PTH)? 1,25-DHCC is produced from a biologically inactive form of Vitamin D after it undergoes several hydroxylations steps in the liver and kidney [6, 7, 8, 9]. The last hydroxilation step in the kidney takes place only under stimulation of PTH. Therefore, the PI action is implemented by the mechanisms underlying the production of these 2 hormones.

### 3.3 Homeostatic System Failure in Milk Fever Animals

In order to relate the failure of the feedback components to milk fever, we need to look at their physiological sources. As mentioned before $V_T = V_{bone} + V_{intestine}$. For the bone calcium, we can write:

$$V_{bone} = \alpha_{bone} V_B \quad (1)$$

where $V_B$ is the quantity of calcium that is available for resorption in bone. Clearly, $0 \leq \alpha_{bone} \leq 1$. We know that PTH stimulates bone resorption , therefore:

$$\alpha_{bone} = f_b([PTH]) \quad (2)$$

When $f_b(\cdot)$ can be adequately described by a linear relation, we would have $f_b([PTH]) = \alpha_b[PTH]$ for some constant $\alpha_b$. On the other hand, we know that at any given time PTH secretion by the parathyroid gland–and hence PTH plasma concentration–is proportional to the $[Ca]_p$ deficiency. Thus, the overall relationship would be:

$$V_{bone} = K_p.e$$

Where $e := r - [Ca]_p$

Similarly, for intestinal absorption we have

$$V_{intestine} = \alpha_{intestine} V_i \quad (3)$$

where $V_i$ is the calcium available in the diet. As before, $0 \leq \alpha_{intenstine} \leq 1$. Since intestinal absorption is stimulated by concentrations of 1,25-DHCC we shall model

$$\alpha_{intestine} = f_i([1,25 - DHCC]) \quad (4)$$

But when $f_i(\cdot)$ can be described adequately by a linear function, we can write $f_i([1,25 - DHCC]) = \alpha_i[1,25 - DHCC]$ for some constant $\alpha_i$. In this case, we have

$$V_{intenstine} = \alpha_i V_i \cdot [1,25 - DHCC]. \quad (5)$$

The relationship between PTH and the 1,25-DHCC production rate could be written as

$$\frac{d}{dt}[1,25 - DHCC] = \alpha_p[PTH]$$

Lumping the above relationships together, we get:

$$V_{intestine} = K_I \int_0^t e d\tau \quad (6)$$

While this model may be adequate to describe the hypocalcemic case, it must be modified by including nonlinear effects inherent to the calcium homeostatic regulation mechanism in order to explain parturient paresis. Nonlinear effects that can be added to our linear model take the form of saturation terms in the PI control block. The physical interpretation of these saturations follows from the observation that PTH and 1,25-DHCC quantities are limited by the physiological capacities of the tissues involved in their production. Another key nonlinear effect introduced into the model reflects the impact of reduced $[Ca]_p$ on the intestinal absorption processes. In [14], Daniel establishes through experimentation that there is a highly significant correlation between plasma calcium level and the amplitude and rate of both gut and abomasal motility in cows. This observation is explained in terms of the general effects of a depression of levels of ionized calcium on smooth muscle contractility and neuromuscular transmission. This reduction in motility is in turn translated into a reduction in intestinal abosrption. Figure 3 shows the dramatic effect of $[Ca]_p$ deficiency on rumen and abomasal motility. Therefore, the effect of low plasma calcium on the supply rate of calcium has been modeled as a nonlinear, monotonically increasing function multiplying the absorption and coefficient and assuming a value of unity at the set point (see Figure 3). This multiplication factor is a quadratic function of $[Ca]_p$ which has been obtained by considering the product of the rate and amplitude linear regression equations for rumen motility given in [14]. This function was then normalized to have unity value at normal $[Ca]_p$ level (considered in the simulation to be 0.08g/l). It should be pointed out here that obtaining an accurate shape

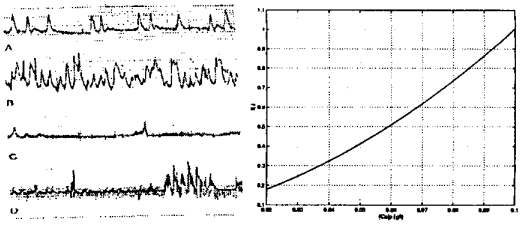

**Figure 3:** 1st Figure: A and B: Typical rumen and abomasal pressure recordings prior to the induction of hypocalcemia in one cow. C and D: Typical rumen and abomasal pressure recordings at the end of the induced hypocalcemic state (taken from [14]). 2nd Figure:Multiplicative reduction factor reflecting the effect of $[Ca]_p$ deficiency on bone resorption and intestinal absorption

of such a multiplication factor is neither practically feasible nor important. The main point here is to study the qualitative effects that such a multiplicative factor may have on the system. The resulting overall nonlinear model is shown in figure 4.

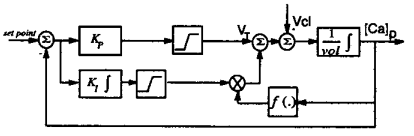


**Figure 4:** Nonlinear closed-loop model

### 3.4 State-Space Representation and Phase Portraits

A state-space description of the system shown in figure 4 could be given by the following:

$$\begin{aligned} \dot{x}_1 &= \frac{1}{vol}[sat_1(K_p(r - x_1)) + f(x_1)sat_2(x_2) - V_{cl}] \\ \dot{x}_2 &= K_I(r - x_1) \end{aligned}$$

where $x_1$ is the output of the calcium pool integrator and $x_2$ is the output of the PI block integrator. $f(.)$ is the nonlinear function corresponding to the effect of excessive decrease of $[Ca]_p$ on the absorption coefficient. The equilibrium point of this system can be easily computed to be:

$$\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} r \\ V_{cl} \end{pmatrix}$$

The phase portraits of the system described above have been numerically computed for $V_{cl} = 70$, $V_i = 100$ and r=0.08 . It is interesting to see (Figure 5) that for $K_p = 4300$ and $K_I = 1800$ (the parameters identified from experimental data for nonmilk fever animals),

the post disturbance solution trajectory goes to the new equilibrium state which correspond to the $[Ca]_p$ set-point and the new clearance rate, while for $K_p = 2500$ and $K_I = 1200$ (figure 6) we see that the solution starting at $\begin{pmatrix} 0.08 \\ 20 \end{pmatrix}$ would go unstable and the regulatory system breaks down, as would be seen in the case of milk fever. These phase portraits correspond to the system operating at its equilibrium (prior to calving) and then being impacted by a constant disturbance of amplitude 70g/day. This effect can be duplicated for other low values of $K_P$ and $K_I$, but does not appear for large values of $K_P$ and $K_I$. In fact, whether or not breakdown takes place for a given disturbance level in this model depends to a great extent on the level of undershoot exhibited by the response of the 2nd order linear system to the disturbance input, on the saturation limits and on the function $f(\cdot)$. Indeed, it could be shown analytically that given $K_p$ and $K_I$, instability would occur for a range of monotonically increasing reduction functions $f(\cdot)$ assuming sufficiently small values at the initial conditions. This result will be reported elsewhere.

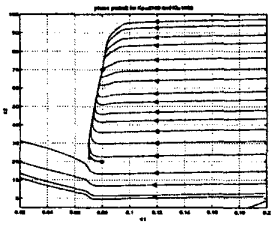

**Figure 5:** Phase portrait for high values of $K_p$ and $K_I$

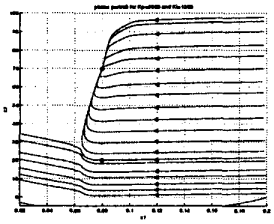

**Figure 6:** Phase portrait for low values of $K_p$ and $K_I$

## 4 Conclusion

In this paper, a study of the calcium homeostatic mechanism with special reference to milk fever in dairy cows was presented. A linear model was developed for the normal hypocalcemic case at parturition. The integral action of the model as well as the proportional action have a physiological basis and can be explained in terms of the interactions of two hormones. Nonlinearities were then added to account for the milk fever recumbency. Those nonlinearities are due to the saturations in PTH and 1,25-DHCC production and to a postulated reduction in calcium intestinal absorption after an excessive decrease in calcium concentration. therefore, the model was able to reproduce both normal and abnormal behavior of the calcium homeostatic mechanism.

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