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DRAFT: A MATHEMATICAL MODEL OF ACUTE RESPONSE OF PARATHYROID HORMONE TO CHANGES IN PLASMA IONIZED CALCIUM IN HUMANS

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ABSTRACT

A complex bio-mechanism, referred to as calcium homeostasis, regulates plasma ionized calcium (Ca^{++}) concentration in the human body to within a narrow physiologic range which is crucial for maintaining normal physiology and metabolism. Various metabolic disorders and pathologic conditions originate from acute and/or chronic disturbances/disorders in calcium homeostatic system. This system relies on numerous subsystems which operate in different time-scales ranging from minutes to weeks. In this thesis we focus on a particular sub-system that operates on the time-scale of minutes; the dynamics involves the response of the parathyroid glands to acute changes in plasma Ca^{++} concentration. We develop a two-pool, linear time-varying model describing the dynamics of the sub-system. We

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show that this model can predict dynamics observed in clinical tests of induced hypo- and hyper- calcemia in normal humans.

NOMENCLATURE

PTH Parathyroid hormone
PTG Parathyroid gland
PTH_P PTH in plasma pool
PTH_C PTH in PTC
Ca_P Ionized calcium in plasma pool
25D 25 hydroxy Vitamin D
$25D_P$ 25D in plasma pool
1,25D 1,25 dihydroxy Vitamin D
$1,25D_P$ 1,25D in plasma pool
DNA Deoxyribonucliec acid
RNA Ribonucliec acid
mRNA Messenger ribonucliec acid
VDR Vitamin D receptor
CaR Calcium receptor
x_1 Amount of parathyroid hormone in PTG pool
$x_{1,SS,N}$ Amount of normal PTH in PTG pool
$x_{1,SS,Max}$ Amount of maximal steady-state PTH in PTG pool
$x_{1,SS,Max}$ Amount of maximal steady-state PTH in PTG pool
$x_{1,SS,Min}$ Amount of minimal steady-state PTH in PTG pool
x_2 Amount of PTH in plasma pool
$x_{2,SS,N}$ Amount of normal PTH in plasma pool
$x_{2,SS,Max}$ Amount of maximal steady-state PTH in plasma pool
$x_{2,SS,Min}$ Amount of minimal steady-state PTH in plasma pool
Ca^{++} Ionized calcium
$Ca(t)$ Ionized calcium concentration in plasma pool
$Ca_{SS,N}$ Normal Ionized calcium concentration in plasma pool
t Time
τ_1 Half-life of PTH in PTG pool
τ_2 Half-life of PTH in plasma pool
λ_1 Decay rate constant of PTH in PTG pool
λ_2 Clearance rate constant of PTH in plasma pool
$\lambda_{Ca}(t)$ secretion rate function of PTH from PTG pool

INTRODUCTION

Calcium homeostasis refers to a complex bio-mechanism that regulates plasma ionized calcium (Ca^{++}) concentration in the human body to within a narrow physiologic range which is crucial for maintaining normal physiology and metabolism. Plasma Ca^{++} plays a vital role in normal functioning of muscles, nerves, platelets, neutrophils, and coagulation factors, cell growth, cell division, secretion of hormones and other regulators [1], and mineralization of bones [2]. This complex bio-system comprises numerous sub-systems interconnected via positive and negative feedback pathways.

Various metabolic disorders and pathologic conditions originate from acute and/or chronic disturbances/disorders in the calcium homeostasis. They can be caused by any one or a combination of the following factors: a) changes in plasma Ca^{++} levels and/or vitamin D levels by a physiologically significant amount, b) impaired synthesis and/or secretion of parathyroid hormone (PTH), and c) pathological conditions of parathyroid glands and kidneys. These disorders may affect normal bone remodeling process causing various metabolic bone diseases, such as osteoporosis, a major public health concern in the United States [3,4], besides causing many other abnormalities and disease conditions (eg., primary and secondary hyperparathyroidism).

The present understanding of calcium homeostasis and its disorders is based on the traditional approach of biological and medical science which involves discovering various signaling pathways, identifying critical bio-markers, and employing statistical analysis. However, calcium homeostasis is a sophisticated bio-system where numerous sub-systems interact at different time-scales. A perturbation in one sub-system has corresponding effects in the interconnected sub-systems and these in turn have effects on the other sub-systems. These cascade-effects propagate in positive and negative feedback pathways in multiple directions. It becomes impractical, if not impossible, to keep track of all of these interactions in order to derive an understanding of the bio-system as a whole using the traditional approach. Systems biology, an emerging science, relies on the integration of mathematical models for individual sub-systems into a single model, enabling us to study the effects of disturbances in the various inputs, pools and processes of the overall bio-system.

We took the systems biology approach in our overall calcium homeostasis modeling efforts. In this paper, we first developed a qualitative model of the overall bio-system in a normal human. We then focus on the sub-system that involves the acute dynamical interaction between plasma Ca^{++} and PTH (called Ca-PTH axis for ease of notation). This model can successfully predict dynamics observed in clinical tests of induced hypo- and hypercalcemic clamp tests.

QUALITATIVE MODEL OF CALCIUM HOMEOSTASIS

A detailed qualitative model describing the interactions between various components and signalling pathways of calcium homeostasis is presented in this section. The intestine, bone, kidney, and plasma are the four major pools of Ca^{++} in the human body. The average total plasma calcium concentration in the human body is 2.1-2.6 mmol/L [5]. At normal physiological state, about 1.1-1.3 mmol/L is ionized calcium, 0.9-1.1 mmol/L is protein-bound calcium, 0.18 mmol/L is complexed calcium and 180 nmol/L is intracellular free calcium [5]. The ionized form of calcium, which is just 0.5% of the total body calcium, is metabolically active and tightly regulated by the homeostatic system. The condition when Ca^{++} level falls below the normal

range is called *hypocalcemia* and the condition when it climbs above the normal range is called *hypercalcemia*. An overall daily Ca^{++} balance in the plasma of a healthy adult is maintained by fluxes of calcium between the plasma and the intestine, bone and kidney (for details see [6]). The fluxes are actively regulated by two chief hormones: the metabolically active form of vitamin D and PTH. The metabolism and regulation of vitamin D and PTH are presented in the next sections, respectively.

Vitamin D Metabolism and Regulation

The general steps in the metabolism of vitamin D are shown in Fig. 1 (the presentation here follows the detailed exposition in [7]). There are two sources of vitamin D in the human body: daily diet and skin. Daily diet provides vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol), whereas in skin, 7-dehydrocholesterol is converted into vitamin D_3 by exposure to uv-light. The biological actions of both forms of vitamin D is considered to be the same, hence, the term vitamin D is used to denote both forms in this work. Vitamin D does not circulate for long in the blood stream. It is immediately taken up by adipose tissue for storage or by liver for 25-hydroxylation to form 25 hydroxy vitamin D[1]. 1,α hydroxylation of 25D occurs in the kidney to form the metabolically active 1,25 dihydroxy vitamin D[2]. In humans, tissue storage of vitamin D can last for months or even years. 25D is the major circulating form of vitamin D.

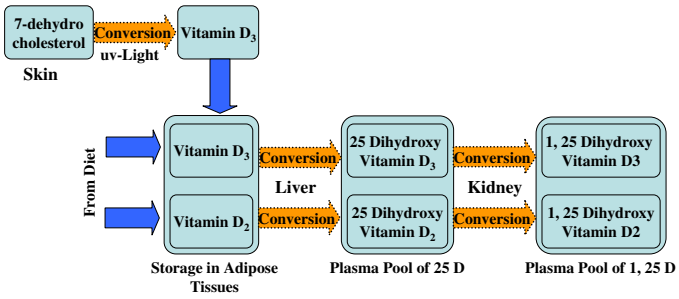


Figure 1. THE GENERAL STEPS IN VITAMIN D METABOLISM. DOTTED ARROWS MEAN CONVERSION AND SOLID ARROWS MEAN TRANSPORTATION.

In a normal individual, there is an ample supply of Vitamin D to plasma directly from diet, skin, and storage in the adipose. The conversion of vitamin D to 25D in the liver is only loosely regulated [7]. However, the conversion of 25D to 1,25D in the kidney is tightly regulated by renal α hydroxylase enzyme and it has been established that the kidney is the major source of the circulating pool of 1,25D [7]. For our modeling purpose, the different steps in the vitamin D metabolism process have been lumped into a high-level schematic diagram as shown in Fig. 3. Next, we present the bio-synthesis and secretion of PTH and their regulations.

PTH Bio-Synthesis and Secretion and Their Regulation

There are four parathyroid glands, each weighing 40 mg on average, located adjacent to the thyroid gland in the neck. The chief cells are the predominant cells in the parathyroid glands. PTH is synthesized and stored in the cytoplasmic vesicles of the chief cells. Normally, only about 20% of the cell population is actively secreting PTH [8].

A simple understanding of the steps involved in the biosynthesis and secretion of PTH is shown in Fig. 2 based on [9, 10]. The first step in the biosynthesis of PTH is the *transcription* process in which genetic information is transferred from the DNA (Deoxyribonucleic acid) to a pre-mRNA (pre-messenger ribonucleic acid) in the nucleus of the parathyroid cell. The *post-transcriptional* process follows. The pre-mRNA matures into an mRNA that is transported to the cytoplasm, the process being called *transportation*. The next step is the *translation* where the genetic information in the mRNA is translated into a specific polypeptide, a larger precursor of PTH, called pre-proPTH containing 115 amino acids. This process occurs in the endoplasmic reticulum-bound polyribosomes. The pre-proPTH is then cleaved in the rough endoplasmic reticulum to produce a 90 amino acid intermediate precursor of PTH called proPTH. This process is called *first cleavage*. The *second cleavage* occurs in the golgi complex in the cytoplasm to finally produce the PTH which accumulates in the vesicles. In response to secretory stimulus caused by decrease in plasma Ca^{++} concentration to calcium sensing receptors (CaR) on the cell membrane [11], the membrane of the storage vesicle fuses with the cell membrane and PTH is released from the cell into circulation. This process is called *exocytosis*.

PTH bio-synthesis is regulated by plasma 1,25D during the transcriptional process [12] and by Ca^{++} during post-transcriptional process [13] as depicted in the Fig. 2. The 1,25D form of vitamin D, with the plasma half-life of 12 to 15 hours [1], regulates the long-term parathyroid secretion function. It has been termed as a day-to-day regulator of calcium homeostasis [1]. Higher concentrations of 1,25D inhibit the transcription of the PTH gene [12] through signalling from the nuclear [5] vitamin D receptor (VDR). The effect occurs within 2 hours [1]. A decrease in PTH mRNA levels to less than 4% of controls was observed within 48 hours in rats that were injected with amounts of 1,25D which did not increase their calcium levels [12]. The time-scale of this regulation of PTH synthesis by 1,25D cannot be pin-pointed. However, a time-scale of hours to days can be assumed based on [1, 12, 14]. Plasma Ca^{++} regulates PTH biosynthesis during the post-transcriptional process. The regula-

[1]We use 25D to denote 25 hydroxy vitamin D.
[2]We use 1,25D to denote 1,25 dihydroxy vitamin D.

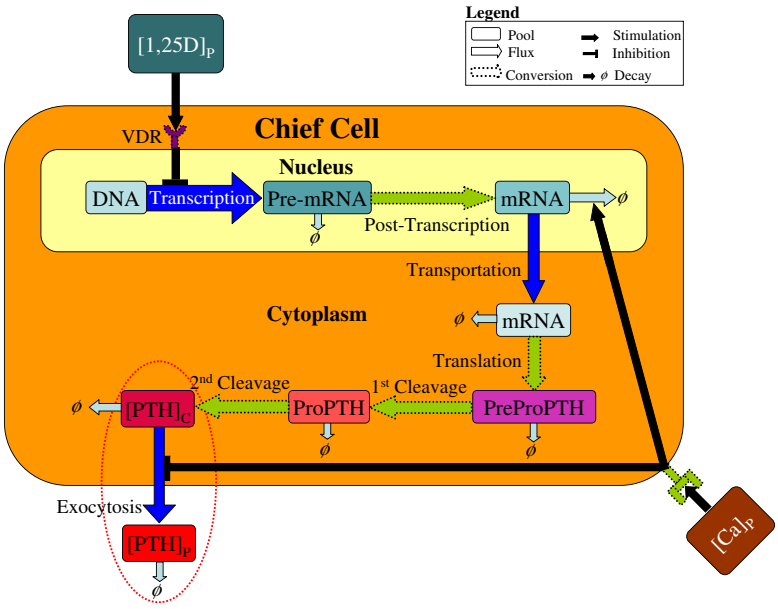


Figure 2. A SCHEMATIC DIAGRAM SHOWING VARIOUS STEPS INVOLVED IN PTH BIOSYNTHESIS AND SECRETION AND THEIR REGULATION BY 1,25D AND CALCIUM.

tion occurs by affecting the mRNA stability [13]. An increase in plasma Ca^{++} concentration decreases the overall PTH bio-synthesis by degrading the mRNA faster. Conversely, a decrease in plasma Ca^{++} concentration increases the overall PTH bio-synthesis by increasing the nuclear mRNA half-life. No known major regulatory effects have been observed at the translational and post-translational levels [9]. The time-scale of this regulation has been suggested to range from hours to days in [1, 9].

The regulation of exocytosis in response to changes in plasma Ca^{++} levels occurs strictly by signaling pathways involving calcium sensing receptors (CaR) located on the cell membrane of the chief cells of the parathyroid glands [11]. An increase in the plasma Ca^{++} concentration results in a decrease in PTH secretion. Conversely, a decrease in the plasma Ca^{++} concentration results in an increase in PTH secretion. The time-scale of the parathyroid gland's response to varying plasma Ca^{++} concentrations ranges from seconds to minutes [11, 15]. In our qualitative model of the calcium homeostasis the above described 1,25D and the plasma Ca^{++} concentration signaling pathways have been lumped together in terms of an overall effect on the exocytosis. Next, we put together a qualitative model of plasma calcium homeostasis.

Qualitative Model of Plasma Calcium homeostasis

The plasma calcium pool size is maintained by a flux balance with the intestine, bone, and kidney. The influx of calcium from the intestine consists of both actively- and passively- regulated channels, whereas the efflux to the intestine is mainly due to passive transportation (Fig. 3). The efflux to the kidney involves ultrafiltration, where the filtration occurs under high pressure in the glomerular capillaries of the kidney. The influx from the kidney involves a passive diffusion and an active reabsorption by the nephrons.

A decrease in the plasma Ca^{++} concentration acutely stimulates (a rise in the plasma Ca^{++} concentration inhibits) PTH secretion by exocytosis from the parathyroid cells in a time-scale of minutes [11]. In the time-scales of hours to days, a decrease in plasma Ca^{++} concentration increases (a rise in the plasma Ca^{++} concentration decreases) bio-synthesis of PTH in the parathyroid cells [9]. PTH in turn stimulates bone calcium resorption and active renal reabsorption of calcium. PTH also upregulates production of renal α hydroxylase enzyme in the kidney which upregulates conversion of 25D into 1,25D in the kidney. 1,25D in turn upregulates active intestinal calcium absorption and active renal calcium reabsorption. It also downregulates PTH bio-synthesis in the parathyroid cells and production of the renal α hydroxylase enzyme, resulting in the downregulation of its own production.

1,25D and PTH play important roles in regulating bone formation and resorption processes [5]. This results in the addition or removal of calcium from the plasma pool and the transportation of it to and from the bone. This process, of course, plays an important role in plasma calcium homeostasis. In fact, the bone acts as a big reservoir to supply calcium to the plasma in case of need. Though the exact function of 1,25D and PTH in the bone remodeling process is not well understood, it has now been generally accepted that 1,25D upregulates calcium trapping

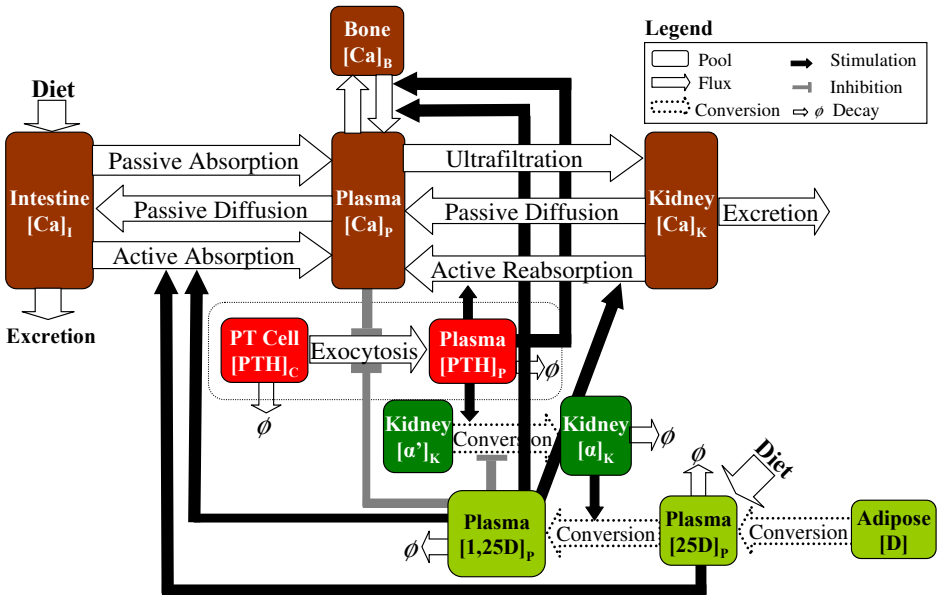


Figure 3. A QUALITATIVE MODEL OF PLASMA CALCIUM HOMEOSTASIS.

for bone formation [5] and an intermittent rise in PTH helps in a net positive bone formation [16, 17] resulting in a net flux of calcium from plasma to bone. A lack of 1,25D and continuous rise in PTH upregulates bone resorption resulting in a net flux of calcium to the plasma. Phosphate in high concentrations stimulates PTH secretion and PTH upregulates phosphate clearance through the kidney. The effect of phosphate on the parathyroid gland is independent of plasma Ca^{++} and vitamin D [13]. Thus, the phosphate pool is not included in the present model.

The response of the parathyroid glands to acute changes in plasma Ca^{++} concentration occurs in time-scales of seconds to minutes [11] which involves the exocytosis process. Because regulation of PTH bio-synthesis by plasma Ca^{++} and 1,25 D in the chief cells and all other signaling pathways in the calcium homeostatic system run in the time-scales of hours to days [12, 13], it is feasible to study the acute response of plasma PTH to changes in the plasma Ca^{++} separately from the overall system. We refer to this isolated sub-system (shown in Fig. 4) of the overall bio-system as the Ca-PTH axis from here on. Given that a reasonable amount of information is available about this axis, this paper focuses on the development of a mathematical model for this axis, which is presented next.

A MATHEMATICAL MODEL OF THE CA-PTH AXIS

In this section we develop a model describing the response of PTH to acute changes in plasma Ca^{++} concentration (Ca-PTH axis) in humans. To fully appreciate this model, we first present a literature review of relevant published models.

Literature Review

Our literature survey unraveled numerous models of calcium homeostasis of varying degrees of details. The earlier works are theoretical or have utilized data from animals and birds whereas the recent investigations have utilized data from humans. A detail literature review can be found in [6]. With the discovery of various receptors and ligands involved in the signalling pathways within individual sub-systems, the understanding of the details of calcium homeostasis has progressed substantially. Hence, most of the recent studies have focussed on modeling particular subsystems of the calcium homeostasis, e.g. Ca-PTH axis [14, 15] and bone remodeling process [16–18].

A relatively recent attempt to model plasma calcium homeostasis consisting of separate pools of calcium, phosphate, PTH, calcitriol in plasma, intracellular phosphate, and parathyroid gland mass was presented in [19]. The exchangeable pools of calcium and phosphate in bone were introduced to model flux exchange between the plasma and bone. Similarly, a renal 1,α hydroxylase pool, a phosphate pool, and an intestinal calcium pool were utilized to capture the dynamics involving the kidney and the intestine. Clinical data from a renal failure case was compared with simulation results with a favorable match. Generally speaking this model seems to have incorporated all the important aspects and recent understanding of calcium homeostasis and signalling pathways. However, this model cannot predict the observed Ca-PTH dynamics for short time-scales of less than 10 minutes. This becomes evident by comparing simulation results presented in the paper with clinical data for shorter time-scales presented in [15]. Moreover, the fact that the model uses a sin-

gle PTH pool rules out the possibility of achieving dynamics observed in clinical data. A mathematical proof of the deficiency of the single PTH pool model is presented in [6]. Short time-scale dynamics may be important in an overall model of plasma calcium homeostasis, especially when we incorporate the interaction with bone because the intermittent change in PTH levels helps in net positive bone formation [16, 17]. A brief review of the two mathematical models that capture short time-scale Ca-PTH interaction are discussed next.

Ca-PTH Axis Models

A multi-parameter deconvolution analysis method suggested in [20] was used to study the tonic and pulsatile nature of PTH secretion in normal humans in [21]. A *two-pool, linear, time-invariant* (LTI) model was arbitrarily assumed to represent the Ca-PTH axis. The model was parameterized using the hypo- and hyper-calcemic clamp test data separately. The parameterized models were used to estimate the tonic and pulsatile PTH secretion.

For the first time, [14] utilized the biological events in the process of PTH secretion to derive a two-pool model of Ca-PTH dynamics for short time-scales (in minutes). Two PTH pools, one in the parathyroid cells and the other in the blood, were considered. An important simplifying assumption that the change in calcium occurs instantaneously was used to render the model into an LTI system. The presentation in [14] differs from the ones in [15,21] in the respect that it utilizes the biological events to explain the origin of the model. This model, parameterized based on a hypocalcemic clamp test, matched the test results. Nevertheless, we note that the assumption of an instantaneous change in plasma calcium levels is not expected to hold in practice. The ability of this model to predict dynamics of a hypercalcemic clamp test was not explored. Next, we briefly present a clinical test called induced calcemic clamp test employed to study the Ca-PTH axis.

Induced Calcemic Clamp Test

A clinical test, referred to as an induced calcemic clamp test, is typically employed to study the status of the Ca-PTH axis. During an induced hypocalcemic clamp test, plasma Ca^{++} concentration is decreased by an intravenous infusion of sodium citrate. Similarly, during an induced hypercalcemic clamp test, plasma Ca^{++} concentration is increased by an intravenous infusion of calcium gluconate [15]. Plasma Ca^{++} concentration and the corresponding plasma PTH concentration are measured at frequent time intervals. Next, we present the dynamical model development.

Model Development

Based on the description of the PTH secretion process and its regulation we consider two pools of PTH: one in the parathyroid glands (PTG) denoted by x_1 and the other in plasma denoted by x_1), as shown in Figure 4. In response to an acute decrease

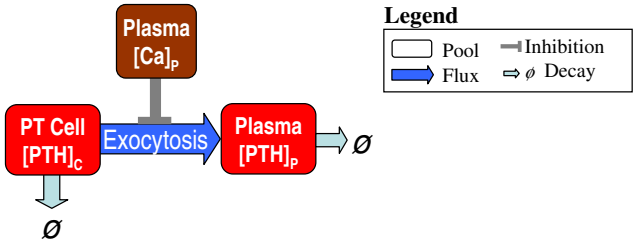


Figure 4. THE CA-PTH AXIS ISOLATED FROM THE QUALITATIVE MODEL OF CALCIUM HOMEOSTASIS SHOWN IN FIG. 3.

(time-scale of minutes) in plasma Ca^{++} concentration, signaling pathways involving calcium sensors on the parathyroid chief cell stimulate exocytosis of the PTH stored in the vesicles of the cells. Similarly, they inhibit exocytosis of the PTH in response to a rise in the plasma Ca^{++} concentration. The PTH response occurs in time-scale of minutes [15]. Since we are considering the response of PTH to acute changes in plasma Ca^{++} concentration, we can assume the bio-synthesis rate of PTH to remain constant because the regulation of PTH bio-synthesis in response to changes in the plasma Ca^{++} concentration occurs in the times-scale of hours to days [1,9,13].

Using mass balance and assuming that we model average dynamics of n active chief cells in the parathyroid glands, the rate of change of PTH in the PTG pool is given by

$$\dot{x_1}(t) = \underbrace{k}_{PTH\ production} - \underbrace{\lambda_{\mathrm{Ca}}(t)x_1(t)}_{\text{Secretion to plasma}} - \underbrace{\lambda_1 x_1(t)}_{\text{Decay}}, \qquad (1)$$

where $x_1(t)$ denotes the total amount of PTH in the PTG pool, k denotes the constant production rate of PTH in the PTG pool, $\lambda_{Ca}(t)$ denotes the secretion rate function which depends on plasma Ca^{++} concentration, and λ_1 denotes the decay rate constant of PTH inside the parathyroid cells. We use the four-parameter reverse-sigmoidal relationship [22] to relate $\lambda_{Ca}(t)$ and plasma Ca^{++} concentration

$$\lambda_{\mathrm{Ca}}(t) = \frac{A-B}{1+\left(\frac{Ca(t)}{S}\right)^m} + B, \qquad (2)$$

where A and B denote maximal and minimal values of the secretion rate constant, $Ca(t)$ denotes plasma Ca^{++} concentration, and S is the value of $Ca(t)$ when $\lambda_{Ca} = \frac{A+B}{2}$, and m gives the slope of the curve at S, respectively. These characteristic features of the reverse sigmoid relationship are depicted in Fig. 5. EM Brown originally used this relationship [22] to relate PTH se-

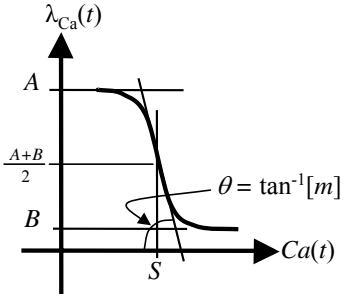


Figure 5. The reverse sigmoid curve.

cretion rate and plasma Ca^{++} concentration. Note that we have used the relationship to relate PTH secretion function ($\lambda_{Ca}(t)$) to plasma Ca^{++} concentration and not PTH secretion (λ_{Ca}) to plasma Ca^{++} concentration. The rate of change of PTH in the plasma pool is given by a mass balance relation

$$\dot{x_2}(t) = \underbrace{\lambda_{\mathrm{Ca}}(t)x_1(t)}_{\text{Secretion from parathyroid glands to plasma}} - \underbrace{\lambda_2 x_2(t)}_{\text{Clearance}}, \quad (3)$$

where $x_2(t)$ denotes the amount of PTH in the plasma pool and λ_2 denotes the biological clearance rate constant for PTH in circulation. Writing Equations (1) and (3) in a matrix form

$$\begin{pmatrix} \dot{x_1} \\ \dot{x_2} \end{pmatrix} = \begin{pmatrix} -(\lambda_{\mathrm{Ca}}(t)+\lambda_1) & 0 \\ \lambda_{\mathrm{Ca}}(t) & \lambda_2 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} + \begin{pmatrix} k & 0 \\ 0 & 0 \end{pmatrix} \begin{pmatrix} 1 \\ 0 \end{pmatrix}, \quad (4)$$

we observe that the two equations form a hierarchy of differential equations. We can solve the first equation, which has a constant forcing function reflecting the assumption of constant rate of PTH production at fast time-scale, to compute $x_1(t)$ and then substitute it into the second equation to solve for $x_2(t)$.

Note that λ_{Ca} is a function of time. Thus the dynamical system (4) is an LTV system. The solution of the system is given by

$$\begin{aligned} x_1(t) &= \phi_1(t,t_0)x_{10} + k\int_{t_0}^{t} \phi_1(t,\sigma)d\sigma \\ x_2(t) &= \phi_2(t,t_0)x_{20} + \int_{t_0}^{t} \phi_2(t,\sigma)\lambda_{\mathrm{Ca}}(\sigma)x_1(\sigma)d\sigma \\ & t \geq t_0,\ x_1(t_0) = x_{10},\ x_2(t_0) = x_{20}, \end{aligned}$$

where, $\phi_1(t,t_0)$, $\phi_2(t,t_0)$, $\phi_1(t,\sigma)$, and $\phi_2(t,\sigma)$ are transition scalars given by

$$\begin{aligned} \phi_1(t,t_0) &= e^{-\int_{t_0}^{t}(\lambda_{\mathrm{Ca}}(\sigma)+\lambda_1)d\sigma} \\ &= e^{-\int_{t_0}^{t}\left(\frac{A-B}{1+\left(\frac{Ca(\sigma)}{S}\right)^m}+\lambda_1\right)d\sigma} \\ \phi_2(t,t_0) &= e^{-\int_{t_0}^{t}\lambda_2 d\sigma} \\ \phi_1(t,\sigma) &= e^{-\int_{\sigma}^{t}(\lambda_{\mathrm{Ca}}(\tau)+\lambda_1)d\tau} \\ &= e^{-\int_{\sigma}^{t}\left(\frac{A-B}{1+\left(\frac{Ca(\tau)}{S}\right)^m}+\lambda_1\right)d\tau} \\ \phi_2(t,\sigma) &= e^{-\int_{\sigma}^{t}\lambda_2 d\tau}. \end{aligned}$$

We have used $Ca(t) = c_1 + c_2 e^{-\lambda t}$ and $Ca(t) = c_3 - c_4 e^{-\lambda t}$ to approximate calcium-time profiles during hypo- and hypercalcemic clamp tests [see Fig. 6(a) and Fig. 7(a)]. Unfortunately, the solution (5) is analytically intractable because the integral terms on the right-hand side cannot be solved in a closed form. One way to simplify the analysis is to assume a step-change in calcium [14], which renders $\lambda_{Ca}(t)$ a constant and thus the system (4) becomes an LTI. But in practice, Ca^{++} concentration changes at a much slower rate than a step. So the step-change assumption in plasma Ca^{++} concentration is not valid. Moreover, plasma PTH response depends on the rate of change of plasma Ca^{++} concentration [23]. Thus a model has to be able to capture the expected time-varying nature of the system (4). Next we present our computational approach for parameterizing the system equations.

Model Parametrization

We start by deriving parameter constraints of the system (1)-(3) at steady-state. We then use both known data and a guided iterative procedure to match clinical tests. At steady-state, (1) becomes

$$k = \left[\frac{A-B}{1+\left(\frac{Ca_{SS}}{S}\right)^m} + B\right] x_{1,SS} + \lambda_1 x_{1,SS}, \quad (5)$$

where $x_{1,\mathrm{SS}}$ and Ca_{SS} denote steady-state values of PTH in the PTG pool and plasma Ca^{++} concentration in plasma, respectively. Similarly, (3) becomes

$$\left[\frac{A-B}{1+\left(\frac{Ca_{SS}}{S}\right)^m} + B\right] x_{1,SS} = \lambda_2 x_{2,\mathrm{SS}}, \quad (6)$$

where $x_{2,\mathrm{SS}}$ denotes steady-state values of PTH concentration in plasma. From (5) and (6) we have

$$k = \lambda_2 x_{2,\mathrm{SS}} + \lambda_1 x_{1,\mathrm{SS}}. \tag{7}$$

Considering normal steady-state[3] values of a healthy individual, 7 becomes

$$k = \lambda_2 x_{2,\mathrm{SS,N}} + \lambda_1 x_{1,\mathrm{SS,N}}, \tag{8}$$

where $x_{1,\mathrm{SS,N}}$ and $x_{2,\mathrm{SS,N}}$ are steady-state values of PTH in the PTG pool and PTH in plasma of a healthy individual, respectively. Since the steady-state PTH secretion rate in response to acute changes in plasma Ca^{++} has maximum and minimum saturation values [22], we assume that there is a maximum or a minimum saturation steady-state value that plasma PTH concentration can attain as well. At extreme values, (7) becomes

$$k = \lambda_2 x_{2,\mathrm{SS,Min}} + \lambda_1 x_{1,\mathrm{SS,Max}}, \tag{9}$$

and

$$k = \lambda_2 x_{2,\mathrm{SS,Max}} + \lambda_1 x_{1,\mathrm{SS,Min}}, \tag{10}$$

where $x_{1,\mathrm{SS,Max}}$ and $x_{1,\mathrm{SS,Min}}$ denote maximum and minimum steady-state values of PTH in the PTG pool, respectively, and $x_{2,\mathrm{SS,Min}}$ and $x_{2,\mathrm{SS,Max}}$ denote minimum and maximum steady-state values of PTH in the plasma pool, respectively. Evaluating (6) at upper and lower plasma Ca^{++} levels we have

$$\lim_{Ca\to 0} A x_{1,\mathrm{SS,Min}} = \lambda_2 x_{2,\mathrm{SS,Max}} \Longrightarrow A = \frac{\lambda_2 x_{2,\mathrm{SS,Max}}}{x_{1,\mathrm{SS,Min}}}, \tag{11}$$

$$\lim_{Ca\to \infty} A x_{1,\mathrm{SS,Max}} = \lambda_2 x_{2,\mathrm{SS,Min}} \Longrightarrow B = \frac{\lambda_2 x_{2,SS,Min}}{x_{1,SS,Max}}. \tag{12}$$

Finally, the set point S can be isolated from (2) as follows

$$S = \exp\left[\log(Ca_{\mathrm{SS}}) - \frac{1}{m}\log\left\{\left(\frac{A-B}{\frac{\lambda_2 x_{2,\mathrm{SS}}}{x_{1,\mathrm{SS}}} - B}\right) - 1\right\}\right]. \tag{13}$$

Relevant steady-state data is listed in Tab. 1 obtained from [15]. Since our model is based on mass balance, the available data in concentration units (pmolL^{-1}) have been multiplied by average adult plasma volume, ≈ 2.75 L, to convert into pmols and listed in Tab. 2.

[3]By normal steady-state we mean the average concentrations of either plasma Ca^{++} or PTH when an individual is not under clamp test.

Variables	Concentration	Units
$x_{2,\mathrm{SS,N}}$	2.41	pmolL^{-1}
$x_{2,\mathrm{SS,Max}}$	5.20	pmolL^{-1}
$x_{2,\mathrm{SS,Min}}$	0.96	pmolL^{-1}
$Ca_{\mathrm{SS,N}}$	1.23	mmolL^{-1}

Table 1. AVERAGE STEADY-STATE PLASMA PTH ($x_{2,\mathrm{SS}}$) AND CA^{++} CONCENTRATIONS FROM 7 HEALTHY INDIVIDUALS OBTAINED FROM FIG. 6 [15].

Variables	Amount	Units
$x_{2,\mathrm{SS,N}}$	6.63	pmol
$x_{2,\mathrm{SS,Max}}$	14.39	pmol
$x_{2,\mathrm{SS,Min}}$	2.65	pmol

Table 2. DATA FROM TAB. 1 CONVERTED INTO PMOLS.

There are 10 unknowns, k, λ_1, λ_2, $x_{1,\mathrm{SS,N}}$, $x_{1,\mathrm{SS,Max}}$, $x_{1,\mathrm{SS,Min}}$, A, B, S, and m, in the 6 equations (8)-(13). If we know the values of λ_1, λ_2, $x_{1,\mathrm{SS,N}}$, and m we can get a closed form solution for the rest of the unknowns. We utilized the guided iterative parametrization scheme described in [6] to find the values of λ_1, λ_2, $x_{1,\mathrm{SS,N}}$, and m. This guided iterative process results in the parameter values listed in Tab. 3. The values of the remaining unknown parameters calculated from the steady-state relations (8)-(13) are listed in Tab. 4. Using these parameters, our simulation result (Fig. 6(b)) matches very well with the plasma PTH response for the calcium input as shown in Fig. 6(a).

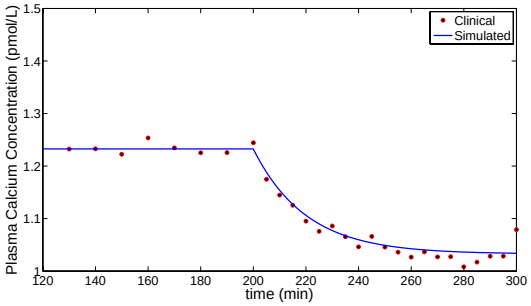
Parameters	Values	Units
τ_1	55.0000	min
λ_1	0.0126	min^{-1}
τ_2	1.8000	min
λ_2	0.3851	min^{-1}
$x_{1,\mathrm{SS,N}}$	321.7500	pmol
m	170.0000	–

Table 3. VALUES OF MODEL PARAMETERS TUNED TO FIT AVERAGE INDUCED HYPOCALCEMIC CLAMP TEST DATA OBTAINED FROM 7 HEALTHY INDIVIDUALS FIG. 6(b) [15].

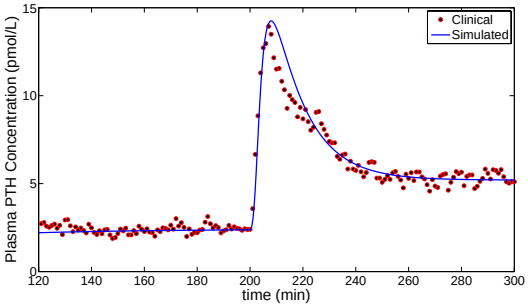
Parameters	Values	Units
k	6.6102	pmol/min
$x_{1,SS,Max}$	443.5062	pmol
$x_{1,SS,Min}$	84.6236	pmol
A	0.0655	pmol/min
B	0.0023	pmol/min
S	1.2159	mmol/L

Table 4. VALUES OF MODEL PARAMETERS CALCULATED USING TAB. 3 AND EQN.S (8)-(13).

Next, we used this model to predict the dynamics of hypercalcemic clamp test conducted on the same set of healthy subjects. The same model, with the same set of parameters as in Tab. 3 successfully predicted plasma PTH response observed in clinical data as seen in Fig. 7(b) for the calcium input as shown in Fig. 7(a).

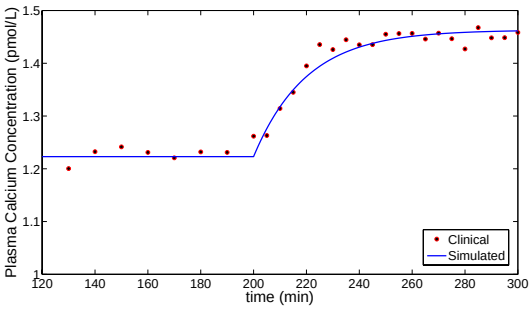


(a) Induced hypocalcemia (input).

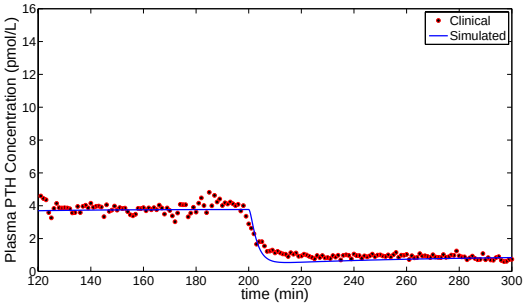


(b) PTH response for induced hypocalcemia (output).

Figure 6. CLINICAL (DOTS) VS. TUNED-MODEL SIMULATION (SOLID LINES) RESULT OF AN INDUCED HYPOCALCEMIC CLAMP TEST. CLINICAL DATA REPRESENTS THE AVERAGE RESPONSE OF 7 HEALTHY SUBJECTS [15].



(a) Induced hypercalcemia (input).



(b) PTH response for induced hypercalcemia (output).

Figure 7. CLINICAL (DOTS) VS. PREDICTION BY TUNED-MODEL (SOLID LINES) OF AN INDUCED HYPERCALCEMIC CLAMP TEST. CLINICAL DATA REPRESENTS AVERAGE RESPONSE OF 7 HEALTHY SUBJECTS [15].

We further tested our model and the guided iterative parametrization scheme successfully using the proprietary data obtained from the lead author of [15], Prof. Claus P Schmitt, Division of Pediatric Nephrology, University of Heidelberg, Germany. These data describe the responses of 3 healthy individuals to hypo- and hyper-calcemic clamp test. The details of the results can be found in [6].

Based on the successful predictive tests presented in this section we conclude that our two-pool, linear, time-varying model (1)-(3) provides a reasonable description of expected dynamics of the Ca-PTH axis. This is the first report of its kind to the best of our knowledge. The guided iterative method that relies on the available clinical data and biologically-driven assumptions provides a simple and an intuitive parametrization of our model.

CONCLUSION

A two-pool, linear, time-varying model was developed to describe the acute Ca-PTH axis dynamics. This model, parameterized based on clinical data from hypocalcemic clamp test successfully predicted PTH response for hypercalcemic clamp test in healthy humans. This model is a good candidate for inclusion in an overall calcium homeostasis model that may be used

to study the health and disease associated with calcium homeostasis.

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REFERENCES

[1] JM Bruder, TA Guise, and GR Mundy. *Endocrinology and metabolism*, chapter Mineral metabolism, pages 1079–1177. McGraw-Hill, New York, 4th edition, 2001.

[2] T Gunther and G Karsenty. *Molecular biology of the parathyroid*, chapter Development of parathyroid glands, pages 1–7. Kluwer Acedemic/Plenum, New York, 1st edition, 2005.

[3] AC Looker, ES Orwoll, CC Johnston Jr., RL Lindsay, HW Wahner, WL Dunn, MS Calvo, TB Harris, and SP Heyse. Prevalence of low femoral bone density in older U.S. adults from NHANES III. *Journal of Bone and Mineral Research*, 12:1761–1768, 1997.

[4] National Osteoporsis Foundation. http://www.nof.org/osteoporosis/diseasefacts.htm. Fast facts on osteoporosis.

[5] D Shoback, R Marcus, and D Bikle. *Basic & clinical endocrinology*, chapter Metabolic bone disease, pages 295–361. Lange Medical Books/McGraw-Hills, New York, 7th edition, 2004.

[6] RP Shrestha. A Mathematical Model of Acute Response of Parathyroid Hormone to Changes in Plasma Ionized Calcium in Normal Humans. MS Thesis, University of Massachusetts, Amherst, MA, Jan 2008.

[7] G Jones, SA Strugneli, and HF DeLuca. Current understanding of the molecular actions of vitamin D. *Physiological Reviews*, 78:1193–1231, 1998.

[8] VA LiVolsi. *The parathyroids basic and clinical concepts*, chapter Embryology, anatomy, and pathology of the parathyroids, pages 1–14. Academic Press, New York, 1st edition, 1994.

[9] JF Habener. Regulation of parathyroid hormone secretion and biosynthesis. *Ann. Rev. Physiol.*, 43:211–223, 1981.

[10] GN Gill. *Endocrinology and metabolism*, chapter Biosynthesis, secretion and metabolism of hormones, pages 29–48. McGraw-Hill, New York, 4th edition, 2001.

[11] S Yano and EM Brown. *Molecular biology of the parathyroid*, chapter The calcium sensing receptor, pages 44–56. Kluwer Acedemic/Plenum, New York, 1st edition, 2005.

[12] T Naveh-Many and J Silver. *Moecular biology of the parathyroid*, chapter Regulation of parathyroid hormone gene expression by 1,25-dihydroxyvitamin D, pages 84–94. Kluwer Academic/Plenum Publishers, New York, 1st edition, 2005.

[13] R Kilav, J Silver, and T Naven-Many. *Molecular biology of the parathyroid*, chapter Regulation of parathyroid hormone mRNA stability by calcium and phosphate, pages 57–67. Kluwer Academic/Plenum Publishers/Landes Bioscience/Eurekah.com, New York, 1st edition, 2005.

[14] G Momsen and P Schwarz. A mathematical/physiological model of parathyroid hormone secretion in response to blood-ionized calcium lowering in vivo. *Scan J Clin Lab Invest*, 57:381–394, 1997.

[15] CP Schmitt, F Schaefer, A Bruch, JD Vel, H Schmidt-Gayk, G Stein, E Ritz, and O Mehls. Control of pulsatile and tonic parathyroid hormone secretion by ionized calcium. *Journal of Clinical Endocrinology and Metabolism*, 81:4236–4243, 1996.

[16] MH Kroll. Parathyroid hormone temporal effects of bone formation and resorption. *Bulletin of Mathematical Biology*, 62:163–187, 2000.

[17] LK Potter, LD Greller, CR Cho, ME Nuttall, GB Stroup, LJ Suva, and FL Tobin. Response to continuous and pulsatile PTH dosing: A mathematical model for parathyroid hormone receptor kinetics. *Bone*, 37:159–169, 2005.

[18] MH Kroll. Modeling the interaction between osteoblast and osteoclast activities in bone remodeling. *Journal of Theoretical Biology*, 229:293–309, 2004.

[19] JF Raposo, LG Sobrinho, and HG Ferreira. A minimal mathematical model of calcium homeostasis. *The Journal of Clinical Endocrinology and Metabolism*, 77:4330–4340, 1993.

[20] J D Veldhuis, ML Carlson, and ML Johnson. The pituitary gland secretes in bursts: Appraising the nature of glandular secretory impulses by simultaneous multiple-parameter deconvolution of plasma hormone concentrations. *Proc. Natl. Acad. Sci*, 84:7686–7690, 1987.

[21] MH Samuels, J Veldhuis, C Cawley, RJ Urban, M Luther, R Bauer, and G Mundy. Pulsatile secretion of parathyroid hormone in normal young subjects: Assessment by deconvolution analysis. *Journal of Clinical Endocrinology and Metabolism*, 57:399–403, 1997.

[22] EM Brown. Four-parameter model of the sigmoidal relationship between parathyroid hormone release and extracellular calcium concentration in normal and abnormal parathyroid tissue. *Journal of Clinical Endocrinology and Metabolism*, 56:572–581, 1983.

[23] FD Grant, PR Conlin, and EM Brown. Rate and concentration dependence of parathyroid hormone dynamics during stepwise changes in serum ionized calcium in normal humans. *Journal of Clinical Endocrinology and Metabolism*, 71:370–378, 1990.