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A control engineering model of calcium regulation

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Abstract: The objective of this work is to develop a comprehensive computational model that will enable quantitative understanding of plasma calcium regulation under normal and pathological conditions. Ca regulation is represented as an engineering control system where physiological sub-processes are mapped onto corresponding block components, and underlying mechanisms represented by differential equations. The resulting model is validated with clinical observations of induced hypo- or hypercalcemia in healthy subjects, and its applicability demonstrated by comparing model predictions of Ca-related pathologies to corresponding clinical data. Our model accurately predicts clinical responses to induced hypo- and hypercalcemia in healthy subjects within a framework that facilitates the representation of Ca-related pathologies in terms of control system component defects. The model also enables a deeper understanding of the emergence of pathologies and the testing of hypotheses about related features of Ca regulation, for example, why Primary Hyperparathyroidism (PHPT) and Hypoparathyroidism (HoPT) arise from "controller defects". The control engineering framework provides an efficient means of organizing the sub-processes constituting Ca regulation, thereby facilitating a fundamental understanding of this complex process. The resulting validated model's predictions are consistent with clinically observed short- and long-term dynamic characteristics of the Ca regulatory system in both healthy and diseased patients. The model also enables simulation of currently infeasible clinical tests, and generates predictions of physiological variables that are currently not measurable.

1. INTRODUCTION

For normal human bodily functions, total extracellular fluid (ECF) Ca concentration is maintained within a narrow range, 2.45 ± 0.25mM (Parfitt, 1993, Kovacs and Ojeda, 2012), which is met through the processes constituting the body's Ca regulatory system. Disorders in the Ca regulatory mechanisms cause abnormal hormonal secretion and contribute to chronic imbalances in Ca levels, often leading to long-term physiological problems (Mundy and Guise, 1999, Kovacs and Ojeda, 2012).

Ca homeostasis is achieved through the coordinated actions of four organs (parathyroid gland (PTG), kidneys, bone, and intestines) and the secretion of three hormones: calcitriol (CTL), calcitonin (CTN) and parathyroid hormone (PTH) (Parfitt, 1993, Kovacs and Ojeda, 2012).

Hormonal regulation of Ca occurs according to the following mechanisms. When plasma Ca is low, Ca-sensing receptors (CaR) located on the surface of the ionized Ca levels and stimulate the production and secretion of PTH (Diaz et al., 2010). In the kidneys, the increased levels of PTH induce two distinct responses: (a) increased production and secretion of CTL; and (b) increased Ca reabsorption in the renal tubules (Parfitt, 1993). Finally, increased levels of PTH, in concert with CTL, stimulate increased bone cell proliferation, causing net bone resorption (i.e. a net transfer of Ca from bone to the plasma). CTL, in turn, inhibits PTH secretion and increases intestinal Ca absorption (Mundy and Guise, 1999, Diaz et al., 2010). The resulting net transfer of Ca from the kidneys, bone and intestines to the plasma increases plasma Ca to basal levels. The opposite response occurs in each organ during hypercalcemia.

The biological control system responsible for Ca regulation may be represented as an engineering control system by identifying the physiological equivalents of each component block as follows: (a) the sensor is the Ca-sensing receptor (CaR); (b) the controlled process is the plasma Ca pool; (c) the controller is the PTG; and (d) the actuators are the kidneys, bone and intestines.

Computational models of human Ca regulation in the literature have been cast in the form of a series of graphical interpolations (Járos et al., 1979) or a single monolithic system of differential equations (Raposo et al., 2002, Peterson and Riggs, 2010). Alternatively, organizing the complete Ca regulatory system into interconnected functional components produces a modular representation that is easier to validate with clinical data module-by-module; it also results in an overall system that is easier to analyse holistically and from which greater fundamental insight can be derived.

2. MATERIALS AND METHODS

The dynamic behaviour of PTH, CTL, bone cell proliferation, and plasma Ca are represented mathematically in the form of nonlinear ordinary differential equations derived from material balances applied to each component sub-process. The resulting equations, relevant parameters, and initial conditions, are summarized in Tables 1 and 2. A detailed

Table 1. Model Equations

Logistic Equation

$$H(x) = (A_x - B_x)/\left[1 + \left({}^{x}/_{S_x}\right)^{m_x}\right] + B_x \quad (1)$$

Process – *Plasma*

$$dCa_{(p)}/dt = Ca_{(i)} + Ca_{(b)} - Ca_{(u)} - Ca_{(d)} \quad (2)$$

$$dPO_{4(p)}/dt = PO_{4(i)} + PO_{4(b)} - PO_{4(u)} - PO_{4(ic)} \quad (3)^{A}$$

Sensor – *Ca-sensing receptor (CaR) on PTG*

$$Ca_{(s)} = K_{sens} Ca_{(p)} \quad (4)$$

Controller – *Parathyroid Gland (PTG)*

$$dPTH/dt = H\left(Ca_{(s)}\right)PTG - k_{PTH}PTH \quad (5)$$

$$\frac{dPTG}{dt} = \frac{\lambda_{PTG}}{PTG_0}\begin{Bmatrix}(PTG_{max} - PTG)[\varphi_{PTG}T^{-}_{PTG} + (1-\varphi_{PTG})] \\ -PTG[\varphi_{PTG}T^{+}_{PTG} + (1-\varphi_{PTG})]\end{Bmatrix} \quad (6)^{B}$$

$$T^{\pm}_{PTG} = 1 \pm tanh[\lambda_{CTL}(CTL - CTL_0)] \quad (7)^{B}$$

Actuator - *Intestines*

$$Ca_{(i)} = \frac{Ca_{meal}}{V}(H(CTL) + \lambda_{Cai}) \quad (8)$$

$$PO_{4(i)} = \lambda_{PO4i} PO_{4meal} \quad (9)$$

Actuator - *Kidneys*

$$dCTL/dt = H_1(PTH)H(PO_4) - k_{CTL}CTL \quad (10)$$

$$Ca_{(u)} = \frac{GFR}{V}\begin{Bmatrix}Ca_{(p)}[0.1 - 0.09H_2(PTH)], & Ca_{(p)} \le Ca_{thr} \\ \left(\alpha_{Cau}Ca_{(p)} + \beta_{Cau}\right), & Ca_{(p)} > Ca_{thr}\end{Bmatrix} \quad (11)$$

$$PO_{4(u)} = \frac{GFR}{V}\alpha_{PO4u}PO_{4(p)} \quad (12)$$

Actuator - *Bone*

$$Ca_{(b)} = \sigma_{Cab}\begin{Bmatrix}(1-\lambda_{Cab}) + \lambda_{Cab}\left[H(OC)\left({}^{RANKL}/_{OC}\right)^{\gamma_{Cab}}\right] \\ -\frac{Ca_{(p)}}{Ca_{(p)0}}\left[(1-\lambda_{Cab}) + \lambda_{Cab}\left(\frac{OB}{OB_0}\right)\right]\end{Bmatrix} \quad (13)^{A}$$

$$\pi_P = \lambda_b\left(\frac{PTH + PTHrP}{PTH_0}\right)\Big/\left[\lambda_b\left(\frac{PTH}{PTH - PTH_0}\right) + PS\right] \quad (14)^{C}$$

$$PO_{4(b)} = \lambda_{PO4b}Ca_{(b)} \quad (15)$$

$$dPO_{4(ic)}/dt = k_{aPO4ic}PO_{4(p)} - k_{bPO4ic}PO_{4(ic)} \quad (16)^{A}$$

[A] Equation taken from (Peterson and Riggs, 2010);

[B] Equation and parameter values taken from (Raposo et al., 2002);

[C] Equation modified from (Lemaire et al., 2004). The complete bone cell proliferation model is described in (Lemaire et al., 2004).

mechanistic description of each component sub-process along with the general assumptions and other considerations follow.

i) All model simulations are carried out using MATLAB® and Simulink®.

ii) All hormones and ions are uniformly distributed in the ECF and their concentrations are identical to that in the plasma.

iii) Consistent with receptor theory and physiological dose-response characteristics (DeLean et al., 1978, Gibaldi and Perrier, 1982), the rates of secretion, production or proliferation, and all hormone/ion dependencies, are described by the logistic function, H(x) given in Eqn. (1). The input variable, x is the stimulus used to elicit the response, H; A_x and B_x are, respectively, the minimum and maximum rates; S_x is the midpoint (the value of x corresponding to a half-maximal response); m_x is the slope of the curve at S_x.

iv) Phosphate regulation is based on the description in reference (Peterson and Riggs, 2010).

v) The effect of calcitonin (CTN) is ignored since its role in Ca regulation is not as important as that of PTH and of CTL (Parfitt, 1993, Kovacs and Ojeda, 2012).

vi) Component defects are implemented as first-order dynamic changes over time in the relevant parameter values.

We estimate the parameter values for each sub-process by performing least squares optimization on the relevant clinical data, normalised based on the reported baseline hormone, or ion, concentration. (Normalising the data allows for avoiding the difficulties often encountered when combining individual blocks into a complete model). Finally, we determine the most critical parameters for each sub-process, and the overall model, through parameter sensitivity analysis.

2.1 Sensor: Calcium-Sensing Receptors (CaR)

Ca sensing by the CaR is represented by a linear relationship where the sensor output, $Ca_{(s)}$, is related to the plasma Ca, $Ca_{(p)}$, by a linear relationship (Eq. 4). The constant of proportionality is the sensor gain, K_{sens}, which represents the CaR detection of $Ca_{(p)}$ and transmission of the signal to the PT cell. For a normal functioning CaR, K_{sens} is unity.

2.2 Controller: The Parathyroid Glands

The PTGs increase PTH secretion via CTL-induced PT cell proliferation and Ca-induced PTH production (Diaz et al., 2010). Therefore, we use the product of two models from the literature (Shrestha et al., 2010, Raposo et al., 2002) to capture these effects (Eq. 5-7). Parameter estimates for the Ca-dependent function, $H\left(Ca_{(s)}\right)$, are determined from published clinical data of PTH responses to induced hypo- and hypercalcemia in healthy subjects (Ramirez et al., 1993, Haden et al., 2000). Parameter values for the CTL-dependent functions (Eq. 6-7) are retained from the reference (Raposo et al., 2002). Additionally, consistent with the literature, the PTH half-life in the plasma (related to the rate of PTH decay, k_{PTH}) is set at 1.3 minutes (Mundy and Guise, 1999).

Table 2. Parameter Estimates

Parameter	Value	Units
$Ca_{(p)0}$*	1.715E+01	mmol
CTL_0*	1.260E+03	pmol
OB_0*	7.282E-04	pM cells
$PO_{4(ic)0}$*	4.516E+04	mmol
$PO_{4(p)0}$*	1.680E+01	mmol
PTG_0*	5.000E-01	Unitless
PTH_0*	5.526E+01	pmol
$\mathrm{Ca_{meal}}$	9.158E-01	mmol.hr^{-1}
$\mathrm{Ca_{thr}}$	3.108E+01	mmol
GFR*	6.000E+00	L.hr^{-1}
$\mathrm{k_{a,PO4ic}}$*	5.180E+01	hr^{-1}
$\mathrm{k_{b,PO4ic}}$*	1.927E-02	hr^{-1}
$\mathrm{k_{CTL}}$*	8.660E-02	hr^{-1}
$\mathrm{k_{PTH}}$*	3.199E+01	hr^{-1}
$\mathrm{k_{PTHrP}}$*	6.932E+00	hr^{-1}
$\mathrm{K_{sens}}$	1.000E+00	Unitless
$\mathrm{PO_{4,meal}}$	5.695E-01	mmol.hr^{-1}
PS*	1.500E+02	Unitless
$\mathrm{PTG_{max}}$*	1.000E+00	Unitless
V*	1.400E+01	L
α_{Cau}	3.146E-01	Unitless
α_{PO4u}	5.545E-02	Unitless
β_{Cau}	-5.710E+00	mmol
γ_{Cab}	6.038E-01	Unitless
λ_{b}	2.907E+00	Unitless
λ_{Cab}	1.500E-01	Unitless
λ_{Cai}	1.500E-01	Unitless
λ_{CTL}*	2.143E-03	pmol^{-1}
λ_{PO4b}	4.640E-01	Unitless
λ_{PO4i}	7.000E-01	Unitless
λ_{PTG}	7.500E-02	hr^{-1}
σ_{Cab}	7.973E-01	hr^{-1}
φ_{PTG}*	8.500E-01	Unitless
$A_{Ca(s)}$	4.641E+02	pmol.hr^{-1}
$A_{Ca(s)}$	6.276E+03	pmol.hr^{-1}
$m_{Ca(s)}A$	-3.000E+01	Unitless
$m_{Ca(s)}B$	-2.500E+02	Unitless
$m_{Ca(s)}m$	-1.500E+02	Unitless
$m_{Ca(s)}S_1$	1.800E+01	mmol
$m_{Ca(s)}S_2$	1.500E+01	mmol
A_{CTL}	4.150E-01	Unitless
B_{CTL}	0.000E+00	Unitless
m_{CTL}	-8.416E+00	Unitless
S_{CTL}	1.306E+03	pmol
$A_{1,PTH}$	3.228E+00	hr^{-1}
$B_{1,PTH}$	1.000E+00	hr^{-1}
$m_{1,PTH}$	-2.000E+01	Unitless
$S_{1,PTH}$	9.823E+01	pmol
$A_{2,PTH}$	1.045E+00	Unitless
$B_{2,PTH}$	0.000E+00	Unitless
$m_{2,PTH}$	-6.520E+00	Unitless
$S_{2,PTH}$	5.186E+01	pmol
A_{PO4}	1.034E+00	Unitless
B_{PO4}	4.182E-01	Unitless
m_{PO4}	1.242E+01	Unitless
S_{PO4}	1.860E+01	mmol
A_{OC}	1.271E+00	Unitless
B_{OC}	9.951E-01	Unitless
m_{OC}	-1.188E+00	Unitless
S_{OC}	9.615E-01	pM cells/pM cells

* Parameter values are taken from (Williams, 1998) or from references outlined in the relevant sub-process in Section 2.

2.3 Actuator: Kidneys – Calcitriol Production

In the kidneys, PTH and plasma phosphate stimulate the production and secretion of CTL which we represent as a product of the PTH–and PO_4–dependent logistic functions (Eq. 10) whose parameter values are estimated from clinical data (Horwitz et al., 2003, Horwitz et al., 2005, Rix et al., 1999). Additionally, we use a CTL half-life of 8 hours in the calculating the CTL elimination rate, k_{CTL}, (Kurbel et al., 2003).

2.4 Actuator: Kidneys – Renal Calcium Reabsorption

"Ca excretion" in the kidneys is the difference between the filtered load and the amount reabsorbed. About 90% of the filtered Ca is reabsorbed by processes linked to sodium reabsorption, and up to 10% of the filtered Ca is further reabsorbed by PTH-dependent processes. Additionally, the Ca reabsorption is limited by the capacity of the renal tubules (Parfitt, 1993). Therefore, beyond a certain plasma Ca threshold, Ca_{thr}, there is no additional reabsorption. As such, Renal Ca excretion is represented in the model by a piecewise continuous curve (Eq. 11) where below the Ca threshold, tubular Ca reabsorption is 90% passive and 10% PTH-dependent and above the threshold, Ca excretion varies linearly with $Ca_{(p)}$ levels. Parameter values are determined from literature data (Peacock and Nordin, 1968).

2.5 Actuator: Intestines – Calcium Absorption

The rate of Ca absorption is regulated through both active and passive pathways. Passive absorption accounts for 15% of total intestinal Ca absorption, while active absorption is CTL-dependent (Parfitt, 1993, McCormick, 2002). Parameter values for CTL-dependent active absorption in Eq. 8 are determined from data published by Heaney et al (Heaney et al., 1997).

2.6 Actuator: Bone Cell Proliferation, Formation, and Resorption

The bone cell proliferation model used in this work is based on reference (Lemaire et al., 2004) which is incorporated into our overall model by normalizing the PTH concentration in the fractional PTH receptor occupation expression (π_P), as shown in Eqn. 14. Finally, the expression linking bone cell proliferation to calcium flux is taken from reference (Peterson and Riggs, 2010) with parameters estimated using clinical data (Parfitt, 1969).

2.7 Process: ECF Calcium and Phosphate

$Ca_{(p)}$ concentration in the plasma is determined from the net ion transfer rates from the kidneys, intestines, bone and any "disturbances" introduced via intravenous infusions.

3. RESULTS

In what follows, the basic model is first validated against clinical data from healthy subjects. Subsequently, the utility of the validated model is demonstrated through a systematic comparison of model predictions of various Ca-related pathologies against corresponding physiological data.

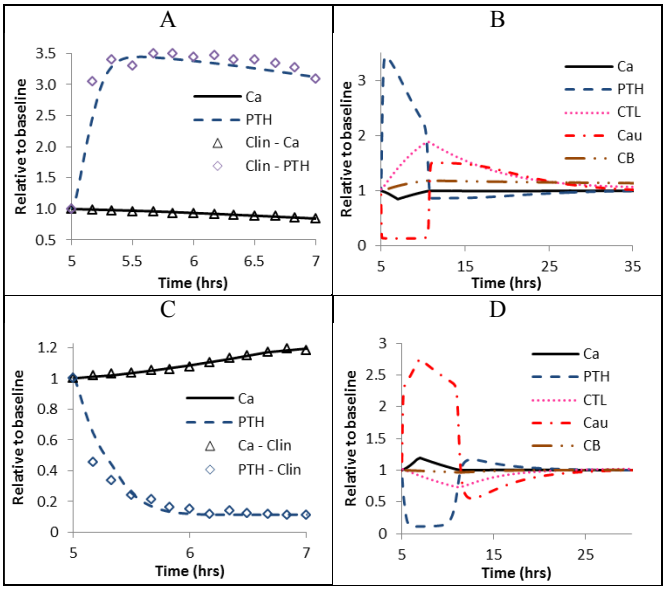

Fig. 1. Response of healthy subjects to induced hypo- and hypercalcemia: (A) Ca and PTH response during 2-hr infusion of sodium citrate (Ramirez et al., 1993); (B) Model prediction of Ca, PTH, CTL, urinary Ca and CB ratio response during and after 2-hr infusion of sodium citrate; (C) Ca and PTH response during 2-hr infusion of calcium gluconate (Goodman et al., 1998); (D) Model predictions of Ca, PTH, CTL, urinary Ca and CB ratio response during and after 2-hr infusion of calcium gluconate.

An important attribute of the model is its ability to predict the dynamic responses of CTL, renal Ca excretion, bone cell proliferation (i.e. osteoblast-to-osteoclast (CB) ratio) and other such physiological variables that are often unavailable for direct measurement but provide additional insight into the overall performance of the Ca regulatory system. For ease of comparison the simulation results are presented not in their usual clinical units but as changes relative to healthy baseline values.

3.1 Model Validation

The datasets used for model validation are from clinically induced hypo- and hypercalcemia in healthy subjects, in response to infusions of sodium citrate or calcium gluconate. The corresponding model simulations are obtained by representing the experimental stimulus as an appropriate $Ca_{(p)}$ disturbance with magnitude and duration matching those of the clinical infusion. The results are shown in Fig 1.

Fig. 1A, shows scaled measurements of the average PTH response of a group of healthy patients to a 2-hour infusion of sodium citrate (Ramirez et al., 1993). In response to the same sodium citrate infusion, Fig. 1B shows the corresponding dynamic profiles of CTL, renal Ca excretion ($Ca_{(u)}$), and CB ratio—quantities not reported in the study. Induced hypocalcemia causes an initial rapid increase in PTH with a corresponding increase in CTL and reduced Ca excretion. Upon removal of the disturbance, the subsequent increase in plasma Ca causes a gradual reduction in PTH with a consequent increase in renal excretion, $Ca_{(u)}$. Owing to its slower dynamics, CTL levels continue to rise long after PTH levels have peaked. Once normocalcemia is achieved, the inhibitory effect of high CTL levels on PTH secretion dominates the Ca-dependent PTH secretory response thus causing PTH to fall to sub-basal levels until CTL returns to baseline. Finally, PTH induces increased bone cell proliferation (CB ratio) resulting in net bone resorption; because bone cell proliferation is a slow process, the CB ratio takes a long time to return to basal levels.

In response to hypercalcemia induced by 2-hr calcium gluconate infusions in healthy subjects (Goodman et al., 1998), Fig 1C shows how our model simulation accurately predicts clinical observations of PTH and Ca. Fig. 1D shows our model prediction of the associated responses of the clinically unreported Ca excretion, CTL and CB profiles during infusion and recovery. The increased Ca inhibits PTH secretion leads to lower CTL secretion, greater Ca excretion, and negligible bone cell proliferation.

With the preceding results validating both our proposed modelling approach and the resulting model of Ca regulation itself, we are now in a position to use the framework to investigate Ca-related pathologies as control system component defects. From the most critical parameters, we can determine which single, or group of, parameter(s) is most likely to play a role in a given pathology. Therefore, understanding a particular pathology in terms of an appropriate control system component failure provides a unique perspective from which effective treatment procedure (targeted to the identified component defect) may be postulated and subsequently tested.

3.2 Investigation of Diseased States as Control System Component Defects: Primary Hyperparathyroidism (PHPT) and Hypoparathyroidism (HoPT) - (Controller Defects)

In PHPT, adenomatous PTGs secrete excess PTH, which induces increased renal Ca reabsorption, bone resorption, and intestinal Ca absorption, leading to hypercalcemia (Kovacs and Ojeda, 2012). Because the PTG is the controller in the control system framework, PHPT therefore arises from a controller defect. This phenomenon is represented in our model by increasing B_{Ca} and A_{Ca} and reducing the slope ($m_{Ca_{(s)}}$) to achieve a 3-fold increase in PTH levels at steady-state (Fig. 2A). The result is an increase in CTL levels, a reduction in renal excretion (Fig. 2B) and a significant increase in CB ratio (higher bone resorption) (Fig. 2B) and ultimately, a 30% increase in $Ca_{(p)}$ (Fig. 2C).

Conversely, HoPT, characterized by inappropriately low PTH secretion, reduced CTL, hypercalciuria and hypocalcemia (Rubin et al., 2010) is reproduced by decreasing A_{Ca} and B_{Ca} to obtain a 25% decrease in PTH from initial basal levels (Fig. 2E). The result is lower CTL secretion, increased Ca excretion and a lower CB ratio (net bone formation) (Fig. 2F), all combining to produce a 30% reduction in $Ca_{(p)}$ (Fig. 2G).

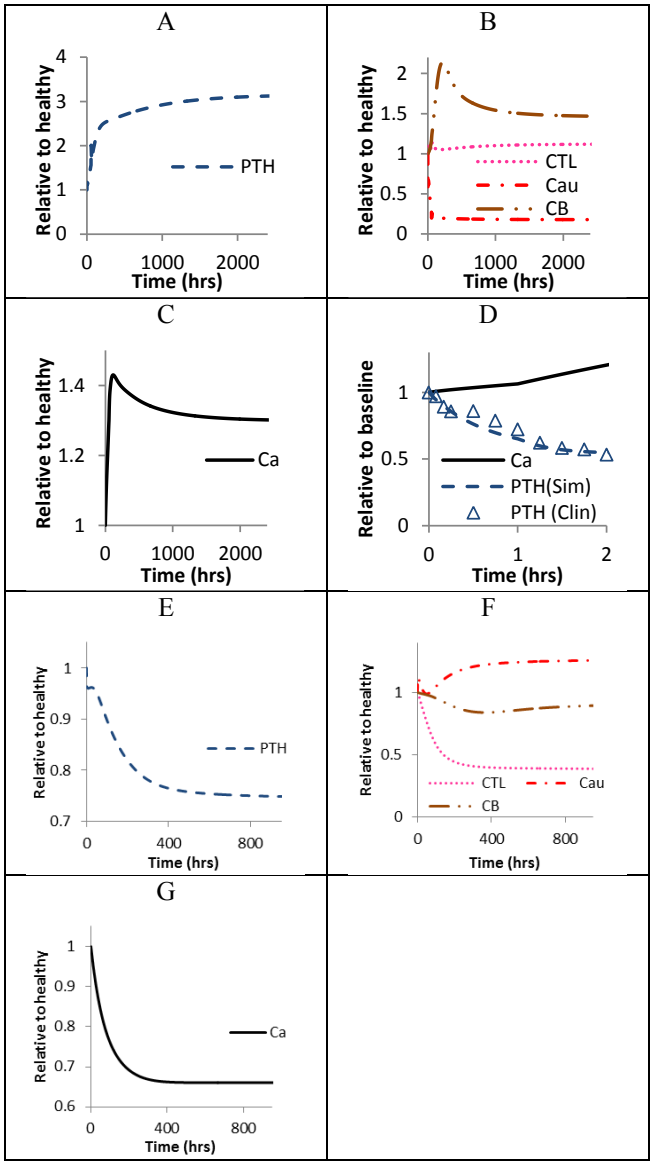

Fig. 2. Simulations of pathologies as ECS component defects: (A–D) PHPT (Controller defect) – Increase in PTH secretion. (A) PTH change trajectory; (B) CTL, urinary Ca and CB ratio responses; (C) Plasma Ca response. (D) Model prediction and clinical observation of Ca and PTH response to 2-hr clinical infusion of calcium gluconate in PHPT (Khosla et al., 1993). (E–G) HoPT (Controller defect) – Decrease in PTH secretion. (E) PTH change trajectory; (F) CTL, urinary Ca, CB ratio responses; (G) Plasma Ca.

4. DISCUSSION AND CONCLUSIONS

Based on the premise that effective regulation of physiological processes is achieved by biological control systems that possess direct analogs with engineering control systems (ECS), we have proposed a modelling and analysis framework for plasma calcium regulation in the form of an ECS. Such an approach achieves two important objectives: (i) the collection of complex sub-processes subtending Ca regulation can be organized into interconnected functional modules, thereby facilitating modelling and analysis of the entire system; and (ii) pathologies can be understood in terms of ineffective regulation caused by identifiable component defects/failures. The unknown parameters within each functional block were estimated using data from relevant clinical tests of healthy subjects; and the overall model was validated with additional clinical data from induced hypo- and hypercalcemia in healthy subjects. We have shown that the resulting model is capable of predicting both short- and long-term physiological changes in the Ca homeostatic environment, under both healthy and pathological conditions.

The PTH oversecretion characteristic of PHPT is modelled by an increase in the maximum (B_{Ca}) and minimum (A_{Ca}) PTH secretory rate parameters. Our simulation results for PHPT (Figs. 2A–D) are consistent with the general clinical observations of the disease (Kovacs and Ojeda, 2012, Rubin et al., 2008), except that the hypocalciuria predicted by our model is consistent with less than 25% of PHPT cases (Younes et al., 2005). In order to predict the PTH response to clinically induced hypercalcemia (2-hr calcium gluconate infusion) in PHPT subjects (Fig. 2D) (Khosla et al., 1993) more accurately, it was necessary also to reduce the hypercalcemic slope ($m_{Ca(s)}A$). The relative change to the slope is therefore an indicator of decreased PTH secretory response to changes in $Ca_{(p)}$ in PHPT compared to the healthy model (Khosla et al., 1993, Malberti et al., 1999) and possibly an indicator of the degree of PHPT.

While qualitatively accurate in general, quantitatively, the model predictions of pathological conditions do not always have an exact match with all clinical observations of calciotropic variables, nor does it account for inter-patient variability. This is due to the following: firstly, our model simulations of pathologies are based on individual component defects in the model of healthy Ca regulation. Secondly, the model does not account for the possible effects of external hormones/ions on Ca regulation under pathological conditions. Thirdly, we assume that the pathologies in question manifest as defects isolated to a single component with no "interactions" with other sub-processes. Finally, owing to the scarcity of clinical data, parameter estimates are determined based on group data rather than the individual patient data, thus limiting model predictions to groups.

Nevertheless, taken together, we have demonstrated how the control engineering framework provides an efficient means for organizing the various physiological sub-processes constituting calcium regulation and facilitates a fundamental understanding of this complex physiological process. The resulting mathematical model adequately predicts the short and long term dynamic characteristics of the Ca regulatory system in both healthy and pathological states. The model provides novel insights into Ca regulation by generating results about physiological variables that are currently unmeasurable. Furthermore, the framework facilitates the testing of hypotheses about mechanisms underlying the emergence of known pathologies. Currently, we are using the model to (a) explore the differential diagnosis of Ca-related pathologies with similar pathophysiologies; and (b) identify potential sites for therapeutic intervention in different Ca-related pathologies.

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