Calcitonin Regulation of Elevated Blood Calcium Levels

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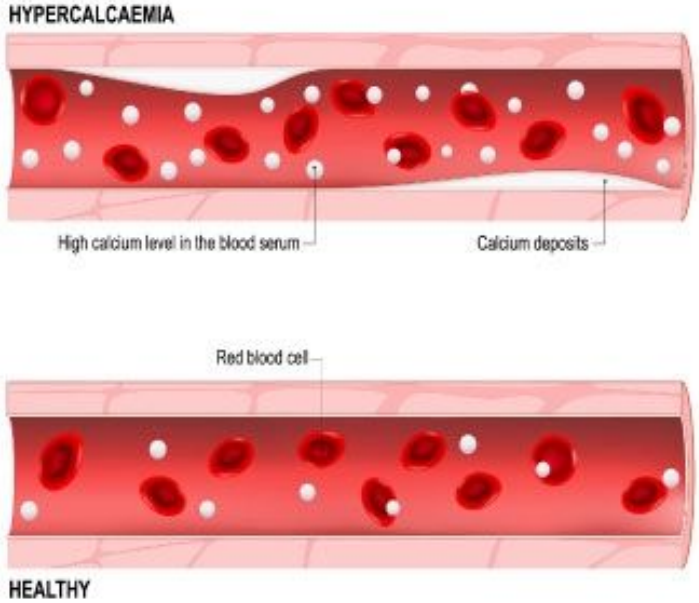
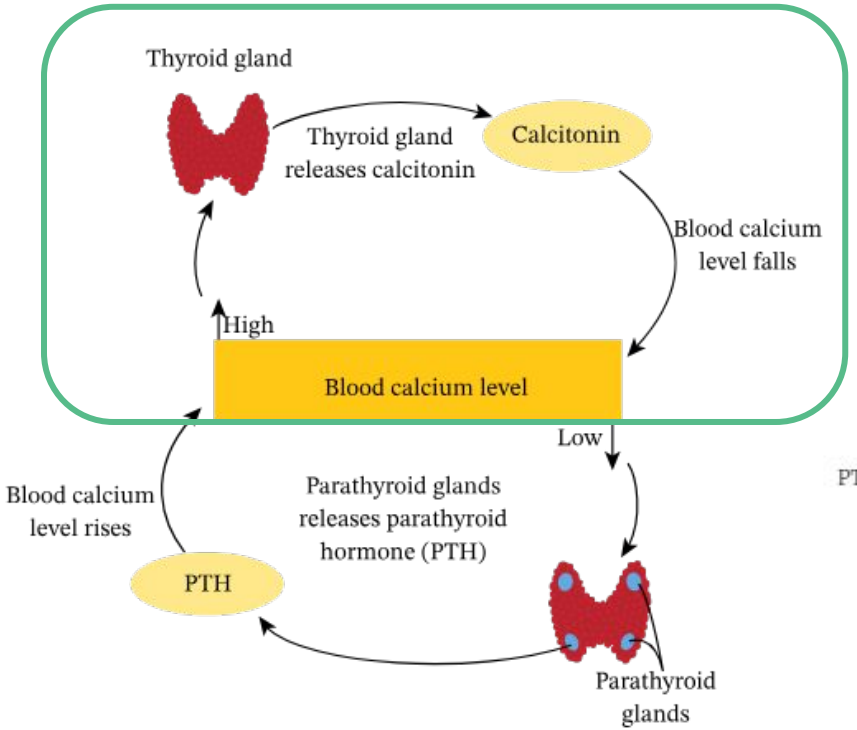
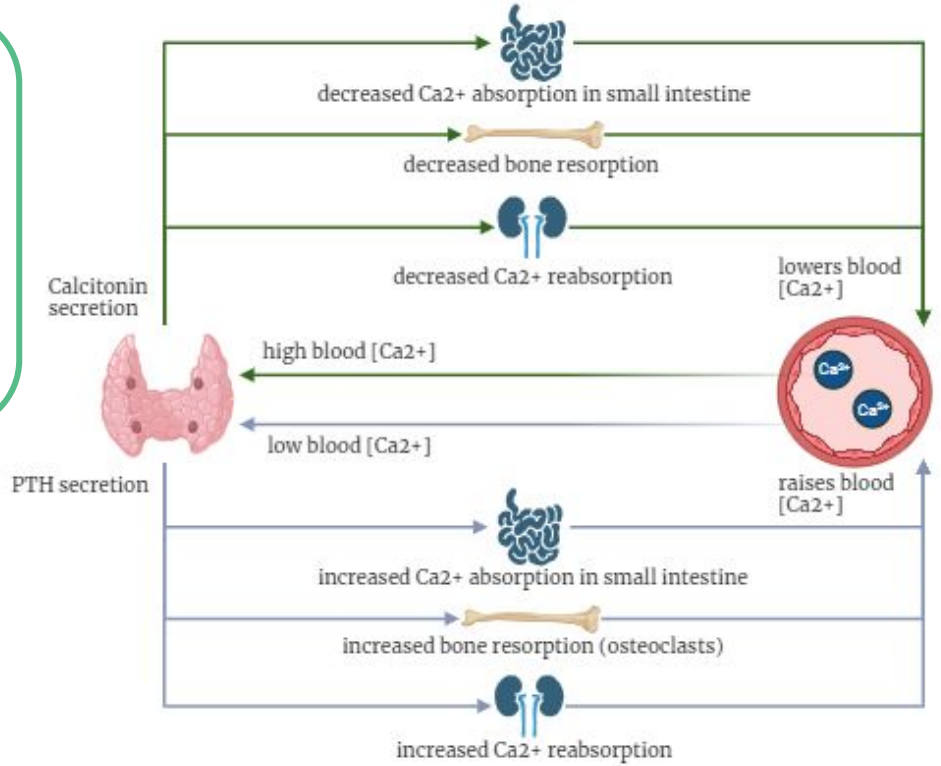
Calcitonin

- Hormone produced by thyroid gland in response to *elevated blood calcium levels*
- Stimulated by calcium-sensing receptors (CaSR) in the parathyroid gland and kidney
- Blocks osteoclast activity to reduce bone resorption
- Decreases calcium reabsorption in the kidneys



Calcium Regulation





Goal & Assumptions

Model the calcitonin response to elevated calcium blood concentration.

1. The scope of the biosystem is limited to calcitonin and parathyroid hormone
2. This model only considers calcium concentrations in the blood
3. The effect of PTH is constant and does not change as a function of the calcium concentration since we are modeling the response to elevated calcium where calcitonin is assumed to have a more significant effect
4. The initial concentrations of calcitonin and calcium are the concentrations at time zero
5. Calcitonin feedback is modeled using a PD controller

Parameters & ODEs

Nonlinear Ordinary Differential Equations:

$$\frac{dC}{dt} = -kC(t)N(t) + \frac{1}{\tau_1}C(t) \quad (1)$$

$$\frac{dN}{dt} = \alpha I(t) - \frac{1}{\tau_2}N(t) \quad (2)$$

$$I(t) = K_p e(t) + K_i \int_{-\infty}^{t} e(t)dt + K_d \frac{d}{dt}e(t) \quad (3)$$

$$e(t) = C_{meas} - T \quad (4)$$

Variable	Value	Units
k	0.3	L/min*mmol
$\tau 1$	276	min
$\tau 2$	1642	min
α	0.20	1/L
T	2.1	mmol/L

C(t) [mmol/L] = calcium concentration

N(t) [mmol/L] = calcitonin concentration

Open Loop Transfer Function

Linearized Ordinary Differential Equations:

$$C(s) = \frac{2kN_oC_o - kC_oN(s) + C_o(1 - \frac{1}{\tau_1})}{s + kN_o - \frac{1}{\tau_1}} \quad ; \quad N(s) = \frac{\alpha I(s) + N_o}{s + \frac{1}{\tau_2}}$$

$$H(s) = \frac{-kC_o\alpha}{s^2 + s(kN_o - \frac{1}{\tau_1} + \frac{1}{\tau_2}) + (\frac{kN_o}{\tau_2} - \frac{1}{\tau_2\tau_1})}$$

$$where\ k_1 = 0.3\,,\ C_o = 2.5\frac{mmol}{L}\,,\ N_o = 2.0482^*\ 10^{-9}\frac{mmol}{L}\,,$$

$$\tau_1 = 4.6\ hr\,,\ \tau_2 = 23.4\ hr\,,\ \alpha = 0.2\frac{1}{L}$$

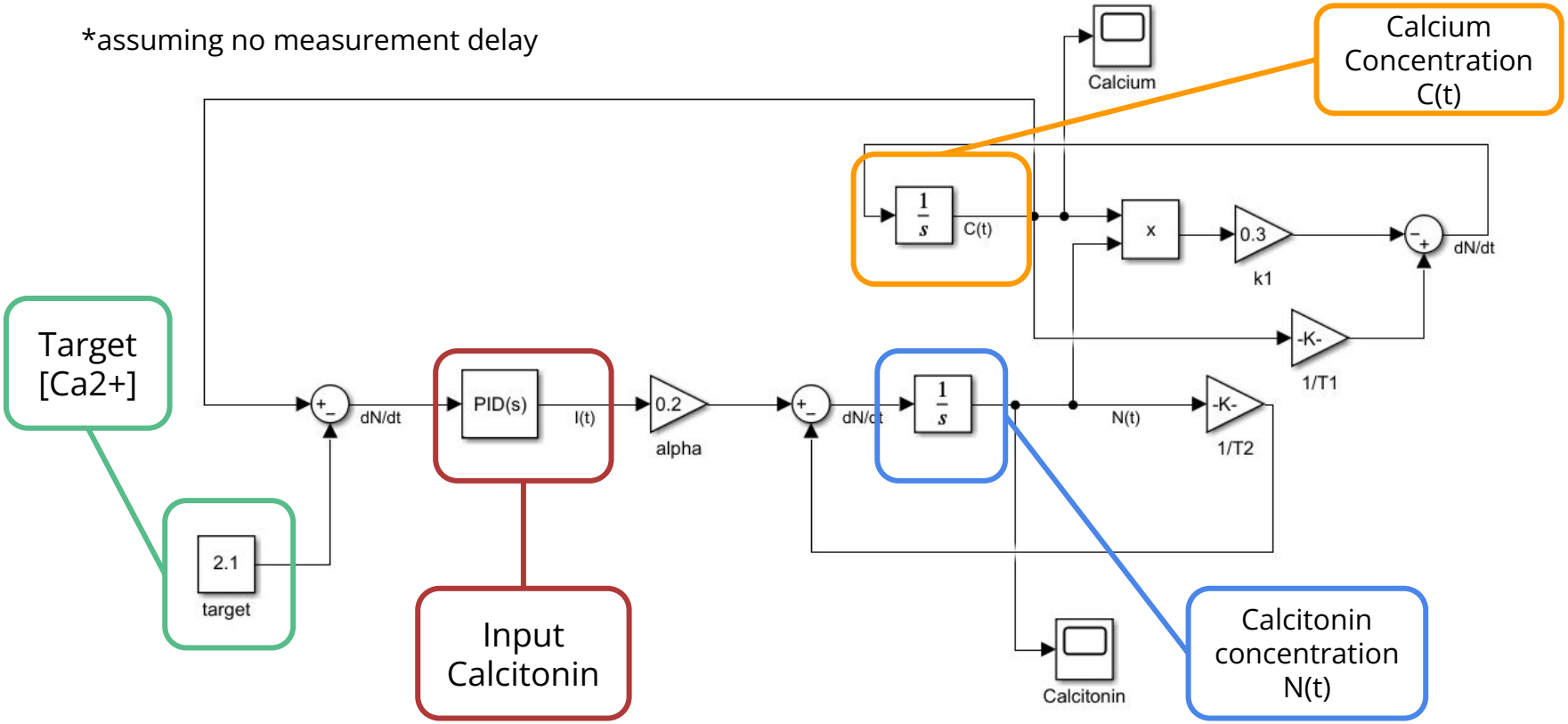
$$\rightarrow \quad H(s) = \frac{-0.15}{s^2 - 0.003014s - 2.207\times10^{-6}}$$

Poles:

s = 0.00362, -0.000609

Block Diagram in Time Domain

*assuming no measurement delay



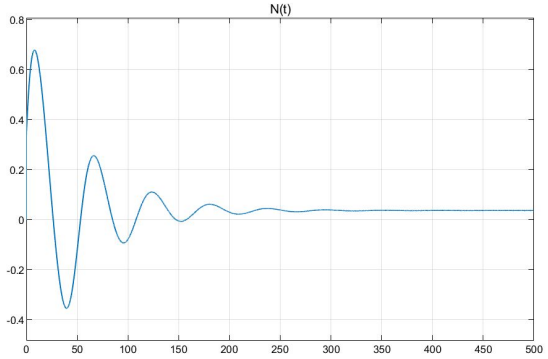
Sensitivity Analysis

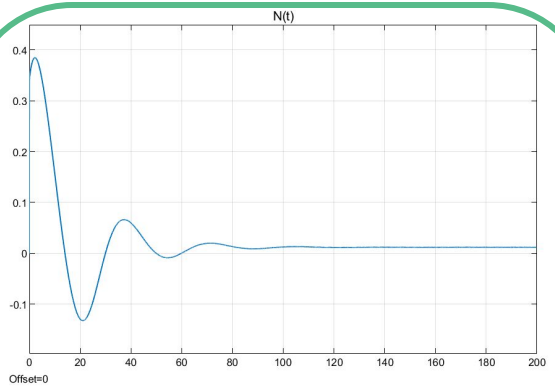
k = 0.1

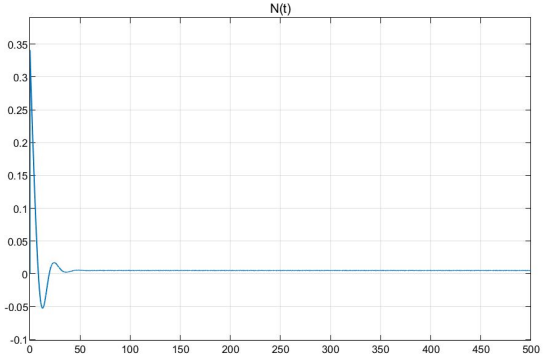
k = 0.3

k = 0.7

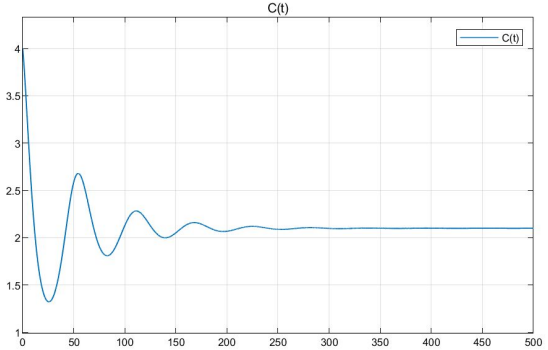
Calcitonin

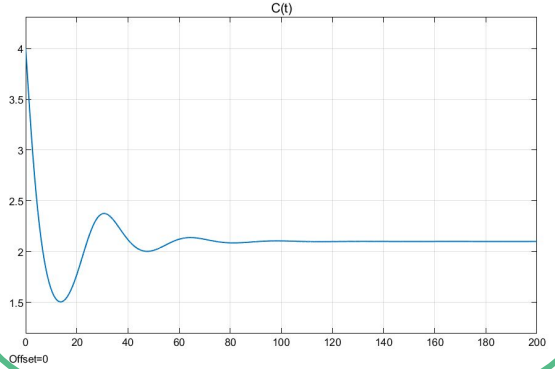


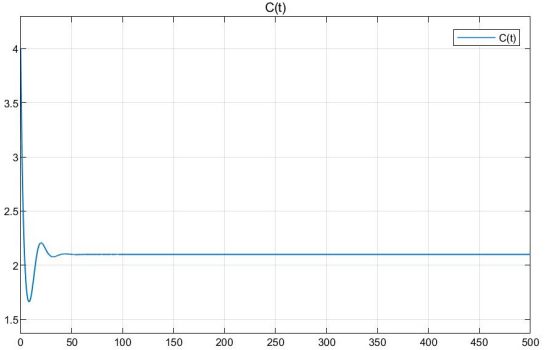




Calcium

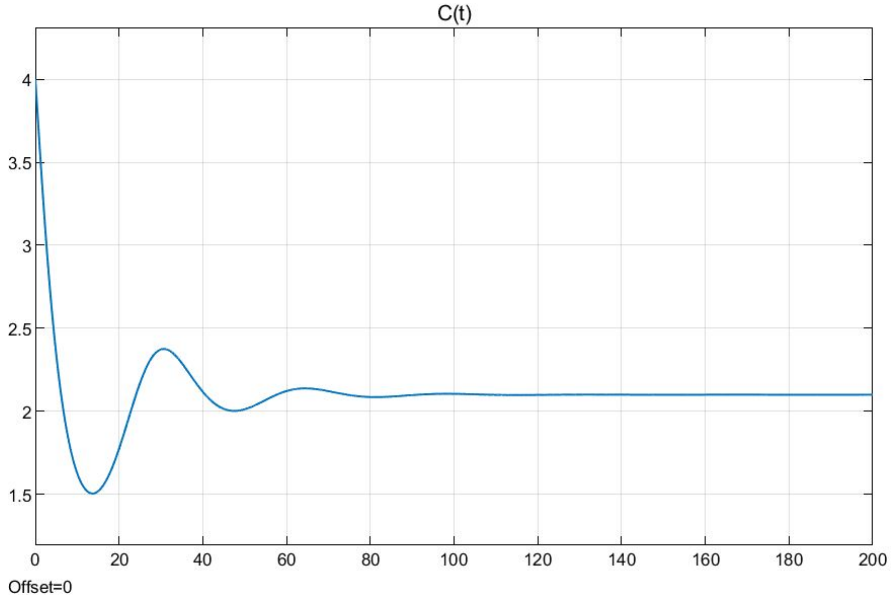




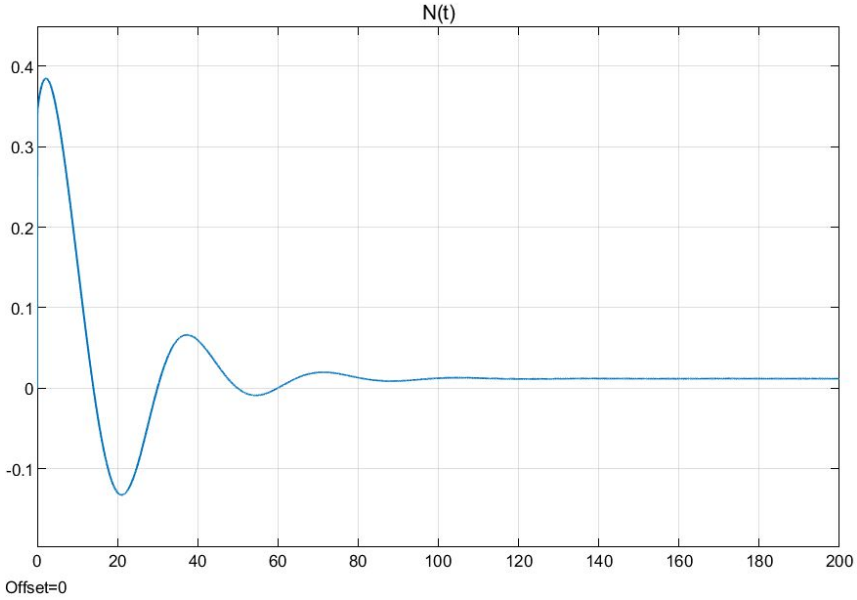


Output Response

Kd	0.3 L/min
Ki	0 L/min^2
Kp	0.9 L



Calcium Concentration

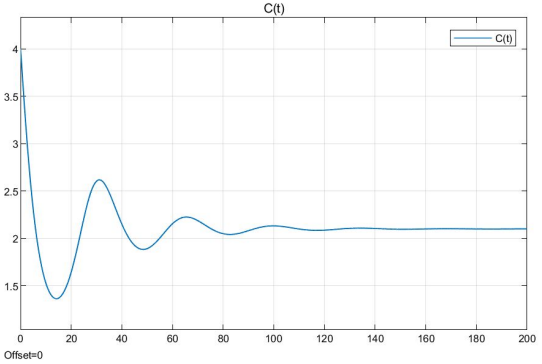


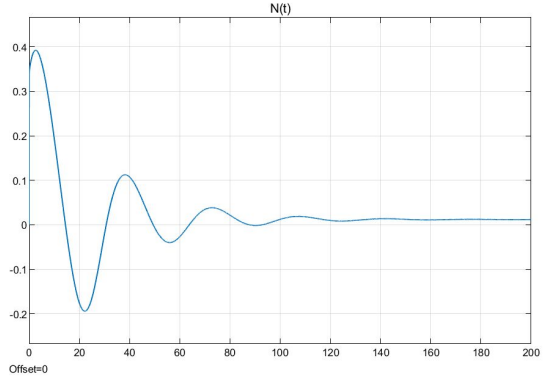
Calcitonin Concentration

Output Response

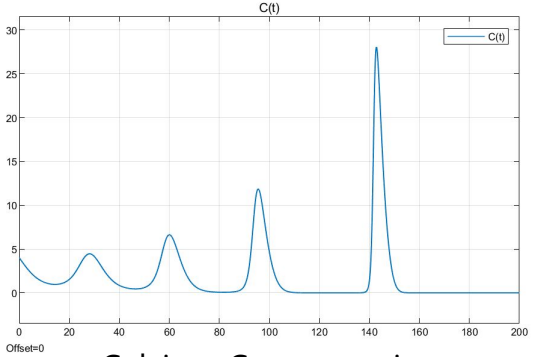
*Adding integral control does not appear to improve the system response

Kd	0.3 L/min
Ki	**0.01 L/min^2**
Kp	0.9 L

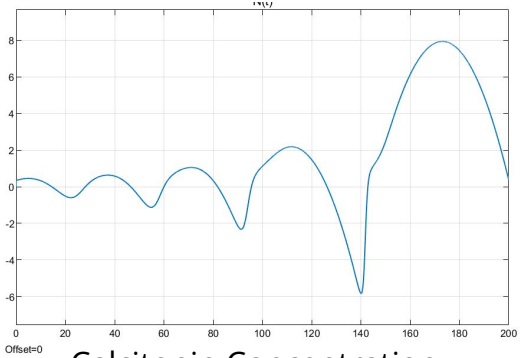




Kd	0.3 L/min
Ki	**0.05 L/min^2**
Kp	0.9 L



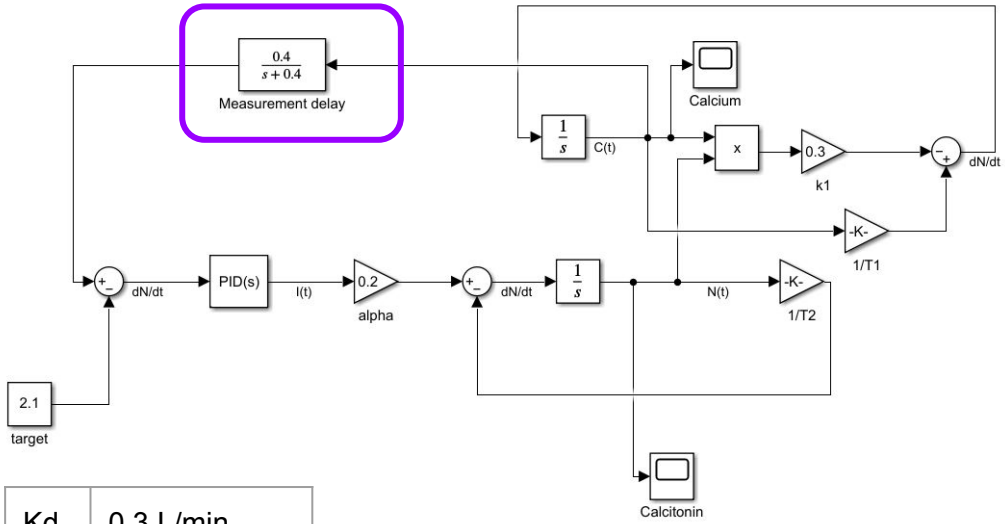
Calcium Concentration



Calcitonin Concentration

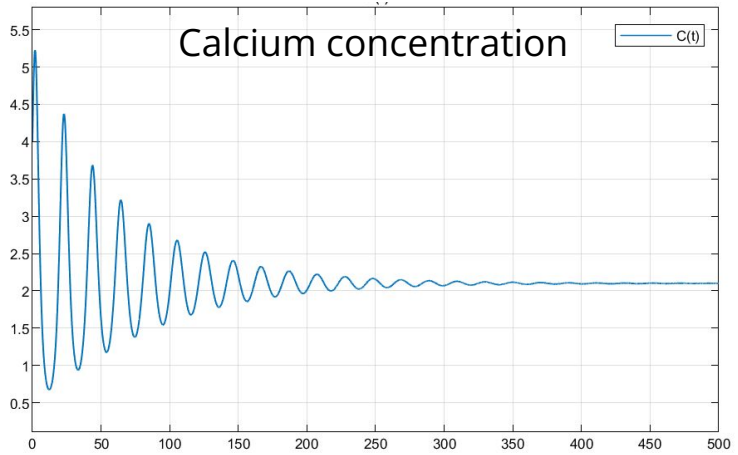
Adding a Measurement Delay

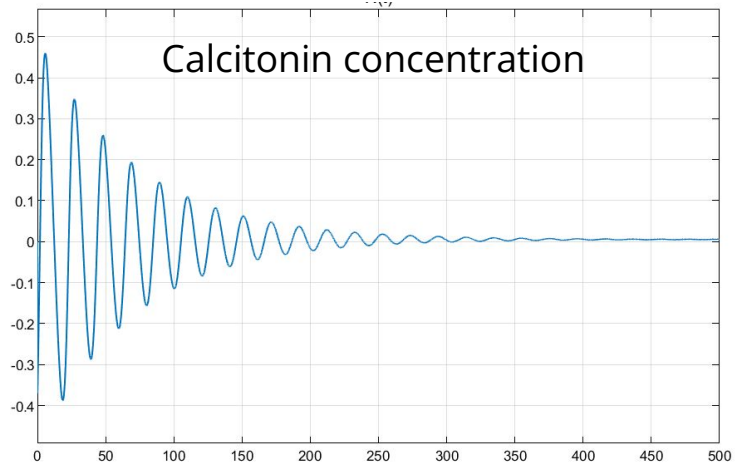
* Considering measurement delay of ~2.5 minutes



Kd	0.3 L/min
Ki	0 L/min^2
Kp	0.9 L

$$\frac{dC_{meas}}{dt} = \frac{1}{\tau_{meas}}(C(t) - C_{meas}(t)) \qquad (5)$$





Closed Loop Transfer Function

Open loop transfer function

$$H(s) = \frac{-0.15}{s^2 - 0.003014s - 2.207\times10^{-6}}$$

Measurement Delay

$$G(s) = \frac{0.4}{s+0.4}$$

Controller

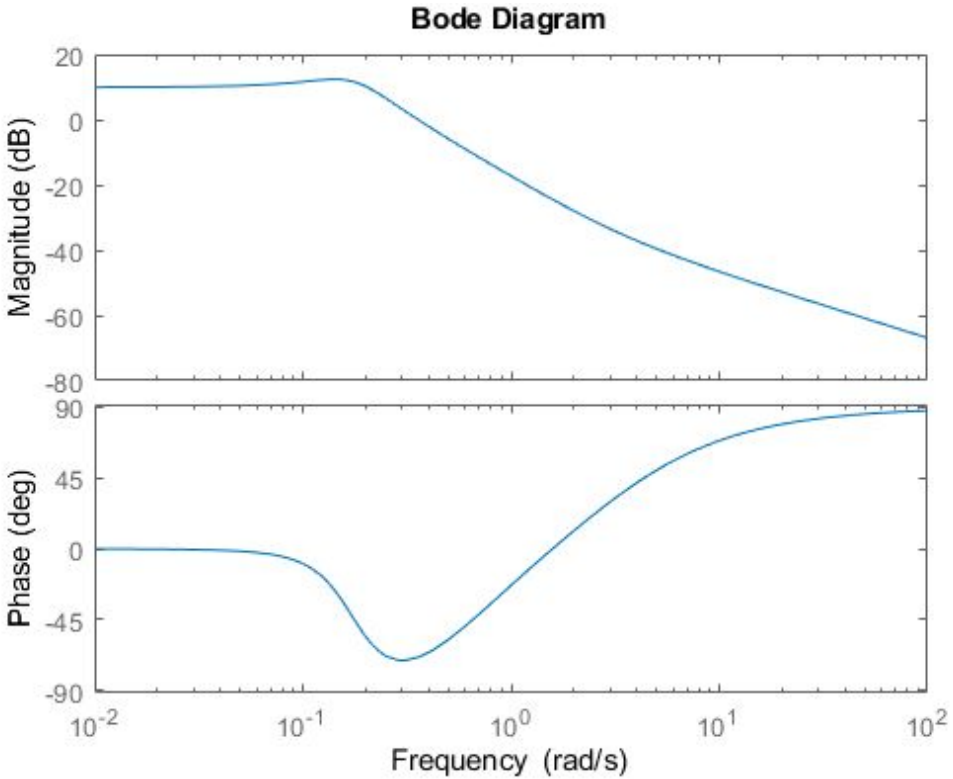
$$F(s) = K_p + K_d s = 0.9 + 0.3s$$

Closed loop transfer function

$$CL(s) = \frac{F(s)H(s)}{1+G(s)F(s)H(s)} \longrightarrow CL(s) = \frac{-0.045s^2 - 0.153s - 0.054}{s^3 - 0.403s^2 - 0.0528s - 0.0172}$$

BODE Plot of Closed Loop System

- System response is stable until 10^{-1} rad/sec
- Downward slope indicates the attenuation of the system at higher frequencies
- Phase shift occurs when response becomes *unstable*



Limitations and Future Design Goals

- Our system only focused on the changes of calcitonin levels in the blood, in the future we could also model parathyroid mechanics which would increase calcium concentration in the blood.
- Manipulating the constants inputted in the transfer functions (ie. k variable) would provide a more stable system

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References

“Lesson Explainer: The Thyroid and Parathyroid Glands | Nagwa.” Nagwa.com, Nagwa, 2023, www.nagwa.com/en/explainers/523154762780/.

Felsenfeld AJ, Levine BS. Calcitonin, the forgotten hormone: does it deserve to be forgotten? Clin Kidney J. 2015 Apr;8(2):180-7. doi: 10.1093/ckj/sfv011. Epub 2015 Mar 20. PMID: 25815174; PMCID: PMC4370311.

“Fractures & Osteoporosis | SSM Health.” Ssmhealth.com, 2023, www.ssmhealth.com/services/orthopedics/fractures-osteoporosis.

Dr Gayatri Sabinkar. “Hypercalcemia: Causes, Symptoms, Treatment, Risks.” Best Hospitals in India | Medicover Hospitals, Medicover Hospitals, 20 May 2022, www.medicoverhospitals.in/diseases/hypercalcemia/.

Goyal, Abhinav, et al. “Hypocalcemia.” Nih.gov, StatPearls Publishing, 15 Oct. 2023, www.ncbi.nlm.nih.gov/books/NBK430912/#:~:text=Most%20laboratories%20report%20total%20serum,are%20considered%20to%20be%20hypocalcemic. Accessed 4 Dec. 2023.

Toledo, A., et al. “Hypercalcitoninemia Is Not Pathognomonic of Medullary Thyroid Carcinoma.” Clinics, vol. 64, no. 7, Elsevier España S.L.U., July 2009, pp. 699–706, https://doi.org/10.1590/s1807-59322009000700015. Accessed 4 Dec. 2023.

Schappacher-Tilp, Gudrun, et al. “A Mathematical Model of Parathyroid Gland Biology.” Physiological Reports, vol. 7, no. 7, Wiley-Blackwell, Mar. 2019, pp. e14045–45, https://doi.org/10.14814/phy2.14045. Accessed 4 Dec. 2023.

Lakshmi Kantham, et al. “The Calcium-Sensing Receptor (CaSR) Defends against Hypercalcemia Independently of Its Regulation of Parathyroid Hormone Secretion.” American Journal of Physiology-Endocrinology and Metabolism, vol. 297, no. 4, American Physiological Society, Oct. 2009, pp. E915–23, https://doi.org/10.1152/ajpendo.00315.2009. Accessed 4 Dec. 2023.