PID Control of Cortisol for Treatment of PTSD

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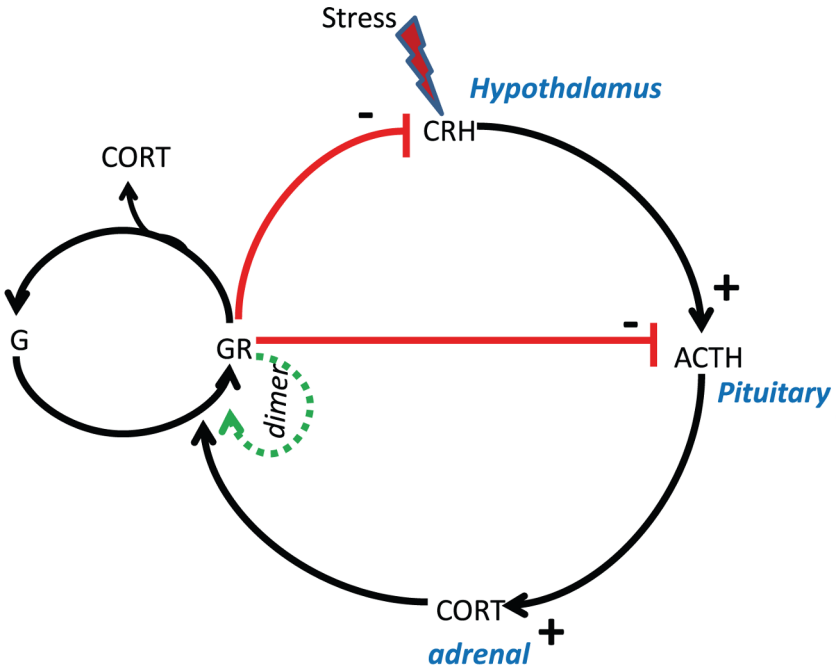
BENG 122A

Background

- HPA Axis
- Cortisol connection to mental illness
  - PTSD
  - Depression



[CRH] = Corticotropin-Releasing Hormone
[GR] = Glucocorticoid Receptor Complex
[ACTH] = Adrenocorticotropin Hormone
[G] = Glucocorticoid Receptor
[G_tot] = Glucocorticoid
[CORT] = Cortisol

Assumptions

01

Autonomous degradation and first order dilution due to hormone transport are considered as one term, while the Michaelis-Menten kinetics are considered separately due to their difference within specific regions of the brain.

02

A sufficient amount of each complex is present for the reactions take place using continuum kinetics.

03

These equations describe the dynamics of the system over 24 hours.

04

The system is not ultradian, and therefore has the same response regardless of time of day.

05

The influence of other hormones or chemical compounds are negligible.

06

Given constants for inhibition, degradation, kinetics, and so on are constant unless specified otherwise. Measurements are ideal.

Defining Our System

Each equation takes into account Michaelis-Menten and autonomous degradation of complexes

$$\frac{d[CRH]}{dt} = k_{stress}\frac{K_i^{n2}}{K_i^{n2}+[GR]^{n2}} - V_{S3}\frac{[CRH]}{K_{m1}+[CRH]} - K_{d1}[CRH] \quad (1)$$

$$\frac{d[ACTH]}{dt} = K_{P2}[CRH]\frac{K_i^{n2}}{K_i^{n2}+[GR]^{n2}} - V_{S4}\frac{[ACTH]}{K_{m2}+[ACTH]} - K_{d2}[ACTH] \quad (2)$$

$$\frac{d[CORT]}{dt} = K_{P3}[ACTH] - V_{S5}\frac{[CORT]}{K_{m3}+[CORT]} - K_{d3}[CORT] \quad (3)$$

$$\frac{d[GR]}{dt} = K_b[CORT]([G_{tot}]-[GR]) + V_{S2}\frac{[GR]^{n1}}{K1^{n1}+[GR]^{n1}} - K_{d5}[GR] \quad (4)$$

$$G_{tot} = G + GR \quad (5)$$

Equations and parameters from Sriram, Rodriguez-Fernandez and Doyle

Linearized Equations

$$\frac{d[\widetilde{CRH}]}{dt} = \left(\frac{K_{stress}K_i^{n2}n2[GR]_{ss}^{n2-1}}{(K_i^{n2}+[GR]_{ss}^{n2})^2}\right)[\widetilde{GR}] + \left(\frac{-V_{s3}K_{m1}}{(K_{m1}+[CRH]_{ss})^2} - K_{d1}\right)[\widetilde{CRH}]$$

$$\frac{d[\widetilde{ACTH}]}{dt} = \left(\frac{-K_{p2}[CRH]_{ss}K_i^{n2}n2[GR]_{ss}^{n2-1}}{(K_i^{n2}+[GR]_{ss}^{n2})^2}\right)[\widetilde{GR}] + \left(-K_d - \frac{V_{s4}K_{m2}}{(K_{m2}+[ACTH]_{ss})^2}\right)[\widetilde{ACTH}] + \left(\frac{K_{p2}K_i^{n2}}{K_i^{n2}+[GR]^{n2}}\right)[\widetilde{CRH}]$$

$$\frac{d\widetilde{CORT}}{dt} = \left(-K_{d3} - V_{S5}\frac{K_{m3}}{(K_{m3}+[\widetilde{CORT}]_{ss})^2}\right)[\widetilde{CORT}] + (K_{P3})[\widetilde{ACTH}]$$

$$\frac{d\widetilde{GR}}{dt} = \left(-K_b[CORT]_{ss} + V_{S2}\frac{K_1^{n1}[GR]_{ss}^{n1-1}}{(K_1^{n1}+[GR]_{ss}^{n1})^2} - K_{d5}\right)[\widetilde{GR}] + (K_b[CORT]_{ss})[\widetilde{G_{tot}}] + K_b([G_{tot}]_{ss} - [GR]_{ss})[\widetilde{CORT}]$$

$$[\widetilde{G_{tot}}] = [G] + [\widetilde{GR}]$$

Evaluating

Parameter	Description	Value
k_{i1}	Inhibition constant for CRH synthesis	0.100
k_{cd}	CRH degradation constant	1.000
k_{i2}	Inhibition constant for ACTH synthesis	0.100
k_{ad}	ACTH degradation constant	10.000
k_{cr}	GR synthesis constant	0.050
k_{rd}	GR degradation constant	0.900
k	Inhibition constant for GR synthesis	0.001

State	Description	Stable Rest Points
x_1	CRH concentration	(0.6261, 0.6610)
x_2	ACTH concentration	(0.0597, 0.0513)
x_3	Free GR concentration	(0.0809, 0.5629)
x_4	Cortisol concentration	(0.0597, 0.0513)

doi:10.1371/journal.pcbi.1000273.t001

Laplace Equations

$$s\widetilde{[CRH]}(s) - [CRH]_0 = -A\widetilde{[GR]}(s) - B\widetilde{[CRH]}(s)$$

$$s\widetilde{[ACTH]}(s) - [ACTH]_0 = -C\widetilde{[GR]}(s) - D\widetilde{[ACTH]}(s) + E\widetilde{[CRH]}(s)$$

$$s\widetilde{[CORT]}(s) - [CORT]_0 = -F\widetilde{[CORT]}(s) + G\widetilde{[ACTH]}(s)$$

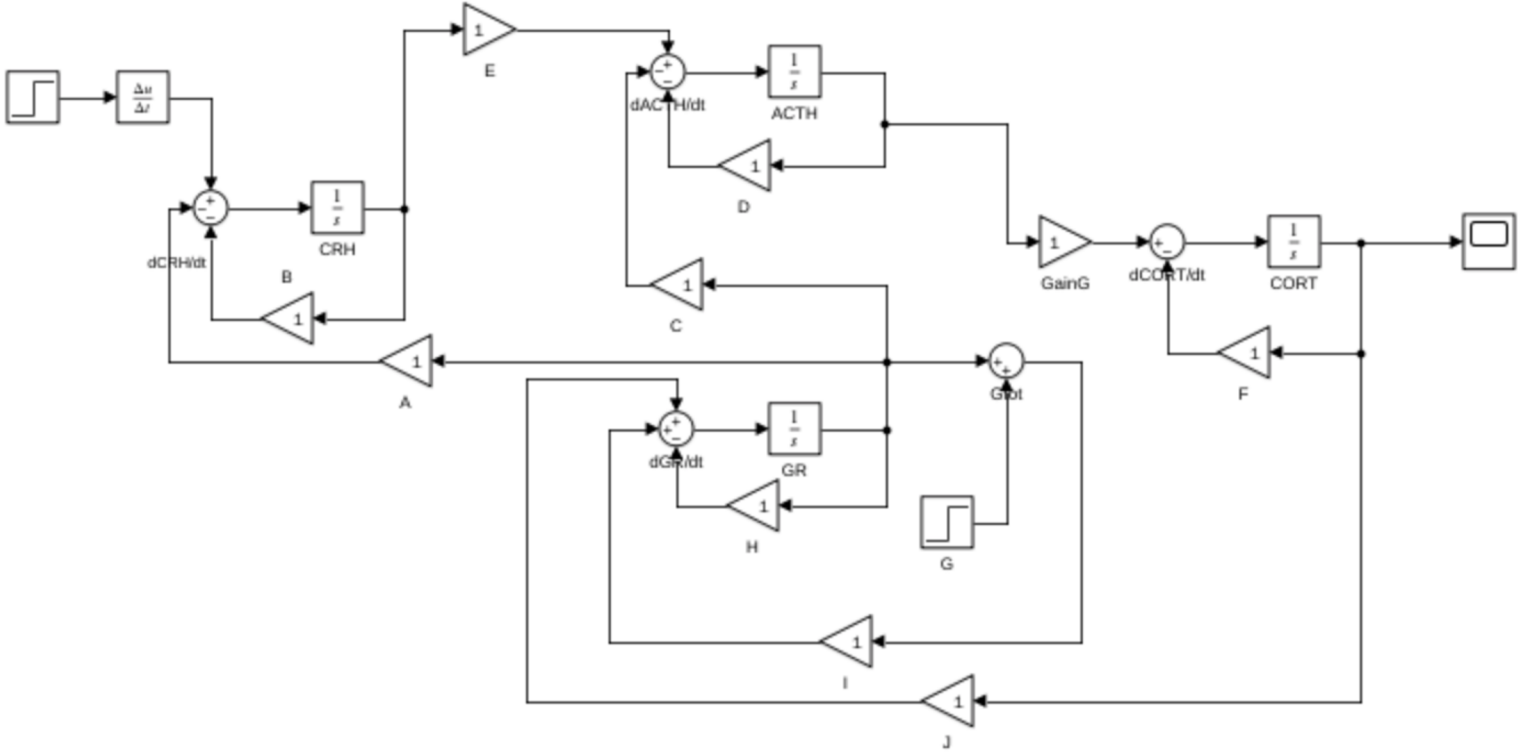
$$s\widetilde{[GR]}(s) - [GR]_0 = -H\widetilde{[GR]}(s) + I\widetilde{[G_{tot})]}(s) + J\widetilde{[CORT]}(s)$$

$$\tilde{[G_{tot}]}(s) = \frac{[G]}{s} + \tilde{[GR]}(s)$$

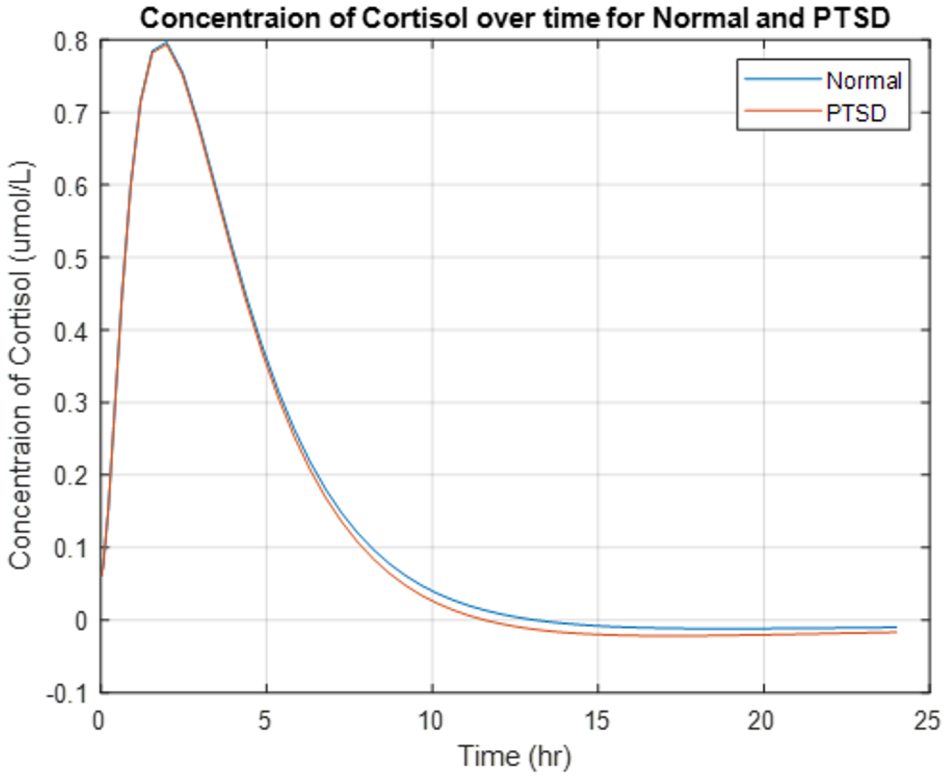
Transfer Function

$$H(s)_1 = \frac{[CORT]}{[CRH]} = G\left(\frac{C(s-B)+EA}{(s-D)(s-F)A}\right)$$

System Block Diagram

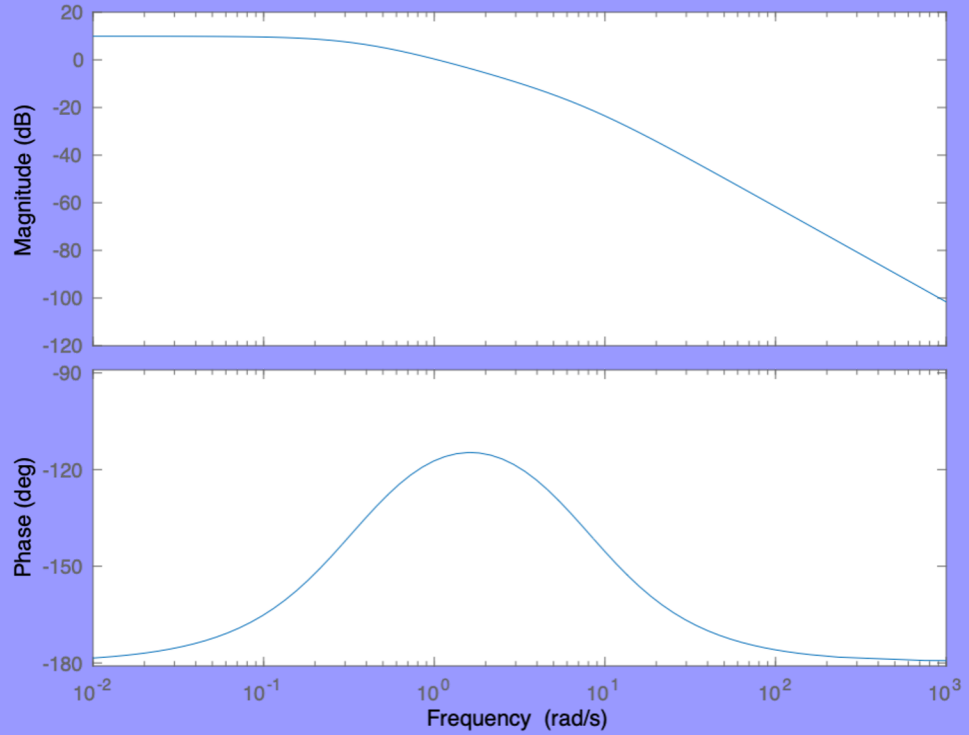


System Response



Bode Plot of System

Same Bode plot for both normal and PTSD



Goal of Controller

1. Reduce steady state error
    a. Causes PTSD response to mimic the normal response
2. Decrease settling time
    a. Quicker return to baseline following occurrence of stress
3. Increase phase margin for improved stability

PD Controller

Closed-Loop Transfer Function:

$$\frac{G(C(s-B)+EA)(K_p+K_ds)}{(s-D)(s-F)a+G(c(s-B)+EA)(K_p+K_ds)}$$

Implementation PD Control

- Helps in reducing the settling time
- Helps in reducing steady state error

Application

- Treatment of PTSD alternative to current pharmaceutical methods
- Better detection of hormone levels

Works Cited

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Thank you!