Proportional-Derivative Control of Cortisol for Treatment of PTSD

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Abstract **- Mental illnesses, such as depression or post-traumatic stress disorder (PTSD), often impact an individual's physiological reaction to stress via their cortisol response. We examine the regulation of cortisol within the hypothalamic-pituitary-adrenal (HPA) axis as a dynamic biosystem. In particular, we investigate the difference between the cortisol regulation of people without mental illness and those who have been diagnosed with PTSD. Additionally, we design and model a proportional-derivative (PD) controller to normalize and improve the stress response of those with PTSD. Such a design may be relevant to improving the treatment of PTSD, as current medical interventions are frequently imprecise and may result in unwanted side effects. The use of a PD controller, in contrast, can be highly measurable and patient-specific.**

I . INTRODUCTION

The goal of this paper is to analyze the biosystem representing the regulation and control of cortisol within the HPA axis in both non-PTSD and PTSD conditions. This analysis will characterize any differences by determining the effect of the altered parameters on key aspects of cortisol control, such as its stability and steady state error. A feedback controller will then be designed that will cause the PTSD response to become, or even improve upon, a normal response. This includes improving the stability of the PTSD response and reducing settling time for a quicker return to a non-stressed state after the occurrence of a stress event. A controller may be implemented into PTSD treatment using a real-time measurement and administration system altering the levels of the targeted hormone.

In the face of the COVID-19 pandemic, there has been a 31% increase from 2019 to 2020 in anxiety or depression symptoms with scientists suggesting only a continuing deterioration in mental health post-pandemic [1]. Stress factors are a product of lack of social interaction (social distancing), familial deaths, economic struggles, and unprecedented devastation [1]. The general catastrophe is a trigger for PTSD - a trauma- and stressor- related disorder. Approximately 90% of people, at some point during their life, experience a major traumatic event that can also result in PTSD [2]. PTSD can be debilitating - hindering work and day-today activities, disrupting relationships and needed social interaction, causing suicidal ideation and deteriorating physical health.

Current pharmaceutical control methods to aid in PTSD treatment - medications, psychotherapy, and natural remedies - are not comprehensive and do not sufficiently and measurably restabilize the system to homeostasis. Medication mainly comes in the form of serotonin reuptake inhibitors and antidepressants [2]. These are dosed out with trial and error as they are not patient-specific. Psychotherapy, while patient-specific, does not tackle the chemical imbalances found in the brain. Natural remedies such as exercising, sleep, and maintaining a positive outlook are at times not only unreasonable to achieve but also ineffective in reduction of cortisol levels. The HPA axis, as described below, provides an accurate, scientifically recognized [3][4][5], representation of the cortisol network and its effects due to stress released in the system. Using this approach, we are able to create a more comprehensive, medically-reliable, and patient-specific process for treatment of PTSD.

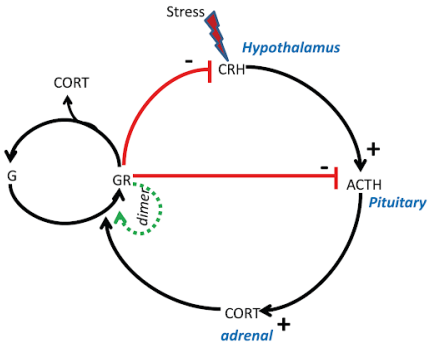

Figure 1: This image [6] shows the HPA axis with regards to cortisol.

The HPA axis is a system of bodies pertaining to the hypothalamus, pituitary gland, and adrenal gland. These bodies work together to activate and discharge hormones as a response to stress, therefore affecting homeostasis within the body. As a result of a stress stimulus, hypophysiotropic neurons in the hypothalamus are alerted to release corticotropin releasing hormone (CRH) to the pituitary gland which then activates the release of adrenocorticotropic hormone (ACTH) [6]. The circulation of ACTH then allows the production of cortisol in the body. The smaller loop on the left in fig. 1, denoted as the GR complex, is created through cortisol's strong affinity for the mineralocorticoid and the glucocorticoid (G) receptors [6]. Through homo-dimerization, an increase in stability and binding affinity, of glucocorticoid and mineralocorticoid, the GR complex activity increases [6]. The complex then down-regulates the production of cortisol by binding to CRH and ACTH [6]. The GR complex acts as a negative feedback

loop that calibrates the additional cortisol needed to be produced in the system to maintain homeostasis [6]. It can be seen that cortisol has a direct representation of stress as it affects the activity of the HPA axis. Additionally, the regulation system is changed by the different production rates as seen in the parameters, consequently affecting the system response.

This analysis was performed by linearizing the system of differential equations from literature. The linearized equations underwent a Laplace transform and were modeled in Matlab Simulink. Simulink was used to generate the system response of both the normal and PTSD conditions to a stress event, modelled as an impulse input to the production of CRH. The open-loop transfer function, and corresponding Bode analysis, of the system was calculated. The system response and Bode analysis were used to characterize each response. We determined the goals of our controller from these responses, and designed it accordingly.

It was determined that the normal response is slightly overdamped with a transfer function of two complex conjugate poles and has a phase margin of approximately 63°, indicating sufficient but not ideal stability. The PTSD response is more overdamped than the normal response with a similar stability. To decrease the overdamping of the PTSD response and increase the overall stability, a proportional-derivative controller was chosen. With the implementation of the PD controller, the stability increased (with an increased phase margin of 272 degrees) and the damping behavior more closely relates to the normal response.

I I I . METHODS

The following system of ordinary differential equations is from prior research [6], and will be used for the remainder of this paper.

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

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

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

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

$$G_{tot} = G + GR$$

Specific parameters are also from [6]; notably, the values of k_{stress} and K_i are dependent on whether they refer to someone with or without PTSD. Each differential equation contains terms describing the production of the hormone as well as terms describing the autonomous degradation and dilution in addition to degradation following Michaelis-Menten kinetics.

Assumptions that have been made for the creation of these equations and dictating the rest of the paper are as follows: (i) Dilution due to hormone transport and autonomous degradation are considered together [6]; (ii) the Michaelis-Menten kinetics - a model for the rate of an enzyme-catalyzed reaction for one substrate - accounts for degradation of the hormones in each specific region of the brain [6]; (iii) There is an adequate amount of each complex that allows the reactions to take place using continuum mechanics [6]; (iv) The system of equations describes the dynamics of the system over 24 hours, and is not ultradian, and therefore has the same response regardless of time of day; (v) The influence of hormones that are not mentioned here are negligible; and (vi) Measurement is ideal.

Linearizing the equations gives the following system of equations:

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

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

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

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

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

The Laplace transform, with simplified parameters, of each linearized equation is as follows, with:

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

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

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

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

$$[\widetilde{G_{tot}}](s) = \frac{1}{s}[G] + [\widetilde{GR}](s)$$

The values of the above parameters and necessary initial conditions are as follows:

Parameter	Represents	Value	
		Without PTSD	With PTSD
A	$\frac{K_{stress}K_i^{n2}n2[GR]_{ss}^{n2-1}}{(K_i^{n2}+[GR]_{ss}^{n2})^2}$	0.0160	0.0218
B	$\frac{-V_{s3}K_{m1}}{(K_{m1}+[CRH]_{ss})^2} - K_{d1}$	1.0139	1.0139
C	$\frac{-K_{p2}[CRH]_{ss}K_i^{n2}n2[GR]_{ss}^{n2-1}}{(K_i^{n2}+[GR]_{ss}^{n2})^2}$	1.0792e-04	8.0328e-05
D	$K_d - \frac{V_{s4}K_{m2}}{(K_{m2}+[ACTH]_{ss})^2}$	3.4549	3.4549
E	$\frac{K_{p2}K_i^{n2}}{K_i^{n2}+[GR]^{n2}}$	8.2934	8.2951
F	$-K_{d3} - V_{S5}\frac{K_{m3}}{(K_{m3}+[\widetilde{CORT}]_{ss})^2}$	0.3781	0.3781
G	K_{P3}	0.9450	0.9450

H	$-K_b[CORT]_{ss} + V_{S2}\frac{K_1^{n1}[GR]_{ss}^{n1-1}}{(K_1^{n1}+[GR]_{ss}^{n1})^2} - K_{d5}$	0.0866	0.0866
I	$K_b[CORT]_{ss}$	0.0012	0.0012
J	$K_b([G_{tot}]_{ss} - [GR]_{ss})$	0.0646	0.0646
$[CRH]_0$	Initial	0.6261 ug/dL	
$[ACTH]_0$	Initial	0.0597 ug/dL	
$[CORT]_0$	Initial	0.0597 ug/dL	
$[GR]_0$	Initial	0.0809 ug/dL	
[G]	Constant	3.2 ug/dL	

Table 1: Values of physiological parameters. Initial conditions are from [6].

The biosystem is represented through a block diagram that is assembled in the Simulink and shows the mathematical relationships presented in the nonlinear ODE equations for the cortisol network.

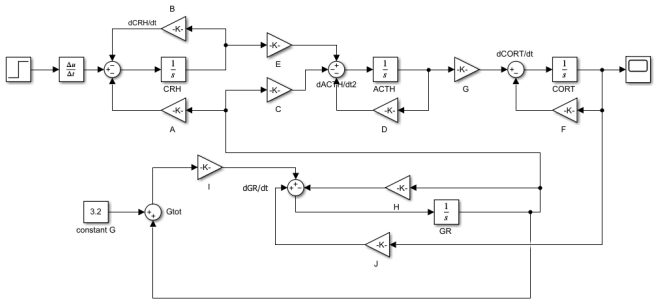

Figure 2: This is the simulink block diagram for the biosystem.

The open loop transfer function for the biosystem as shown below is calculated from the Laplace transformed equations where [CRH] is the input and changes directly in response to stress input and [CORT] is the output of our biosystem. The open loop transfer function has one zero and two poles.

$$H_1(s) = \frac{GCs - G(CB + EA)}{As^2 + A(F - D) - ADF}$$

The open loop transfer function was obtained using the equation $H_2(s) = H_1(s)F(s)$ where $H_1(s)$ is the transfer function and $F(s)$ is the Laplace transform of the biosystem PD controller. The proportional control increases the unity gain and overall response of the system, while the derivative control introduces a zero that counteracts one of the poles of the biosystem, increasing the system bandwidth and therefore stability

$$H_2(s) = \frac{K_dGCs^s + (K_pGC - K_dG(CB + EA))s - K_p(CB + EA)}{As^2 + A(F - D) - ADF}$$

I V. RESULTS

With the given transfer functions and block diagrams, the simulated circuits were run in SIMULINK to yield the cortisol concentration outputs for normal and PTSD cases.

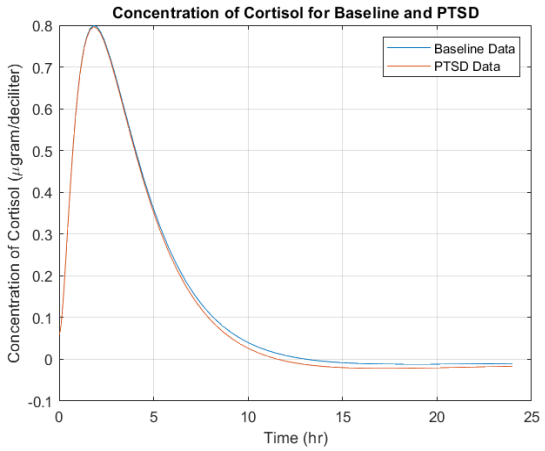

Figure 3: The concentration levels of cortisol output from the Baseline and PTSD models. The blue and red lines represent respectively the response of the baseline and PTSD data.

From these responses, we observe that the largest divergence in PTSD patients from relative normal cases of cortisol starts from about six hours and forth, as PTSD patients seem to experience more of an undershoot in negative feedback, with a lower settling time.

This led to the decision to apply a PD controller in the GR Complex to correct the negative feedback of the HPA axis, as it indirectly affects the level of cortisol, and is already targeted via pharmaceuticals. The PD controller values were chosen to both fix the undershoot in feedback for the PTSD model and increase stability via the phase margin. K_p was found by fine tuning the system until there was a near perfect overlap with the normal. K_d was derived using a natural frequency and pole calculation to find a value that matched our desired parameters, such as phase margin, settling time.

Thus, the determined values are K_p = -40 and K_d = 11.309.

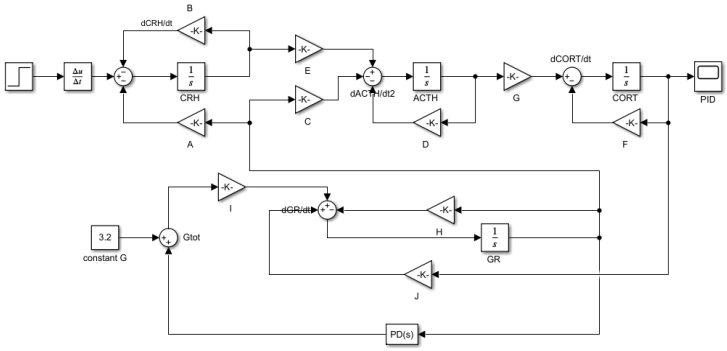

Figure 4: The block diagram of the modeled PTSD model with the PD controller. The biosystem is defined on the top portion of the diagram, whereas the feedback is the lower half. The controller is the block at the lowest point, labeled "PD(s)", connecting to the Gtot block. Impulse represents a stress response input.

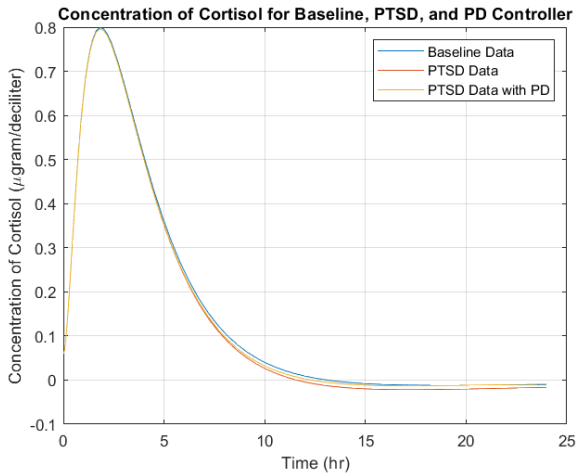

Figure 5: The concentration levels of cortisol output from the Baseline, PTSD, and PID models. The blue, red and yellow lines represent respectively the output response for the baseline, PTSD and PTSD Data with the PD controller. We can see the yellow line closely overlaps with the baseline data in blue.

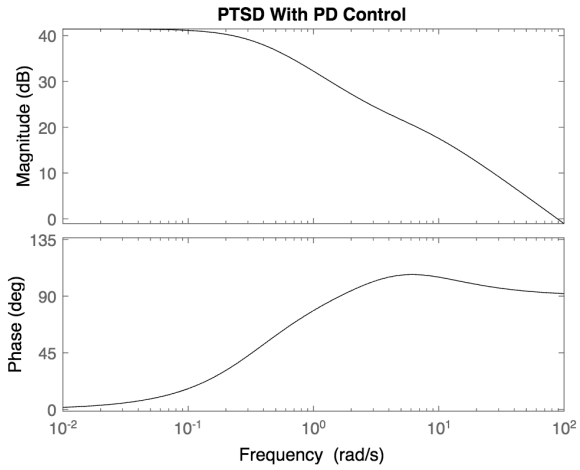

Figure 6: Bode plot of the PTSD data with PD control. The top image represents magnitude, and the lower represents the phase.

V. DISCUSSION

The goals of the controller were to reduce steady state error and increase the phase margin. This was achieved through a proportional-derivative (PD) controller. The steady state portion of the cortisol graph of a person without mental disorders was set as the target value. With $K_p = -40$ the target was achieved as can be seen in Fig. 5. The phase margin was improved with a value of $K_d = 11.903$. The bode plot of the biosystem initially had a phase margin of 63.2025° degrees for both normal and PTSD cortisol secretion. It was improved to a value of 272.3° after the derivative control was added. The greater the phase margin, the greater the stability of the system.

In PTSD patients there is a strong negative feedback which can cause a phenomenon known as adrenal fatigue. This leads to side effects such as increased irritability, depression, and constant fatigue [7] . The HPA axis is a sensitive biosystem, and slight changes can make a great physiological difference [3]. The inspiration behind this design was aimed at studying the physiological effects of patients with PTSD to ultimately come up with a solution for the imbalanced secretion of the popular stress hormone, cortisol.

There are current solutions such as pharmaceuticals that help people control certain hormone levels, but they often come at a disadvantage with unwanted side effects. Doses of these pharmaceuticals are not an exact measurement of a required concentration, and are more often estimates of how much a patient needs. This can be a long, painful process with people with mental illness to discover the right doses that work with their body. The PD controller is used at the metabolic cycle with glucocorticoid as seen in Fig. 1. In this instance of the 24 hour period, the system is assumed to be an ideal measurement which detects the undershoot of cortisol from the target value. Glucocorticoid is an inhibitor to ACTH and CRH [8], and attaching a controller there can correct the strong feedback experienced in the HPA axis of a person with PTSD. The importance of this design is being able to use a hormone already present in the biosystem at a level that is no more or less than what is needed to prevent further issues or complications in the patient.

Some of the limitations experienced in this design involve the assumption of the ideal measurement. A typical measurement system would not be perfect, so to apply the design in a real-life application a measurement would have to be made. In future development of the design the goal would be to incorporate a target value within a device that is tailored to each patient. The controller will cause the same stress response in a person with PTSD than a person without mental illness. This device can be attached to a person's body in a similar way that an insulin pump would be [9]. In future studies this can be applied to other mental health issues such as anxiety and depression as an alternative to pharmaceuticals, and will aid in the avoidance of becoming dependent on drugs by only injecting treatment when necessary at precise values that are needed in the body.

VI. REFERENCES

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