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STRESS ESTIMATION USING AN HYPOTHALAMIC-PITUITARY-ADRENAL AXIS MODEL

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1. Introduction

The hypothalamic-pituitary-adrenal (HPA) axis is a part of the endocrine system. The endocrine system as well as its subsystem, the HPA axis, uses hormones to communicate between the regions of the body. The regulation of hormones maintains homeostasis the process by which bodily functions are maintained at a constant level. This leads to a definition of stress as a state of disharmony in which the homeostasis of the organism is threatened. Another approach to define stress was proposed by McEwen [1] in 2002. To define stress McEwen introduced a notion of allostasis, the process by which the body functions change in response to surrounding stimuli. The term allostasis is the opposite to the notion of homeostasis. An example of allostais is the fight-or-flight response in which the sympathetic nervous system as well as the HPA axis are involved. Dysregulation of the HPA axis is associated with a number of neuroimmune disorders such as chronic fatigue syndrome (CFS), depression, Gulf War illness (GWI), or posttraumatic stress disorder (PTSD), among other stress related diseases [2]. At present, it is not clear what causes dysregulation of the HPA axis. Irrespective of how we define stress, in order to be able to devise effective treatment strategies preventing the adverse effects of stress, it is desirable to have a means of measuring stress. One way to get closer to this goal is through the mathematical modeling of subsystems of the endocrine system that are linked to stress.

A number of mathematical models of the HPA axis were proposed in the last six decades. Building on the previous models, Bingzhen, Zhenye, and Lainsong [3] proposed a third-order dynamical model and tested it on clinical data. This model was later improved by Liu et al. [4]. Kyrylov, Severyanova and Vieira [5] modified the model of Liu et al. [4] to include additional properties of the HPA axis. Conrad et al. [6] proposed and analyzed a second-order non-linear mathematical model of the HPA axis. Lenbury and Pornsawad [7] used delay-differential equations in their HPA axis model to account for the delays associated with the action of the glands in response to the stimulating hormones. Gupta et al. [8], on the other hand, proposed a fourth-order non-linear state-space model of the HPA axis in which the effect of stress on the HPA axis dynamical behavior is modeled. Ben-Zvi, Vernon, and Broderick [2] modified the model of Gupta et al. [8] by adding the control input representing the treatment. The HPA model proposed by Ben-Zvi et al. [2] can be viewed as a dynamical system with unknown input.

In the paper, we use the model of Ben-Zvi et al. [2] to construct a stress estimator using the theory of the unknown input observer (UIO). For a comparative study of different UIO architectures, the reader may wish to consult [9]. Specifically, using only information about applied treatment and one of the hormone measurements, the proposed observer calculates concentrations of three other hormones involved and estimates the stress affecting the individual. We are convinced that the availability of the stress estimate can be employed in the design of effective treatment strategies of stress related diseases. In the next section we discuss the HPA model used in this paper.

2. The HPA model

The HPA model used by us in this paper was proposed by Gupta et al. [8] and modified by Ben-Zvi et al. in [2]. A simplified schematic diagram of the HPA is shown in Figure 1. The HPA axis is responsible for a rapid response to stress stimuli. An activation of the hypothalamus by a stressor causes the release of the corticotropin releasing hormone (CRH).

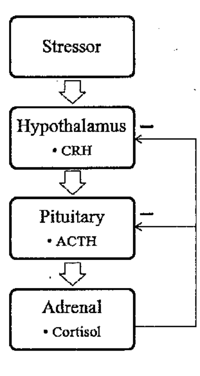

Fig. 1. A simplified schematic diagram of the HPA axis

The hypothalamus is the control center of most of the body's hormonal systems. Upon reaching the pituitary gland, the CRH hormone induces the release of the adrenocorticotropic hormone (ACTH) by the pituitary into the circulation that reaches the adrenal glands that are located on top of the kidneys. The ACTH stimulates the secretion of cortisol by the adrenals. The release of cortisol initiates metabolic effects to fight the harmful effects of stress through negative feedback to the hypothalamus and pituitary see Figure 1. Once the state of stress subsides, the concentration of ACTH and cortisol decreases. In their model, Gupta et al. [8] also include the dynamics of the glucocorticoid receptor (GR) that enables to demonstrate bistability in the HPA axis dynamics, which is compatible with clinical observations. The variables used in the HPA axis modeling are described in Table 1.

Tab. 1. Description of variables in the HPA model

Variable	Description
x_1	CRH concentration
x_2	ACTH concentration
x_3	Free GR concentration
x_4	Cortisol concentration
d	Unknown input modeling stress action
u	Control variable modeling treatment action

This model has the form

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \end{bmatrix} = \begin{bmatrix} \dfrac{1}{1+\dfrac{x_4}{k_{i1}}} - k_{cd}x_1 \\ \dfrac{x_1}{1+\dfrac{x_1x_4}{k_{i2}}} - k_{ad}x_2 \\ \dfrac{(x_1x_4)^2}{k+(x_3x_4)^2} - k_{rd}x_3 \\ x_2 - x_4 \end{bmatrix} + \begin{bmatrix} \dfrac{1}{1+\dfrac{x_4}{k_{i1}}} \\ 0 \\ 0 \\ 0 \end{bmatrix} d + \begin{bmatrix} 0 \\ 0 \\ 0 \\ 1 \end{bmatrix} u \qquad (1)$$

The parameter values we use are the same as in Ben-Zvi et al. [2] and are given in Table 2.

Following the approach of Ben-Zvi et al. [2], we obtain steady-state values of the state variables as a function of the external stressor d. The obtained plots are shown in Figures 2 and 3.

Tab. 2. Parameter values in the HPA model

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

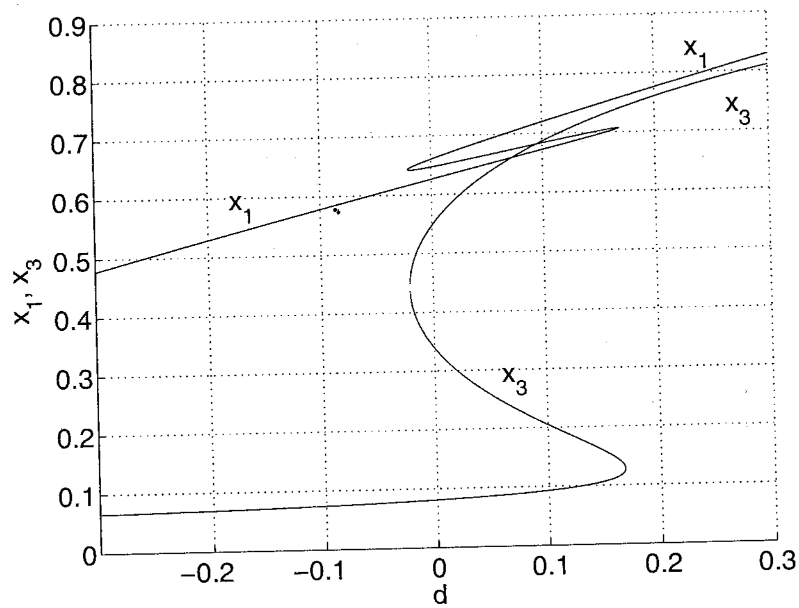

Fig. 2. Plots of the steady-state values of x_1 and x_3 versus d

We note that in a chronically stressed individual, cortisol concentration, x_4, is very low. Thus a healthy individual subjected to a prolonged extreme stress, $d > 0.168$, would settle down in a stable equilibrium state corresponding to depressed cortisol concentration, x_4, corresponding to the lower branch of the curve in Figure 3. When the stress subsides, that is, $d = 0$, the individual will stay in the new equilibrium state corresponding to a depressed cortisol concentration. This is because the equilibrium corresponding to $d = 0$ is asymptotically stable and so states "close" to it will be attracted by this asymptotically stable low cortisol equilibrium. Ben-Zvi et al. [2] propose a treatment strategy whereby the chronically stressed individual is moved to the healthy state corresponding to the normal cortisol concentration, by moving the individual into a negative stress region, after which internal regulatory processes translates the individual into the healthy equilibrium which is asymptotically stable and maintains it there. Effective treatment can be accomplished when the states as well as stress levels are available. In the following section, we propose a method to estimate state variables as well as the stress level.

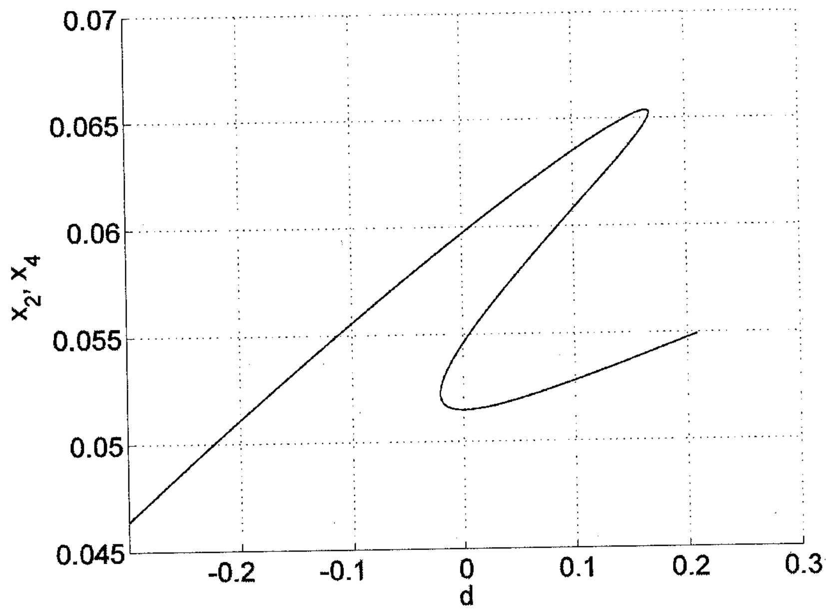

Fig. 3. Plots of the steady-state values of x_2 and x_4 versus d

3. Construction of the stress estimator

We use the unknown input observer (UIO) theory to construct a state and stress estimator. The first observer was proposed by Luenberger in the early nineteen sixties [10, 11, 12] for the purpose of estimating the state of a dynamical system, referred to as a plant, based on limited measurements of that system. More specifically, an observer is a deterministic dynamical system that can generate an estimate of the plant's state using that plant's input and output signals. A block diagram of a general observer structure is depicted in Figure 4.

Observers can be used as „software" or "virtual" sensors as opposed to hardware sensing devices directly measuring physical variables, thus augmenting or replacing sensors in a control system [13]. Generalizations of the Luenberger's observer to plants with unknown inputs resulted in several unknown input observer (UIO) architectures [9, 14-26].

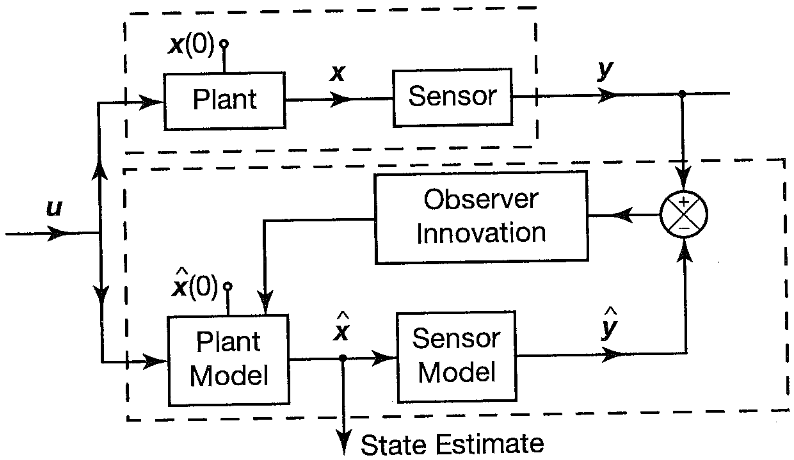

Fig. 4. General observer architecture

To proceed, we represent the HPA model given by (1) in a compact format as

$$\dot{x} = f(x) + b_1 u + b_2(x) d \tag{2}$$

We view the above model as the patient's model. We assume that we can measure the ACTH concentration, that is, x_2. Therefore our output is

$$y = x_2 = [0 \quad 1 \quad 0 \quad 0] x = cx$$

Let $e_y = y - \hat{y} = cx - c\hat{x}$. Consider the following dynamical system

$$\dot{\hat{x}} = f(\hat{x}) + b_1 u + b_2(\hat{x}) E(e_y) \tag{3}$$

where $\hat{x}$ is the state estimate and $E(e_y)$ is the innovation term to be determined - see Figure 4.

Definition 1. A dynamical system (3) is an observer of the system (2) if $\lim_{t \to \infty} \hat{x}(t) = \hat{x}(t)$ for a set of initial conditions $x(0)$ and $\hat{x}(0)$.

Let $e = x - \hat{x}$ denote the state observation error. Then the dynamics of the observation error is governed by the following differential equation

$$\dot{e} = f(x) - f(\hat{x}) + b_2(x) d - b_2(\hat{x}) E(e_y)$$

Taking into account that $e = x - \hat{x}$, we obtain

$$\dot{e} = f(e + \hat{x}) - f(\hat{x}) + b_2(e + \hat{x}) d - b_2(\hat{x}) E(e_y) = h(e) \tag{4}$$

The system (3) is an unknown input observer for the system (2) if the above error system has an asymptotically stable equilibrium state at $e = 0$. To proceed, we analyze the patient's model dynamics given by (2). We assume that $u = 0$. Then, for an operating constant value of the stress level, we select a stable equilibrium state x_{eq}. We then perform Taylor's linearization of (2) about the equilibrium point

$$(x_{eq}, u_{eq} = 0, d_{eq}) \tag{5}$$

We obtain

$$\frac{d}{dt}(x - x_{eq}) = f(x) + b_1 u + b_2(x)d \approx A(x - x_{eq}) + b_1 u + b_2(x_{eq})(d - d_{eq})$$

where A is the Jacobian matrix of $(f(x) + b_2(x)d)$ with respect to x evaluated at the equilibrium point (5). Note that $b_2(x_{eq})$ is the Jacobian matrix of $(f(x) + b_2(x)d)$ with respect to the input d evaluated at the equilibrium point (5). We next perform Taylor's linearization of the observer dynamics (3) to obtain

$$\frac{d}{dt}(x - x_{eq}) = A(x - x_{eq}) + b_1 u + b_2(x_{eq})(E(e_y) - d_{eq}) \tag{6}$$

The dynamics of the linearized observation error are

$$\dot{e} = A(x - x_{eq}) + b_2(x_{eq})(d - d_{eq}) - \left(A(x - x_{eq}) + b_2(x_{eq})(E(e_y) - d_{eq})\right)$$

Performing simple manipulations gives

$$\dot{e} = Ae + b_2(x_{eq})(d - E(e_y)) \tag{7}$$

Suppose now that $d(0) - E(0) = 0$ and that $|d - E| \le \mu\|e\|$ for some $\mu \ge 0$. The matrix A was assumed to be asymptotically stable. Hence, by the Lyapunov's theorem, for any real positive definite matrix $Q = Q^T > 0$ the solution $P = P^T > 0$ to the Lyapunov matrix equation, $A^T P + PA = -2Q$, is positive definite, see, for example [27, p. 338] or [28, p. 155]. We take $V = 0.5e^T Pe$ as the Lypaunov function candidate for (7) and evaluate its Lyapunov derivative on its trajectories to obtain, $\dot{V} \le -e^T Qe + \|Pb_2\|\|e\||d - E|$. Taking into account (8) gives

$$\dot{V} \le -(\lambda_{\min}(Q) - \mu\|Pb_2\|)\|e\|^2$$

where $\lambda_{\min}(Q)$ is the minimal eigenvalue of Q. For $\dot{V}$ to be negative-definite it is sufficient that

$$\mu < \frac{\lambda_{\min}(Q)}{\|Pb_2\|}$$

If μ satisfies the above constraint, then $e = 0$ is a globally asymptotically stable equilibrium state of the observation error system (8). In the steady-state, $\dot{e} = e = 0$, and therefore $b_2(x_{eq})(d - E(e_y)) = 0$. Because $b_2(x_{eq})$ has a full column rank, that is, its null space is trivial, for the above to hold we have to have

$$E(e_y) = d \tag{9}$$

A possible implementation of $E(e_y)$ can have the form of a high gain feedback, $E(e_y) = ke_y$, where $k > 0$ is a "high gain". Another implementation of $E(e_y)$ is to use the relay element as a "high gain" element, that is, $E(e_y) = \rho$ sign (e_y), where $\rho > 0$ is a design parameter. The reason that the relay can be considered as a high gain element is that for $e_y = 0$ the slope of a "tangent" is ∞.

4. Simulations

We present the results of two numerical experiments involving two different types of stress estimators. In the first simulation, we used a linear implementation of the element $E(e_y) = 750e_y$. In the second simulation we tested a non-linear implementation of the element $E(e_y) = 4$ sign (e_y) of the stress estimator. We applied a treatment strategy, $u = 0.27$ for $0 < t < 10$ and $u = 0$ for $t \geq 10$. The initial condition of the patient model was selected to be

$$x(0) = [0.1 \quad 0.01 \quad 0.1 \quad 0.01]^T$$

We selected zero initial conditions for the observer. The stress profile, using the MATLAB notation can be described as $d = 0.1 * ((t > 5) \& (t < 12)) + 0.5 * (t > 20)$. In Figure 5, we show a plot of the estimated stress, $\hat{d}$, versus time as well as a plot of the "actual" stress, d, versus time. After transient decay, the observer tracks the actual stress very well.

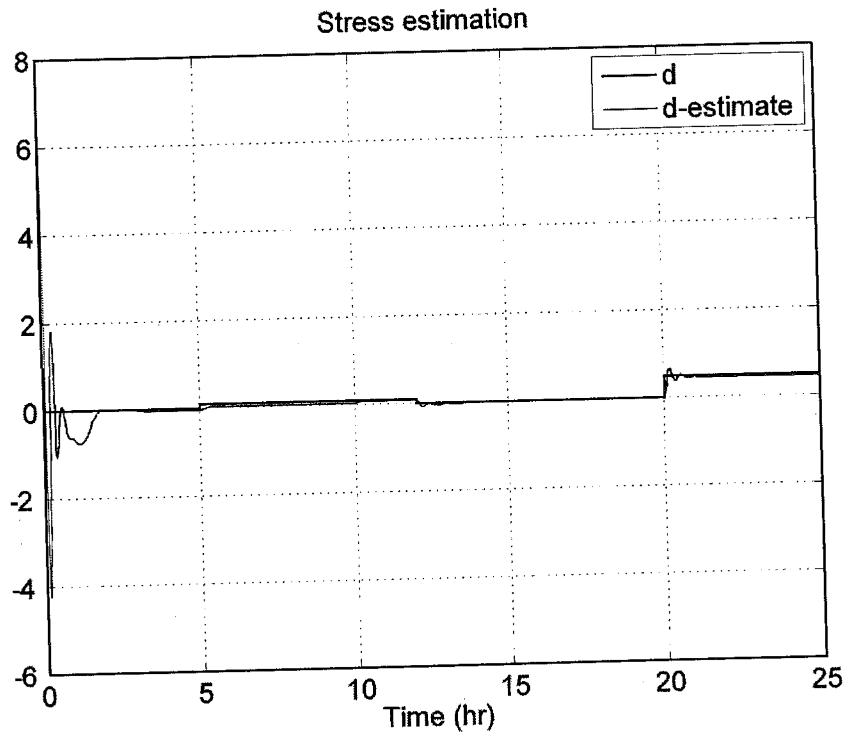

Fig. 5. Plots of the stress d and its estimate versus time for $E(e_y) = ke_y$

In the second simulation, we implemented the element $E(e_y) = 4$ sign (e_y). The initial conditions were the same as in the previous simulation. In our simulations we approximated the rely function with a sigmoid-like function, that is, we used the approximation, $\mathrm{sign}(e_y) \approx \dfrac{e_y}{|e_y| + \nu}$, where we used $\nu = 0.001$. The reason for this approximation is the relay function is discontinuous at 0, which yields a lot of chattering and slows down simulations. Note that as $\nu \to 0$, the sigmoid-like function tends pointwise to the relay function. A plot of the estimated stress, $\hat{d}$, versus time as well as a plot of the "actual" stress, d, versus time for the case when $E(e_y) = 4$ sign (e_y) are shown in Figure 6.

As can be seen from this figure, the stress estimator works even better than in the previous case.

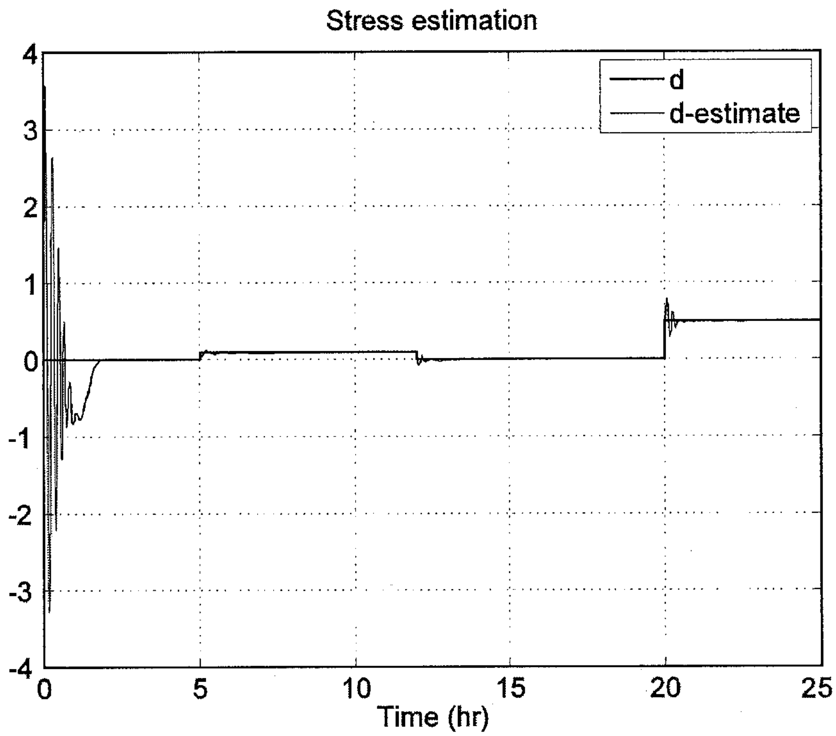

Fig. 6. Plots of the stress d and its estimate versus time for $E(e_y) = \rho$ sign (e_y)

5. Conclusions

Stress may be responsible for symptoms as diverse as disorders of mood and memory, skin lesions, excess acidity that impairs digestion and absorption, inability to detoxify systemic poisons, and neurotransmitter malfunctions among many other symptoms [29, p. 201]. According the American Institute of Stress (AIS), stress is America's leading health problem. Stress has been with us from the beginning of the human race. Yet, even now in the 21st century we do not have one commonly accepted definition of stress. Stress is something that we can feel. Even though stress may be a highly subjective phenomenon, we need to find a way to measure, or quantitatively estimate stress. In this paper, we proposed an approach to model-based stress estimation using the HPA axis mathematical model of Ben-Zvi et al [2]. Our next step is to apply our approach, that is based on the theory of the unknown input observers, to a more detailed model of the HPA axis that account for the delays in the endocrine system.

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