Stress Estimation Using Unknown Input Observer

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***Abstract*— The hypothalamic-pituitary-adrenal (HPA) axis is the body's primary stress management system. The role of the HPA axis is to maintain bodily functions in the presence of physical and mental stressors. This is accomplished by controlling the body's cortisol level. A non-linear mathematical model of the HPA axis from the literature is used to construct a stressor estimator. The mathematical model of the HPA axis is in the state-space format containing an unknown input that models the stressor acting on the body. The controlled input variable models external treatment. The unknown input observer (UIO) is constructed to estimate the unknown input modeling the stressor and its mathematical analysis is provied. Availability of the stressor estimate can be employed in the design of effective treatment strategies for stress related diseases. Simulations studies illustrate the effectiveness of the proposed observer-based stressor estimator.**

I. 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.

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. In the past, the term stress was used to denote both the causes and effects of the pressures. Recently the term stressor has been used for the stimulus that provokes a stress response.

A number of mathematical models of the HPA axis were proposed in the last six decades. For an overview of the HPA axis modeling, see [2]. In this paper, we utilize the HPA model proposed by Ben-Zvi et al. [3], which can be viewed as a dynamical system with unknown input. Using this model, we construct a stressor estimator applying the theory of the unknown input observer (UIO). (For a recent development of the UIO theory, the reader may wish to consult [4].) Specifically, using only information about applied treatment and one of the hormone measurements, the proposed observer calculates concentrations of the three other hormones involved and estimates the stressor affecting the individual.

In the next section we discuss the HPA model used in this paper.

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II. The HPA model

The HPA model used by us in this paper was proposed by Gupta et al. [5] and modified by Ben-Zvi et al. [3]. A simplified schematic diagram of the HPA is shown in Figure 1.

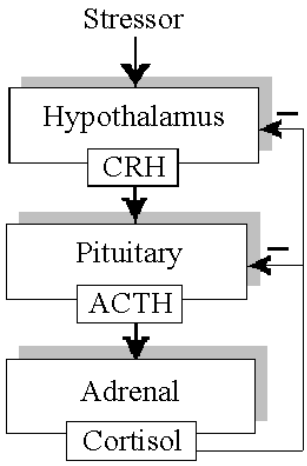

Fig. 1. A simplified schematic diagram of the HPA axis.

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). 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.

The variables used in the HPA axis modeling are described in Table I.

TABLE I

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

TABLE II

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

This model has the form,

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

The parameter values we use are the same as in Ben-Zvi et al. [3] and are given in Table II.

Following the approach of Ben-Zvi et al. [3], we can obtain steady-state values of the state variables as a function of the external stressor, d. In Figure 2, we show plots of the steady-state values of x_1 and x_3 versus d. In Figure 3, we show plots of the steady-state values of x_2 and x_4 versus d. 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

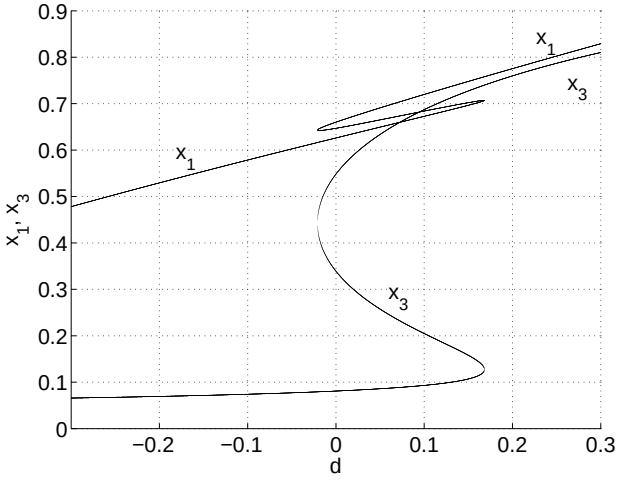

Fig. 2. Plots of the steady-state values of x_1 and x_3 versus d.

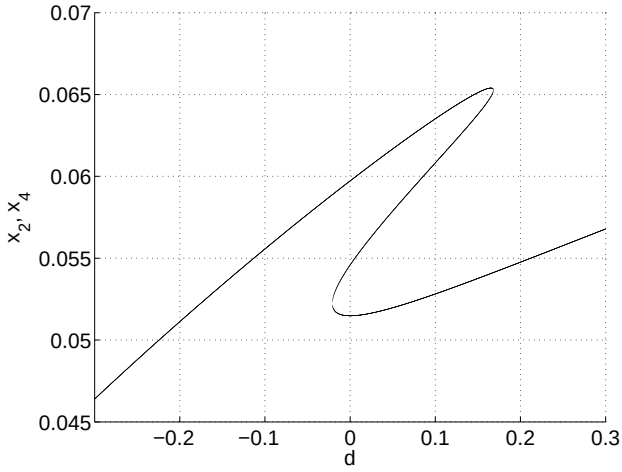

Fig. 3. Plots of the steady-state values of x_2 and x_4 versus d.

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. 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.

III. CONSTRUCTION OF THE STATE AND 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 [6], [7], [8] 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.

Generalizations of the Luenberger's observer to plants with unknown inputs resulted in several unknown input observer (UIO) architectures [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [4].

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

$$\dot{\boldsymbol{x}} = \boldsymbol{f}(\boldsymbol{x}) + \boldsymbol{b}_1 u + \boldsymbol{b}_2(\boldsymbol{x})d. \tag{2}$$

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

$$\begin{aligned} y &= x_2 = \begin{bmatrix} 0 & 1 & 0 & 0 \end{bmatrix} \boldsymbol{x} \\ &= \boldsymbol{c}\boldsymbol{x}. \end{aligned}$$

Let

$$e_y = y - \hat{y} = \boldsymbol{c}\boldsymbol{x} - \boldsymbol{c}\hat{\boldsymbol{x}}.$$

Consider the following dynamical system,

$$\dot{\hat{\boldsymbol{x}}} = \boldsymbol{f}(\hat{\boldsymbol{x}}) + \boldsymbol{b}_1 u + \boldsymbol{b}_2(\hat{\boldsymbol{x}})E(e_y), \tag{3}$$

where $\hat{\boldsymbol{x}}$ is the state estimate and the term $E(e_y)$, called the injection term, is to be determined.

Definition 1: Dynamical system (3) is an observer of system (2) if

$$\lim_{t\to\infty} \hat{\boldsymbol{x}}(t) = \boldsymbol{x}(t)$$

for a set of initial conditions $\boldsymbol{x}(0)$ and $\hat{\boldsymbol{x}}(0)$.
Let

$$\boldsymbol{e} = \boldsymbol{x} - \hat{\boldsymbol{x}}$$

denote the state observation error. Then the dynamics of the observation error are governed by the following differential equation,

$$\begin{aligned} \dot{\boldsymbol{e}} &= \boldsymbol{f}(\boldsymbol{x}) - \boldsymbol{f}(\hat{\boldsymbol{x}}) + \boldsymbol{b}_2(\boldsymbol{x})d - \boldsymbol{b}_2(\hat{\boldsymbol{x}})E \\ &= \boldsymbol{f}(\boldsymbol{e}+\hat{\boldsymbol{x}}) - \boldsymbol{f}(\hat{\boldsymbol{x}}) + \boldsymbol{b}_2(\boldsymbol{e}+\hat{\boldsymbol{x}})d - \boldsymbol{b}_2(\hat{\boldsymbol{x}})E \\ &= \boldsymbol{h}(\boldsymbol{e}). \end{aligned} \tag{4}$$

System (3) is an unknown input observer for system (2) if the above error system has an asymptotically stable equilibrium state at $\boldsymbol{e} = \boldsymbol{0}$.

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 $\boldsymbol{x}_{eq}$. We then perform Taylor's linearization of (2) about the equilibrium point

$$(\boldsymbol{x}_{eq},\ u_{eq} = 0,\ d_{eq}). \tag{5}$$

We obtain

$$\begin{aligned} \frac{d}{dt}(\boldsymbol{x} - \boldsymbol{x}_{eq}) &= \boldsymbol{f}(\boldsymbol{x}) + \boldsymbol{b}_1 u + \boldsymbol{b}_2(\boldsymbol{x})d \\ &\approx \boldsymbol{A}(\boldsymbol{x} - \boldsymbol{x}_{eq}) + \boldsymbol{b}_1 u \\ &\quad + \boldsymbol{b}_2(\boldsymbol{x}_{eq})(d - d_{eq}), \end{aligned} \tag{6}$$

where $\boldsymbol{A}$ is the Jacobian matrix of $(\boldsymbol{f}(\boldsymbol{x}) + \boldsymbol{b}_2(\boldsymbol{x})d)$ with respect to $\boldsymbol{x}$ evaluated at the equilibrium point (5). Note that $\boldsymbol{b}_2(\boldsymbol{x}_{eq})$ is the Jacobian matrix of $(\boldsymbol{f}(\boldsymbol{x})+\boldsymbol{b}_2(\boldsymbol{x})d)$ 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,

$$\frac{d}{dt}(\hat{\boldsymbol{x}}-\boldsymbol{x}_{eq}) = \boldsymbol{A}(\hat{\boldsymbol{x}}-\boldsymbol{x}_{eq})+\boldsymbol{b}_1 u+\boldsymbol{b}_2(\boldsymbol{x}_{eq})(E(e_y)-d_{eq}), \tag{7}$$

The dynamics of the linearized observation error are,

$$\begin{aligned} \dot{\boldsymbol{e}} &= \boldsymbol{A}(\boldsymbol{x} - \boldsymbol{x}_{eq}) + \boldsymbol{b}_2(\boldsymbol{x}_{eq})(d - d_{eq}) \\ &\quad -(\boldsymbol{A}(\hat{\boldsymbol{x}} - \boldsymbol{x}_{eq}) + \boldsymbol{b}_2(\boldsymbol{x}_{eq})(E - d_{eq})) \\ &= \boldsymbol{A}\boldsymbol{e} + \boldsymbol{b}_2(\boldsymbol{x}_{eq})(d - E(e_y)). \end{aligned} \tag{8}$$

Suppose now that $d(0) - E(0) = 0$ and that

$$|d - E| \le \mu\|\boldsymbol{e}\| \tag{9}$$

for some $\mu \ge 0$. The matrix $\boldsymbol{A}$ was assumed to be asymptotically stable. Hence, by the Lyapunov's theorem, see, for example [22, p. 155], for any real positive definite matrix $\boldsymbol{Q} = \boldsymbol{Q}^\top > 0$ the solution $\boldsymbol{P} = \boldsymbol{P}^\top$ to the Lyapunov matrix equation, $\boldsymbol{A}^\top\boldsymbol{P} + \boldsymbol{P}\boldsymbol{A} = -2\boldsymbol{Q}$, is positive definite. We take

$$V = \frac{1}{2}\boldsymbol{e}^\top\boldsymbol{P}\boldsymbol{e}$$

as the Lypaunov function candidate for system (8) and evaluate its Lyapunov derivative on the trajectories of (8) to obtain

$$\begin{aligned} \dot{V} &= \boldsymbol{e}^\top\boldsymbol{P}\dot{\boldsymbol{e}} \\ &= \boldsymbol{e}^\top\boldsymbol{P}\left(\boldsymbol{A}\boldsymbol{e} + \boldsymbol{b}_2(\boldsymbol{x}_{eq})(d - E)\right) \\ &= \frac{1}{2}\boldsymbol{e}^\top\left(\boldsymbol{A}^\top\boldsymbol{P} + \boldsymbol{P}\boldsymbol{A}\right)\boldsymbol{e} + \boldsymbol{e}^\top\boldsymbol{P}\boldsymbol{b}_2(\boldsymbol{x}_{eq})(d - E) \\ &\le -\boldsymbol{e}^\top\boldsymbol{Q}\boldsymbol{e} + \|\boldsymbol{P}\boldsymbol{b}_2\|\|\boldsymbol{e}\||d - E|. \end{aligned}$$

Taking into account (9) gives

$$\begin{aligned} \dot{V} &\le -\lambda_{\min}(\boldsymbol{Q})\|\boldsymbol{e}\|^2 + \mu\|\boldsymbol{P}\boldsymbol{b}_2\|\|\boldsymbol{e}\|^2 \\ &= -\left(\lambda_{\min}(\boldsymbol{Q}) - \mu\|\boldsymbol{P}\boldsymbol{b}_2\|\right)\|\boldsymbol{e}\|^2, \end{aligned}$$

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

$$\mu < \frac{\lambda_{\min}(\boldsymbol{Q})}{\|\boldsymbol{P}\boldsymbol{b}_2\|}. \tag{10}$$

If μ satisfies the above constraint, then $\boldsymbol{e} = \boldsymbol{0}$ is a globally asymptotically stable equilibrium state of the observation error system (8).

IV. Stress estimator analysis

A. Switching Injection Term

In this section, we discuss the estimation of the unknown input using a switching injection term. We have shown that, in the steady-state, the error $\boldsymbol{e} \to \boldsymbol{0}$, and because of the switching nature of the injection term E that we will use, $\boldsymbol{e} = \boldsymbol{0}$ only at isolated points in time. Therefore $\dot{\boldsymbol{e}}$ is zeros only at isolated points in time. We next show that d can be estimated by lowpass filtering E.

Let ϕ be a smooth (infinitely differentiable) non-negative function defined on the real line such that $\phi(t) = 0$ for $|t| > a$ and that

$$\int_{-\infty}^{\infty} \phi(\tau)\, d\tau = 1.$$

Let

$$M = \int_{-\infty}^{\infty} |\dot{\phi}(\tau)|\, d\tau$$

Since ϕ is smooth, M is finite and is determined by the choice of ϕ, which can be considered as a design parameter. For each $\epsilon > 0$, let

$$\phi_\epsilon(t) = \frac{1}{\epsilon}\phi\left(\frac{t}{\epsilon}\right).$$

It is easy to see that ϕ_ϵ and $\dot{\phi}_\epsilon$ are only nonzero on the interval $[-\epsilon a, \epsilon a]$. As $\epsilon \to 0$, the length of the support interval for ϕ_ϵ and $\dot{\phi}_\epsilon$ also tend to zero. A straightforward computation shows that

$$\int_{-\infty}^{\infty} \phi_\epsilon(\tau)\, d\tau = 1$$

and

$$\int_{-\infty}^{\infty} |\dot{\phi}_\epsilon(\tau)|\, d\tau = \frac{M}{\epsilon}.$$

Since the solution of Equation (8) is absolutely continuous (see for example Equation (85) and Theorem 8 of Filipov [23]), we can apply integration by parts to obtain from Equation (8) that, for any t,

$$\int_{-\infty}^{\infty} \phi_\epsilon(t-\tau)\dot{\boldsymbol{e}}(\tau)\,d\tau = \int_{-\infty}^{\infty} \dot{\phi}_\epsilon(t-\tau)\boldsymbol{e}(\tau)\,d\tau$$

It follows from Equation (8) that

$$\begin{aligned} & \boldsymbol{b}_2(\boldsymbol{x}_{eq}) \int_{-\infty}^{\infty} \phi_\epsilon(t-\tau)(d(\tau)-E(\tau))\,d\tau \\ = & \int_{-\infty}^{\infty} \dot{\phi}_\epsilon(t-\tau)\boldsymbol{e}(\tau)\,d\tau + \boldsymbol{A}\int_{-\infty}^{\infty} \phi_\epsilon(t-\tau)\boldsymbol{e}(\tau)\;d\tau. \end{aligned}$$

Because $\boldsymbol{b}_2(\boldsymbol{x}_{eq})$ has a full column rank, its left inverse is the same as its pseudoinverse $\boldsymbol{b}_2^\dagger$. We premultiply the above equation by $\boldsymbol{b}_2^\dagger$ to obtain

$$\begin{aligned} & \int_{-\infty}^{\infty} \phi_\epsilon(t-\tau)d(\tau)\,d\tau - \int_{-\infty}^{\infty} \phi_\epsilon(t-\tau)E(\tau)\,d\tau \\ = & \boldsymbol{b}_2^\dagger \int_{-\infty}^{\infty} \dot{\phi}_\epsilon(t-\tau)\boldsymbol{e}(\tau)\,d\tau + \boldsymbol{b}_2^\dagger\boldsymbol{A}\int_{-\infty}^{\infty} \phi_\epsilon(t-\tau)\boldsymbol{e}(\tau)\;d\tau. \end{aligned}$$

We have

$$\left\| \int_{-\infty}^{\infty} \dot{\phi}_\epsilon(t-\tau)\boldsymbol{e}(\tau)\,d\tau \right\| \le \frac{M}{\epsilon} \sup_{\tau\in[t-\epsilon a, t+\epsilon a]} \|\boldsymbol{e}(\tau)\|$$

and

$$\left\| \int_{-\infty}^{\infty} \phi_\epsilon(t-\tau)\boldsymbol{e}(\tau)\;d\tau \right\| \le \sup_{\tau\in[t-\epsilon a, t+\epsilon a]} \|\boldsymbol{e}(\tau)\|.$$

For a fixed ϵ, it is clear that

$$\sup_{\tau\in[t-\epsilon a, t+\epsilon a]} \|\boldsymbol{e}(\tau)\| \to 0$$

and that

$$\frac{M}{\epsilon} \sup_{\tau\in[t-\epsilon a, t+\epsilon a]} \|\boldsymbol{e}(\tau)\| \to 0$$

as $t \to \infty$ because $\boldsymbol{e}$ tends asymptotically to $\mathbf{0}$. Note that the rate of convergence will depend on the design parameter ϵ. We can now conclude that for large t,

$$\int_{-\infty}^{\infty} \phi_\epsilon(t-\tau)d(\tau)\,d\tau \approx \int_{-\infty}^{\infty} \phi_\epsilon(t-\tau)E(\tau)\,d\tau.$$

One interpretation of the above is that the lowpassed outputs of d and E are approximately equal. If d is slowly varying relatively to E, then by choosing the appropriate ϕ and ϵ, we have

$$d(t) \approx \int_{-\infty}^{\infty} \phi_\epsilon(t-\tau)E(\tau)\,d\tau \tag{11}$$

for large t.

Our implementation of $E(e_y)$ uses the relay element

$$E(e_y) = \rho \text{sign}(e_y),$$

where

$$\text{sign}(e_y) = \begin{cases} 1 & \text{if} \quad e_y > 0 \\ 0 & \text{if} \quad e_y = 0 \\ -1 & \text{if} \quad e_y < 0 \end{cases}$$

and $\rho > 0$ is a design parameter. We will see in Section IV-B that a high gain linear injection term can be used to obtain an estimate of d. We note here that the relay can also be considered a high gain element because for $e_y = 0$, the slope of the "tangent" is ∞.

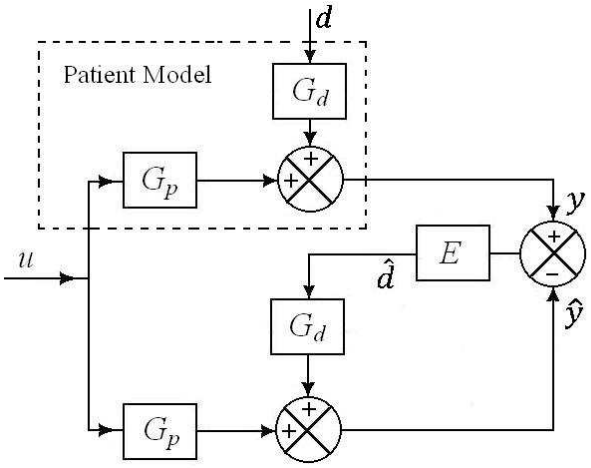

Fig. 4. Observer-based stressor estimator analysis using linearized models of the HPA axis and the observer.

B. Linear Injection Term

In Section IV-A, we showed that d can be estimated by lowpass filtering of the output of the switching injection term. We next show that a linear injection element can also be used. We perform our analysis in the Laplace transform domain and, for convenience, we use the same symbol for the functions in both the time and transform domains.

Our stressor estimator can be represented by the block diagram shown in Figure 4, where

$$G_p = \boldsymbol{c}\,[s\boldsymbol{I}_4 - \boldsymbol{A}]^{-1}\,\boldsymbol{b}_1, \quad G_d = \boldsymbol{c}\,[s\boldsymbol{I}_4 - \boldsymbol{A}]^{-1}\,\boldsymbol{b}_2(\boldsymbol{x}_{eq}).$$

From the diagram and using the linearity of E, we see that

$$\begin{aligned} \hat{d} &= E(y-\hat{y}) \\ &= E(G_p u + G_d d) - E(G_p u - G_d \hat{d}) \\ &= EG_d(d-\hat{d}). \end{aligned}$$

Therefore,

$$\hat{d} = \frac{EG_d}{1+EG_d} d. \tag{12}$$

It follows from the above that if E is large for all s in the spectrum of d, then

$$\hat{d} = Ee_y \approx d,$$

which is the linear analogue of (11) in the Laplace transform domain. One possible E, in the Laplace transform domain, is $E(s) = k$, where k is a large positive gain. This corresponds in the time domain to the input-output relationship

$$E(e_y) = ke_y,$$

which is simply a proportional control with a large gain. Of course, more sophisticated E's can used to take into the account the spectral properties of d and G_d and possibly improve the performance of the estimator.

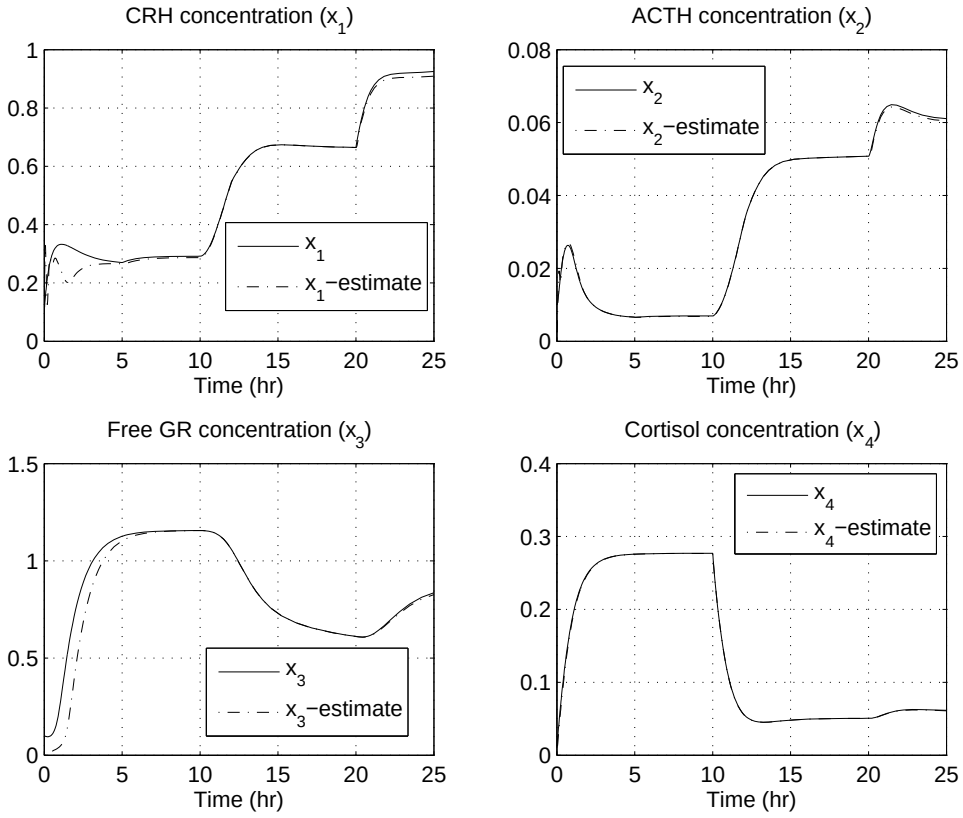

Fig. 5. Plots of the states versus time for $E(e_y) = ke_y$.

V. Simulation Experiments

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 $E(e_y)$. In the second simulation we tested a non-linear implementation of the element $E(e_y)$ of the stressor estimator.

A. $E(e_y) = ke_y$

In the first simulation experiment, we used $E(e_y) = ke_y$, where we include the results of our simulations for $k = 750$. We also applied a treatment strategy in the form

$$u = \begin{cases} 0.27 & \text{for} \quad 0 < t < 10 \\ 0 & \text{for} \quad t \geq 10. \end{cases}$$

The initial condition of the patient model was selected to be

$$\boldsymbol{x}(0) = \begin{bmatrix} 0.1 & 0.01 & 0.1 & 0.01 \end{bmatrix}^\top.$$

We selected zero initial conditions for the observer. The stress profile, using the MATLAB notation can be described as

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d=0.1*((t>5)&(t<12))+0.5*(t>20).
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In Figure 5, we show plots of the HPA axis actual and estimated states versus time. In Figure 6, 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 stressor with a steady-state error that depends on the gain k.

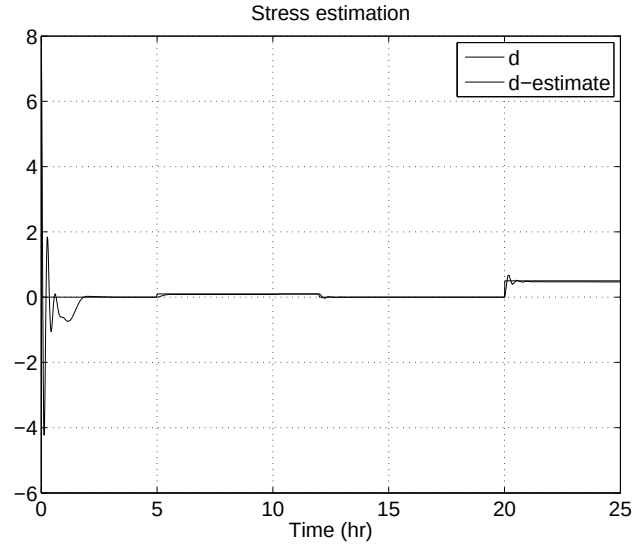

Fig. 6. Plots of the stressor d and its estimate versus time for $E(e_y) = ke_y$.

B. $E(e_y) = \rho\, sign(e_y)$

In this simulation experiment, we implemented the element $E(e_y)$ as $E(e_y) = \rho\,\text{sign}(e_y)$, where $\rho = 4$. The initial conditions were the same as in the previous simulation. In our simulations we approximated the rely function with a sigmoid-

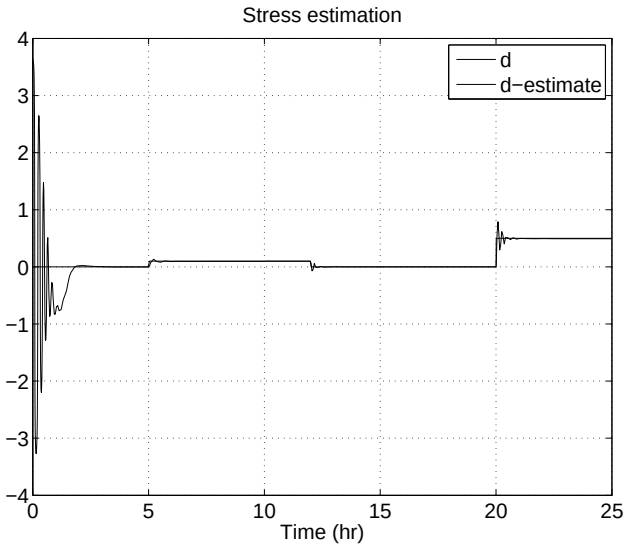

Fig. 7. Plots of the stressor d and its estimate versus time for $E(e_y) = \rho\,\text{sign}(e_y)$.

like function, that is, we used the following approximation,

$$\text{sign}(e_y) \approx \frac{e_y}{|e_y| + \nu},$$

where we used $\nu = 0.001$. The reason for this approximation is the 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.

The plots of states versus time were very similar to those in the previous simulation—see Figure 5. A plot of the estimated stressor, $\hat{d}$, versus time as well as a plot of the "actual" stressor, d, versus time for the case when $E(e_y) = \rho\,\text{sign}(e_y)$ are shown in Figure 7. As can be seen from this figure, the stress estimator works even better than in the previous case.

VI. 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 [24, p. 201]. According the 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 21-st 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 [3].

The model used by us in this paper focuses on a single hormone, cortisol, which is somewhat biologically limiting, despite the fact that cortisol is a major stress hormone. 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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