33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

A Feedback Control Model for Cortisol Secretion

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Abstract— **Existing mathematical models for cortisol secretion do not describe the entire cortisol secretion process, from the neural firing of corticotropin releasing hormone (CRH) in the hypothalamus to cortisol concentration in the plasma. In this paper, we lay the groundwork to construct a more comprehensive model, relating CRH, Adrenocorticotropic hormone (ACTH), and cortisol. We start with an existing mathematical model for cortisol secretion, and combine it with a simplified neural firing model that describes CRH and ACTH release. This simplified neural firing model is obtained using the extended FitzHugh-Nagumo (FHN) model, which includes a time-varying spiking threshold [3]. A key feature of our model is the presence of a feedback loop from cortisol secretion to ACTH secretion.**

I. Introduction

Hormones could be considered as chemical messengers, relaying signals from one group of cells to another. Hormone secretion is governed by the circadian rhythm, which is a biological clock with a period of 24 hours [12]. Hormone secretion can be stimulated by neurons in the hypothalamus. In neurons, oscillatory changes in the membrane potentials as well as the intracellular Ca^{2+} oscillations result in neurosecretion in a pulsatile manner [14]. Neurosecretion is the coupling of electrical activity to hormone release, and the amount of hormone released by spiking increases as the frequency of spikes increases [13]. In other words, the periodic increase in hormone release is a consequence of synchronization in hormone generating neurons as well as increase in firing activity in individual neurons instead of activation of new neurons [14]. Pulsatile neurosecretion results from synchronized bursting activity of neuroendocrine cells [13], and intracellular chemical concentrations play an important role in releasing hormones. For example, the coupling of electrical activity to hormone release in Luteinizing Hormone-Releasing Hormone (LHRH) neurons is as follows. High K^+ results in neurosecretion, which is followed by an increase in Ca^{2+}, and oscillatory changes in membrane potentials. Moreover, Nitric Oxide (NO) mediates the release of the LHRH [14]. In this paper, we study cortisol, a steroid hormone, and cortisol secretion, from neural firing to cortisol concentration in the plasma and propose a feedback control model for cortisol secretion.

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This work was supported in part by NSF 0836720. Rose T. Faghih's work was also supported in part by MIT Fellowship in Control and NSF Graduate Fellowship.

II. Cortisol Secretion

Cortisol is a steroid hormone that regulates the metabolism and the body's reaction to stress and inflammation [1]. Stress can be physical, such as infection, thermal exposure, and dehydration, or psychological, such as fear and anticipation [5]. Cortisol relays rhythmic signals from the suprachiasmatic nucleus (SCN), the circadian pacemaker, to synchronize bodily systems with environmental variations [10]. Cortisol secretion can be stimulated by calcium oscillations and changes in the membrane potential of the hypothalamus neurons. Ultradian analysis of cortisol shows significant periods of 24 hours, 12 hours, and 2 hours. The first two significant periods (24 hours and 12 hours) correspond to the circadian pattern. In addition to the circadian pattern, there is a shorter periodicity in the observed cortisol pattern [6]. The 24-hour plasma cortisol profile consists of episodic release of 15 to 21 secretory events with varying magnitudes in a regular diurnal pattern, with the lowest amplitude occurring between 8pm and 2am, increasing rapidly throughout the late night, with the highest amplitude between 8am and 10am, and then, the amplitude declines throughout the day [1].
Cortisol secretion is controlled by the hypothalamic pituitary adrenal axis (HPA), which is a self-regulated dynamic feedback neuroendocrine system [5]. In the hypothalamus, SCN sends a harmonic circadian signal to the paraventricular nuclei (PVN), which leads to release of CRH. CRH secreted into the hypophyseal portal blood vessels induces release of ACTH from the anterior pituitary [1]. ACTH is synthesized and stored in the anterior pituitary gland. Synthesis and release can occur independently, and are stimulated by CRH [2]. Then, via stimulation of adrenal gland by ACTH, adrenal gland produces and secretes cortisol [7], [1]. After synthesis, cortisol diffuses into the circulation and is absorbed from the blood plasma by different tissues where it implements regulatory functions as a steroid hormone. Then, cortisol is cleared from the plasma by the liver [1]. Moreover, cortisol has a negative feedback effect on the hypothalamus and pituitary as well as CRH and ACTH secretion [5], [7], [1].

A. Mathematical Models for Cortisol Secretion

Different mathematical models of the HPA and cortisol secretion have been proposed in the literature. Comparing models by Brown et al. [1], Savic and Jelic [10], and Gupta et al. [5], the equation describing cortisol synthesis in the adrenal glands and infusion of cortisol from the adrenal glands to plasma given by these three models are in agreement, with the only difference that the rate of cortisol synthesis in the adrenal glands and the rate of infusion of cortisol from the adrenal glands are different in these models.

Considering that the model by Brown et al. [1] is the only model that uses unstimulated physiological data to estimate the synthesis and infusion rates, we use this model as a starting point.

Brown et al. [1] introduce a stochastic differential equation model of diurnal cortisol patterns, assuming first-order kinetics for synthesis of cortisol in the adrenal gland, infusion of cortisol from adrenal gland to plasma, and clearance of cortisol from plasma by the liver, while making use of the timing of secretory events and circadian modulation of the amplitude of secretory events:

$$\frac{dC_a}{dt} = -\beta_I C_a + C_s \ , \ \frac{dC_p}{dt} = \beta_I C_a - \beta_C C_p \quad (Model\ I)$$

where C_a is the cortisol concentration in the adrenal gland and C_p is the cortisol concentration in the plasma space. Moreover, β_I and β_C are normal random variables with mean and variance obtained using cortisol data; C_s is a doubly stochastic pulsatile input which has a Gaussian circadian amplitude with a two-harmonic mean, and a mean-dependent variance, and a secretory event timing with gamma distributed interarrival times. Since cortisol synthesis is initiated by ACTH and is highly coupled to ACTH, it is possible to replace C_s with ACTH (variable A). In this model, Gaussian noise is added to C_p to obtain the cortisol profile. The simulations obtained using this model have a plasma cortisol diurnal pattern, which agrees with the physiology.

B. Mathematical Models for ACTH and CRH Release

In the literature, we found the following mathematical models for ACTH release via CRH regulation: [8] investigates ACTH secretion via CRH regulation using the Hodgkin-Huxley (HH) mathematical model that results from the intracellular signaling system. In a later paper, [9] reduces the model in [8] to one with three differential equations. Later on, [11] includes a K^+ current which takes two values depending on the value of the action potential in the model in [8]. These models only include the ACTH release, and do not include a model for ACTH regulating cortisol release and for cortisol secretion. Moreover, the neural firing models used in these papers are more complicated, and we suspect a simpler model (e.g. the extended FHN with time-varying spiking threshold [3]) could be used for such modeling.

The following is the extended FHN model, which includes a time-varying spiking threshold:

$$\frac{dv}{dt} = a(-v(v-1)(v-b) - w + I), \ \frac{dw}{dt} = v - cw, \ \frac{db}{dt} = g(t)$$

where v is the membrane potential, w is the recovery variable, a and c are scaling parameters, and I is a constant stimulus current. Moreover, b is the spiking threshold, and physiologically, it might be the case that this threshold is varying throughout the day changing the firing frequency. The spiking modes that this model can generate are discussed in detail in [4].

C. From CRH Release to Cortisol Secretion

As discussed before, reviewing the literature, we could not find a paper that provides a mathematical model for cortisol secretion that includes the entire process, starting from a neural firing model for secretion of CRH in the hypothalamus to cortisol secretion. In the next section, we propose a more comprehensive model by bringing more pieces together and propose a feedback control model. Considering that *Model I* describes the physiology and is capable of generating the fluctuations observed in the cortisol profile, we will use *Model I* as a starting point for this study. Then, we will employ the FHN model with time-varying spiking threshold to study ACTH release. Our proposed model is different from *Model I* in the sense that *Model I* uses a doubly stochastic model for the input (C_s) to the system while we use a dynamical model, which includes a neural firing piece, and such model allows to study the kind of pulsatile mechanism the body uses for hormone secretion. Also, cortisol has a negative feedback effect on the ACTH secretion [5], [7], [1], and we include the negative feedback effect of cortisol in our model while it is not included in *Model I*. Moreover, our proposed ACTH secretion model is simpler than the existing dynamical models for ACTH secretion.

III. A Feedback Control Model for Cortisol Secretion

In this section, we propose a feedback control model for cortisol secretion, which, to the best of our knowledge, is the first proposed mathematical model that includes the entire process, starting from a neural firing model for secretion of CRH in the hypothalamus to cortisol concentration in the plasma, with an output that is in agreement with the actual diurnal cortisol profile. Considering that *Model I* [1] describes the physiology and is capable of generating the fluctuations observed in the cortisol profile, we will use *Model I* to model this part of the cortisol secretion process. *Model I* [1] estimates β_I and β_C to be normal random variables with mean values 2.71 and 0.646, respectively. We will assume that these mean values are the parameter values in the described model. Moreover, cortisol has a negative feedback effect on the pituitary as well as ACTH secretion [5], [7], [1], and we include this negative feedback effect in modeling the cortisol secretion.

A. Obtaining the Input to Model I

When cortisol data is available, the cortisol level in plasma (C_p) is available and the input to *Model I* (C_s) should be estimated. The solutions to the linear time-invariant state equations in *Model I* are as follows:

$$C_a(t) = e^{-\beta_I t} C_a(t_0) + \int_0^t e^{-\beta_I (t-\tau)} C_s d\tau \ (Adrenal\ Gland) \quad (1)$$

$$C_p(t) = e^{-\beta_C t} C_p(t_0) + \int_0^t e^{-\beta_C (t-\tau)} \beta_I C_a d\tau \ (Plasma) \quad (2)$$

The integrals in the above system can be replaced by convolutions. Then, considering that the cortisol datasets are discrete, each continuous convolution can be approximated

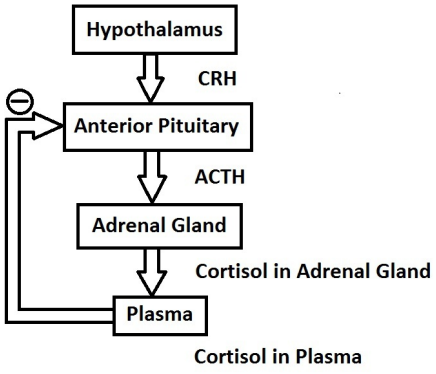

Fig. 1. Cortisol Secretion Process

by a discrete convolution. Let G_a and G_p be the Toeplitz matrices that correspond to the discrete convolution in equations (1) and (2), respectively.

$$G_a = \begin{pmatrix} e^{-\beta_I t_0} & 0 & 0 & \cdots & 0 \\ e^{-\beta_I t_1} & e^{-\beta_I t_0} & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ e^{-\beta_I t_n} & e^{-\beta_I t_{n-1}} & e^{-\beta_I t_{n-2}} & \cdots & e^{-\beta_I t_0} \end{pmatrix}$$

$$G_p = \begin{pmatrix} \beta_I e^{-\beta_C t_0} & 0 & 0 & \cdots & 0 \\ \beta_I e^{-\beta_C t_1} & \beta_I e^{-\beta_C t_0} & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \beta_I e^{-\beta_C t_n} & \beta_I e^{-\beta_C t_{n-1}} & \beta_I e^{-\beta_C t_{n-2}} & \cdots & \beta_I e^{-\beta_C t_0} \end{pmatrix}$$

Let $u_p = C_p(t_0)[e^{-\beta_C t_0} \quad \cdots \quad e^{-\beta_C t_n}]^T$ and $u_a = C_a(t_0)[e^{-\beta_I t_0} \quad \cdots \quad e^{-\beta_I t_n}]^T$. When cortisol data is available at times t_0, t_1, ... , t_n, one could rewrite equations (1) and (2) as $C_a = u_a + G_a C_s$ and $C_p = u_p + G_p C_a$.

When one has access to the cortisol data, $C_p(t_0)$ is available, and hence, u_p is a known quantity. Then, by formulating the optimization problem in (3), it is possible to solve for C_a; therefore, $C_a(t_0)$ and u_a will be known quantities, and it is possible to solve for C_s:

$$\min_{C_a \succ 0} \|C_p - u_p - G_p C_a\|^2 \ , \ \min_{C_s \succ 0} \|C_a - u_a - G_a C_s\|^2 \qquad (3)$$

The value of C_s obtained using this formulation is an estimate of the pulsatile input to the system in *Model I*.

B. Modeling the Pulsatile Input that Induces C_s Secretion

As mentioned in the previous section, C_s secretion is highly coupled to ACTH secretion, and ACTH is induced by CRH. Considering that CRH has a varying frequency secretion profile, it is possible to model CRH secretion using the extended FHN model with a two-harmonic spiking threshold (the varying frequency neural firing model described in [3]). Considering that the circadian rhythm plays an important role in the cortisol secretion, periods T=24 and T=12 could be used as the periods of such a two-harmonic function. Let v_{in} be the output of the FHN model with a two-harmonic spiking threshold. Then, let the CRH secreted be C_r=max(2.5v_{in},0). C_r induces the ACTH secretion; however, the ACTH secretion is affected by the negative feedback effect of the cortisol level. Next, we will describe how one could model this negative effect.

C. Negative Feedback Effect of Cortisol Level

Our goal is to model C_s by using a neural spiking model as well as feedback control. We postulate that the negative feedback effect of the cortisol level in plasma on ACTH secretion and cortisol secretion can be modeled using a reference trajectory. In other words, if the cortisol level is below a certain time-varying threshold, there will be ACTH secretion, and if the cortisol level is above a certain threshold, the negative feedback effect of the cortisol level prevents any ACTH secretion and hence no more cortisol will be secreted. In order to obtain such time-varying threshold, we first inspect the C_s time-series plot (obtained by solving (3)) to obtain the times at which there is a pulsatile secretion. Next, form a dataset that includes the plasma cortisol levels (C_p) corresponding to the time at which there is a pulsatile secretion in C_s. Then, using multiple regression, we fit this new dataset to a three-harmonic function of the form: $y_{thresh} = \alpha + \beta cos(\frac{2\pi t}{24}) + \gamma sin(\frac{2\pi t}{24}) + \zeta cos(\frac{2\pi t}{12}) + \kappa sin(\frac{2\pi t}{12}) + \varsigma cos(\frac{2\pi t}{2}) + \rho sin(\frac{2\pi t}{2})$

Periods 24, 12, and 2 are chosen because as mentioned before, the ultradian analysis of cortisol shows significant periods of 24 hours, 12 hours, and 2 hours [6]. The ACTH profile (A) is induced by the secreted CRH and is suppressed by the cortisol level. Hence, one could model the ACTH profile as:

$$A(t) = \begin{cases} C_r(t) & C_p \leq y_{thresh} \\ 0 & y_{thresh} < C_p \end{cases}$$

Moreover, $C_s(t) = kA(t)$, where k is a constant gain.

D. Simulation of Cortisol Secretion Model

Fig. 2 is a block diagram of the described model. We solved the inverse problem using a sample dataset and obtained parameters $\alpha, \beta, \gamma, \zeta, \kappa, \varsigma, \rho$ of y_{thresh}. Moreover, we obtained the function b that corresponds to the two-harmonic spiking threshold. Then, using these values, we simulated the 24-hour cortisol profile. In the FHN part of the model, a=100, I=1, and c=0.28 were used, and b was defined as: $b = \frac{1}{25}[10 - 6cos(\frac{2\pi}{24}(t+9)) + 3.5sin(\frac{2\pi}{24}(t+9)) - 3.5cos(\frac{2\pi}{12}(t+9)) - 1.1720sin(\frac{2\pi}{12}(t+9))]$
Moreover, we used a gain of $k = 100$ and $y_{thresh} = 6.5595 - 5.8071cos(\frac{2\pi t}{24}) - 1.1020sin(\frac{2\pi t}{24}) - 0.9184cos(\frac{2\pi t}{12}) - 2.8927sin(\frac{2\pi t}{12}) + 0.1259cos(\frac{2\pi t}{2}) + 0.6564sin(\frac{2\pi t}{2})$

Fig. 3 shows the 24-hour cortisol and ACTH profiles obtained using this simulation. This closely resembles a typical cortisol profile, i.e. cortisol level is at the highest amplitude between 8am and 10am, and declines throughout the day; then, increases rapidly through the late night (e.g. Fig. 8 in [1]).

IV. Conclusion and Future Work

In this paper, a more comprehensive model for cortisol secretion was proposed by extending the model in [1] and

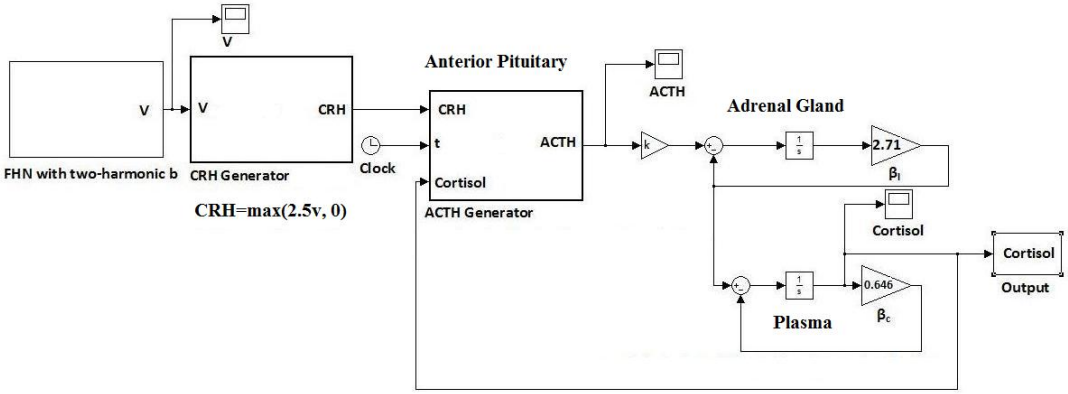

Fig. 2. Simulink Block Diagram of the Cortisol Feedback Control Model

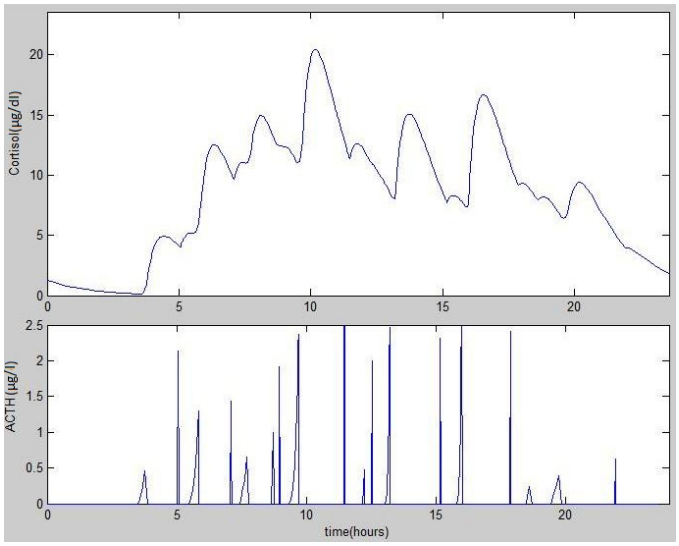

Fig. 3. Simulated 24-hour Cortisol Profile in Plasma (top) and ACTH Profile (bottom)

adding neural spiking to the model, including the negative feedback effect of cortisol, and looking at the cortisol secretion process as a tracking problem. A similar approach can be used to study growth hormone, luteinizing hormone, follicle-stimulating hormone, or thyroid hormone.

In our future work, we will obtain cortisol data to implement our feedback control model on cortisol data, and analytically investigate trackability in the cortisol secretion process. We will also add to the current feedback control model of cortisol another piece that includes the negative feedback effect of cortisol on CRH secretion and study why the body uses a pulsatile mechanism for hormone secretion, and why such a mechanism is efficient in conserving energy in the body.

ACKNOWLEDGMENTS

Rose T. Faghih would like to thank Dr. Michael Rinehart for useful discussions.

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