A Wearable Brain Machine Interface Architecture for Regulation of Energy in Hypercortisolism

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***Abstract*— Hypercortisolism is associated with tiredness and fatigue during the day and disturbed sleep at night. Our goal is to employ a wearable brain machine interface architecture to regulate one's energy in hypercortisolism. First, we present a state-space model to infer a hidden cognitive energy-related state from one's cortisol secretion patterns. Particularly, we consider circadian upper and lower bound envelope curves on cortisol levels, and timings of hypothalamic pulsatile activity underlying cortisol secretion as observations. We then use Bayesian filtering to estimate the hidden cognitive energy-related state. Finally, we close the loop using a knowledge-based control approach. In a simulation study based on experimental data, we illustrate the feasibility of designing a wearable brain machine interface architecture for energy regulation in hypercortisolism. In this architecture, we infer one's cognitive energy-related state seamlessly rather than monitoring the brain activity directly and close the loop using fuzzy control. This simulation study is a first step towards the ultimate goal of managing hypercortisolism in real-world situations.**

I. INTRODUCTION

Cortisol, a glucocorticoid hormone, is released in pulsatile manner [1], [2]. Abnormal secretion of cortisol can lead to irregular daily energy patterns [3]. An example is hypercortisolism, a disorder caused by excessive levels of cortisol. Patients with hypercortisolism (e.g., Cushing's disease) suffer from tiredness and fatigue during the day, while experiencing disrupted sleep at night [4], [5], [6]. Other symptoms associated with hypercortisolism include thirst, muscle weakness, obesity, high blood pressure, high sugar level, and sleep disorders [7], [8], [9]. Moreover, elevated cortisol levels are related to depression and psychiatric disorders [10], [11], [12]. Although Cushing's disease is occasionally treated by surgery, medical therapy is sometimes unavoidable due to the delayed or unsuccessful surgery [13], [14]. Furthermore, in case of early detection of this disease, there are medications that can be efficiently used for treatment [15], [16], [17].

Given that cortisol secretion plays an crucial role in regulating one's energy level, we relate the hidden cognitive energy-related state to one's Corticotropin-releasing hormone (CRH) secretion patterns using the state-space approach [18]. To treat hypercortisolism disease, we consider medications that can both decrease and increase the cortisol levels [15], [16]. Our main objective here is to design a wearable brain machine interface architecture [19] to control cortisol levels and achieve energy regulation.

In this regard, we first present a state-space model to infer a hidden cognitive energy-related state from one's CRH secretion patterns [18]. We then use Bayesian filtering for the state estimation process [20]. Finally, by simulating medication dynamics and employing knowledge-based control approaches, we close the loop in our proposed architecture [19]. We take advantage of the flexibility and knowledge-based nature of the fuzzy logic [19], [21] in designing control and close the loop. In this closed-loop architecture, the estimated cognitive energy-related state is the input to the controller, and the required medication timing and dosage (actuation policy) are the control outputs. Compared to brain-machine interface architectures, which collect brain signals directly, the wearable brain machine interface architecture here utilizes non-brain physiological signals [22], [23] to infer neural activity [24], [25]. The envisioned wearable brain machine interface architecture presented in Figure 1 (i) collects data from a wearable cortisol sensor, (ii) infers the underlying brain activity, (iii) models circadian upper and lower bound envelope curves on cortisol levels, (iv) estimates a hidden cognitive energy-related state, (v) models actuation dynamics, and (vi) designs closed-loop control for medication timings and dosage to regulate energy in hypercortisolism.

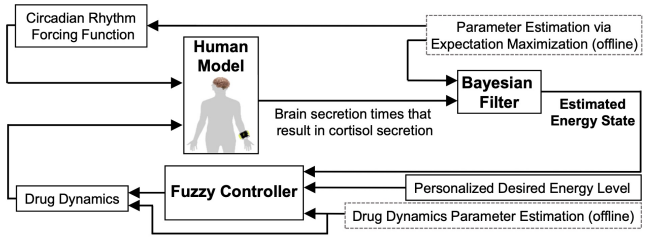

Fig. 1. Wearable Brain Machine Interface Architecture. A wearable device measures cortisol data from the human in the loop. Then, a decoder estimates the cognitive energy-related state based on brain secretion times that result in cortisol secretion, upper, and lower envelops generated using an offline expectation maximization algorithm. Finally, based on drug dynamics and a personalized target level, the controller regulates the energy-related state by suggesting proper medicines usage. The dashed lines and boxes depict the offline processes.

In this study, we first simulate multi-day cortisol data based on experimental values in the literature [26], [27]. Specifically, we simulate cortisol profiles in both healthy subjects and patients who suffer from Cushing's disease. We then present a model to simulate CRH secretion events. Next, we estimate the hidden cognitive energy-related state using Bayesian filtering. Then, we simulate medicine dynamics and

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implement fuzzy control structure. Finally, we present our closed-loop results. In particular, we consider one open-loop (i.e. a healthy subject) and two closed-loop scenarios (i.e. Cushing's patients with and without circadian rhythm in their cortisol profiles) for our analysis.

II. Methods

A. Data Simulation

Due to the lack of multi-day experimental data for both healthy subjects and Cushing's patients, following [18], [26], [27], we simulate cortisol profile data for a healthy subject and the subjects with the Cushing's disease.

1) Healthy: We simulate the cortisol profile using gamma distribution for the pulse inter-arrival time and Gaussian distribution for the pulse amplitudes. The corresponding parameters for gamma distribution are $\alpha = 54, \beta = 39$. The pulse amplitude follows a Gaussian distribution $H_k \sim \mathcal{N}(\mu_k, k_k^2)$, where $\mu_k = 6.1 + 3.93\sin\left(\frac{2\pi k}{1440}\right) - 4.75\cos\left(\frac{2\pi k}{1440}\right) - 2.53\sin\left(\frac{4\pi k}{1440}\right) - 3.76\cos\left(\frac{4\pi k}{1440}\right)$ and $k_k = 0.1\sqrt{\mu_k}$. We consider a second-order stochastic differential equation to simulate diurnal cortisol patterns [28]. To do so, we use $0.0751\,\mathrm{min}^{-1}$ and $0.0086\,\mathrm{min}^{-1}$ for cortisol infusion and clearance rates based on the median rate parameters [28].

2) Cushing's patient without circadian rhythm: Following [26], [29], inter-arrival times and the amplitudes of the pulse occurrences can be assumed to be 59 ± 11 min and 38 ± 2.5 $\mu g dL^{-1}\,\mathrm{min}^{-1}$, respectively. Considering above parameters as the mean and standard deviation in Gamma and Gaussian distributions [18], we simulate data for a Cushing's patient without circadian rhythm.

3) Cushing's patient with circadian rhythm: In some Cushing's patients, there exists circadian rhythm in their cortisol profile [29]. Compared to the other two cases, we employ $\mu_k = 38.5 + 1.93\sin\left(\frac{2\pi k}{1440}\right) - 1.6\cos\left(\frac{2\pi k}{1440}\right) - 1.5\sin\left(\frac{4\pi k}{1440}\right) - 3.5\cos\left(\frac{4\pi k}{1440}\right)$, $k_k = \frac{2.5}{\sqrt{38\mu_k}}$, and the same Gamma inter-arrival distribution to simulate data for a Cushing's patient with circadian rhythm.

Assuming a vector input of pulse timings and amplitudes, we follow the solution of coupled differential equations in regulating the secretion of cortisol outlined in [27], [28], [30] to obtain the serum cortisol profiles over five days for each simulated data-set.

B. State Estimation

Considering the simulated cortisol profile as the observation, the next step is to infer hidden cognitive energy-related state for our further analysis. We do this task using the state-space approach [18], [31]:

$$x_k = \rho x_{k-1} + u_k + \epsilon_k + I_k, \tag{1}$$

where x_k is the hidden energy-related state, u_k is the control input, $\epsilon_k \sim \mathcal{N}(0, \sigma_\epsilon^2)$ is the process noise and I_k is the forcing function that keeps the energy variations during wakefulness and sleep in a 24 h period at k-th time step [18]:

$$I_k = \sum_{i=1}^{2} m_i \sin\left(\frac{2\pi i k}{1440}\right) + n_i \cos\left(\frac{2\pi i k}{1440}\right), \tag{2}$$

where the coefficients m_i and n_i are estimated using the Expectation Maximization (EM) algorithm presented in [18]. The corresponding parameters in (2) are presented in Table I.

TABLE I

Parameters used to generate forcing function I_k in (2) .

Profile	m_1	n_1	m_2	n_2
Healthy	0.00531	0.00192	0.00031	−0.00636
Cushing's without circadian	0.00934	−0.00048	0.00359	−0.00610
Cushing's with circadian	−0.00194	−0.00086	0.00121	0.00059

We model presence or absence of the CRH pulses using Bernoulli distribution:

$$P(c_k|p_k) = p_k^{c_k}(1-p_k)^{1-c_k}, \tag{3}$$

where p_k is computed by the following logistic relationship:

$$p_k = \frac{1}{1+e^{-(\gamma_0+\gamma_1 x_k)}}. \tag{4}$$

This model relates the probability p_k of observing a CRH pulse event c_k to the energy-related state x_k through person-specific baseline parameters γ_0 and γ_1. In order to estimate x_k, we use the upper and the lower bound envelopes of the blood cortisol measurements. We label these two upper and lower bound envelopes as R_k and S_k, respectively. We assume that there exists a linear relationship between these envelopes and the corresponding state x_k:

$$R_k = r_0 + r_1 x_k + v_k, \tag{5}$$

$$S_k = s_0 + s_1 x_k + w_k, \tag{6}$$

where $v_k \sim \mathcal{N}(0, \sigma_v^2)$, $w_k \sim \mathcal{N}(0, \sigma_w^2)$, and r_0, r_1, s_0, s_1 are regression coefficients that are driven by EM algorithm [18].

Taking the CRH pulse event c_k, the upper and lower envelopes R_k and S_k as the observations, we follow the Bayesian filtering approach [32] to estimate hidden cognitive energy-related state x_k.

Prediction step:

$$\hat{x}_k = \rho x_{k-1} + I_k, \tag{7}$$

$$\hat{\sigma}_k^2 = \rho^2\sigma_{k-1}^2 + \sigma_\epsilon^2. \tag{8}$$

Update step:

$$A_k = \frac{\hat{\sigma}_k^2}{\sigma_v^2\sigma_w^2 + \hat{\sigma}_k^2(r_1^2\sigma_w^2 + s_1^2\sigma_v^2)}, \tag{9}$$

$$\begin{aligned} x_k = \hat{x}_k + A_k\Big[&\gamma_1\sigma_v^2(c_k - p_k) \\ &+ r_1^2\sigma_w^2(R_k - r_0 - r_1\hat{x}_k) \\ &+ s_1^2\sigma_v^2(S_k - s_0 - s_1\hat{x}_k)\Big], \end{aligned} \tag{10}$$

$$\sigma_k^2 = \left[\frac{1}{\hat{\sigma}_k^2} + \gamma_1^2 p_k(1-p_k) + \frac{r_1^2}{\sigma_v^2} + \frac{s_1^2}{\sigma_w^2}\right]^{-1}. \tag{11}$$

Since p_k, which is presented in (10), is related to the x_k as noted in (4), x_k is present on both sides of (10). Hence, Newton's method is employed to solve update equations. Consequently, the hidden cognitive energy-related state is estimated.

C. Drug Dynamic Parameter Estimation and Control Design

By estimating the cognitive energy-related state, the next step is to design the control algorithm for closing the loop. Based on the simulated data and studies in [13], [33], [34], we consider that two different types of medications should be suggested per day: one for regulating the energy level for daily activity (i.e. excitation effect), and one for helping subjects to sleep well at night (i.e. inhibition effect). This results in the cognitive energy-related state to have a desired circadian rhythm. In this part, based on the known medications' responses, we simulate their dynamics to include them in the control design process and close the loop.

1) Drug Dynamic Parameter Estimation: In order to simulate the effect of medication, we use a second-order state-space representation:

$$\begin{bmatrix}\dot{z}_1(t)\\ \dot{z}_2(t)\end{bmatrix} = \begin{bmatrix}-\theta_{i1} & 0\\ \theta_{i1} & -\theta_{i2}\end{bmatrix}\begin{bmatrix}z_1(t)\\ z_2(t)\end{bmatrix} + \begin{bmatrix}\eta\\ 0\end{bmatrix} q(t), \tag{12}$$

where $i = 1, 2$ denotes the type of medication/actuation that is supposed to be used for regulating the circadian cortisol rhythm. $\theta_{\mathbf{i}} = \begin{bmatrix}\theta_{i1} & \theta_{i2}\end{bmatrix}$ denotes the rise time and the decay time of each assumed medication i, respectively. In the state-space representation, $q(t) = q_i^* \, \delta(t - \tau_i^*)$ is the actuation input signal where the parameters τ^* and q^* describe the time and the dosage of the corresponding drug [28], [35]. The η term also determines if the actuation should be excitation (i.e. $\eta = +1$ for elevating the cortisol level) or inhibition (i.e. $\eta = -1$ for lowering the cortisol level). Solving the state-space equation (12) and considering the output equation $y(t) = z_2(t)$, we derive the output at each time step j as:

$$y_j = a_j y_0 + \boldsymbol{b_j}\mathbf{q}. \tag{13}$$

where $a_j = e^{-\theta_{i2} j}$ and $\boldsymbol{b_j} = \frac{\theta_{i1}}{\theta_{i1}-\theta_{i2}}\big[(e^{-\theta_{i2} j} - e^{-\theta_{i1} j}) \;\; (e^{-\theta_{i2}(j-1)} - e^{-\theta_{i1}(j-1)}) \;\; \cdots \;\; (e^{-\theta_{i2}} - e^{-\theta_{i1}}) \;\; \underbrace{0 \;\; \cdots \;\; 0}_{N-j}\big]'$; the vector input $\mathbf{q}$ consists of one non-zero element (i.e. $\mathbf{q} = [q_1 \cdots q_N]$, where $q_j = 0, \forall j$ except the one element q_i^* at time τ_i^*). Considering the output for whole time horizon N, we form the vector representation $\mathbf{y}$ as:

$$\mathbf{y} = \mathbf{A}_\theta y_0 + \mathbf{B}_\theta \mathbf{q}, \tag{14}$$

where $\mathbf{y} = \begin{bmatrix} y_1 & y_2 & \cdots & y_N \end{bmatrix}'$, $\mathbf{A}_\theta = \begin{bmatrix} a_1 & a_2 & \cdots & a_N \end{bmatrix}'$, $\mathbf{B}_\theta = \begin{bmatrix} \boldsymbol{b_1} & \boldsymbol{b_2} & \cdots & \boldsymbol{b_N} \end{bmatrix}'$.

Given that in our formulation $\mathbf{q}$, we consider the constraint $||\mathbf{q}||_0 = 1$ in the following parameter estimation process. To find the optimum parameters, we solve the following optimization problem:

$$\min_{\substack{\theta_{\mathbf{i}}, \mathbf{q} \\ ||\mathbf{q}||_0 = 1}} \; J = \frac{1}{2}||\mathbf{y} - \mathbf{A}_\theta y_0 - \mathbf{B}_\theta \mathbf{q}||_2^2. \tag{15}$$

Consequently, by knowing $\mathbf{y}$ we find the optimal $\mathbf{A}_\theta$, $\mathbf{B}_\theta$ (i.e. contain $\theta_{\mathbf{i}}$), and $\mathbf{q}$ to derive the actuation dynamics [36]. Employing the actuation dynamics, the control system decides the dosage and the time of desired medicine.

2) Control Design: Fuzzy logic, as an intelligent approach, is a powerful bridge from the expertise inference to the real world [21]. In fact, fuzzy control systems employ knowledge about the system and the actuation mechanism to perform inference and make real-time decisions [19]. Each fuzzy control system consists of four main parts: fuzzifier, rule base, inference engine, and defuzzifier. Using fuzzification, the system translates the linguistic input variables to the crisp values. By forming the comprehensive rule base, all the cases will be covered [37]. Consequently, rule base enables us to impose all required constraints in the control design process. Employing the inference engine, fuzzy output will be generated in real-time. The very last part is defuzzification which converts the fuzzy output to the actual control decision. In this specific problem, the input of the fuzzy control system is the estimated cognitive energy-related state, while the control output is the time and the dosage of the required medicine.

Analyzing the simulated cortisol profiles, we need to regulate the energy-related state in two stages: first stage is day time regulation of energy to help a subject have enough energy for daily activity, and the second stage is night time regulation of energy to help the patients sleep well. As a result, we set to have two control inputs per day: one in the morning which increases cortisol level, and one that is used in the evening to lower the cortisol which results in better sleep cycle to ultimately solve sleep disorder in hypercortisolism. We generate rule base and membership functions of the fuzzy controller using the insight about the system which is generated in simulations. The corresponding membership functions are presented in Figure 2.

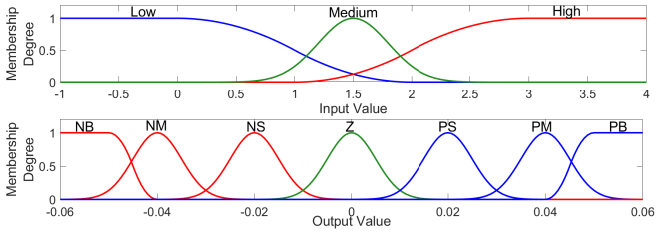

Fig. 2. Input and Output Membership Functions. The top-panel shows the input membership functions (i.e. estimated energy-related state). The bottom-panel shows the membership functions for the output (i.e. control signal u_k). The abbreviations P, N, Z, S, M, and B stand for "Positive," "Negative," "Zero," "Small," "Medium," and "Big", respectively.

As observed in this figure, we create three membership functions for the input and seven membership functions for the output values to cover all conditions in the rule base. We form rules such as:

- If the estimated energy state is *low*, and the time is *early* in the morning then control is *positive big*;
- If the estimated energy state is *high*, and the time is *early* in the morning then control is *positive small*;
- If the estimated energy state is *medium*, and the time is *early* in the morning then control is *positive medium*;
- If the estimated energy state is *high*, and the time is *early* in the evening then control is *negative big*.

In our proposed fuzzy controller, we use *Mamdani inference engine* [38] and *centroid* defuzzification method [37].

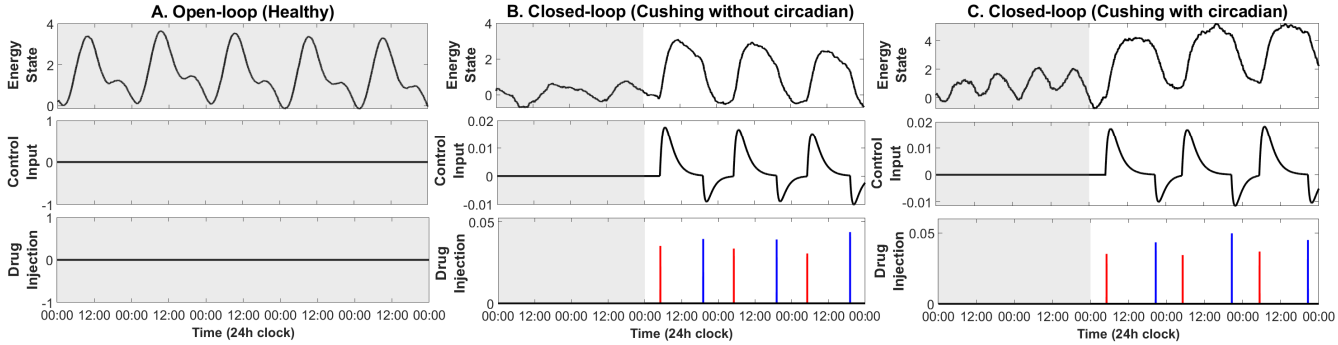

Fig. 3. **Simulated Energy Regulation Results.** Panel A displays the open-loop results. Panel B shows closed-loop results for the Cushing's patients without circadian rhythm, while panel C shows closed-loop results for the Cushing's patients with circadian rhythm. In each panel: the top sub-panel shows the estimated cognitive energy-related state, the middle sub-panel displays the control input, and the bottom sub-panel depicts the drug injections. Red pulses are related to excitation and the blue pulses are related to inhibition. The grey background indicates open-loop simulation (i.e. $u = 0$), while white background implies the closed-loop results.

III. Results

In this section, we present the results for three different cases: open-loop healthy subject and closed-loop Cushing's patients with and without circadian rhythm. In each case, we present the control signal and the controlled cognitive energy-related state (Figure 3).

A. Open-loop (Healthy subject)

We aim to track one's cognitive energy-related state when no control input is applied $(u_k = 0)$. In the upper sub-panel of panel A in Figure 3, it is depicted that the estimated energy state is at its peak during the working time (06:00 - 16:00), and it drops during the night.

B. Closed-loop (Cushing's patient without circadian rhythm)

We simulated five days; during the first two days no control was implemented. In the closed-loop architecture (last three days), our system detects low energy during the wake time; then, the control signal increases the energy state for the day time activity (Red pulses in the third sub-panel of panel B in Figure 3). On the other hand, the control decreases the energy state during the sleep time (i.e. 22:00 - 06:00) (Blue pulses in the third sub-panel of panel B in Figure 3).

C. Closed-loop (Cushing's with circadian rhythm)

Similar to case B, our system detects energy dysregulation both during wake and sleep. Then, the control algorithm regulates the cognitive energy-related state (Panel C of Figure 3).

IV. Discussion and Conclusions

With the goal of energy regulation in hypercortisolism, we proposed wearable brain machine interface architecture, by first simulating cortisol profile data, then employing the state-space approach. Then, we related CRH secretion observation to one's hidden cognitive energy-related state. Thereafter, we modeled drug dynamics and used a fuzzy control approach to design the actuation policy and regulate the energy state. To the best of our knowledge, this study is one of the very first simulations in the area of regulating patients' cognitive energy-related state by using cortisol profile measurements. We illustrated that we can achieve energy regulation in hypercortisolism, and our simulated results indicate that the proposed method has great potential to be implemented and used in daily life.

In the first case, we showed how our approach can track a healthy person's cognitive energy-related state by taking the cortisol profile as the observation. Then, for the case of Cushing's disease, we designed a colsed-loop approach for energy regulation using medications. When we observe a low level of energy in the morning, excitatory medication is used to elevate cortisol levels. Medications such as Mifepristone [33], [39], [40], [41] and Benzodiazepin [42] may be used to increase the cortisol level in the morning. On the other hand, the problem of insomnia (i.e. having sleep issues during nights) might be caused by high serum cortisol level in the evenings, due to lack of normal diurnal variation in the cortisol secretion. Medications such as Ketoconazole [43] and Metyrapone [34] may be used to inhibit cortisol secretion. These medication could be used to lower cortisol levels in the evening to help lower the energy during sleep to avoid unwanted wake at night.

Future work would include incorporating all possible medications and designing the control algorithms with the capability to choose from them. This system design could potentially enable cortisol regulation efficiently with minimal medical side-effects to eventually treat hypercortisolism in real-world situations.

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