A System Theoretic Investigation of Cortisol Dysregulation in Fibromyalgia Patients with Chronic Fatigue

Divesh Deepak Pednekar, *Student Member, IEEE*, Md. Rafiul Amin, *Student Member, IEEE*, Hamid Fekri Azgomi, *Student Member, IEEE*, Kirstin Aschbacher, Leslie J. Crofford, and Rose T. Faghih*, *Member, IEEE*

***Abstract*— Fibromyalgia Syndrome (FMS) and Chronic Fatigue Syndrome (CFS) are complex medical conditions with similar symptoms such as anxiety, fatigue, depression, headaches, muscle aches and joint pain. The etiology of both these syndromes is unknown. The objective of this study is to characterize FMS, both in the presence and in the absence of CFS, by analyzing variations in cortisol secretion patterns, timings, amplitudes, and the number of the underlying pulses as well as infusion and clearance rates. The comparison is performed against matched healthy control subjects. We estimate the hormonal secretory events by deconvolving cortisol data using a two-step coordinate descent approach. The first step implements a sparse recovery approach to infer the amplitudes and the timings of the cortisol secretion events from limited cortisol hormone data. The main advantage of this method is estimating the cortisol secretory events using a system theoretic approach. The second step is to estimate the physiological system parameters (i.e. infusion and clearance rates). This approach has been verified on healthy individuals previously. Our results show that the clearance rate of cortisol by the liver is relatively lower in patients as compared to the matched healthy individuals. This suggests that there is a relatively higher accumulation of serum cortisol in patients when compared to matched healthy subjects.**

I. Introduction

Fibromyalgia Syndrome (FMS), also known as fibrositis syndrome, is a complex medical condition characterized by widespread musculoskeletal pain in combination with tenderness at 11 or more out of the 18 specific tender points [1]. It affects about 2% of the population and is more common in females than in males [2]. The prevalence of this syndrome increases with age and is highest in 60-79 age group. Chronic Fatigue Syndrome (CFS) is defined by the Centers for Disease Control and Prevention (CDC) as a complex condition characterized by prolonged disabling fatigue [3]. Similar to FMS, CFS is also more prevalent in females (75.4% of all CFS patients are females) than in males [4]. Bakken *et al.* [4] observed two distinct peaks for age groups between 10-19 and 30-39 years, being true for both genders. Different symptoms associated with FMS include anxiety, difficulty sleeping, pain, tender points, fatigue, depression, morning stiffness and decreased cognitive function, while those associated with CFS include headaches, sore throats, fever, muscle aches and joint pain [5], [2], [6].

Widespread musculoskeletal pain is the most common symptom that patients with CFS and FMS share [5]. Persistent stimulation of psychological stress responses have the potential to affect systemic cortisol secretion over time [7], [8]. As FMS and CFS patients are more prone to such psychological stress, they might have altered cortisol levels as compared to healthy individuals. Therefore, in this study, we hypothesize that understanding cortisol patterns in both these syndromes may be a crucial factor in characterizing FMS and CFS in order to generate testable hypotheses about causal mechanisms. An individual's response to psychological stress induces significant hypothalamic-pituitary-adrenal (HPA) axis responses across all ages and genders [9]. HPA axis activity is accomplished by the secretion of corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) from the hypothalamus. This triggers the secretion of adrenocorticotropic hormone (ACTH) from the pituitary, which finally simulates the secretion of glucocorticoids (cortisol is a type of glucocorticoid) [10]. A negative feedback mechanism prevents cortisol overproduction [11]. If there is any dysfunction with the above mechanism, the person is more likely to develop CFS and/or FMS.

Various hypotheses have been investigated concerning cortisol levels in FMS. Klerman *et al.* [12], found no differences in the circadian variation of serum cortisol levels in patients with FMS compared to healthy controls. On the contrary, Riva *et al.* [13] state that FMS is associated with hypocortisolism. These differences can be due to variations in experimental procedures such as the steps taken to minimize responses to environmental stimuli (e.g. light, rest, medication) or the presence of secondary syndromes such as CFS. For CFS though, most studies suggest lower serum cortisol levels [14], [15]. As a result, an investigation of cortisol patterns becomes essential for a better characterization of FMS and CFS. Cortisol patterns are highly influenced by the circadian rhythm of an individual [16]. Since different individuals have distinctive circadian rhythms, the cortisol patterns of different individuals are, therefore, distinct. Traditionally, in analyzing cortisol data, an average of the cortisol patterns of different individuals is considered; this could lead to the loss of some

Divesh Deepak Pednekar, Md. Rafiul Amin, Hamid Fekri Azgomi, and Rose T. Faghih are with the Department of Electrical and Computer Engineering at the University of Houston, Houston, TX 77004 USA (e-mail:{dpednekar, mamin, hfekriazgomi, rtfaghih}@uh.edu). Kirstin Aschbacher is with the Division of Cardiology at the University of California, San Francisco, CA 94158 USA (e-mail:Kirstin.Aschbacher@ucsf.edu). Leslie J. Crofford is with the Division of Rheumatology & Immunology Vanderbilt University, Nashville, TN 37232 USA (e-mail: leslie.j.crofford@vumc.org). This work was supported in part by NSF grant 1755780 – CRII: CPS: Wearable-Machine Interface Architectures.

*Rose T. Faghih served as the senior author.

critical information in cortisol data. To avoid such cases in this study, we plan to consider each subject's cortisol pattern separately using a system theoretic approach.

As the first step in understanding the etiology of these syndromes, we analyze the cortisol response in both patients and healthy control subjects. Healthy control subjects with normal physiology have a cortisol response with variations due to circadian modulation of the amplitude of secretory events and ultradian modulation of the timing of secretory events [16]. Circadian rhythm of every organism depends on various factors such as body temperature, exposure to light, diet and posture [17]. Since cortisol secretary events are a function of the circadian rhythm [16], and each individual has a distinct circadian rhythm, we consider every patient's serum cortisol response separately. The studies in [18] and [19] use mathematical modeling to understand HPA behavior and to characterize FMS patients [18]. Physiological evidence from investigation of human subjects shows that the diurnal variations in blood cortisol levels are a result of three factors: (I) ultradian modulation of the timings of hormonal secretory events; (II) circadian alteration of the amplitudes of these events; and (III) infusion rate of cortisol into blood by the adrenal glands and clearance rate of cortisol by the liver [20]. We use the model and deconvolution algorithm provided by Faghih *et al.* [21], [22], [23], [24], [25] to investigate cortisol levels in both adrenal glands and serum, as it also allows us to estimate the amplitude, number and timing of hormonal secretary events along with the model parameters. According to this algorithm, the sparsity characteristic of the hormone pulses is exploited to recover the timings and the amplitudes of hormone pulses using compressed sensing. A coordinate descent approach is used to estimate the cortisol secretory events and model parameters. Similar to [21], we use generalized cross-validation to find the number of pulses such that there is a balance between the sparsity level and residual error. The estimated hormonal secretory events and model parameters are then used to compare the cortisol variations in patients and matched healthy subjects.

II. Methods

A. Dataset

In this study, we use the serum cortisol level data of the patients suffering from FMS only or both FMS and CFS, and their matched healthy control subjects [14]. All subjects are between 18-65 years of age. They have no significant medical conditions other than FMS or both FMS and CFS. As mentioned earlier in the introduction, FMS is more prevalent in females, therefore, the FMS dataset in [14] contains only measurements from female subjects. Healthy control subjects and patients were matched according to their age and menstrual status.

This study was carried out in a controlled environment. The subjects were familiarized to the study environment at least two months prior to the commencement of the study. The subjects were acquainted with the blood transfusion process to lower any disturbances in their circadian rhythm during the study. All subjects were admitted the evening prior to taking samples. The 24-hour cortisol level measurements started at 9 a.m. The sleep period of all subjects was between 11 p.m. to 8 a.m. Blood samples (2.8 ml) were collected every 10 minutes for the next 24 hours. Duplicate serum ACTH samples were quantified using a dual-immunoradiometric assay and the serum cortisol concentrations were measured by radioimmunoassay. The data includes 72 subjects (36 age-matched healthy control subjects and 36 patients) [14]. Informed consent was obtained from healthy subjects and patients based on the approval by the institutional review board of the University of Michigan. In this research, we consider the cortisol data of patients suffering from FMS only and from both FMS and CFS. Here, we study 8 subject pairs, out of which 3 pairs have patients with FMS only and the other 5 subject pairs have patients suffering from both FMS and CFS.

B. Model Formulation

According to Faghih *et al.* [21], the sparse nature of the hormonal secretory events and other physiological constraints make it possible to recover and estimate the amplitudes and timings of the secretory events as well as the physiological system parameters. The rate of change of cortisol concentration in the adrenal glands is equal to the difference between the rate of cortisol synthesis and the infusion rate of cortisol into the blood from the adrenal glands. Similarly, the rate of change of cortisol concentration in the blood is equal to the difference between the cortisol infusion rate from the adrenal glands into the blood and the rate at which the liver clears cortisol [20]. We use the cortisol secretion dynamics model in [21] which is represented as follows:

$$\frac{dx_1(t)}{dt} = -\phi_1 x_1(t) + u(t) \qquad \text{(Adrenal Glands)} \qquad (1)$$

$$\frac{dx_2(t)}{dt} = \phi_1 x_1(t) - \phi_2 x_2(t) \qquad \text{(Serum)} \qquad (2)$$

where $x_1(t)$ is the cortisol concentration in the adrenal glands, $x_2(t)$ is the serum cortisol concentration, and ϕ_1 and ϕ_2 are model parameters which represent the infusion rate of cortisol from the adrenal glands into the blood and the clearance rate of cortisol by the liver (clearance rate here differs from the way biologists assess phenomena such as clearance through functional in vitro assays or in vivo tests), respectively. The input $u(t)$ represents the hormone pulses that result in cortisol secretion, i.e. $u(t) = \sum_{j=1}^{N} q_j \delta(t - \tau_j)$ where q_j represents the amplitude of a hormone pulse initiated at time τ_j; q_j is a positive value where there is a hormone pulse and zero if there is no hormone pulse. We assume that the hormone pulses may occur at integer minutes, i.e., there are 1440 different locations for the occurrence of hormone pulses in 24 hours (N = 1440) [21]. Blood was collected every 10 minutes, for M samples (M = 144). The output which refers to the measurement is represented as follows:

$$y_{t_i} = x_2(t_i) + v_{t_i} \qquad (3)$$

where y_{t_i} and v_{t_i} represent the observed serum cortisol level

and the measurement error in the i^{th} sample, respectively. Considering that the initial condition of the cortisol concentration in the adrenal glands and blood are zero (due to *de novo* cortisol synthesis) and y_0, respectively, the system can be represented as,

$$\boldsymbol{y} = \boldsymbol{A_\phi} y_0 + \boldsymbol{B_\phi} \boldsymbol{u} + \boldsymbol{v} \tag{4}$$

where $\boldsymbol{y} = \begin{bmatrix} y_{t_{10}} & y_{t_{20}} & \cdots & y_{t_{10M}} \end{bmatrix}'$, $\boldsymbol{\phi} = \begin{bmatrix} \phi_1 & \phi_2 \end{bmatrix}'$, $\boldsymbol{A_\phi} = \begin{bmatrix} a_{t_{10}} & a_{t_{20}} & \cdots & a_{t_{10M}} \end{bmatrix}'$, $\boldsymbol{B_\phi} = \begin{bmatrix} b_{t_{10}} & b_{t_{20}} & \cdots & b_{t_{10M}} \end{bmatrix}'$, $\boldsymbol{u} = \begin{bmatrix} q_1 & q_2 & \cdots & q_N \end{bmatrix}'$, $\boldsymbol{v} = \begin{bmatrix} v_{t_{10}} & v_{t_{20}} & \cdots & v_{t_{10M}} \end{bmatrix}'$, $a_{t_i} = e^{-\phi_2 i}$ and $\boldsymbol{b_{t_i}} = \begin{bmatrix} \frac{\phi_1}{\phi_1-\phi_2}(e^{\phi_2 i} - e^{\phi_1 i}) & \frac{\phi_1}{\phi_1-\phi_2}(e^{\phi_2(i-1)} - e^{\phi_1(i-1)}) & \cdots & \frac{\phi_1}{\phi_1-\phi_2}(e^{\phi_2} - e^{\phi_1}) & \underbrace{0 \quad \cdots \quad 0}_{N-i} \end{bmatrix}'$.

C. Estimation

To estimate the model parameters, we assume that the infusion rate of cortisol from the adrenal glands is at least four times the clearance rate of cortisol by the liver (i.e., $4\phi_2 \leq \phi_1$) [21]. Also, previous studies suggest that there are 15 to 22 secretory events (i.e., $15 \leq ||\boldsymbol{u}||_0 \leq 22, \boldsymbol{u} \geq 0$) in 24 hours [20], [16]. We can therefore state this optimization problem as,

$$\min_{\substack{\boldsymbol{u}\geq 0 \\ \boldsymbol{R\phi}\leq \boldsymbol{s}}} \boldsymbol{J_\lambda(\phi, u)} = \frac{\mathbf{1}}{\mathbf{2}}||\boldsymbol{y} - \boldsymbol{A_\phi y_0} - \boldsymbol{B_\phi u}||_{\mathbf{2}}^{\mathbf{2}} + \boldsymbol{\lambda}||\boldsymbol{u}||_{\boldsymbol{p}}^{\boldsymbol{p}} \tag{5}$$

where $$\boldsymbol{R} = \begin{bmatrix} -1 & 4 \\ -1 & 0 \\ 0 & -1 \end{bmatrix}, \quad \boldsymbol{s} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}.$$

λ is the regularization parameter. λ can be chosen in such a way that the sparsity level of $\boldsymbol{u}$ is within the physiologically plausible range. Using a coordinate descent approach this problem can be solved using the following steps until convergence is achieved:

$$\boldsymbol{u^{(k+1)}} = \mathbf{arg}\min_{\boldsymbol{u}\geq \mathbf{0}} \boldsymbol{J_\lambda(\phi^{(k)}, u)} \tag{6}$$

$$\boldsymbol{\phi^{(k+1)}} = \mathbf{arg}\min_{\boldsymbol{R\phi}\leq \mathbf{s}} \boldsymbol{J_\lambda(\phi, u^{(k+1)})} \tag{7}$$

The optimization problem in (6) is a sparse recovery problem and can be solved efficiently using an Iterative Re-weighted Least Square (IRLS) approach. A variant of the IRLS algorithm is the FOCal Under-determined System Solver (FOCUSS) [26]. We use FOCUSS+ [27], an extension of the FOCUSS algorithm, which solves for non-negative solutions. The combination of the Generalized Cross-Validation (GCV) technique and FOCUSS+ enables us to find a reasonable choice for λ which further helps us to filter out noise to solve for $\boldsymbol{u}$ [21], [28].

The algorithm is as follows:

Algorithm 1 Deconvolution Algorithm

1: Initialize $\bar{\boldsymbol{\phi}}^{\mathbf{o}}$ by sampling a uniform random variable z on [0,1] and let $\bar{\boldsymbol{\phi}}^{\mathbf{o}}$=[$z$ $\frac{z}{4}$].
2: **for** `r= 1,2,3,...,30` **do**
3: Set $\bar{\boldsymbol{\phi}}$ equal to $\bar{\boldsymbol{\phi}}^{r-1}$; using FOCUSS+ [27], solve for $\bar{\boldsymbol{u}}^{\boldsymbol{r}}$ by initializing the optimization problem in (6) at a vector of all ones
4: Set $\bar{\boldsymbol{u}}$ equal to $\bar{\boldsymbol{u}}^{\boldsymbol{r}}$; using the interior point method, solve for $\bar{\boldsymbol{\phi}}^{\boldsymbol{r}}$ by initializing the optimization problem in (7) at $\bar{\boldsymbol{\phi}}^{\boldsymbol{r-1}}$
5: **end for**
6: Initialize $\bar{\boldsymbol{u}}^{\mathbf{0}}$ and $\bar{\boldsymbol{\phi}}^{\mathbf{0}}$ by setting them equal to $\bar{\boldsymbol{u}}^{\boldsymbol{r}}$ and $\bar{\boldsymbol{\phi}}^{\boldsymbol{r}}$, respectively
7: **while** until convergence **do**
8: Set $\bar{\boldsymbol{\phi}}$ equal to $\bar{\boldsymbol{\phi}}^{\boldsymbol{m-1}}$; using GCV-FOCUSS+ [21], solve for $\bar{\boldsymbol{u}}^{\boldsymbol{m}}$ by initializing the optimization problem (6) at $\bar{\boldsymbol{u}}^{\boldsymbol{m-1}}$
9: Set $\bar{\boldsymbol{u}}$ equal to $\bar{\boldsymbol{u}}^{\boldsymbol{m}}$; using the interior point method, solve for $\bar{\boldsymbol{\phi}}^{\boldsymbol{m}}$ by initializing the optimization problem in (7) at $\bar{\boldsymbol{\phi}}^{\boldsymbol{m-1}}$
10: **end while**
11: Repeat the above steps for several initializations and set the estimated model parameter $\overline{\boldsymbol{\phi}}$ and input $\overline{\boldsymbol{u}}$ equal to values that minimize J_λ in (5).

After we estimate the model parameter $\boldsymbol{\phi}$ and cortisol pulses $\boldsymbol{u}$, we analyze the estimated data. Analysis for phase difference included the study of the upper and lower envelopes of the cortisol data. The upper and lower envelopes are harmonic in nature because of the circadian rhythm of cortisol secretion and can be written as a sum of significant harmonics [29] as:

$$\begin{aligned} h_\psi(t_i) = h_{\psi,1} + h_{\psi,2}\sin(\omega t_i/N) + h_{\psi,3}\cos(\omega t_i/N) \\ + h_{\psi,4}\sin(2\omega t_i/N) + h_{\psi,5}\cos(2\omega t_i/N) \end{aligned} \tag{8}$$

where $\omega = 2\pi$ and $\psi \in \{\text{low}, \text{up}\}$. We formulate two optimization problems for estimating the coefficients in (8) to find the upper and lower envelopes of the cortisol data. For the lower envelope, the optimization formulation is given as

$$\min_{\boldsymbol{h}_{\text{low}}} ||\boldsymbol{y} - \boldsymbol{D}\boldsymbol{h}_{\text{low}}||_2^2 \qquad \text{s.t.} \quad \boldsymbol{D}\boldsymbol{h}_{\text{low}} \leq \boldsymbol{y} \tag{9}$$

For the upper envelope, the optimization formulation is given as

$$\min_{\boldsymbol{h}_{\text{up}}} ||\boldsymbol{y} - \boldsymbol{D}\boldsymbol{h}_{\text{up}}||_2^2 \qquad \text{s.t.} \quad \boldsymbol{D}\boldsymbol{h}_{\text{up}} \geq \boldsymbol{y} \tag{10}$$

where, $\boldsymbol{h_\psi} = \begin{bmatrix} h_{\psi,1} & h_{\psi,2} & h_{\psi,3} & h_{\psi,4} & h_{\psi,5} \end{bmatrix}$, $\boldsymbol{D} = \begin{bmatrix} d_1 & d_2 & d_3 & d_4 & d_5 \end{bmatrix}$, $d_1 = \begin{bmatrix} 1 & 1 & 1 & \cdots & 1 \end{bmatrix}'$, $\boldsymbol{d}_2 = \begin{bmatrix} \sin(2\pi t_{10}/N) & \sin(2\pi t_{20}/N) & \cdots & \sin(2\pi t_{10M}/N) \end{bmatrix}'$, $\boldsymbol{d}_3 = \begin{bmatrix} \cos(2\pi t_{10}/N) & \cos(2\pi t_{20}/N) & \cdots & \cos(2\pi t_{10M}/N) \end{bmatrix}'$, $\boldsymbol{d}_4 = \begin{bmatrix} \sin(4\pi t_{10}/N) & \sin(4\pi t_{20}/N) & \cdots & \sin(4\pi t_{10M}/N) \end{bmatrix}'$ and $\boldsymbol{d}_5 = \begin{bmatrix} \cos(4\pi t_{10}/N) & \cos(4\pi t_{20}/N) & \cdots & \cos(4\pi t_{10M}/N) \end{bmatrix}'$

We can further express (8) as:

$$\begin{aligned} h_\psi(t_i) = A_{\psi,1} + A_{\psi,2}\sin(\omega t_i/N + \theta_{\psi,1}) \\ + A_{\psi,3}\sin(2\omega t_i/N + \theta_{\psi,2}) \end{aligned} \tag{11}$$

where, $A_{\psi,1} = h_{\psi,1}$, $A_{\psi,2} = \sqrt{h_{\psi,2}^2 + h_{\psi,3}^2}$, $A_{\psi,3} = \sqrt{h_{\psi,4}^2 + h_{\psi,5}^2}$, $\theta_{\psi,1} = \tan^{-1}(\frac{h_{\psi,3}}{h_{\psi,2}})$ and $\theta_{\psi,2} = \tan^{-1}(\frac{h_{\psi,5}}{h_{\psi,4}})$.

III. Results

Figure 1 shows the comparison between the measured and reconstructed serum cortisol levels of patients and corresponding matched healthy subjects. It shows the estimated amplitudes and timings of hormonal secretory events, for both patients and matched healthy subjects. The amplitude variations of the pulses are demonstrated by the circadian rhythm of underlying cortisol release, and the variations in the timings are due to the ultradian rhythm [20]. The black diamonds in Figure 1 represent the measured cortisol level obtained from blood samples. After deconvolution we obtain the hormone secretion pulses $\boldsymbol{u}$ (blue vertical lines in Figure 1), which are used to obtain the reconstructed signal (red curve in Figure 1). The number of estimated hormone secretion events for all subjects are within physiologically plausible ranges with a square of the multiple correlation coefficient (R^2) above 0.86.

TABLE I: **The Estimated Model Parameters for Patients and Matched Healthy Control Subjects.**

Subject	Healthy		Patient	
	ϕ_1 (min^{-1})	ϕ_2 (min^{-1})	ϕ_1 (min^{-1})	ϕ_2 (min^{-1})
1	0.2687	0.0097	0.1833	0.0097
2	0.1655	0.0133	0.1909	0.0104
3	0.2178	0.0066	0.3681	0.0044
4	0.1968	0.0083	0.2282	0.0065
5	0.1477	0.0103	0.2394	0.0072
6	0.2767	0.0073	0.2727	0.0069
7	0.1482	0.0048	0.1042	0.0066
8	0.1397	0.0076	0.00981	0.0074

Table I shows the estimated model parameters obtained from deconvolution of experimental cortisol measurements. The model parameters obtained are the serum cortisol infusion rate (ϕ_1) and the clearance rate (ϕ_2).

Figure 2 shows the upper and lower envelopes of the cortisol pattern of both a healthy subject and a patient using the optimization formulation in (9) and (10), respectively.

Figure 3 shows the sample distribution of the paired differences of the clearance rate of cortisol by liver in the left box-plot. The median for this box-plot is greater than zero. Performing Wilcoxon signed-rank test on the $\phi_2^{\text{healthy}} - \phi_2^{\text{patient}}$ sample distribution revealed that the differences between the clearance rates of the healthy control subjects and patients have median difference significantly greater than zero using a one tailed test ($p = 0.0294$).

Additionally, Figure 3 shows the sample distribution of the paired differences of the hormonal secretion events during sleep in the central box-plot respectively. The median for this box-plot is greater than zero. Similarly a Wilcoxon signed-rank test on the sample distribution the number of pulses for healthy subjects and patients during the sleep cycle revealed that the median difference is significantly greater than zero using a one tailed test ($p = 0.0364$).

Lastly,the right box-plot in Figure 3 shows the sample distribution of the paired differences of the phase change in the upper envelope for the healthy subjects and patients (i.e. $\theta_{\text{up},1}^{\text{healthy}} - \theta_{\text{up},1}^{\text{patient}}$) illustrated in Figure 2. The median for this box-plot is greater than zero. Similar to earlier cases, Wilcoxon signed-rank test on the phase differences of the lower harmonics of upper envelope between healthy controls and patients ($\theta_{\text{up},1}^{\text{healthy}} - \theta_{\text{up},1}^{\text{patient}}$) revealed that the sample distribution of phase differences have median significantly greater than zero using a one tailed test ($p = 0.0391$).

IV. Discussion

A complete model for description of cortisol variations must include all intrinsic parameters such as forward and backward linkages between the hypothalamus, anterior pituitary, adrenal gland, and liver as well as extrinsic factors like stress, sleep, light and food. A simultaneous study of all these events is challenging in humans. Therefore, Brown *et al.* [20] suggest that a minimal model can be devised for healthy individuals and patients. The model used in [21] is based on the stochastic model of diurnal cortisol patterns provided in [20]. They successfully implemented this model for simulated cortisol data. Similarly, Faghih *et al.* [21] successfully developed a deconvolution algorithm based on this model and verified this for cortisol data from 10 healthy female subjects. Both these studies obtained good fits suggesting the validity of this model for estimation.

From our results and statistical analysis, it is evident that for this controlled environment, the clearance rate of cortisol by the liver in patients is found to be relatively lower than that of matched healthy subjects. This suggests that since the blood cortisol in healthy control subjects is getting cleared at a faster rate as compared to the matched patients they show a relatively lower cortisol concentration. The liver produces C-reactive protein (CRP) and inflammatory cytokines [18]. Hence, the liver could be triggering neuroinflammatory responses via afferent nervous system pathways. Cortisol uses phosphorylation (glucocorticoid receptor) for feedback signaling, but cytokines can weaken the receptor; thus, reciprocal effects stay the same [18].

We also aim to understand how the hormonal secretory event behavior in patients deviates from that of healthy subjects. To investigate if there are any differences between the FMS patients and healthy subjects, we calculate the number of pulses (l_0-norm), the sum of amplitudes (l_1-norm), and energy (l_2-norm) of $\boldsymbol{u}$ as well as the time interval between pulses. No consistent differences were observed. We further perform analysis to check if there is any delay in the ultradian rhythm of the FMS patients as compared to the healthy control subjects. In this regard, we check the baseline of the upper and lower envelopes, but there was no significant difference. We also obtain the l_0-norm, l_1-norm and l_2-norm of $\boldsymbol{u}$ in the wake and sleep cycles of all patients and healthy control subjects. As mentioned earlier, statistical analysis shows that the patients have a relatively

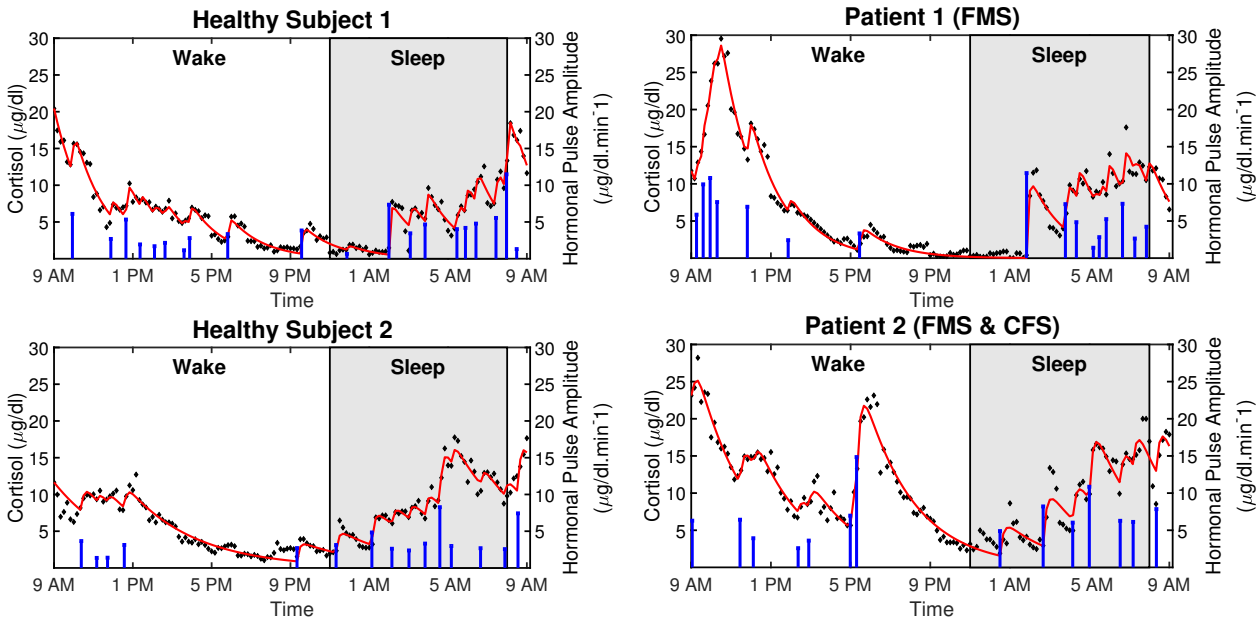

Fig. 1: **Comparison between Deconvolved Experimental Twenty-Four-Hour Cortisol Levels in a Matched Pair consisting of a Healthy Control Subject and a Patient.** Each subplot shows the measured 24-hour cortisol time series (black diamonds), the reconstructed cortisol levels (red curve), the estimated pulse timings and amplitudes (blue vertical lines).

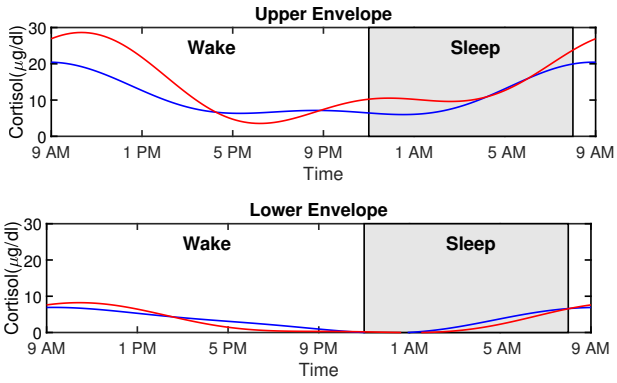

Fig. 2: **Comparison between Upper and Lower Envelopes of a Healthy Control Subject and a Patient.** Each subplot shows the comparison between the patient (the red curve) and the corresponding age-matched healthy control subject (the blue curve).

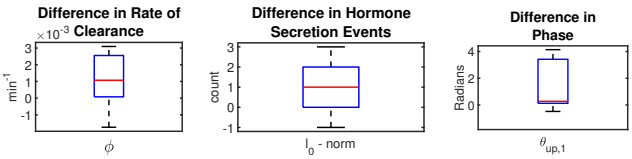

Fig. 3: **Box-plot of Paired Differences of the Clearance Rate, the Number of Hormone Secretion Events during Sleep and the Phase.** Left, central and right subplots, respectively illustrate the sample distribution of the paired differences of the clearance rate, the number of hormone secretion events (during sleep) and the phase, depicting the median (red line), the lower (Q1) to upper (Q3) quartile range (blue rectangle), and 9 to 91 percentile range (black line and black dashed line).

lower number of secretory events than the healthy subjects during the sleep cycle. Cortisol levels are highest when a person wakes and decrease as the day progresses [21]. The relatively lower number of hormone pulses in patients during sleep could be due to the lower cortisol clearance rates. As the patients have lower cortisol clearance rates, there is relatively higher cortisol residue in patients when compared to the matched healthy subjects. Therefore, patients produce less cortisol secretory events during sleep as they have some serum cortisol residue. Crofford *et al.* [14] claimed that there is a delayed decline in cortisol levels from peak to crest in patients when compared to matched healthy control subjects. According to our results and statistical analysis we see that there is a positive phase difference between the upper envelope of healthy subjects and patients. As mentioned earlier, we see relatively higher cortisol residue in patients due to lower clearance rates. The relative delay in cortisol levels in patients can be, therefore, explained as an outcome of relatively lower clearance rates.

Although our study suggests some potential pathological mechanisms for FMS patients, further verification is necessary. The data used in this study is limited and the dataset is obtained from a controlled study. This preliminary evidence suggests that further inclusion of subjects and rigorous experiments under different conditions and perturbations can lead to a more general conclusion for FMS patients.

The change in cortisol alone does not imply a pathophysiological mechanism. The change may be an outcome of a counter-regulatory mechanism that the body follows adaptively to bolster cognitive function, elicit the synthesis

of glucose, or suppress inflammation. We should not use any drug until the pathological mechanism is confirmed. The serum cortisol level is only a marker. If the principal issue is lower clearance rate, we should understand it with respect to a key tissue and investigate which of the biological mechanisms that breakdown cortisol are affected.

V. Conclusion and Future Work

In this research, we have deconvolved the cortisol data to obtain hormonal secretory events and model parameters. The model parameters include the infusion rate of cortisol by adrenal gland and the clearance rate by the liver. The cortisol clearance rate from the blood was relatively lower for the patients than for healthy control subjects. In addition, there is a delayed cortisol decline response in patients compared to healthy subjects. This delay is an outcome of relatively higher serum cortisol concentration and lower clearance rates in patients.

In future work, we plan to include ACTH data in our analysis and investigate the differences in ACTH and cortisol secretion dynamics in patients and healthy subjects using a system theoretic approach.

References

[1] F. Wolfe, H. A. Smythe, M. B. Yunus, R. M. Bennett, C. Bombardier, D. L. Goldenberg, P. Tugwell, S. M. Campbell, M. Abeles, P. Clark, *et al.*, "The american college of rheumatology 1990 criteria for the classification of fibromyalgia," *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, vol. 33, no. 2, pp. 160–172, 1990.

[2] F. Wolfe, K. Ross, J. Anderson, I. J. Russell, and L. Hebert, "The prevalence and characteristics of fibromyalgia in the general population," *Arthritis & Rheumatism*, vol. 38, no. 1, pp. 19–28, 1995.

[3] K. Fukuda, S. E. Straus, I. Hickie, M. C. Sharpe, J. G. Dobbins, and A. Komaroff, "The chronic fatigue syndrome: a comprehensive approach to its definition and study," *Annals of internal medicine*, vol. 121, no. 12, pp. 953–959, 1994.

[4] I. J. Bakken, K. Tveito, N. Gunnes, S. Ghaderi, C. Stoltenberg, L. Trogstad, P. Magnus, *et al.*, "Two age peaks in the incidence of chronic fatigue syndrome/myalgic encephalomyelitis: a population-based registry study from norway 2008-2012," *BMC medicine*, vol. 12, no. 1, p. 167, 2014.

[5] M. Meeus and J. Nijs, "Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome," *Clinical rheumatology*, vol. 26, no. 4, pp. 465–473, 2007.

[6] K. Malin and G. O. Littlejohn, "Psychological factors mediate key symptoms of fibromyalgia through their influence on stress," *Clinical rheumatology*, vol. 35, no. 9, pp. 2353–2357, 2016.

[7] S. S. Dickerson and M. E. Kemeny, "Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research.," *Psychological bulletin*, vol. 130, no. 3, p. 355, 2004.

[8] K. Aschbacher, A. ODonovan, O. M. Wolkowitz, F. S. Dhabhar, Y. Su, and E. Epel, "Good stress, bad stress and oxidative stress: insights from anticipatory cortisol reactivity," *Psychoneuroendocrinology*, vol. 38, no. 9, pp. 1698–1708, 2013.

[9] B. Kudielka, A. Buske-Kirschbaum, D. Hellhammer, and C. Kirschbaum, "HPA axis responses to laboratory psychosocial stress in healthy elderly adults, younger adults, and children: impact of age and gender," *Psychoneuroendocrinology*, vol. 29, no. 1, pp. 83–98, 2004.

[10] C. M. Pariante and S. L. Lightman, "The HPA axis in major depression: classical theories and new developments," *Trends in neurosciences*, vol. 31, no. 9, pp. 464–468, 2008.

[11] R. T. Faghih, K. Savla, M. A. Dahleh, and E. N. Brown, "A feedback control model for cortisol secretion," in *Engineering in Medicine and Biology Society, EMBC, 2011 Annual International Conference of the IEEE*, pp. 716–719, IEEE, 2011.

[12] E. B. Klerman, D. L. Goldenberg, E. N. Brown, A. M. Maliszewski, and G. K. Adler, "Circadian rhythms of women with fibromyalgia," *The Journal of Clinical Endocrinology & Metabolism*, vol. 86, no. 3, pp. 1034–1039, 2001.

[13] R. Riva, P. J. Mork, R. H. Westgaard, M. Rø, and U. Lundberg, "Fibromyalgia syndrome is associated with hypocortisolism," *International journal of behavioral medicine*, vol. 17, no. 3, pp. 223–233, 2010.

[14] L. J. Crofford, E. A. Young, N. C. Engleberg, A. Korszun, C. B. Brucksch, L. A. McClure, M. B. Brown, and M. A. Demitrack, "Basal circadian and pulsatile ACTH and cortisol secretion in patients with fibromyalgia and/or chronic fatigue syndrome," *Brain, behavior, and immunity*, vol. 18, no. 4, pp. 314–325, 2004.

[15] S. L. Nijhof, J. M. Rutten, C. S. Uiterwaal, G. Bleijenberg, J. L. Kimpen, and E. M. van de Putte, "The role of hypocortisolism in chronic fatigue syndrome," *Psychoneuroendocrinology*, vol. 42, pp. 199–206, 2014.

[16] J. D. Veldhuis, A. Iranmanesh, G. Lizarralde, and M. L. Johnson, "Amplitude modulation of a burstlike mode of cortisol secretion subserves the circadian glucocorticoid rhythm," *American Journal of Physiology-Endocrinology And Metabolism*, vol. 257, no. 1, pp. E6–E14, 1989.

[17] J. Aschoff, "Circadian rhythms in man," *Science*, vol. 148, no. 3676, pp. 1427–1432, 1965.

[18] K. Aschbacher, E. K. Adam, L. J. Crofford, M. E. Kemeny, M. A. Demitrack, and A. Ben-Zvi, "Linking disease symptoms and subtypes with personalized systems-based phenotypes: a proof of concept study," *Brain, behavior, and immunity*, vol. 26, no. 7, pp. 1047–1056, 2012.

[19] K. Aschbacher, M. Rodriguez-Fernandez, H. van Wietmarschen, A. J. Tomiyama, S. Jain, E. Epel, F. J. Doyle III, and J. van der Greef, "The hypothalamic–pituitary–adrenal–leptin axis and metabolic health: a systems approach to resilience, robustness and control," *Interface focus*, vol. 4, no. 5, p. 20140020, 2014.

[20] E. N. Brown, P. M. Meehan, and A. P. Dempster, "A stochastic differential equation model of diurnal cortisol patterns," *American Journal of Physiology-Endocrinology And Metabolism*, vol. 280, no. 3, pp. E450–E461, 2001.

[21] R. T. Faghih, M. A. Dahleh, G. K. Adler, E. B. Klerman, and E. N. Brown, "Deconvolution of serum cortisol levels by using compressed sensing," *PloS one*, vol. 9, no. 1, p. e85204, 2014.

[22] R. T. Faghih, M. A. Dahleh, G. K. Adler, E. B. Klerman, and E. N. Brown, "Quantifying pituitary-adrenal dynamics and deconvolution of concurrent cortisol and adrenocorticotropic hormone data by compressed sensing," *IEEE Transactions on Biomedical Engineering*, vol. 62, no. 10, pp. 2379–2388, 2015.

[23] R. T. Faghih, "From physiological signals to pulsatile dynamics: a sparse system identification approach," in *Dynamic Neuroscience*, pp. 239–265, Springer, 2018.

[24] R. T. Faghih, *System identification of cortisol secretion: Characterizing pulsatile dynamics*. PhD thesis, Massachusetts Institute of Technology, 2014.

[25] R. T. Faghih, P. A. Stokes, M.-F. Marin, R. G. Zsido, S. Zorowitz, B. L. Rosenbaum, H. Song, M. R. Milad, D. D. Dougherty, E. N. Eskandar, *et al.*, "Characterization of fear conditioning and fear extinction by analysis of electrodermal activity," in *Engineering in Medicine and Biology Society (EMBC), 2015 37th Annual International Conference of the IEEE*, pp. 7814–7818, IEEE, 2015.

[26] I. F. Gorodnitsky and B. D. Rao, "Sparse signal reconstruction from limited data using focuss: A re-weighted minimum norm algorithm," *IEEE Transactions on signal processing*, vol. 45, no. 3, pp. 600–616, 1997.

[27] J. F. Murray, *Visual recognition, inference and coding using learned sparse overcomplete representations*. PhD thesis, University of California, San Diego, 2005.

[28] R. Zdunek and A. Cichocki, "Improved M-FOCUSS algorithm with overlapping blocks for locally smooth sparse signals," *IEEE Transactions on Signal Processing*, vol. 56, no. 10, pp. 4752–4761, 2008.

[29] R. T. Faghih, M. A. Dahleh, and E. N. Brown, "An optimization formulation for characterization of pulsatile cortisol secretion," *Frontiers in neuroscience*, vol. 9, p. 228, 2015.