Characterization of Cortisol Dysregulation in Fibromyalgia and Chronic Fatigue Syndromes: A State-Space Approach

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Abstract*—*Objective: **Fibromyalgia syndrome (FMS) and chronic fatigue syndrome (CFS) are complicated medical disorders, with little known etiologies. The purpose of this research is to characterize FMS and CFS by studying the variations in cortisol secretion patterns, timings, amplitudes, the number of underlying pulses, as well as infusion and clearance rates of cortisol.** ***Methods:*** **Using a physiological state-space model with plausible constraints, we estimate the hormonal secretory events and the physiological system parameters (i.e., infusion and clearance rates).** ***Results:*** **Our results show that the clearance rate of cortisol is lower in FMS patients as compared to their matched healthy individuals based on a simplified cortisol secretion model. Moreover, the number, magnitude, and energy of hormonal secretory events are lower in FMS patients. During early morning hours, the magnitude and energy of the hormonal secretory events are higher in CFS patients.** ***Conclusion:*** **Due to lower cortisol clearance rate, there is a higher accumulation of cortisol in FMS patients as compared to their matched healthy subjects. As the FMS patient accumulates higher cortisol residues, internal inhibitory feedback regulates the hormonal secretory events. Therefore, the FMS patients show a lower number, magnitude, and energy of hormonal secretory events. Though CFS patients have the same number of secretory events, they secrete lower quantities during early morning hours. When we compare the results for CFS patients against FMS patients, we observe different cortisol alteration patterns.** ***Significance:*** **Characterizing CFS and FMS based on the cortisol alteration will help us to develop novel methods for treating these disorders.**

Index Terms: **Biomedical signal processing, deconvolution, system identification, state-space methods, statistical analysis**

I. Introduction

Fibromyalgia syndrome (FMS) or fibrositis syndrome, is a complicated medical condition characterized by widespread musculoskeletal pain in combination with tenderness at 11 or more out of the 18 specific tender points [2]. It is 7 times more prevalent in females than in males [3]. Symptoms associated with FMS include anxiety, difficulty sleeping, pain and tender points, fatigue, depression, morning stiffness, and decreased cognitive function. On the other hand, another chronic pain condition called chronic fatigue syndrome (CFS) is defined by the Centers for Disease Control and Prevention as a complex condition characterized by prolonged disabling fatigue [4]. Similar to FMS, CFS is also two times more prevalent in females than in males [5]. The symptoms associated with CFS are headaches, sore throats, fever, muscle aches, and joint pain [6], [7].

The most common symptom shared by FMS and CFS patients is widespread pain [6]. Despite similar symptoms, there are certain differences between these syndromes. For example, a regulated Ribonucleic Acid (RNA) pathway known as the 2-5A/RNase L pathway contributes to the anti-tumor and anti-viral activities of interferons [8]. An abnormal 2-5A synthetase/RNase L pathway has been seen in CFS patients but not in FMS patients [9]. Furthermore, Meeus *et al.* [6] reports the differences between the patterns of brain function activity of FMS and CFS patients. Variations in cortisol secretory patterns can result from persistent stimulation of physiological stress responses [10]. Since FMS and CFS patients are more likely to suffer from such physiological stress, they might have altered cortisol levels as compared to their matched healthy individuals. Therefore, in this research, we believe that understanding cortisol patterns in both these syndromes may be a vital factor to understand and characterize FMS, in both presence or absence of CFS, and could result in the generation of testable hypotheses about causal mechanisms.

Cortisol is a very important glucocorticoid in humans to regulate stress and sleep-wake cycle [11]. The hypothalamus-pituitary-adrenal (HPA) axis connects the central nervous system to the endocrine system. Across all age and gender groups, an individual's physiological stress responses can induce significant HPA axis responses [12]. The secretion of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) from the hypothalamus results in HPA axis activity. This activity further triggers the secretion of adrenocorticotropic hormone (ACTH) from the pituitary, resulting in the secretion of glucocorticoids. A negative feedback mechanism prevents the overproduction of serum cortisol [13]. Figure 1-A shows a pictorial depicition of the cortisol secretion and regualtion model.

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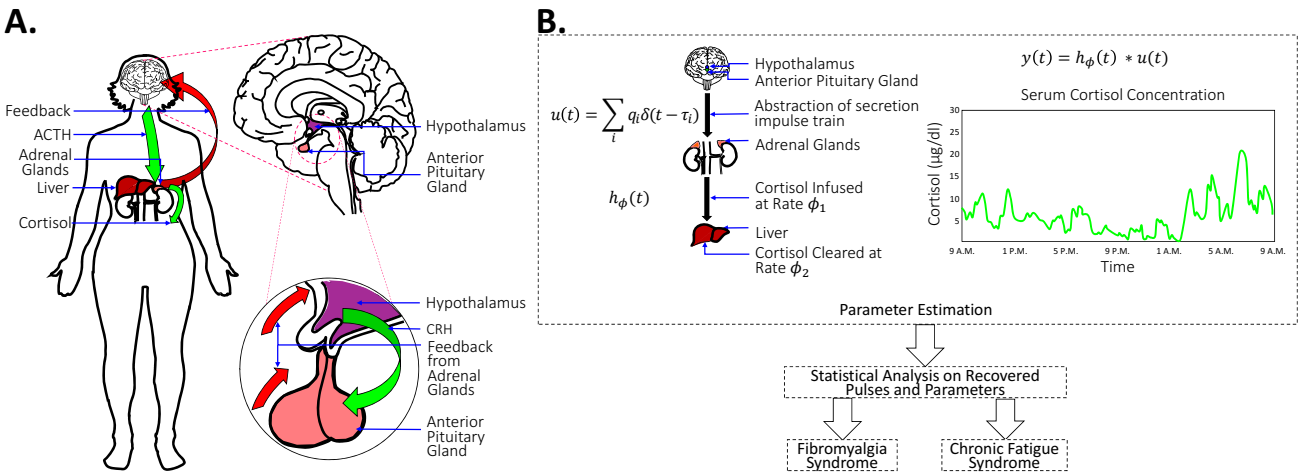

Fig. 1: **An Overview of the System-Theoretic Approach.** (**A**) shows the cortisol secretion & regulation model. The cortisol secretion starts in the hypothalamus. The CRH released by hypothalamus triggers the release of ACTH by the anterior pituitary, which in turn results in production of cortisol by the adrenal glands. (**B**) shows the overall approach used in this study. A state-space model with physiological constraints is designed. A co-ordinate descent approach is then used to estimate the secretion events and the physiological parameters. A statistical analysis is done on the estimations to categorize CFS from FMS.

The central idea of this research is to categorize CFS and FMS based on the estimated underlying pulses and the cortisol infusion and clearance rate. We further perform statistical analysis on these estimated pulses and rates. Traditional approaches study and compare the serum cortisol levels by comparing the averages or the levels directly. Klerman *et al.* [3] found no variations in the circadian rhythm followed by serum cortisol levels in FMS patients compared to healthy controls. On the contrary, Riva *et al.* [14] observed that the FMS patients show cortisol deficiency [15]. These differences in studies can be due to variations in the experimental procedures, like steps taken to minimize responses to factors such as light, sleep, medication, or presence of other secondary syndromes such as CFS. Unlike FMS, most studies reported hypocortisolism in CFS patients [16], [17]. Every individual has a distinct cortisol secretion pattern [18]. Traditional studies analyze cortisol data by averaging the cortisol patterns of different individuals, which could lead to the loss of some vital information. To avoid the loss of such critical information, we propose to consider each subject's cortisol pattern independently using a system-theoretic approach. Since we use a state-space model based on the human physiology, it is easier to identify the possible tissues, or organs responsible in causing the syndromes.

Figure 1-B shows a pictorial representation of the overall approach used in this research. In this study, we study the etiologies of FMS and/or CFS based on the underlying pulses and the physiological parameters. Understanding the underlying pulses and physiological parameters using a state-space model based on human physiology, allows us to take a closer look and observe which human tissue or organ is responsible in causing the syndromes. These underlying pulses are estimates of the signals arriving from the HPA-axis. The physiological parameters are estimates of the cortisol infusion rate by the adrenal glands and the cortisol clearance rate by the liver. As the first step in characterizing FMS and/or CFS, we analyze the cortisol response in both patients and healthy control subjects. Aschbacher *et al.* [19], [20] used a differential model to predict the rate of change in the future level of cortisol as a function of time and the current levels of cortisol and ACTH, to characterize the FMS and/or CFS patients. The diurnal variations in blood cortisol levels are a result of three factors as shown by the physiological evidence of human subjects: the timings of hormonal secretory events undergoing ultradian modulation, the amplitudes of these events undergoing circadian alteration, and the cortisol infusion rate into blood by the adrenal glands and the cortisol clearance rate by the liver [18]. Brown *et al.* [18] proposed a stochastic model based on the diurnal cortisol patterns to explain cortisol secretion process. State-space modelling and sparse deconvolution to understand pulsatile physiological signals including cortisol levels have been investigated in [21], [22], [23], [24], [25], [26], [27], [28], [29]. With physiologically plausible constraints, the model leads to a tractable optimization problem to estimate the amplitude, number, and time of hormonal secretory events along with the model parameters. In this framework, the sparsity characteristic of the hormone pulses is utilized to recover the timings and the amplitudes of hormone pulses. A coordinate-descent approach is used to estimate the cortisol secretory events and model parameters.

In this study, we use a similar model and approach with 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 various aspects of cortisol secretion in patients against their matched healthy subjects. The circadian rhythm dynamics of the patients is compared against the healthy individuals by formulating an optimization problem. The physiological model parameters and the different norms of hormonal secretory events of patients are compared against their matched healthy individuals using statistical

testing analysis. Since CFS and FMS might have different sources of dysregulations in cortisol patterns, a comparison directly amongst them would not be appropriate, therefore, in this study we first compare FMS and/or CFS against their healthy matched subject and then compare the results. As the state-space model used in this research is based on the human physiology, statistically analysing the estimated underlying pulses, infusion, and clearance rates may potentially help us to locate possible tissues or organs responsible to cause the syndrome.

II. Methods

A. Experiment

In this research, we use the serum cortisol level data of the FMS and/or CFS patients, and their matched control subjects to understand if cortisol plays any role in causing FMS [16]. All patients were recruited from clinics in the University of Michigan Medical Center. Diagnoses were done using the 1990 American College of Rheumatology Criteria and the 1988 Center for Disease Control and Prevention, respectively [16]. All subjects are within an age range of 18 to 65 years. Other than FMS and/or CFS, they have no other reported significant medical disorder. As mentioned in the introduction, FMS and CFS is more prevalent in females, therefore, the dataset in [16] contains only females. Control subjects and patients were matched according to their age and menstrual status.

All subjects were admitted the evening prior to having blood samples drawn to get them accustomed to the conditions. The 24-hour cortisol level measurement was started at 9 a.m. The dataset includes 72 subjects (36 age-matched healthy control subjects and 36 patients) [16]. Informed consent was obtained from healthy subjects and patients based on the approval by the institutional review board of the University of Michigan. Detailed description of the experiment is provided in [16]. In this study, we analyze data from 31 subject pairs (patients and their healthy control subjects), out of which 3 pairs are patients with FMS only, 15 subject pairs are patients suffering from both FMS and CFS, and 13 subject pairs are suffering from CFS only. For the premise of this study, we do not consider 5 subject pairs, for which the data was highly corrupted in either the patients or the matched healthy subjects.

B. Model Formulation

Faghih *et al.* [21] utilizes the sparse nature of hormonal secretory events and other physiological constraints along with a state-space model to estimate the amplitude and timings of the secretory events as well as the physiological system parameters. Their model is based on the stochastic differential equation model of diurnal cortisol patterns in [18]. The rate of change of cortisol concentration in the adrenal glands is equivalent to the difference between the cortisol synthesis rate and the infusion rate of cortisol from the adrenal glands into the blood. Similarly, the rate of change of cortisol concentration in the blood is equivalent to the difference between the cortisol infusion rate by the adrenal glands and the cortisol clearance rate by the liver [18]. We use the cortisol secretion dynamics model in [21] which is represented as follows:

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

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

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

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

where y_{t_i} and v_{t_i} represent the observed cortisol level in the serum and the error of measurement, respectively. We consider that the initial condition of concentration of the cortisol in adrenal glands and serum as zero and y_0, respectively. The system can be expressed as follows:

$$\boldsymbol{y} = \boldsymbol{A_\phi} y_0 + \boldsymbol{B_\phi} \mathbf{u} + \boldsymbol{v} \quad (4)$$

where $\boldsymbol{y} = \begin{bmatrix} y_{t_{10}} & y_{t_{20}} & \cdots & y_{t_{10M}} \end{bmatrix}'$, $\boldsymbol{\phi} = \begin{bmatrix} \phi_1 & \phi_2 \end{bmatrix}'$, $\boldsymbol{A_\phi} = \begin{bmatrix} a_{t_{10}} & a_{t_{20}} & \cdots & a_{t_{10M}} \end{bmatrix}'$, $\boldsymbol{B_\phi} = \begin{bmatrix} b_{t_{10}} & b_{t_{20}} & \cdots & b_{t_{10M}} \end{bmatrix}'$, $\mathbf{u} = \begin{bmatrix} q_1 & q_2 & \cdots & q_N \end{bmatrix}'$, $\boldsymbol{v} = \begin{bmatrix} v_{t_{10}} & v_{t_{20}} & \cdots & v_{t_{10M}} \end{bmatrix}'$, $a_{t_i} = e^{-\phi_2 i}$ 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 cortisol infusion rate from adrenal glands is at least four times the cortisol clearance rate by liver (i.e., $4\phi_2 \leq \phi_1$) [21]. Previous studies in [18], [30] suggest that there are 15 to 22 cortisol secretory events (i.e., $15 \leq ||\mathbf{u}||_0 \leq 22, \mathbf{u} \geq 0_{N\times 1}$) in 24 hours. We can therefore assume cortisol secretory events are sparse and state this optimization problem as

$$\min_{\substack{\mathbf{u}\geq 0_{N\times 1} \\ \mathbf{R}\boldsymbol{\phi}\leq 0_{3\times 1}}} J_\lambda(\boldsymbol{\phi}, \mathbf{u}) = \frac{1}{2}||y - \mathbf{A}_{\boldsymbol{\phi}} y_0 - \mathbf{B}_{\boldsymbol{\phi}}\mathbf{u}||_2^2 + \lambda||\mathbf{u}||_p^p \quad (5)$$

where $\mathbf{R} = \begin{bmatrix} -1 & -1 & 0 \\ 4 & 0 & -1 \end{bmatrix}^\top$.

The regularization parameter, i.e., λ is selected such that the sparsity level of $\mathbf{u}$ remains within the physiologically plausible range. The l_p-norm is chosen an approximation for the l_0-norm, i.e, the number of non-zero elements in $\mathbf{u}$ ($0 < p \leq 2$). This problem can be solved using a deconvolution algorithm,

which uses the coordinate-descent approach until we achieve convergence. We iterate between the following steps:

$$\mathbf{u}^{(m+1)} = \underset{\mathbf{u}\geq 0_{N\times 1}}{\operatorname{argmin}} J_\lambda(\boldsymbol{\phi}^{(m)}, \mathbf{u}) \tag{6}$$

$$\boldsymbol{\phi}^{(m+1)} = \underset{\mathbf{R}\boldsymbol{\phi}\leq 0_{3\times 1}}{\operatorname{argmin}} J_\lambda(\boldsymbol{\phi}, \mathbf{u}^{(m+1)}). \tag{7}$$

To obtain good estimates for $\mathbf{u}$ and $\boldsymbol{\phi}$ we use the initialization algorithm provided in the supplementary information. Equation (5) shows an optimization problem, which is a sparse recovery problem and can be solved using a variant of the Iterative Re-weighted Least Square algorithm called FOCal Under-determined System Solver (FOCUSS) [31]. FOCUSS+ [32] is an extension of the FOCUSS algorithm which solves for non-negative solutions while constraining the maximum number of non-zero elements in $\mathbf{u}$. The maximum sparsity for $\mathbf{u}$ is constrained at n (where n is 22 for healthy individuals and since we are unaware of the maximum sparsity for patients, we relax the constraint on the number of pulses to 30. The regularization parameter is set using generalized cross validation. When we obtained the estimate, we observed that for all the patients the pulses were between the range given for healthy subjects, i.e, 15 to 22 pulses. Hence, we gradually decreased the constraints on the problem. We gradually decrease the upper bound on the number of pulses to 25 for the patients, to be less conservative). The initialization algorithm uses FOCUSS+ to obtain good initializations. Although we obtain an estimate for $\boldsymbol{\phi}$ and $\mathbf{u}$ by iteratively solving for it, we need to find a good estimate for λ such that there is a balanced trade-off between λ and the sparsity of $\mathbf{u}$. The Generalized Cross-Validation (GCV) technique is used to find a good estimate for the regularization parameter [33]. FOCUSS+ algorithm and GCV technique are further provided in the supplementary material. Figure 2 shows the flowchart for deconvolution algorithm.

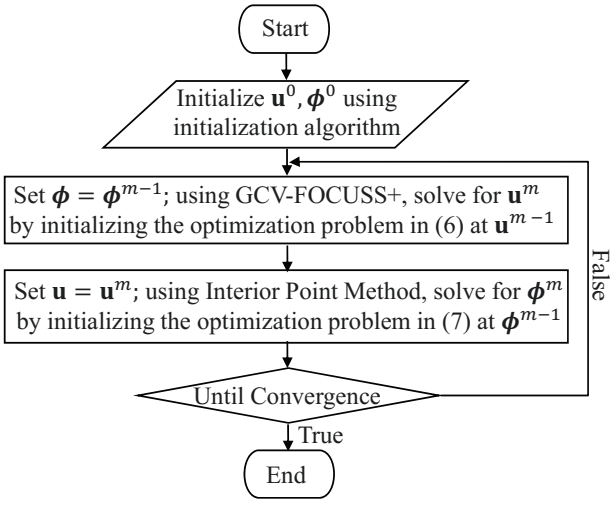

Fig. 2: **Flowchart of Deconvolution Algorithm [21]**

D. Analysis of Circadian Rhythm

The circadian rhythm of an individual is the process that regulates the sleep and wake cycle and repeats itself every 24 hours [3]. As cortisol secretion pattern is also regulated by the circadian rhythm, we analyze the circadian rhythm of the secretion pattern by examining the upper and lower envelopes of the cortisol time series. The timings and amplitudes of the hormonal secretory events vary throughout the day. We assume that the amplitude variations are due to the circadian rhythm with periods of 12 and 24h [13], and the assumption is only considering the most significant release. Therefore, we formulate the upper and lower envelopes as a sum of two significant harmonics similar to [34]. It is given 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 $\omega = 2\pi$, $t_i \in (0, T]$ and $\psi \in \{\text{low}, \text{up}\}, \boldsymbol{h_\psi} = \begin{bmatrix} h_{\psi,1} & h_{\psi,2} & h_{\psi,3} & h_{\psi,4} & h_{\psi,5} \end{bmatrix}$.
To find the upper and lower envelope of the cortisol data, we formulate two optimization problems for estimating the coefficients in (8).

The optimization formulation for the lower envelope is given as

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

Similarly, the optimization formulation for the upper envelope 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,
$\boldsymbol{D} = \begin{bmatrix} d_1 & d_2 & d_3 & d_4 & d_5 \end{bmatrix}$, $d_1 = \begin{bmatrix} 1 & 1 & 1 & \cdots & 1 \end{bmatrix}'$,
$d_2 = \begin{bmatrix} \sin(2\pi t_{10}/N) & \sin(2\pi t_{20}/N) & \cdots & \sin(2\pi t_{10M}/N) \end{bmatrix}'$,
$d_3 = \begin{bmatrix} \cos(2\pi t_{10}/N) & \cos(2\pi t_{20}/N) & \cdots & \cos(2\pi t_{10M}/N) \end{bmatrix}'$,
$d_4 = \begin{bmatrix} \sin(4\pi t_{10}/N) & \sin(4\pi t_{20}/N) & \cdots & \sin(4\pi t_{10M}/N) \end{bmatrix}'$,
and $d_5 = \begin{bmatrix} \cos(4\pi t_{10}/N) & \cos(4\pi t_{20}/N) & \cdots & \cos(4\pi t_{10M}/N) \end{bmatrix}'$
We solve the optimization problems in (9) and (10) using the interior point method.

III. Results

Figure 3 shows the comparison between the measured serum cortisol and reconstructed serum cortisol levels of ~~FMS~~ patients and healthy matched control subjects for two subject pairs. Each subject's subplot consists of:

1) The black diamonds in the upper plot of Figure 3 represent the measured cortisol level obtained from blood samples. After deconvolution, we obtain the reconstructed signal (black curve) obtained from hormone secretion pulses $\mathbf{u}$.
2) The central plot of Figure 3 shows the hormone secretion pulses $\mathbf{u}$ (black vertical lines), reconstructed from estimated amplitudes and timings obtained using deconvolution. 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 0.80.
3) Lastly, the lower plot of Figure 3 shows the quantile-quantile plot of the model residuals for both patients and matched healthy subjects. Slight deviations from the straight line are observed for the extreme values of residuals in the quantile-quantile plots for some patients. We explain this in detail in the discussion section. The

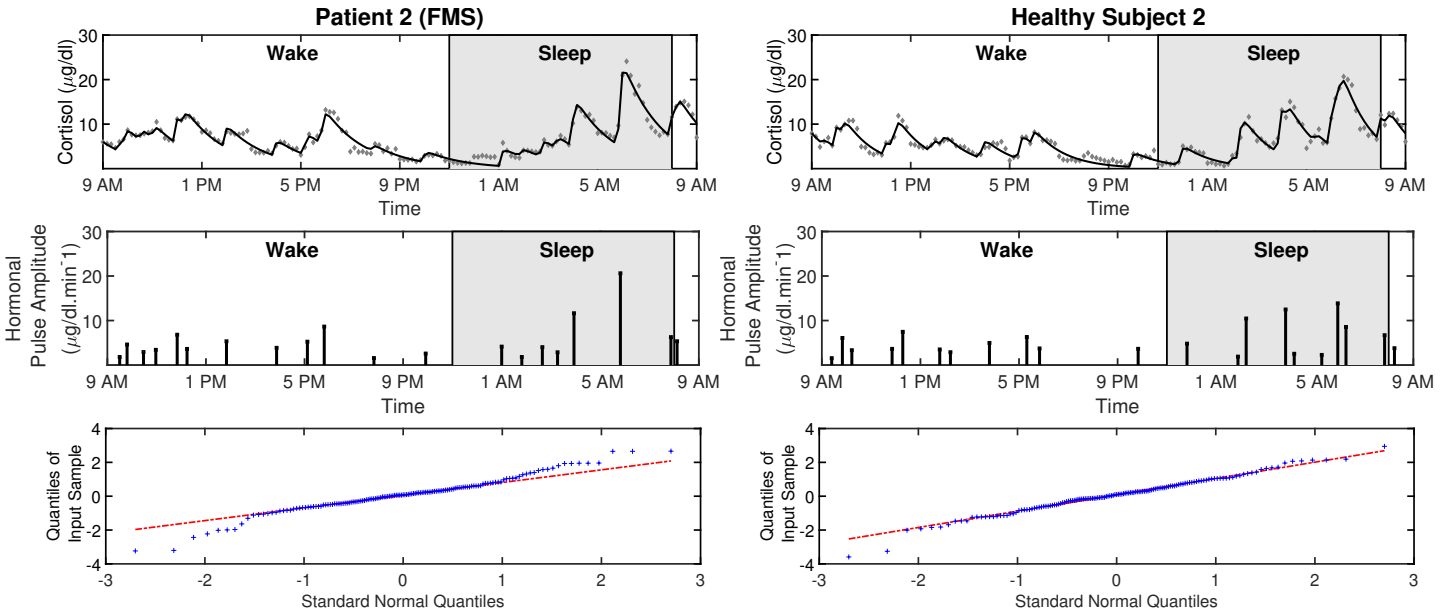

Fig. 3: **Comparison between Deconvolved Experimental Twenty-Four-Hour Cortisol Levels in Matched Subject Pairs consisting of a Healthy Control Subject and a Patient.** Each subplot shows (i) the measured 24-hour cortisol time series (gray diamonds), the reconstructed cortisol levels (black curve), (ii) the estimated pulse timings and amplitudes (black vertical lines) , (iii) Quantile-quantile plot of the model residuals for both patients and matched healthy subjects show that the residuals are Gaussian.

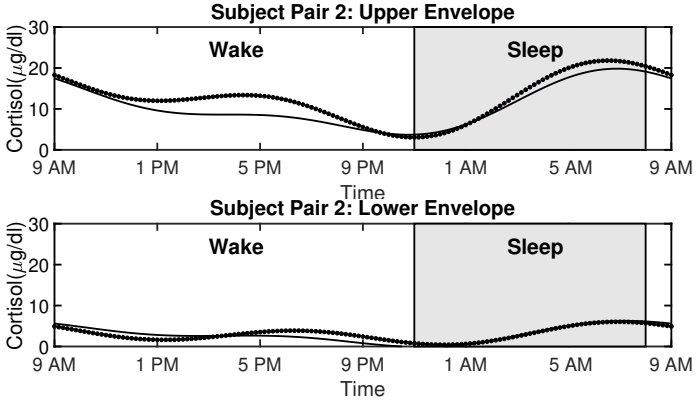

Fig. 4: **Comparison between Upper and Lower Envelopes of a Healthy Control Subject and a Patient for Matched Subject Pairs.** Each subplot shows the comparison between the patient (the black dots) and the corresponding age-matched healthy control subject (the black curve).

residuals follow a straight line in the quantile-quantile plots of the healthy subjects.

Using the optimization formulation in (9) and (10), we obtain the upper and lower envelopes of the estimated cortisol pattern for both the patient and its matched healthy subject as shown in Figure 4 (Subject pair 2 is provided here, rest are in the supplementary information).

Subject pairs comparing FMS patients against their matched healthy subjects:

1) Statistical Analysis of Physiological Parameters (serum infusion rate and clearance rate): We perform the two-tailed variant of the Wilcoxon signed-rank test (WSR) on the paired differences between the clearance rates of healthy control subjects and FMS patients [35]. This test was done considering all 18 subject pairs. We observe that the medians of ϕ_2^{healthy} and ϕ_2^{patient} (clearance rate of serum cortisol) are significantly different ($p = 0.0013$). The box-plot (a) in Figure 5 shows the sample distribution of the paired differences of the cortisol clearance rate. From this box-plot, we can verify that the median difference is greater than zero. We did a similar test involving only the 15 subject pairs in which the FMS patient also qualified for chronic fatigue (FMS & CFS both). Considering these 15 subject pairs yields a similar result ($p = 0.0052$). The box-plot is provided in the supplementary information.

2) Statistical Analysis of Hormonal Secretory Events: We perform WSR on the sample distribution of the different norms of hormonal secretion events associated with hormonal secretion patterns of healthy subjects and FMS patients. It is evident that the median for the number of hormone secretion events distribution ($||\mathbf{u}||_0^{\text{healthy}}$ and $||\mathbf{u}||_0^{\text{patient}}$) as well as for the magnitudes of hormonal secretory events ($||\mathbf{u}||_1^{\text{healthy}}$ and $||\mathbf{u}||_1^{\text{patient}}$) is different for FMS patients and healthy subjects with p-values 0.0455 and 0.0249. The box-plot (b) and box-plot (c) in Figure 5 shows the sample distribution of the paired differences of the number of hormone secretion events and the absolute value of the hormone secretion events. We observe that the median for this distribution is greater than zero. We further consider this distribution of number of hormone secretion events for 15 subject pairs (FMS & CFS both), but do not see similar results. When we consider the absolute value of hormonal secretion events in 15 subject pairs (FMS & CFS both), we obtain similar results ($p = 0.0231$). The box-plot is

provided in the supplementary information.

We do not observe significant difference for 18 subject pairs when we perform WSR on the distribution of energy of the hormonal secretory events ($||\mathbf{u}||_2^{\text{healthy}}$ & $||\mathbf{u}||_2^{\text{patient}}$). But when we consider the 15 subject pairs (FMS & CFS both), we observe that the medians are different ($p = 0.0468$). The box-plot is provided in the supplementary information.

Additionally, when we analyze the distribution of magnitudes of hormonal secretory events during sleep cycle ($||\mathbf{u}||_{1(\text{sleep})}^{\text{healthy}}$ and $||\mathbf{u}||_{1(\text{sleep})}^{\text{patient}}$) and energy of hormonal secretory events during sleep ($||\mathbf{u}||_{2(\text{sleep})}^{\text{healthy}}$ and $||\mathbf{u}||_{2(\text{sleep})}^{\text{patient}}$) using WSR we observe that the medians of the FMS patients and the healthy subjects are significantly different p-values 0.0043 and 0.00386. The box-plot (d) and box-plot (e) in Figure 5 shows the sample distribution of the paired differences of the absolute value of the hormone secretion events and of the energy of the hormone secretion events during sleep, respectively. We observe that the median is greater for this distribution. When we consider both these distribution for 15 subject pairs (FMS & CFS both), we obtain similar results with p-values 0.0054 and 0.0231. The box-plots are provided in the supplementary information.

3) Statistical Analysis on Circadian Rhythm: Similar to earlier cases, we perform the two-tailed variant of WSR on the phase differences of the lower harmonics of the upper envelope between healthy controls and patients. The test reveals that the medians of ($\theta_{\text{up},1}^{\text{healthy}}$ and $\theta_{\text{up},1}^{\text{patient}}$) are different ($p = 0.0198$). Finally, the box-plot (f) in Figure 5 shows the sample distribution of the paired differences of the phase change in the upper envelope for the healthy subjects and patients (i.e. $\theta_{\text{up},1}^{\text{healthy}} - \theta_{\text{up},1}^{\text{patient}}$). The median for this distribution is greater than zero. We obtain similar results when we perform this test on 15 subject pairs (FMS & CFS both) ($p = 0.0468$). The box-plot is provided in the supplementary information. We analyzed both the upper and lower envelopes. The lower envelopes did not show any significant differences. The upper envelopes show differences because of the amplitude variations on account of the circadian rhythm.

Subject pairs comparing CFS patients against their matched healthy subjects:

4) Statistical Analysis of Hormonal Secretory Events: We perform the two-tailed variant of the Wilcoxon signed-rank test (WSR) on the paired differences of the absolute value of hormonal secretory events in the period 4 AM to 9 AM [35]. We see that the median of $||\mathbf{u}||_1^{\text{healthy}}$ and $||\mathbf{u}||_1^{\text{patient}}$ are significantly different ($p = 0.0464$) in this time period. The left box-plot in Figure 6 shows the sample distribution of the paired differences of the absolute value of cortisol secretion events between 4 AM and 9 AM. From this box-plot, we can verify that the median difference is lower than zero. Therefore, we observe that the sum of amplitudes of hormonal secretory events during this period is lower for patients compared to their matched healthy individuals.

Similarly, we perform WSR on the paired differences of the energy of hormonal secretory events in the time period 4 AM to 9 AM [35]. We see that the median of $||\mathbf{u}||_2^{\text{healthy}}$ and $||\mathbf{u}||_2^{\text{patient}}$ are significantly different ($p = 0.0277$) in this time period. The right box-plot in Figure 6 shows the sample distribution of the paired differences of the energy of cortisol secretion events between 4 AM and 9 AM. From this box-plot, we can verify that the median difference is lower than zero. Therefore, we observe that the energy of hormonal secretory events during this time period is lower for patients than their matched healthy individuals.

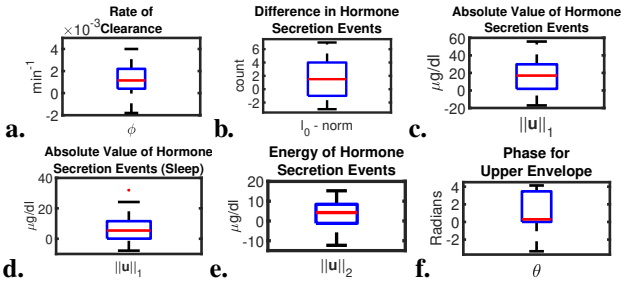

Fig. 5: **Box-plot of Paired Differences for FMS subject pairs** Subplots, respectively illustrate the sample distribution of the paired differences of **(a)** the clearance rate, **(b)** the number of hormone secretion events, **(c)** the absolute value of hormone secretion events, **(d)** the absolute value of hormone secretion events during sleep, **(e)** energy of hormone secretion events during sleep and **(f)** the phase of upper envelope, depicting the median (red line), the lower (Q1) to upper (Q3) quartile range (black rectangle), and 9 to 91 percentile range (black line and black dashed line).

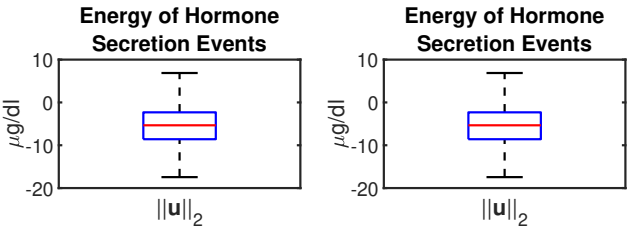

Fig. 6: **Box-plot of the Absolute Value and Energy of the Hormonal Secretory Events between 4 AM and 9 AM for CFS subject pairs** Left and right subplots, respectively illustrate the sample distribution of the paired differences of the absolute value and energy of the hormonal secretory events, depicting 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).

IV. Discussion

Understanding the cortisol secretion dynamics in FMS and/or CFS patients and designing a model to understand their irregularities with respect to healthy control subjects is a difficult and challenging problem due to various reasons.

1) For healthy subjects, the pulse range for cortisol is between 15 and 22 but, no range is known or defined for patients. Since we have no prior knowledge about the exact range in FMS and/or CFS patients, we relax the constraints on pulse range. We relax the upper and lower limits of this problem while preventing overfitting using GCV-FOCUSS+ to find λ. Although the upper limit on the number of pulses was set to 30, we obtained

no more than 22 pulses for all the patients; generalized cross validation prevents overfitting.

2) The cortisol secretion process is distinct for every individual. As a result, the comparison between healthy subjects and patients is challenging. To investigate these differences in circadian rhythms, we obtain the upper and lower envelopes.

A comprehensive model for the representation of cortisol variations must include all essential parameters such as forward and backward linkages between the hypothalamus, anterior pituitary, adrenal gland, and liver as well as external factors like stress, sleep, light, and food. It is challenging to consider all these factors while working on human data. To overcome this difficulty, Brown *et al.* [18] suggests a minimal model for both healthy individuals and patients. The model used in [21] is obtained from the stochastic model of diurnal cortisol patterns provided in [18]. Brown *et al.* [18] successfully realized this model for simulated cortisol data. Similarly, Faghih *et al.* [21] successfully developed a deconvolution algorithm based on this model and verified it on cortisol data from 10 healthy female subjects. Both these studies obtained good fits suggesting the validity of this model for estimation.

We perform statistical analysis on the number, amplitude, and energy of hormonal secretory events, and the physiological parameters. Based on the statistical analysis of our results obtained from the simplified cortisol secretion model, it is evident that for this controlled environment, the clearance rate of cortisol in patients is found to be relatively lower than that of matched healthy subjects. A higher clearance rate suggests that the blood cortisol in healthy control subjects is getting cleared at an accelerated pace as compared to their matched patients. Therefore, due to the higher clearance rate, healthy individuals show a relatively lower cortisol concentration. Immune cells exposed to psychological stress and/or higher diurnal cortisol exhibit decreased glucocorticoid sensitivity, and consequently, they exhibit increased production of inflammatory cytokines and reductions in pro-resolving immune functions [36]. Consequently, when psychological stress elicits secretion of inflammatory cytokines [37], cortisol will be less effective in inhibiting and appropriately resolving inflammation. Hence, as others have suggested [19], the kinds of alterations in cortisol clearance that this model identifies as a characteristic of patients with fibromyalgia may contribute to excess inflammation in the periphery. In turn, it is well demonstrated that peripheral cytokines, elicited by stress or endotoxin, can contribute to neuroinflammation, and consequent symptoms of fatigue, depression, sleep problems, poor concentration, and pain, all of which are common symptoms of patients with fibromyalgia [38], [39].

We further aim to understand how the hormonal pulse behavior in FMS patients differs from that of their healthy subjects. To investigate if there is any difference in the hormonal secretory behavior of FMS patients as opposed to their matched healthy subjects, we calculate the number of pulses ($||\mathbf{u}||_0$), the sum of amplitudes ($||\mathbf{u}||_1$), and the energy ($||\mathbf{u}||_2$). Based on our statistical analysis for all 18 subject pairs, we observe that the number of pulses are lower in FMS patients as compared to their matched healthy control subjects. Analyzing the magnitude of hormone secretion events, we further see that the FMS patients have a lower sum of amplitudes or magnitudes as opposed to their matched healthy subjects. We also obtain the $||\mathbf{u}||_0$, $||\mathbf{u}||_1$, and $||\mathbf{u}||_2$ in the wake and sleep cycles of all patients and healthy control subjects. We observe that the magnitude of hormone secretion events during sleep cycle is lower in FMS patients as compared to their matched healthy subjects. Also, the energy of the secretory events during sleep is lower in FMS patients.

From the statistical analysis, it is evident that the patients have a lower number of secretory events than the healthy subjects. The lower number of hormone pulses in patients can be associated with lower cortisol clearance rates. Because the FMS patients have lower cortisol clearance rates, they have higher cortisol residue than the matched healthy subjects. Therefore, due to the inhibitory feedback, patients produce fewer cortisol secretory events with lower magnitudes as they have some serum cortisol residue. Cortisol levels are highest when a person wakes, and they descend as the day progresses [21]. Since FMS patients still have cortisol residue in plasma, the new secretion amplitudes are relatively lower, which is also consistent during the sleep cycle.

If the cortisol clearance rate by the liver is low or there are fewer number of hormonal secretory events, it may potentially influence the immune system in such a way that, it promotes inflammation, pain, and other related symptoms. The increase in cortisol residue due to lower cortisol clearance rate as discussed earlier may contribute to a relative decrease in glucocorticoid sensitivity in immune cells like monocytes that secrete pro-inflammatory cytokines [40]. Further, no anti-inflammatory signal may be transmitted due to reduced glucocorticoid sensitivity and fewer number of hormonal secretory events. There may not be suppression of anti-inflammatory signal. Hence, when stress or other provocation triggers an acute inflammatory response, cortisol may be less effective in the termination of the response.

Crofford *et al.* [16] pointed out that there is a delayed decline in cortisol levels from peak to crest in patients when compared to matched healthy control subjects. We, therefore, retrieved information from the circadian rhythm. In this regard, we check the phase difference in the baseline of the upper and lower envelopes. We obtain the phase of both the patients and their matched control subjects by solving optimization problems (9) and (10). From statistical analysis it can be seen that the phase concerning the first harmonic of upper envelope is greater in control subjects as compared to their matched healthy subjects. As explained earlier, based on the simplified cortisol secretion model, control subjects have a higher cortisol clearance rate by the liver resulting in lower serum cortisol concentration. Due to this lower cortisol concentration, control subjects tend to show secretory events earlier than the patients, leading to a phase shift in the rhythm. Figure 5 shows the sample distribution of the paired differences in the phase of matched pairs in a box-plot. Another possible explanation for the phase difference may be as follows; at the start of the wake cycle, arousal from sleep increases the concentration of ACTH and cortisol in the body [41]. This increment starts an

hour prior to the time when an individual usually wakes up. But if an individual is taken by surprise, i.e., the individual is unaware of the time when he has to wake up, there is a higher increase in the concentration [41]. When an individual suffers from FMS, there is a possibility that the individual's body does not anticipate the wake-up timing leading to a delay in the time of cortisol secretion.

When we consider hormonal secretory events only for 15 subject pairs (FMS & CFS both), we observe the exact same results when it comes to the clearance rate of cortisol by the liver based on the minimal model used in this paper and phase lag in the circadian rhythm. We observe no statistical differences in the number of pulses, but we obtain similar results for magnitude of hormonal secretory events. We also obtain similar results for magnitude and energy of hormonal secretory events during the sleep cycle.

Our previous study in [1] follows a similar approach and shows some preliminary results for 8 subject pairs. Since the number of subject pairs we considered earlier was limited, we had fewer observations. We included more subjects to further verify our earlier results. The results of this study are in agreement with our previous results.

We perform WSR on the paired differences of number of secretory events ($||\mathbf{u}||_0$), the sum of amplitudes of hormonal secretory events ($||\mathbf{u}||_1$), the energy of hormonal secretory events ($||\mathbf{u}||_2$), but do not see any significant differences. We further investigated the hormonal secretory events during the wake and sleep cycle. Here, we also do not see significant differences when we perform WSR on $||\mathbf{u}||_0$, $||\mathbf{u}||_1$, and $||\mathbf{u}||_2$ during sleep and wake cycle. This shows that the cortisol secretion pattern for the patients and the corresponding matched healthy subject are similar during these periods.

When we examined the hormonal secretory events during early morning hours, we observe significant differences. As a result, the sum of amplitudes of hormonal secretory events between the period 4 AM and 9 AM was higher for the patients as compared to their matched healthy subjects. We observed similar results when we analyzed the energy of the hormonal pulses in this period. We observed no significant differences in the number of secretory events. Therefore, there could be some differences in the amplitudes of pulses during this period. According to the box-plot in Figure 6, since the median of the paired differences between healthy subjects and patients is lower than zero, patients might have higher secretory events during these early morning hours. The higher secretion events of cortisol could be associated with lower serum cortisol accumulation during this period. Crofford *et al.* [16], identified lower serum cortisol levels in CFS patients as compared to their matched healthy subjects. Similar to our results, studies in [42], [17] suggest that hypocortisolism (low cortisol levels) could play an essential role in CFS. Van *et al.* [43] suggested that HPA-axis hypofunction can be conceived as prolonged dysfunction of the neurobiological stress system. Fries *et al.* [42] observed that hypocortisolism might be an outcome of hyperactivity of the HPA-axis due to chronic stress. Nijhof *et al.* [17] related hypocortisolism in CFS patients to the amount of sleep.

One potential interpretation of the hypocortisolism might be decreased efficiency of the HPA axis to produce as much cortisol as the body requires during early morning hours. It is hypothesized that hypoactivity of the HPA axis is could be responsible for lower cortisol levels in the morning. Instead, we observe that the sum of the amplitudes of cortisol secretion events is higher during this period. The possibility might the feedback is faulty and unable to detect the requirement of cortisol in the body, or due to higher levels of fatigue.

Comparing FMS & CFS: Previously, we explained the lower number and amplitudes of cortisol secretion events based on a lower clearance rate of cortisol. From Figure 5, since the median of box-plot (a) is greater than 0, we see that the FMS patients have a higher clearance rate in comparison to their matched healthy subjects. Similarly, they show higher number and sum of amplitudes in cortisol secretion events. This shows that due to lower clearance rates, FMS patients may accumulate higher levels of cortisol in comparison to the healthy subjects. Although this study was not designed to directly study the cortisol variations in CFS patients against FMS patients, we can compare the outcomes. When we compare the cortisol alterations in FMS and CFS patients, we see differences in cortisol alteration. There is no significant difference observed in the infusion rate and the clearance rate of cortisol in CFS patients. We see statistical differences in the number and the amplitude of cortisol secretion events for FMS patients, but in CFS we only observe such statistical differences during early morning hours. In FMS, patients accumulate more cortisol, while in CFS, patients have lower secretion of cortisol.

During data collection, there are possibilities of measurement errors. We model the measurement errors as i.i.d Gaussian random variables. The quantile-quantile plot verifies that the residuals have a Gaussian structure. For some patients there are deviations in the quantile-quantile plot from standard normal plot. Although the model works for healthy population, slight deviation of errors from Gaussian structure suggest that there is some scope of improvement in the model used to understand the FMS and/or CFS patients.

Furthermore, the change in phase of cortisol pattern may be an outcome of the peripheral or central nervous system. The data is obtained from a controlled study and is is limited. This preliminary evidence suggests that a more general conclusion can be obtained from further inclusion of subjects and rigorous experiments under different conditions and perturbations. Cortisol dysfunction alone does not imply a pathophysiological mechanism. The change in cortisol may be a result of a counter-regulatory mechanism that the body follows adaptively for purposes, such as assisting cognitive function, eliciting the synthesis of glucose, or suppressing inflammation. Further, it is difficult to conclude whether FMS is a consequence of the abnormality in cortisol regulation or is itself a causative factor. Several studies have been concentrating on the association between fatigue and circulating cytokines, but as all these studies have large differences due to signal processing, sample handling, and recruitment of subjects, the results are inconsistent. For e.g., while studying the relationship between interleukin-1 and fatigue, some studies showed a direct correspondence while some showed no variations at all. Moreover,

depending on the duration for which the patients suffered from fatigue, the outcomes vary [44]. Therefore, to study different cytokines alongside cortisol may be a good approach to further unveil the etiology of FMS. Before any further medication is prescribed, the pathophysiological mechanism of FMS should be confirmed. The serum cortisol level is only a marker. If the key issue is a lower clearance rate, we should understand it with respect to tissue and investigate which of the biological mechanisms responsible for the breakdown of cortisol are affected.

Finally, physiological stress is a symptom of FMS and CFS, which might be resulting in the alteration in hormonal secretory events. Therefore, understanding the relation between these two needs consideration. This research is a first step towards understanding the cortisol behavior in a system theoretic approach to reveal the etiology FMS and CFS syndromes based on the underlying pulses.

V. Conclusion and Future Work

The purpose of this research is to characterize CFS and FMS based on the estimated underlying pulses, infusion, and clearance rates. In this research, we obtained the hormonal secretory events and model parameters by using a state-space model and then by deconvolving the cortisol time series to quantify the cortisol secretion dynamics. We see that the model residuals are Gaussian distributed. The model parameters include the cortisol infusion rate by the adrenal gland and cortisol clearance rate by the liver. The clearance rate of cortisol from the blood was lower for the FMS patients as compared to their matched healthy individuals. When an individual has higher cortisol residue in the blood than required, negative feedback occurs to keep the cortisol secretion regulated. The delayed decline may be an outcome of higher serum cortisol residue and lower clearance rates in patients. We also see a lower number, magnitude, and energy of hormonal secretory events in FMS patients. When we only consider the subject pairs consisting of FMS subjects with CFS we obtain similar results. From our analysis, we observe significant evidence of FMS patients having a delayed decline in cortisol concentration and a shift in the circadian rhythm as opposed to their matched healthy subjects. Further, we observe that CFS patients have lower serum cortisol accumulation in the morning period as compared to their matched healthy subjects. We observe differences in the sum of amplitude of cortisol secretion events and the energy of cortisol secretion events.

In future work, using a system-theoretic approach we plan to include ACTH data in our analysis and investigate the differences in ACTH and cortisol secretion dynamics in patients and healthy subjects. ACTH is a responsible factor in cortisol synthesis and it strengthens our understanding.

References

[1] D. D. Pednekar, M. R. Amin, H. Fekri, C. L. J. Aschbacher, Kirstin, and R. T. Faghih, "A system theoretic investigation of cortisol dysregulation in fibromyalgia patients with chronic fatigue," in *Engineering in Medicine and Biology Society (EMBC), 2019 41st Annual International Conference of the IEEE*, IEEE, 2019.

[2] 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.

[3] 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.

[4] 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.

[5] D. Buchwald, T. Pearlman, P. Kith, and K. Schmaling, "Gender differences in patients with chronic fatigue syndrome," *Journal of general internal medicine*, vol. 9, no. 7, pp. 397–401, 1994.

[6] 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.

[7] 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.

[8] R. H. Silverman, "A scientific journey through the 2-5a/rnase l system," *Cytokine & growth factor reviews*, vol. 18, no. 5-6, pp. 381–388, 2007.

[9] J. NIJS and K. DE MEIRLEIR, "Impairments of the 2-5a synthetase/rnase l pathway in chronic fatigue syndrome," *In Vivo*, vol. 19, no. 6, pp. 1013–1021, 2005.

[10] K. Aschbacher, A. O'Donovan, 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.

[11] 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.

[12] 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.

[13] 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.

[14] 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.

[15] L. D. Edwards, A. H. Heyman, and S. Swidan, "Hypocortisolism: an evidence-based review," *Integrative Medicine*, vol. 10, no. 4, p. 30, 2011.

[16] 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.

[17] 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.

[18] 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.

[19] 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.

[20] 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.

[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] M. R. Amin and R. T. Faghih, "Sparse deconvolution of electrodermal activity via continuous-time system identification," *IEEE Transactions on Biomedical Engineering*, 2019.

[27] D. S. Wickramasuriya, M. Amin, R. T. Faghih, *et al.*, "Skin conductance as a viable alternative for closing the deep brain stimulation loop in neuropsychiatric disorders," *Frontiers in Neuroscience*, vol. 13, p. 780, 2019.

[28] M. R. Amin and R. T. Faghih, "Inferring autonomic nervous system stimulation from hand and foot skin conductance measurements," in *2018 52nd Asilomar Conference on Signals, Systems, and Computers*, pp. 655–660, IEEE, 2018.

[29] M. R. Amin and R. T. Faghih, "Tonic and phasic decomposition of skin conductance data: A generalized-cross-validation-based block coordinate descent approach," in *Engineering in Medicine and Biology Society (EMBC), 2019 41st Annual International Conference of the IEEE*, IEEE, 2019.

[30] 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.

[31] 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.

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

[33] G. H. Golub, M. Heath, and G. Wahba, "Generalized cross-validation as a method for choosing a good ridge parameter," *Technometrics*, vol. 21, no. 2, pp. 215–223, 1979.

[34] 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.

[35] R. Woolson, "Wilcoxon signed-rank test," *Wiley encyclopedia of clinical trials*, pp. 1–3, 2007.

[36] G. E. Miller, E. Chen, J. Sze, T. Marin, J. M. Arevalo, R. Doll, R. Ma, and S. W. Cole, "A functional genomic fingerprint of chronic stress in humans: blunted glucocorticoid and increased nf-κb signaling," *Biological psychiatry*, vol. 64, no. 4, pp. 266–272, 2008.

[37] A. Steptoe, M. Hamer, and Y. Chida, "The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis," *Brain, behavior, and immunity*, vol. 21, no. 7, pp. 901–912, 2007.

[38] A. H. Miller and C. L. Raison, "The role of inflammation in depression: from evolutionary imperative to modern treatment target," *Nature reviews immunology*, vol. 16, no. 1, p. 22, 2016.

[39] K. Aschbacher, E. Epel, O. Wolkowitz, A. Prather, E. Puterman, and F. Dhabhar, "Maintenance of a positive outlook during acute stress protects against pro-inflammatory reactivity and future depressive symptoms," *Brain, behavior, and immunity*, vol. 26, no. 2, pp. 346–352, 2012.

[40] K. Aschbacher, R. Derakhshandeh, A. J. Flores, S. Narayan, W. B. Mendes, and M. L. Springer, "Circulating angiogenic cell function is inhibited by cortisol in vitro and associated with psychological stress and cortisol in vivo," *Psychoneuroendocrinology*, vol. 67, pp. 216–223, 2016.

[41] J. Born, K. Hansen, L. Marshall, M. Mölle, and H. L. Fehm, "Timing the end of nocturnal sleep," *Nature*, vol. 397, no. 6714, p. 29, 1999.

[42] E. Fries, J. Hesse, J. Hellhammer, and D. H. Hellhammer, "A new view on hypocortisolism," *Psychoneuroendocrinology*, vol. 30, no. 10, pp. 1010–1016, 2005.

[43] B. Van Houdenhove, F. Van Den Eede, and P. Luyten, "Does hypothalamic–pituitary–adrenal axis hypofunction in chronic fatigue syndrome reflect a 'crash'in the stress system?," *Medical hypotheses*, vol. 72, no. 6, pp. 701–705, 2009.

[44] M. E. Roerink, M. E. Van der Schaaf, C. A. Dinarello, H. Knoop, and J. W. Van der Meer, "Interleukin-1 as a mediator of fatigue in disease: a narrative review," *Journal of neuroinflammation*, vol. 14, no. 1, p. 16, 2017.