A SYSTEM-THEORETIC INVESTIGATION OF HORMONE DYNAMICS IN CHRONIC FATIGUE SYNDROME, FIBROMYALGIA SYNDROME, AND OBESITY

by
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ABSTRACT

Fibromyalgia syndrome (FMS), chronic fatigue syndrome (CFS), and obesity are complicated medical disorders with little known etiologies. The purpose of this research is to characterize FMS, CFS, and obesity by studying the variations in hormonal secretion patterns, timings, amplitudes, the number of underlying pulses, as well as infusion and clearance rates of hormones such as cortisol, and leptin. Employing 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). The first outcome of our research shows 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 the energy levels of cortisol secretory events are lower in FMS patients. During early morning hours, the magnitude and the energy levels of the cortisol secretory events are higher in CFS patients. Due to the lower cortisol clearance rate, there is a higher accumulation of cortisol in FMS patients as compared to their matched healthy subjects. As the FMS patients accumulate higher cortisol residues, internal inhibitory feedback regulates the hormonal secretory events. Therefore, the FMS patients show a lower number, magnitude, and the energy levels of hormonal secretory events. Though CFS patients have the same number of secretory events, the secretion quantity is lower during early morning hours. When we compare the results for CFS patients against FMS patients, we observe different cortisol alteration patterns. In the second part of this thesis, we propose a simplified minimal leptin secretion model and study the correlation between estimated parameters of leptin and cortisol. The hunger hormone leptin and stress hormone cortisol are closely associated with obesity. Traditionally, a leptin-cortisol antagonism is observed in obese patients. We also observe a leptin-cortisol

antagonism when we compare the reconstructed leptin and cortisol levels, hence, further validating the model. The proposed model can potentially be employed to study leptin variations in obese patients against their matched healthy subjects. Characterizing CFS, FMS, and obesity based on the hormonal alterations will help us develop effective methods for treating these disorders.

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1 Introduction

1.1 General Overview of Chronic Fatigue Syndrome, Fibromyalgia Syndrome, and Obesity

Until a few decades ago, the human race underwent many difficulties due to epidemics of communicable diseases such as tuberculosis, plague, and cholera [61, 77, 89]. Today, we are facing a COVID-19 pandemic [87]. Such communicable diseases spread at a very rapid rate and the symptoms are much more visible, therefore, are studied extensively [19, 45]. Although, there are a lot of studies on communicable diseases, there are still a class group of diseases called non-communicable diseases that needs rigorous study. Non-communicable diseases include heart diseases, obesity, and chronic illness. According to a 2018 study, non-communicable diseases result in 41 million people each year, equivalent to 71% of deaths worldwide [72]. Also, there is increasing association between communicable and non-communicable diseases [45]. It is observed that obese patients are more vulnerable to contract Corona virus disease (COVID-19), but further research is necessary. The number of patients diagnosed with conditions such as obesity, fibromyalgia, and chronic fatigue syndromes is increasing day by day [50, 62]. Many such non-communicable diseases have been linked to hormonal dysregulation [20, 37]. In this research, we therefore intend to study hormonal dysregulation in syndromes such as fibromyalgia, chronic fatigue, and obesity. We attempt to investigate potential underlying causes by studying various hormones related to these syndromes [36].

1.1.1 Fibromyalgia and Chronic Fatigue Syndromes-Background

Fibromyalgia Syndrome (FMS), also known as fibrositis syndrome, is a complex medical condition characterized by widespread musculoskeletal pain accompanied by tenderness at 11 or more out of the 18 specific tender points [100]. Chronic Fatigue Syndrome (CFS) is defined by the Centers for Disease Control and Prevention (CDC) as a complex condition characterized by prolonged disabling fatigue [35]. CFS and FMS each affect approximately 2% of people worldwide [78, 99]. FMS and CFS are more prevalent in females than in males [12, 21]. The prevalence of FMS increases with age and is highest in 60-79 age group [21]. For CFS, two distinct peaks were observed for age groups between 10-19 and 30-39 years, being true for both genders [12]. 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 [59, 63, 99]. The etiologies (i.e., causes) of both these syndromes are unknown. Since they have overlapping symptoms, it becomes difficult to characterize them [1]. Currently, CFS and FMS patients are given medications to reduce the discomfort caused by symptoms [43]. There is no known cure for these syndromes [51, 95]. By isolating the cause and designing an approach to distinguish between the syndromes, one may potentially develop approaches to treat them. Widespread pain is the most common symptom in FMS and CFS patients [21]. Since pain and fatigue are types of physiological stress, they are often linked to the stress hormone, cortisol [21]. We, therefore, propose an investigation of cortisol behavior in FMS and CFS patients.

Traditional approaches study and compare the serum cortisol levels by comparing the averages or the levels directly. Klerman *et al.* [53] 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.* [79] observed that the FMS patients show cortisol deficiency [26]. 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 [21, 69]. Every individual has a distinct cortisol secretion pattern [15]. 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.

1.1.2 Obesity-Background

Another non-communicable condition nowadays, especially in United States, with a high prevalence rate is obesity. Obesity dubbed the "Global Epidemic" by the World Health Organization, is said to cause or aggravate various other health problems, worsening one's life expectancy [68, 71]. The prevalence of obesity is increasing worldwide at an alarming rate. Estimates show that 4% of the world population is obese [47]. Different studies suggest different approaches for treating obesity, such as a low-calorie diet, therapy, and surgery [24, 93]. These pathogenic (treating factors which cause a condition) approaches are often used to treat the condition, but a salutogenic (i.e., factors supporting human health and well-being) model may be more effective as both a preventive and remedial measure [71]. Very few studies have been done to identify the cause behind obesity [10, 48, 88]. Identifying the hormones and tissues responsible for causing obesity will potentially help

us to prevent and cure the conditions. Obesity is often linked to hormones such as cortisol, leptin, ghrelin, and insulin [40]. Since, obesity is very closely associated with the polypeptide hormone, leptin [17, 48, 60], and the glucocorticoid hormone, cortisol [13, 67], studying them will prove vital in designing an approach to treating it. This model can be further generalized to include other hormones.

1.2 Thesis Outline

In this research, we study hormones such as cortisol and leptin based on their pulsatile nature. Cortisol secretion and variations are the result of hormonal pulses induced by the Hypothalamic-Pituitary-Adrenal (HPA) axis [30]. Similarly, leptin variations are induced by adipose tissue [10]. This research was conducted in two parts:

1. The first part is dedicated to studying the cortisol dynamics and variations in FMS and CFS patients against their matched healthy subjects.

2. The second part is dedicated to studying both the leptin-cortisol dynamics in obese patients and understanding the correlation.

1.2.1 Characterization of Cortisol Dysregulation in Fibromyalgia and Chronic Fatigue Syndromes

As the first step in understanding the etiology of CFS and FMS, we propose to 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 [92]. We use the model and deconvolution algorithm developed by Faghih *et al.* [27, 28, 29, 30, 33] to investigate cortisol levels

in both adrenal glands and serum. The approach allows us to estimate the amplitude, number and timing of hormonal secretary events along with the physiological parameters. The sparsity characteristic of the hormone pulses underlying cortisol release is exploited to recover the timings and the amplitudes of hormone pulses using compressed sensing [29]. A coordinate descent approach is used to estimate the cortisol secretory events and model parameters [29, 30]. Similar to [29], 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.

1.2.2 Characterization of Leptin and Cortisol Dynamics in Obese Patients

To study the leptin-glucocorticoid behaviour in obese patients, we propose to observe the underlying pulses and estimate the physiological infusion and clearance rates in the system. The identification of a dynamic system model for leptin concentration over time makes it possible to recover the number of leptin pulses. It further allows us to recover information about the pulse amplitudes and intervals of occurrence from collected subject data. The system identification for leptin in this research is based on the method for deconvolution of cortisol levels mentioned above [29]. The leptin and cortisol pulses are considered to be sparse signals due to the limited number of secretory events that occur each day. A better understanding of the behavior of leptin in the body can be obtained through the signal and pulse recovery techniques that we use in this research. Determining a system model for the relationship between leptin and cortisol concentrations provides us with a more

comprehensive understanding of the biological system's true behavior. This model can provide insight into the effects of the relationship of the hormones on weight gain.

1.3 Scientific Significance

In the first part of the research, we study the underlying pulses resulting in cortisol secretion and the physiological parameters such as infusion rate by the adrenal glands, clearance rate by the liver. Understanding these parameters will not only help us to gain insight into the possible etiology of CFS and FMS but also to distinguish between them. Previous studies characterized FMS and CFS based on symptoms, but due to overlapping symptoms, this approach maybe misleading. Characterization of FMS and CFS based on cortisol secretion may help us design a more promising approach as well as help us to unveil their etiologies. Based on the results, if hypocortisolism or hypercortisolism, is observed in these syndromes, medications such as Mifepristone and Benzodiazepine may be used to inhibit cortisol secretion [42, 73]. Another possible approach may be to regulate the energy levels in hypercortisolism by employing a wearable brain machine interface architecture [11].

Similarly for obesity, our goal is to understand the leptin-glucocortcoid behavior by understanding the underlying pulses and other physiological parameters such as infusion rate by adipose tissue and clearance rate by the renal system. Leptin was successfully discovered in 1994 [2], so it is a new hormone when compared to other hormones such as cortisol, ACTH, and insulin. Very few studies exist which investigate both cortisol and leptin behavior. Previous studies either investigate leptin or cortisol individually, however, did not include investigation of the underlying pulses

resulting in the secretion. The leptin model proposed in this part of the research, is minimal and more simplified as compared to the previously proposed models. This leptin model can be further used to study leptin behaviour in obese patients against their matched healthy subjects.

Obtaining the pulses coming from the brain and hypothalamus-pituitary-adrenal axis is a challenge. The approach mentioned in this research, can help us to estimate these underlying pulses. This research can be further generalized to study ACTH, cortisol and leptin behavior in other syndromes such as Thyroid, and Addison disease. Exploiting the pulsatile nature of these hormones and understanding the behavior we can relate these syndromes to the HPA axis, thus obtain the root cause and devise a treatment for them. Moreover, it will further help us to understand the role of hypothalamus and other neural activities responsible for causing the syndromes.

2 Characterization of Cortisol Dysregulation in Fibromyalgia and Chronic Fatigue Syndromes

2.1 An Overview of Fibromyalgia Syndrome, Chronic Fatigue Syndrome, and the System-Theoretic Approach

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 [100]. It is 7 times more prevalent in females than in males [53]. 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 [35]. Similar to FMS, CFS is also two times more prevalent in females than in males [16]. The symptoms associated with CFS are headaches, sore throats, fever, muscle aches, and joint pain [59, 63].

The most common symptom shared by FMS and CFS patients is widespread pain [63]. 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 [83]. An abnormal 2-5A synthetase/RNase L pathway has been seen in CFS patients but not in FMS patients [70]. Furthermore, Meeus *et al.* [63]

This paper was presented in part at the proceedings of the IEEE Engineering in Medicine and Biology Society Conference [76]. Chapter adopted from Pednekar, Divesh Deepak, et al. "Characterization of Cortisol Dysregulation in Fibromyalgia and Chronic Fatigue Syndromes: A State-Space Approach." IEEE Transactions on Biomedical Engineering (2020).

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 [9]. 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.

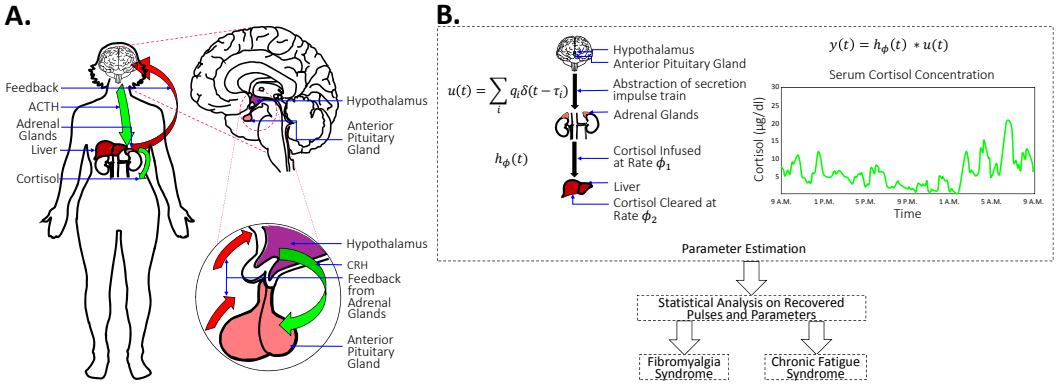


Figure 1: **An Overview of the System-Theoretic Approach.** (**A**) shows the cortisol secretion & regulation model. (**B**) shows the overall approach used in this study.

Cortisol is a very important glucocorticoid in humans to regulate stress and sleep-wake cycle [74]. 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 [55]. Figure 1-A shows the cortisol secretion & regulation model. 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 [32]. Figure 1-A shows a pictorial depicition of the cortisol secretion and regualtion model.

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.* [53] 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.* [79] observed that the FMS patients show cortisol deficiency [26]. 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 [21, 69]. Every individual has a distinct cortisol secretion pattern [15]. 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. A state-space model with physiological constraints is designed. A coordinate 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. In this research, 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.* [6, 10] 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 [15]. Brown *et al.* [15] 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 [3, 4, 5, 27, 28, 29, 30, 33, 96]. 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.

2.2 Methods

2.2.1 Experiment: Cortisol Serum Measurements in Healthy and Diseased Population

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 [21]. 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 [21]. 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 [21] 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) [21]. 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 [21]. 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.

2.2.2 Cortisol Model Formulation for Healthy and Diseased Population

Faghih *et al.* [29] 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 [15]. 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 [15]. We use the cortisol secretion dynamics model in [29] which is represented as

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

and

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

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 ($N = 1440$) [29]. Every 10 minutes the blood was collected, for M samples ($M = 144$). The output, which refers to the

measurement, is presented as

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

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

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

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

2.2.3 Cortisol Parameter 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., $4\phi_2 \leq \phi_1$) [29]. Previous studies in [15, 92] 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

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

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

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

and

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

To obtain good estimates for $\mathbf{u}$ and $\boldsymbol{\phi}$ we use the initialization algorithm provided in 2.2.4. Equation (16) 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) [41]. FOCUSS+ [66] 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 [39]. FOCUSS+ algorithm and GCV technique are further provided in the supplementary material. Figure 2 shows the flowchart for deconvolution algorithm.

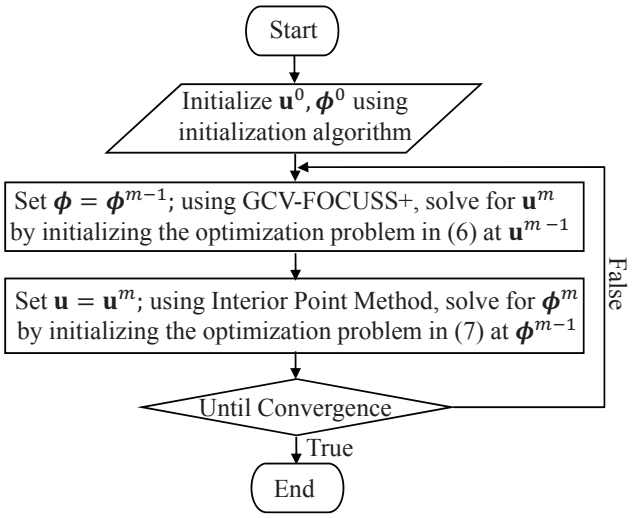


Figure 2: **Flowchart of Deconvolution Algorithm [29].**

2.2.4 Sparse Recovery with Iterative Re-weighted Least Square Approach: (FOCal Under-determined System Solver+)

FOCUSS+ [66] is an extension of the FOCUSS algorithm [41] which solves for non-negative solutions. FOCUSS+ allows us to maintain the maximum sparsity of $\mathbf{u}$. This algorithm uses a heuristic approach to update the λ. By updating λ iteratively until it reaches maximum regularization $\lambda_{\max}$, we can maintain the trade-off between residual error and sparsity. The residual error $||\boldsymbol{y}_{\boldsymbol{\phi}} - B_{\phi}\mathbf{u}||$ reduces with every iteration.

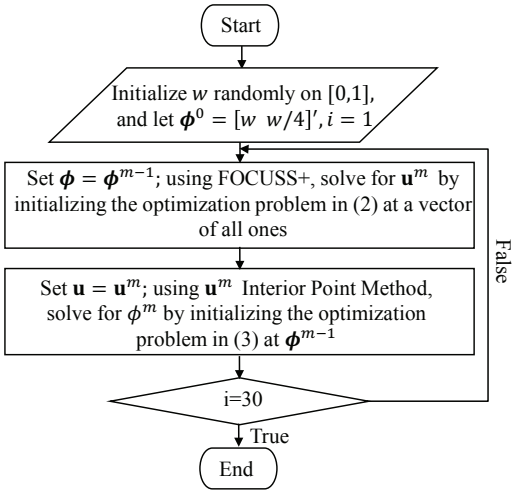


Figure 3: **Flowchart of Initialization Algorithm [29].**

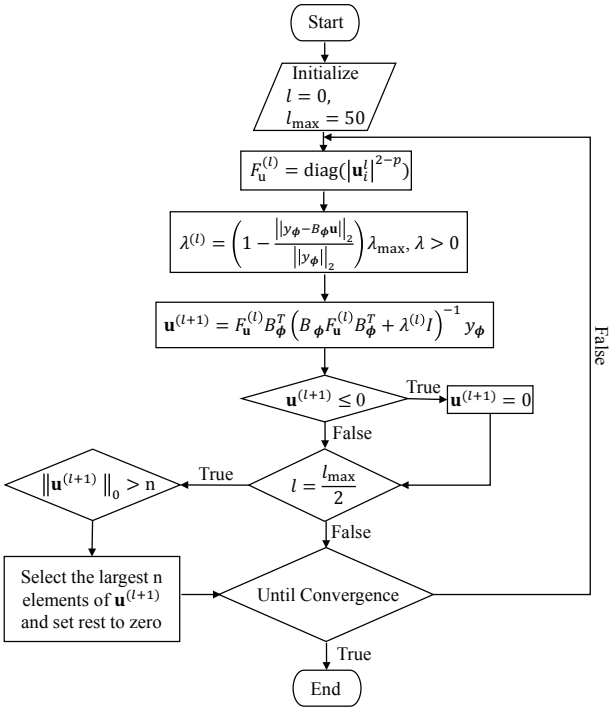


Figure 4: **Flowchart of FOCUSS+ [66].**

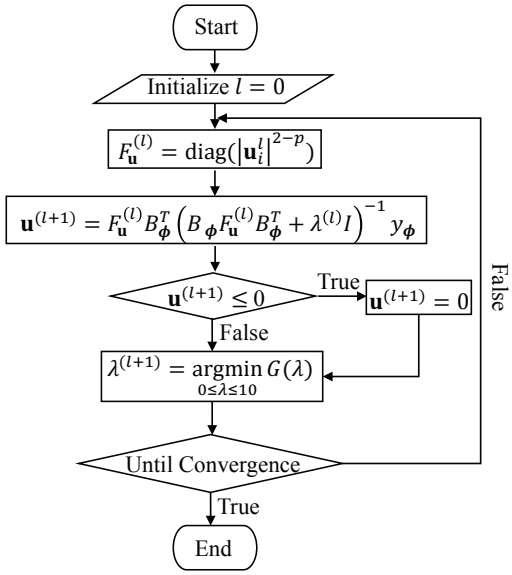


Figure 5: **Flowchart of GCV-FOCUSS+ [104].**

FOCUSS+ takes about 10 to 50 iterations to converge [66]. The initialization algorithm uses FOCUSS+ to obtain good initializations. FOCUSS+ algorithm is also provided in the supplementary material. 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 GCV technique is used to find a good estimate for the regularization parameter [39]. GCV function is given as

$$G(\lambda) = \frac{L||(1-\boldsymbol{B_\phi F_u^{(l)} B_\phi^T (B_\phi F_u^{(l)} B_\phi^T + \lambda^{(l)} I)^{-1}) y_\phi}||^2}{(\text{trace}(1-\boldsymbol{B_\phi F_u^{(l)} B_\phi^T (B_\phi F_u^{(l)} B_\phi^T + \lambda^{(l)} I)^{-1}}))^2}$$

where F_u is $\text{diag}(|\mathbf{u}_i|^{2-p})$, l refers to the estimated values at l^{th} iteration of FOCUSS+ algorithm, and L is the number of data points. The combination of GCV technique and FOCUSS+ allows us to find a reasonable choice for λ, which further helps us to filter out noise to solve for $\mathbf{u}$ [29, 104]. The GCV function is used for this purpose. Figure 5 shows the flowchart for GCV-FOCUSS+.

2.2.5 Analysis of Circadian Rhythms

The circadian rhythm of an individual is the process that regulates the sleep and wake cycle and repeats itself every 24 hours [53]. 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 [32], 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 [31]. 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 can further express (8) as

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

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 $\theta_{\psi,2} = \tan^{-1}(\frac{h_{\psi,5}}{h_{\psi,4}})$.

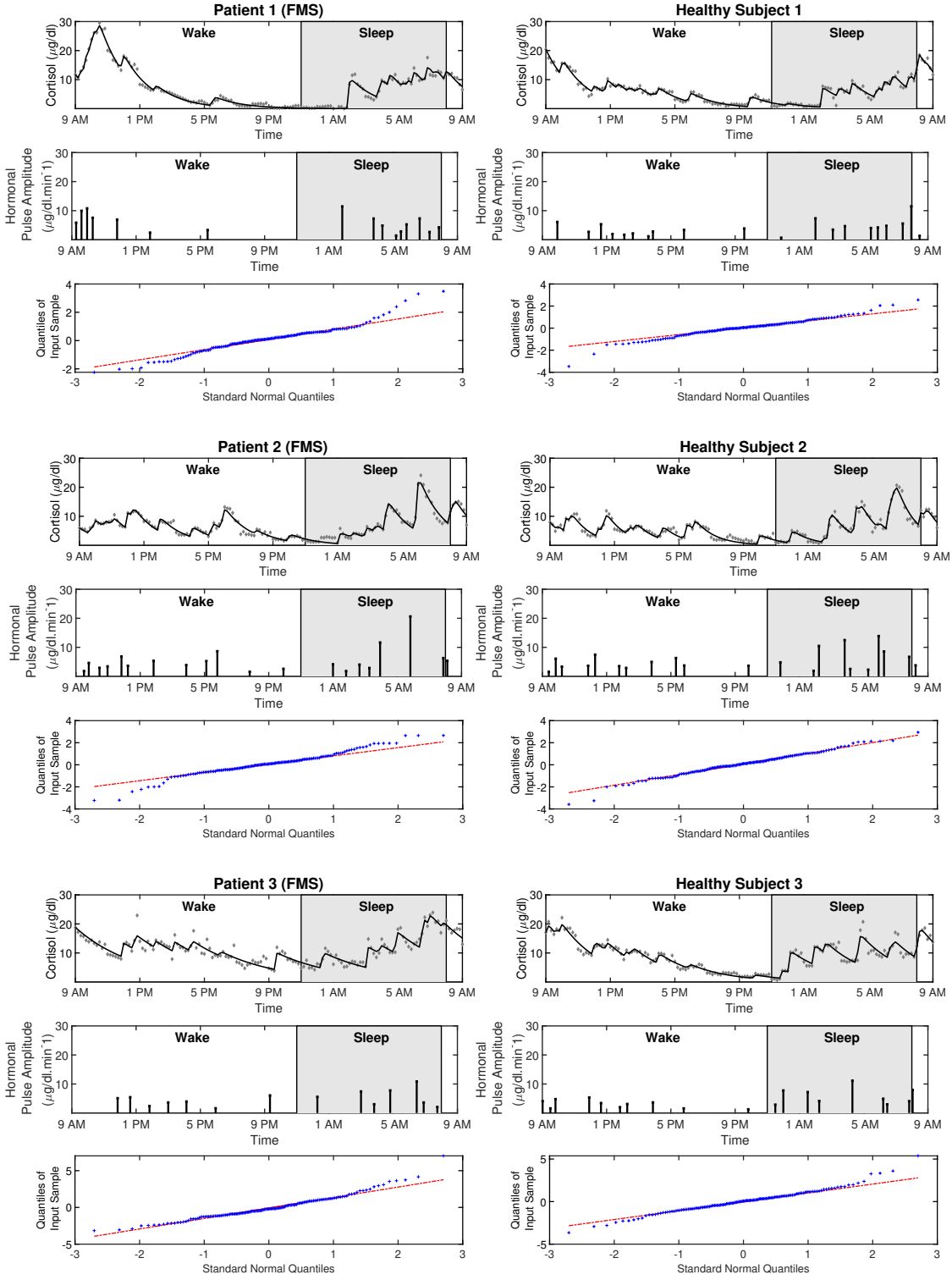
We solve the optimization problems in (9) and (10) using the interior point method.

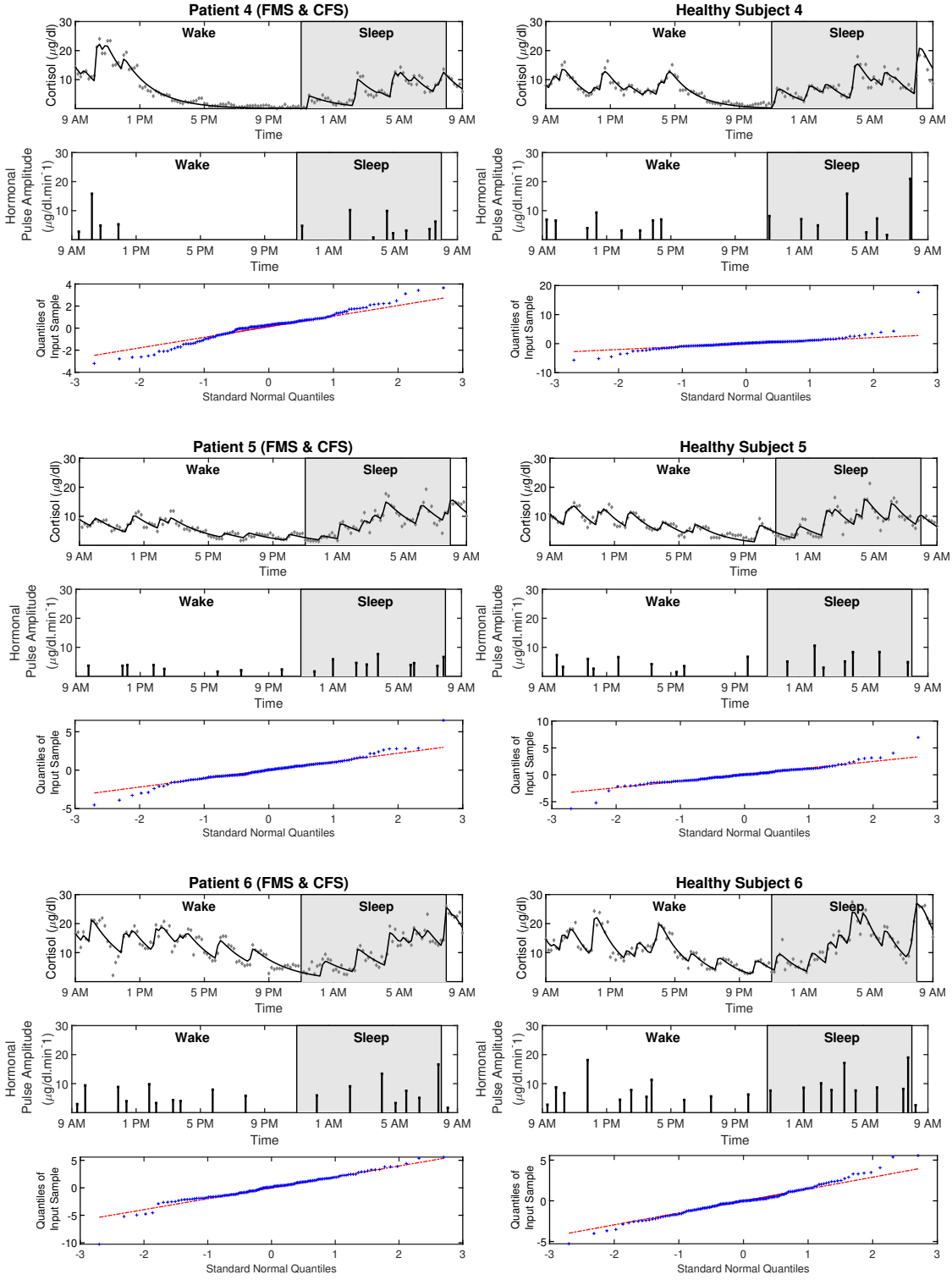
2.3 Results

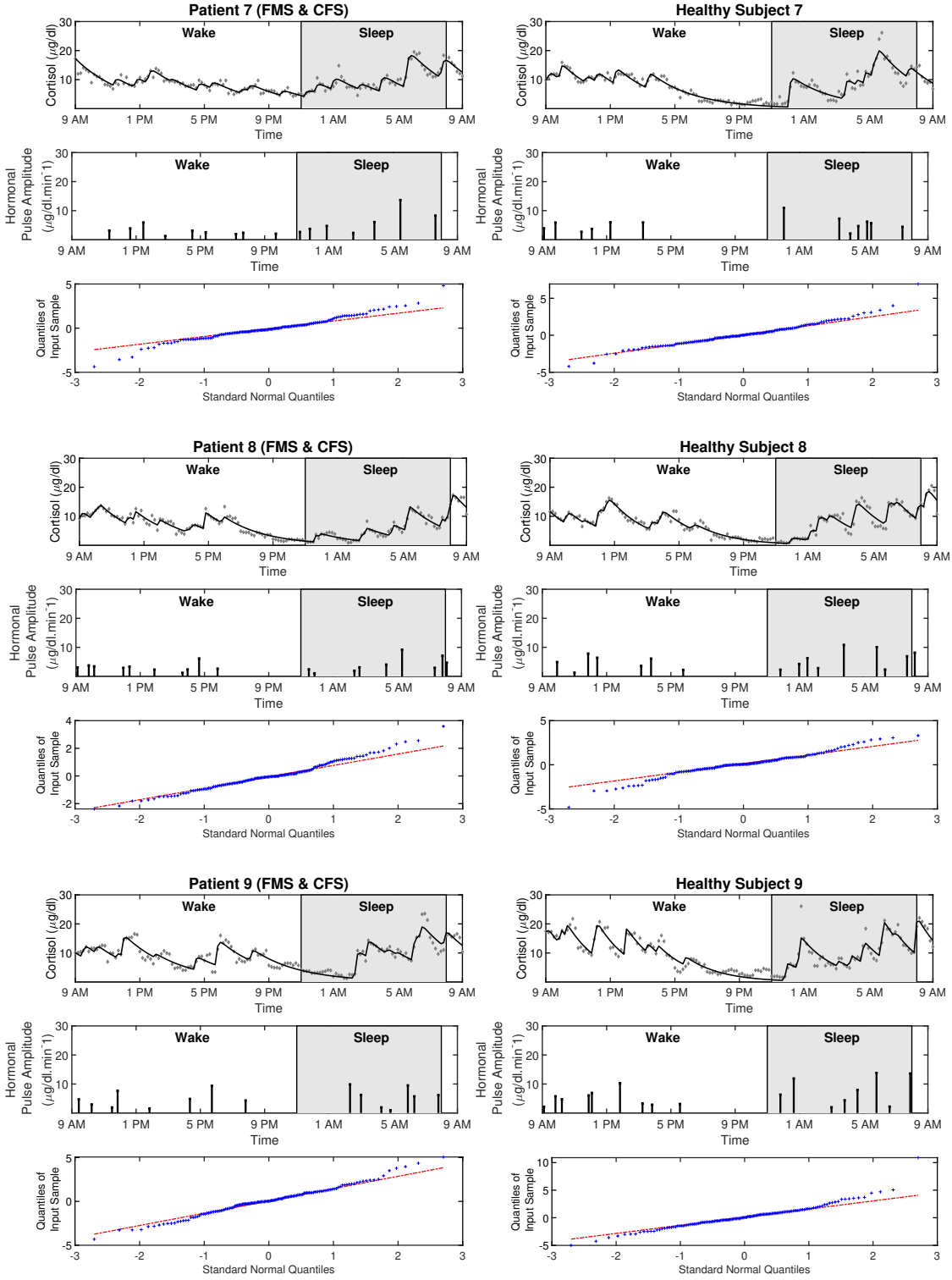
Figure 6 shows the comparison between the measured serum cortisol and reconstructed serum cortisol levels of patients and healthy matched control subjects for two subject pairs. Each subject's subplot consists of:

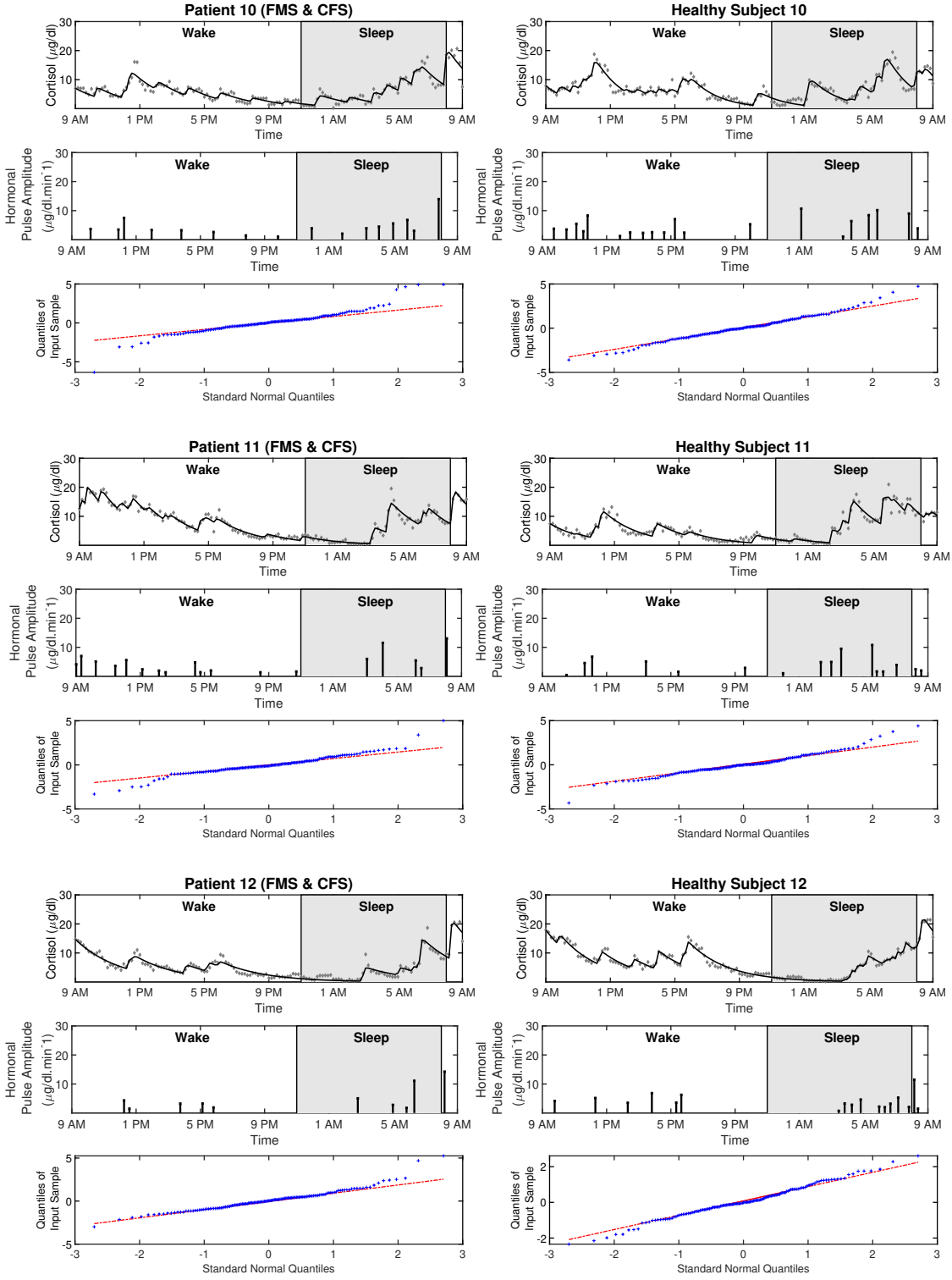
1. The black diamonds in the upper plot of Figure 6 represent the measured cortisol level obtained from blood samples. After deconvolution, we obtain the reconstructed signal (black curve) obtained from hormone secretion pulses **u**.

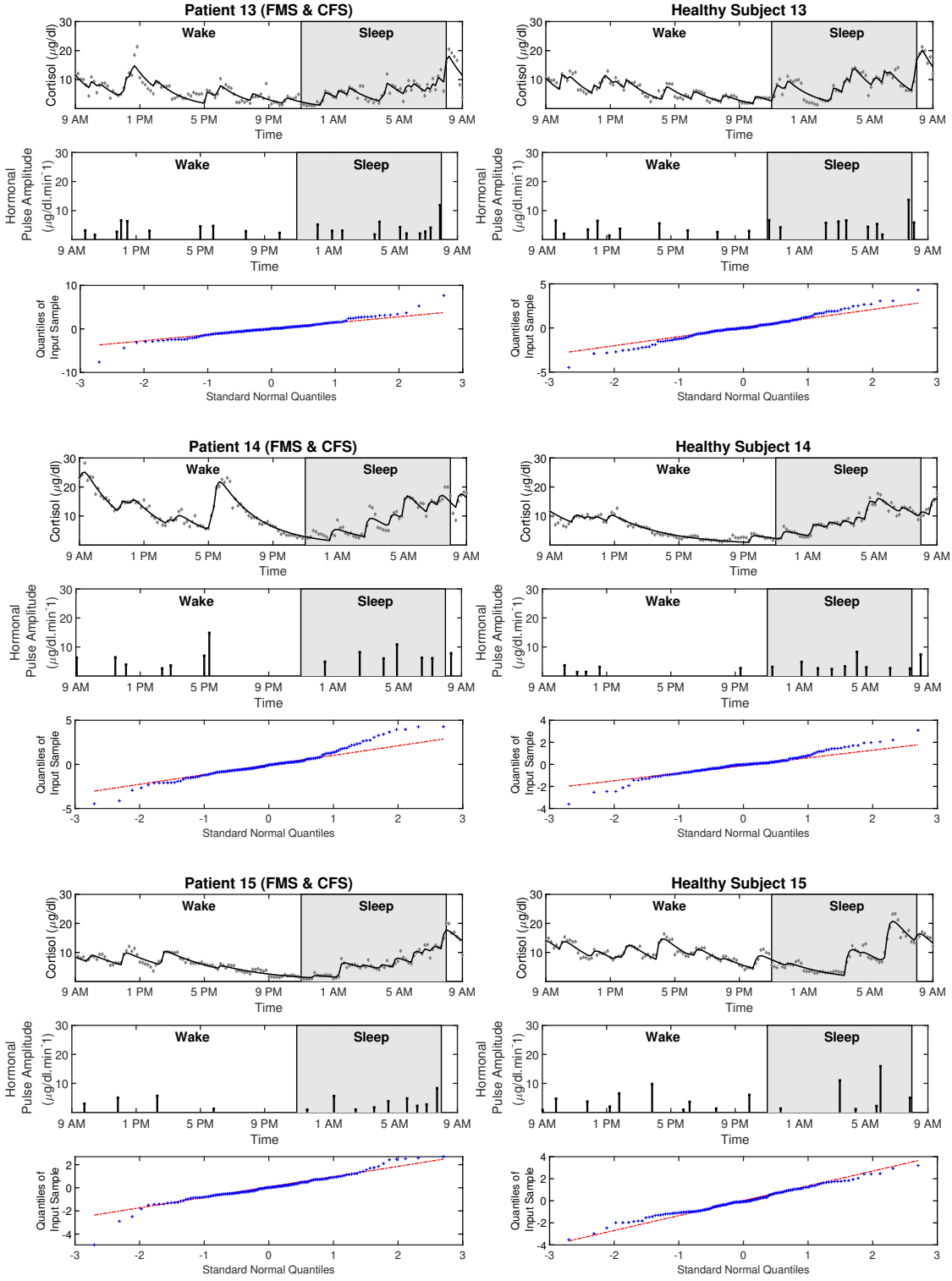
2. The central plot of Figure 6 shows the hormone secretion pulses **u** (black

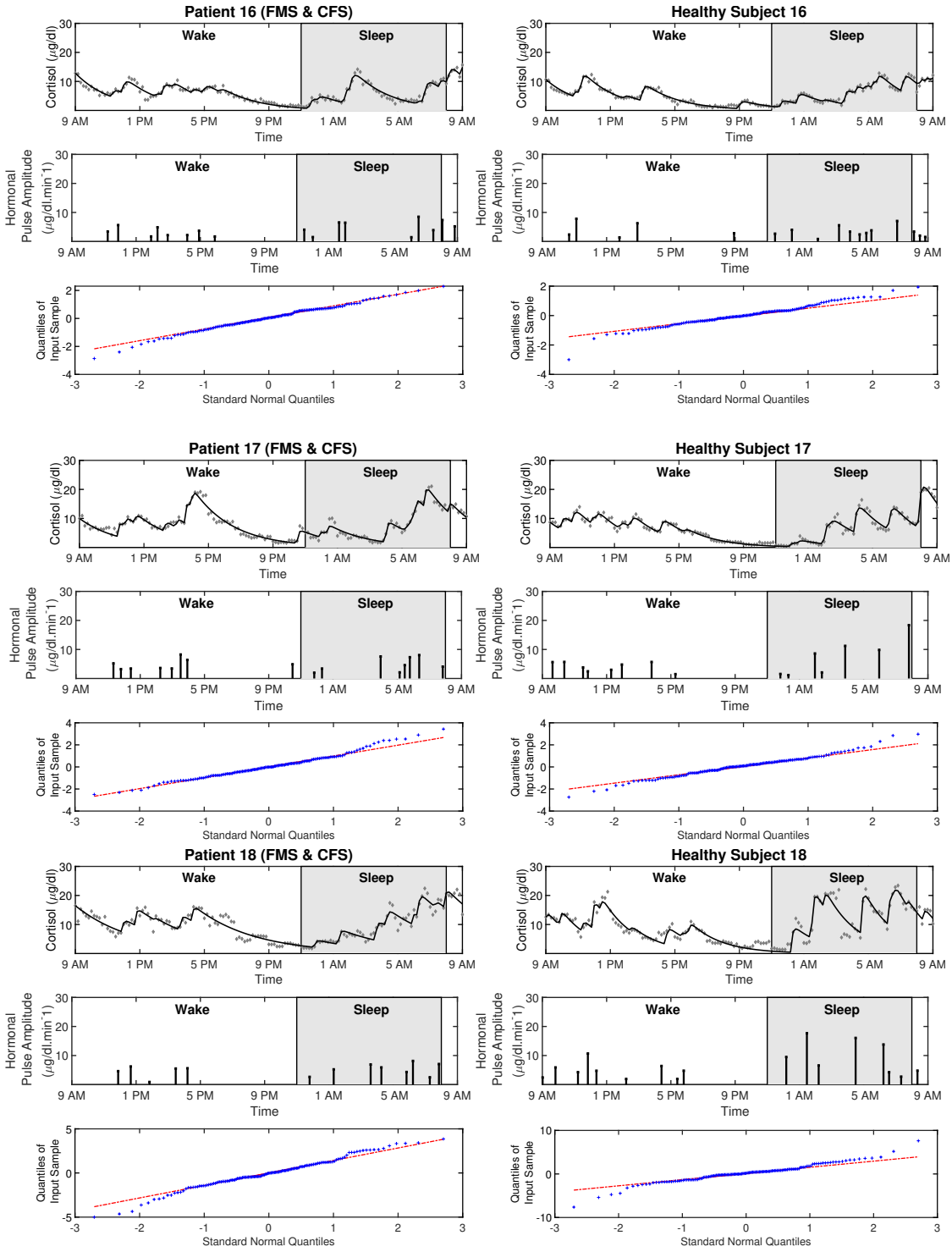

Patient 1 (FMS)
Healthy Subject 1
Patient 2 (FMS)
Healthy Subject 2
Patient 3 (FMS)
Healthy Subject 3
Wake
Sleep
Cortisol (μg/dl)
Hormonal Pulse Amplitude (μg/dl.min⁻¹)
Time
9 AM
1 PM
5 PM
9 PM
1 AM
5 AM
Quantiles of Input Sample
Standard Normal Quantiles

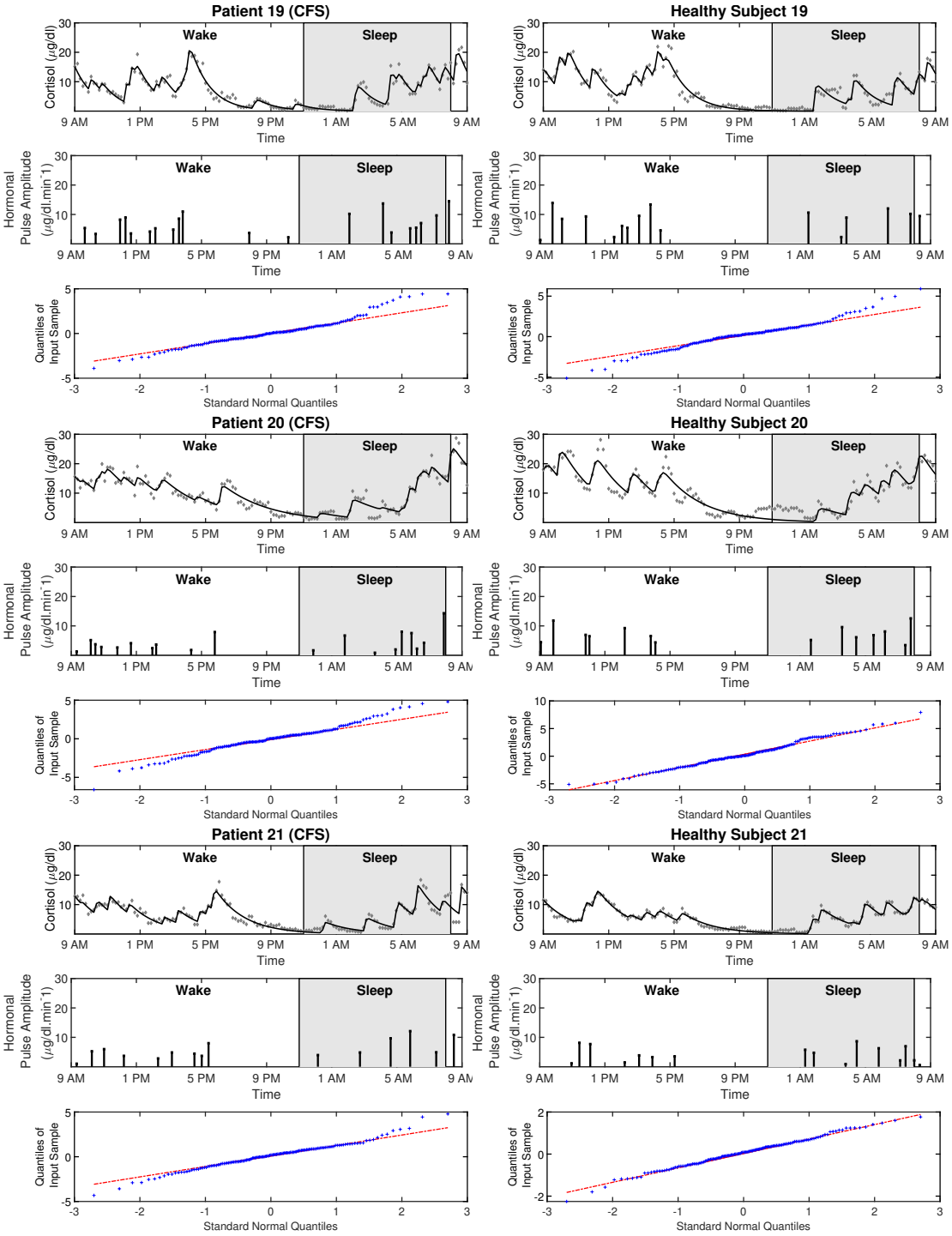

Patient 4 (FMS & CFS)
Healthy Subject 4
Patient 5 (FMS & CFS)
Healthy Subject 5
Patient 6 (FMS & CFS)
Healthy Subject 6
Wake
Sleep
Cortisol (μg/dl)
Hormonal Pulse Amplitude (μg/dl.min⁻¹)
Time
9 AM
1 PM
5 PM
9 PM
1 AM
5 AM
Quantiles of Input Sample
Standard Normal Quantiles

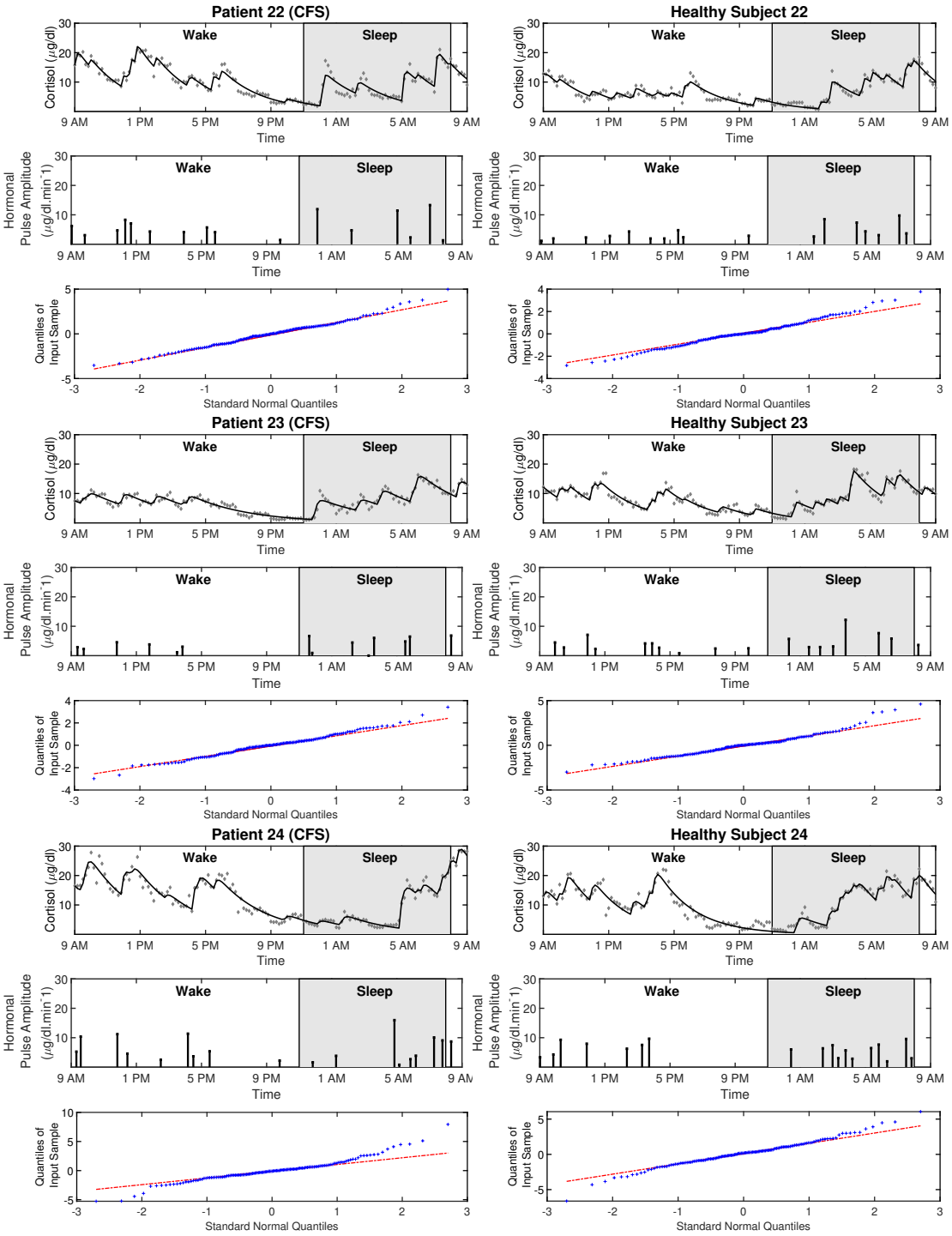

Patient 7 (FMS & CFS)
Healthy Subject 7
Patient 8 (FMS & CFS)
Healthy Subject 8
Patient 9 (FMS & CFS)
Healthy Subject 9
Wake
Sleep
Cortisol (μg/dl)
Hormonal Pulse Amplitude (μg/dl.min-1)
Quantiles of Input Sample
Time
Standard Normal Quantiles
9 AM
1 PM
5 PM
9 PM
1 AM
5 AM

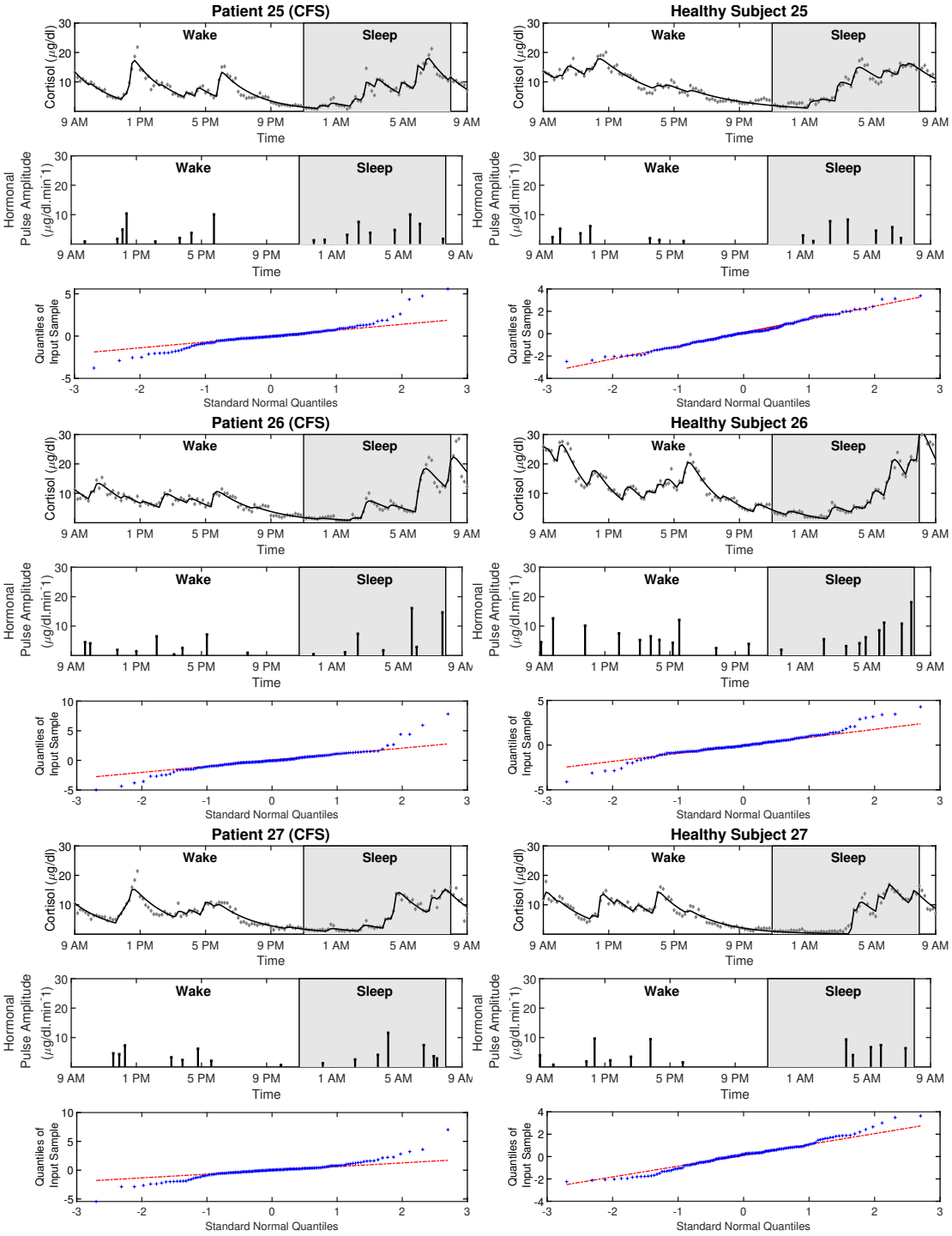

Patient 10 (FMS & CFS)
Healthy Subject 10
Patient 11 (FMS & CFS)
Healthy Subject 11
Patient 12 (FMS & CFS)
Healthy Subject 12
Wake
Sleep
Cortisol (μg/dl)
Hormonal Pulse Amplitude (μg/dl.min-1)
Quantiles of Input Sample
Standard Normal Quantiles
Time
9 AM
1 PM
5 PM
9 PM
1 AM
5 AM
9 AM

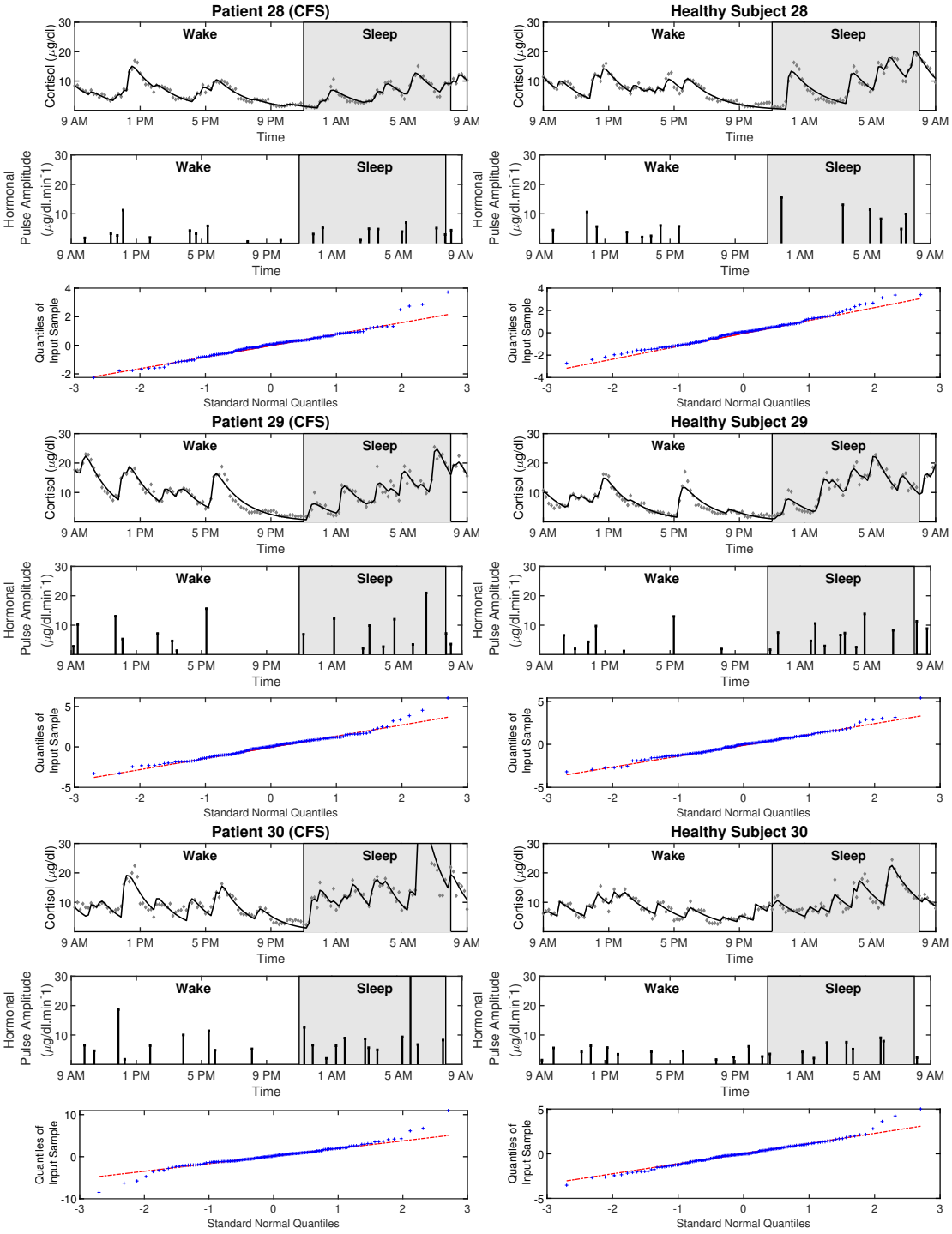

Patient 13 (FMS & CFS)
Healthy Subject 13
Patient 14 (FMS & CFS)
Healthy Subject 14
Patient 15 (FMS & CFS)
Healthy Subject 15
Wake
Sleep
Cortisol (μg/dl)
Hormonal Pulse Amplitude (μg/dl.min⁻¹)
Quantiles of Input Sample
Standard Normal Quantiles
Time
9 AM
1 PM
5 PM
9 PM
1 AM
5 AM
9 AM


Patient 16 (FMS & CFS)
Healthy Subject 16
Patient 17 (FMS & CFS)
Healthy Subject 17
Patient 18 (FMS & CFS)
Healthy Subject 18
Wake
Sleep
Cortisol (μg/dl)
Hormonal Pulse Amplitude (μg/dl.min-1)
Time
9 AM
1 PM
5 PM
9 PM
1 AM
5 AM
Quantiles of Input Sample
Standard Normal Quantiles


Patient 19 (CFS)
Healthy Subject 19
Patient 20 (CFS)
Healthy Subject 20
Patient 21 (CFS)
Healthy Subject 21
Wake
Sleep
Cortisol (μg/dl)
Hormonal Pulse Amplitude (μg/dl.min⁻¹)
Time
9 AM
1 PM
5 PM
9 PM
1 AM
5 AM
Quantiles of Input Sample
Standard Normal Quantiles


Patient 22 (CFS)
Healthy Subject 22
Patient 23 (CFS)
Healthy Subject 23
Patient 24 (CFS)
Healthy Subject 24
Wake
Sleep
Cortisol (μg/dl)
Hormonal Pulse Amplitude (μg/dl.min⁻¹)
Quantiles of Input Sample
Standard Normal Quantiles
Time
9 AM
1 PM
5 PM
9 PM
1 AM
5 AM


Patient 25 (CFS)
Healthy Subject 25
Patient 26 (CFS)
Healthy Subject 26
Patient 27 (CFS)
Healthy Subject 27
Wake
Sleep
Cortisol (μg/dl)
Hormonal Pulse Amplitude (μg/dl.min⁻¹)
Time
9 AM
1 PM
5 PM
9 PM
1 AM
5 AM
Quantiles of Input Sample
Standard Normal Quantiles


Patient 28 (CFS)
Healthy Subject 28
Patient 29 (CFS)
Healthy Subject 29
Patient 30 (CFS)
Healthy Subject 30
Wake
Sleep
Cortisol (μg/dl)
Hormonal Pulse Amplitude (μg/dl.min⁻¹)
Quantiles of Input Sample
Standard Normal Quantiles
Time
9 AM
1 PM
5 PM
9 PM
1 AM
5 AM

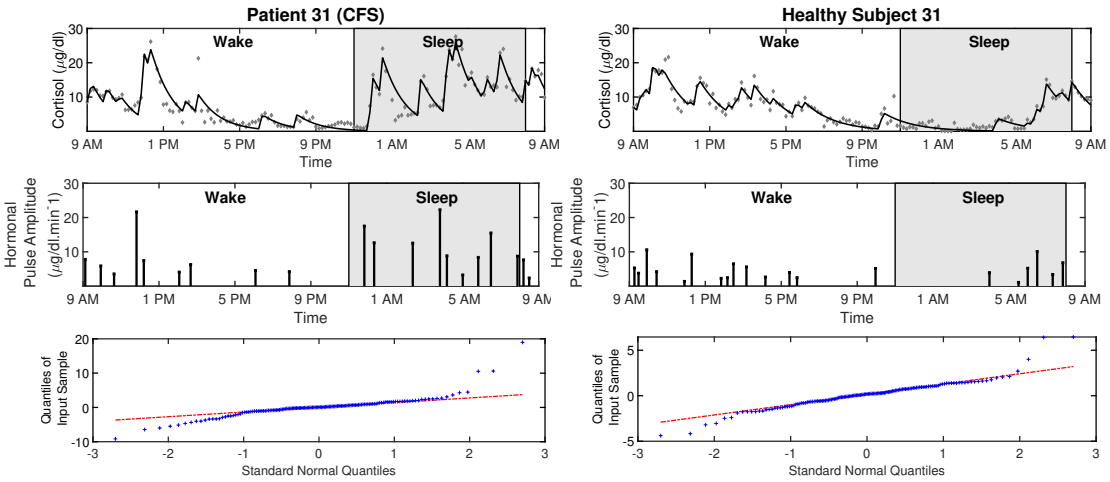
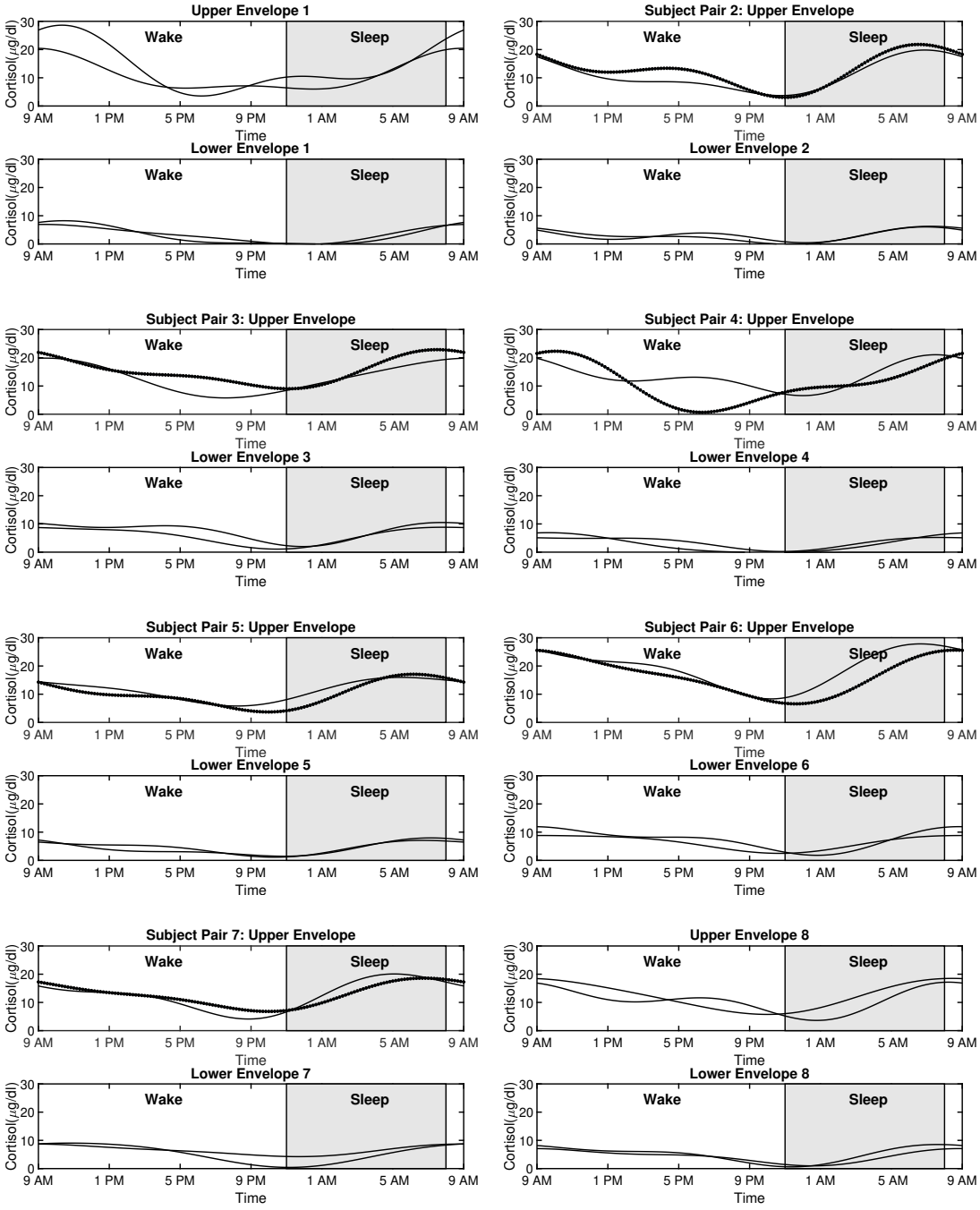


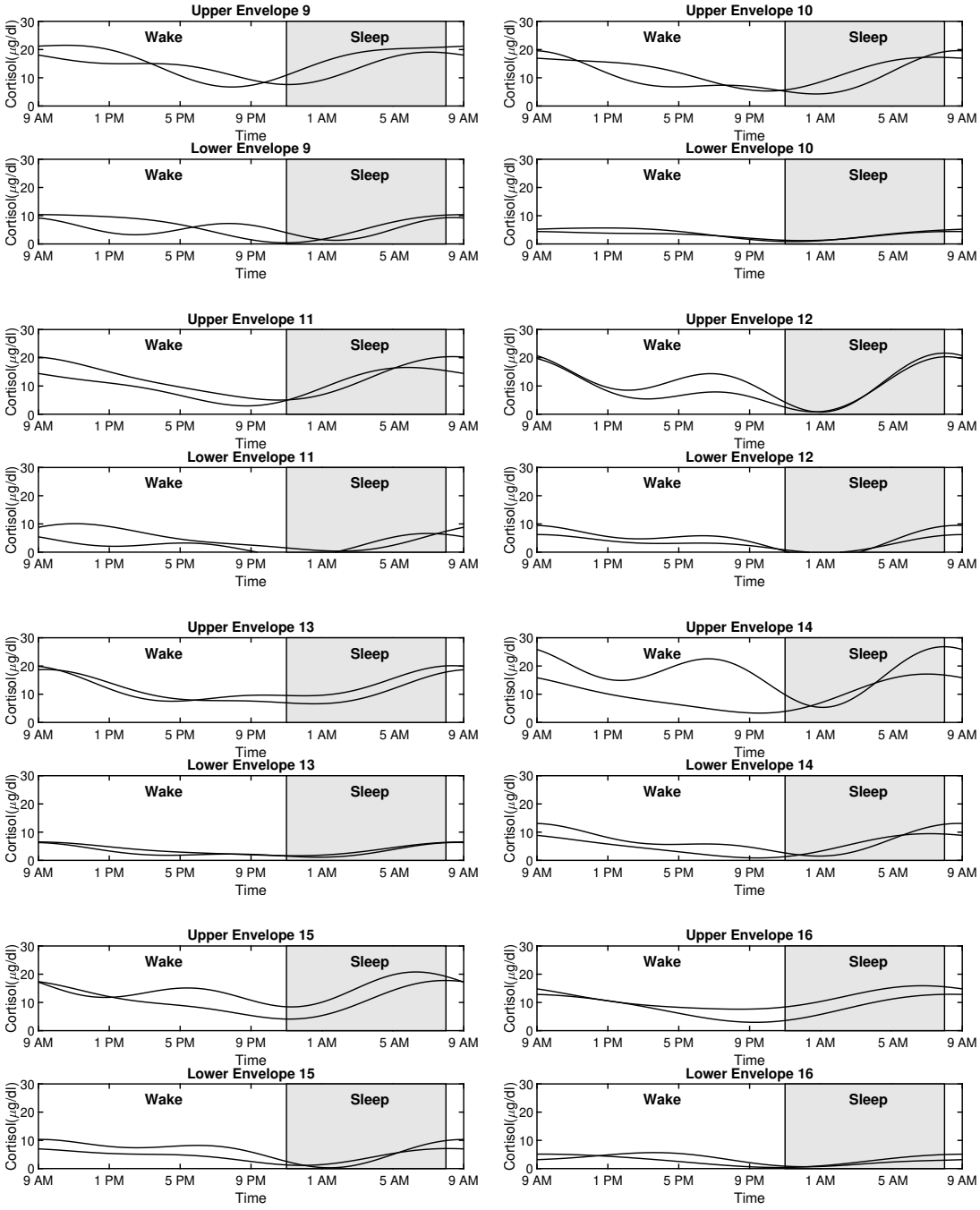
Figure 6: **Comparison between Deconvolved Experimental Twenty-Four-Hour Cortisol Levels in Matched Subject Pairs consisting of a Healthy Control Subject and a Patient.**

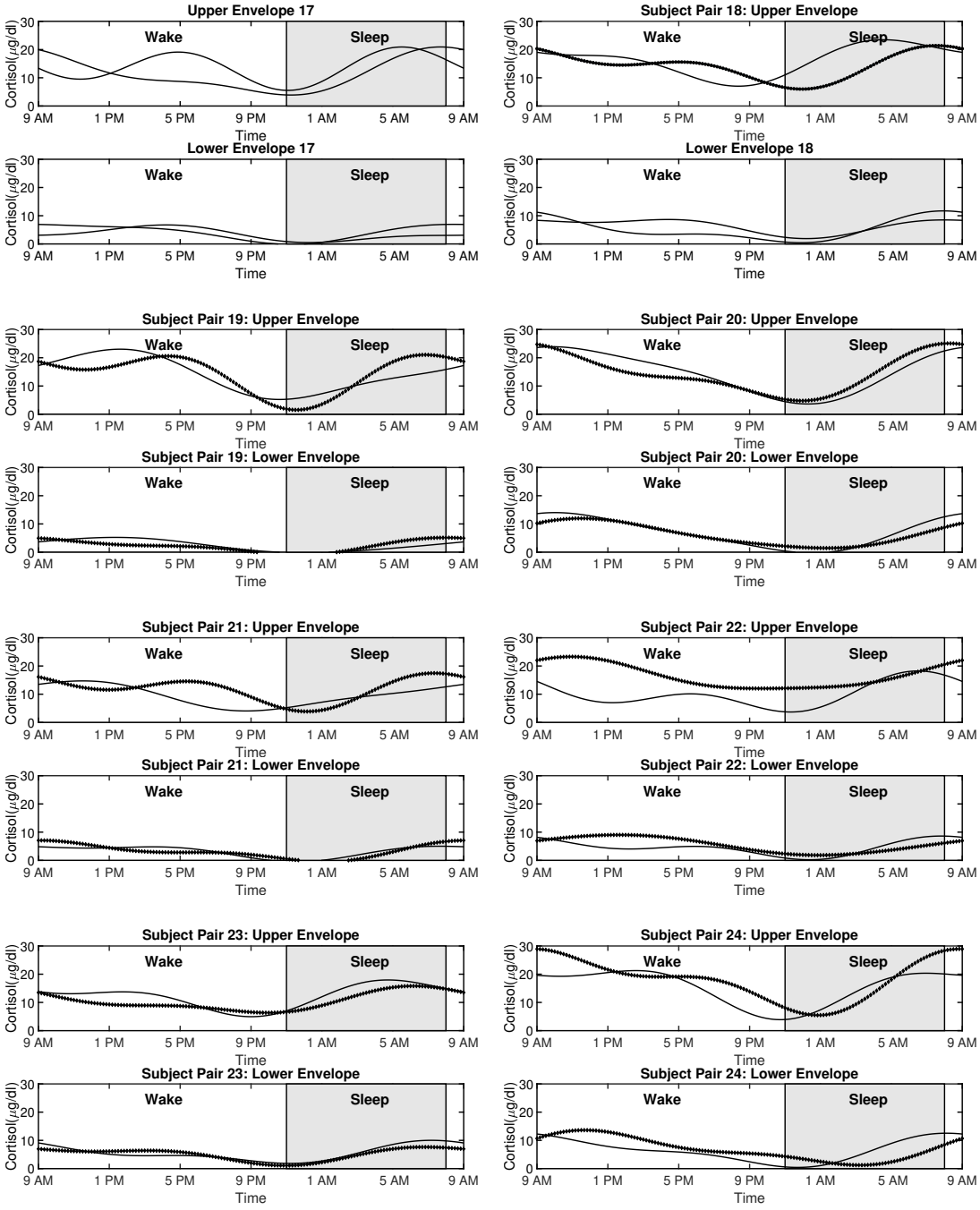
vertical lines), reconstructed from estimated amplitudes and timings obtained using deconvolution. The number of estimated hormone secretion events for all subjects are within physiologically plausible ranges with a square of the multiple correlation coefficient (R^2) above 0.80.

3. Lastly, the lower plot of Figure 6 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 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 7.


Upper Envelope 1
Subject Pair 2: Upper Envelope
Lower Envelope 1
Lower Envelope 2
Subject Pair 3: Upper Envelope
Subject Pair 4: Upper Envelope
Lower Envelope 3
Lower Envelope 4
Subject Pair 5: Upper Envelope
Subject Pair 6: Upper Envelope
Lower Envelope 5
Lower Envelope 6
Subject Pair 7: Upper Envelope
Upper Envelope 8
Lower Envelope 7
Lower Envelope 8
Wake
Sleep
Cortisol(μg/dl)
Time
9 AM
1 PM
5 PM
9 PM
1 AM
5 AM
0
10
20
30


Upper Envelope 9
Upper Envelope 10
Lower Envelope 9
Lower Envelope 10
Upper Envelope 11
Upper Envelope 12
Lower Envelope 11
Lower Envelope 12
Upper Envelope 13
Upper Envelope 14
Lower Envelope 13
Lower Envelope 14
Upper Envelope 15
Upper Envelope 16
Lower Envelope 15
Lower Envelope 16
Wake
Sleep
Cortisol(μg/dl)
0
10
20
30
9 AM
1 PM
5 PM
9 PM
1 AM
5 AM
9 AM
Time


Upper Envelope 17
Subject Pair 18: Upper Envelope
Lower Envelope 17
Lower Envelope 18
Subject Pair 19: Upper Envelope
Subject Pair 20: Upper Envelope
Subject Pair 19: Lower Envelope
Subject Pair 20: Lower Envelope
Subject Pair 21: Upper Envelope
Subject Pair 22: Upper Envelope
Subject Pair 21: Lower Envelope
Subject Pair 22: Lower Envelope
Subject Pair 23: Upper Envelope
Subject Pair 24: Upper Envelope
Subject Pair 23: Lower Envelope
Subject Pair 24: Lower Envelope
Wake
Sleep
Cortisol(μg/dl)
Time
9 AM
1 PM
5 PM
9 PM
1 AM
5 AM
9 AM
0
10
20
30

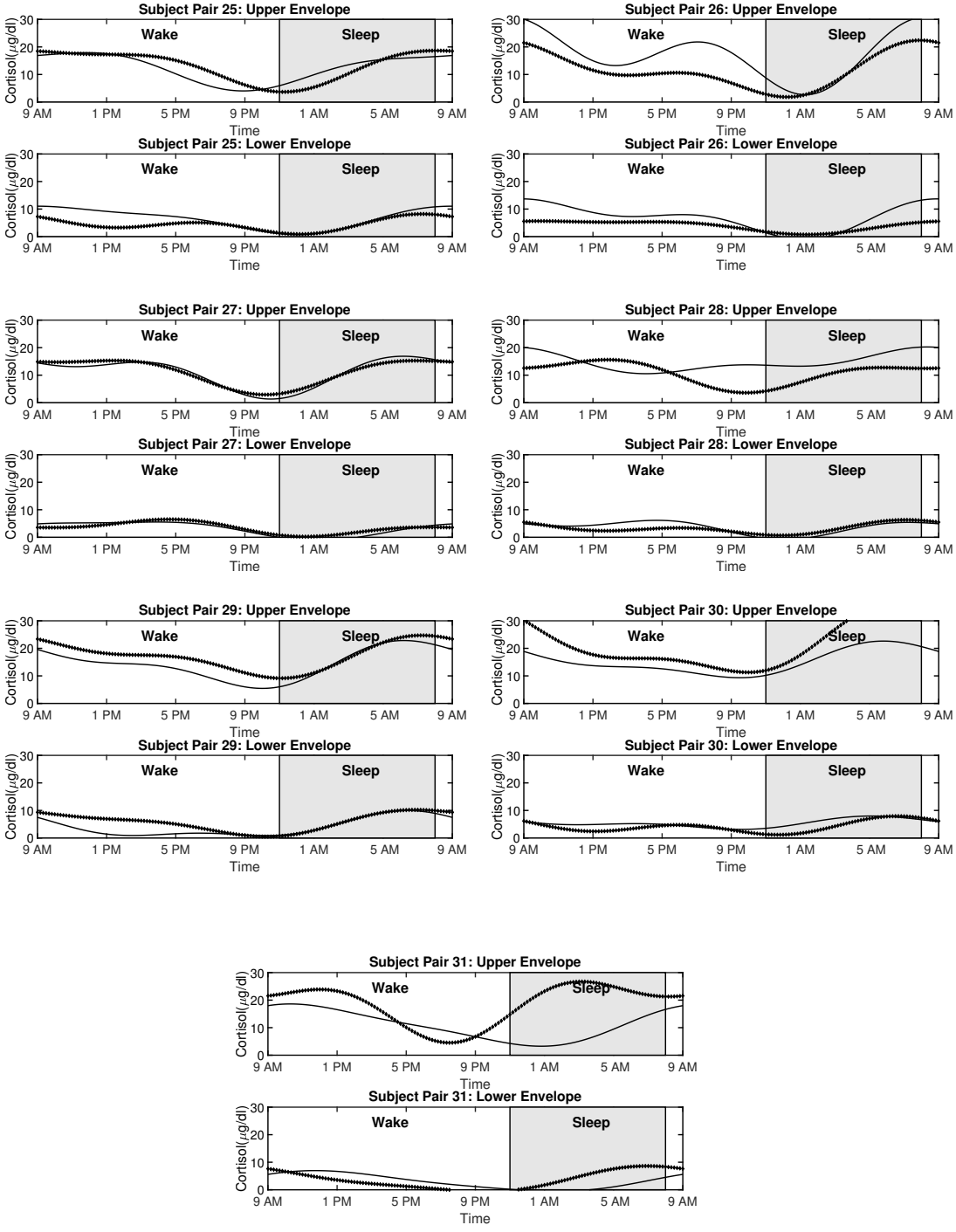


Figure 7: **Comparison between Upper and Lower Envelopes of a Healthy Control Subject and a Patient.**

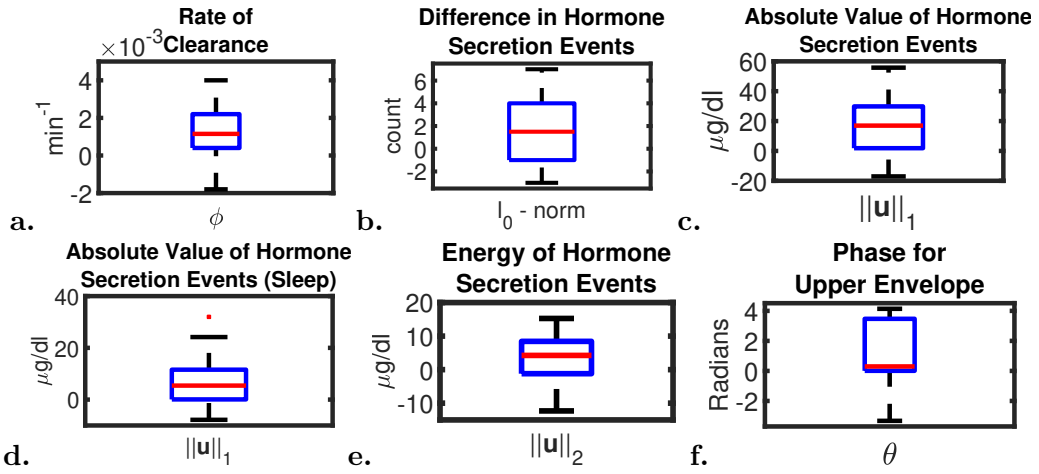


Figure 8: **Box-plot of Paired Differences for FMS subject pairs.**

2.3.1 Observed Cortisol Dysregulation/Secretion Abnormalities in Fibromyalgia Patients

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 [101]. 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 8 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.

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 8 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 do not observe significant difference for 18 subject pairs when we perform WSR on the distribution of energy of the hormonal secretory events ($||\mathbf{u}||_2^{\text{healthy}}$ & $||\mathbf{u}||_2^{\text{patient}}$).

Additionally, when we analyze the distribution of sum 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 8 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.

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 8 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 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.

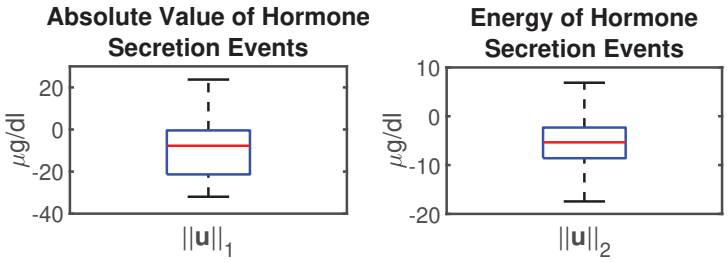


Figure 9: **Box-plot of the Absolute Value and Energy of the Hormonal Secretory Events between 4 AM and 9 AM for CFS subject pairs**.

2.3.2 Observed Cortisol Dysregulation/Secretion Abnormalities in Chronic Fatigue Patients

Statistical Analysis of Hormonal Secretory Events: We perform the two-tailed variant of the Wilcoxon signed-rank test on the paired differences of the absolute value of hormonal secretory events in the period 4 AM to 9 AM [101]. 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 9 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 [101]. 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 9 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.

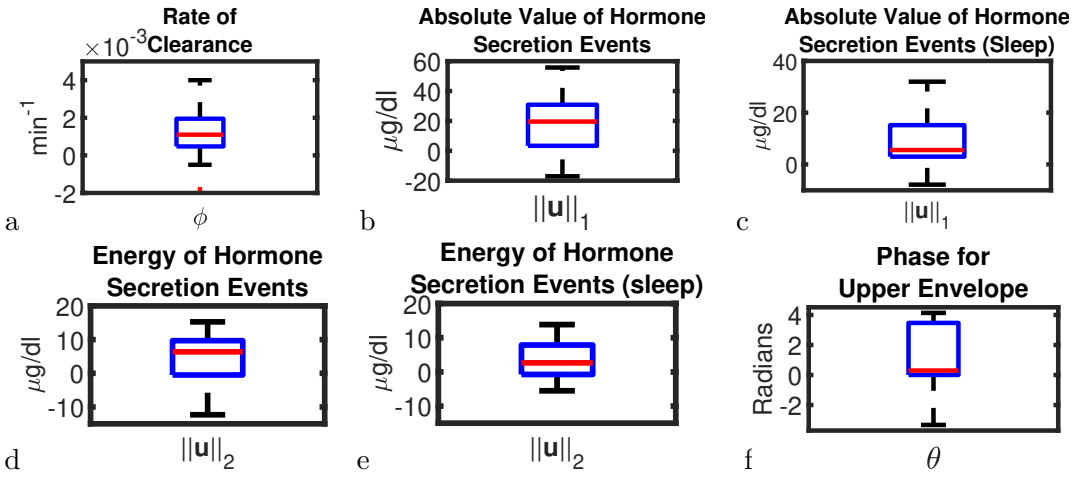


Figure 10: **Box-plot of Paired Differences for patients with both FMS and CFS.**

2.3.3 Observed Cortisol Dysregulation/Secretion Abnormalities in Patients with both Fibromyalgia and Chronic Fatigue

Statistical Analysis of Physiological Parameters: We perform the two-tailed variant of the Wilcoxon signed-rank test on the paired differences between the clearance rates of healthy control subjects and FMS patients (ϕ_2^{healthy} and ϕ_2^{patient}). This test was done considering all the 15 subject pairs (FMS & CFS both). We observe that the medians of ϕ_2^{healthy} and ϕ_2^{patient} are significantly different ($p = 0.0052$). The box-plot (a) in Figure 10 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.

Statistical Analysis of Hormonal Secretory Events: When we perform the two-tailed variant of the Wilcoxon signed-rank test on the distribution of magnitudes of hormonal secretory events ($||\mathbf{u}||_1^{\text{healthy}}$ and $||\mathbf{u}||_1^{\text{patient}}$) for 15 subject pairs (FMS & CFS both), we observe that the median of the FMS patients and the healthy subjects are different as well ($p = 0.0231$). The box-plot (b) in Figure 10 shows the sample distribution of the paired differences of the absolute value of the hormone secretion events, respectively. We observe that the median is greater for this distribution.

Additionally, when we analyze the distribution of magnitudes of hormonal secretory events during sleep cycle ($||\mathbf{u}||_1^{\text{healthy}}{}_{\text{sleep}}$ and $||\mathbf{u}||_1^{\text{patient}}{}_{\text{sleep)}}$ using the two-tailed variant of the Wilcoxon signed-rank test for 15 subject pairs (FMS & CFS both), we observe that the medians of the FMS patients and the healthy subjects are significantly different ($p = 0.0054$). The box-plot (c) in Figure 10 shows the sample distribution of the paired differences of the absolute value of the hormone secretion events during sleep cycle, respectively. We observe that the median is greater for this distribution.

Moreover, we analyze the distribution of energy of the hormonal secretory events ($||\mathbf{u}||_2^{\text{healthy}}$ and $||\mathbf{u}||_2^{\text{patient}}$) using the two-tailed variant of the Wilcoxon signed-rank test. When we consider 15 subject pairs (FMS & CFS both), we observe that the medians are different ($p = 0.0468$). The box-plot (d) in Figure 10 shows the sample distribution of the paired differences of the energy of the hormone secretion events during sleep, respectively. We observe that the median is greater for this distribution.

Lastly, When we perform the two-tailed variant of the Wilcoxon signed-rank test on the distribution of energy of hormonal secretory events during sleep ($||\mathbf{u}||_2^{\text{healthy}}{}_{\text{sleep}}$ and $||\mathbf{u}||_2^{\text{patient}}{}_{\text{sleep}}$), we observe that the median of the FMS patients and the healthy subjects are different ($p = 0.0231$). This test was done considering all the 15 subject pairs (FMS & CFS both). The box-plot (e) in Figure 10 shows the sample distribution of the paired differences of the energy of the hormone secretion events during sleep, respectively. We observe that the median is greater for this distribution as well.

Statistical Analysis on Circadian Rhythm: Similar to earlier cases, we again perform the two-tailed variant of Wilcoxon signed-rank test 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 ($p = 0.0468$). This test was done considering all the 15 subject pairs (FMS & CFS both). Finally, the box-plot (f) in Figure 10 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.

2.4 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.* [15] suggests a minimal model for both healthy individuals and patients. The model used in [29] is obtained from the stochastic model of diurnal cortisol patterns provided in [15]. Brown *et al.* [15] successfully realized this model for simulated cortisol data. Similarly, Faghih *et al.* [29] 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 [65]. Consequently, when psychological stress elicits secretion of inflammatory cytokines [86], cortisol will be less effective in inhibiting and appropriately resolving inflammation. Hence, as others have suggested [6], 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 [64, 8].

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 [29]. 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 [7]. 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.* [21] 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 8 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 [14]. 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 [14]. 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 [76] 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 Wilcoxon sign-rank test 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 9, 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. [21], identified lower serum cortisol levels in CFS patients as compared to their matched healthy subjects. Similar to our results, studies in [34, 69] suggest that hypocortisolism (low cortisol levels) could play an essential role in CFS. Van *et al.* [91] suggested that HPA-axis hypofunction can be conceived as prolonged dysfunction of the neurobiological stress system. Fries *et al.* [34] observed that hypocortisolism might be an outcome of hyperactivity of the HPA-axis due to chronic stress. Nijhof *et al.* [69] 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 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 8, 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 [80]. 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.

3 Characterization of Leptin and Cortisol Dynamics in Obese Patients

3.1 An Overview of Obestiy and Its relation with Leptin and Cortisol Secretion Dynamics

Obesity dubbed the "Global Epidemic" by the World Health Organization, which is said to cause or aggravate various other health problems, worsening one's life expectancy [68, 94]. The prevalence of obesity is increasing worldwide at an alarming rate. The estimate shows that about 4% of the world population are obese [49]. Different studies suggest different approaches for treating obesity, such as a low-calorie diet, therapy, and surgery [24, 93]. These pathogenic approaches are often used to treat the condition, but a salutogenic model may be more effective as both a preventive and remedial measure [71]. Identifying the hormones and tissues responsible for causing obesity will not only help us cure the disease but also prevent it. The hormones mainly studied to understand obesity are leptin, cortisol, growth hormone, insulin, and ghrelin [40]. In this research, we propose models to understand leptin and cortisol behavior, which can further be generalized for other hormones.

Leptin is a signaling hormone essential to activate central nervous system (CNS) networks, suppress appetite, alter immune function as well as is responsible for food intake, metabolism, energy expenditure in the human body, and body weight [60]. Studies show an irregular production of leptin in the body can result in weight gain [48]. Blood leptin levels also correlate to the changes in the fat stores [2]. The HPA-axis is the interaction between the hypothalamus, pituitary glands, and adrenal glands, and together is the system responsible for the body's reactions to stress, energy regulation, and energy usage [17]. Leptin is a hormone produced and

secreted primarily by adipocytes [10]. Excessive amounts of adipose tissue in the body correspond to an increased leptin production rate, and thus, higher serum leptin levels [60].

Similar to leptin, cortisol is responsible to signal the CNS. It is a steroid hormone responsible for the stress response in the body. [82]. Cortisol is a much-studied hormone when it comes to obesity [13]. In response to physiological stress, significant HPA-axis responses are induced across all ages and genders [55]. Björntorp *et al.* [13] compared several studies and concluded that the association between obesity and cortisol is complicated. They also suggest that it is necessary to examine the cortisol secretion process to further get a better insight about obesity [13].

In an attempt to study obesity, various models based on ordinary differential equations considering regulations in energy and metabolism [18, 23, 44, 46] and the effects of different hormones such as ghrelin, cholecystokinin, and leptin have been hypothesized. Traditional studies perform statistical analysis on the measured serum hormone levels. Some models include leptin, leptin resistance, and leptin receptors to understand obesity [22, 48, 88], other studies show the association of glucocorticoids and weight gain [85, 90], however this is not enough. Since, obesity is highly associated with the polypeptide hormone, leptin [17, 48, 60], and the glucocorticoid hormone, cortisol [13, 67], studying them will prove vital in designing an approach to treating it.

Aschbacher *et al.* [10] propose a mathematical model based on the systems-level understanding of the HPA-leptin axis. Incorporating leptin in the model helped

them to obtain three parameters: (I) inhibitory cortisol feedback signal, (II) Adrenocorticotropic hormone (ACTH)-adrenal interaction, and (III) leptin-cortisol proportionality. It concludes that the leptin-cortisol relationship may be crucial in understanding the neuroendocrine starvation response essential to understand obesity. The mathematical model mentioned in research by Aschbacher *et al.* [10] explains the rate of change in cortisol with respect to cortisol, ACTH, and leptin dynamics. The model used in this research is an extension of the HPA system dynamics model used previously in [6], incorporating leptin's impact on cortisol. Though leptin regulation is dependent on its relation with different hormones, understanding its behavior requires the study of leptin secretion and regulation. Inspecting the cortisol and leptin separately based on their physiology will be a vital option in interpreting how they behave concerning each other and other systems of the body. Jacquier *et al.* [48] introduce a mathematical model to study leptin resistance based on leptin synthesis and receptor activity. They study the changes in plasma leptin concentration, the density of leptin receptors, and food intake by varying leptin infusion and food consumption. This model studies leptin resistance dynamics based on many parameters such as leptin receptors, food intake, fat mass, and leptin hormone. However, sometimes it is challenging to simultaneously consider multiple observations while collecting human data, and therefore we propose a simplified model considering only plasma leptin levels as the observation. Since leptin secretion is pulsatile, we intend to exploit this characteristic. In this research, we propose a simplified method to understand leptin regulation by exploiting the sparse nature of leptin secretion. If plasma leptin levels are sampled at a 10-minute sampling rate over 24-hours, we obtain a maximum of 40 leptin secretion events out

of a total of 1440 secretion possibilities (considering 1-minute resolution for secretion timing), therefore, the nature being sparse. The sparse system identification of leptin dynamics over time makes it possible to recover the number of leptin pulses and estimating the amplitudes and timings of leptin secretory events. For an extensive understanding of leptin secretion, it is necessary to unveil the pulses originating from the hypothalamus as an outcome to leptin signaling. The pulses resulting in leptin regulation and secretion are an outcome of several contributing factors such as the effects of other hormones on leptin regulation, the density of leptin receptors, and food intake. Similar to leptin, cortisol is also sparse [29]. Sparse system identification of cortisol will help us recover the abstraction of secretion events coming from the HPA-axis and the way it is infused by the adrenal glands and cleared by the liver. This approach has been verified for cortisol in healthy subjects [29] and also on patients suffering from chronic fatigue syndrome and fibromyalgia syndrome in Chapter 2 [76]. We suggest studying the leptin-cortisol behavior by first observing the underlying pulses and estimating the physiological infusion and clearance rates in the system using two separate regulatory minimal leptin and cortisol models, to further investigate the relationship between them.

Figure 11-A shows a pictorial representation of the leptin regulation and secretion model. Figure 11-B shows a pictorial representation of the overview of our work. The leptin model yields three important parameters: the timing and amplitudes of the leptin secretion events, the infusion rate of leptin by the adipose tissue and the clearance rate by the renal system. We further conduct statistical analysis on the recovered parameters. These hormonal secretory events are abstraction of the pulsatile nature of the cortisol and leptin hormones and provide a good estimation of the pulses originating in the CNS. An investigation on these events could further

help us to understand the role of the CNS as well as kidneys and liver in causing obesity.

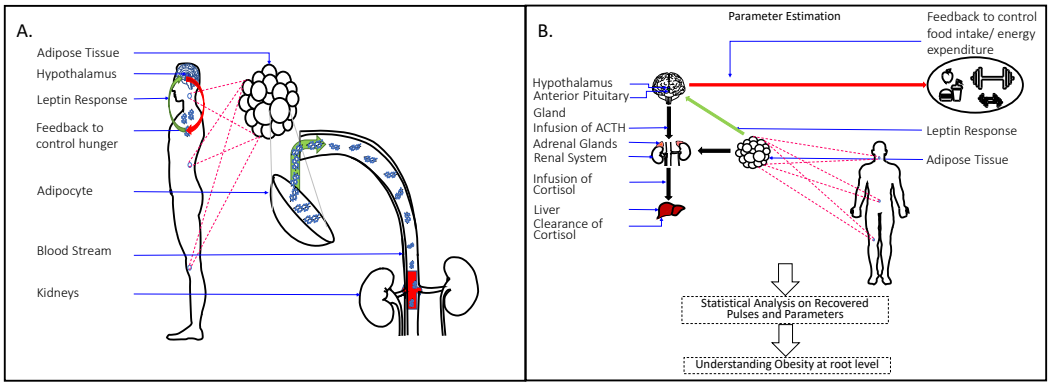


Figure 11: **Leptin Regulation Model and an Overview of System-Theoretic Approach.** (**A**) shows the leptin secretion & regulation model. (**B**) shows the overall approach used in this study.

Determining a system model for the relationship between leptin and cortisol concentrations provides us with a more comprehensive understanding of the biological system's behavior. This model can provide insight into the effects of the relationship of the hormones on weight gain.

Bioscience technology applies life processes to practical uses, such as the development of drugs and new medical devices. There are several bioscience and biosystem technologies used presently to simplify laboratory procedures and ease human life [81, 38]. Shortly, there will be bioscience technologies that would be able to obtain the leptin levels in the human body, similar to those available to obtain the insulin levels in the human body [25]. By deconvolving leptin levels and obtaining the hormonal pulses, we can further use expectation-maximization framework to obtain hunger states. Wickramasuriya *et al.* use the known fact that cortisol secretion in healthy humans has a circadian nature [97]. They derive multi-day data and observe

differences between healthy humans and patients. A similar study can be done for leptin, since leptin secretion is also influenced by the circadian rhythm. Similarly, another possible outcome of this study is to understand the leptin regulation behavior in obese patients against their matched healthy subjects. In Chapter 2, we used deconvolution to obtain the underlying hormonal pulses from cortisol data for fibromyalgia and chronic fatigue syndrome and their matched healthy subjects [75]. The healthy subjects are matched to the patients based on several factors such as age, sex, and weight. The comparison between the parameters and pulses obtained from the patients against their matched healthy subjects showed significant differences in clearance rates and hormonal pulses. A similar study can be done in the future, using leptin assays in obese and other related patients.

3.2 Methods

3.2.1 Experiment: Leptin and Cortisol Serum Measurements in Obese Patients

In this research, we use the serum leptin and cortisol data of the obese patients to better understand the role of leptin-cortisol dynamics in causing obesity [10]. Dataset contains 18 obese premenopausal women over a 24-hour period with 10-minute sampling frequency [10]. The subjects were within an age-group of 22-51 and with Body Mass Index between 30-41 kg /m^2. Each subject followed a consistent schedule with breakfast, lunch, and dinner provided, and had an 8.5 hour sleeping period between 23:00 and 7:30. The blood samples were collected without waking the subjects during this period. The above study was approved by the Medical Ethics Committee of Leiden University [10]. Participants were required to be free of chronic disease, and exclusion criteria were fixed, such as shift-work, depression,

alcohol abuse, and oral contraceptives. The blood samples were assayed every 10 minutes for cortisol, and every 20 minutes for leptin and intermediate points were interpolated. A detailed description of the experiment is provided in [10, 54].

3.2.2 Modeling Leptin Dynamics

The state-space model introduced in this research considers the first-order differential system of equations for leptin synthesis in the adipose tissue and clearance by the renal system. In a period of 24 hours, the blood samples were collected at a 10 minutes interval, i.e., 1440 events in a day (considering 1-minute resolution for secretion timing). In a discrete space of 1440 events, we observe between 20 to 40 pulses making it sparse in nature. In this model, we intend to utilize the sparse nature of the hormonal secretory events along with the other physiological constraints in a state-space model to estimate the amplitude and frequency of hormonal secretory events. The rate of change in leptin concentration of the adipose tissue is equal to the difference between the leptin synthesis rate and the leptin infusion rate from adipose tissue into the blood. Similarly, the rate of change of leptin concentration in the serum is equal to the difference between the leptin infusion rate from adipose tissue into the blood and the leptin clearance rate by the renal system [98]. The leptin secretion dynamics are represented as

$$\frac{dx_1(t)}{dt} = -\gamma_1 x_1(t) + u_l(t) \qquad \text{(Adipose Tissue)} \tag{12}$$

and

$$\frac{dx_2(t)}{dt} = \gamma_1 x_1(t) - \gamma_2 x_2(t) \qquad \text{(Serum)} \tag{13}$$

where $x_1(t)$ and $x_2(t)$ represent the effective leptin concentrations inside adipose tissues and leptin concentration in the blood serum, respectively. The model parameters γ_1 and γ_2 represent the infusion rate of leptin by the adipose tissue and the clearance rate of leptin by the kidneys, respectively. Input $u_l(t)$ represent the abstraction of effective pulses mainly produced by the adipose tissue. $u_l(t)$ can be modeled as a summation of delta functions with $u_l(t) = \sum_{i=1}^{N} q_i \delta(t - \tau_i)$ where q_i is the magnitude of the pulse initiated at time τ_i. If no pulse occurs at τ_i, q_i is equal to zero. The pulses are assumed to occur at integer minutes, i.e., in a 24-hour period, there are 1440 distinct locations ($N = 1440$). The blood samples are collected every 20 minutes and intermediate points are interpolated, for M samples ($M = 144$). Blood samples were collected, beginning at y_{l_0} and then assayed for leptin. Let $y_{t_{10}}, y_{t_{20}}, \ldots, y_{t_{10M}}$, $t_k : k = 10, 20, \ldots, 10M$. Also, $y_{l_0} = y_{t_{10}}$.

$$\mathrm{y}_{t_k} = x_2(t_k) + \nu_{t_k} \tag{14}$$

where y_{t_k} and v_{t_k} represent the observed leptin level and hormone measurement error at a time t_k, respectively. We model v_{t_k} random variables as Gaussian random variable. Then, we assume that the observed output value at time t_k will be equal to the previous value, y_{l_0}, multiplied by a decay term and added to a secretion value and the error term. We can represent the solution for every time point t_k with the following equation

$$\mathrm{y}_{l_{t_k}} = \mathrm{a}_{t_k}\mathrm{y}_{l_0} + \mathbf{b_{t_k}}\mathbf{u}_l + \boldsymbol{\nu}_{t_k}. \tag{15}$$

We then solve for a_{t_k} and $\mathbf{b_{t_k}}$ using a forced solution approach, multiplying each side of the equation by e^{-at} and using mathematical methods to obtain the solutions.

Here, $\mathbf{b_{t_k}} = \big[\frac{\gamma_1}{\gamma_1-\gamma_2}(e^{-\gamma_2 k}-e^{-\gamma_1 k}) \quad \frac{\gamma_1}{\gamma_1-\gamma_2}(e^{-\gamma_2(k-1)}-e^{-\gamma_1(k-1)}) \quad \cdots \quad \frac{\gamma_1}{\gamma_1-\gamma_2}(e^{-\gamma_2}-e^{-\gamma_1})$
$\underbrace{0 \quad \cdots \quad 0}_{N-k}\big]'$, $a_{t_k} = e^{-\gamma_2 k}$
and with $\mathbf{u}_l$ representing the input over the entire 24-hour sampling period, with values q_i over $i = 1, \ldots, 1440$. From these matrices, we can form a combined representation for the system at any time, using $\mathbf{y}_l = \begin{bmatrix} y_{t_{10}} & y_{t_{20}} & \cdots & y_{t_{10M}} \end{bmatrix}'$, $\mathbf{u}_l = \begin{bmatrix} q_1 & q_2 & \cdots & q_N \end{bmatrix}'$, $\boldsymbol{v} = \begin{bmatrix} v_{t_{10}} & v_{t_{20}} & \cdots & v_{t_{10M}} \end{bmatrix}'$, $\boldsymbol{\gamma} = \begin{bmatrix} \gamma_1 & \gamma_2 \end{bmatrix}'$ $\boldsymbol{A_\gamma} = \begin{bmatrix} a_{t_{10}} & a_{t_{20}} & \cdots & a_{t_{10M}} \end{bmatrix}'$, $\boldsymbol{B_\gamma} = \begin{bmatrix} \boldsymbol{b_{t_{10}}} & \boldsymbol{b_{t_{20}}} & \cdots & \boldsymbol{b_{t_{10M}}} \end{bmatrix}'$.

We then represent the system output as

$$\mathbf{y}_l = \boldsymbol{A_\gamma} y_{l_0} + \boldsymbol{B_\gamma} \mathbf{u}_l + \boldsymbol{\nu}_l$$

where output vector $\mathbf{y}_l$ is dependent on the initial signal value, the input pulses, and the error term. The values of matrices $\boldsymbol{A_\gamma}$ and $\boldsymbol{B_\gamma}$ are dependent on the values of γ for the given subject.

3.2.3 Leptin Parameter Estimation

Sparse signal reconstruction allows us to recover information on the timing and amplitude of hormone pulses beginning with a discrete-time sampled signal. Following data reported by [52], we develop a relationship between γ_1 and γ_2 assuming that the infusion rate for leptin from the adipose tissue is at least greater than or equal to the rate of leptin clearance from circulation by the kidneys. We use this relationship in our estimation of our model parameters, with $\gamma_1 \geq \gamma_2$. The values of the infusion and clearance rates are assumed to be non-negative $\gamma_1, \gamma_2 \geq 0$.

The study by [56] compared the leptin levels of obese women against healthy women and found that the concentration of independent pulsatile parameters of leptin, such as the pulse duration and frequency remained consistent between the groups, and that the excessive leptin levels in the obese persons were due only to an increased pulse height during secretion. The average number of leptin secretory events was found to be 32.0 ± 1.8 per day with 7-minute sampling in [56], within a range of 29 to 39 pulses among the subjects. In a study done the following year, [57] found the average number of leptin pulses to be 30.0 ± 1 with the range of pulses between 21 to 39 over a 24 hour sampling period. These studies give a likely average of around 30 pulses per day of leptin, with a range between 20 to 40 being a possibility. We assumed there to be between 20-40 secretory events during a 24-hour period, represented by the non-zero elements of our input function $u(t)$. We than formulate an optimization problem, generating values for u and γ that result in the minimum error for the output value. We consider the minimization of $\frac{1}{2}||\mathbf{y}_l - \boldsymbol{A}_{\boldsymbol{\gamma}} \mathrm{y}_{l_0} - \boldsymbol{B}_{\boldsymbol{\gamma}} \mathbf{u}_l||_2^2$ which we can see from the previous section is equivalent to the error term $\boldsymbol{v}_l$. We also constrain the optimization problem with the physiological boundary conditions imposed that $20 \leq ||\mathbf{u}_l||_0 \leq 40$ and $\mathbf{u}_l \succeq 0$.

We consider the amplitude of hormonal pulses to be greater than zero because these effective abstraction of pulses leads to secretion of the hormone, and we cannot have negative pulses leading to secretion of hormone.

Using the relationship between γ_1 and γ_2, we form the additional constraint that $C\gamma \preceq b$ where, $C = \begin{bmatrix} -1 & -1 & 0 \\ 1 & 0 & -1 \end{bmatrix}^\top, b = \begin{bmatrix} 0 & 0 & 0 \end{bmatrix}^\top$. Each row of C and b are formed based on the physiological constraints on γ_1 and γ_2.

We solve this problem by using an extension of the FOCal Under-determined

System Solver (FOCUSS) [41] algorithm. The optimization problem is given as

$$\min_{C\gamma \preceq b} J_{\lambda}(\gamma, \mathbf{u}_l) = \frac{1}{2}||y - A_{\gamma} y_0 - B_{\gamma}\mathbf{u}_l||_2^2 + \lambda||\mathbf{u}_l||_p^p \tag{16}$$

The optimization problem is NP-hard. We consider the l_p-norm as an approximation to the l_0-norm, where p is 0.5. Here the value of λ is chosen to contain the number of pulses between 20 and 40. If λ is large, the minimization of the cost function will focus on the term in which it is contained, and if λ is zero, we will have the original error minimization problem. This term balances the minimization of the error with returning the maximum sparsity for the input.

We solve this optimization problem iteratively by using a coordinate descent algorithm. We iterate between

$$\mathbf{u}_l^{(m+1)} = \arg\min_{\mathbf{u}_l \succeq 0} J_{\lambda}(\boldsymbol{\gamma}^{(m)}, \mathbf{u}_l) \tag{17}$$

and

$$\boldsymbol{\gamma}^{(m+1)} = \arg\min_{C\boldsymbol{\gamma} \preceq \mathbf{b}} J_{\lambda}(\boldsymbol{\gamma}, \mathbf{u}_l^{(m+1)}). \tag{18}$$

3.2.4 Cortisol Model Formulation in Obese Patients

In this research, we use the cortisol secretion model provided by Faghih *et al.* [29]. It exploits the sparse nature of hormonal secretory events and other physiological constraints to estimate the amplitude and timings of the secretory events using a state-space model. The rate at which cortisol concentration changes in the adrenal glands is equal to the difference between the rate at which it is infused in the blood and the rate at which it is secreted. The rate of change in serum cortisol

concentration is equal to the difference between the rate at which it is infused by the adrenal gland into the blood and the rate at which it is cleared by the liver from the blood.

$$\frac{dx_3(t)}{dt} = -\psi_1 x_3(t) + u_c(t) \qquad \text{(Adrenal Glands)} \tag{19}$$

and

$$\frac{dx_4(t)}{dt} = \psi_1 x_3(t) - \psi_2 x_4(t) \qquad \text{(Serum)} \tag{20}$$

where $x_3(t)$ and $x_4(t)$ represent the cortisol concentrations in the adrenal glands and the blood serum, respectively. The physiological model parameters ψ_1 and ψ_2 represent the infusion rate of cortisol by the adrenal glands and the cortisol clearance rate by the liver respectively. Input $u_c(t)$ represents the abstraction of pulses coming from the hypothalamus responsible for the production of cortisol. Input $u_c(t)$ can be modeled as a summation of delta functions with $u_c(t) = \sum_{i=1}^{N} q_i \delta(t - \tau_i)$. q_i is the magnitude of the pulse initiated at time τ_i. If no pulse occurs at τ_i, q_i will equal zero. The pulses are assumed to occur at integer minutes, i.e., in a 24-hour period, there are 1440 distinct locations ($N = 1440$). The blood samples are collected every 10 minutes, for M samples ($M = 144$). As explained in Section 3.2.2 the output, i.e. the measurement can be represented as

$$\mathrm{y}_{c_{t_k}} = x_4(t_k) + \omega_{t_k} \tag{21}$$

where y_{t_k} and ω_{t_k} are the observed cortisol concentration and the measurement

error, respectively. The initial concentration of cortisol in adrenal glands and serum is assumed to be zero and y_{c_0}. The system is further expressed as

$$\mathbf{y}_c = \boldsymbol{A}_{\boldsymbol{\psi}} \mathrm{y}_{c_0} + \boldsymbol{B}_{\boldsymbol{\psi}} \mathbf{u}_c + \boldsymbol{\omega}_c \tag{22}$$

where, $\mathbf{y}_c = \begin{bmatrix} \mathrm{y}_{t_{10}} & \mathrm{y}_{t_{20}} & \cdots & \mathrm{y}_{t_{10M}} \end{bmatrix}'$, $\boldsymbol{A}_{\boldsymbol{\psi}} = \begin{bmatrix} a_{t_{10}} & a_{t_{20}} & \cdots & a_{t_{10M}} \end{bmatrix}'$, $\boldsymbol{B}_{\boldsymbol{\psi}} = \begin{bmatrix} \boldsymbol{b_{t_{10}}} & \boldsymbol{b_{t_{20}}} & \cdots & \boldsymbol{b_{t_{10M}}} \end{bmatrix}'$, $\mathbf{u} = \begin{bmatrix} q_1 & q_2 & \cdots & q_N \end{bmatrix}'$, $\boldsymbol{\psi} = \begin{bmatrix} \psi_1 & \psi_2 \end{bmatrix}'$, $\boldsymbol{v_c} = \begin{bmatrix} \boldsymbol{v_{t_{10}}} & \boldsymbol{v_{t_{20}}} & \boldsymbol{\cdots} & \boldsymbol{v_{t_{10M}}} \end{bmatrix}'$, $a_{t_i} = e^{-\psi_2 i}$ and $\boldsymbol{b_{t_i}} = \begin{bmatrix} \frac{\psi_1}{\psi_1 - \psi_2}(e^{-\psi_2 i} - e^{-\psi_1 i}) & \frac{\psi_1}{\psi_1 - \psi_2} (e^{-\psi_2 (i-1)} - e^{-\psi_1 (i-1)}) & \cdots & \frac{\psi_1}{\psi_1 - \psi_2}(e^{-\psi_2} - e^{-\psi_1}) & \underbrace{0 \quad \cdots \quad 0}_{N-i} \end{bmatrix}'$.

3.2.5 Cortisol Parameter Estimation

To estimate the model parameters, timings, and amplitudes of hormonal secretory events, we impose corresponding constraints on (22). The infusion rate of the cortisol from adrenal glands is at least four times the clearance rate of cortisol by the liver (i.e., $4\psi_2 \leq \psi_1$) [29]. [15, 92] show that there are between 15 to 22 cortisol secretory events (i.e., $15 \leq ||\mathbf{u}_c||_0 \leq 22, \mathbf{u}_c \geq 0$) in a 24-hour period. We therefore state the optimization problem as

$$\min_{\substack{\mathbf{u_c} \succeq 0 \\ \boldsymbol{D\psi} \preceq e}} \boldsymbol{J_\lambda(\psi, \mathbf{u_c})} = \frac{\mathbf{1}}{\mathbf{2}} ||\mathbf{y_c} - \boldsymbol{A_\psi} \mathrm{y}_{\boldsymbol{c_0}} - \boldsymbol{B_\psi} \mathbf{u_c}||_{\mathbf{2}}^{\mathbf{2}} + \boldsymbol{\lambda} ||\mathbf{u_c}||_{\boldsymbol{p}}^{\boldsymbol{p}} \tag{23}$$

where $\boldsymbol{D} = \begin{bmatrix} -1 & -1 & 0 \\ 4 & 0 & -1 \end{bmatrix}^\top$, $\boldsymbol{e} = \begin{bmatrix} 0 & 0 & 0 \end{bmatrix}^\top$.

Similar to Section 3.2.3, the regularization parameter, i.e., λ, is selected such that the sparsity level of pulses, i.e. $||\mathbf{u}_c||_0$ remains within the physiologically plausible

range. We choose the approximation for the l_0-norm as l_p-norm $(0 < p \leq 2)$. This problem can be solved using a deconvolution algorithm, which uses the coordinate-descent approach until we achieve convergence. We iterate between

$$\mathbf{u}^{(n+1)} = \arg \min_{\boldsymbol{u}_c \succeq 0} J_\lambda(\boldsymbol{\psi}^{(n)}, \mathbf{u}_c) \tag{24}$$

and

$$\boldsymbol{\psi}^{(n+1)} = \arg \min_{\boldsymbol{D}\boldsymbol{\psi} \preceq \mathbf{e}} J_\lambda(\boldsymbol{\psi}, \mathbf{u}_c^{(n+1)}). \tag{25}$$

Cortisol parameter estimation is explained in more detail in 2.2.3.

3.2.6 Sparse Recovery with Iterative Re-weighted Least Square Approach: (FOCal Under-determined System Solver+)

The same approach is used to solve the optimization problems for both leptin and cortisol but with different constraints. The FOCUSS algorithm can be used to solve the optimization problem in (17) and in (24) [41]. This algorithm uses a re-weighted norm minimization approach. The FOCUSS algorithm use the l_2-norm of the cost function in order to solve the minimization problem [41]. The deconvolution can be split into two stages with an initialization step using FOCUSS+, which is an extension of the FOCUSS algorithm, followed by a coordinate descent step using GCV - FOCUSS [39]. The coordinate descent approach minimizes multi-variable along one coordinate direction at a time [102]. A detailed explanation is provided in 2.2.4.

Table 1: **Clinical Characteristics of the Participants.** This table includes Body Mass Index (BMI) and Age for all participants.

Participant	BMI	Age
1	32.661	34
2	40.522	33
3	30.119	44
4	38.365	34
5	33.798	38
6	30.258	36
7	30.964	40
8	32.204	46
9	35.116	25
10	31.809	37
11	31.108	22
12	34.258	45
13	35.322	38
14	31.405	32
15	33.309	51
16	31.569	39
17	31.153	43
18	32.694	38

3.3 Results

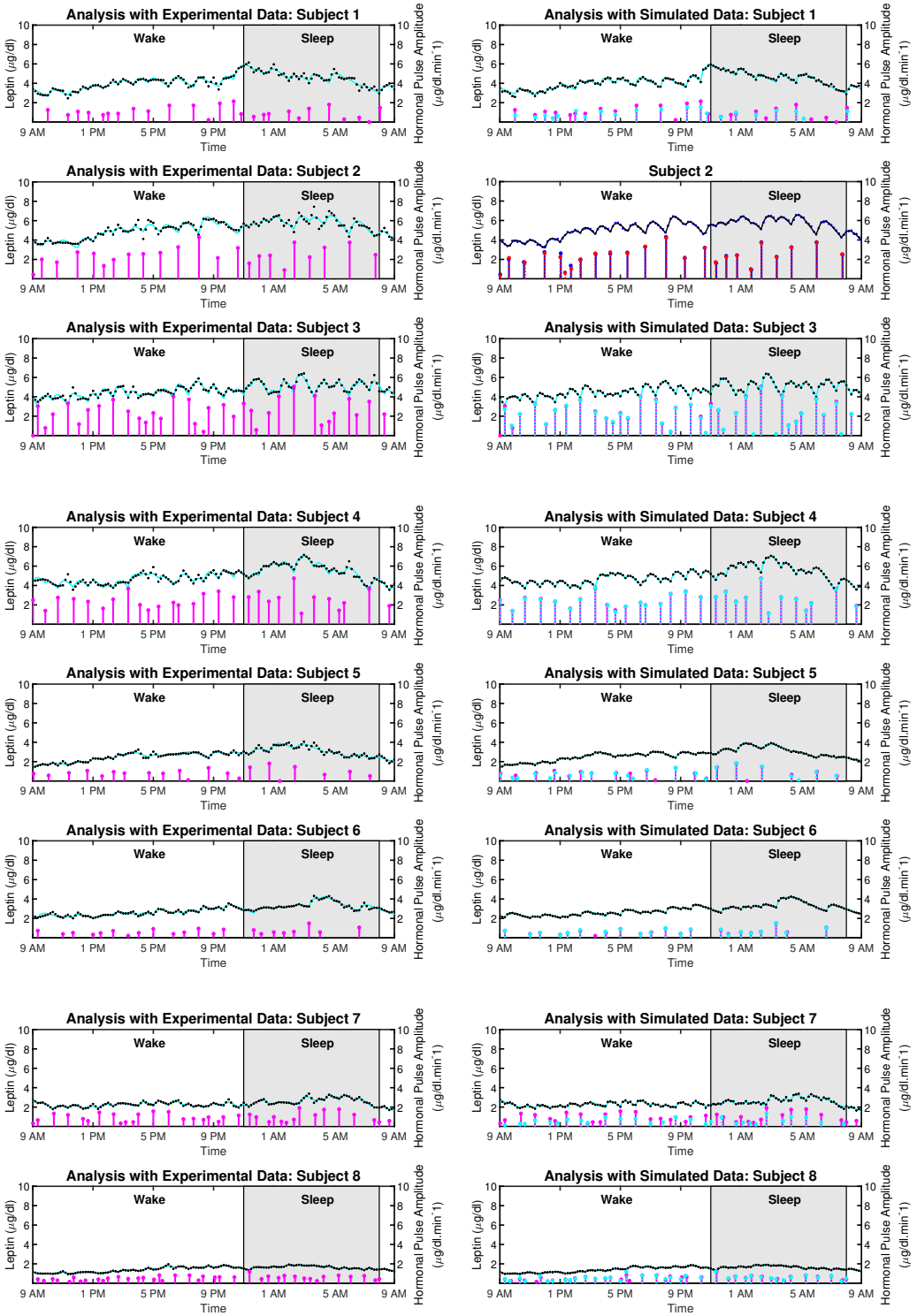
3.3.1 Estimated Leptin Secretion Events and Physiological Parameters

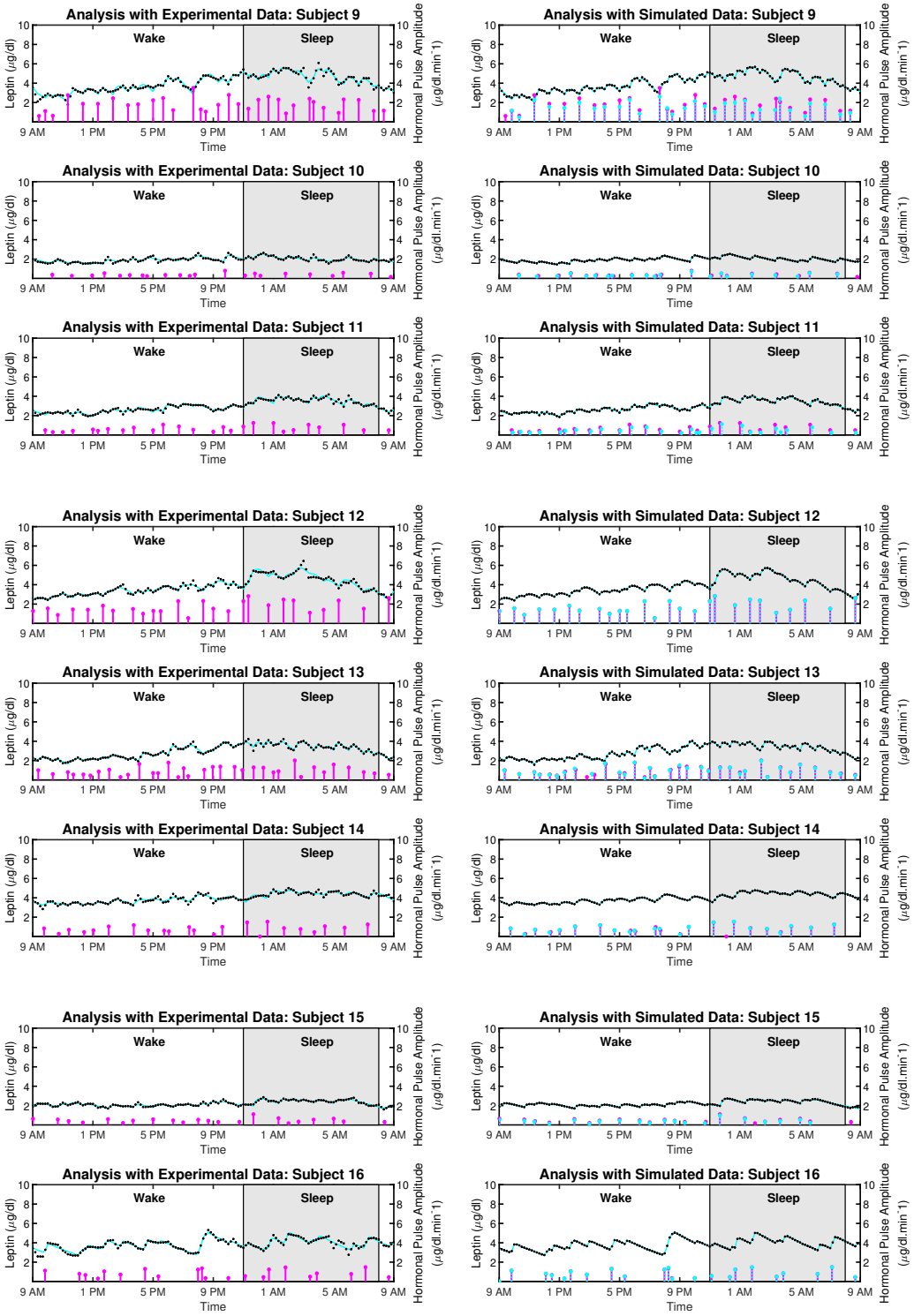
Table 1 shows the clinical characteristics, i.e., the age and body mass index (BMI) of all the participants. Participants with more than 30 kg/m^2 are considered to be obese. Figure 12-a shows the measured and reconstructed blood leptin levels of obese patients for experimental data. It exhibits the estimated amplitudes and timings of hormonal secretory events, experimental leptin data and estimates predicted by the model. The variations in amplitudes of the pulses are due to the circadian rhythm of underlying leptin release, and the variations in the timings are because of the ultradian rhythm [84]. The number of recovered secretory events for

all the patients were within the physiologically plausible range. This experimental data includes 18 obese patients. The black diamonds in Figure 12-a represent the measured leptin level obtained from blood samples. After deconvolution we obtain the hormonal secretory pulses, which are used to obtain the reconstructed signal. The square of the multiple correlation coefficient (R^2) is between 0.8327 and 0.98603. γ_1 and γ_2 are the infusion rate of leptin by adipose tissue and clearance rate of leptin by renal system in experimental subjects. $\hat{\gamma_1}$ and $\hat{\gamma_2}$ are the infusion rate and clearance rate of leptin in simulated subjects. The number of recovered pulses for the experimental data is between the pulse range 20-40.

In this research, we simulated data to further validate the proposed leptin model. We simulated 18 leptin datasets, each corresponds to an experimental dataset. The datasets are simulated from the estimated pulses of the experimental dataset shown in Figure 12-b. We have added Gaussian noise with standard deviation based on interassay co-efficient of variability (σ) provided in [10]. Figure 12-b shows the ground truth of the sparse input, the estimated input and the simulated leptin data. The blue stars show the estimated 24-hour leptin data, the black curve shows the estimated leptin levels, the vertical blue lines show the amplitudes and timings of the simulated data, and the vertical red lines show the amplitudes and timings of estimated hormone secretory events.

Figure 13 shows the sample distribution for infusion and clearance rates for simulated and experimental leptin levels.


Analysis with Experimental Data: Subject 1
Analysis with Simulated Data: Subject 1
Analysis with Experimental Data: Subject 2
Subject 2
Analysis with Experimental Data: Subject 3
Analysis with Simulated Data: Subject 3
Analysis with Experimental Data: Subject 4
Analysis with Simulated Data: Subject 4
Analysis with Experimental Data: Subject 5
Analysis with Simulated Data: Subject 5
Analysis with Experimental Data: Subject 6
Analysis with Simulated Data: Subject 6
Analysis with Experimental Data: Subject 7
Analysis with Simulated Data: Subject 7
Analysis with Experimental Data: Subject 8
Analysis with Simulated Data: Subject 8
Wake
Sleep
Leptin (μg/dl)
Hormonal Pulse Amplitude (μg/dl.min-1)
Time
9 AM
1 PM
5 PM
9 PM
1 AM
5 AM
9 AM


Analysis with Experimental Data: Subject 9
Analysis with Simulated Data: Subject 9
Analysis with Experimental Data: Subject 10
Analysis with Simulated Data: Subject 10
Analysis with Experimental Data: Subject 11
Analysis with Simulated Data: Subject 11
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Analysis with Simulated Data: Subject 12
Analysis with Experimental Data: Subject 13
Analysis with Simulated Data: Subject 13
Analysis with Experimental Data: Subject 14
Analysis with Simulated Data: Subject 14
Analysis with Experimental Data: Subject 15
Analysis with Simulated Data: Subject 15
Analysis with Experimental Data: Subject 16
Analysis with Simulated Data: Subject 16
Wake
Sleep
Leptin (μg/dl)
Hormonal Pulse Amplitude (μg/dl.min-1)
9 AM
1 PM
5 PM
9 PM
1 AM
5 AM
9 AM
Time

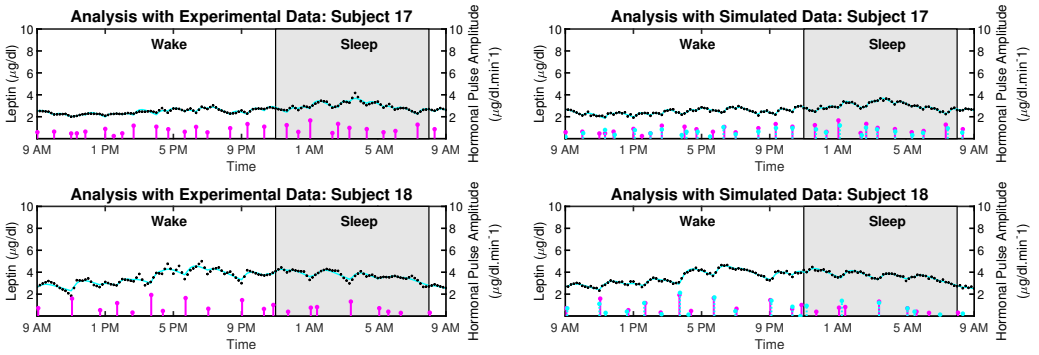


Figure 12: **Deconvolved Twenty-Four Hours Leptin Levels in Obese Patient.** (a) Sub-plot shows the measured 24-hour leptin time series. (b) Sub-plot shows the simulated 24-hour leptin time series.

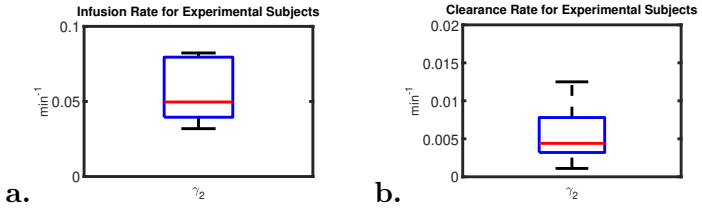
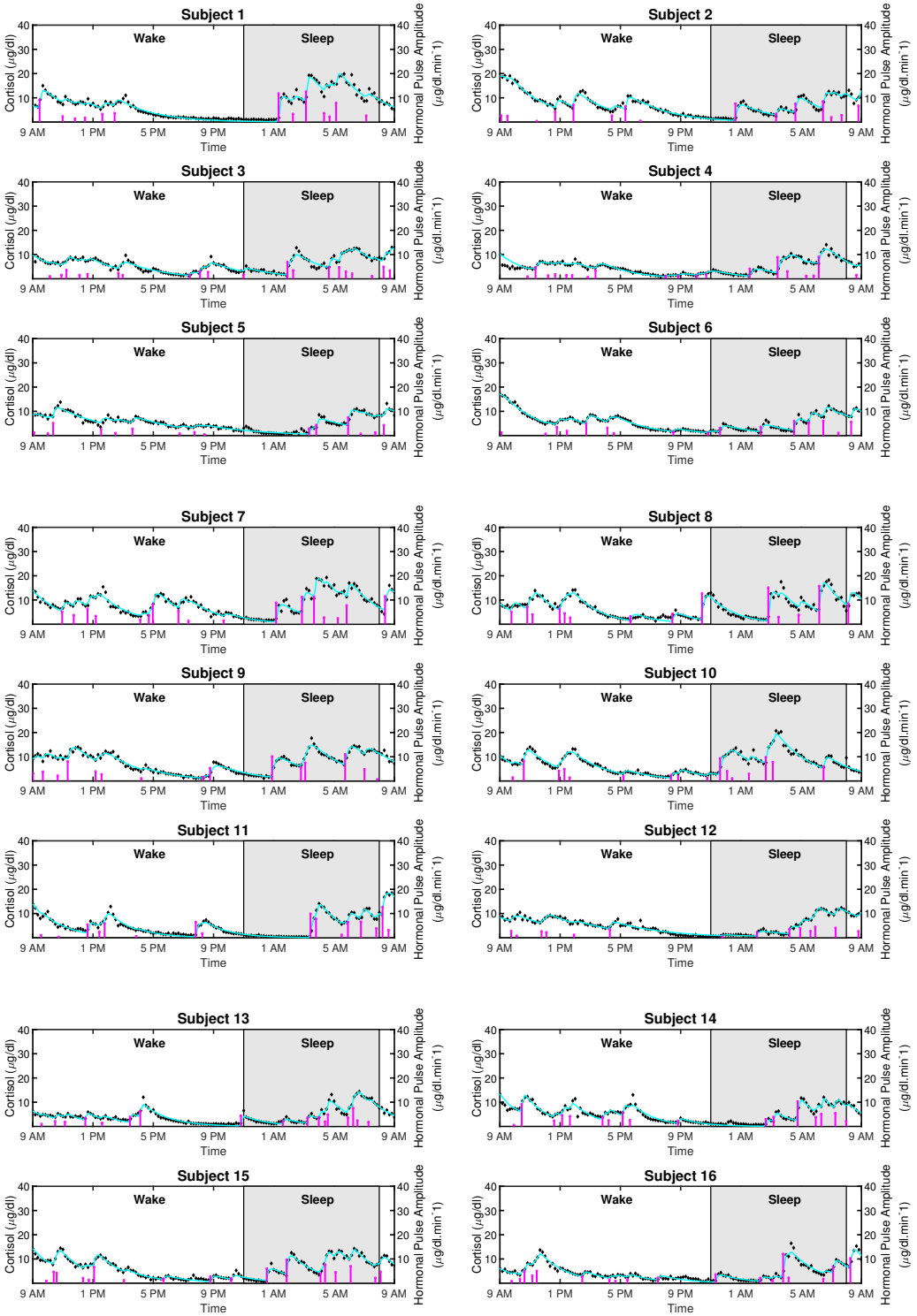


Figure 13: **Box-plot of Physiological Parameters of Leptin Levels.**

3.3.2 Estimated Cortisol Secretion Events and Physiological Parameters

Figure 14 shows the measured and reconstructed blood cortisol levels of obese patients. It shows the measured cortisol levels, reconstructed cortisol levels, estimated amplitudes and timings of hormonal secretory events, for the patients. The amplitude and timing variations of the pulses are due to the circadian rhythm and ultradian rhythm of underlying cortisol release [15]. The black diamonds in Figure 14 represent the measured cortisol level obtained from blood samples. After deconvolution, we obtain the abstraction of hormonal secretory events (blue vertical lines in Figure 14), which are used to obtain the reconstructed signal (red curve in Figure 14). The square of the multiple correlation coefficient (R^2) between 0.87557 and 0.98023. The model has been previously validated in previous studies [29, 30, 76].


Subject 1
Subject 2
Subject 3
Subject 4
Subject 5
Subject 6
Subject 7
Subject 8
Subject 9
Subject 10
Subject 11
Subject 12
Subject 13
Subject 14
Subject 15
Subject 16
Wake
Sleep
Cortisol (μg/dl)
Hormonal Pulse Amplitude (μg/dl.min^-1)
Time
9 AM
1 PM
5 PM
9 PM
1 AM
5 AM
9 AM

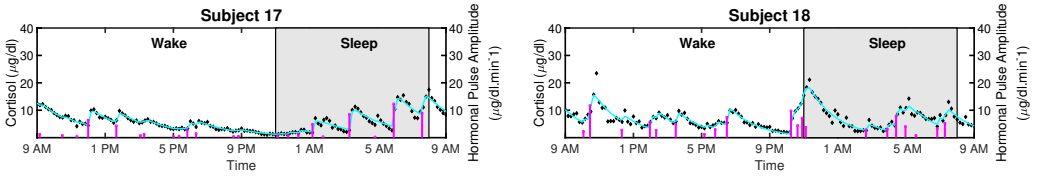


Figure 14: **Deconvolved Experimental Twenty-Four Hours Cortisol Levels in Obese Patient.**

3.3.3 Leptin-cortisol antagonism

The Pearson correlation coefficient is a measure of the strength of a linear association between two variables. Table 2 shows the Pearson correlation coefficient between measured leptin levels and measured cortisol levels for 18 participants. It also shows correlation coefficients for estimated as well as measured leptin and cortisol levels. The outcome for both these cases is very similar, and shows that the proposed model retain the properties previously known. We observe a leptin-cortisol antagonism.

Furthermore, we tried to visualize the correlation between the hormonal pulses against BMI and age, but we do not observe any significant differences.

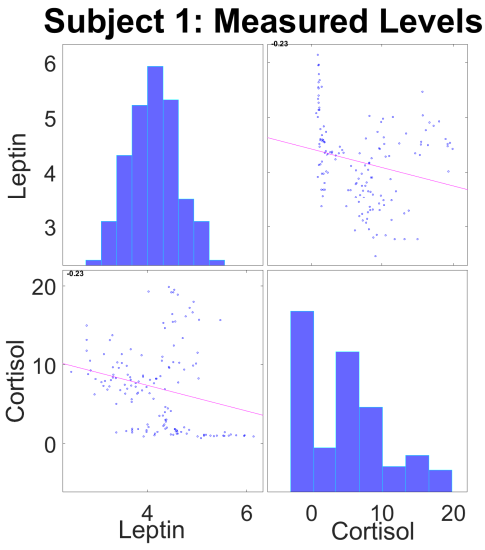
Figure 15 shows the correlation plots for leptin and cortisol levels. We plot for both the measured and estimated levels to show the similarities. Except for subjects 3, 10, 15, 17, and 18, we observe significant differences in the participants (i.e., $p \leq 0.05$).

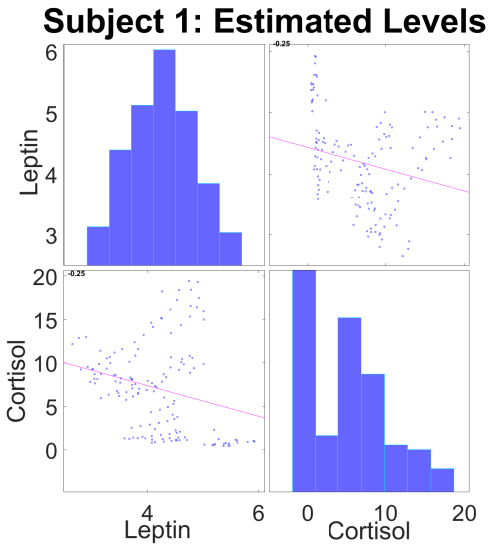
3.4 Discussion

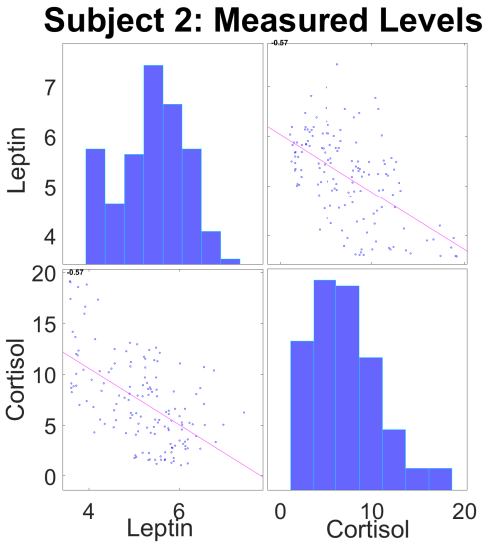
The primary objective of this research is to model the leptin secretion dynamics with respect to the adipose tissue and the renal system. The secondary objective of this research is to understand the leptin-cortisol interaction. The CNS regulates the

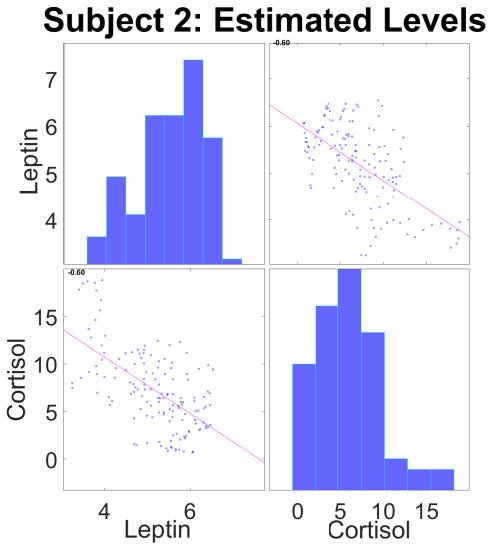
Table 2: **Comparison of Pearson Correlation.** Comparing Pearson correlation coefficients between the measured serum leptin and cortisol levels and the model estimated leptin and cortisol levels.

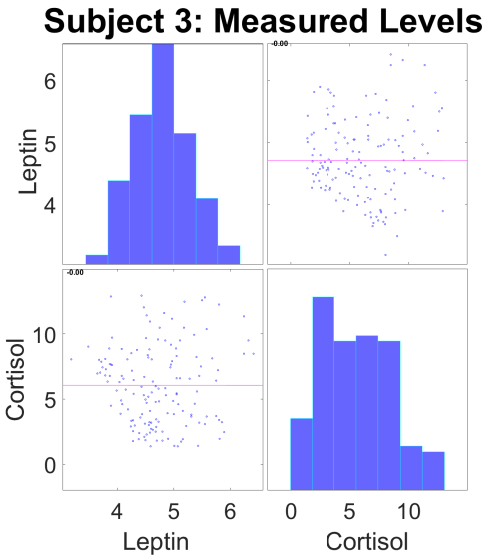
Participant	Coefficient for measured levels	p-value	Coefficient for estimated levels	p-value
1	-0.2336	0.0047	-0.2502	0.0024
2	-0.5661	1.653×10^{-13}	-0.5992	1.69×10^{-15}
3	-0.0004	0.9961	-0.0233	0.7807
4	-0.2624	0.0014	-0.2554	0.0019
5	-0.7407	1.7697×10^{-26}	-0.7903	3.15×10^{-32}
6	-0.4000	6.23×10^{-7}	-0.3944	9.19×10^{-7}
7	0.3810	2.2769×10^{-6}	0.3855	1.687×10^{-6}
8	-0.3882	1.4041×10^{-6}	-0.4012	5.705×10^{-7}
9	-0.2605	0.0016	-0.2379	0.0040
10	-0.0701	0.4021	-0.1138	0.1729
11	-0.1841	0.0267	-0.1860	0.0251
12	-0.6131	2.4763×10^{-16}	-0.6499	9.16×10^{-19}
13	-0.1784	0.0318	-0.2004	0.0156
14	-0.2792	6.7071×10^{-4}	-0.3044	1.97×10^{-4}
15	0.0590	0.4806	0.0689	0.4102
16	-0.1515	0.0690	-0.1425	0.0872
17	-0.0587	0.4832	-0.0770	0.3573
18	-0.1308	0.1168	-0.1015	0.2242

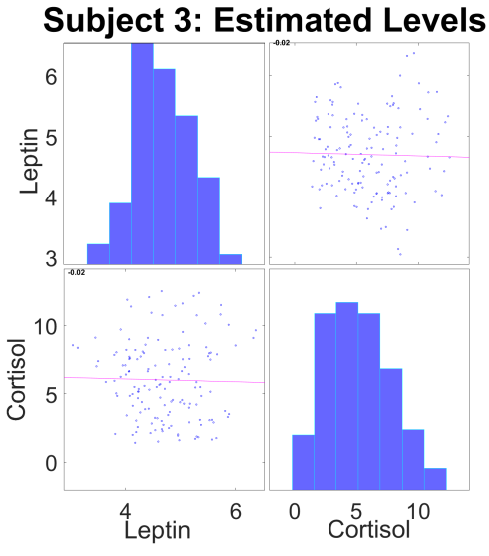

Subject 1: Measured Levels
Leptin
Cortisol
-0.23
-0.23
Leptin
Cortisol


Subject 1: Estimated Levels
Leptin
Cortisol
-0.25
-0.25
Leptin
Cortisol


Subject 2: Measured Levels
Leptin
Cortisol
-0.57
-0.57
Leptin
Cortisol


Subject 2: Estimated Levels
Leptin
Cortisol
-0.60
-0.60
Leptin
Cortisol


Subject 3: Measured Levels
Leptin
Cortisol
-0.00
-0.00
Leptin
Cortisol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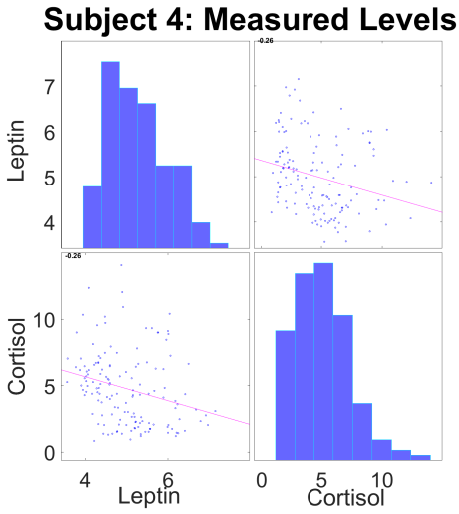
Leptin
Cortisol
-0.02
-0.02
Leptin
Cortisol


Subject 4: Measured Levels
Leptin
Cortisol
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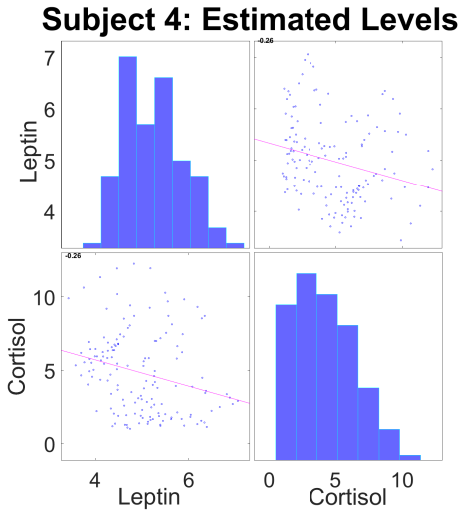
-0.26
-0.26
4
5
6
7
0
5
10
4
6
0
5
10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Leptin
Cortisol
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7
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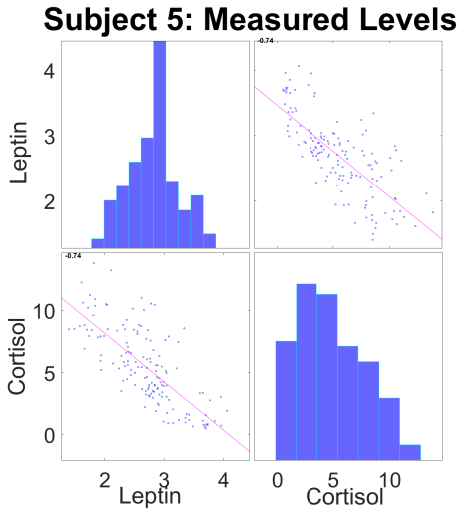
5
10
4
6
0
5
10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Cortisol
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-0.74
-0.74
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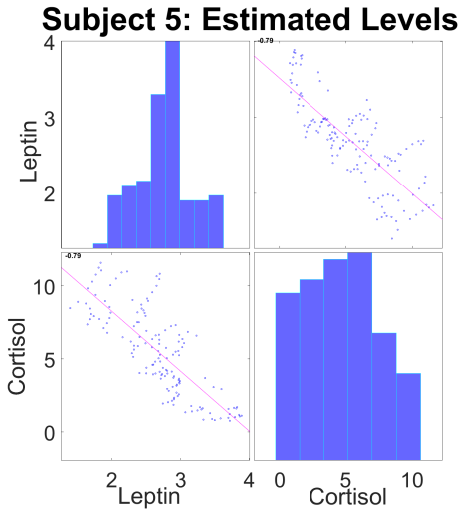
3
4
0
5
10
2
3
4
0
5
10


Subject 5: Estimated Levels
Leptin
Cortisol
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-0.79
-0.79
2
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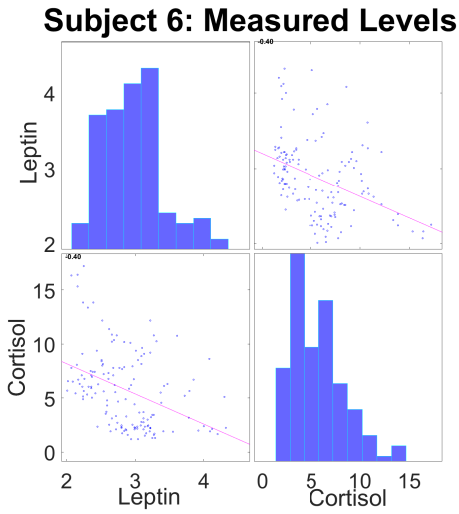
4
0
5
10
2
3
4
0
5
10


Subject 6: Measured Levels
Leptin
Cortisol
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-0.40
-0.40
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3
4
0
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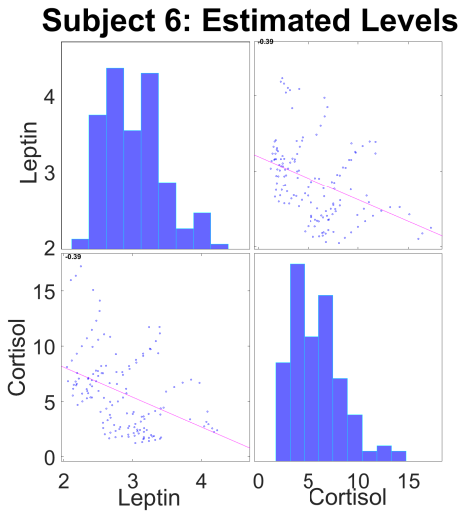
10
15
2
3
4
0
5
10
15


Subject 6: Estimated Levels
Leptin
Cortisol
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-0.39
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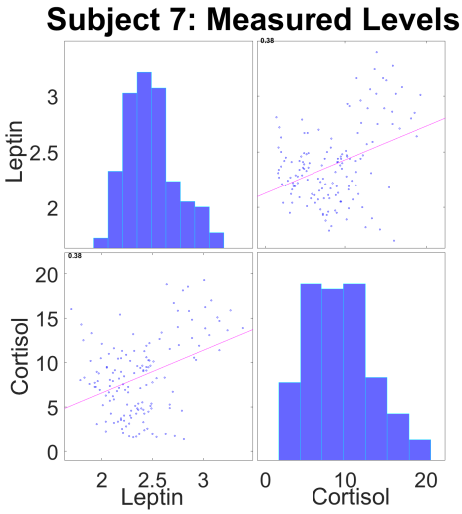
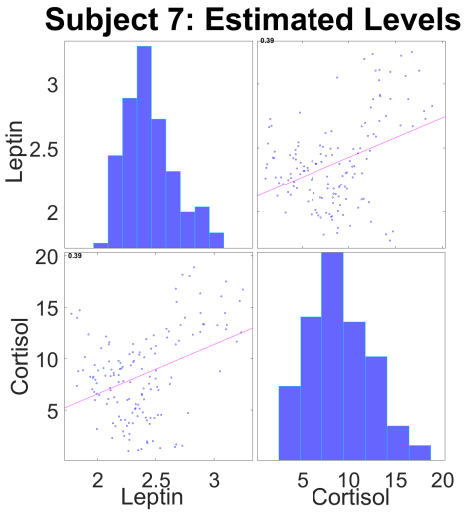
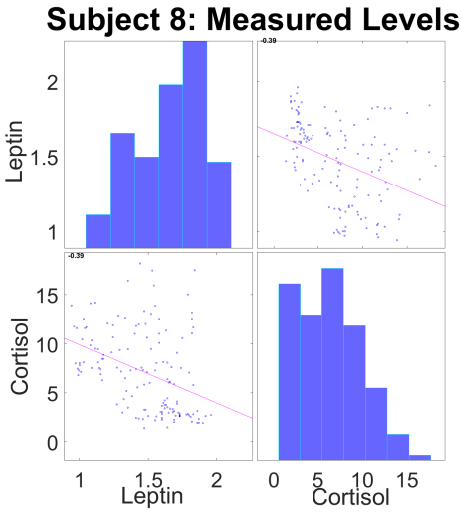
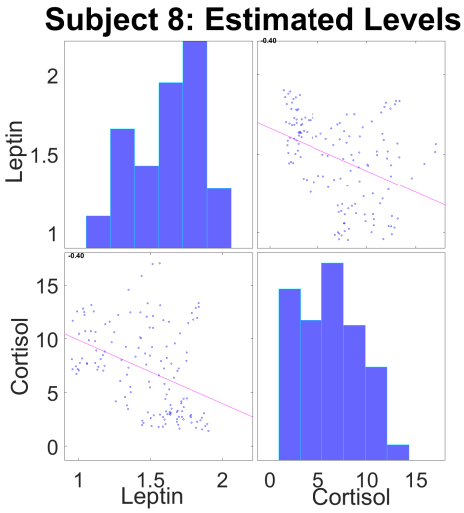
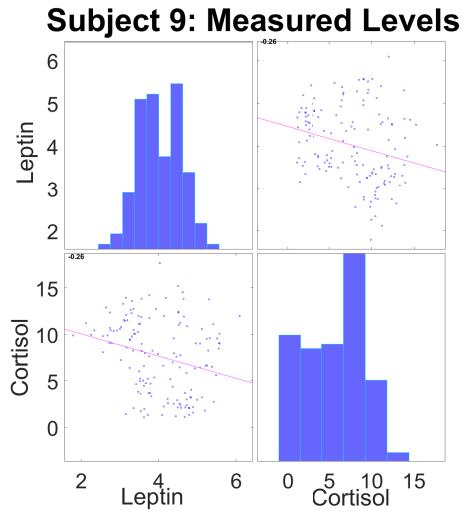
3
4
0
5
10
15
2
3
4
0
5
10
15

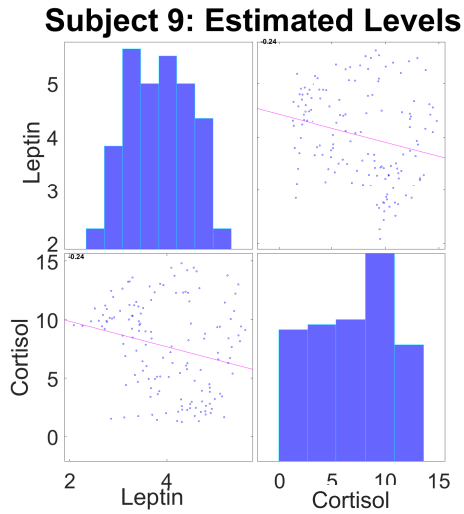

Subject 7: Measured Levels
Leptin
Cortisol
0.38
0.38


Subject 7: Estimated Levels
Leptin
Cortisol
0.39
0.39

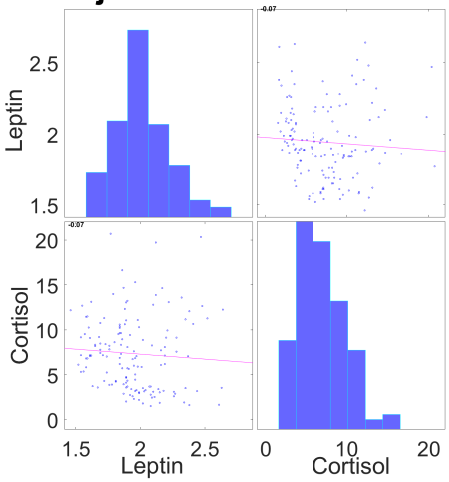

Subject 8: Measured Levels
Leptin
Cortisol
-0.39
-0.39


Subject 8: Estimated Levels
Leptin
Cortisol
-0.40
-0.40

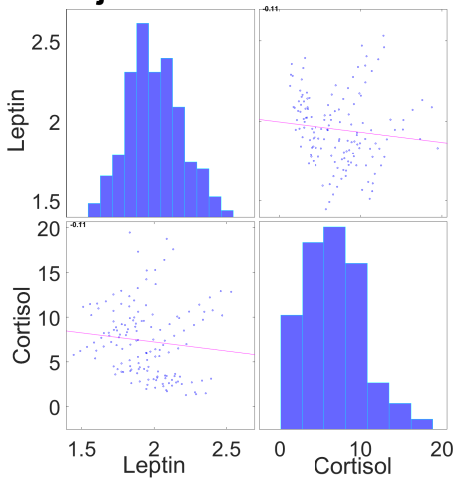

Subject 9: Measured Levels
Leptin
Cortisol
-0.26
-0.26


Subject 9: Estimated Levels
Leptin
Cortisol
-0.24
-0.24

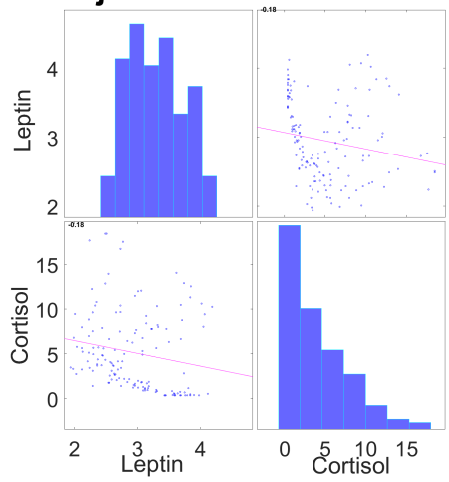
Subject 10: Measured Levels



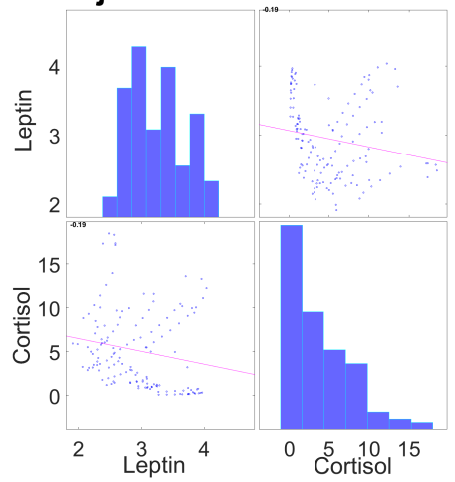
Subject 10: Estimated Levels



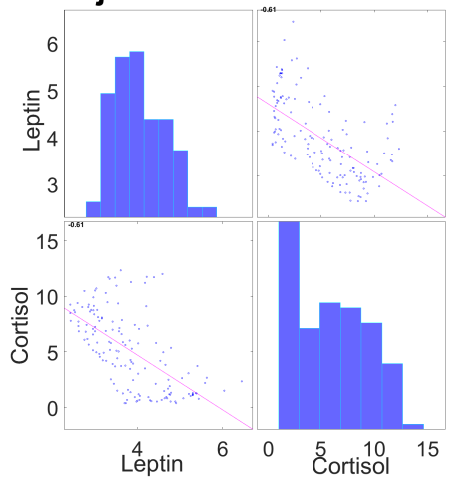
Subject 11: Measured Levels



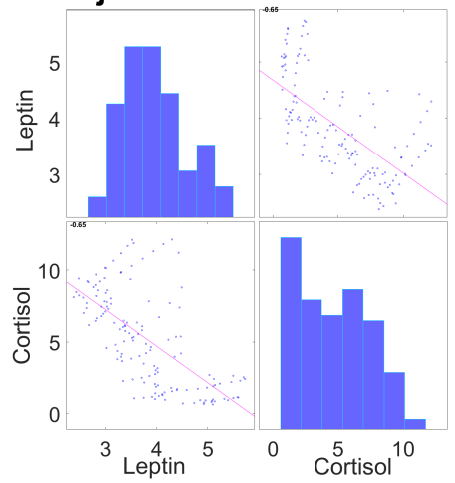
Subject 11: Estimated Levels

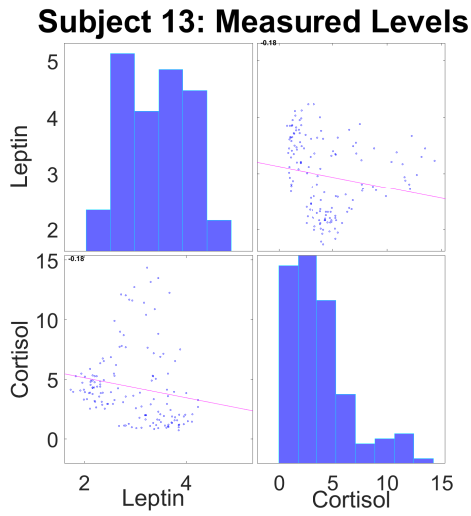


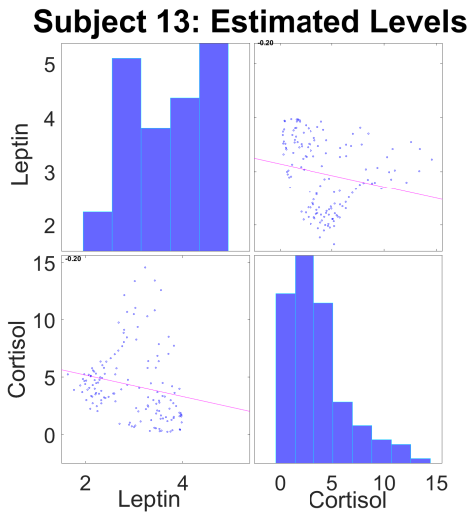
Subject 12: Measured Levels

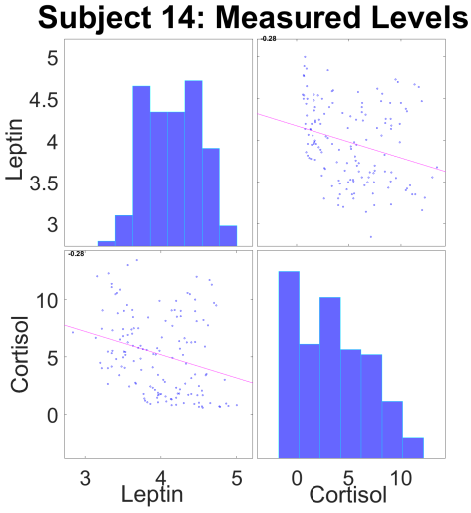


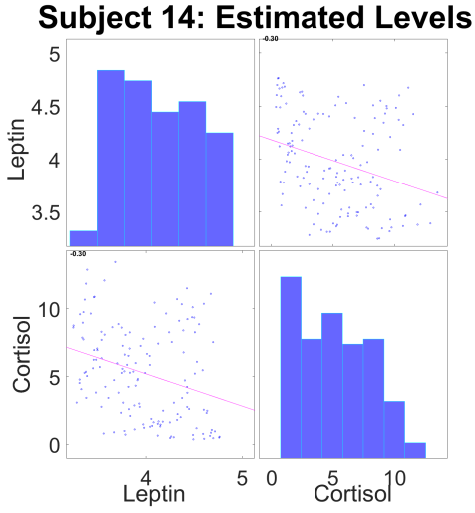
Subject 12: Estimated Levels

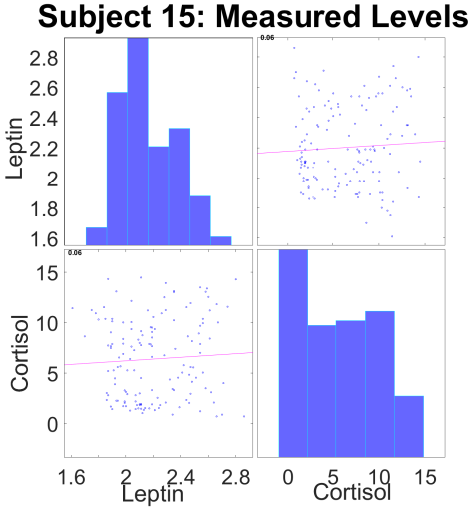


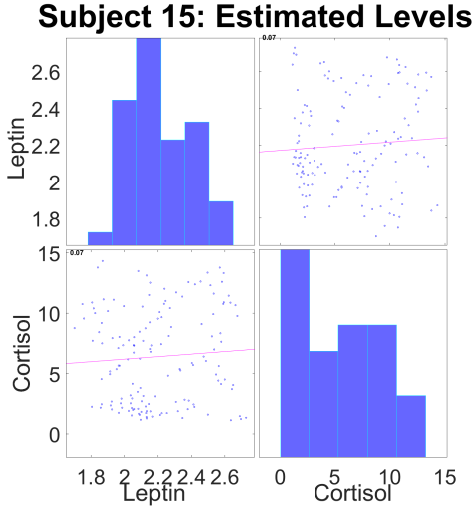

Subject 13: Measured Levels
Leptin
Cortisol
-0.18
-0.18


Subject 13: Estimated Levels
Leptin
Cortisol
-0.20
-0.20


Subject 14: Measured Levels
Leptin
Cortisol
-0.28
-0.28


Subject 14: Estimated Levels
Leptin
Cortisol
-0.30
-0.30


Subject 15: Measured Levels
Leptin
Cortisol
0.06
0.06


Subject 15: Estimated Levels
Leptin
Cortisol
0.07
0.07

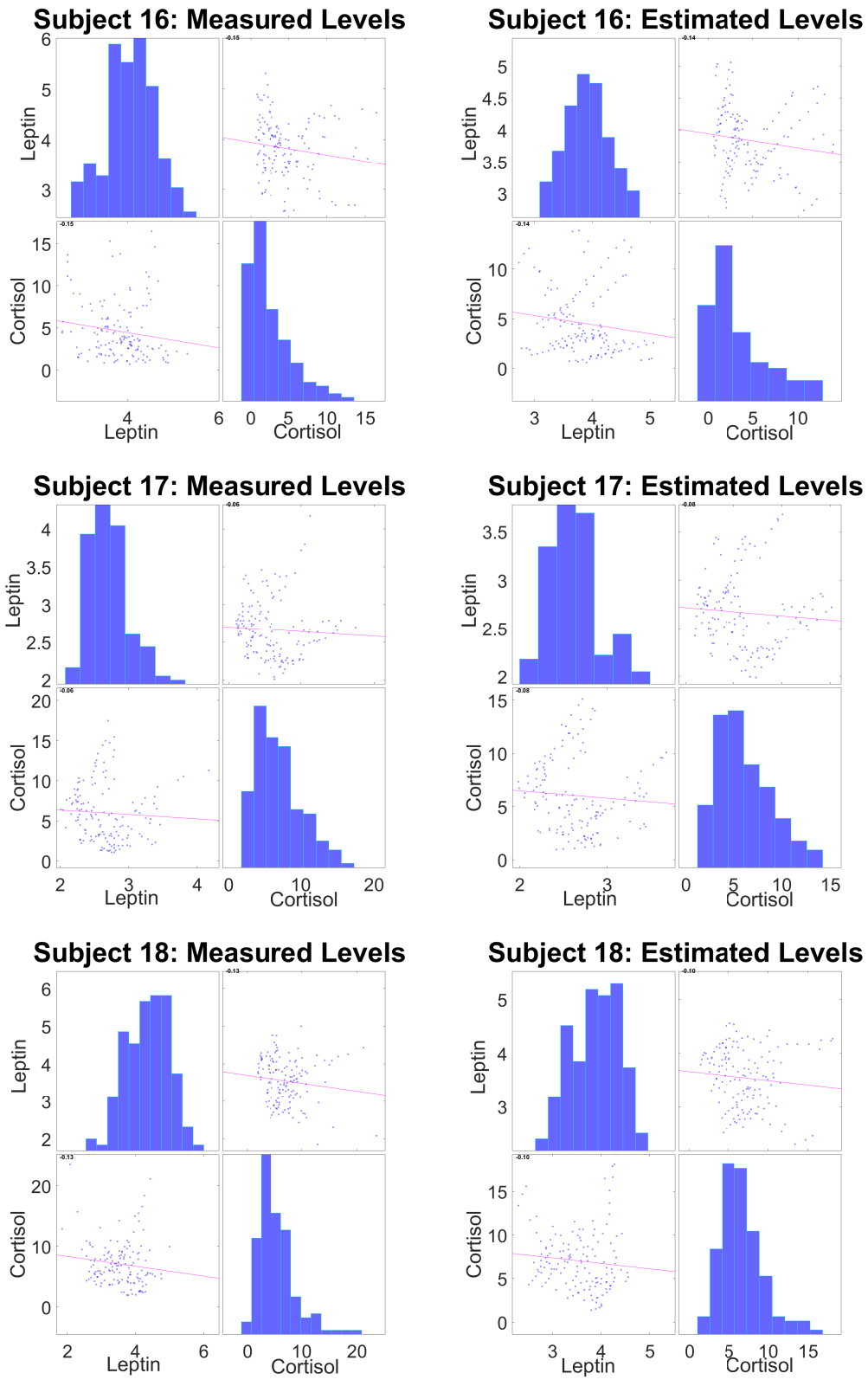


Figure 15: **Correlation Plot between Leptin and Cortisol Levels in Obese Patients.** The plots on the left show the correlation between measured serum levels and the plots on right show the recovered levels.

leptin levels in the body by signalling the adipose tissue to release leptin in form of pulses. Using the state-space model, we estimate the time and amplitude of these pulses. As shown in Figure 11-A, the renal system is responsible to clear the leptin from the system depending on the energy expended. We also recover the infusion rate of leptin by the adipose tissue in the plasma and the clearance rate of leptin from the plasma by the renal system. Leptin regulation can be studied in more details based on these three parameters. Leptin has been studied previously by associating it with different hormones, but these studies do not consider leptin as an independent entity. This model can be then further utilized to understand the leptin variations in obese patients as compared to their matched healthy subjects and also be extended to incorporate effects of other entities. A complete model for the representation of hormonal variations must include all important intrinsic parameters such as forward and backward linkages between the hypothalamus, adipose tissue, anterior pituitary, adrenal gland, renal system, and liver as well as extrinsic parameters like stress, sleep, light, and food [15]. It is a challenge to include all these factors while collecting human data, therefore, we propose this simplified minimal model considering the leptin measurements only. This study is the first step and needs to be extended in future studies.

In this research, We use the coordinate descent approach to recover the model parameters and the pulses exploiting the sparse nature of the input [29]. Understanding the secretion dynamics of leptin and cortisol in obese subjects and designing a model to understand their irregularities is a difficult and challenging problem due to the following reasons:

1. The number of leptin secretion events over a 24-hour period has not been accurately established. The study by [56] compared the leptin levels of obese

women against healthy women and found that the concentration of independent pulsatile parameters of leptin, such as the pulse duration and frequency remained consistent between the groups, and that the excessive leptin levels in the obese persons were due to an increased pulse height during secretion. The average number of leptin secretory events was found to be 32.0 ± 1.5 per day [56], within a range of 29 to 39 pulses among the subjects. Another study found the average number of leptin pulses to be 30.0 ± 1 with the number of pulses between 21 to 39 over a 24 hour sampling period [57]. These studies give a likely average of around 30 pulses per day of leptin, with a range between 20 to 40 being a possibility. We assumed there to be between 20-40 secretory events during a 24-hour period.

2. Since there is no prior knowledge about the exact range of secretion events in obese patients, we relax the constraints on the pulse range. We relaxed the upper and lower limits of this problem while taking care of the overfitting. We use GCV to obtain reasonable sparsity level balancing the model fit and the residual error. Although the upper limit was set to 50, we obtained no more than 40 pulses for all the patients.

Unlike leptin, cortisol is a more widely studied problem. Using the coordinate descent approach, we recover the underlying pulses for cortisol along with the infusion rate of cortisol into plasma by the adrenal glands , and the clearance by the liver.

After recovering the underlying leptin and cortisol pulses, we check the relation between them. As compared to cortisol measurements, the leptin measurements have lower levels, making it more challenging to deconvolve. Aschbacher *et al.*

observed a leptin-cortisol antagonism [10]. This research further suggests that neuroendocrine starvation response may be a possible reason behind such antagonism [10]. Based on our statistical analysis, we observe negative correlation for 16 out of 18 subjects between measured leptin and cortisol levels, as well as a negative correlation between the estimated leptin and cortisol levels. These results show that leptin and cortisol do in fact display an inverse relationship with the ability to inhibit the secretion of one another. Therefore, this approach of using a simplified minimal model to study cortisol and leptin, and then finding the relationship between them, retains previous properties, further validating the approach. Therefore, exploiting the sparse and pulsatile nature of these hormones provides us with a more coherent approach.

The leptin regulation model, used in this research, might be further useful to understand the regulation dynamics in different symptoms such as leptin congential deficiency, Alzheimer's disease, and metabolic syndrome [103, 58]. The advantages of using a model based on human physiology is that it can be used to further isolate the organs or tissues responsible in causing a particular deficiency.

4 Conclusion and Future Work

4.1 Conclusion

Understanding the release and dynamics of endocrine hormones, further, helps us to understand their role in causing corresponding syndromes. The first part of this thesis examines cortisol secretion in FMS and CFS syndromes. In the second part of the thesis, we proposed a simplified minimal model to study leptin secretion. We perform statistical analysis on the estimated secretion events and physiological parameters, i.e., the infusion rate and clearance rate of hormones, and based on the observations characterize the syndromes.

4.1.1 Characterization of Cortisol Dysregulation in Fibromyalgia and Chronic Fatigue Syndromes

In the first part of this thesis, 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 approximately follow a Gaussian structure. 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 patients with both FMS and CFS we obtain similar

results. The difference we observe between patients with FMS only and with both FMS and CFS is in the number of cortisol secretion events. 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 the CFS patients have lower serum cortisol accumulation in the morning period as compared to their matched healthy subjects. We also observe differences in the sum of amplitude of cortisol secretion events and the energy of cortisol secretion events for CFS patients.

4.1.2 Characterization of Leptin and Cortisol Dynamics in Obese Patients

The simplified minimal leptin regulation model proposed in this research aids us to obtain the underlying abstraction of leptin secretion pulses as well as the leptin infusion and clearance rate by the adipose tissue and the renal system. Unlike the traditional approaches, in the proposed minimal leptin secretion model we only consider serum leptin levels. 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 used a similar state-space model to understand cortisol regulation and obtain the underlying cortisol secretory events alongside the cortisol infusion rate by adrenal glands, and the cortisol clearance rate by the liver. This model provided a simplistic approach while still retaining the properties of previous models. When we statistically analyze the correlation between leptin and cortisol, we observe a leptin-cortisol antagonism.

4.2 Future Scope

The model used in this thesis can be further generalized to other hormones with pulsatile nature and developed to incorporate more hormones and understand their relationships. In future work, a system-theoretic approach can be used to include ACTH measurement in the analysis to investigate the differences in ACTH and cortisol secretion dynamics in FMS and CFS patients against healthy subjects. As ACTH is a responsible factor in cortisol synthesis, it strengthens our understanding. The leptin model can be further used to identify leptin dysregulation, to compare the leptin secretion and dynamics in obese patients against their matched healthy control subjects. Eventually, a combined model can be obtained based on the leptin-cortisol dynamics.

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