Characterization of Leptin Secretion in Premenopausal Obese Women Treated with Bromocriptine

Revanth Reddy*, *Student Member, IEEE*, Yaxin Guo*, Vidya Raju, *Member, IEEE* and Rose T. Faghih, *Senior Member, IEEE*

***Abstract*— Leptin, a hormone secreted by adipose tissue, is primarily responsible for inhibiting hunger and maintaining energy balance. Improper leptin secretion may result in hyperleptinemia (excess secretion of leptin) or leptin resistance, both of which contribute to obesity. Diagnosing abnormal leptin secretion may help treat this underlying cause of obesity. Therefore, continuous monitoring of the level of leptin may help characterize its secretion dynamics and also help devise an appropriate treatment. In this research, we consider leptin hormone concentration data taken over a 24 hour time period from eighteen healthy premenopausal obese women before and after treatment with a dopamine agonist, bromocriptine, and deconvolve the observed leptin hormone levels to estimate the number, timing, and magnitude of the underlying leptin secretory pulses. We find that there is an overall decrease in leptin secretion, particularly during sleep, but the changes in the secretory and clearance rates, and the number of pulses underlying the secretion process are not statistically significant.**

***Clinical relevance*— This work seeks to understand the effect of bromocriptine on leptin secretory dynamics and will help further current understanding of the effect of bromocriptine in relation to obesity.**

I. INTRODUCTION

Leptin is a hormone that is responsible for inhibiting hunger to maintain energy balance in the body. It is secreted mainly by white adipose tissue, and the levels are highly correlated with energy expenditure [1], and the amount of body fat [2]. Leptin controls body fat levels by signaling the brain about the current energy levels and inhibiting hunger levels when energy is sufficient, which in turn reduces fat storage in adipose tissue. Extended periods of fasting and starvation decrease leptin levels and increase hunger [3]. On the other hand, excessive food consumption causes increased leptin levels and decreases hunger [3]. Studies have even shown that decrease in leptin levels due to starvation can inhibit the production of certain hormones, including low reproductive, thyroid, and insulin-like growth factor (IGF) hormones [4], [5]. Since changes in the leptin levels are sensed by the central nervous system to modulate hunger and satiation, the altered leptin secretion also has a direct effect in driving obesity [6].

Leptin's role in energy intake and expenditure makes it a particularly important hormone to study in relation to obesity. In common obesity, leptin resistance or deficiency causes leptin to lose its ability to signal in a negative feedback manner to downregulate energy intake, causing obese patients to perpetually feel hungry [7]. In leptin resistance, a build-up of leptin concentration levels with the severity of obesity eventually compromises its ability to signal satiation and regulate hunger [8]. Leptin deficiency, on the other hand, can be congenital or activated by environmental factors and occurs when the body is unable to produce sufficient amounts of leptin or if the leptin signaling pathway is compromised. This also results in a constant need for energy intake and subsequently leads to obesity [9]. These factors make understanding the dynamics of leptin and its effect on hunger crucial for monitoring the health of patients and devising treatments for obesity.

Bromocriptine is a dopamine agonist that is commonly used to treat disorders of the neuroendocrine system and many other diseases [10]. Importantly, its dopaminergic effect directly decreases prolactin secretion, and hence, it is used to treat hyperprolactinemia [11]. Previous investigations to study the effect of bromocriptine on energy metabolism have shown that the drug is capable of reducing blood glucose and insulin levels [12]. In addition, bromocriptine was found to significantly increase oxygen consumption and energy expenditure in patients [12]. These clinical studies motivate the investigation of the influence of bromocriptine in obese patients, in relation to alterations in energy balance and hunger. Understanding bromocriptine's effect on leptin secretion dynamics can reveal more about the impact of this drug on leptin irregularities and thereby, obesity. In this work, we use leptin concentration data from both before and after bromocriptine treatment to determine the changes in leptin secretion for healthy premenopausal obese women.

A. Dataset

Leptin data used in this investigation are from a previously published clinical study [12], [13] where plasma levels of leptin were collected from eighteen healthy, obese premenopausal women (BMI 30.1–40.5 kg/m^2, mean age 37.5 ± 1.7, ranging between 22–51 years). The subjects went through initial medical screening for excluding those with acute or chronic illness, under medication, with history of drug abuse, or participation in another clinical trial, and other confounding factors which may influence endocrine regulation. In addition, all of the subjects were premenopausal with

* Equal contribution.

The work was supported in part by NSF under Grant 2226123 - CAREER: MINDWATCH: Multimodal Intelligent Noninvasive brain state Decoder for Wearable AdapTive Closed-loop arcHitectures and in part by NYU start-up funds. R. T. Faghih served as the senior author.

Revanth Reddy, Yaxin Guo, Vidya Raju, and Rose T. Faghih are with Department of Biomedical Engineering, New York University, USA (e-mail: rfaghih@nyu.edu). Rose T. Faghih served as the senior author.

regular menstrual cycles and the data was collected during the early follicular phase of the menstrual cycle. Each subject was studied twice with a 4-week interval between the two studies. In the first study, all subjects were studied for a 24-hour period (starting at 9 AM) after 7 days of placebo treatment. Hormone concentration levels were measured in 10-minute intervals throughout the study period. A eucaloric diet and regular sleep schedules were also kept consistent for all the subjects, where each subject was required to go to sleep at 2300 h and woken up at 0730 h. In the second study performed after 4 weeks, each subject was given a 2.5 mg bromocriptine dose twice a day for 7 days, and then 24-hour blood sampling was performed in 10-minute intervals again from 9 AM. Leptin concentrations were measured from the blood samples using radioimmunoassay with a detection limit of 0.5 ng/L.

II. Model

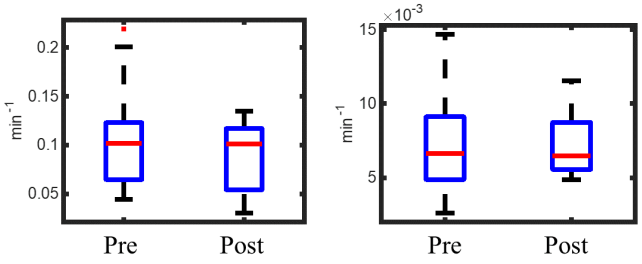
Hormone deconvolution methods developed over the past decades have enabled analysis of hormone secretory characteristics [14]–[20]. Recently, system-theoretic deconvolution methods have been successfully used to mathematically characterize the secretory behaviors of many hormones such as cortisol [20]–[22], leptin [23], growth hormone [24] etc. In a similar vein, we use a second-order state-space model with physiological constraints to infer the nature of secretory pulses that underlie leptin secretion throughout the day. This model assumes a first-order kinetics for leptin synthesis in adipose tissue and its subsequent diffusion into the blood, followed by another first-order dynamics that tracks its abundance in the blood, subject to clearance by the renal system [25]. The dynamics of leptin secretion and the discrete measurement sampling ($y(t_i)$ at time instants t_i) is given by:

$$\frac{dx_1(t)}{dt} = -\theta_1 x_1(t) + u(t) \quad \text{(Adipose Tissue)} \tag{1}$$

$$\frac{dx_2(t)}{dt} = \theta_1 x_1(t) - \theta_2 x_2(t) \quad \text{(Plasma)} \tag{2}$$

$$y(t_i) = x_2(t_i) + v(t_i),\ i = 1, \ldots, N \tag{3}$$

where x_1 and x_2 are respectively the instantaneous leptin concentration in adipose tissue and plasma. θ_1 and θ_2, respectively, represent the rate of infusion into plasma and the rate of its renal clearance, and N is the total number of measurements. The measurements at discrete time instants are given by $y(t_i)$, and $v(t_i)$ is a term used to model noises that cause imprecise measurements. In the dataset, leptin levels were measured every ten minutes ($T_y = 10$ min) and in our work, we recover its level every minute with y_{t_0} denoting the initial condition of the plasma leptin concentration by recovering the underlying secretory stimuli at a one-minute sampling interval ($T_u = 1$ min), for M samples ($M = 1440 = 10N$). In this case, the discrete state $x[k]$ at time t_k can be represented as follows $x[k+1] = \Lambda x[k] + \Gamma u[k]$, where $\Lambda = \exp AT_u$, $\Gamma = \int_0^{T_u} \exp(A(T_u - \sigma))Bd\sigma$, where $u(t) = \sum_{i=1}^{N} q_i \delta(t - \tau_i)$ with the measurement being



(a) Infusion Rate (b) Clearance Rate

Fig. 1: Box plots of pre-treatment and post-treatment rates of (a) infusion and (b) clearance for leptin shows the median (red line) value, the lower (Q1) to upper (Q3) quartile range (blue rectangle), and 9 to 91 percentile range (black line and black dashed line) of the parameters.

$y(t_k) = Cx(t_k) + \eta(t_k)$, where $\eta(t_k)$ is an additive noise term which we assume is Gaussian distributed. Therefore, commensurate with the frequency of blood sampling, we get $T_y = LT_u$, where $L = 10$, and letting $A_d = \Lambda^L$, $B_d = [\Lambda^{L-1}\Gamma\ \Lambda^{L-2}\Gamma\ \ldots\ \Gamma]$, $u_d[k] = [u[Lk]\ u[Lk+1]\ \ldots\ u[Lk+L-1]]^T$, $\eta_d[k] = \eta[Lk]$ so that the solution to the discrete state equation can be written as

$$x_d[k] = A_d x_d[0] + B_d u_d[k] \tag{4}$$

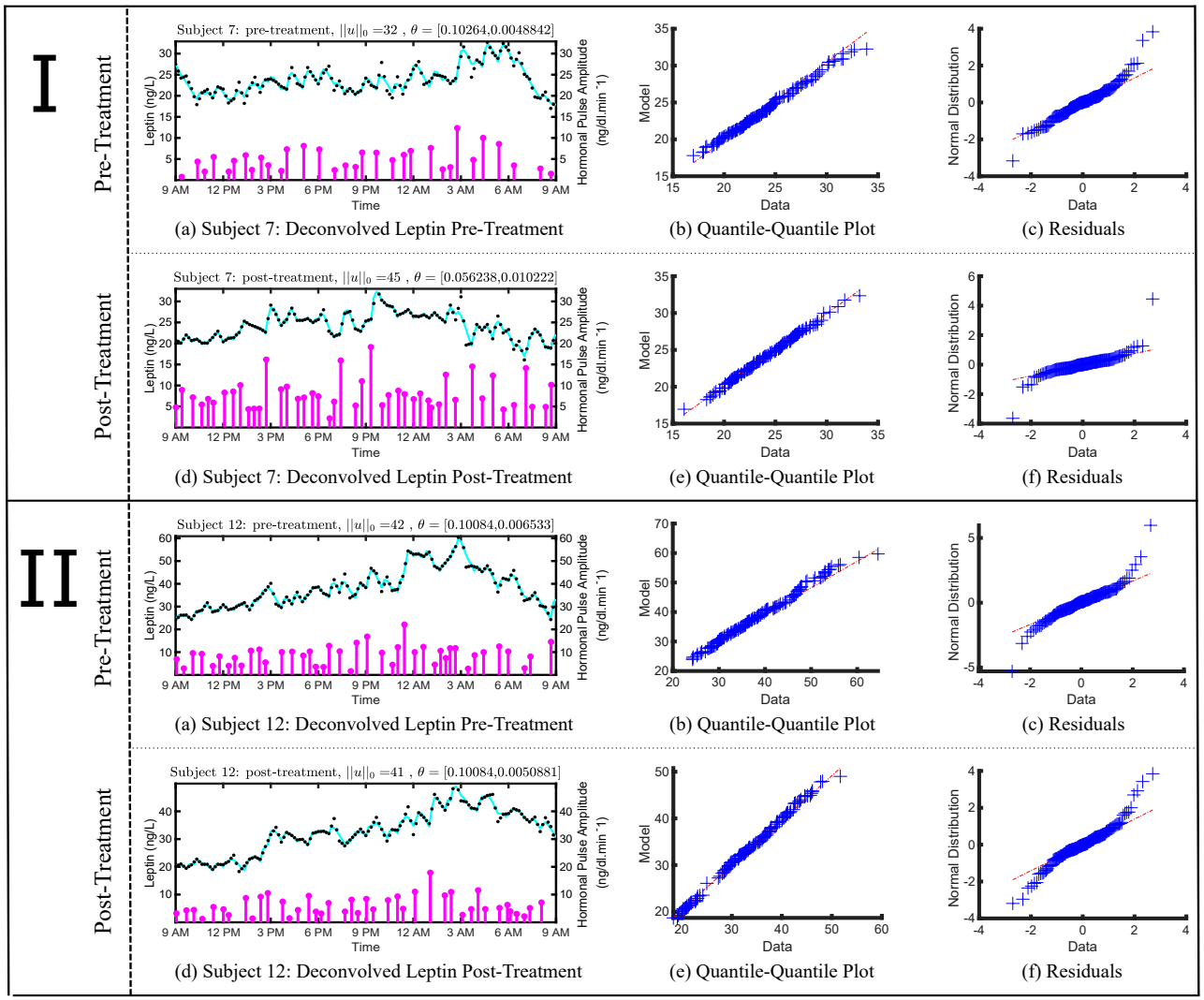
$$y[k] = Cx_d[k] + \eta_d[k] \tag{5}$$

Solving this equation and concatenating the values of measurements, we write the following equation representing the effect of initial condition $y_0 = x_d[0]$, underlying secretory pulses and the noise on the measured leptin levels:

$$\mathrm{y} = \mathbf{F}_\theta y_0 + \mathbf{D}_\theta \mathbf{u} + \eta \tag{6}$$

A. Deconvolution

In order to recover the leptin secretory pulses as well as the rate parameters governing its temporal dynamics, we perform deconvolution by taking into account our model of leptin synthesis and clearance. We cast the process of identifying the parameters θ_1, θ_2 together with sparse secretory pulses u to explain the observed leptin levels as an optimization problem subject to constraints that ensure physiological plausibility. Leptin secretion, like that of other hormones, is known to be sparse, with about 20-40 hormone pulses occurring in a day [26]. This sparsity criterion is imposed as a constraint on the total number of underlying secretory events. To account for alterations in leptin secretory activity before and after treatment with bromocriptine, we consider an upper bound of 45 for the subjects in this study, out of the 1440 time instants over which we determine the secretory events. We add constraints on the infusion and clearance rates: (i) $\theta_1 \geq 0$, $\theta_2 \geq 0$ to impose positivity of these parameters and (ii) we also assume that the infusion rate is greater than or equal to the clearance rate, i.e., $\theta_1 \geq \theta_2$. This formulation



(a) Subject 7: Deconvolved Leptin Pre-Treatment (b) Quantile-Quantile Plot (c) Residuals

(d) Subject 7: Deconvolved Leptin Post-Treatment (e) Quantile-Quantile Plot (f) Residuals

(a) Subject 12: Deconvolved Leptin Pre-Treatment (b) Quantile-Quantile Plot (c) Residuals

(d) Subject 12: Deconvolved Leptin Post-Treatment (e) Quantile-Quantile Plot (f) Residuals

Fig. 2: Leptin deconvolution results for both pre-treatment and post-treatment are shown for subject 7 (**I**) and subject 12 (**II**). (a) depicts the leptin deconvolution results including leptin concentration (black), recovered pulses (pink), and reconstructed signal (blue). (b) depicts the quantile-quantile plots which represents the relationship between the measured data and the reconstructed leptin signal. (c) shows the residuals plot indicating the model's estimation error plotted against samples from a normal distribution. (d) - (f) represent the deconvolution results performed for post-treatment in the same subject.

is similar to the deconvolution of leptin [25], cortisol [20]–[22], [27], [28], electrodermal activity [22], [23], [29]–[34], and growth hormone [24] in earlier work and is subject to the same computational complexity as those.

To estimate the model parameters, we follow the method used in [20], and formulate an optimization problem:

$$\text{minimize } \|\mathrm{y} - \mathbf{F}_\theta y_0 - \mathbf{D}_\theta \mathrm{u}\|_2^2 \tag{7}$$

$$\text{subject to: } 20 \le \|\mathrm{u}\|_0 \le 45,\ \mathrm{u} \ge 0,\ C\theta \le b \tag{8}$$

where $C = \begin{bmatrix} -1 & -1 & 0 \\ 1 & 0 & -1 \end{bmatrix}', b = \begin{bmatrix} 0 & 0 & 0 \end{bmatrix}'$. Here, the constraints on the recovered secretory pulses refer to the non-negativity of pulse amplitudes and the rate parameters, and ensure that the infusion rate is higher than the clearance rate. This optimization problem to simultaneously find the parameters and the sparse stimuli in general is computationally complex [20]. We therefore solve a relaxation of the original optimization problem as follows:

$$\min \quad J_\lambda(\theta, \mathrm{u}) = \frac{1}{2}\|\mathrm{y} - \mathbf{F}_\theta y_0 - \mathbf{D}_\theta \mathrm{u}\|_2^2 + \lambda \|\mathrm{u}\|_p^p \tag{9}$$

$$\mathrm{u}^{(l+1)} = \underset{\mathrm{u}\ge 0}{\operatorname{argmin}} \quad J_\lambda\left(\theta^{(l)}, \mathrm{u}\right) \tag{10}$$

$$\theta^{(l+1)} = \underset{C\theta \le b}{\operatorname{argmin}} \quad J_\lambda\left(\theta, \mathrm{u}^{(l+1)}\right) \tag{11}$$

B. Optimization

We solve this optimization problem using the FOCUSS+ algorithm [35] and subsequently FOCUSS+ together with Generalized Cross Validation (GCV) [36]. In this method, the values of λ and u are iteratively updated until convergence is achieved, with GCV additionally enabling the sparsification of the recovered stimuli by refining the regularization

parameter λ which tunes the sparsity of u in relation to the residual error of the reconstructed signal.

We use the GCV technique for updating the regularization term [36]. The GCV function is defined as:

$$G(\lambda) = \frac{N \left\| (I - H_\lambda)\, \mathrm{y}_\theta \right\|^2}{(\text{trace } (I - H_\lambda))^2} \tag{12}$$

where N is the number of data points, $H_\lambda = \mathbf{D}_\theta P_\mathrm{u} \mathbf{D}_\theta^T \left(\mathbf{D}_\theta P_\mathrm{u} \mathbf{D}_\theta^T + \lambda I \right)^{-1}$ is the influence matrix, following [20]. A summary of the algorithm is as follows [20], where y_θ denotes the residual error $\mathrm{y} - \mathbf{F}_\theta y_0$:

1. $P_\mathrm{u}^{(r)} = \mathrm{diag}\left(\left| \mathrm{u}_\mathrm{i}^{(r)} \right|^{2-p} \right)$
2. $\mathrm{u}^{(r+1)} = P_\mathrm{u}^{(r)} \mathbf{D}_\theta^T \left(\mathbf{D}_\theta P_\mathrm{u}^{(r)} \mathbf{D}_\theta^T + \lambda^{(r)} I \right)^{-1} \mathrm{y}_\theta$
3. $\mathrm{u}_\mathrm{i}^{(r+1)} \leq 0 \rightarrow \mathrm{u}_\mathrm{i}^{(r+1)} = 0$
4. $\lambda^{(r+1)} = \underset{0 \leq \lambda \leq \lambda_{max}}{\mathrm{argmin}}\ G(\lambda)$
5. Iterate until convergence

θ_1 and θ_2 are initialized using a uniform random variable w sampled from the interval $[8.3 \times 10^{-4}, 1]$, where $\theta_1(0) = 5\theta_2(0) = w$. To account for inter-subject variability in leptin secretion dynamics, for each subject, we begin with an initial trial of $\lambda_{max} = 10$. Then, we decrease λ_{max} by a factor of ten until we observe a high-fidelity fit of the leptin data, without overfitting. The λ_{max} values used for each subject is reported in Table I.

III. RESULTS AND DISCUSSION

In this study, plasma leptin concentration levels were successfully deconvolved to retrieve the underlying secretory pulse timings and magnitudes using the proposed algorithm. A summary of the rate parameters, recovered number of pulses and the coefficient of determination (R^2) are reported in table I. We see that the total number of recovered pulses satisfied the cardinality constraint, and were between 20-45, as set in the algorithm. Moreover, the rate parameters satisfied the constraint that the infusion rate be higher than the rate of clearance. The statistics of the rate parameters across all subjects is shown in the box plots in Figure 1. The deconvolution results for two subjects both pre-treatment and post-treatment are shown in Figure 2. The quantile-quantile plots show that the residuals in the recovered signal follow an approximately normal distribution, indicating a good fit. The deconvolution results all follow the physiological constraints that the infusion rate is greater than the clearance rate, and the number of pulses recovered for each subject satisfy the criterion of being within 45 leptin secretion pulses, as can be seen in table I.

The relatively high values of the multiple correlation coefficients ($R^2 > 0.90$ for all subjects) between the recovered signals based on the secretion pulses and the experimental data indicate that our method is capable of estimating leptin secretion information that is both physiologically plausible and accurate. Leptin secretion events appear to follow a circadian rhythm with leptin levels typically increasing during the sleep period, though there is high subject variability in terms of the number of pulses, pulse magnitude, and infusion/clearance rates. We also calculated other metrics considered typically in literature, including the number of pulses (during wake, sleep, and total hours of study), the sum of pulse amplitudes (during wake, sleep, and total duration of the study), mean leptin levels over the time intervals, and the area under the curve during wake, sleep or the total 24 hours.

We performed paired Wilcoxon signed rank test to examine differences induced by bromocriptine treatment in each of these metrics. The Wilcoxon signed-rank test is a non-parametric test used to determine statistical differences between two populations with paired observations [37]. The summary of the statistics from this study in Table II suggests a statistically significant change of mean leptin secretion profile due to bromocriptine treatment and the leptin area under the curve during sleep. We did not find any significant change in the remaining metrics. Given the complex nature of interactions between the various hormones and the fact that other metabolic markers were shown in previous studies to be improved due to treatment with bromocriptine, it is possible that these observations may be better explained by considering the totality of the changes in all the other measured hormones induced by bromocriptine [13]. For example, bromocriptine has been shown to decrease prolactin levels and has been used to treat hyperprolactinemia [11]. The assessment of its influence on neuroendocrine function will address the overall effect of bromocriptine in these obese patients.

Based on our deconvolution results, it appears that plasma leptin concentrations follow both fast and slow dynamics in these subjects. Previous studies have also shown that leptin plays a key role in maintaining sleep cycles and leptin deficiencies can cause dysregulation in the sleep cycle [38]. Our analysis (table II) shows a marked difference during sleep in the area under leptin curve. It is possible that models that can incorporate aspects of both dynamics make for a better model of leptin secretion. To obtain further insight, it will be useful to measure and analyze plasma leptin concentration levels retrieved from healthy non-obese individuals.

IV. CONCLUSION AND FUTURE WORK

In this research, we modeled the leptin secretory process by second-order dynamics and used a coordinate descent approach to perform deconvolution, parameter estimation, and recovery of the sparse stimuli underlying leptin secretion. From the results of our deconvolution analysis, we found that overall leptin secretion decreased on average across all subjects, as was the leptin area under the curve during sleep, but did not find other significant markers of altered leptin secretion that could be attributed to treatment with bromocriptine. We intend to extend this work in the future in two directions. The first is to incorporate our observations of fast and slow processes governing leptin secretion, which happens from adipose tissues throughout the body, and expand the model to include them. The second is a combined analysis of interactions between the various hormones, such

TABLE I: Parameters governing leptin production before (pre) and after (post) treatment with bromocriptine: infusion rate θ_1, clearance rate θ_2, number of secretory pulses $||\mathrm{u}||_0$, multiple correlation coefficient R^2, and λ_{max}.

Sub No.	θ_1 **(pre)** (min^{-1})	θ_2 **(pre)** (min^{-1})	$\|\|\mathrm{u}\|\|_0$ **(pre)**	$\|\|\mathrm{u}\|\|_0$ **(pre) (sleep)**	R^2 **(pre)**	λ_{max} **(pre)**	θ_1 **(post)** (min^{-1})	θ_2 **(post)** (min^{-1})	$\|\|\mathrm{u}\|\|_0$	$\|\|\mathrm{u}\|\|_0$ **(post) (sleep)**	R^2 **(post)**	λ_{max} **(post)**
1	0.1008	0.0067	38	13	0.9740	1	0.1348	0.0063	39	14	0.9354	1
2	0.0606	0.0121	42	14	0.9715	1	0.1169	0.0069	40	13	0.9706	1
3	0.0647	0.0122	42	13	0.9558	1	0.1050	0.0067	42	14	0.9555	1
4	0.1229	0.0059	40	15	0.9644	1	0.1027	0.0060	42	14	0.9836	1
5	0.1547	0.0061	40	13	0.9780	1	0.1244	0.0048	36	12	0.9863	1
6	0.2007	0.0035	37	14	0.9776	1	0.0653	0.0106	45	16	0.9752	0.1
7	0.1026	0.0049	32	10	0.9297	1	0.0562	0.0102	45	14	0.9578	0.1
8	0.0445	0.0091	41	15	0.9852	0.1	0.1068	0.0051	38	12	0.9526	0.1
9	0.0620	0.0147	44	15	0.9830	1	0.0543	0.0116	40	12	0.9833	1
10	0.2188	0.0049	33	11	0.9047	1	0.0360	0.0064	35	13	0.9651	0.1
11	0.1191	0.0049	38	14	0.9712	1	0.1305	0.0053	34	13	0.9657	1
12	0.1008	0.0065	42	14	0.9810	1	0.1008	0.0051	41	14	0.9834	1
13	0.1165	0.0075	40	13	0.9790	1	0.0529	0.0092	42	15	0.9894	0.1
14	0.1008	0.0046	39	15	0.9553	1	0.0362	0.0056	26	10	0.9683	1
15	0.0561	0.0113	45	17	0.9811	0.1	0.0601	0.0087	41	15	0.9720	0.1
16	0.1036	0.0068	39	13	0.9592	1	0.1008	0.0065	40	15	0.9731	1
17	0.1392	0.0026	29	10	0.9393	1	0.0304	0.0060	24	9	0.9485	1
18	0.1008	0.0069	40	15	0.9683	1	0.1181	0.0066	40	13	0.9641	1

TABLE II: Results of paired Wilcoxon signed rank test for measures of leptin secretion pre- and post- treatment with bromocriptine

Parameter	**Mean ± S.D. (pre-treatment)**	**Mean ± S.D. (post-treatment)**	**p-value**
Infusion rate θ_I (min^{-1})	0.1094 ± 0.0470	0.0851 ± 0.0355	0.2311
Clearance rate θ_C (min^{-1})	0.0073 ± 0.0033	0.0071 ± 0.0021	0.7439
No. of pulses $\|\|u\|\|_0$ (sleep)	13.5556 ± 1.8222	13.2222 ± 1.7675	0.6146
No. of pulses $\|\|u\|\|_0$ (wake)	25.3889 ± 2.7255	25.1111 ± 4.2272	0.5100
No. of pulses $\|\|u\|\|_0$ (total)	38.9444 ± 4.1084	38.3333 ± 5.6776	0.3500
Sum of pulse amplitudes $\|\|u\|\|_1$ (sleep) (ng/L.min^{-1})	2.8788 ± 9.3062	2.0019 ± 4.6279	0.8438
Sum of pulse amplitudes $\|\|u\|\|_1$ (wake) (ng/L.min^{-1})	366.7855 ± 243.4978	317.1822 ± 146.8222	0.1701
Sum of pulse amplitudes $\|\|u\|\|_1$ (total) (ng/L.min^{-1})	369.6643 ± 248.1543	319.1841 ± 149.6031	0.1841
Leptin area under curve (sleep) (ng/L.min)	$1.9634 \times 10^3 \pm 620.2569$	$1.7787 \times 10^3 \pm 630.0866$	**0.0386**
Leptin area under curve (wake) (ng/L.min)	$2.8792 \times 10^3 \pm 922.7463$	$2.6264 \times 10^3 \pm 918.3443$	0.0582
Leptin area under curve (total) (ng/L.min)	$4.8426 \times 10^3 \pm 1.5336 \times 10^3$	$4.4050 \times 10^3 \pm 1.5293 \times 10^3$	0.0526
Leptin mean (sleep)(ng/L)	37.6857 ± 11.9106	34.1768 ± 12.1042	**0.0386**
Leptin mean (wake) (ng/L)	31.2321 ± 10.0016	28.4845 ± 9.9624	0.0582
Leptin mean (total) (ng/L)	33.5910 ± 10.6348	30.5651 ± 10.6123	0.0526
Leptin mean profile (across all subjects)	-	-	**<0.01**

as growth hormone, which regulates body fat mass and lipolysis [13].

ACKNOWLEDGMENT

The authors would like to thank Dr. Daniel J. Vis for sharing the data used in this paper.

REFERENCES

[1] R. Pandit, S. Beerens, and R. A. Adan, "Role of leptin in energy expenditure: the hypothalamic perspective," *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, vol. 312, no. 6, pp. R938–R947, 2017.

[2] R. V. Considine, M. K. Sinha, M. L. Heiman, A. Kriauciunas, T. W. Stephens, M. R. Nyce, J. P. Ohannesian, C. C. Marco, L. J. McKee, T. L. Bauer, *et al.*, "Serum immunoreactive-leptin concentrations in normal-weight and obese humans," *New England Journal of Medicine*, vol. 334, no. 5, pp. 292–295, 1996.

[3] J. W. Kolaczynski, R. V. Considine, J. Ohannesian, C. Marco, I. Opentanova, M. R. Nyce, M. Myint, and J. F. Caro, "Responses of leptin to short-term fasting and refeeding in humans: a link with ketogenesis but not ketones themselves," *Diabetes*, vol. 45, no. 11, pp. 1511–1515, 1996.

[4] J. L. Chan, K. Heist, A. M. DePaoli, J. D. Veldhuis, C. S. Mantzoros, *et al.*, "The role of falling leptin levels in the neuroendocrine and metabolic adaptation to short-term starvation in healthy men," *The Journal of clinical investigation*, vol. 111, no. 9, pp. 1409–1421, 2003.

[5] J. L. Chan and C. S. Mantzoros, "Role of leptin in energy-deprivation states: normal human physiology and clinical implications for hypothalamic amenorrhoea and anorexia nervosa," *The lancet*, vol. 366, no. 9479, pp. 74–85, 2005.

[6] C. A. LeDuc, A. A. Skowronski, and M. Rosenbaum, "The role of leptin in the development of energy homeostatic systems and the maintenance of body weight," *Frontiers in Physiology*, p. 2229, 2021.

[7] A. G. Izquierdo, A. B. Crujeiras, F. F. Casanueva, and M. C. Carreira, "Leptin, obesity, and leptin resistance: where are we 25 years later?," *Nutrients*, vol. 11, no. 11, p. 2704, 2019.

[8] P. J. Enriori, A. E. Evans, P. Sinnayah, and M. A. Cowley, "Leptin resistance and obesity," *Obesity*, vol. 14, no. S8, pp. 254S–258S, 2006.

[9] M. Wasim, F. R. Awan, S. S. Najam, A. R. Khan, and H. N. Khan, "Role of leptin deficiency, inefficiency, and leptin receptors in obesity," *Biochemical Genetics*, vol. 54, pp. 565–572, 2016.

[10] F. Naz, A. Malik, M. Riaz, Q. Mahmood, M. H. Mehmood, G. Rasool, Z. Mahmood, and M. Abbas, "Bromocriptine therapy: Review of mechanism of action, safety and tolerability," *Clinical and Experimental Pharmacology and Physiology*, vol. 49, no. 8, pp. 903–922, 2022.

[11] A. Colao, A. Di Sarno, E. Guerra, M. De Leo, A. Mentone, and G. Lombardi, "Drug insight: Cabergoline and bromocriptine in the

treatment of hyperprolactinemia in men and women," *Nature clinical practice Endocrinology & metabolism*, vol. 2, no. 4, pp. 200–210, 2006.

[12] P. Kok, F. Roelfsema, M. Frolich, J. van Pelt, A. E. Meinders, and H. Pijl, "Activation of dopamine d2 receptors lowers circadian leptin concentrations in obese women," *The Journal of Clinical Endocrinology & Metabolism*, vol. 91, no. 8, pp. 3236–3240, 2006.

[13] D. J. Vis, J. A. Westerhuis, H. C. Hoefsloot, F. Roelfsema, J. Van der Greef, M. M. Hendriks, and A. K. Smilde, "Network identification of hormonal regulation," *PLoS One*, vol. 9, no. 5, p. e96284, 2014.

[14] J. D. Veldhuis, V. Guardabasso, A. D. Rogol, W. S. Evans, K. E. Oerter, M. L. Johnson, and D. Rodbard, "Appraising the nature of luteinizing hormone secretory events in men," *American Journal of Physiology-Endocrinology and Metabolism*, vol. 252, no. 5, pp. E599–E605, 1987.

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

[16] C. Cobelli, A. Mari, S. Del Prato, S. De Kreutzenberg, R. Nosadini, and I. Jensen, "Reconstructing the rate of appearance of subcutaneous insulin by deconvolution," *American Journal of Physiology-Endocrinology And Metabolism*, vol. 253, no. 5, pp. E584–E590, 1987.

[17] G. Sparacino and C. Cobelli, "A stochastic deconvolution method to reconstruct insulin secretion rate after a glucose stimulus," *IEEE Transactions on Biomedical Engineering*, vol. 43, no. 5, pp. 512–529, 1996.

[18] M. Bergendahl, A. Iranmanesh, T. Mulligan, and J. Veldhuis, "Impact of age on cortisol secretory dynamics basally and as driven by nutrient-withdrawal stress," *The Journal of Clinical Endocrinology & Metabolism*, vol. 85, no. 6, pp. 2203–2214, 2000.

[19] G. Sparacino, G. Pillonetto, M. Capello, G. De Nicolao, and C. Cobelli, "Winstodec: a stochastic deconvolution interactive program for physiological and pharmacokinetic systems," *Computer methods and programs in biomedicine*, vol. 67, no. 1, pp. 67–77, 2002.

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

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

[22] R. T. Faghih, "From physiological signals to pulsatile dynamics: a sparse system identification approach," *Dynamic Neuroscience: Statistics, Modeling, and Control*, pp. 239–265, 2018.

[23] M. R. Amin and R. T. Faghih, "Sparse deconvolution of electrodermal activity via continuous-time system identification," *IEEE Transactions on Biomedical Engineering*, vol. 66, no. 9, pp. 2585–2595, 2019.

[24] J. X. Genty, M. R. Amin, N. D. Shaw, E. B. Klerman, and R. T. Faghih, "Sparse deconvolution of pulsatile growth hormone secretion in adolescents," *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, vol. 19, no. 4, pp. 2463–2470, 2021.

[25] M. Amin, D. D. Pednekar, H. F. Azgomi, H. van Wietmarschen, K. Aschbacher, R. T. Faghih, *et al.*, "Sparse system identification of leptin dynamics in women with obesity," *Frontiers in Endocrinology*, vol. 13, p. 157, 2022.

[26] J. Licinio, C. Mantzoros, A. B. Negrão, G. Cizza, M.-L. Wong, P. B. Bongiorno, G. P. Chrousos, B. Karp, C. Allen, J. S. Flier, *et al.*, "Human leptin levels are pulsatile and inversely related to pituitary–ardenal function," *Nature medicine*, vol. 3, no. 5, pp. 575–579, 1997.

[27] D. D. Pednekar, M. R. Amin, H. F. Azgomi, K. Aschbacher, L. J. Crofford, and R. T. Faghih, "A system theoretic investigation of cortisol dysregulation in fibromyalgia patients with chronic fatigue," in *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, pp. 6896–6901, IEEE, 2019.

[28] D. D. Pednekar, M. R. Amin, H. F. Azgomi, K. Aschbacher, L. J. Crofford, and R. T. Faghih, "Characterization of cortisol dysregulation in fibromyalgia and chronic fatigue syndromes: a state-space approach," *IEEE Transactions on Biomedical Engineering*, vol. 67, no. 11, pp. 3163–3172, 2020.

[29] M. R. Amin and R. T. Faghih, "Robust inference of autonomic nervous system activation using skin conductance measurements: A multi-channel sparse system identification approach," *IEEE Access*, vol. 7, pp. 173419–173437, 2019.

[30] M. R. Amin, D. S. Wickramasuriya, and R. T. Faghih, "A wearable exam stress dataset for predicting grades using physiological signals," in *2022 IEEE Healthcare Innovations and Point of Care Technologies (HI-POCT)*, pp. 30–36, IEEE, 2022.

[31] S. Khazaei, M. R. Amin, and R. T. Faghih, "Decoding a neurofeedback-modulated cognitive arousal state to investigate performance regulation by the yerkes-dodson law," in *2021 43rd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC)*, pp. 6551–6557, IEEE, 2021.

[32] H. F. Azgomi, I. Cajigas, and R. T. Faghih, "Closed-loop cognitive stress regulation using fuzzy control in wearable-machine interface architectures," *IEEE Access*, vol. 9, pp. 106202–106219, 2021.

[33] D. S. Wickramasuriya, C. Qi, and R. T. Faghih, "A state-space approach for detecting stress from electrodermal activity," in *2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, pp. 3562–3567, IEEE, 2018.

[34] A. Yaghmour, M. R. Amin, and R. T. Faghih, "Decoding a music-modulated cognitive arousal state using electrodermal activity and functional near-infrared spectroscopy measurements," in *2021 43rd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC)*, pp. 1055–1060, IEEE, 2021.

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

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

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

[38] A. D. Laposky, J. Shelton, J. Bass, C. Dugovic, N. Perrino, and F. W. Turek, "Altered sleep regulation in leptin-deficient mice," *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, vol. 290, no. 4, pp. R894–R903, 2006.