Nonlinear Smoothing of Data with Random Gaps and Outliers (DRAGO) Improves Estimation of Circadian Rhythm

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***Abstract*—Core body temperature measurement using an ingestible pill has been proven effective for field-based ambulatory applications. The ingestible pill overcomes many impracticalities related with traditional methods of assessing core body temperature, however, it suffers from two key issues: random gaps due to missing data and outliers due to electromagnetic intereference. In this paper, we propose a principled convex optimization based framework for preprocessing the raw core body temperature signal. The proposed framework assumes that the raw core body temperature signal consists of two components: a smooth low-frequency component and a transient component with sparse outliers. We derive a computationally efficient algorithm using the majorization-minimization procedure and show its performance on simulated data. Finally, we demonstrate utility of the proposed method for estimating the circadian rhythm of core body temperature in cognitively normal elderly.**

I. Introduction

Circadian rhythms are physiologic and behavioral cycles with a recurring periodicity of approximately twenty-four hours in healthy individuals [17]. The biological processes of sleep-wake cycle and body temperature are controlled by the circadian rhythms and disruptions in these rhythms can lead to circadian rhythm disorders such as an irregular sleep-wake rhythm disorder, which is prevalent in subjects with traumatic brain injury [18]. Moreover, circadian rhythm alterations are observed in age-related diseases such as Alzheimer's disease [2], [9], [13], [18].

Core body temperature (CBT) is considered an objective measure of the circadian rhythm and is known to characterize their circadian phase [15]. The CBT is typically measured from either the esophagus, naso-pharynx, rectum or tympanum/auditory meatus [6]. There is growing interest in utilizing ingestible capsules such as the CorTemp ingestible pill (CorTemp® HQ Inc., Palmetto, FL, USA.) for measuring CBT [10]. The CorTemp® ingestible pill sensor wirelessly transmits temperature measurements to a recorder worn on the waist as it travels through the digestive tract. The CBT measured using the ingestible pill has a good agreement with the rectal core body temperature, which is a gold standard method of circadian rhythm measurement [1], [3]. One of the major challenges in measuring circadian rhythm using the CorTemp pill is that the raw CBT signal often contains random gaps and/or outliers [7]. Furthermore, in some subjects the pill passes in less than 24 hours due to which estimating circadian rhythm becomes difficult. The presence of random gaps and outliers in the raw CBT signal can lead to inaccurate measurements of several features of an individual's circadian rhythm, (e.g., period, mean temperature, timing of peak and nadir temperatures etc.) [11]. As a result, the data is often discarded. Among the causes of outliers in the raw CBT signal, the common ones are 1) close proximity to electronic devices and 2) ingestion of liquids at a higher (likewise lower) temperature than the room temperature [16]. In addition to these outliers, the CBT signal often contains missing data when the waist-worn receiver is out of range, particularly during showers as the receiver is not waterproof.

Missing data upto a few samples can be imputed based on traditional methods such as averaging, similar response pattern imputation, and maximum likelihood estimation [4]. However, most of these methods assume that the underlying data is stationary, which is not met in the case of CBT signals. In addition, traditional methods for outlier removal consist of either replacing them with more moderate values (e.g., mean of few preceding samples) or treating them as missing values and imputing as above. However, if the data are not missing completely at random, which is the case for the CBT signals, such outliers removal techniques bias the underlying signal model. Further, it is also possible to use the Lomb-Scargle periodogram [8], [12] to estimate period in the presence of missing values or non-uniformly sampled data. However, in the event of a sub-optimal signal-to-noise ratio (SNR), these estimates are not accurate [14].

In this paper we propose a principled convex optimization based framework for nonlinear smoothing of the circadian rhythm data with missing values. To our knowledge, this is the first such unified framework proposed for preprocessing the CBT signal that is capable of tackling both random gaps and outliers in a single pass. We hypothesize that the proposed framework improves SNR of the CBT signal thereby leading to a better estimate of the period using the Lomb-Scargle Periodogram.

II. Preliminaries

A. Notation

We denote vectors and matrices by lower and upper case letters respectively. The N-point signal y is represented by the vector

$$y = \left[y_0, \ldots, y_{N-1}\right]^T, \qquad y \in \mathbb{R}^N, \tag{1}$$

where $[\cdot]^T$ represents the transpose. The ℓ_1 and ℓ_2 norm of the vector y are defined as

$$\|y\|_1 := \sum_n |y_n|, \qquad \|y\|_2 := \left(\sum_n |y_n|^2\right)^{1/2} \tag{2}$$

We define the second order difference matrix D as

$$D = \begin{bmatrix} 1 & -2 & 1 & & & \\ & 1 & -2 & 1 & & \\ & & \ddots & & \ddots & \\ & & & 1 & -2 & 1 \end{bmatrix}. \tag{3}$$

Using the matrix D of size $(N-1) \times N$, the second-order difference of an N-point discrete signal x is given by Dx.

B. Encoding random gaps in the input signal

Suppose only K samples of an N-point input signal q are observed, where $K < N$. This is particularly true when a given signal q contains gaps that are randomly distributed or when non-uniformly sampled data is regridded to a uniform grid. We express the observed values $\hat{q}$ as

$$\hat{q} = Sq, \qquad \hat{q} \in \mathbb{R}^K, q \in \mathbb{R}^N, \tag{4}$$

where $S \in \mathbb{R}^{K \times N}$ is a sampling matrix. As an example, if only the first, second and last elements of a 5-point signal q are observed, then the matrix S is given by

$$S = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}, \tag{5}$$

Note that the matrix S is deduced from the input data by simply deleting the relevant rows from an N- by-N identity matrix. For the example shown above, the third and fourth rows of a 5-by-5 identity matrix are deleted to derive the matrix S. The matrix S satisfies the properties listed below. We will use these properties throughout the paper.

1) The matrix S satisfies the following identities,

$$SS^T = I, \tag{6}$$

where I is the $K \times K$ identity matrix. In addition,

$$S^T S = \mathrm{diag}(s), \qquad s \in \mathbb{R}^N, \tag{7}$$

where $\mathrm{diag}(s)$ denotes a diagonal matrix with s as its diagonal.

2) The matrix S^T represents zero-filling. As an example, for the matrix S in (5), we have

$$S^T y = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix} \cdot \begin{bmatrix} y_0 \\ y_1 \\ y_2 \end{bmatrix} = \begin{bmatrix} y_0 \\ y_1 \\ 0 \\ 0 \\ y_2 \end{bmatrix}. \tag{8}$$

III. Nonlinear Smoothing of Data with Random Gaps and Outliers

A. Problem formulation

Let y be the N-point observed signal with random gaps and outliers in presence of Gaussian noise. The signal model can be written as

$$Sy = Sf + x + w, \tag{9}$$

where f is the smooth signal, x is the sparse signal representing outliers, S is the given sampling matrix and w represents additive white Gaussian noise with a standard deviation of σ. The matrix S encodes the position of the gaps and we assume it to be known. In order to estimate the underlying smooth signal f, we consider the following sparse-regularized optimization problem

$$\{\hat{f}, \hat{x}\} = \arg\min_{f,x} \bigg\{ F(f,x) := \frac{1}{2}\|Sy - Sf - x\|_2^2 + \frac{\lambda_1}{2}\|x\|_1 + \frac{\lambda_2}{2}\|Df\|_2^2 \bigg\}, \tag{10}$$

where λ_1 and λ_2 are the regularization parameters. The objective function in (10) promotes the sparsity of the signal x using the ℓ_1 norm, while preserving the smoothness of f using the ℓ_2 norm over its second-order difference. It is worth noting that the proposed objective function does not require the input signal to be stationary.

B. Algorithm

We derive an algorithm for the proposed objective function in (10) using the Majorization-Minimization (MM) procedure [5]. Note that the proposed objective function (10) is convex and hence global minimum of (10) can be reliably obtained. The MM principle is well-established and consists of the iteration

$$\{f^{(i+1)}, x^{(i+1)}\} = \arg\min_{f,x} F^{\mathrm{M}}(f, x; x^{(i)}), \tag{11}$$

where i is the iteration index and F^{M} denotes a majorizer of the objective function F. In particular, we have

$$F^{\mathrm{M}}(f, x; v) \geqslant F(f, x), \qquad \text{for all} \quad f, x, v, \tag{12}$$

$$F^{\mathrm{M}}(f, v; v) = F(f, v), \qquad \text{for all} \quad v. \tag{13}$$

We define the majorizer F^{M} as

$$F^{\mathrm{M}}(f, x; v) := \frac{1}{2}\|S(y - f) - x\|_2^2 + \frac{\lambda_2}{2}\|Df\|_2^2 + \frac{\lambda_1}{2} x^T \big[W(v)\big] x, \tag{14}$$

where $W(v)$ is a diagonal matrix defined as

$$\big[W(v)\big]_{n,n} = \frac{1}{|v_n|}. \tag{15}$$

To obtain the solution to (11), we minimize (11) with respect to f and x alternatively. Minimizing F^{M} with respect to x gives

$$x = \big(I + \lambda_1[W(v)]\big)^{-1} S(y - f). \tag{16}$$

Equivalently,

$$x_n = \frac{1}{1 + \lambda_1[W(v)_{n,n}]}\,[S(y-f)]_{n,n} \tag{17}$$

$$= \frac{1}{1 + \lambda_1/|v_n|}\,[S(y-f)]_{n,n} \tag{18}$$

$$= \frac{|v_n|}{|v_n| + \lambda_1}\,[S(y-f)]_{n,n}\,. \tag{19}$$

Using (16) in (14) gives

$$\begin{aligned} F^{\mathrm{M}}(f; v) &= \frac{1}{2}\|S(y-f) - \big(I + \lambda_1[W(v)]\big)^{-1} S(y-f)\|_2^2 \\ &+ \frac{\lambda_2}{2}\|Df\|_2^2 + \Bigg(\frac{\lambda_1}{2}(y-f)^T S^T \big(I + \lambda_1[W(v)]\big)^{-1} \\ &\times [W(v)]\big(I + \lambda_1[W(v)]\big)^{-1} S(y-f)\Bigg), \end{aligned} \tag{20}$$

which can be re-written as

$$\begin{aligned} F^{\mathrm{M}}(f; v) &= \frac{1}{2}\|A_1(v)S(y-f)\|_2^2 + \frac{\lambda_2}{2}\|Df\|_2^2 \\ &+ \frac{1}{2}(y-f)^T S^T [A_2(v)] S(y-f), \end{aligned} \tag{21}$$

where A_1 and A_2 are diagonal matrices defined as

$$[A_1(v)] := I - \Big(I + \lambda_1[W(v)]\Big)^{-1} \tag{22}$$

$$\begin{aligned} [A_2(v)] &:= \lambda_1\Big(I + \lambda_1[W(v)]\Big)^{-1} \times \\ &[W(v)]\Big(I + \lambda_1[W(v)]\Big)^{-1} \end{aligned} \tag{23}$$

The matrices A_1 and A_2 can be written alternatively using (19) as

$$[A_1(v)]_{n,n} = \frac{\lambda_1}{|v_n| + \lambda_1}, \tag{24}$$

$$[A_2(v)]_{n,n} = \frac{\lambda_1|v_n|}{(|v_n| + \lambda_1)^2}. \tag{25}$$

On the other hand, minimizing F^{M} with respect to f gives

$$\begin{aligned} f &= \big[S^T([A_1(v)]^2 + [A_2(v)])S + \lambda_2 D^T D\big]^{-1} \\ &\times S^T([A_1(v)]^2 + [A_2(v)])Sy. \end{aligned} \tag{26}$$

Note that

$$[A_1(v)]_{n,n}^2 + [A_2(v)]_{n,n} = \left(\frac{\lambda_1}{|v_n| + \lambda_1}\right)^2 + \frac{\lambda_1|v_n|}{(|v_n| + \lambda_1)^2} \tag{27}$$

$$= \frac{\lambda_1}{|v_n| + \lambda_1}. \tag{28}$$

Algorithm 1 DRAGO iterative algorithm for smoothing of data with random gaps and outliers. The objective function is given in (10)

input: $y \in \mathbb{R}^N, \lambda_1, \lambda_2$
initialize: $x = Sy$
repeat
  $A_{n,n} = \lambda_1/(|x_n| + \lambda_1)$
  $B = S^T A S + \lambda_2 D^T D$
  $f = B^{-1} S^T A S y$
  $x_n = |x_n|\,[S(y-f)]_n\,/\,(|x_n| + \lambda_1)$
until convergence

As a result, we have

$$f = \Big(S^T[A(v)]S + \lambda_2 D^T D\Big)^{-1} S^T [A(v)] S y, \tag{29}$$

where $[A(v)]$ is a diagonal matrix with entries

$$[A(v)]_{n,n} = \frac{\lambda_1}{|v(n) + \lambda_1|}. \tag{30}$$

Note that the matrix to be inverted in (29) is banded[1]. As a result, the equation (29) can be implemented efficiently. The MM procedure (11) gives rise to the following iterative algorithm for smoothing of data with random gaps and outliers (DRAGO), which is also summarized in Table 1.

$$[A^{(i)}]_{n,n} = \frac{\lambda_1}{|x_n^{(i)}| + \lambda_1}, \tag{31a}$$

$$f^{(i+1)} = \Big(S^T A^{(i)} S + \lambda_2 D^T D\Big)^{-1} S^T A^{(i)} S y, \tag{31b}$$

$$x_n^{(i+1)} = \frac{|x_n^{(i)}|}{|x_n^{(i)}| + \lambda_1}\Big[S(y - f^{(i+1)})\Big]_{n,n}. \tag{31c}$$

In order to avoid the zero-locking issue, wherein a chosen value for $x^{(0)}$ results in all subsequent iterations to be zero, i.e., $x_n^{i+1} = 0, i > 0,$ for all n, we set the initial value for the iterative algorithm as $x^{(0)} = Sy$.

C. Example

We illustrate the performance of the proposed DRAGO method for smoothing data with random gaps and outliers using the following synthetic example. Shown in Fig. 1(a) is the simulated data which consists of two low-frequency sinusoids that are uniformly sampled. The Lomb-Scargle power spectral density (PSD) estimate is shown in Fig. 2(a). The Lomb-Scargle periodogram method does not require the underlying data to be uniformly sampled and can handle missing values [8], [12]. Note that the Lomb-Scargle PSD estimate shows prominent peaks (red circles in Fig. 2(a)) at the two frequencies of x. Figure 1b shows the noisy data y with random gaps (45% missing) and outliers. The Lomb-Scargle PSD estimate of y is shown

[1] A banded matrix is a sparse matrix whose non-zero entries are confined to a diagonal band and zero or more diagonals on either side.

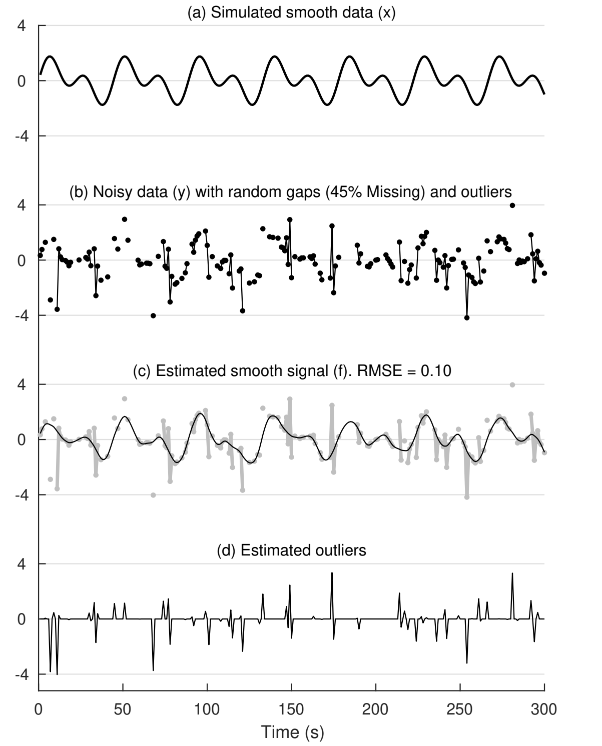

Figure 1: Illustration of the proposed DRAGO method on simulated data.

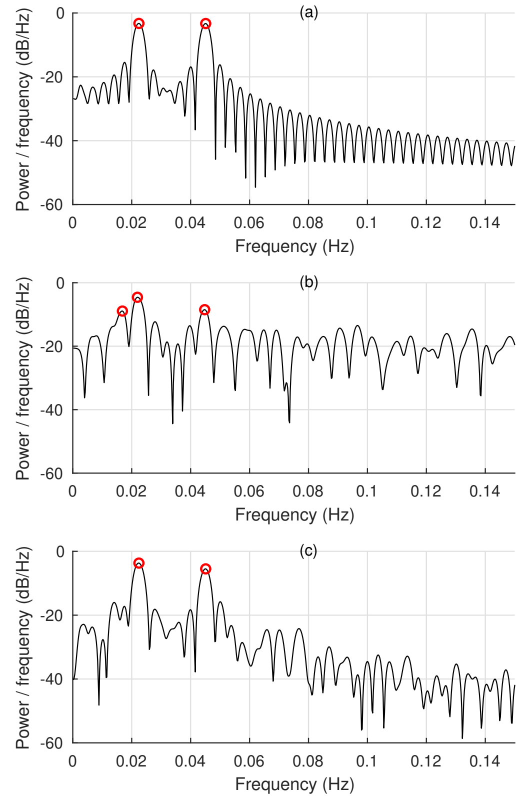

Figure 2: Lomb-Scargle power spectral density estimates for the (a) synthetic smooth data, (b) noisy data with random gaps and outliers and (c) smooth signal estimate using DRAGO.

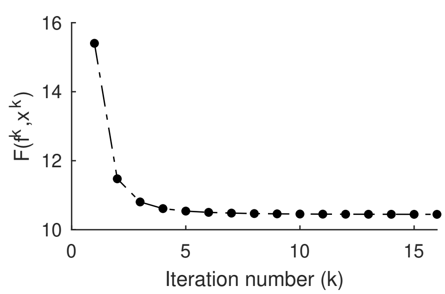

Figure 3: Value of the objective function in (10) for every iteration using the synthetic data in Fig. 1 as an example.

in Fig. 2(b). Note that the peaks are no longer prominent and a false peak appears at 0.018 Hz. Although lowering the threshold for peak detection eliminates the false peak, it also eliminates the true peak at 0.045 Hz. We set the value of the regularization parameters λ_1 and λ_2 manually to obtain the lowest denoising and smoothing error using the root mean square error (RMSE) which is defined as

$$\text{RMSE}(x_{\text{org}}, x_{\text{est}}) := \frac{\|x_{\text{org}} - x_{\text{est}}\|_2^2}{\|x_{\text{org}}\|_2^2}. \tag{32}$$

Figure 1(c) shows the estimated smooth signal using DRAGO and the obtained RMSE. The outliers estimated are shown in Fig. 1(c). It is worth noting that the estimated smooth signal does not contain any outliers. Shown in Fig. 2(c) is the Lomb-Scargle PSD estimate of the estimated smooth signal f. Notice that the two peaks are distinctly visible and the power/frequency ratio decays with increasing frequency values. The value of the objective function in (10) after each iteration of the DRAGO iterative algorithm using the MM procedure is shown in Fig. 3.

It can be seen that the DRAGO iterative algorithm converges in about 5 iterations.

IV. Estimating Circadian Rhythm using DRAGO processed Core Body Temperature Signal

We now illustrate the application of the DRAGO iterative algoritm for estimating circadian rhythm from raw CorTemp pill data. Figures 4(a) and 4(c) show the raw data from two fully entrained subjects who participated in a study on orexin and tau pathology in cognitively normal elderly. The circadian rhythm i.e., period of the CorTemp data, estimated using the Lomb-Scargle PSD estimate is shown in Fig. 5(a) and Fig. 5(c) for Subject 1 and 2 respectively. These subjects were fully entrained in a 24hr environment, confirmed with 7-day actigraphy, and had no complaints of circadian rhythm sleep disorders. Entrainment is defined as alignment of the circadian system to the 24hr day. As a result, these subjects are expected to demonstrate roughly a 24hr circadian rhythm. The subjects were administered the pill on the first night of their scheduled 2 night in-lab polysomnography visits and the data was collected until the pill was passed by the body (approx. 36-40 hours). The sampling rate for the CorTemp data was fixed at 1 sample per 25 seconds. Note that the sampling rate is not uniform since datapoints are recorded

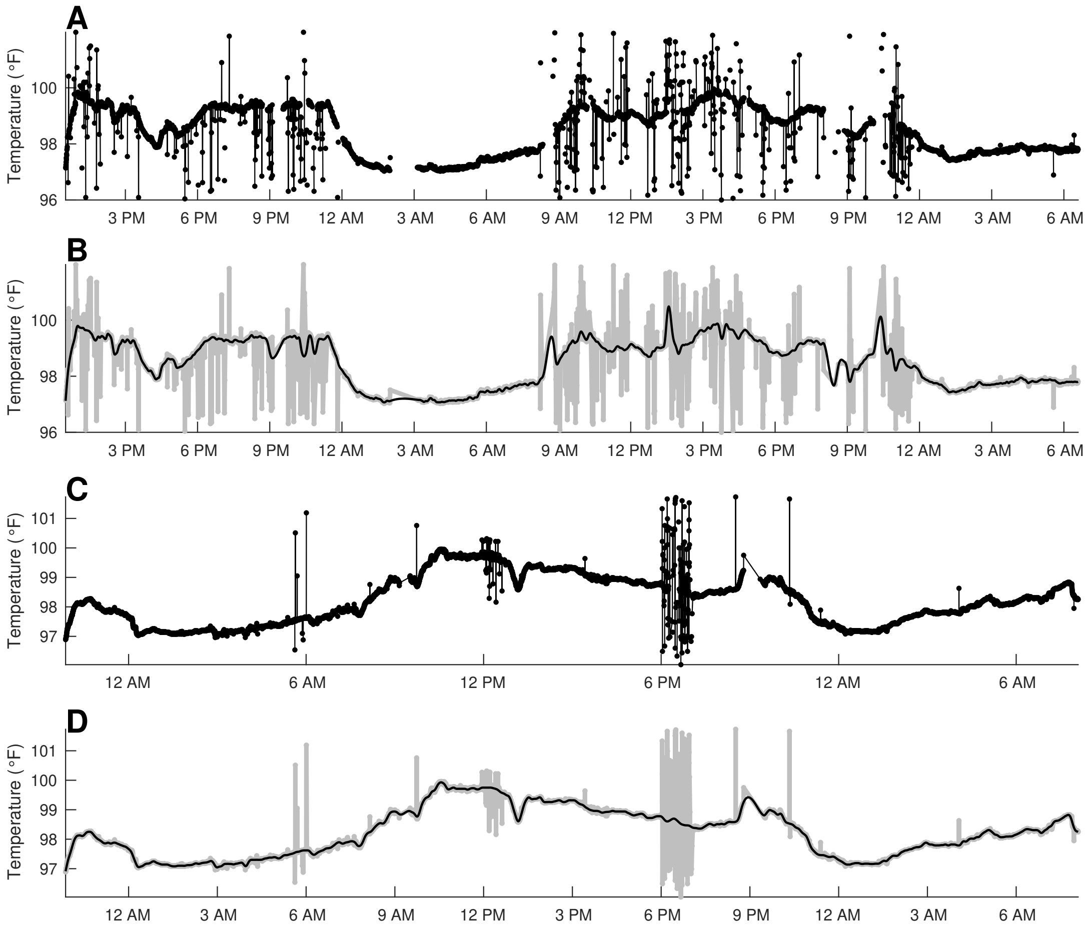

Figure 4: Core body temperature data using CorTemp ingestible pill from fully entrained cognitively normal subjects (a) and (c). The DRAGO smoothed signal is shown in (b) and (d) for the two subjects respectively.

when the subjects manually read the temperature data. All subjects signed informed consent documents and the protocol for the study was approved by the NYU IRB and the Mount Sinai IRB.

Figures 4(b) and 4(d) show the result of using the DRAGO iterative algorithm on the raw CorTemp data. Note that the data has been regridded to a sampling rate of 1 sample per second. It can be seen that the estimated smooth data contains no outliers (e.g., significant outliers in Fig. 4(c) around 6PM) and the missing data has been approximated with a smooth segment (e.g., the segment of missing data in Fig. 4(a) around 3AM on Night 1). It worth noting that estimates of the mean temperature from the smooth signal estimated using DRAGO are more accurate due to the absence of outliers. The estimated circadian rhythm using the smoothed CorTemp data for the Subjects 1 and 2 can be seen in Fig. 5(b) and Fig. 5(d) respectively. Figure 6 shows the circadian rhythm estimated from the raw data and the DRAGO processed data for all the 18 subjects who participated in the parent study. It can be seen that processing the CBT signal using DRAGO provides better circadian rhythm estimates than using the raw signal alone. The DRAGO iterative algorithm takes on an average 0.67 ± 0.02 seconds for a CBT signal with a duration of approx. 45 hours.

One of the limitations of the proposed DRAGO framework is that it requires the setting of two regularization parameters λ_1 and λ_2. For simulated data where the ground-truth is available, often the parameters are set so as to minimize the error criteria (RMSE). However, when no ground-truth data is available, a suggested method is to synthetically set a segment of raw data as missing and/or with outliers and tune the two parameters so as to obtain the lowest RMSE for that segment. We used this method for processing the CBT signals from the 18 participants shown in Fig. 6. In addition, as is seen often with imputation methods, when a significantly large segment of data is missing, the reconstructed signal using the proposed DRAGO framework may not be accurate. Our ongoing work is directed toward developing a theoretical framework for the setting of regularization parameters as well as deriving bounds on the length of missing data when the reconstructed signal using DRAGO may not be reliable.

V. Conclusion

Ingestible pills allow feasible monitoring of core body temperature in a home-based ambulatory setting. However, the presence of random gaps and outliers hinders the

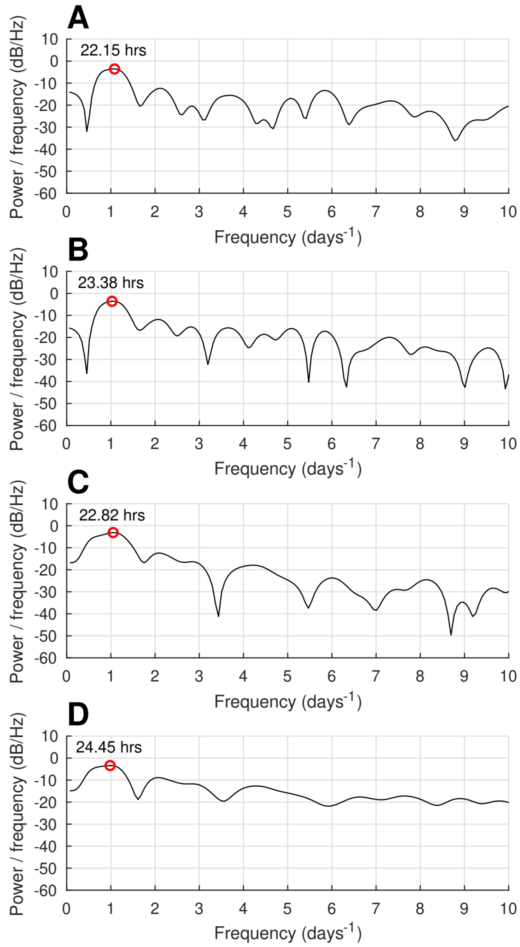

Figure 5: Lomb Scargle PSD estimates for the corresponding data in Fig. 4. Note that the circadian rhythm calculcated from the raw data in Fig. 4(a) and Fig. 4(c) is inaccurate as we expect a roughly 24hr circadian rhythm.

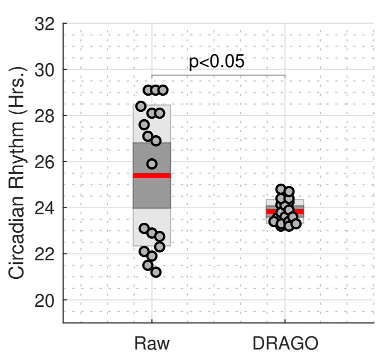

Figure 6: Circadian rhythm estimates using Lomb-Scargle Periodogram directly on the raw and on the DRAGO processed CBT signal from N=18 participants.

assessment of circadian rhythm and its features. In this paper we develop a principled convex optimization based framework for smoothing the core body temperature data with random gaps and outliers (DRAGO). We propose a convex objective function utilizing the sparsity of the outliers and the smoothness of the underlying signal. We derive a computationally efficient iterative algorithm using the majorization-minimization procedure and demonstrate its performance on simulated data as well as on actual data from fully entrained subjects with an expected 24hr circadian rhythm. We show that the proposed method can reliably estimate the underlying CBT signal and its features such as the period and phase.

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