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Dealing with Methodological Issues in the Functional Data Analysis of Actigraphy Data

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Abstract

This article examines several methodological issues we have encountered when using functional data analysis (FDA) to analyze actigraphy data. For example, we discuss and compare methods used for handling missing actigraphy data, and how to determine the optimal number of basic functions to use when applying FDA. Curves fit to actigraphy data must take on non-negative values, so we also discuss how to restrict FDA curves so that they have no negative values. The methods and issues we discuss are illustrated using actigraphy data from our study of the utility of a rest-activity biomarker to predict responsiveness to antidepressants.

Keywords: Basis functions; Missing data; Imputation; Biomarker; Validation; Rest-activity data

Introduction

In this article, we describe methodological issues that we encountered when using functional data analysis (FDA) in our examination of the utility of rest-activity biomarkers to predict responsiveness to antidepressants. We considered the following biomarkers: (1) Bathyphase (clock-time of lowest activity) and (2) Acrophase (clock-time of greatest activity). Both are based on actigraph-obtained activity levels during a given 24-hour period.

Description of Clinical Study

Our investigation used data from the "Reducing Suicidal Ideation through Treatment of Insomnia" (REST-IT) randomized clinical trial (RCT) [1]. Adult patients with major depressive disorder (MDD) complicated by insomnia and suicidal ideation were recruited for this study. The primary goal of REST-IT was to evaluate targeted insomnia treatment in hopes of reducing suicidal ideation. The eligibility criteria were as follows: (1) Adults aged 18-65 years suffering with MDD, (2) 24-item Hamilton Rating Scale for Depression (HRSD) scores of ≥ 20, (3) Insomnia Severity Index (ISI) scores > 7, and (4) Scale for Suicide Ideation (SSI) scores ≥ 3.

Patients with cognitive disorders, history of substance abuse, and schizophrenia were excluded. All participants completed either a portable in-home test for sleep apnea or an in-lab polysomnogram the week before starting the RCT. All patients were free of all psychotropic medications for $\geq$ 1 week prior to beginning the RCT. REST-IT consisted of open-label Prozac™ 20 mg every morning, along with 1:1 randomization to either Ambien CR™ extended-release 6.25 mg or placebo at bedtime.

The collection of the actigraphy data that were used in our study was from the first 1-2 weeks of drug treatment in the RCT. Activity data were collected using either the Philips Actiwatch 2 or the Philips Actiwatch Score. The Philips Actiwatch 2 is pictured in Figure 1.

The particular watch that an individual study participant received was based upon what the study site already had on hand. The internal mechanics and scoring of each watch were identical and interchangeable, and assumed to produce exactly the same actigraphy results. The watches were set to medium sensitivity, with 30 second recording epochs. Patients were instructed to wear the devices continuously, including during bathing, swimming, etc.

Functional Data Analysis

A good operational definition of functional data is the following: "Observations on subjects that you can imagine as $X_i(s_i)$, where s_i is continuous" [2]; for example, $X_i(t)$, $0 \leq t \leq 2880$, where 2880 is the number of 30-second epochs in a 24-hour period. However, this notation is conceptual; observations are actually made on a finite discrete grid. Thus, each observation in a sample of functional data is a vector.

Functional data are intrinsically high dimensional and this poses challenges for theory and computation. The second author has been actively involved in research studies in which FDA curves were fit to actigraphy data [3]. An example is given in Figure 2.

Methodological Issues We Encountered

We analyzed data on 47 REST-IT patients with 3 to 12 nights

Figure 1: Philips Actiwatch 2.

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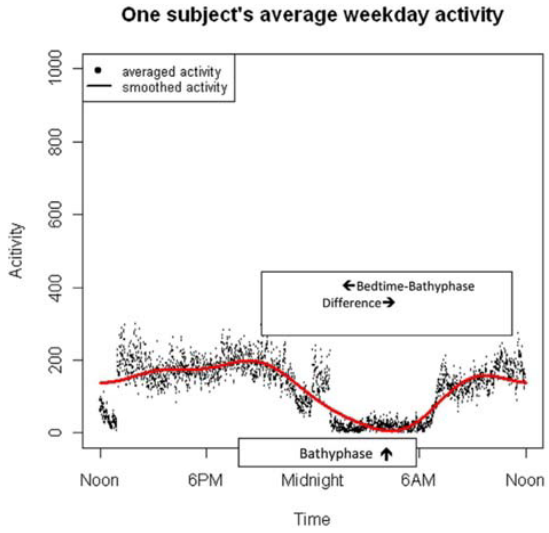

Figure 2: Smoothed curve for one week of actigraphy data in a single subject.

of actigraphy data per patient. All functional data analyses of the actigraphy data were performed using R 3.2.2 (The R Foundation for Statistical Computing, 2016), and the following R components were used: the *fda* package, the *Actigraphy* package, the *create.fourier.basis* function, the *smooth.basis* function, the *smooth.pos* function, and the *eval.posfd* function.

In our application of FDA to actigraphy data, we considered the following issues: (1) missing actigraphy data, (2) determination of optimal number and type of basis functions to use when applying FDA, (3) whether or not to apply a roughness penalty, and (4) restricting fitted FDA curves so that they have no negative values. We will discuss each of these issues separately in the sections below.

Handling missing data

Due to software/hardware errors in the actigraphy watches, there were missing activity data throughout the study. We developed the following strategy for dealing with missing data: if the total amount of missing data exceeded 60 minutes in a day, we removed the entire day from the analysis for that subject. If the total amount of missing data was less than 60 minutes in a day, we compared 2 methods: (1) Impute missing data using the Predictive Mean Matching (PMM) method [4] and (2) Replace missing data with 0. We analyzed the data using both methods and found that there was very little meaningful difference between the final FDA results obtained using the two methods. However, since the primary goal of the FDA of the actigraphy data was to estimate the bathyphase for each subject, we decided to use PMM rather than replace the missing values with 0 since it is possible that imputing a value of 0 could lead to biased estimates of the bathyphase. Activity data (as measured by actigraphy) can be very close to zero; however, even when subjects are asleep, there are very slight movements. Thus, imputing a value of 0 for missing actigraphy data might result in a fitted FDA curve that does not provide a realistic representation of near-zero activity levels, thereby leading to a biased estimate of the time at which the lowest activity level occurred (i.e., the bathyphase).

Choosing basis functions

The application of FDA requires the analyst to select an appropriate set of basis functions. According to Ramsay and Silverman [5], "A basis function system is a set of known functions φ_k that are mathematically independent of each other and that have the property that we can approximate arbitrarily well any function by taking a weighted sum or linear combination of a sufficiently large number K of these functions." We considered several different types of basis functions (Fourier, splines, etc.) and, under visual examination, Fourier appeared to fit the data best. This is consistent with the belief that circadian data are periodic in nature. In addition to selecting the type of basis functions, the analyst must also select the appropriate number of functions. We considered several different numbers of basis functions (between 7 and 65, inclusive), and decided to use 15. As discussed by Ramsey and Silverman [5], there is no gold standard method for choosing the number of basis functions. We initially eliminated some choices for the number of basis functions that consistently yielded larger total mean-squared error (MSE) than other choices. However, we were then left with several choices that had very similar results for MSE. Some had larger bias while others had larger variance. This bias/variance trade-off is inherently subjective; thus, we needed another criterion in order to make the final decision concerning the number of basis functions to use. Visual examination by the clinical investigator (the 2nd author) indicated that 15 Fourier basis functions yielded FDA curves that were most useful in identifying the most important clinical features of the activity patterns, especially in terms of the bathyphase.

Since the estimate of the bathyphase obtained from the FDA analysis was to be incorporated into the clinical treatment of the study subjects, we felt that it would be best to use this subjective approach, rather than apply some objective criterion that might not yield results that were clinically intuitive and useful.

Roughness penalty

To avoid overfitting the data, we considered imposing a roughness penalty on the fitted curve. We decided to use a roughness penalty that penalized the integral of the square of the second derivative, or the total curvature: $PEN_2 = \int \left[D^2 x(t) \right]^2 dt$, where $x(t)$=the smoothing function at time t. This provides smoothing because wherever the function is highly variable, the square of the second derivative is large. This gives us a compound fitting criterion of

$$F(c) = \sum_{j=1}^{T} \left[y_j - x(t_j) \right]^2 + \lambda \int \left[D^2 x(t) \right]^2 dt,$$

where T: Number of time points,

λ: Smoothing parameter,

y_j: Activity value obtained from the Actiwatch, and

$x(t_j)$: Smoothing function at time t_j.

To identify the appropriate value of the smoothing parameter λ, we used the generalized cross-validation measure GCV [6]. The GCV criterion is given by:

$$GCV(\lambda) = \left[\frac{T}{T - df(\lambda)} \right] \left[\frac{SSE}{T - df(\lambda)} \right],$$

where df: Degrees of freedom, and

SSE: Sum of squared errors.

We chose the value of the smoothing parameter that minimized the GCV (λ=10^4).

Restricting to non-negative values

By definition, activity values obtained using actigraphy should always be non-negative. However, many of the FDA curves we fit to

the activity values dipped below 0. To remedy this, we used the *smooth.pos* function in R to satisfy the non-negativity constraint. We then used the resulting positive smoothed curve to find values for the timing and amplitude of the daily bathyphase and acrophase for each patient in the study.

Example

In this section, we provide an example of the FDA curves fitted to one day's worth of actigraphy data for a single patient ("Patient X"). The data for Day 4 are plotted in Figure 3.

In Figure 4, we provide the FDA curve fitted to these data using 15 Fourier basis functions and the roughness penalty described previously. In Figure 5, we provide the FDA curve fitted to these data using 15 Fourier basis functions, the roughness penalty, and positive smoothing.

In Figure 6, we indicate the bathyphase (vertical blue line) and acrophase (vertical green line) obtained from the fitted curve. The bathyphase occurred at 4:30:00 a.m., with a fitted activity level of 0.182, and the acrophase occurred at 3:38:30 p.m., with a fitted activity level of 279.13.

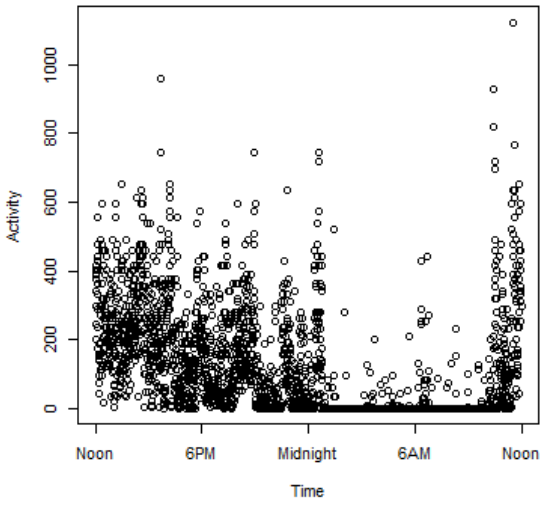

Figure 3: Actigraphy data for patient X, day 4, plotted in time order from noon to 11:59 a.m. of the following day.

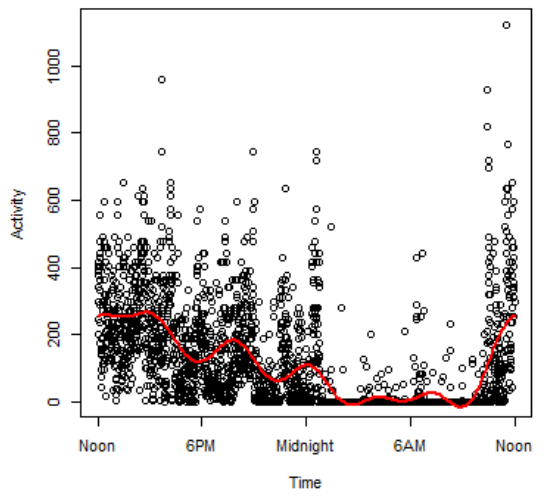

Figure 4: Actigraphy data for patient X, day 4, with fitted FDA curve in red (FDA curve based on 15 Fourier basis functions and includes a roughness penalty).

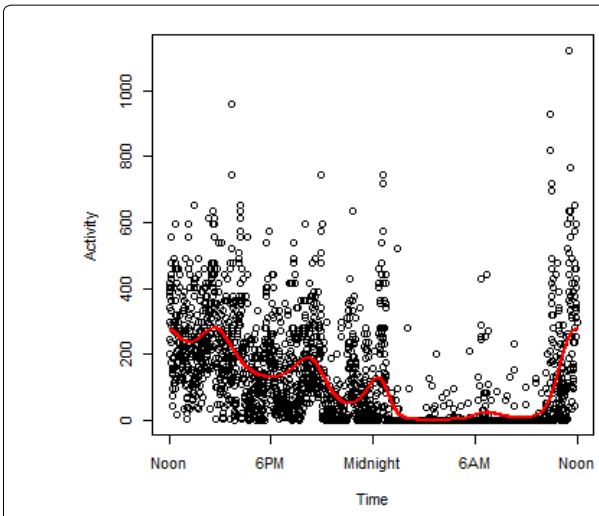

Figure 5: Actigraphy data for patient X, day 4, with fitted FDA curve in red (FDA curve based on 15 Fourier basis functions and includes a roughness penalty and positive smoothing).

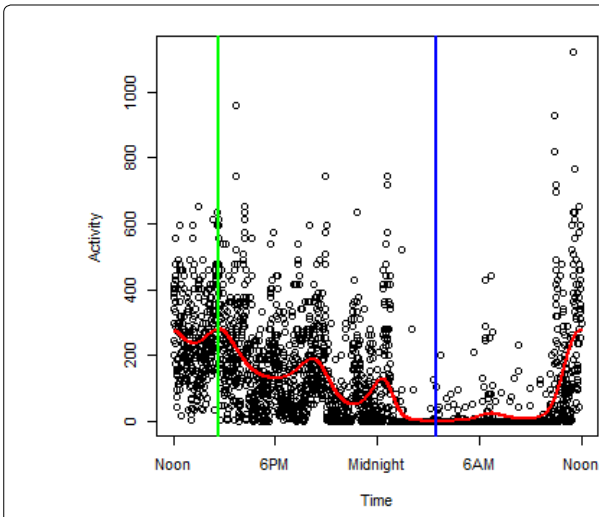

Figure 6: Actigraphy data for patient X, day 4, with fitted FDA curve in red, estimated bathyphase (vertical blue line) and estimated acrophase (vertical green line).

Summary and Discussion

We encountered several methodological issues when attempting to use FDA to analyze human activity data as measured by actigraphy. Of primary concern to us were determining workable strategies for dealing with missing activity data and negative fitted values for the FDA curves. Early in our analysis, we realized that fitting FDA curves to activity data required one to pay careful attention to "tuning"; in particular, determining the optimal type and number of basis functions and deciding whether or not to apply a roughness penalty and, if so, what type of roughness penalty to use.

In developing our analysis strategy, we decided to address these

methodological issues by: (1) removing the entire day if missing data for that day exceeded 60 min, (2) using Predictive Mean Matching to impute missing data if the total amount of missing data was less than 60 min, (3) using 15 Fourier basis functions, (4) applying a roughness penalty, and (5) using the *smooth.pos* function in R.

Functional data analysis of actigraphy data can be quite challenging, but if done carefully, it can yield interpretable measures of overall activity level. However, analysts should be aware that "canned" statistical analysis packages (even in R) may not yield interpretable results.

The limitations of our analysis included the fact that the data we analyzed were obtained from depressed insomniacs during their first week of treatment. Different results might have been obtained from healthy normals, or from depressed insomniacs during a medication-free interval. As with any FDA analysis, our results were dependent upon our final choice of the number and type of basis functions. However, our sensitivity analyses indicated that approximately the same results were obtained as with other choices.

In terms of future work, we plan to replicate our FDA results using actigraphy data from healthy normals. As part of the validation of our approach to analyzing actigraphy data, we also plan to compare values of bathyphase and acrophase obtained using FDA with values obtained using more commonly used methods such as cosinor analysis [7]. We also plan to validate the bathyphase as a biomarker of "morningness-eveningness" or other measures of circadian timing such as dim light melatonin onset (DLMO).

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