Powerful Actigraphy Data Through Functional Representation

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Actigraphy is an emerging clinical technology to evaluate sleep, daytime activity, and circadian activity rhythms in people. An actigraph is a watch-like device, usually attached to the wrist or leg, that contains accelerometers to measure movements in the form of activity counts every minute or every few seconds. Common actigraphs can be viewed at *www.actiwatch.respironics.com*. They document sleep/wake patterns, sleep disorders, circadian rhythms disorders, basic activity levels, and compliance with exercise routines. It is usually worn for multiple days to give an overall pattern of the person's activity level.

Because of less invasive data acquisition, low cost, and portability, actigraphy is recommended as an adjuvant to some studies of sleep by the American Academy of Sleep Medicine reports.

The restorative power of sleep is a universal experience. A good night's sleep is a requirement for optimal functioning during waking hours. Feeling tired after a poor night's sleep is also a universal experience. While an occasional bad night may merely be a nuisance, for the millions of Americans with sleep disorders, inadequate sleep becomes a serious health problem leading to adverse personal and social health consequences, impaired quality of life, and economic burdens.

Obstructive sleep apnea (OSA) syndrome is a disorder characterized by repetitive occlusions of the upper airway during sleep. This results in sleep fragmentation, oxygen desaturations, and elevated sympathetic tone. Symptoms include fatigue, sleepiness, and cognitive impairment. Adverse health consequences include increased risk of hypertension, cardiovascular disease, stroke, and mortality. Risks of diabetes and depression may be increased, and patients with OSA have a two- to seven-fold increased risk of automobile accidents. Between 2% and 4% of the general population has OSA, with the vast majority remaining undiagnosed. It is estimated that one in four Americans should be tested for OSA.

Restless legs syndrome (RLS) presents with four cardinal features: an urge to move the leg usually associated with parasthesias such as a creepy crawly feeling; this urge is precipitated by rest and relieved by movement; increased motor activity is present; and symptoms exhibit a circadian rhythm, being most severe near bedtime. Prevalence is estimated at 5% of the general population. Patients may have severe difficulty sleeping, and simple things such as sitting through an evening movie or taking a plane ride may be impossible. The overall impact on quality of life as measured by the SF-36, a health survey with only 36 questions, is comparable to that of other chronic diseases such as type II diabetes or osteoarthritis.

Insomnia, defined as difficulty initiating or maintaining sleep resulting in daytime consequences such as fatigue or concentration problems, is the most common sleep disorder, present in about 10% of the population. Insomnia is an expensive disorder, with direct costs such as physician visits and medications totaling $13.58 billion and total costs, including accidents and absenteeism, estimated at $77 to $92 billion in 1995.

Inadequate sleep from a variety of causes is such a pervasive problem in our society that the scope of the problem is difficult to overstate, as indicated by a statement from a presidential commission on sleep disorders research stating: "In sum, a substantial number of Americans, perhaps the majority, are functionally handicapped by sleep deprivation on any given day."

The high prevalence and significant impact of sleep disorders suggest the need for readily available, inexpensive diagnostic tools. The sleep medicine field, however, has relied on expensive, limited availability procedures such as the all-night polysomnogram (ANPSG), which is the gold standard for diagnosing and verifying adequate treatment of OSA, or a subjective symptom-based approach with inconsistently applied objective monitoring, as in RLS and insomnia. During an ANPSG, the patient spends a night in a sleep laboratory with electrodes placed on the scalp and face for sleep staging and is monitored by a technician. A variety of monitors are placed to measure respiration, electrocardiogram (ECG), oxygen saturation, leg movement, body position, and snoring intensity while the subject is videotaped.

Polysomnography has the advantage of being able to simultaneously monitor multiple physiological variables, and treatment may be initiated during the study. Disadvantages include the artificial laboratory setting that may affect sleep variables; the one-night limitation, which may miss the night-to-night variability present in sleep disorders; the lack of information on daytime function; and expense.

Actigraphy, on the other hand, can be used in the home sleep environment with virtually no impact on sleep, can be used for weeks at a time, provides information about daytime activity, and is inexpensive. It has been shown that actigraphy has about 90% agreement (with respect to sleep versus waking) with ANPSG. While the role of the ANPSG will always be limited in the evaluation of RLS and insomnia, new methods of data analysis for actigraphy may lead to valuable new objective measures for evaluating patients with RLS, insomnia, and OSA.

There is also a great interest in using actigraphy as a tool for measuring fatigue, which is one of the most common complaints in primary medical practices. Fatigue has been defined as a "lack of energy" or "control" for the timely initiation or maintenance of a desired behavior and has a negative impact on a person's quality of life. Due to the prevalence of fatigue and its effect on quality of life, many studies have attempted to correlate fatigue with objective actigraphic measures. In this article, we show how functional data analysis (FDA) could become a possible natural approach for the statistical analysis of actigraphy data.

Actigraphy Measurement

Activity-level data and clinical data are being collected for 750 patients who are treated at the Washington University Sleep Medicine Center for sleep apnea, insomnia, or restless legs syndrome. Pregnant women and individuals who report working an evening or overnight shift are excluded from participation. These data are collected in accordance with the standards of the American Academy of Sleep Medicine and are reviewed by a board-certified sleep physician.

Traditionally, activity levels of patients, as measured by actigraphs, are displayed via actigrams for several consecutive days, such as in Figure 1. Here, the activities of a patient are plotted from Friday to Thursday. The horizontal axis indicates the time of day, and the vertical axis indicates the activity level. Higher values correspond to higher activity. Each spike on the plot represents the patient's activity, which is accumulated over one-minute intervals. From this actigram, it is clear there is considerable minute-to-minute variability within each day and even more considerable day-to-day variability for this patient. As expected, low activity levels are recorded between 11 p.m. and 6 a.m. The actigram also reveals that no further activities were recorded past 5 p.m. on Thursday, which is eliminated from further graphical and numerical assessments for convenience.

Although the information collected by actigraphy devices is abundant, as shown in the actigram, much research and clinical use of actigraphy data are limited to simple summary statistics such as total sleep time, sleep efficiency, and acrophase.

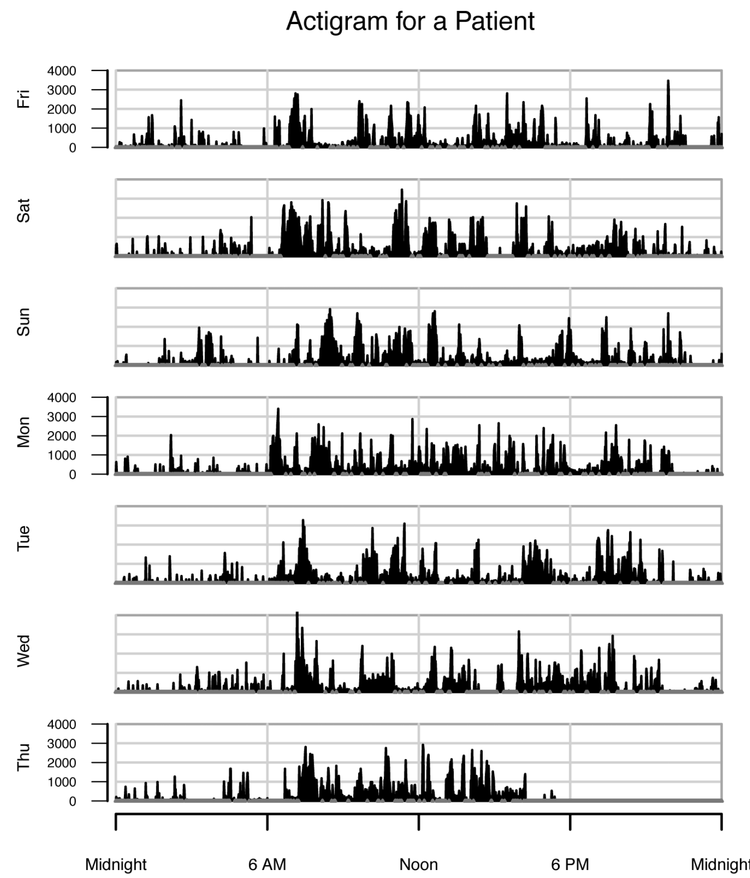

Figure 1. Actigraphy data for a patient over a seven-day period displayed in an actigram. Each row represents a 24-hour period from midnight to midnight. Data are shown for each minute. Rather than just showing the activity level as a time series, the area between the actual data and horizontal axis typically is filled in black in an actigram. The activity level shown on the vertical axis is unitless and depends on the actigraph model. A small gray triangle is shown on the horizontal axis when the activity level is zero over a one-minute interval.

Functional Representation

FDA is a more powerful tool than simple summary statistics for actigraphy data. Using the classical approach, the plot of averaged activity levels over several days (Figure 2(a)) shows tremendous noise that makes it hard to describe the pattern of activity other than noticing lower activity during the night (11 p.m. to 6 a.m.) and higher activity during the day. On the other hand, the FDA approach shows the smoothed activity

Functional Data Analysis (FDA)

In statistical terms, FDA is a technique that deals with a function or curve that may vary over time or across locations. For example, temperature over the year is a function of time and was analyzed as functional data in J. O. Ramsay and B. W. Silverman's *Functional Data Analysis*. Gene expression level at different stages is another example of functional data.

Our actigraphy data could also be naturally described as curves, as shown in Section 3. In general, a functional linear model could be written as

$$y_i(t) = Z_i(t)\beta(t) + \epsilon_i(t), \; i = 1, \ldots, n,$$

where $y_i(t)$ is the curve (functional data) from the ith subject, $Z_i(t)$ is the covariate vector of the ith subject, and $\beta(t)$ is the coefficient (treatment effect) associated with the covariate. This falls into the framework of general linear models, but with an infinite or very high dimensional response variable or covariate. Viewing data as a function allows us to investigate not only the expectation of curves but also functional features such as derivatives and curvatures of curves. One of the key ideas of FDA is dimension reduction. FDA techniques are often used to explore the pattern of the data and quantitatively investigate the source of variation.

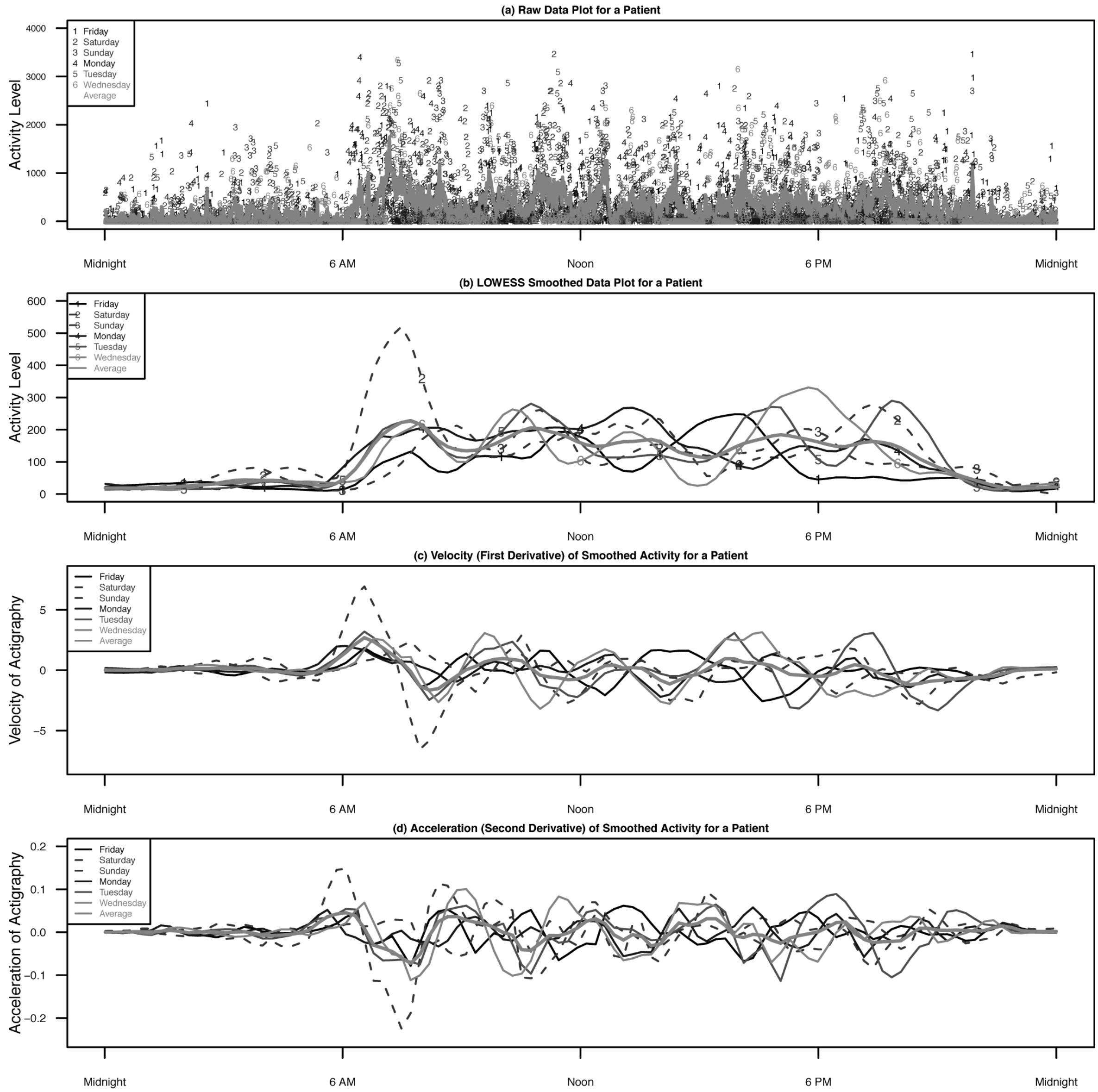

Figure 2. (a) raw daily activity levels; (b) smoothed activity levels based on a LOWESS smoother; (c) the first derivatives of the smoothed activity levels; and (d) the second derivatives of the smoothed activity levels. Shown are data for the same patient as in Figure 1 for six consecutive days (from Friday to Wednesday), omitting the partial data from day seven (Thursday). In each plot, the mean curve is overlaid as a solid thick line. The horizontal axis represents a 24-hour period from midnight to midnight. Data were collected every minute and are shown continuously in functional form.

curves (Figure 2(b)) that make the activity structure much more apparent.

These LOWESS smoothed curves show expected "normal" patterns of low activity levels from 11 p.m. to 6 a.m. when the patient is sleeping, increased activity levels in the morning when the patient wakes up, relatively high and constant activity levels during the day, and activity levels that slowly go back to low in the evening. By displaying daily smoothed curves (thin lines) with the smoothed mean curve (solid thick line), the variation of activity levels within the patient is revealed. Different activity levels early in the morning (in particular on Saturday) and substantially different evening activities (on Saturday and Tuesday) are observable in Figure 2(b). This transformation from raw activity levels into function curves allows us to identify patterns not easily seen in the raw data shown in Figure 2(a).

A functional view of actigraphy data also allows us to check some characteristics only available in the functional space. For example, the first derivatives of the LOWESS functions (Figure 2(c)) indicate the change of activity, called velocity, and the second derivatives (Figure 2(d)) indicate the speed of the change, called acceleration. Based on the velocity plot, we observe that most of the changes occur from 6 a.m. to 10 p.m. The mean of the first derivatives is negative between 7:30 a.m. and 9:30 a.m. This implies that the patient, after an active early morning, settles down in the middle of the morning. It would be worthwhile to investigate whether this patient has a sedentary job. The acceleration (Figure 2(d)) only varies slightly within each day, but it varies a lot between days. Saturday is the most unusual day, with rather high and low values for acceleration, indicating quite extreme changes in activity levels.

Besides individual functional curves, we also could investigate the population patterns of the activity levels in different patient subgroups. For instance, in a study of depression, patients filled out the Patient Health Questionnaire (PHQ-9), one of several existing ways to evaluate the level of depression. The clinician hypothesized that actigraphy levels are negatively correlated with depression levels. On the PHQ-9 scale, the higher the depression score, the more severely depressed the patient is. Patients with PHQ-9 scores equal to or higher than 15 are identified as moderately severely and severely depressed, and patients with PHQ-9 scores less than 5 are identified as normal (i.e., no depression). The others are identified as mildly and moderately depressed.

Figure 3 shows a decrease in average daytime activity levels for higher PHQ-9 scores. In particular, we observe slightly lower average daytime activity levels of the mild and moderate depression group, compared with the no depression group. The moderately severely and severely depressed patients on average seem to have considerable sleep disturbances and less, but unchanging, activity levels during the day in comparison with the mild and moderate depression and the no depression groups. These results seem to suggest that daytime activity levels are negatively correlated with the depression level and nighttime activity levels are positively correlated with the depression level. However, Figure 3 is only based on a pilot study of a small sample of 52 patients collected at the beginning of the study, and the full study of all 750 patients would be needed to confirm this hypothesis.

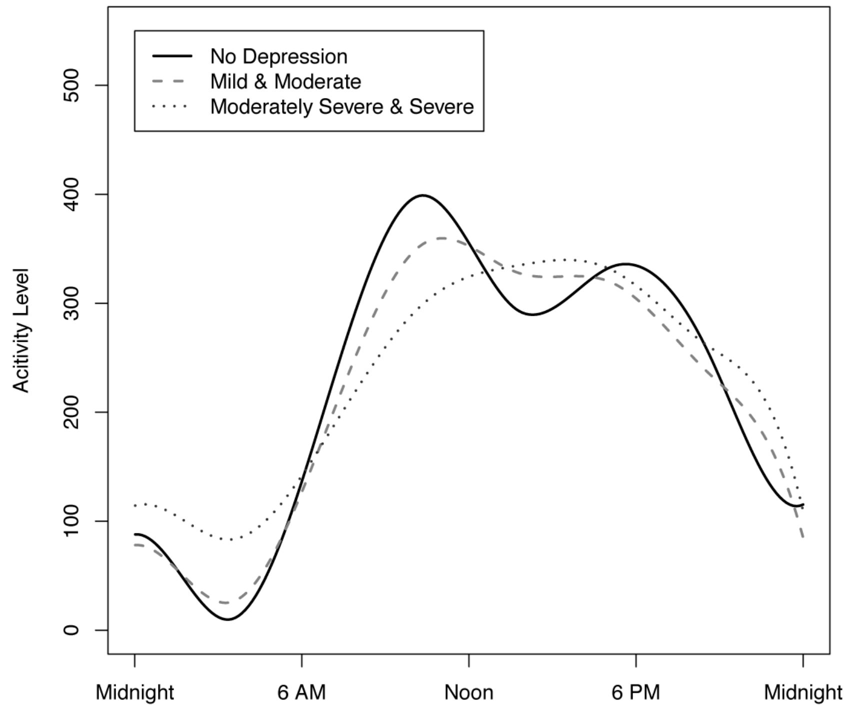

Figure 3. Mean activity levels of patients with three levels of depression, based on $n = 15$ patients with no depression (solid curve), $n = 26$ patients with mild and moderate depression (dashed curve), and $n = 11$ patients with moderately severe and severe depression (dotted curve). The horizontal axis represents a 24-hour period from midnight to midnight. Data were collected every minute and are shown continuously in functional form.

Variation Assessment

We previously showed how raw activity data can be transformed into smooth functions to extract information, which may not be obvious in simple summary statistics such as a mean function or histogram. From the functional mean curves in Figure 3, important clinical questions arise naturally: (1) Do activity patterns really differ for people with different levels of depression? (2) How should one assess the variation of activity levels among patients for hypothesis testing purposes? Functional principal components analysis

Functional Principal Components Analysis

In classical (nonfunctional) principal components analysis (PCA), the data are linearly transformed into new coordinates so only a few dimensions contain the major information (variation) of the data. Usually, the first dimension, referred to as the first principal component, has the largest information content (most of the variance) about the original data; the second principal component contains the second-largest information content, and so forth. Each principal component is independent of the other components and can therefore be analyzed separately.

In the functional case, we would like to achieve the same goal, but in the functional space, where the resulting principal components are not vectors, as in classical PCA, but functions.

The original data are represented by a weighted sum of the calculated principal components (i.e., a linear combination of eigenfunctions). The principal components (vectors or functions) imply the direction of variation. The associated weights, often referred to as scores or loadings, describe the amplitude of variation in that direction. Details about FPCA can be found in J. O. Ramsay and B. W. Silverman's *Functional Data Analysis*.

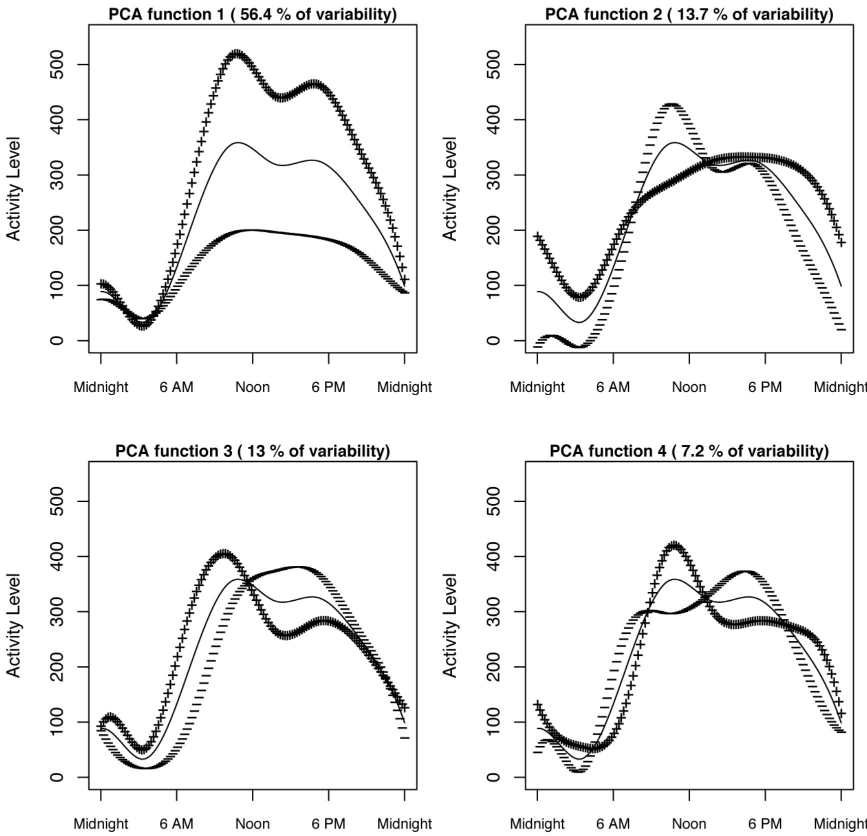

Figure 4. The population mean activity level (solid line) and the effects of adding (+) and subtracting (−) a suitable multiple of each PCA curve, shown for the first four principal components from FPCA

VARIMAX Algorithm

In PCA, the VARIMAX algorithm is a rotation of the original principal components to maximize the sum of variances of the squared scores (loadings). The linear space spanned by the rotated principal components is the same as that spanned by the original principal components. Hence, the VARIMAX rotation reserves all functional features obtained through FPCA. Meanwhile, the VARIMAX rotation makes the scores of each subject concentrated on only a few rotated principal components.

(FPCA), a modern statistical technique for functional data, can be applied to actigraphy data to help answer these questions.

Further development of functional data analysis strategies for analyzing actigraphy data would allow the variation among sets of functions to be (1) decomposed into patient subgroups that may correlate with measures of depression and other clinically important conditions (e.g., different levels of depression or fatigue), (2) used to assess treatment response by accurately measuring changes in activity level over time after treatment (e.g., measure treatment impact to improve a patient's ability to increase daily activity), and (3) analyzed to identify circadian activity pattern abnormalities (e.g., identify unusual patterns throughout the day, such as sleep fragmentation, that correlate with disease severity and activity level).

We apply FPCA to aforementioned actigraphy data in the pilot study of 52 subjects with six days of complete activity recordings each that were already used as the basis for Figure 3. We identify four major distinct patterns of activity functions explaining 56.4% + 13.7% + 13% + 7.2% = 90.3% of the total variation shown in Figure 4.

To plot the eigenfunctions in a more illustrative way, we plot the population mean function as a solid line, and we also plot positive and negative multiples for each eigenfunction using plus and minus signs. For instance, a patient with the first PC score equal to one and all other PC scores equal to zero will have the profile identical to the plus-sign line shown in the upper left panel of Figure 4. Hence, the lines drawn with the plus and minus signs represent the principal variation away from the population mean.

The first principal component (upper left panel) shows that the largest variation among patients occurs along the population mean trend. The second principal component (upper right panel) shows that the next largest variation exists in the activity shift from morning to evening. The two outer lines of this PCA function cross over at about 7 a.m. and 1 p.m. This indicates that patients with a high score associated with PCA function 2 (corresponding to the line labeled with "+" signs) are more active in the afternoons and nights between 1 p.m. and 7 a.m., but less active in the mornings between 7 a.m. and 1 p.m. Patients with low scores associated with PCA function 2 exhibit the opposite pattern: active in the mornings, but less afternoon and night activity.

The ability to score each patient for each principal component may allow us to correlate these specific activity patterns with clinical variables. Similarly, the third principal component (lower left panel) takes a similar amount of variation and represents the activity trade-off between early mornings and afternoons. The fourth principal component (lower right panel) shows a similar pattern as the third principal component, but it is shifted by a few hours.

To make the result more interpretable and easier to understand, we further rotate the first four principal components using the VARIMAX algorithm. The rotated principal components are shown in Figure 5. PCA function 1 (upper left panel) shows that 32.7% variation among the patients exists in the afternoon and evening (between noon and 10 p.m.), PCA function 2 (upper right panel) shows that 15.3% variation exists during night and sleep time (between 6 p.m. and 6 a.m.), PCA function 3 (lower left panel) shows that 13.8% variation exists during the early morning (between 4 a.m. to 11 a.m.), and PCA function 4 (lower right panel) shows that 28.4% variation exists in the morning only (between 7 a.m. and noon).

FPCA also could be used to identify outliers and extreme individuals. For instance, the plot of the first PC scores against the second PC scores in Figure 6 (left panel) shows that subject A stands out with an extremely large second PC score. The plot of the third PC scores against the fourth PC scores in Figure 6 (right panel) shows that subject B stands out with large third and fourth PC scores. In fact, when we checked the original data, we noticed that subject A had some suspiciously high activity levels in the recordings during the last morning, which seems to be a possible outlier. On the other hand, subject B had a regular sleep time every day from noon to 8 p.m., assuming that activity levels around zero over several hours are an indicator for sleep. Therefore, subject B might have a special work schedule.

Discussion and Remarks

A detailed analysis of actigraphy data is possible with functional data analysis methods. This goes beyond results obtained from classical statistical methods, such as histograms and numerical summary statistics. We have been able to move from simple activity counts-per-minute comparisons distinguishing among highly active and less active patients to potentially understanding patient behavior as related to activity patterns and possibly to fatigue and disease. The above pilot analysis was done in R (version 2.11.1), using the fda R package

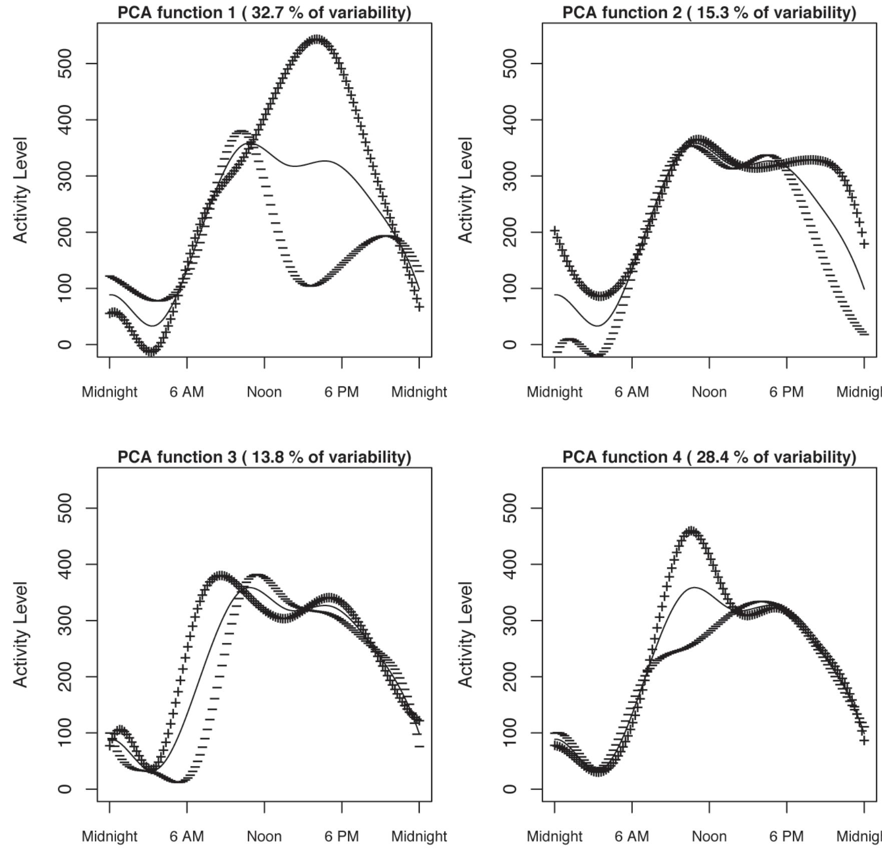

Figure 5. The population mean activity level (solid line) and the effects of adding (+) and subtracting (−) a suitable multiple of each PCA curve after a VARIMAX rotation, shown for the first four principal components from FPCA

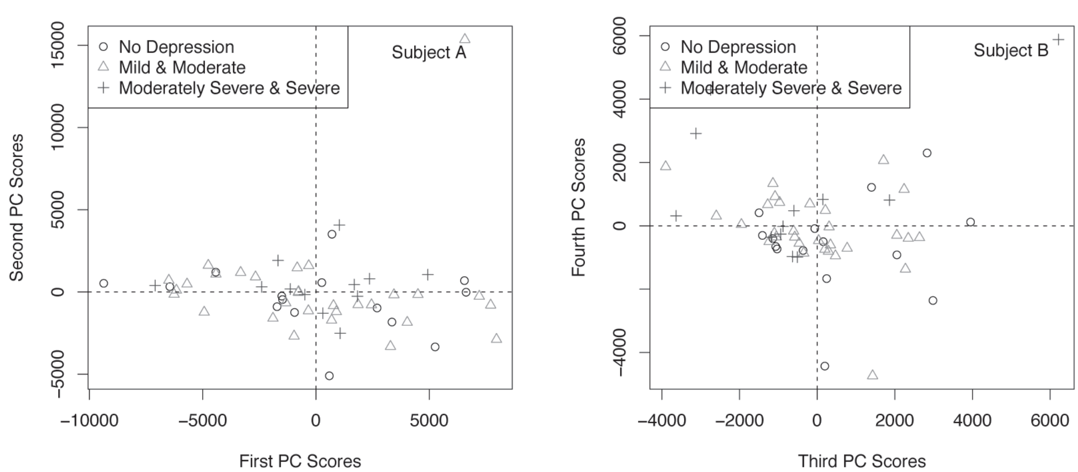

Figure 6: Outliers identified by extreme PC scores. Different symbols are used to distinguish between the three depression levels, but there is no indication in these two plots that there is any clustering of PC scores that relates to the different depression levels.

and additional R code developed by the contributing authors.

This preliminary analysis of a pilot study illustrates the type of information we expect to obtain from developing a full functional data analysis approach toward actigraphy data. We have shown that this type of approach provides more details for an individual patient's activity level profiles than simple summary statistics of counts-per-minute data. We also have shown that statistical tools, such as functional principal components analysis, could be used to identify patient subgroup activity patterns and to test hypotheses. Most importantly, functional principal components analysis could help us examine fatigue, sleep, and activity levels as related to diseases. By fully developing functional data analysis for actigraphy data, we believe there could be a great potential to increase actigraphy as an important tool for objectively measuring fatigue and sleep disorders across a broad group of patients and disease groups.

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Further Reading

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