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Journal

Statistics in Medicine, 33(8)

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Publication Date

2014-04-15

DOI

10.1002/sim.6038

Peer reviewed

Published in final edited form as:
Stat Med. 2014 April 15; 33(8): 1383–1394. doi:10.1002/sim.6038.

Nonparametric Spectral Analysis of Heart Rate Variability Through Penalized Sum of Squares

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Abstract

Frequency domain properties of heart rate variability (HRV), or the elapsed time between consecutive heart beats, are utilized by biomedical researchers in a variety of fields. HRV is measured from the electrocardiograph signal through the interbeat interval series. Popular approaches for estimating power spectra from these interval data apply common spectral analysis methods that are designed for the analysis of evenly sampled time series. The application of these methods to the interbeat interval series, which is indexed over an uneven time grid, requires a bias inducing transformation. The goal of this article is to explore the use of penalized sum of squares for nonparametric estimation of the spectrum of HRV directly from the interbeat intervals. A novel cross-validation procedure is introduced for smoothing parameter selection. Empirical properties of the proposed estimation procedure are explored and compared to popular methods in a simulation study. The proposed method is used in an analysis of data from an insomnia study which seeks to illuminate the association between the power spectrum of HRV during different periods of sleep with response to behavioral therapy.

Keywords

Cross-Validation; Frequency Domain; Heart Rate Variability; Signal Processing; Smoothing Spline; Time Series

1. Introduction

The cyclical patterns of heart rate variability (HRV) have been shown to be associated with a variety of diseases and clinical events such as myocardial infarction, hypertension, congestive heart failure, insomnia, depression, psychological stress, and all cause mortality [1, 2, 3, 4]. By providing an indirect measure of autonomic nervous system modulation, the spectral analysis of HRV provides a means to elucidate the pathways through which nervous system activity and stress affect health [1, 5].

This article is motivated by a study that seeks to better understand how behavioral therapies designed to improve sleep can aid older adults with insomnia. Prior to treatment, study participants completed clinical assessments of sleep, mental and physical health. These

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assessments included in-home polysomnongraphy (PSG), a comprehensive recording of electrophysiological activity during sleep, that contained an electrocardiogram (ECG) from which HRV could be computed. Following baseline assessments, participants underwent manualized Brief Behavioral Treatment of Insomnia (BBTI) [6]. Measures were repeated within one month of completing BBTI. Our goal is to use these data to evaluate the extent to which cardiac autonomic tone, as indexed by the power spectrum of HRV across different sleep periods, predicts the efficacy of BBTI, as measured by decreased subjective sleep complaints, a hallmark symptom of insomnia.

The analysis of HRV from a recorded ECG begins with the identification of time points t_j that mark the peak of the R-waves as the locations of the upward deflection of the ECG associated with each heartbeat. Figure 1 displays a sample epoch of ECG to illustrate these time points. These points are used to compute interbeat intervals (IBIs), $X(t_j) = t_{j-1} - t_j$, as a measure of elapsed time between consecutive heart beats. The top panels of Figure 2 display IBI series from a study participant at three periods of sleep. Theoretical HRV X is modeled as a continuous process over time that is observed at the discreet times t_j through $X(t_j)$. The frequency domain properties of the process X must be estimated from the IBI series.

The spectral analysis of HRV may be divided into two categories: the analysis of approximately stationary short term epochs under specific physiological conditions and the time-frequency analysis of long term nonstationary epochs. Our motivating study is concerned with the spectral analysis of HRV during specific periods of sleep and falls into the former category. Consequently, this article focuses on the spectral analysis of short term epochs where HRV X is second order stationary. Traditional approaches to the spectral analysis of sort term HRV use methods, such as Fourier periodograms, that are well studied for the spectral analysis of integer indexed time series and for evenly sampled continuous processes [1]. The application of these methods to the analysis of HRV from an IBI series $\{X(t_1), \ldots, X(t_N)\}$, which is unevenly indexed as a function of time, requires transformations which are known to bias estimates of the power spectrum.

Huang *et al*. [7] developed a method for estimating the power spectrum of a continuous process from data observed over an uneven grid through the minimization of a penalized sum of squares. This penalized sum of squares is comprised of a time domain sum of squares, which provides a measure of fit of a power spectrum to the observed time domain data, and a penalty, which provides a measure of roughness of the power spectrum. The primary goal of this article is to explore the use of penalized sum of squares as a tool for the nonparametric spectral analysis of HRV. Critically, this approach circumvents the biases incurred by traditional methods. Key to the performance of any penalized method is the selection of tuning parameters. A novel cross-validation procedure based on the Lomb periodogram [8] is developed for smoothing parameter selection and to provide an automated nonparametric estimation procedure.

Estimating power spectra is a first step in the majority of studies that are interested in the frequency domain properties of HRV. Most studies are concerned with determining how HRV spectra are associated with other study variables, such as response to treatment. We explore the use of penalized sum-of-squares spectral estimation in evaluating the association between HRV and study outcomes in a three stage analysis of the data from our motivating insomnia study. After power spectra are estimated through penalized sum of squares, the second stage of this analysis fits a functional linear model [9, Chapter 15] regressing response to treatment onto the estimated log-spectra. Historically, relationships between HRV spectra and outcome variables are evaluated via a finite number of preselected spectral summary measures. However, there exist debate as to which spectral measures should be considered [10]. The functional regression model, which inherently requires accurate

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estimates of continuous power spectra, allows one to evaluate the relationship between outcomes and the entire spectra and to identify summary measures that are important to the problem at hand. In the final step of our analysis, the relationship between response to treatment and the summary measure illuminated by the functional regression model is further explored.

The rest of the article is organized as follows. Section 2 describes popular approaches to the spectral analysis of HRV, Section 3 presents the penalized sum-of-squares method conditional on smoothing parameter, and Section 4 develops Lomb based cross-validation for smoothing parameter selection. Results of a simulation study are presented in Section 5 while the data from the insomnia study are analyzed in Section 6. A discussion is presented in Section 7.

2. Popular Approaches for Estimating HRV Spectra

The most common tool for the spectral analysis of a second order stationary process is the discrete Fourier transform and its associated periodogram. Properties of the Fourier periodogram have been well studied for integer indexed time series and for continuous time processes sampled over even grids [11]. The inherent variability in the elapsed time between heart beats implies that the locations of the peaks of the R-waves are not evenly spaced and that IBI series provide observations of the continuous time HRV processes over uneven grids. Although periodograms could be computed from the IBIs as series indexed by beat number, known as interval tachograms, the resulting spectral estimates would be in units of time-squared per cycles/beat while the desired power spectrum of X is in units of time-squared per Hz. To assure interpretability and avoid distortion and spurious harmonics, established guidelines recommend that the IBI series be spline interpolated and evenly sampled before computing Fourier periodograms [1]. Fourier periodograms provide noisy estimators of the power spectrum at any given frequency. To reduce this noise, Fourier periodogram based analyses of HRV commonly employ Welch's method to achieve a consistent estimator by averaging periodograms from overlapping intervals [1, 12].

The spline interpolation of the IBI series is equivalent to applying a low-pass filter that distorts the ratio of power from low frequencies versus power from high frequencies [13]. The ratio in power between low frequencies from 0.05–0.15 Hz versus high frequencies from 0.15–0.40 Hz is of clinical importance in many studies that examine the spectral properties of HRV [1, 3]. The autonomic nervous system is classically divided into two dynamically balanced branches: the parasympathetic branch and the sympathetic branch. The parasympathetic branch is responsible for the maintenance of the body at rest while the sympathetic branch is associated with the flight-or-flight response. The ratio in power from low frequencies to power from high frequencies is an indirect measure of the relative modulation of the sympathetic branch as compared to the parasympathetic branch and is often interpreted as a physiological measure of stress [4, 5]. The bias induced by sampling the spline interpolation of the IBI series is rather undesirable in studies, such as our motivating insomnia study, where the ratio of power from low frequencies to power from high frequencies is of scientific interest.

To circumvent the bias incurred through interpolation, least squares based Lomb periodograms have been used for the spectral analysis of HRV [13]. The Lomb periodogram produces an unbiased but noisy estimate of the power spectrum at any given frequency. The estimation of power collapsed within a given frequency band by combining noisy Lomb periodograms across frequency is unbiased and consistent. The Lomb periodogram can only be used for the analysis of integral functions of the power spectrum and cannot be used to investigate the power spectrum itself.

In addition to these nonparametric techniques, parametric autoregressive models (AR) are also popular [1, 14]. Estimation via AR models has been observed to perform better than Welch's method for estimating the entire power spectrum as a continuous function [1]. However, AR models are subject to parametric linear assumptions that are often difficult to verify. Additionally, popular approaches to fitting AR models require an evenly sampled series, much in the same manner as estimation under Fourier periodogram based methods, and consequently require bias inducing transformations of the IBI series [1, 14].

This article investigates the use of penalized sum of squares for the spectral analysis of HRV to overcome many of the drawbacks of current popular methods by providing a method that is nonparametric, obtains estimates directly from the IBI series, and produces smooth estimates of the entire power spectrum.

3. Penalized Sum-of-Squares Estimation

This section considers estimation of the power spectrum of a second order stationary continuous HRV process X from the IBI series $\{X(t_1), \ldots, X(t_N)\}$ where $0 < t_j < t_{j+1}$ and $t_N = T$. The theoretical HRV X is a real valued stochastic process over $\mathbb{R}$ with mean $\mu = E[X(t)]$, autocovariance function $\Gamma(s) = E[X(t) - \mu][X(t + s) - \mu]$, and power spectrum $f(\omega) = \int_{-\infty}^{\infty} \Gamma(t) e^{-2\pi i \omega t} dt$. Although we aspire to estimate f over the entire real line, we are restricted by the smallest IBI. The average Nyquist frequency is given by $\nu = N/(2T)$ [8] and, since f is an even function, we seek to estimate $f(\omega)$ for $\omega \in [0, \nu]$. The power spectrum of HRV is smooth and we assume that f is in the space $W_1^2[0,\nu]$ that consists of all absolutely continuous real valued functions on $[0, \nu]$ with square integrable first derivatives [15].

Consider the product pairs

$$y_{ij} = \left[X(t_i) - \overline{X}\right]\left[X(t_j) - \overline{X}\right], \ 1 \le i \le j \le N$$

that provide estimates of $\Gamma(t_j - t_i)$. Noting that $\Gamma(t) = 2\int_0^{\infty} f(\omega)\cos(2\pi\omega t)\, d\omega$, an estimator $\hat{f}$ of f can be obtained by minimizing some measure of discrepancy between the time domain quantities y_{ij} and $2\int_0^{\nu}\cos[2\pi\omega(t_j - t_i)]\hat{f}(\omega)\, d\omega$. Since there is variation in the elapsed time between consecutive heart beats, $t_j - t_i$ are unique for $i \neq j$ so that an estimate $\hat{f}$ can always be found such that $2\int_0^{\nu}\cos[2\pi\omega(t_j - t_i)]\hat{f}(\omega)\, d\omega = y_{ij}$ for every $i \neq = j$. A regularized solution to this problem was proposed by Huang *et al*. [7] by defining the estimate $\hat{f}_\lambda$ of f as the function in $W_1^2[0,\nu]$ that minimizes the penalized sum of squares

$$\sum_{1 \le i \le j \le N} \{y_{ij} - 2\int_0^{\nu}\cos[2\pi\omega(t_j - t_i)] f(\omega)\, d\omega\}^2 + \lambda\int_0^{\nu} f'(\omega)^2 df \qquad (1)$$

given a smoothing parameter $\lambda > 0$. The smoothing parameter λ controls the smoothness of the spectral estimate such that $\hat{f}_\lambda$ approaches a constant as $\lambda \to \infty$ while $\hat{f}_\lambda$ becomes excessively rough as $\lambda \to 0$. A data-driven cross-validation procedure for selecting λ is given in Section 4.

Minimizing this penalized sum of squares is part of the general smoothing spline problem discussed in detail by Wahba [15]. As a general smoothing spline problem, the solution to (1) can be found via Theorem 1.3.1 of Wahba [15]. We present the solution here and direct readers to Huang *et al*. [7] for further details and consistency results. To compute the solution, let $P = N + N(N - 1)/2$ be the number of distinct product pairs and define

$$Y=[(y_{11},\ldots,y_{1N}),\ldots(y_{ii},\ldots,y_{iN}),\ldots,y_{NN}]',$$

$$\mathscr{T}=[(\tau_{11},\ldots,\tau_{1N}),\ldots(\tau_{ii},\ldots,\tau_{iN}),\ldots,\tau_{NN}]'$$

as the P-vectors of these pairs and their lag times $\tau_{ij} = \tau_j - \tau_i$. Further, define ξ as the P-vector valued function over [0,1] with pth element

$$\xi_p(u)=\begin{cases} u-0.5u^2 & \mathscr{T}_p=0 \\ \frac{2\pi\nu\mathscr{T}_p u\sin(2\pi\nu\mathscr{T}_p)+\cos(2\pi\nu\mathscr{T}_p u)-1}{(2\pi\mathscr{T}_p)^2} & \mathscr{T}_p\neq 0 \end{cases},$$

Q as the P-vector with pth element $\int_0^1 \cos(2\pi\mathscr{T}_p u)\,du$, and Σ as the $P \times P$ matrix with pqth element $\int_0^1 \cos(2\pi\mathscr{T}_p u)\,\xi_q(u)\,du$. For $\omega \in [0, \nu]$,

$$\hat{f}_\lambda(\omega)=\frac{1}{2\nu}\left[d+\sum_{p=1}^{P}c_p\xi_p(\omega/\nu)\right] \quad (2)$$

where $C = (c_1, \ldots, c_P)'$ and d solve the system

$$\begin{aligned}(\Sigma+\lambda I)C+Qd &=Y\\ Q'C &=0.\end{aligned}$$

It should be noted that there is no guarantee that $\hat{f}_\lambda(\omega)$ is non-negative for all $\omega \in [0, \nu]$ and in practice we set the negative values to zero.

4. Smoothing Parameter Selection

A popular method for the automated selection of smoothing parameters in smoothing spline estimation is the generalized cross validation (GCV) discussed in Chapter 3 of Wahba [15]. The GCV is known to have poor performance if the observations being smoothed are correlated, such as y_{ij}, and this correlation is not accounted for [16, 17, 18]. Huang *et al*. [7] modified the GCV to account for correlation among product pairs in penalized sum-of-squares estimation of power spectra. In the simulation study of realistic epochs of short term heart rate variability described in Section 5, we found that the modified GCV greatly overfit the data and produced spectral estimates that were nearly identical to the Lomb periodogram. We hypothesize that the modified GCV has good asymptotic properties that require time series of lengths much larger than those observed for short term HRV. Huang *et al*. [7] demonstrated that the modified GCV has good empirical performance in a simulation study with time series epochs of 2000 observations. The IBI series from short term heart rate variability will usually have much smaller length. For instance, if the heart rate is 60 beats per minute and we observe an epoch of the maximally suggested length of 5 minutes [1], then we would expect to have an IBI series with 300 observations.

K-fold cross-validation is a common procedure for the selection of tuning parameters in a variety of settings [19]. A complication in using K-fold cross-validation to select λ is that IBI are observed on the time scale whereas f is in the frequency domain. To overcome this obstacle, we use the Lomb periodogram, which has been shown to be an approximately unbiased estimate of $f(\omega)$ [13], to allow the observed data within a given fold to be used to assess the performance of the spectral estimate obtained from the remaining folds.

Given a positive integer K, the proposed procedure divides the time interval $[0, T]$ into the K intervals

$$I_k = \left(\frac{(k-1)T}{K}, \frac{kT}{K}\right], k=1,\ldots,K$$

and lets $H_k = \{X(t_j)\}_{t_j \in I_k}$ be the IBI data from the kth fold. Compute $\hat{f}_\lambda^{[-k]}$ through (2) using smoothing parameter λ and only the data in $\bigcup_{j \neq k} H_j$. The Lomb periodograms from the kth fold are computed as

$$L_k(\omega) = \frac{\left\{\Sigma_{t_j \in I_k}\left[X(t_j) - \overline{X}_k\right]\cos\left[2\pi\omega(t_j-\theta_k)\right]\right\}^2}{2s_k^2\Sigma_{t_j \in I_k}\cos^2\left[2\pi\omega(t_j-\theta_k)\right]} + \frac{\left\{\Sigma_{t_j \in I_k}\left[X(t_j) - \overline{X}_k\right]\sin\left[2\pi\omega(t_j-\theta_k)\right]\right\}^2}{2s_k^2\Sigma_{t_j \in I_k}\sin^2\left[2\pi\omega(t_j-\theta_k)\right]}$$

where $\overline{X}_k$, s_k^2 are the sample mean and variance of H_k and θ_k is defined as

$$\tan(4\pi\omega\theta_k) = \left[\sum_{t_j \in I_k}\sin(4\pi\omega t_j)\right] / \left[\sum_{t_j \in I_k}\cos(4\pi\omega t_j)\right].$$

We use $G_k(\lambda) = \sum_{\ell=1}^{\lfloor N_k/2 \rfloor}\left[L(\omega_{k\ell}) - \hat{f}_\lambda^{[-k]}(\omega_{k\ell})\right]^2$ as a measure of discrepancy between $\hat{f}_\lambda^{[-k]}$ and the data in H_k where N_k is the number of observations in the kth fold, $[N_k/2]$ is the integer part of $N_k/2$, and $\omega_{k\ell} = (\ell - 1)\nu/\lfloor N_k/2 \rfloor$. The smoothing parameter λ is selected as the minimizer of the spectral prediction over all folds as

$$\lambda = \underset{\lambda_0}{\operatorname{argmin}}\left\{\sum_{k=1}^{K} G_k(\lambda_0)\right\}.$$

In simulation studies and in analyzing data from the insomnia study, we found the performance of the Lomb periodogram K-fold estimator to be insensitive to K, with $K = 5$, 10, 15, 20 providing similar spectral estimators. This similarity is illustrated by the $K = 5$ and $K = 10$ fold cross-validated spectral estimates displayed in the top left panel of Figure 4. In light of this insensitivity, we suggest following the general recommendation given in Chapter 7.10.1 of Hastie *et al*. [19] and use either $K = 5$ or $K = 10$.

5. Simulation Study

We illustrate the empirical properties of penalized sum of squares for the spectral analysis of HRV through an analysis of simulated realistic epochs of ECG under two settings. The simulation method developed by McSharry *et al*. [20] was used to generate 500 independent and identically distributed ECG epochs per setting of length 5 minutes with mean heart rate

60 bpm and standard deviation 1 bpm. A mixture of Gaussian densities was used to represent the power spectrum such that f is proportional to $3\varphi\,[0.02\pi(\omega - 0.02)] + \varphi\,[0.02\pi(\omega - 0.095)] + \rho\varphi\,[0.02\pi(\omega - 0.275)]$ where φ is the standard Gaussian density and ρ is a low frequency/high frequency ratio. The first setting has $\rho = 0.5$ while the second setting has $\rho = 2.0$. A simulated epoch from the setting with $\rho = 2.0$ is displayed in Figure 3.

The performance of the proposed estimation procedure was compared to three popular spectral estimation procedures discussed in Section 2: the Lomb periodogram, Welch's periodogram method, and AR estimation. For Welch's periodogram method and AR estimation, the IBI series were interpolated with a cubic spline then sampled at 4 Hz. Welch's periodogram method was implemented with a Hamming window and GCV span selection [11]. AR parameters were estimated via Yule-Walker equations and order was selected though the AICc [21]. Estimates of the power spectrum from the simulated epoch displayed in Figure 3 are given in Figure 4.

Performance of the estimation procedures were evaluated through four measures: a measure of fit of the entire power spectrum and three measures of relative power within frequency bands that are commonly utilized by clinical researchers [10]. The three measures of relative power considered are the low to high frequency ratio LF/HF defined as the ratio in power from frequencies between 0.05–0.15 Hz versus power from frequencies between 0.15–0.40 Hz, normalized low frequency power LF_{μ} defined as the ratio of power at frequencies between 0.05–0.15 Hz versus power at frequencies between 0.05–0.40 Hz, and normalized high frequency power HF_{μ} defined as the ratio of power at frequencies between 0.15–0.40 Hz versus power at frequencies between 0.05–0.40 Hz. The accuracy in estimating the entire power spectrum was evaluated through the across-the-curve square error (ASE) by averaging square-errors across the grid of 5000 equally spaced frequencies between 0 and 0.4 Hz. Since the Lomb periodogram produces an inconsistent estimate of $f(\omega)$ at any given frequency ω, we do not report its performance for estimating the entire power spectrum. The mean and standard deviations of the LF/HF, LF_{μ}, and HF_{μ} estimates and of the ASE are given in Table 1. Results for the penalized sum-of-squares estimator are reported when λ is selected through $K = 5$-fold Lomb periodogram cross-validation.

The penalized sum-of-squares method and Lomb periodogram demonstrated similar, approximately unbiased, performance in the estimation of LF/HF, LF_{μ}, and HF_{μ}. Both Welch's periodogram method and AR estimation had a positive bias in the estimation of LF/HF. This result, that Welch's method and AR estimation tend to over estimate LF/HF, and that the Lomb periodogram produces noisy estimates of the spectrum are illustrated in the estimates from a simulated epoch in Figure 4. The penalized sum-of-squares estimator had a smaller mean and standard deviation in the ASE than either Welch's method or AR estimation. The simulation results indicate that the proposed penalized sum-of-squares method offers a procedure for the spectral analysis of HRV that possesses the approximately unbiased properties of the Lomb periodogram for estimating relative power within clinical frequency bands while providing an accurate estimate of the entire power spectrum.

6. Analysis of Data from the Insomnia Study

6.1. Study Design and Data Collection

Insomnia affects an estimated 15% – 35% of older adults and has been shown to be associated with reduced quality of life and increased risk for falls and hip fractures [22]. We consider data collected as part of the study described in Buysse *et al.* [6] that seeks to assess the efficacy BBTI on improving sleep in older adults with insomnia. The analysis considered in this section explores the association between pre-treatment indices of cardiac autonomic tone and improvement in self-reported sleep quality.

We consider data from 31 men and women between 60–89 years of age who were clinically diagnosed with primary insomnia. Prior to treatment, study participants completed a self-report sleep quality questionnaire and participated in an overnight in-home sleep study using ambulatory PSG monitors. The questionnaire was used to compute the 18-item Pittsburgh Sleep Quality Index (PSQI), a widely used measure of self-reported sleep quality complaints that has been shown to be associated with a variety of medical conditions such as sleep disorders and depression [23]. The PSQI takes values from 0 to 21 with higher values reflecting greater subjective sleep quality complaints; scores greater than 5 are indicative of clinically disturbed sleep [23, 24].

The ambulatory PSG in our study included a modified 2-lead electrode placement for the continuous collection of ECG throughout the night at 512 Hz. Digitized ECG signals were stored for off-line processing according to established guidelines [1], the IBI series were computed, and a Savitzky-Golay filter was applied to the interval tachogram for trend removal. The PSG signals were used by a trained technician to visually score sleep in 20 second intervals of wakefulness, rapid eye movement sleep (REM), and non-rapid eye movement sleep (NREM). The IBI series were temporally aligned with the visually scored sleep to allow for the identification of the first three minutes of HRV from each of the first three periods of NREM sleep.

Study participants were assessed again approximately four weeks after completing BBTI to evaluate treatment efficacy. Our outcome of interest is change in subjective sleep quality complaints as measured by the PSQI, where negative values represent reduced sleep complaints, indicative of improved sleep quality. Define D_ℓ as the change in PSQI after treatment in the ℓth participant. In our sample, D_ℓ ranges from −8 to 2 with a mean of −3.81 and a standard deviation of 2.66. We desire an analysis which illuminates the association between the pre-treatment spectrum of HRV during the first three period of NREM and the change in PSQI post-treatment.

6.2. Spectral Estimation

Let $f_{\ell m}$ be the HRV power spectrum for participant $\ell = 1, \ldots, 31$ at NREM period $m = 1, 2, 3$. The proposed data driven penalized sum-of-squares estimator was computed for each of the 93 epochs of HRV with smoothing parameters selected through $K = 5$ fold Lomb periodogram cross-validation to obtain the estimates $\widehat{f}_{\ell m}$. The bottom panel of Figure 2 displays the estimated power spectra for a participant. Since the variability in the power spectra from a population are proportional to the mean and since ratios of power are often of clinical interest, power spectra are often analyzed on the log-scale [25, 26]. Define the estimated log-spectrum at frequency ω for participant ℓ at NREM period m as $F_{\ell m}(\omega) = \log\left[\widehat{f}_{\ell m}(\omega)\right]$. Figure 5 displays the estimated log-spectra during each NREM period from the 31 participants.

6.3. Functional Data Analysis of Log-Spectra

To assess the association between the power spectrum at each period of NREM and treatment response, we regressed the change in PSQI on the estimated log-spectra through the scalar-on-functional model

$$D_\ell = \beta_0 + \sum_{m=1}^{3} \int_0^{0.4} \beta_m(\omega) F_{\ell m}(\omega)\, d\omega + \epsilon_\ell,\ \ell = 1, \ldots, 31$$

where $\in_\ell$ are independent and identically distributed mean zero Gaussian random variables. We used the penalized spline approach discussed in Chapter 15 of Ramsay and Silverman [9] to fit the model. Let *B* be the span of the set of 3rd order B-spline bases over [0, 0.4] with 20 equally spaces knots. The regression coefficients were estimated as the minimizers of the penalized sum of squares

$$\left(\widehat{\beta}_0,\widehat{\beta}_1,\widehat{\beta}_2,\widehat{\beta}_3\right)=\underset{\beta_0\in\quad;\beta_1,\beta_2,\beta_3\in\mathscr{B}}{\operatorname{argmin}}\left\{\sum_{\ell=1}^{31}\left[D_\ell-\beta_0-\sum_{m=1}^{3}\int_0^{0.4}\beta_m(\omega)\,F_{\ell m}(\omega)\,d\omega\right]^2+\sum_{m=1}^{3}\theta_m\int_0^{0.4}\beta_m'(\omega)^2d\omega\right\}.$$

where the smoothing parameters θ_1, θ_2, $\theta_3 > 0$ were selected via cross-validation [9, Chapter 15.6].

Figure 6 displays the estimated functional regression coefficients with approximate point-wise 95% Gaussian confidence intervals [9, Chapter 15.5.2]. Each coefficient represents a contrast between log-power at different frequencies. The estimated coefficient for the first period is a contrast between log-power at frequencies less than 0.07 Hz and greater than 0.27 Hz versus log-power at frequencies between 0.07 – 0.27 Hz. The estimated coefficient for the second period is a contrast between log-power less than than 0.1 Hz versus log-power greater than 0.1 Hz while the coefficient for the third period is a contrast between log-power greater than 0.17 Hz versus less than 0.17 Hz. Recall that this analysis is on the log-scale so that the contrast presented in $\widehat{\beta}_3$ is equivalent to a ratio between power at high frequencies versus power at low frequencies. This ratio is the measure that our simulation study found to be distorted by evenly sampling a spline interpolation of the IBI series prior to analysis.

6.4. Analysis of Sympathovagal Balance

The fitted functional linear model suggests ratios of power from low and high frequency bands are associated with response to treatment. To provide an analysis that produces clinically interpretable information to illuminate the pathway through which BBTI reduces sleep complaints, we regressed the change in PSQI on the log ratio of power from low frequencies versus power from high frequencies. Define the log-ratio for participant $\ell = 1, \ldots, 31$ at period $m = 1, 2, 3$ as

$$R_{\ell m}=\log\left[\int_{0.04}^{0.15}\widehat{f}_{\ell m}(\omega)\,d\omega\right]-\log\left[\int_{0.15}^{0.04}\widehat{f}_{\ell m}(\omega)\,d\omega\right].$$

We fit the linear model

$$D_\ell=\gamma_0+\sum_{m=1}^{3}\gamma_m R_{\ell m}+\delta_\ell,\ \ell=1,\ldots,31,$$

where δ_ℓ are independent and identically distributed mean zero Gaussian random variables. The first column of Table 2 displays the maximum likelihood estimates of the regression coefficients, their standard errors and two-sided p-values when spectra are estimated through penalized sum of squares. These estimates show that the ratio of power between low frequencies and high frequencies during the first two NREM periods are not associated with change in PSQI when controlling for power at other periods. In contrast, when controlling for HRV during the first two NREM periods, increases in the low frequency/high frequency ratio during the third NREM period are associated with larger decreases in PSQI after treatment.

Our analysis indicates that BBTI is most efficacious, as measured by improvements in subjective sleep quality, in individuals with insomnia who demonstrate increased sympathovagal tone during the latter part of the night prior to treatment. This altered cardiac autonomic tone profile is not unprecedented. It has been shown to be elevated during NREM in insomniacs as compared to good sleepers [27] and in response to a pre-sleep experimental stress manipulation [2]. Future studies are needed to evaluate the extent to which baseline stress profiles predict response to BBTI and other treatments of insomnia.

In addition, we computed estimated log-ratios through the three other estimation procedures previously discussed: Lomb periodograms, Welch's method, and AR modeling. The results of the fitted regression models using these estimates are also displayed in Table 2. Although similar results are obtained, estimated coefficients are shrunk towards the null when using Welch's method and AR estimation, which are biased, as opposed to penalized sum of squares and Lomb periodograms, which were found to be approximately unbiased in simulations.

7. Discussion

This article considered the use penalized sum of squares for estimating the power spectrum of short term HRV. A novel cross-validation procedure was developed for the automated selection of smoothing parameters. Simulation studies demonstrated that, in a manner similar to Lomb periodograms, the proposed procedure avoids the biases of Welch's periodogram method and AR modeling for the estimation of clinical frequency bands while, in contrast to Lomb periodograms, providing good estimates of the entire power spectrum. The proposed method was used in a study of physiological predictors of BBTI treatment efficacy in older adults with insomnia. Results suggest treatment efficacy is associated with pre-treatment sympathovagal tone during the latter part of the night.

Smoothing spline estimates of power spectra based on Fourier periodograms have been previously developed. Wahba [28] minimized a penalized sum of squares to smooth the log-periodogram while Pawitan and O'Sullivan [29] and Qin and Wang [30] minimize negative penalized Whittle likelihoods. Since Fourier periodograms require time series that are indexed over an equally spaced time grid, these approaches are not applicable to IBI series without applying a transformation, such as the bias inducing even sampling of a spline interpolation.

This article only considered the spectral analysis of short term HRV under the assumption of stationarity. The time-frequency analysis of long term epochs of HRV under changing conditions are of interest in a variety of applications for risk stratification of clinical outcomes [1, 3]. The extension of the proposed estimation procedure for the time-frequency analysis of nonstationary HRV will be the subject of future research. Although initial results using the stationary penalized sum-of-squares estimator in rolling windows are promising, both computational feasibility in the face of massive data sets and the simultaneous selection of the temporal window length and frequency domain smoothing parameter could present non-trivial obstacles.

Acknowledgments

This work is supported by NSF grant DMS0805050 and NIH grants AG02067, R01104607, and RR024153. The authors would like to thank Anne Germain, Sati Mazumdar, Timothy Monk and Eric Nofzinger for their contributions to the AgeWise study.

References

1. Task Force of the ESC/ASPE. Heart rate variability - standards of measurement, physiological interpretation, and clinical use. Circulation. 1996; 93:1043–1065. [PubMed: 8598068]
2. Hall M, Vasko R, Buysse D, Ombao H, Chen Q, Cashmere J, Kupfer D, Thayer J. Acute stress affects heart rate variability during sleep. Psychosomatic Medicine. 2004; 66:56–62. [PubMed: 14747638]
3. Kleiger RE, Stein PK, Bigger JT Jr. Heart rate variability: Measurement and clinical utility. Annals of Noninvasive Electrocardiology. 2005; 10:88–101. [PubMed: 15649244]
4. Hall M, Thayer J, Germain A, Moul D, Vasko R, Puhl M, Miewald J, Buysse D. Psychological stress is associated with heightened physiological arousal during NREM sleep in primary insomnia. Behavioral Sleep Medicine. 2007; 5:178–193. [PubMed: 17680730]
5. Montano N, Porta A, Cogliati C, Costantino G, Tobaldini E, Casali KR, Iellamo F. Heart rate variability explored in the frequency domain: A tool to investigate the link between heart and behavior. Neuroscience & Biobehavioral Reviews. 2009; 33:71–80. [PubMed: 18706440]
6. Buysse DJ, Germain A, Moul DE, Franzen PL, Brar LK, Flecher ME, Begley A, Houck PR, Mazumdar S, Reynolds CF III, Monk TH. Efficacy of brief behaviour treatments for chronic insomnia in older adults. Archives of Internal Medicine. 2011; 171:887–895. [PubMed: 21263078]
7. Huang C, Hsing T, Cressie N. Spectral density estimation through a regularized inverse problem. Statistica Sinica. 2011; 21:1115–1144.
8. Scargle JD. Studies in astronomical time series analysis. II - Statistical aspects of spectral analysis of unevenly spaced data. Astrophysical Journal. 1982; 263:835–853.
9. Ramsay, JO.; Silverman, BW. Functional Data Analysis. 2nd ed.. Springer; 2005. Springer Series in Statistics
10. Burr RL. Interpretation of normalized spectral heart rate variability indices in sleep research: a critical review. Sleep. 2007; 30:913–919. [PubMed: 17682663]
11. Priestley, MB. Spectral Analysis and Time Series: Vol. I and II. Academic Press; London: 1982.
12. Welch P. The use of fast Fourier transform for the estimation of power spectra: A method based on time averaging over short, modified periodograms. IEEE Transactions on Audio and Electroacoustics. 1967; 15(2):70–73.
13. Laguna P, Moody G, Mark R. Power spectral density of unevenly sampled data by least-square analysis: performance and application to heart rate signals. IEEE Transactions on Biomedical Engineering. 1998; 45(6):698–715. [PubMed: 9609935]
14. Boardman A, Schlindwein FS, Rocha AP, Leite A. A study on the optimum order of autoregressive models for heart rate variability. Physiological Measurement. 2002; 23(2):325. [PubMed: 12051304]
15. Wahba, G. Spline Models for Observational Data. SIAM; Philadelphia: 1990. CBMS-NSF Regional Conference Series in Applied Mathematics
16. Wang Y. Smoothing spline models with correlated random errors. Journal of the American Statistical Association. 1998; 60:159–174.
17. Krivobokova T, Kauermann G. A note on penalized spline smoothing with correlated errors. Journal of the American Statistical Association. 2007; 102:1328–1337.
18. Han C, Gu C. Optimal smoothing with correlated data. Sankhya. 2008; 70:38–72.
19. Hastie, T.; Tibshirani, R.; Friedman, JH. The Elements of Statistical Learning: Data Mining, Inference, and Prediction. Springer; New York: 2009.
20. McSharry PE, Clifford GD, Tarassenko L, Smith LA. A dynamical model for generating synthetic electrocardiogram signals. IEEE Transactions on Biomedical Engineering. 2003; 50:289–294. [PubMed: 12669985]
21. Brockwell, PJ.; Davis, RA. Time Series: Theory and Methods. Springer; New York: 2006.
22. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Medicine Reviews. 2002; 6:97–111. [PubMed: 12531146]

23. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index (PSQI): A new instrument for psychiatric research and practice. Psychiatry Research. 1989; 28:193–213. [PubMed: 2748771]
24. Cole J, Motivala S, Buysse D, Oxman M, Levin M, Irwin M. Validation of a 3-factor scoring model for the Pittsburgh Sleep Quality Index in older adults. Sleep. 2006; 29:112–116. [PubMed: 16453989]
25. Krafty RT, Hall M, Guo W. Functional mixed effects spectral analysis. Biometrika. 2011; 98:583–598.
26. Krafty RT, Hall M. Canonical correlation analysis between time series and static outcomes, with application to the spectral analysis of heart rate variability. Annals of Applied Statistics. 2013; 7:570–587.
27. Bonnet MH, Arand DL. Heart rate variability in insomniacs and matched normal sleepers. Psychosomatic Medicine. 1998; 60:610–615. [PubMed: 9773766]
28. Wahba G. Automatic smoothing of the log-periodogram. Journal of the American Statistical Association. 1980; 75:122–132.
29. Pawitan Y, O'Sullivan F. Nonparametric spectral density estimation using penalized whittle likelihood. Journal of the American Statistical Association. 1994; 89:600–610.
30. Qin L, Wang Y. Nonparametric spectral analysis with applications to seizure characterization using EEG time series. Annals of Applied Statistics. 2008; 2:1432–1451.

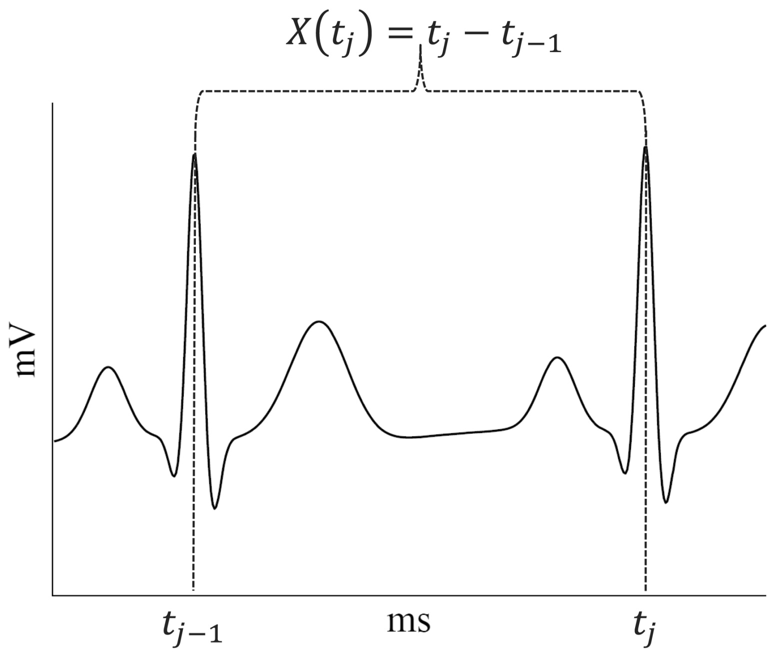

Figure 1.
An ECG epoch with the (j – 1)th and jth R-waves and the jth IBI identified

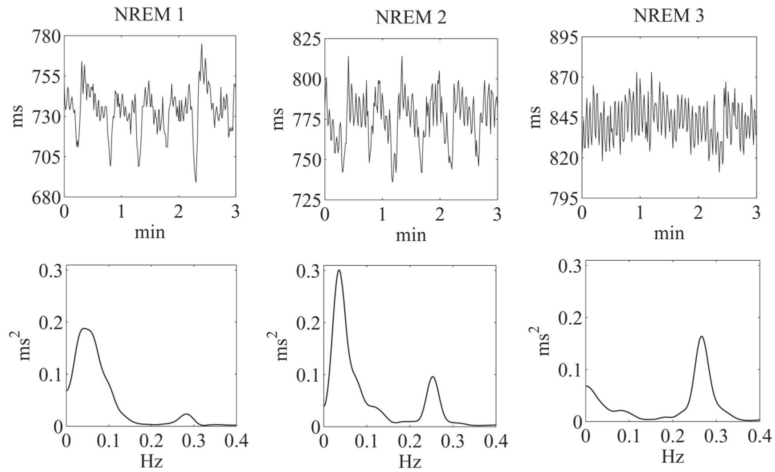

Figure 2.

IBI series (top row) and estimated power spectra (bottom row) for the first three periods of NREM sleep from a participant suffering from insomnia whose PSQI decreased by 2 points after treatment.

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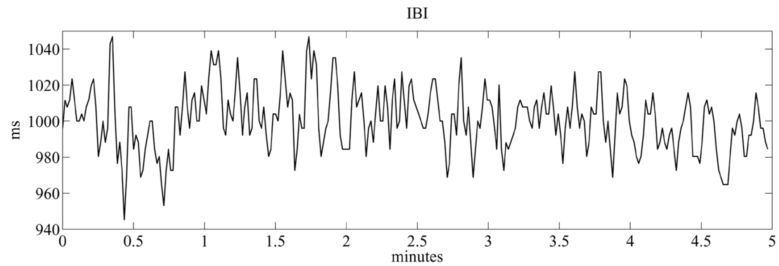

Figure 3.

A simulated HRV epoch with LF/HF ratio ρ = 2.0.

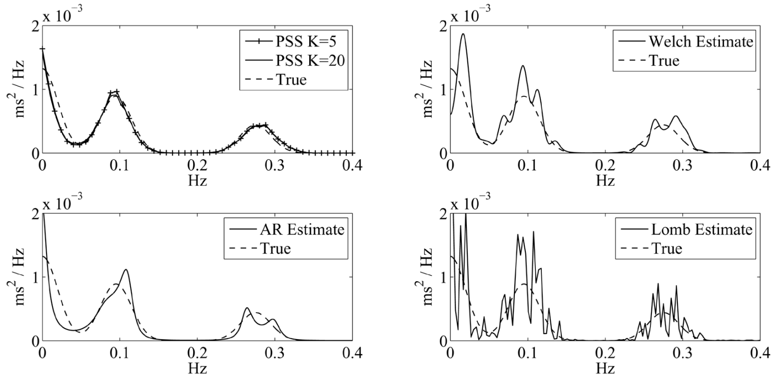

Figure 4.

Estimates of the power spectrum from the HRV epoch displayed in Figure 3 using the proposed sum-of-squares estimator with smoothing parameters selected via $K = 5$ and $K = 20$ fold cross-validation, Welch's periodogram methods, AR estimation, and the Lomb periodogram.

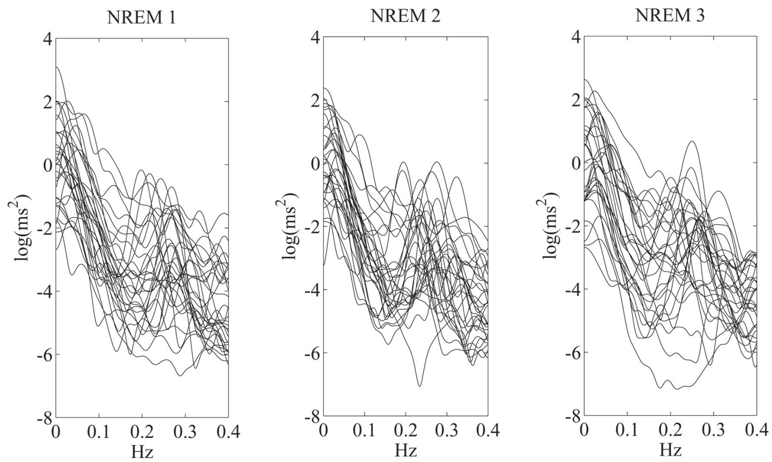

Figure 5.
Estimated HRV log-spectra during the first three periods of NREM from the 31 participants in the insomnia study.

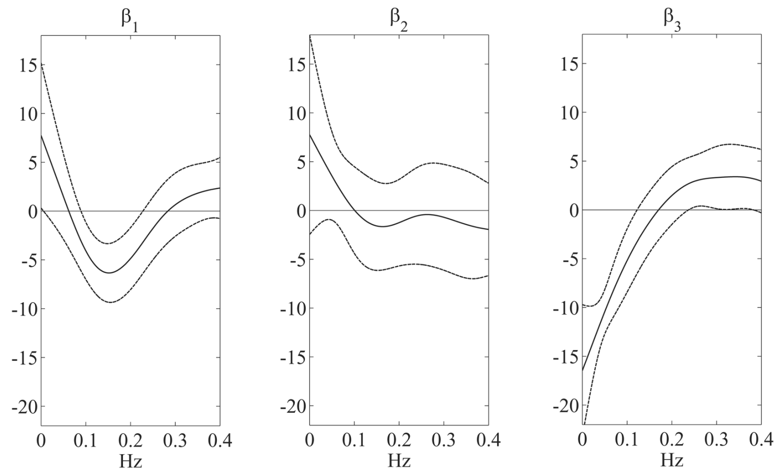

Figure 6.
Estimated functional coefficients and asymptotic point-wise 95% confidence intervals from the functional linear model regressing change in PSQI onto log-spectra.

Table 1

Results of the simulation studies.

	PSS	Lomb	FFT	AR
Setting 1: LF/HF=0.50, LF_μ=0.33, HF_μ = 0.67				
LF/HF	0.50 (0.17)	0.50 (0.17)	0.59 (0.35)	0.54 (0.29)
LF_μ	0.34 (0.07)	0.34 (0.07)	0.35 (0.14)	0.35 (0.10)
HF_μ	0.66 (0.07)	0.66 (0.07)	0.65 (0.11)	0.65 (0.10)
ASE	0.18 (0.10)	− (−)	0.80 (0.61)	0.22 (0.11)
Setting 2: LF/HF=2.00, LF_μ=0.67, HF_μ = 0.33				
LF/HF	2.02 (0.60)	2.01 (0.60)	2.36 (1.29)	2.31 (0.97)
LF_μ	0.67 (0.06)	0.66 (0.06)	0.67 (0.11)	0.67 (0.10)
HF_μ	0.34 (0.06)	0.34 (0.06)	0.33 (0.11)	0.34 (0.10)
ASE	0.19 (0.11)	− (−)	0.50 (0.29)	0.31 (0.18)

The mean (and standard deviation) of LF/HF, LF_μ, and HF_μ estimates and of the across-the-curve ASE. Four estimation procedures are implemented: the proposed penalized sum-of-squares estimator (PSS), Lomb's periodogram (Lomb), Welch's Fourier periodogram method (FFT), and autoregressive estimation (AR).

Table 2

Maximum likelihood estimates, standard errors, and two sided p-values for the coefficients of the regression of change in PSQI onto log low-frequency/high-frequency ratios.

		PSS	Lomb	FFT	AR
γ_0	Estimate	−3.55	−3.56	−3.03	−3.19
	Standard Error	0.63	0.62	0.69	0.61
	P-Value	<0.01	<0.01	<0.01	<0.01
γ_1	Estimate	0.14	0.09	−0.01	0.01
	Standard Error	0.42	0.39	0.41	0.42
	P-Value	0.75	0.81	0.98	0.98
γ_2	Estimate	0.20	0.02	−0.01	−0.02
	Standard Error	0.42	0.43	0.41	0.39
	P-Value	0.63	0.63	0.97	0.96
γ_3	Estimate	−1.05	−1.03	−0.99	−1.00
	Standard Error	0.40	0.43	0.52	0.50
	P-Value	0.01	0.02	0.07	0.05

Four separate models were fit where the low-frequency/high-frequency ratios were computed by the proposed penalized sum-of-squares estimator (PSS), Lomb's periodogram (Lomb), Welch's Fourier periodogram method (FFT), and autoregressive estimation (AR).