Functional Mixed Effects Spectral Analysis

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Abstract

In many experiments, time series data can be collected from multiple units and multiple time series segments can be collected from the same unit. This article introduces a mixed effects Cramér spectral representation which can be used to model the effects of design covariates on the second order power spectrum while accounting for potential correlations among the time series segments collected from the same unit. The transfer function is composed of a deterministic component to account for the population-average effects and a random component to account for the unit-specific deviations. The resultant log-spectrum has a functional mixed effects representation where both the fixed effects and random effects are functions in the frequency domain. It is shown that, when the replicate-specific spectra are smooth, the log-periodograms converge to a functional mixed effects model. A data driven iterative estimation procedure is offered for the periodic smoothing spline estimation of the fixed effects, penalized estimation of the functional covariance of the random effects, and unit-specific random effects prediction via the best linear unbiased predictor.

Keywords: Cramér Representation; Mixed Effects Model; Smoothing Spline; Spectral Analysis; Replicated Time Series

1 Introduction

In biomedical experiments, it is common to collect time series data from multiple subjects and use the time series as the basic unit in the analysis to study the effects of design covariates. These studies can include multiple time series segments collected from the same unit, which can be potentially correlated. The motivating study considered in this article measures three epochs of heart rate variability from subjects during three stages of sleep where it is believed that the heart rate variability spectra are are associated with sleep stage and presence of disease (Malik et al., 1996; Hall et al., 2004). When the focus of the analysis is on the effects of the design covariates on the first moment, such data can be modeled by mixed effects models. However, existing methods are preliminary when the interest is on the second order spectra.

This article introduces a mixed effects Cramér spectral representation to model a collection of time series by defining the transfer function as the product of a deterministic component and a random component. Both the deterministic component, which accounts for the population-average effects, and the random component, which accounts for the unit-specific deviations, are semi-parametrically indexed by design covariates. The resultant log-spectrum has a functional linear mixed effects representation in which both the fixed effects and random effects are functions over the frequency domain.

To fit the mixed effects model for the log-periodograms, we propose an iterative algorithm that begins with an initial smoothing spline estimator of the log-spectral fixed effects. This initial estimator is obtained by approximating the minimizer of a penalized sum-of-squares which ignores the within-unit log-spectral correlation and can be viewed as an extension of the estimators of Cogburn & Davis (1974) and Wahba (1980) to the regression setting. Despite the empirical findings of Qin & Wang (2008) which show that the negative penalized Whittle-likelihood under the proper selection of smoothing parameters can produce more efficient spectral estimates than the penalized sum-of-squares for a single deterministic spectrum, we base our fixed effects estimator on a penalized sum-of-squares because of its computational feasibility and transparent form as a multivariate low-pass filter applied to the ordinary least squares estimates of the log-periodograms at each frequency.

2 Model

2.1 Mixed Effects Cramér Spectral Representation

We introduce the mixed effects Cramér spectral representation for modeling a collection of $n = \sum_{j=1}^{N} n_j$ time series from N independent units where n_j time series are observed from the jth unit. This model consists of a stochastic transfer function that is composed of population fixed effects and unit-specific random effects. Let $U_{jk} = (u_{jk1}, \ldots, u_{jkP})^T \in \mathcal{U}$ and $V_{jk} = (v_{jk1}, \ldots, v_{jkQ})^T \in \mathcal{V}$ be vectors of covariates for the kth replicate of the jth independent unit which index the fixed effects and the unit-specific random effects, respectively. These covariates can include continuous covariates as well as indicator variables for categorical variables. Our motivating study of heart rate variability that is discussed in greater detail in §4 consists of $n = 375$ epochs of heart rate variability measured at $n_j = 3$ different sleep stages from $N = 125$ independent subjects. In addition to its dependence on sleep stage, the expected spectrum of heart rate variability is hypothesized to be associated with the presence of insomnia. The fixed covariates are modeled with $P = 6$ by indicator variables to indicate the presence of insomnia and stage of sleep. The covariates of the random effects are modeled with $Q = 2$ to capture the variation in the across-the-night average heart rate variability between different subjects and the correlation in the heart rate variability from the same subject at different stages of sleep.

The transfer function of the kth replicate of the jth independent unit is decomposed into $A_0(\omega; U_{jk})A_j(\omega; V_{jk})$ where A_0 is a fixed effects term and A_j is a random effects term. To formally define our model, let the population fixed effects term A_0 be a complex valued function over $\mathbb{R} \times \mathcal{U}$ such that for every $U_{jk} \in \mathcal{U}$, $A_0(\cdot; U_{jk})$ is Hermitian, square-integrable over $[-1/2, 1/2]$, and has period 1 as a function of frequency. The unit-specific random terms are defined for $j = 1, \ldots, N$ as the complex valued random functions A_j over $\mathbb{R} \times \mathcal{V}$ such that for every $V_{jk} \in \mathcal{V}$, $A_j(\cdot; V_{jk})$ are Hermitian, square-integrable over $[-1/2, 1/2]$, and have period 1 as trajectories over frequency. Additionally, A_j and $A_{j'}$ for $j, j' \neq 0$ are independent and identically distributed conditional on V_{jk} when $j \neq j'$, and it is assumed that $\sup_{\omega \in \mathbb{R}, V_{jk} \in \mathcal{V}} E\left\{|A_j(\omega; V_{jk})|^2\right\} < \infty$.

The mixed effects Cramér spectral representation defines the kth replicate time series of the jth independent unit $\{X_{jkt}\}$ for $k = 1, \ldots, n_j$ and $j = 1, \ldots, N$ as:

$$X_{jkt} = \int_{-1/2}^{1/2} A_0(\omega; U_{jk})A_j(\omega; V_{jk})e^{2\pi i\omega t} dZ_{jk}(\omega) \qquad (1)$$

where Z_{jk} are mutually independent identically distributed mean-zero orthogonal increment processes over $[-1/2, 1/2]$ that are independent of $A_{j'}$ for all j and j', and $E\left\{|dZ_{jk}(\omega)|^2\right\} = d\omega$. The time series $\{X_{jkt}\}$ exists with probability one, is mean zero second order stationary, and has spectral density $|A_0(\omega; U_{jk})|^2 E\left\{|A_j(\omega; V_{jk})|^2\right\}$. To examine which second order stationary time series have a (not necessarily unique) mixed effects Cramér spectral representation, note that any second order stationary time series with a spectral density has a traditional Cramér representation with a unit-variance orthogonal increment processes and a transfer function that is the square root of its spectral density. Since the proposed model allows for $A_j(\omega; V_{jk}) = 1$ with probability 1 for all ω and V_{jk}, any second order stationary time series with a spectral density, such as the popular stationary autoregressive moving average models, possess a mixed effects Cramér spectral representation. Conditional on A_j, the time series $\{X_{jkt}\}$ is also mean zero second order stationary and we define the replicate-specific spectra as the random functions

$$f_{jk}(\omega; U_{jk}, V_{jk}) = |A_0(\omega; U_{jk})|^2 \, |A_j(\omega; V_{jk})|^2. \tag{2}$$

We focus on inference on the log-spectral scale and without loss of generality assume that the replicate-specific spectra are parameterized such that $E\left\{\log |A_j(\omega; V_{jk})|^2\right\} = 0$ for all $\omega \in \mathbb{R}$ and $V_{jk} \in \mathcal{V}$.

2.2 Semi-Parametric Log-Spectral Model

We will assume semi-parametric models for both the fixed and random components of the transfer functions. The semi-parametric model of the fixed effects component of the transfer function is defined for $U_{jk} = (u_{jk1}, \ldots, u_{jkP})^T$ as $A_0(\omega; U_{jk}) = \prod_{p=1}^{P} h_p^0(\omega)^{u_{jkp}}$ where h_p^0 are deterministic Hermitian functions over $\mathbb{R}$ with period 1 that are bounded away from zero. The random component of the unit-specific transfer functions are defined for $V_{jk} = (v_{jk1}, \ldots, v_{jkQ})^T \in \mathcal{V}$ as $A_j(\omega; V_{jk}) = \prod_{q=1}^{Q} h_{jq}(\omega)^{v_{jkq}}$ where h_{jq} are mutually independent Hermitian random functions with period 1 that are bounded away from zero, h_{jq} and $h_{j'q}$ are independent and identically distributed for $j \neq j'$, and $E\left\{|h_{jq}(\omega)|^4\right\} < \infty$. Define the functions $\beta_p(\omega) = \log |h_p^0(\omega)|^2$ and $\alpha_{jq}(\omega) = \log |h_{jq}(\omega)|^2$ as well as the P-dimensional vectors $\beta(\omega) = \{\beta_1(\omega), \ldots, \beta_P(\omega)\}^T$ and the Q-dimensional vectors $\alpha_j(\omega) = \{\alpha_{j1}(\omega), \ldots, \alpha_{jQ}(\omega)\}^T$. This transfer function model induces the semi-parametric mixed effects model on the replicate-specific log-spectra

$$\log f_{jk}(\omega; U_{jk}, V_{jk}) = U_{jk}^T \beta(\omega) + V_{jk}^T \alpha_j(\omega). \tag{3}$$

If we define the covariance function for the qth log-spectral random effect as $\Gamma_q(\omega, \nu) = E\{\alpha_{jq}(\omega)\alpha_{jq}(\nu)\}$ and let $\Gamma(\omega, \nu) = \text{diag}\{\Gamma_1(\omega, \nu), \ldots, \Gamma_Q(\omega, \nu)\}$ be the diagonal $Q \times Q$ matrix of these covariances, the first two central moments of log-spectra are

$$\begin{aligned} \mathrm{E}\{\log f_{jk}(\omega; U_{jk}, V_{jk})\} &= U_{jk}^T \beta(\omega) \\ \mathrm{cov}\{\log f_{jk}(\omega; U_{jk}, V_{jk}), \log f_{j\ell}(\nu; U_{j\ell}, V_{j\ell})\} &= V_{jk}^T \Gamma(\omega, \nu) V_{j\ell}. \end{aligned}$$

3 Estimation

3.1 Log-Periodogram Mixed Effects Model

Let $T = 2L$ for a positive integer L and assume that we observe epochs of length T of a collection of time series $\{X_{jk1}, \ldots, X_{jkT}\}$ that follow a mixed effects Cramér spectral representation for $k = 1, \ldots, n_j$ and $j = 1, \ldots, N$. Let $\omega_\ell = \ell/T$ for $\ell = (1-L), \ldots, L$ be the Fourier frequencies and define the finite Fourier transforms as $d_{jk\ell} = T^{-1/2} \sum_{t=1}^{T} X_{jkt} e^{-2\pi i \omega_\ell t}$ and subsequent periodograms as $I_{jk\ell} = |d_{jk\ell}|^2$. Theorem 1 establishes asymptotic properties of the log-periodograms when the replicate-specific spectra are in $W_{2,per}^2$ and allows the log-periodograms to be approximated by a functional mixed effects model.

Letting $y_{jk\ell} = \log I_{jk\ell} + \gamma_\ell$, the log-periodograms approximately follow the functional mixed effects model

$$y_{jk\ell} \approx U_{jk}^T \beta(\omega_\ell) + V_{jk}^T \alpha_j(\omega_\ell) + \epsilon_{jk\ell} \tag{4}$$

where $\epsilon_{jk\ell}$ are mean-zero independent random variables for $\ell = 0, \ldots, L$ with $\operatorname{var}(\epsilon_{jk\ell}) = \sigma_\ell^2$. The second part of Theorem 1 provides the uniform convergence of the first two moments of this smooth signal plus noise model and subsequently allows functional mixed effects modeling techniques to be applied to (4) to obtain consistent estimates of β_p, Γ_q and α_{jq}.

3.2 Fixed Effects

The proposed estimator of β is based on minimizing the penalized sums-of-squares

$$\frac{1}{nT} \sum_{j=1}^{N} \sum_{k=1}^{n_j} \sum_{\ell=1-L}^{L} \left\{ y_{jk\ell} - U_{jk}^T \beta(\omega_\ell) \right\}^2 + \sum_{p=1}^{P} \lambda_p \int_{-1/2}^{1/2} \beta_p''(\omega)^2 \, d\omega \tag{5}$$

over $\otimes^P W_{2,per}^2$ given smoothing parameters $\lambda_p \geq 0$. By the representer lemma for smoothing splines, if U_j are the $n_j \times P$ matrices with kpth elements u_{jkp} and $U = (U_1^T, \ldots, U_N^T)^T$ is full rank, then a unique solution exists. To find this solution, let $Y_{j\ell} = (y_{j1\ell}, \ldots, y_{jn_j\ell})^T$, $Y_\ell = (Y_{1\ell}^T, \ldots, Y_{N\ell}^T)^T$, and $Y = \left(Y_{1-L}^T, \ldots, Y_L^T\right)^T$. The estimate $\beta(\omega)$ with

$$\hat{\beta}(\omega) = \frac{1}{T} \sum_{\ell=1-L}^{L} \sum_{m=1-L}^{L} \left\{ U^T U + n(2\pi m)^4 \Lambda \right\}^{-1} U^T Y_\ell e^{2\pi i m(\omega - \omega_\ell)}. \tag{6}$$

When $n = 1$ and $P = 1$, the proposed estimator is equivalent to the estimator proposed by Wahba (1980) and is subsequently a generalization of this well studied estimator to the regression setting with multiple log-spectra. Using simple algebra to express

$$\left\{ U^T U + n(2\pi m)^4 \Lambda \right\}^{-1} U^T Y_\ell = \left\{ I_P + n(2\pi m)^4 (U^T U)^{-1} \Lambda \right\}^{-1} \left\{ (U^T U)^{-1} U^T Y_\ell \right\}$$

illuminates that the proposed estimate is a type of multivariate low-pass filter applied to the ordinary least squares estimates at each frequency. It is dependent on the smoothing parameters such that as $\max \lambda_j \to 0$, $\hat{\beta}$ approaches a spline interpolation of the ordinary least squares estimates. Theorem 2 establishes the optimal decay of λ_j if both the number of independent units and the number of time points is large as well as the point-wise consistency of $\hat{\beta}$.

3.3 Functional Covariance

We propose an estimate of the functional covariance of the log-spectral random effects conditional on the estimate $\hat{\beta}$ through the outer product of smoothed unit-specific quantities. Define the residuals $y_{jk\ell}^* = y_{jk\ell} - U_{jk}^T \hat{\beta}(\omega_\ell)$ and $Y_{j\ell}^* = (y_{j1\ell}^*, \ldots, y_{jn_j\ell}^*)^T$. We propose to estimate $\Gamma_q(\omega, \nu)$ for $\omega, \nu \in \mathbb{R}$ as

$$\hat{\Gamma}_q(\omega, \nu) \quad = \quad N^{-1} \sum_{j=1}^{N} \tilde{\alpha}_{jq}(\omega) \tilde{\alpha}_{jq}(\nu) \tag{7}$$

where $\tilde{\alpha}_j = (\tilde{\alpha}_{j1}, \ldots, \tilde{\alpha}_{jQ})^T$ is based on minimizing

$$\frac{1}{n_j T} \sum_{k=1}^{n_j} \sum_{\ell=1-L}^{L} \left\{ y^*_{jk\ell} - V_{jk}^T \alpha_j(\omega_\ell) \right\}^2 + \sum_{q=1}^{Q} \theta_q \int_{-1/2}^{1/2} \alpha''_{jq}(\omega)^2 \, d\omega$$

over $\otimes^Q W^2_{2,per}$ given the smoothing parameters $\theta_q \geq 0$. Approximating the solution to the penalized sums-of-squares, we estimate $\hat{\Gamma}_q(\omega, \nu)$ as the qth diagonal element of the $Q \times Q$ matrix

$$\frac{1}{NT^2} \sum_{j=1}^{N} \sum_{\ell,m,r,s=1-L}^{L} \left\{ V_j^T V_j + n_j (2\pi m)^4 \Theta \right\}^{-1} V_j^T Y^*_{j\ell} Y^{*T}_{jr} V_j$$
$$\times \left\{ V_j^T V_j + n_j (2\pi s)^4 \Theta \right\}^{-1} e^{2\pi i m(\omega - \omega_\ell) + 2\pi i s(\nu - \omega_r)}$$

where V_j is the $n_j \times Q$ matrix with kqth element v_{jkq} and $\Theta = \text{diag}(\theta_1, \ldots, \theta_Q)$. Theorem 3 finds the optimal decay of the smoothing parameters θ_q for the estimation of Γ_q as well as the point-wise mean-squared consistency of the estimate of Γ_q.

4 Analysis of Heart Rate Variability

Heart rate variability is the measure of variability in the elapsed time between consecutive heart beats. The spectral analysis of heart rate variability is important in the study of various physiological outcomes and provides indirect measures of autonomic nervous system activity (Malik et al., 1996). Researchers have devised methods to assess heart rate variability continuously and non-invasively throughout sleep (Hall et al., 2004, 2007). In the present study, sleep and heart rate variability were concurrently assessed in a sample of N=125 men and women between the ages of 60 and 89 years of age. Data were collected in participants' homes to enhance the ecological validity of study measures. Of these participants, 76 were poor sleepers due to insomnia while 49 were poor sleepers due to the emotional strain of caregiving for a spouse with advanced dementia. The present analysis uses epochs of heart rate variability tachograms, or the series of the elapsed time between consecutive heart beats indexed by beat number, of the first 500 continuous heart beats during each of the first three periods of non-rapid eye movement (NREM). The data for each subject are comprised of patient type (either insomnia or caregiver) and three time series (heart rate variability for the first three periods of NREM).

The goal of our analysis is to quantify the expected differences in heart rate variability spectra between individuals with insomnia and caregivers during different NREM periods. We model the heart rate variability log-spectrum for the $j = 1, \ldots, 129$ subjects at the first $k = 1, 2, 3$ periods of NREM as $\log f_{jk}(\omega; U_{jk}, V_{jk}) = U_{jk}^T \beta(\omega) + V_{jk}^T \alpha_j(\omega)$ where

$$\begin{bmatrix} U_{j1}^T \\ U_{j2}^T \\ U_{j3}^T \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 & S_j & 0 & 0 \\ 0 & 1 & 0 & 0 & S_j & 0 \\ 0 & 0 & 1 & 0 & 0 & S_j \end{bmatrix}, \qquad \begin{bmatrix} V_{j1}^T \\ V_{j2}^T \\ V_{j3}^T \end{bmatrix} = \begin{bmatrix} 1 & -1 \\ 1 & 0 \\ 1 & 1 \end{bmatrix}$$

and S_j is the indicator variable for the jth subject being an insomniac. The fixed effects $\beta_1, \beta_2, \beta_3$ are the mean log-spectrum at NREM periods 1, 2, and 3 respectively for caregivers, $\beta_4, \beta_5, \beta_6$ are the differences in the mean log-spectra between caregivers and individuals with insomnia at NREM periods 1, 2, and 3 respectively, Γ_1 accounts for the variability in the across-the-night average log-spectra among subjects, and Γ_2 is the covariance kernel among adjacent NREM periods within a subject.

5 Discussion

The model and estimation procedure introduced in this article offer tools for analyzing collections of time series from designed studies and can be extended in several directions to encompass other popular settings. We have focused on estimation based on the first two moments of the log-spectra. It is possible to extend our procedure to Whittle-likelihood based inference. In addition, many applications involve the analysis of replicated time series that are not necessarily stationary. The incorporation of the tensor-product design employed by Guo et al. (2003) into our proposed model to allow for the spectral analysis of replicated non-stationary time series could provide a useful tool for the analysis of replicated locally stationary time series. We hypothesize that the computational burden associated with Whittle-likelihood based inference and the tensor-product analysis of locally stationary time series for a collection of time series could make these two extensions non-trivial tasks. Although the mixed effects Cramér spectral representation holds when unit-specific spectra are not necessarily smooth, our estimation procedure is formulated for applications such as the analysis of heart rate variability where a global smoothness criterion is appropriate.

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