Application of spectral methods to representative data sets in electrophysiology and functional neuroimaging

Society for Neuroscience Short Course III

14 November 2008 (revised 17 November 2008)
Five examples of the utility and implementation of spectral methods

(1) Variation in the power of high-frequency cortical oscillations from human LFP
   Emphasizes frequency-domain concepts such as the spectrogram

(2) Synaptic connectivity between neurons in the leech swim network
   Emphasizes spectral coherence and the associated confidence level

(3) Discovery of neurons, in rat vM1 cortex, that report the pitch of vibrissa movement
   Emphasizes spectral power density as the sum of pure tones and pink noise

(4) Denoising of imaging data in the study of calcium waves
   Emphasizes space-time correlation in multisite measurements and the time-domain SVD

(5) Delineation of electrical wave phenomena in turtle visual cortex
   Emphasizes space-frequency correlation in multisite measurements and the complex frequency SVD

Focus is on the explanation of the analysis and not on the scientific questions *per se.*
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<th>Laboratory units</th>
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<td>T/N transforms to 1</td>
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<tr>
<td>(minimum time)</td>
<td>(minimum time)</td>
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<tr>
<td>Record length</td>
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<td>(maximum time)</td>
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<td>Temporal range</td>
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<td>Raleigh frequency ($f_R$)</td>
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<td>Bandwidth product</td>
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How to deduce variation in the power of a high-frequency cortical oscillation from human LFP

Think frequency-domain concepts, e.g., spectrogram.
Human intracranial LFP

\[ T = 300 \, \text{s} \]
\[ N = 300,000 \]
\[ f_{\text{Nyquist}} = 500 \, \text{Hz} \]

How do we start?

The mean value is removed to form

$$\delta V(t) = V(t) - \frac{1}{T} \int_0^T dt \ V(t) \xrightarrow{\text{discrete units}} V(t) - \frac{1}{N} \sum_{t=0}^N V(t).$$

Fourier transform of this signal with respect to the k-th Slepian, $w^{(k)}(t)$, is

$$\delta \tilde{V}^{(k)}(f) = \frac{1}{\sqrt{T}} \int_0^T dt \ e^{-i 2\pi f t} \ w^{(k)}(t) \ \delta V(t) \xrightarrow{\text{discrete variables}} \frac{1}{\sqrt{N}} \sum_{t=0}^N e^{-i 2\pi f t} \ w^{(k)}(t) \ \delta V(t).$$

The spectral power density (units of amplitude$^2$/Hz) is an average over tapers, i.e.,

$$S(f) \equiv \frac{1}{K} \sum_{k=1}^K \left| \delta \tilde{V}^{(k)}(f) \right|^2.$$
Human intracranial LFP

\[ T = 300 \text{ s} \]
\[ N = 300,000 \]
\[ f_{\text{Nyquist}} = 500 \text{ Hz} \]

Laboratory units

Discrete units


Human intracranial LFP

$T = 300 \text{ s}$

$N = 300,000$

$f_{\text{Nyquist}} = 500 \text{ Hz}$

Laboratory units

Discrete units


How do we characterize the variations in power in the $\gamma$-band?

Treat the logarithm of the power in a band as a new signal, \textit{i.e.},

$$V_\gamma(t) \equiv \frac{1}{f_2 - f_1} \int_{f_1}^{f_2} df \log \{S(f; t)\} \text{ discrete units} \rightarrow \frac{1}{f_2 - f_1} \sum_{f=f_1}^{f_2} \log \{S(f; t)\}.$$

Spectrum of the new time series is called the “second-spectrum”, \textit{i.e.},

$$S_\gamma(f) \equiv \frac{1}{K} \sum_{k=1}^{K} \left| \tilde{V}_{\gamma}^{(k)}(f) \right|^2.$$
Human intracranial LFP

T = 300 s
N = 300,000
f_{Nyquist} = 500 Hz

Laboratory units

Discrete units

Human intracranial LFP

Laboratory units
Discrete units

How do we calculate confidence intervals? Jackknife!

We compute the standard error in terms of "delete-one" means, i.e.,

$$S^{(n)}(f) \equiv \frac{1}{K-1} \sum_{k=1 \atop k \neq n}^{K} \sum_{k=1}^{K} \left| \tilde{V}^{(k)}_{\gamma}(f) \right|^2 \quad \forall n.$$  

As amplitudes are defined on $[0, \infty)$, not $(-\infty, \infty)$, the delete-one estimates are replaced with

$$g[S(f)] = \log[S(f)].$$

The mean and standard error of the transformed variable are

$$\mu_{\gamma}(f) = \frac{1}{K} \sum_{n=1}^{K} g\{S^{(n)}_{\gamma}(f)\} \quad \text{and} \quad \sigma_{\gamma}(f) = \sqrt{\frac{K-1}{K} \sum_{n=1}^{K} g\{S^{(n)}_{\gamma}(f)\} - \mu_{\gamma}(f)}.$$  

The 95% confidence interval for the spectral power is thus

$$\left[ e^{\mu_{\text{Mag}} - 2\sigma_{\text{Mag}}}, e^{\mu_{\text{Mag}} + 2\sigma_{\text{Mag}}} \right].$$
Human intracranial LFP

$T = 300 \text{ s}$
$N = 300,000$
$f_{\text{Nyquist}} = 500 \text{ Hz}$

Laboratory units
Discrete units

How to deduce synaptic connectivity between neurons in the leech swim network

2

Think multisite measurements

Think spectral coherence and confidence levels
Circuit Analysis with FRET-based Voltage Sensitive Dyes

- **Depolarized** ($V \gg 0$)
  - Pump
  - Direct Emission

- **Hyperpolarized** ($V \ll 0$)
  - Emission via FRET

O = Oxonol  C = CC1 or CC3 Coumarin

![Graph showing sensitivity vs. holding potential](image)

Sensitivity, ($v = 1$ Hz), (-ΔF/F per 10 mV × 10^-3)

Holding Potential (mV)

Idea:
Drive one cell and optically measure response in all others

Example pair-wise data
How do we calculate coherence?

\[
C(f) = \frac{\frac{1}{K} \sum_{k=1}^{K} V^{(k)}(f) \left[ U^{(k)}(f) \right]^*}{\sqrt{\left( \frac{1}{K} \sum_{k=1}^{K} |V^{(k)}(f)|^2 \right) \left( \frac{1}{K} \sum_{k=1}^{K} |U^{(k)}(f)|^2 \right)}}
\]
How do we calculate confidence intervals? Jackknife again!

Compute delete-one averages of coherence, i.e.,

$$C_i^{(n)}(f) = \frac{1}{K-1} \sum_{k=1 \atop k \neq n}^K \bar{V}_i^{(k)}(f) \left[ \bar{U}_i^{(k)}(f) \right]^*$$

$$\forall \ n.$$ 

As magnitudes are defined on [0,1], not (-∞, ∞), the delete-one estimates are replaced with

$$g\{|C_i|\} = \log \left( \frac{|C_i|^2}{1 - |C_i|^2} \right).$$

The mean and standard error of the transformed variable are

$$\mu_{i; \text{Mag}}(f) = \frac{1}{K} \sum_{n=1}^K g\{C_i^{(n)}(f)\} \quad \text{and} \quad \sigma_{i; \text{Mag}}(f) = \sqrt{\frac{K-1}{K} \sum_{n=1}^K g\{C_i^{(n)}(f)\} - \mu_{i; \text{Mag}}(f)^2}.$$ 

The 95% confidence interval for the coherence is thus

$$\left[ -\sqrt{1+e^{-\mu_{i; \text{Mag}} - 2\sigma_{i; \text{Mag}}}}, -\sqrt{1+e^{-\mu_{i; \text{Mag}} + 2\sigma_{i; \text{Mag}}}} \right].$$
How do we calculate confidence intervals for the phase? Jackknife on unit vectors!

Idea is to compute the variation in the relative directions of the delete-one unit vectors, \textit{i.e.},

\[ \sigma_{i;\text{Phase}}(f) = \sqrt{\frac{2}{K} \left( K - \sum_{n=1}^{K} \frac{C_i^{(n)}(f)}{C_i^{(n)}(f)} \right)} \quad \forall \; n. \]
FRET-based Voltage Sensitive Dyes and Phase-Sensitive Detection for the Discovery of Novel Followers in Leech

How to deduce neuronal coding for the pitch of vibrissa movement

Think spectral power as the sum of pure tones, and slowly evolving pink background noise
Consecutive Video Rate Fields (60 Hz acquisition) of a free ranging rat (blindfolded) that is whisking in air in search of a foodtube
The Frequency of Whisking is Constant within an Epoch but Broadly Distributed from Epoch to Epoch

O'Connor, Berg and Kleinfeld 2001
Stimulus Induced Spiking in M1 vs. S1 Vibrissa Cortex in the Aroused Rat
Response of Motor (M1) versus Sensory (S1) Cortical Units

Kleinfeld, Sachdev, Merchant, Jarvis and Ebner - 2002
The Response of Units in M1 Vibrissa Cortex is Sinusoidal (Fundamental Frequency of a Harmonic Spectrum) For a Broad Range of Stimulation Frequencies

Kleinfeld, Sachdev, Merchant, Jarvis and Ebner - 2002
How do we model a rhythmically driven process?

Output as linear response plus noise, \textit{i.e.},

\[ V(t) = A_1 \cos(2 \pi f_1 t + \phi_1) + \eta(t). \]

The goal is to determine coefficients \( A_1 \) and \( \phi_1 \) by regression.

With the replacement \( B_1 = \frac{A_1}{2} e^{i \phi_1} \), we have a computationally convenient form

\[ V(t) = B_1 e^{i 2 \pi f_1 t} + B_1^* e^{-i 2 \pi f_1 t} + \eta(t). \]

The Fourier transform of \( V(t) \) with respect to the \( k \)-th taper yields

\[ \tilde{V}^{(k)}(f) = B_1 \tilde{w}^{(k)}(f - f_1) + B_1^* \tilde{w}^{(k)}(f + f_1) + \tilde{\eta}^{(k)}(f), \]

where

\[ \tilde{w}^{(k)}(f) = \frac{1}{\sqrt{N}} \sum_{t=1}^{N} e^{-i 2 \pi f t} w^{(k)}(t) \quad \text{and} \quad \tilde{\eta}^{(k)}(f) = \frac{1}{\sqrt{N}} \sum_{t=1}^{N} e^{-i 2 \pi f t} w^{(k)}(t) \eta(t). \]
At \( f = f_1 \), the frequency of interest, \( \tilde{w}^{(k)}(2f_1) = 0 \) since \( 2f_1 > f_1 + W \) and

\[
\tilde{V}^{(k)}(f_1) = \begin{cases} 
B_1 \tilde{w}^{(k)}(0) + \tilde{\eta}^{(k)}(f_1) & \text{for } k = 1, 3, 5, \ldots \\
\tilde{\eta}^{(k)}(f_1) & \text{for } k = 2, 4, 6, \ldots 
\end{cases}
\]

This specifies a regression for \( B_1 \).

The \( \tilde{V}^{(k)}(f_1) \) are the dependent variables and the \( \tilde{w}^{(k)}(0) \) are the independent variables.

The least-squares estimate of \( B_1 \) is

\[
\hat{B}_1 = \frac{\sum_{k = 1, 3, 5, \ldots}^{K} \tilde{w}^{(k)}(0) \tilde{V}^{(k)}(f_1)}{\sum_{k = 1, 3, 5, \ldots}^{K} \left[ \tilde{w}^{(k)}(0) \right]^2}
\]

and the associated F-statistic, to determine significance, is (Thomson, 1982)

\[
F_{2, 2K-2} = \left| \hat{B}_1 \right|^2 \frac{(K-1) \sum_{k = 1}^{K} \left| \tilde{w}^{(k)}(0) \right|^2}{\sum_{k = 1}^{K} \left| \tilde{V}^{(k)}(f_1) - \tilde{V}^{(k)}(f_1) \right|^2}
\]
Spectral Analysis (Power and Transfer Functions) of Spike Trains

Spectral Power Density [Spikes²/Hz]

= Driven Density [Spikes²/Hz]

+ Residual Density [Spikes²/Hz]
Response of Units in M1 Vibrissa Cortex is Sinusoidal
(Fundamental Frequency of a Harmonic Spectrum) for a Broad Range of Stimulation Frequencies

\[
\hat{C}(f_1) = \frac{|\hat{B}(f_1)|^2}{\sum_{m=1}^{M} |\hat{B}(mf_1)|^2}
\]

Fraction of response at stimulus frequency

Kleinfeld, Sachdev, Merchant, Jarvis and Ebner - 2002
How to denoise confocal imaging data in the study of calcium waves

Think singular value decomposition (SVD) to represent space-time correlations in multi-site measurements.
In Vitro Neocortical Slice Preparation
Optical Properties of Ca-Green 2

Absorption

Fluorescent Emission

Wavelength (nm)

350 400 450 500 550 600 650

Ex = 488 nm

500 μM free Ca²⁺
39.8
9.0
6.0
3.0
1.35
1.00
0.60
0.10
0.0

Fluorescence emission

Wavelength (nm)
Intracellular Calcium in Acute Hippocampal Slice

Strictly Raw
How do we model imaging data?

Express space in terms of a pixel index, \( s \), so data define a space-time matrix, \( i.e. \),

\[
V(s, t) = \sum_{n=1}^{\text{rank}\{V\}} \lambda_n \ F_n(s) \ G_n(t)
\]

where the rank is the smaller of the pixel or time dimensions.

Temporal functions satisfy the eigenvalue equation

\[
\sum_{t'=1}^{N_t} G_n(t') \left[ \sum_{s=1}^{N_s} V(s, t) V(s, t') \right] = \lambda_n^2 G_n(t)
\]

where

\[
\sum_{t=1}^{N_t} G_m(t) G_n(t) = \delta_{nm} \quad \text{and} \quad \sum_{s=1}^{N_s} F_m(s) F_n(s) = \delta_{nm}.
\]

The spatial function that accompanies each temporal function are

\[
F_n(s) = \frac{1}{\lambda_n} \sum_{t=1}^{N_t} V(s, t) G_n(t).
\]
Spatial and Temporal Modes for Ca^{2+} Imaging Data
Spatial and Temporal Modes for Ca$^{2+}$ Imaging Data

![Graph showing spatial and temporal modes for Ca$^{2+}$ imaging data. The graph plots the index of eigenvalue against the eigenvalue squared ($\lambda^2$) with a logarithmic scale on the y-axis and a linear scale on the x-axis. The graph demonstrates the decay of eigenvalues as the index increases.]
How do we denoise data?

Utility of SVD is that only the lower-order modes carry information.

Reconstruct the data matrix from only these modes and thus remove the “fast” noise, i.e.,

\[
V^{\text{reconstructed}} (s, t) = \sum_{n = 1}^{\text{largest significant mode}} \lambda_n F_n(s) G_n(t).
\]
Intracellular Calcium in Acute Hippocampal Slice

The Raw

The Cooked
How to delineate electrical wave phenomena in turtle visual cortex

Think SVD to represent space-frequency correlations across multi-site measurements
Voltage Sensitive Dye Imaging of Turtle Visual Cortex

[Diagram showing experimental setup with detectors, source, electrodes, and brain section with labels D1 and D2, as well as LFP and Optical signal plots over time.]
How do we model propagating waves?

Idea is to look for spatial shifts in the phase of a rhythmic process.

Space-time data $V(s, t)$ are first projected into a local frequency domain, *i.e.*, 

$$
\tilde{V}^{(k)}(s, f) = \frac{1}{\sqrt{N}} \sum_{t=0}^{N} e^{i 2\pi f t} \, w^{(k)}(t) \, V(s, t)
$$

where the index $k$ defines a local frequency index in the band $[f - W, f + W]$.

For a fixed frequency, $f_0$, an SVD is performed on this complex matrix:

$$
\tilde{V}(s, k; f_0) \equiv \left[ \tilde{V}^{(1)}(s, f_0), \ldots, \tilde{V}^{(K)}(s, f_0) \right].
$$

This yields

$$
\tilde{V}(s, k; f_0) = \sum_{n=1}^{\text{rank}\{\tilde{V}\}} \lambda_n \, \tilde{F}_n(s) \, \tilde{G}_n(k)
$$

where the rank is invariably set by $K$. 
Dominant Modes from a SVD in Space and Temporal Frequency

\[ \hat{C}(f_0) = \frac{\lambda_1^2(f_0)}{\sum_{k=1}^{K} \lambda_k^2(f_0)} \]

Prechtl, Cohen, Mitra, Pesaran and Kleinfeld (1997)
Application of spectral methods to representative data sets in electrophysiology and functional neuroimaging

Thank you for your attention!