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*.

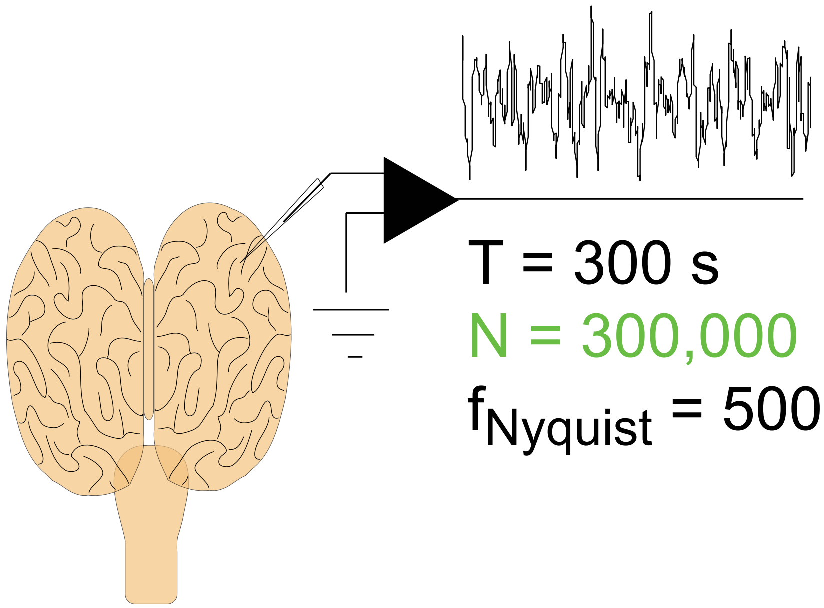
	Laboratory units		**Discrete units**
Sample time (Δt) (minimum time)	T/N	transforms to	1
Record length (maximum time)	T	transforms to	N
Temporal range	[0, T]	transforms to	[0, N]
Raleigh frequency (f_R) (minimum frequency)	1/T	transforms to	1/N
Nyquist frequency (f_N) (maximum frequency)	N/2T	transforms to	1/2
Spectral range	[0, N/2T]	transforms to	[-1/2, +1/2]
Bandwidth (W)	p/T	transforms to	p/N
Time-bandwidth product	p	is invariant	p

How to deduce variation in the power of a high-frequency cortical oscillation from human LFP

1

Think frequency-domain concepts, *e.g.*, spectrogram

Human intracranial LFP



$T = 300$ s

$N = 300{,}000$

$f_{Nyquist} = 500$ Hz

Nir, Mukamel, Dinstein, Privman, Harel, Fisch, Gelbard-Sagiv, Kipervasser, Andelman, Neufeld, Kramer, Arieli, Fried and Malach R (2008)

Drew, Duyn, Galanov and Kleinfeld (2008)

How do we start?

The mean value is removed to form

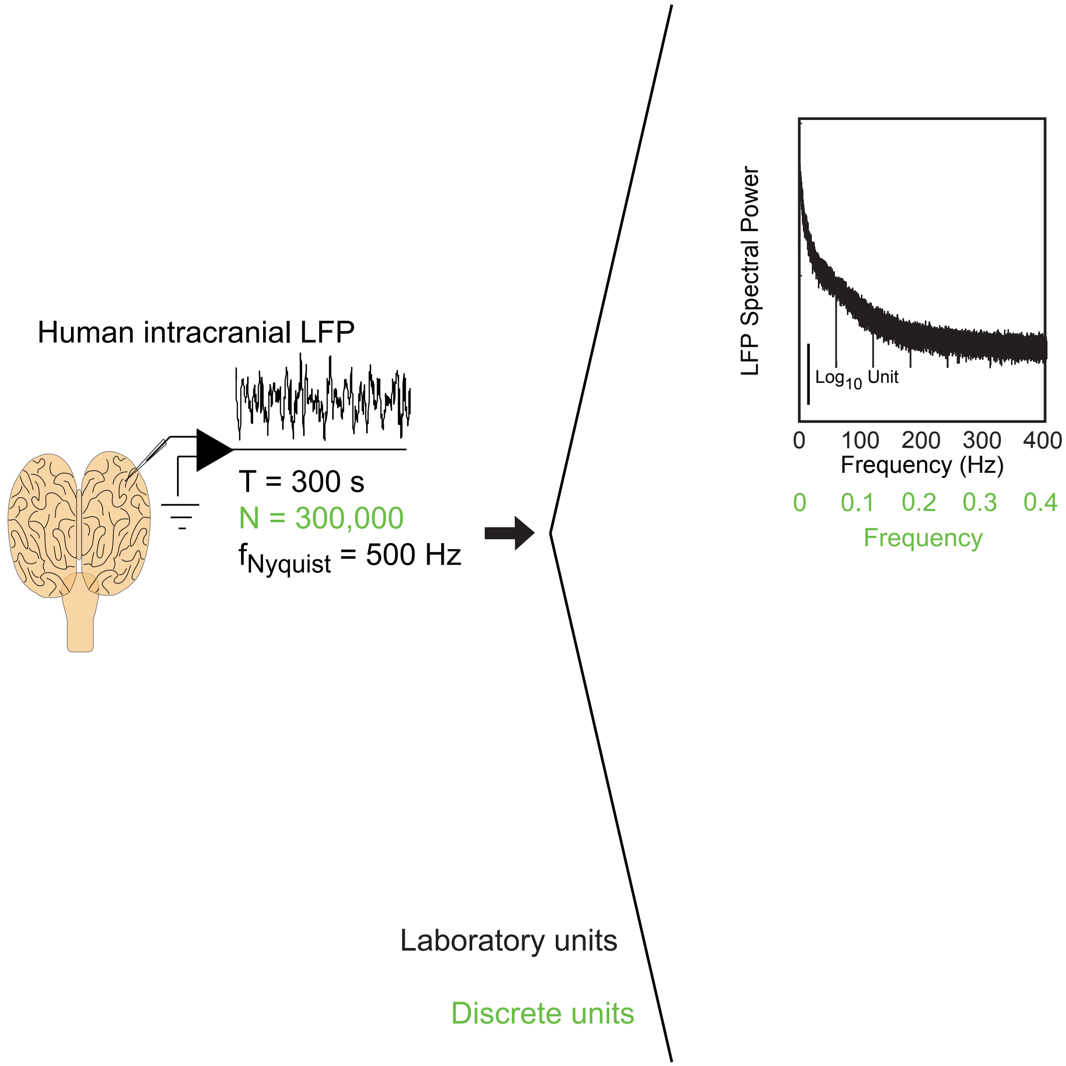
$$\delta V(t) = V(t) - \frac{1}{T}\int_0^T dt\, V(t) \xrightarrow[\text{units}]{\text{discrete}} V(t) - \frac{1}{N}\sum_{t=0}^{N} V(t) \quad .$$

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

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

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

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



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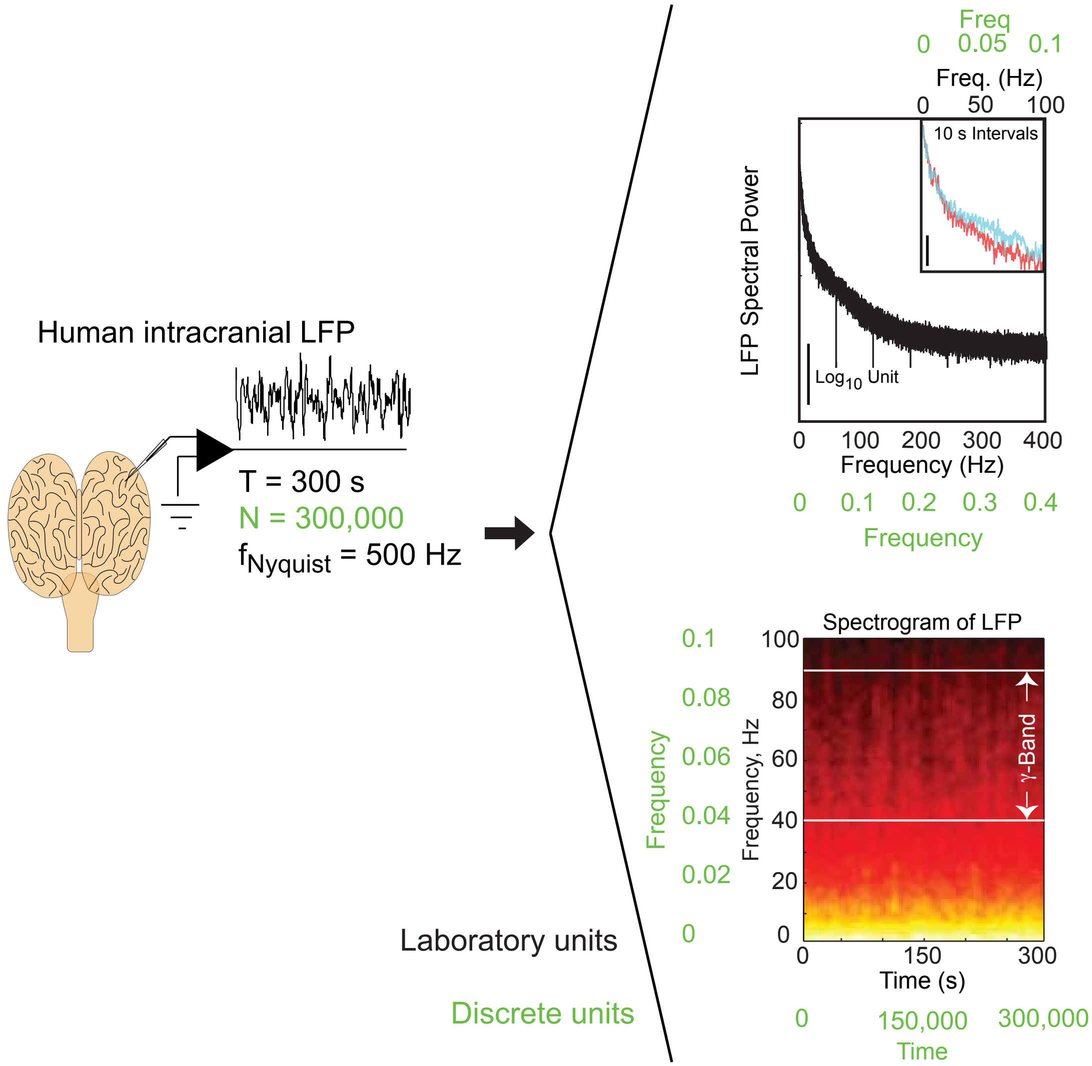

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Drew, Duyn, Galanov and Kleinfeld (2008)

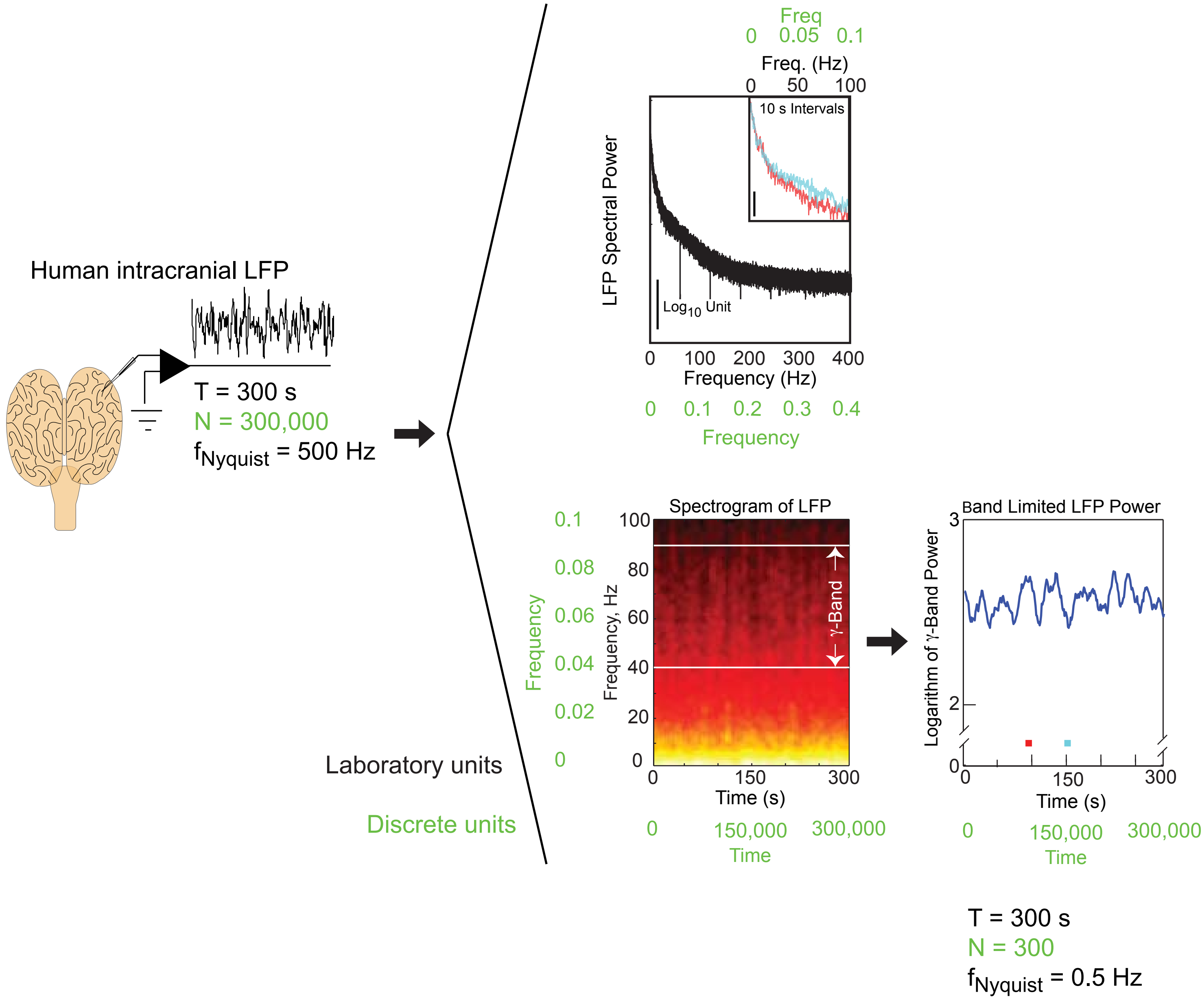
How do we characterize the variations in power in the γ-band?

Treat the logarithm of the power in a band as a new signal, *i.e.*,

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

Spectrum of the new time series is called the "second-spectrum", *i.e.*,

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



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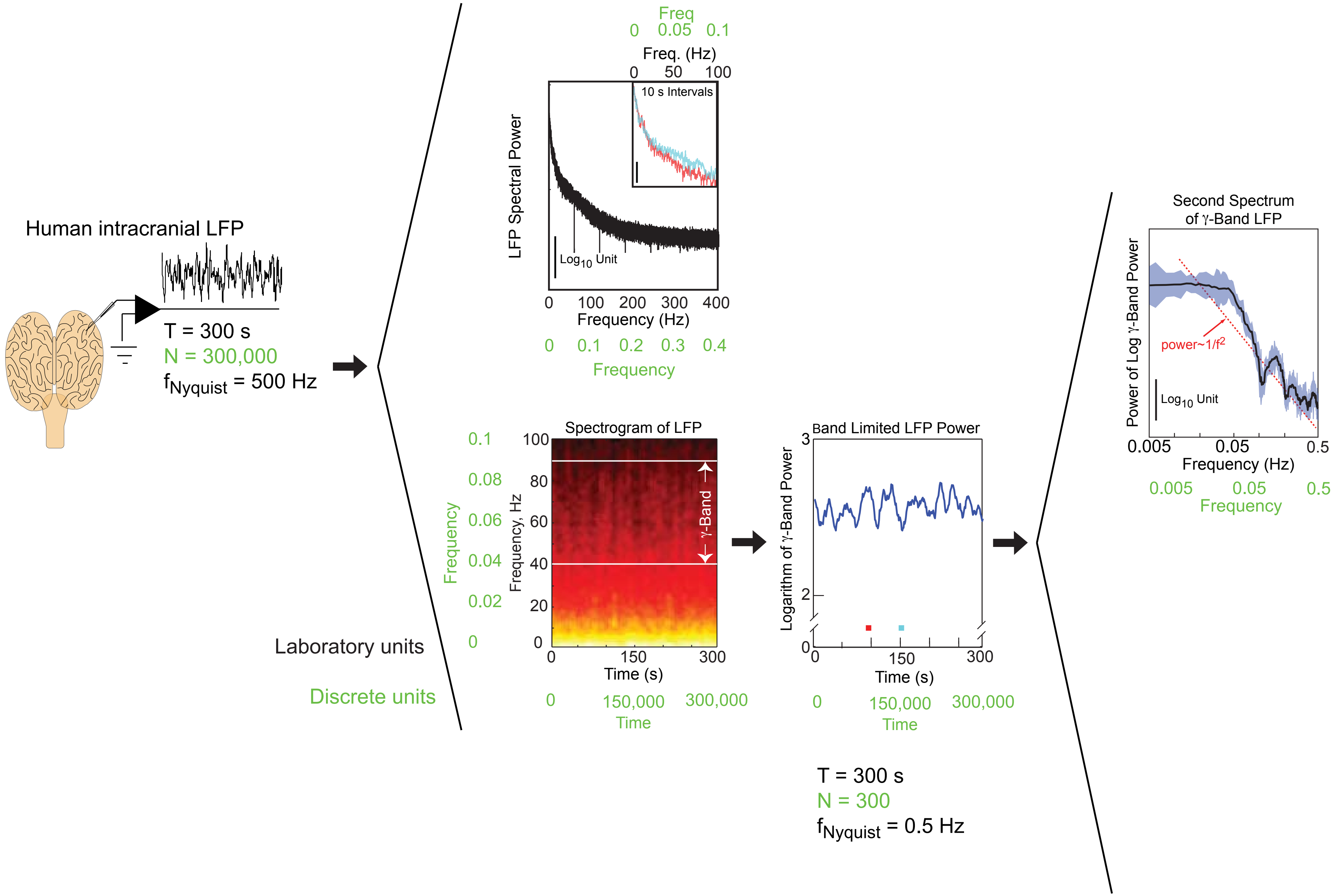


Nir, Mukamel, Dinstein, Privman, Harel, Fisch, Gelbard-Sagiv, Kipervasser, Andelman, Neufeld, Kramer, Arieli, Fried and Malach R (2008)
Drew, Duyn, Galanov and Kleinfeld (2008)

How do we calculate confidence intervals? Jackknife!

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

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

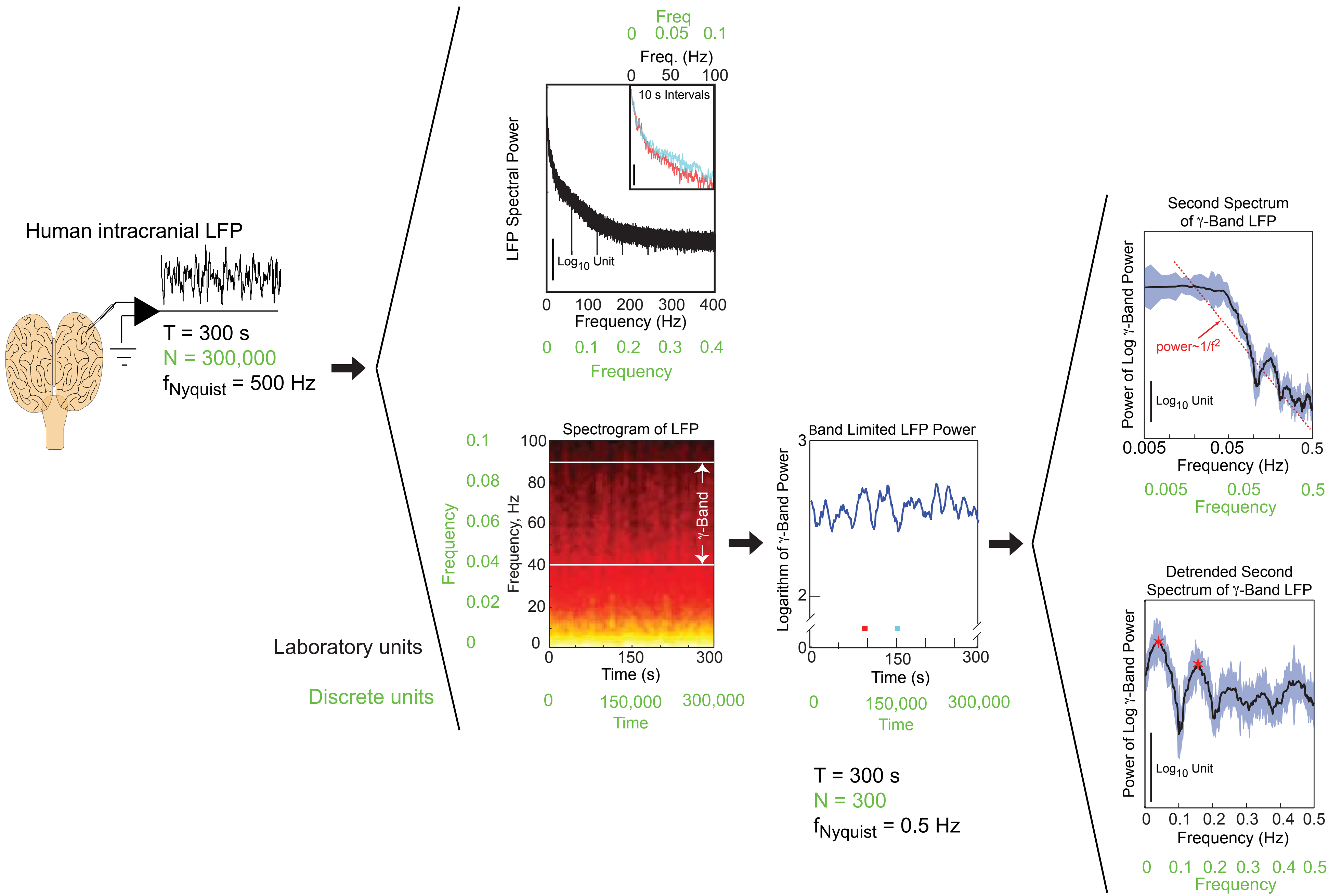
As amplitudes are defined on [0, ∞), not (-∞, ∞), the delete-one estimates are replaced with

$$g\left\{S(f)\right\} = \mathit{log}[S(f)] .$$

The mean and standard error of the transformed variable are

$$\mu_\gamma(f) = \frac{1}{K} \sum_{n=1}^{K} g\left\{S_\gamma^{(n)}(f)\right\} \text{ and } \sigma_\gamma(f) = \sqrt{\frac{K-1}{K} \sum_{n=1}^{K} \left| g\left\{S_\gamma^{(n)}(f)\right\} - \mu_\gamma(f) \right|^2} \quad .$$

The 95% confidence interval for the spectral power is thus $\left[e^{\mu_{i;Mag} - 2\sigma_{i;Mag}} , e^{\mu_{i;Mag} + 2\sigma_{i;Mag}} \right]$.



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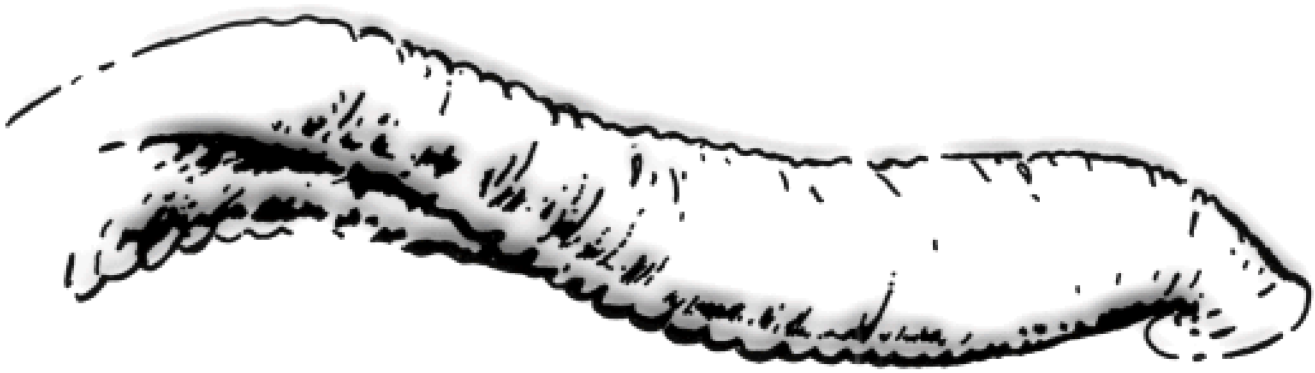
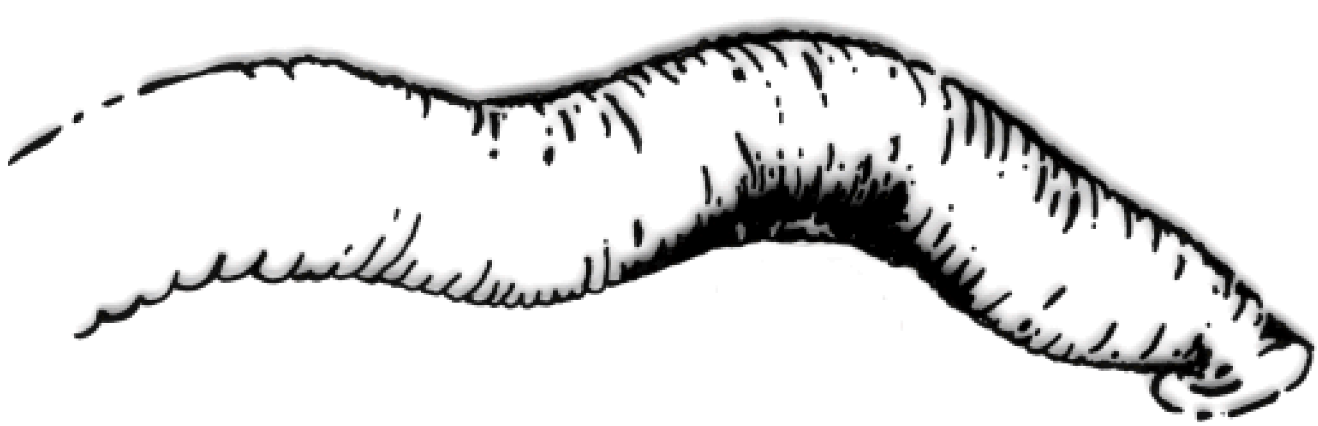
How to deduce synaptic connectivity between neurons in the leech swim network

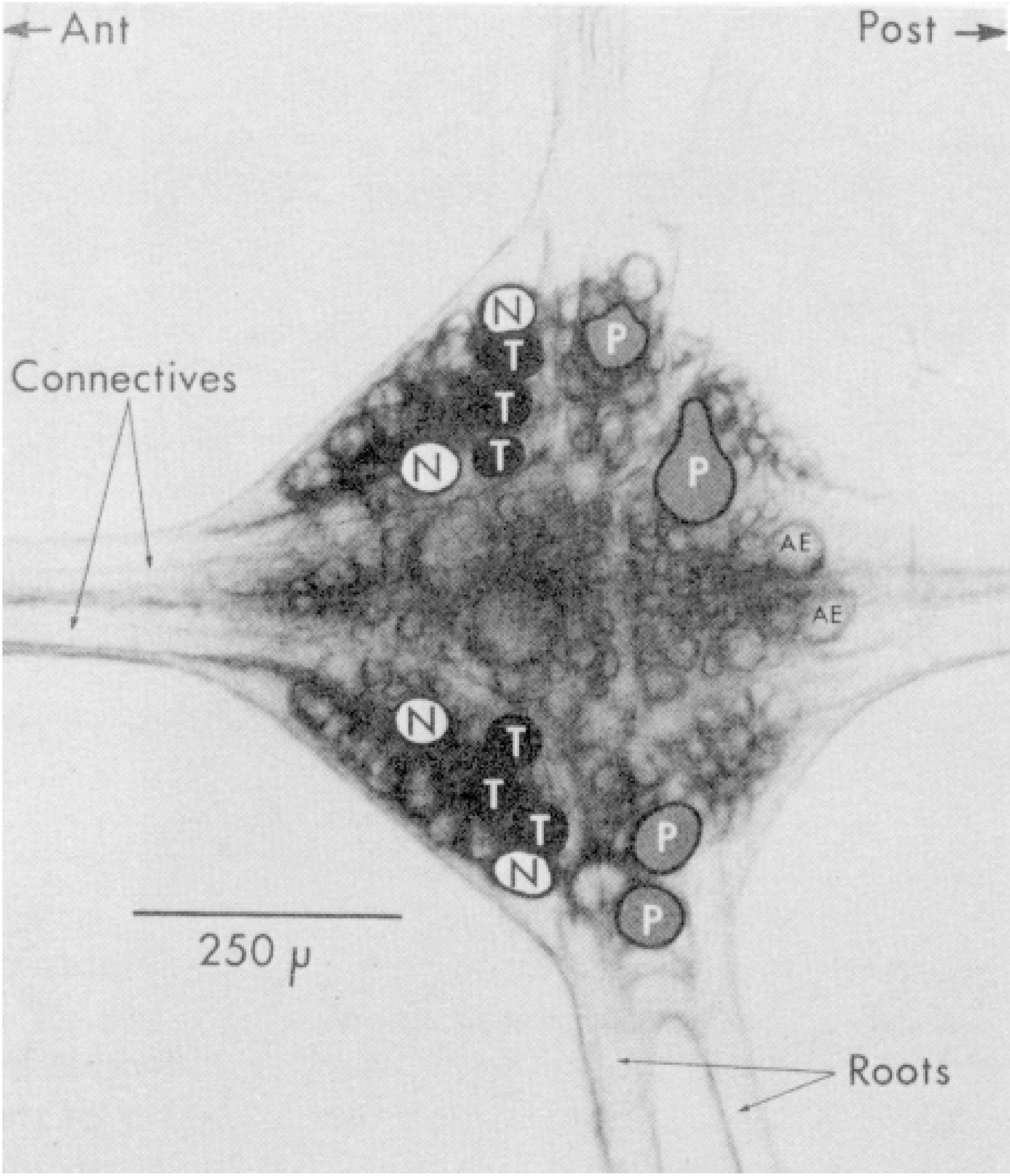
2

Think multisite measurements

Think spectral coherence and confidence levels







← Ant
Post →
Connectives
N
T
T
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N
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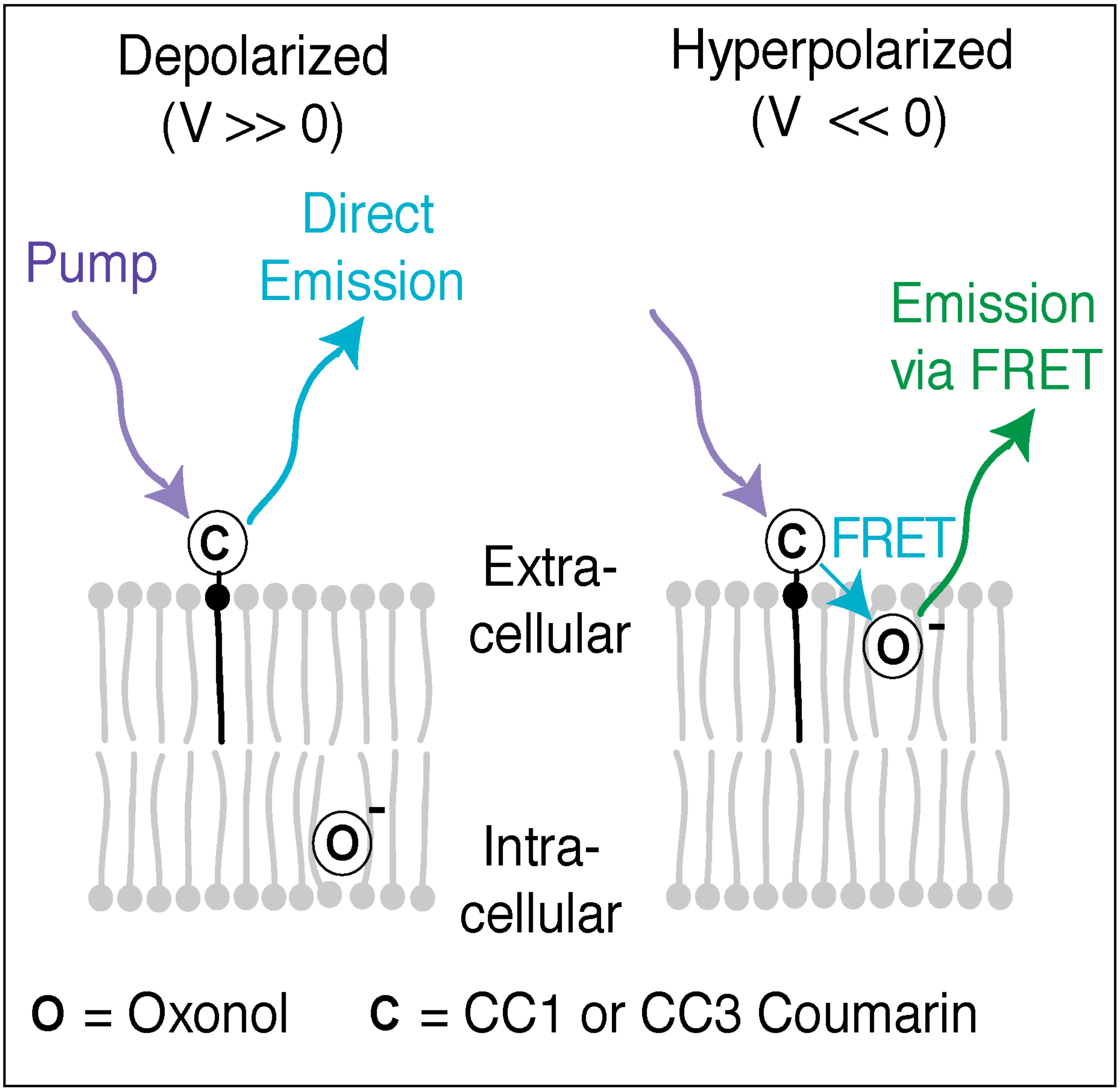
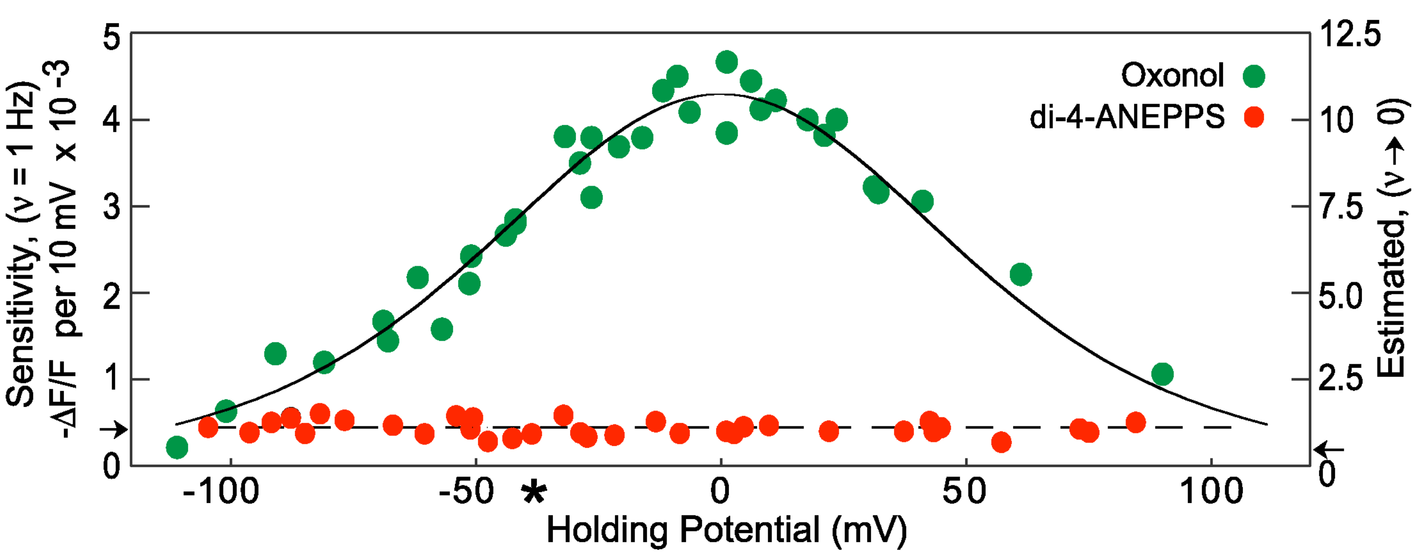
250 μ
Roots

Circuit Analysis with FRET-based Voltage Sensitive Dyes

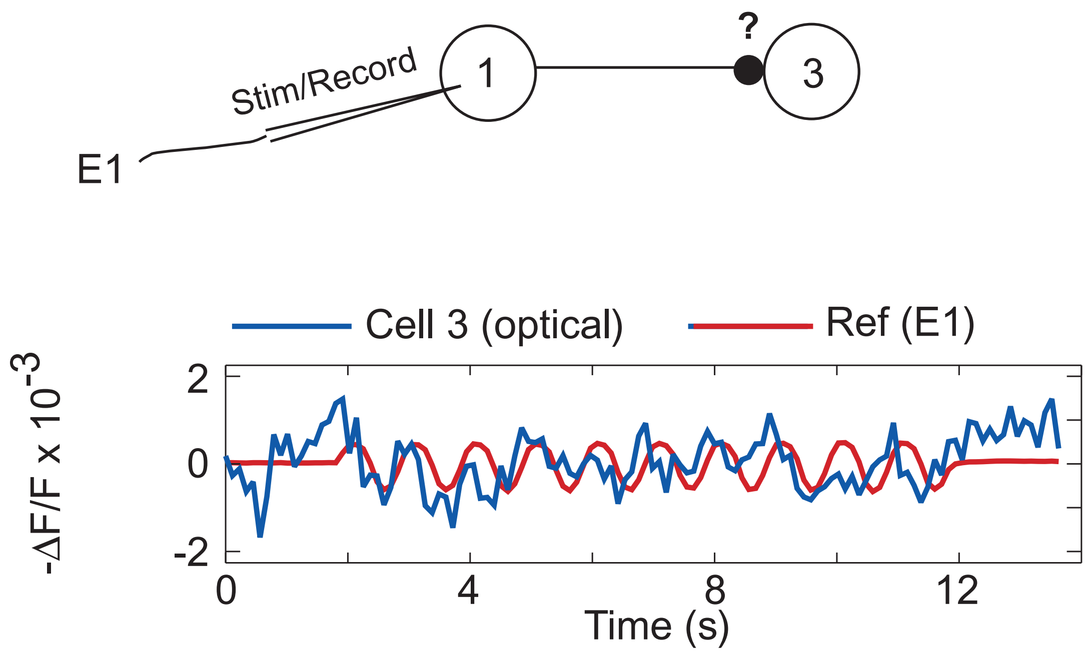




Cacciatore, Brodfueher, Gonzalez, Jiang, Adams, Tsien, Kristan Jr. and Kleinfeld (1999)

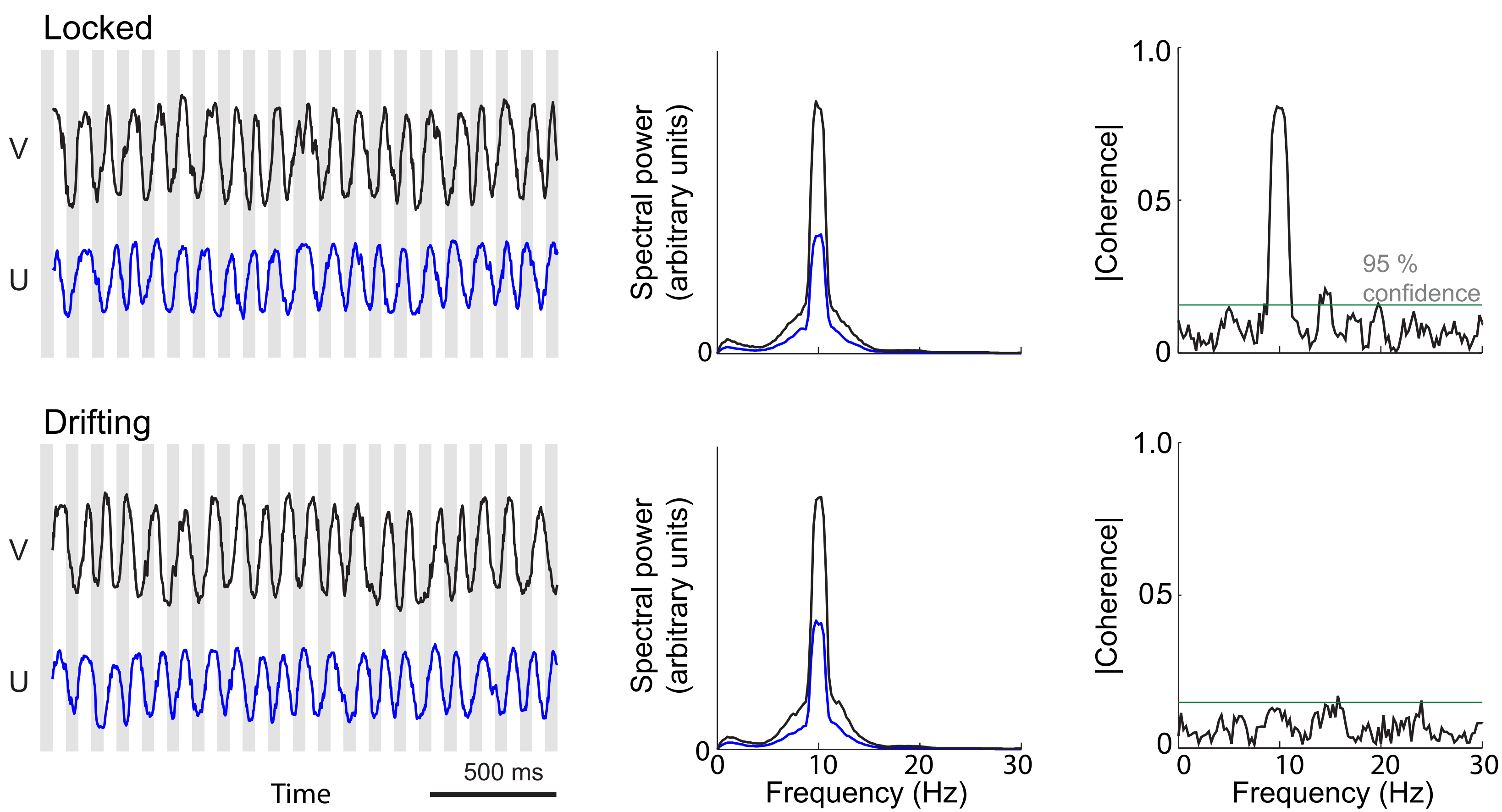
Idea:
Drive one cell and optically measure response in all others

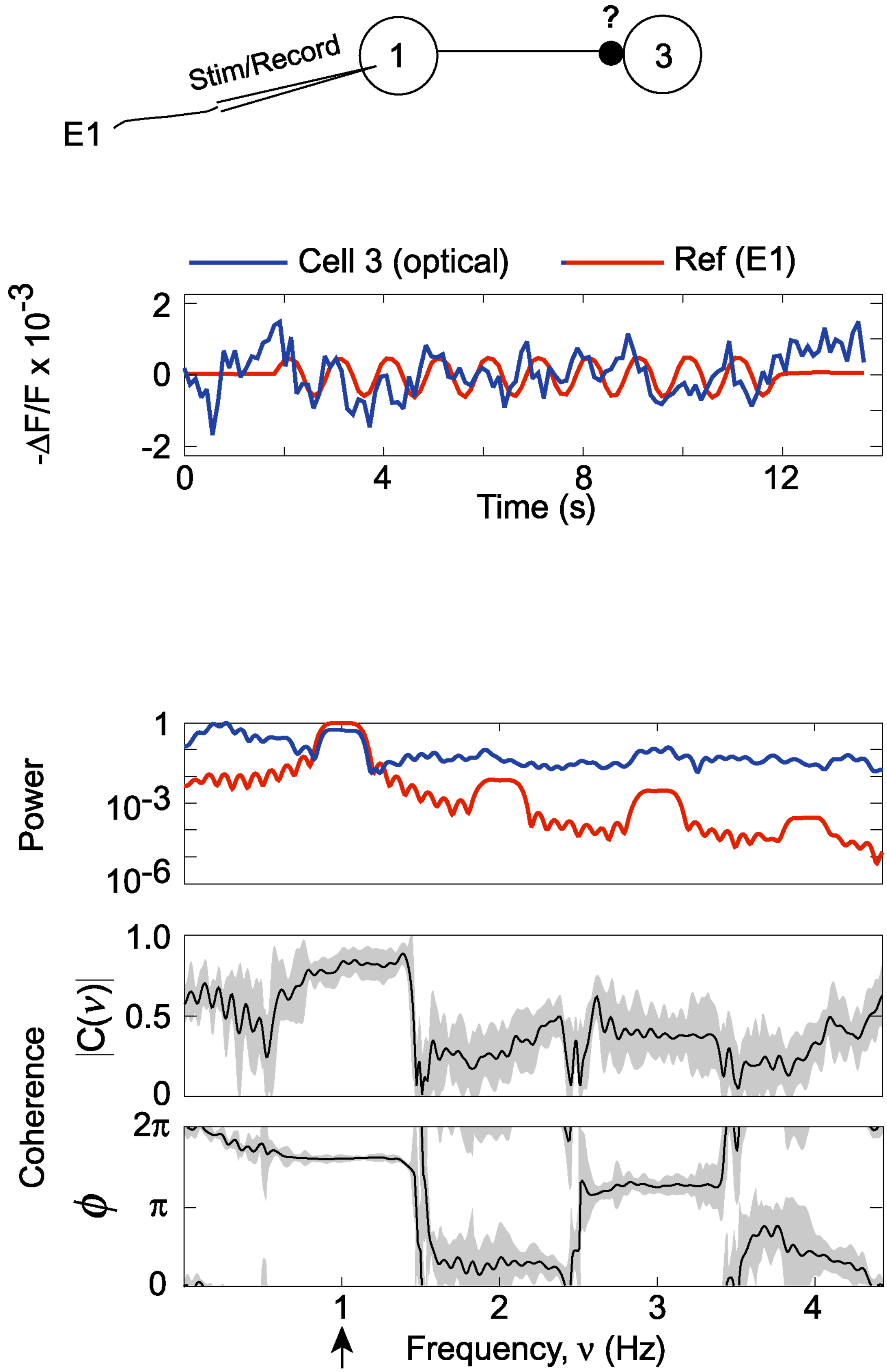
Example pair-wise data



How do we calculate coherence?

$$C\left(f\right) = \frac{\frac{1}{K}\sum_{k=1}^{K}\tilde{V}^{(k)}(f)\left[\tilde{U}^{(k)}(f)\right]^{*}}{\sqrt{\left(\frac{1}{K}\sum_{k=1}^{K}\left|\tilde{V}^{(k)}(f)\right|^{2}\right)\left(\frac{1}{K}\sum_{k=1}^{K}\left|\tilde{U}^{(k)}(f)\right|^{2}\right)}}$$





Stim/Record
E1
1
?
3
Cell 3 (optical)
Ref (E1)
-ΔF/F x 10-3
2
0
-2
0
4
8
12
Time (s)
Power
1
10-3
10-6
Coherence
|C(ν)|
1.0
0.5
0
φ
2π
π
0
1
2
3
4
Frequency, ν (Hz)

How do we calculate confidence intervals? Jackknife again!

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

$$C_i^{(n)}(f) = \frac{\frac{1}{K-1}\sum_{\substack{k=1\\k\neq n}}^{K} \tilde{V}_i^{(k)}(f)\left[\tilde{U}^{(k)}(f)\right]^*}{\sqrt{\left(\frac{1}{K-1}\sum_{\substack{k=1\\k\neq n}}^{K}\left|\tilde{V}_i^{(k)}(f)\right|^2\right)\left(\frac{1}{K-1}\sum_{\substack{k=1\\k\neq n}}^{K}\left|\tilde{U}^{(k)}(f)\right|^2\right)}} \quad \forall\, n.$$

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

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

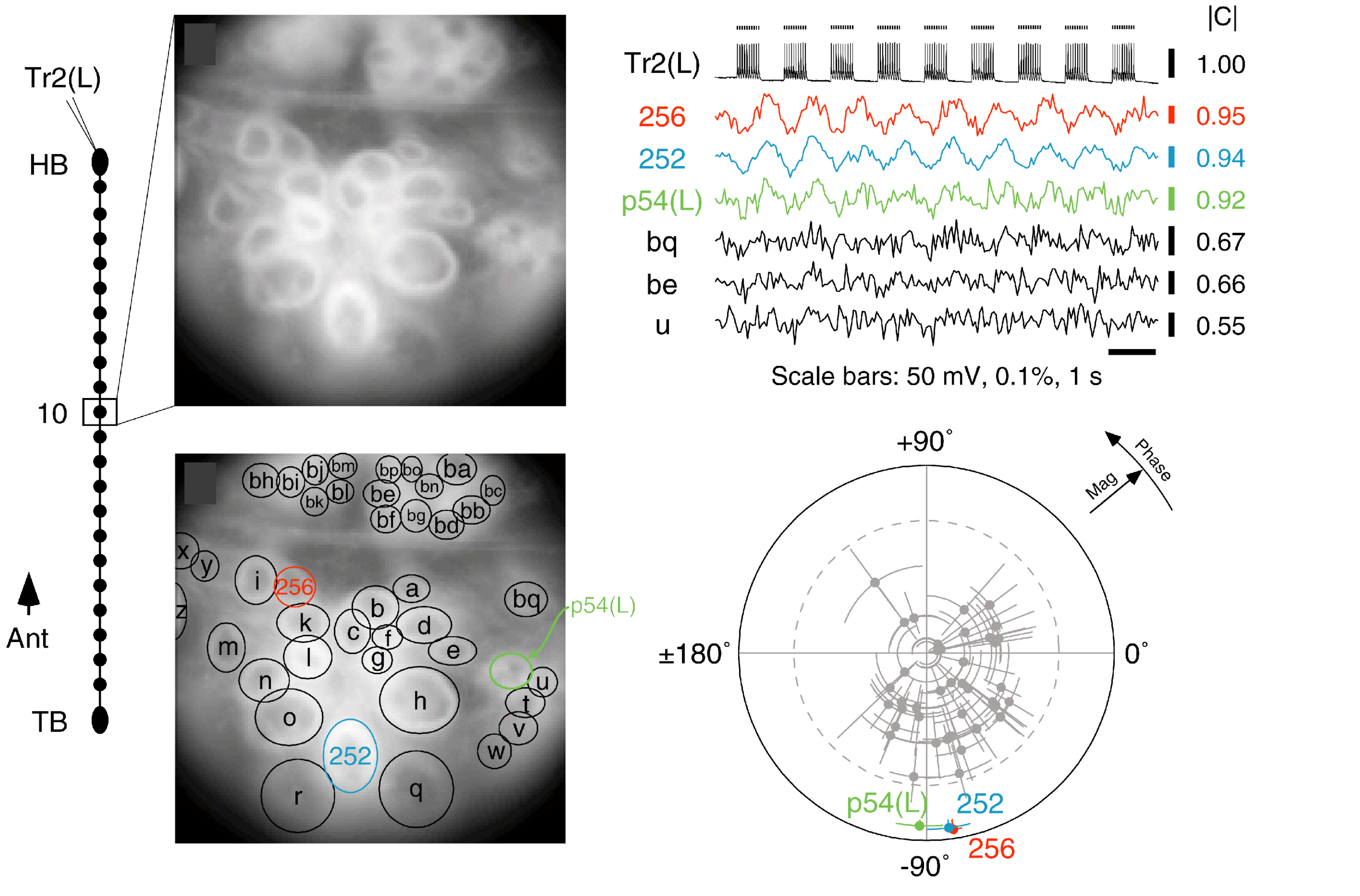
The 95% confidence interval for the coherence is thus $\left[\sqrt[-1]{1+e^{-(\mu_{i;Mag} - 2\sigma_{i;Mag})}},\ \sqrt[-1]{1+e^{-(\mu_{i;Mag} + 2\sigma_{i;Mag})}}\right]$.

How do we calculate confidence intervals for the phase? Jackknife on unit vectors!

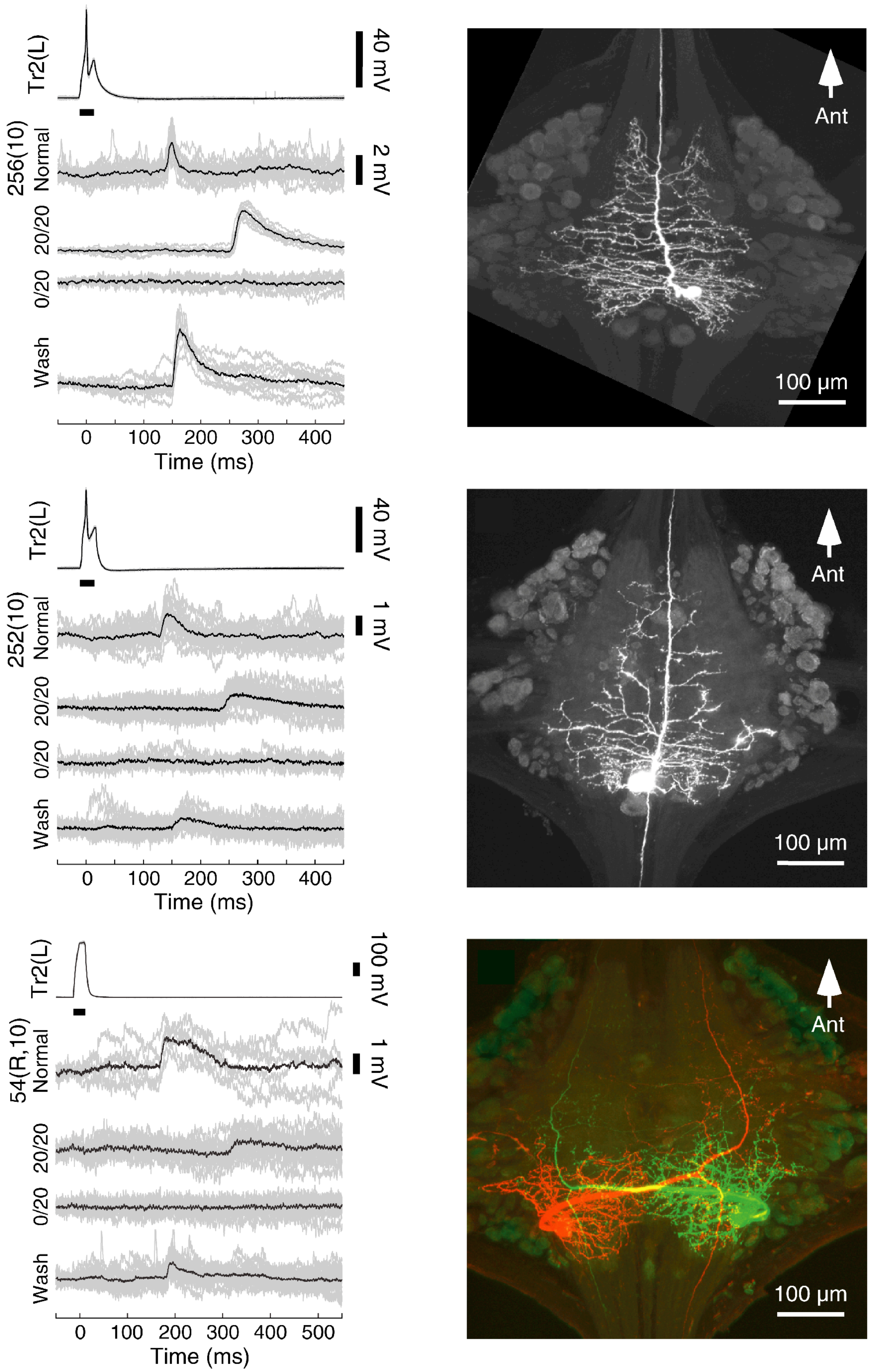
Idea is to compute the variation in the relative directions of the delete-one unit vectors, *i.e.*,

$$\sigma_{i;\,\text{Phase}}(f) = \sqrt{2\,\frac{K-1}{K}\left(K - \left|\sum_{n=1}^{K} \frac{C_i^{(n)}(f)}{\left|C_i^{(n)}(f)\right|}\right|\right)} \quad \forall\, n .$$

FRET-based Voltage Sensitive Dyes and Phase-Sensitive Detection for the Discovery of Novel Followers in Leech



Taylor, Cottrell , Kleinfeld and Kristan (2003)



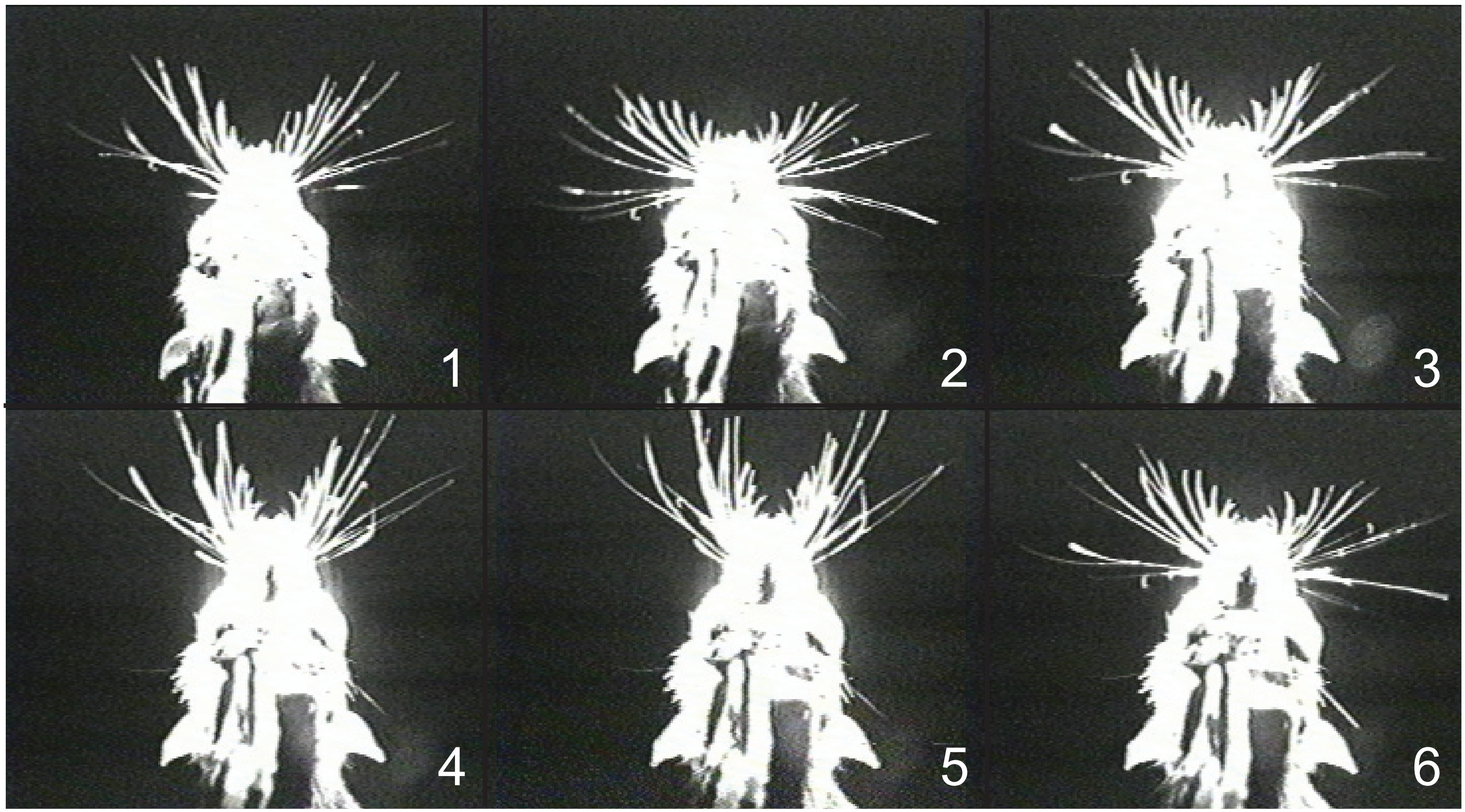
Taylor, Cottrell, Kleinfeld and Kristan (2003)

How to deduce neuronal coding for the pitch of vibrissa movement

3

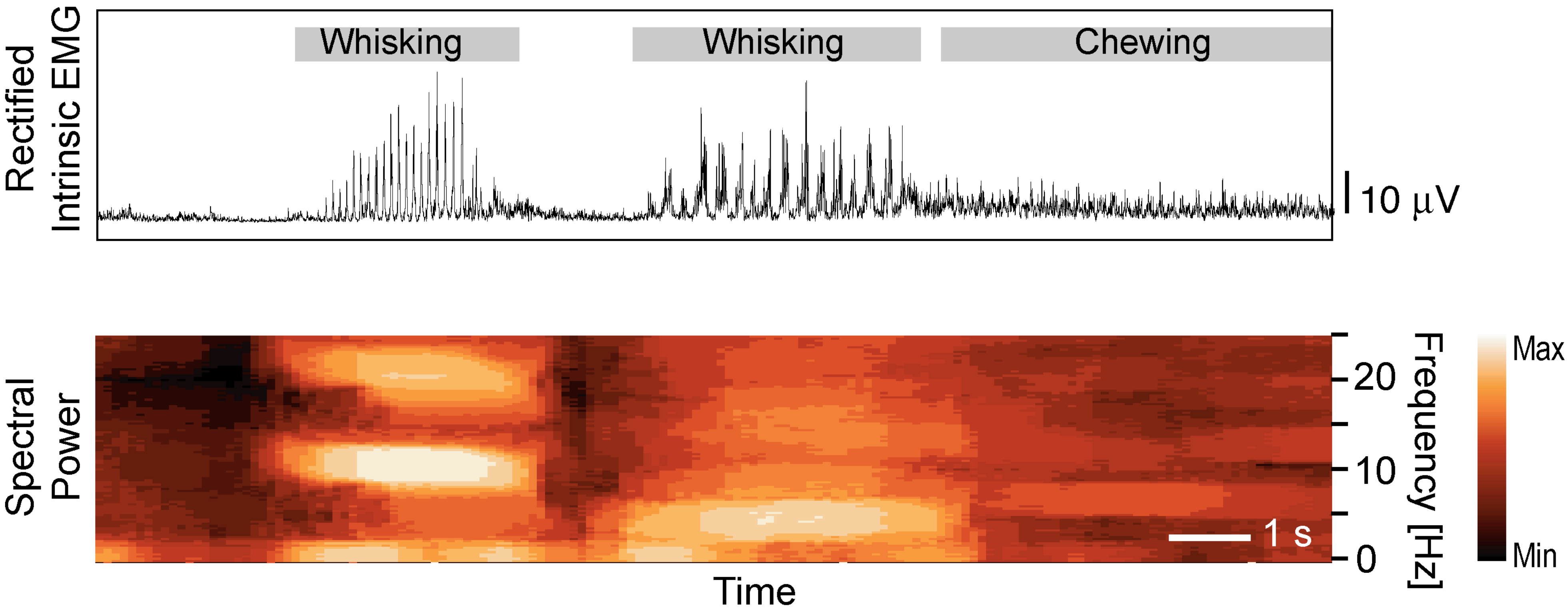
Think spectral power as the sum of pure tones, and slowly evolving pink background noise

The Fusion of Touch and Motion Signals in the Rat Vibrissa Sensorimotor System



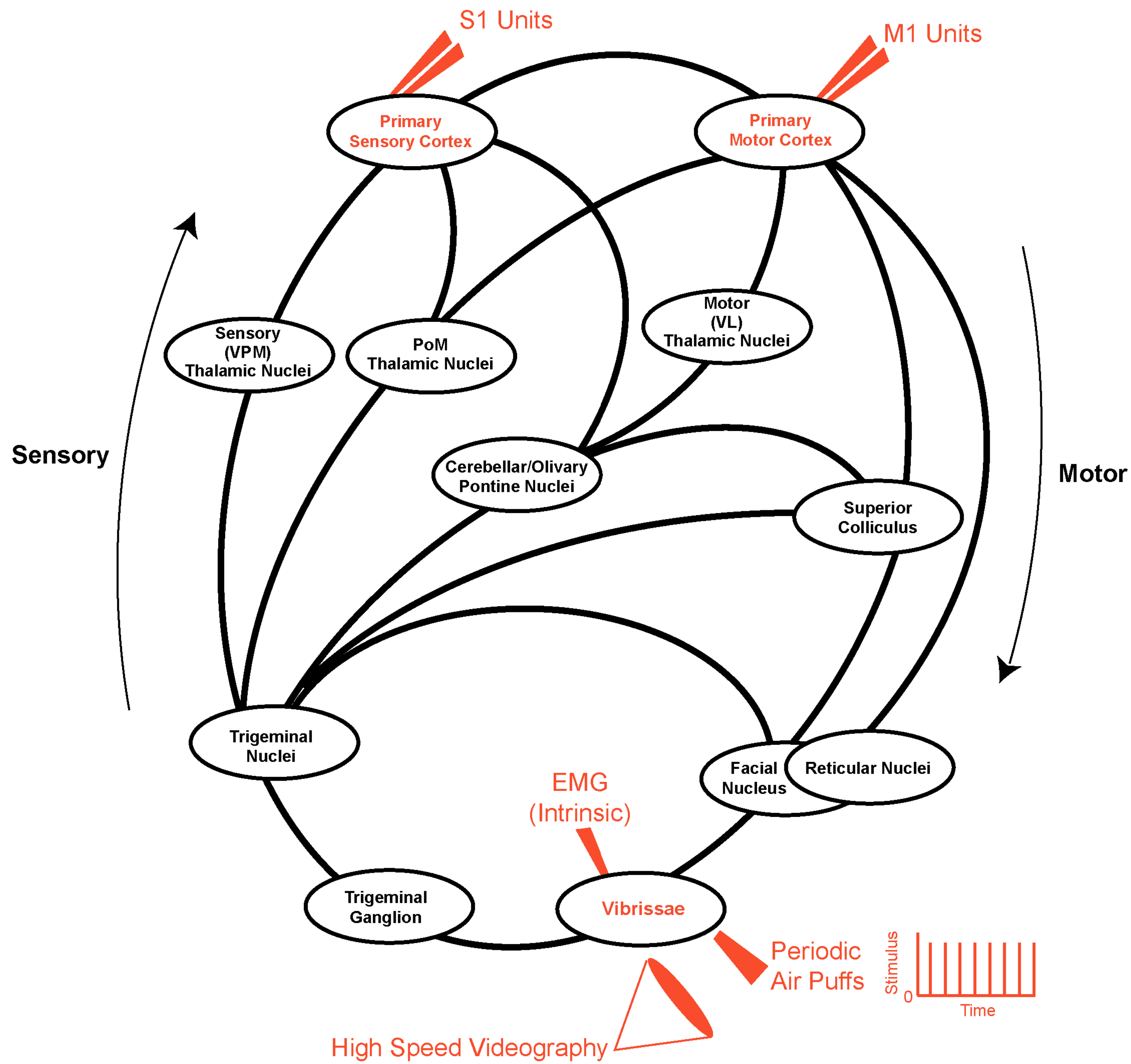
Consecutive Video Rate Fields (60 Hz acquisition) of a free ranging rat (blindfolded) that is whisking in air in search of a foodtube

The Frequency of Whisking is Constant within an Epoch but Broadly Distributed from Epoch to Epoch

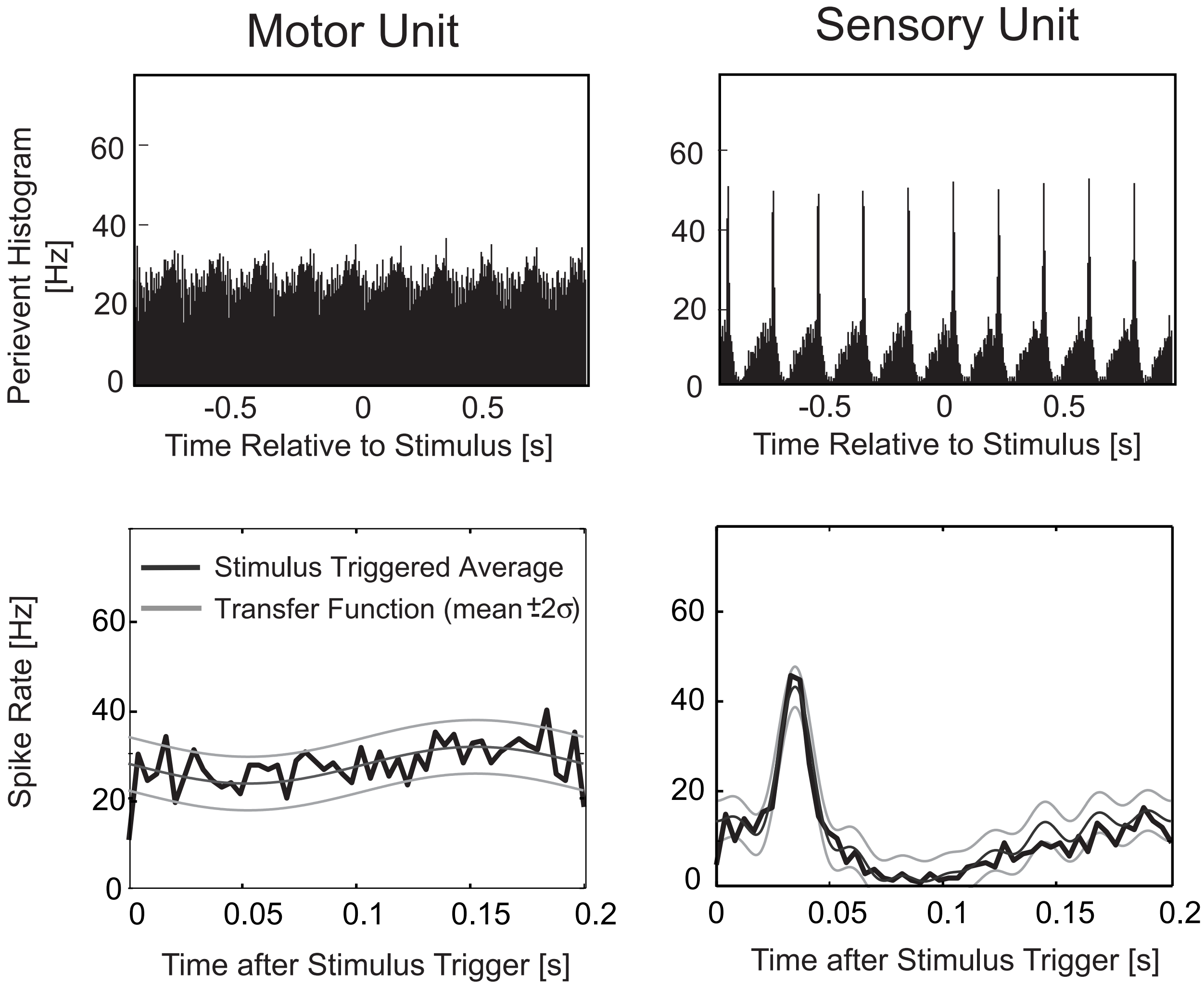


O'Connor, Berg and Kleinfeld 2001

Stimulus Induced Spiking in M1 vs. S1 Vibrissa Cortex in the Aroused Rat

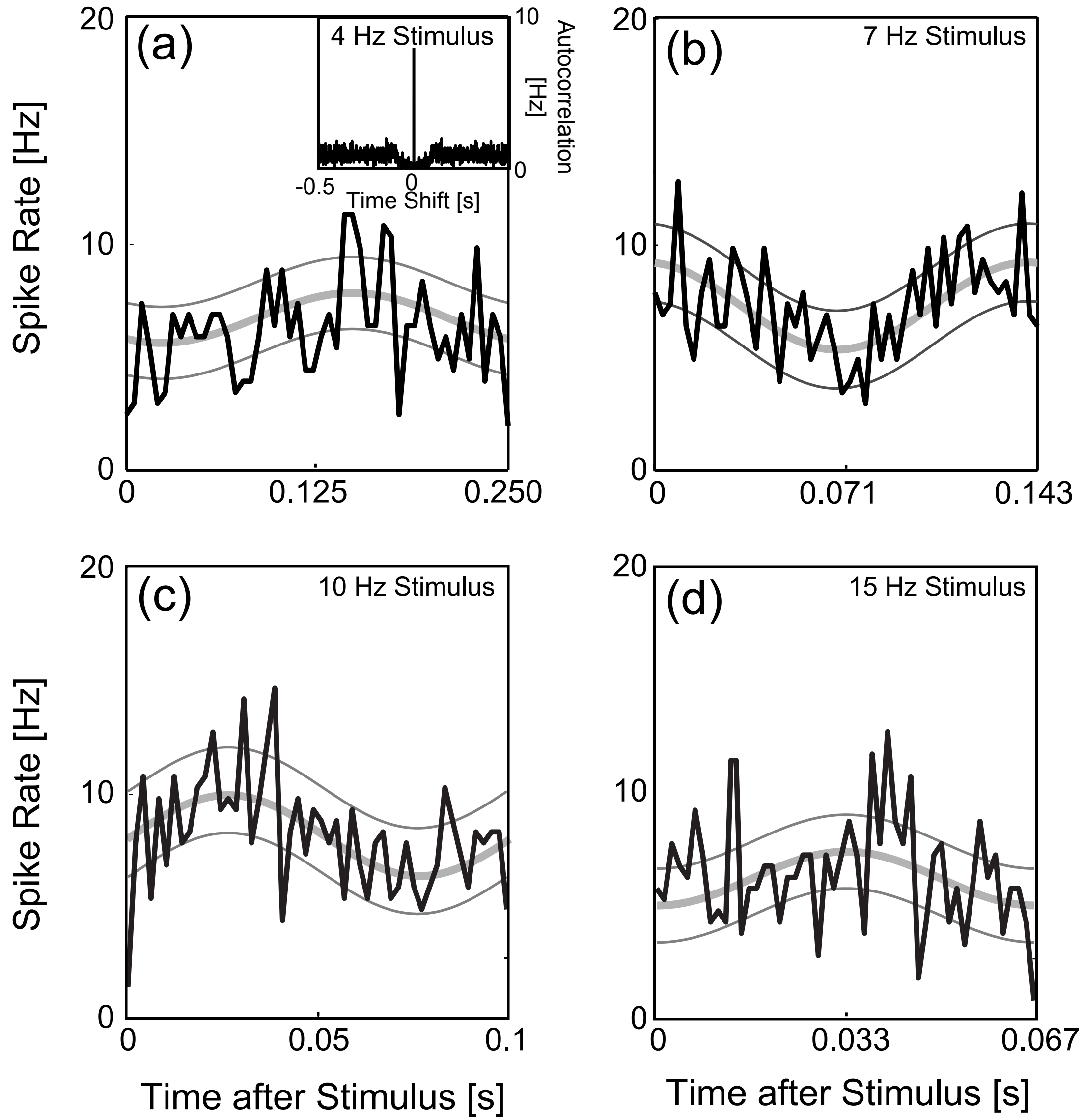


Response of Motor (M1) versus Sensory (S1) Cortical Units



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, *i.e.*,

$$V(t) = A_1 \, cos(2\pi f_1 t + \varphi_1) + \eta(t).$$

The goal is to determine coefficientsA_1 and ϕ_1 by regression.

With the replacement $B_1 = \frac{A_1}{2} e^{i\varphi_1}$ 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 $2 f_1 > f_1 + W$ 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.

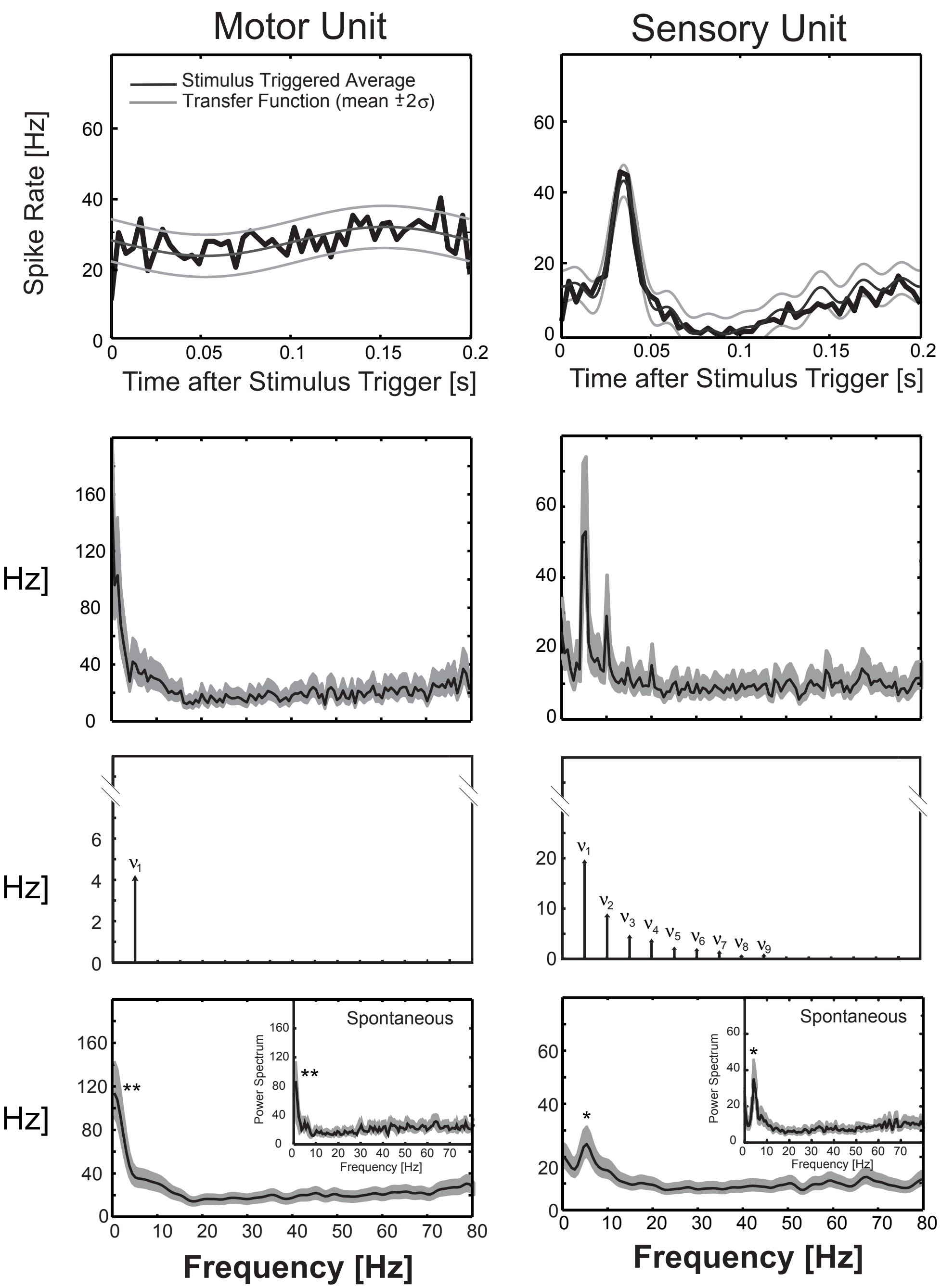
The least-squares estimate of B_1 is

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

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

$$F_{2,\,2K\text{-}2} = \left|\hat{B}_1\right|^2 \frac{(K\text{-}1)\sum_{k=1}^{K}\left|\tilde{w}^{(k)}(0)\right|^2}{\sum_{k=1}^{K}\left|\tilde{V}^{(k)}(f_1) - \hat{V}^{(k)}(f_1)\right|^2}$$

Spectral Analysis (Power and Transfer Functions) of Spike Trains



Spectral Power Density [Spikes ^{2}/ Hz]

= Driven Density [Spikes ^{2}/ Hz]

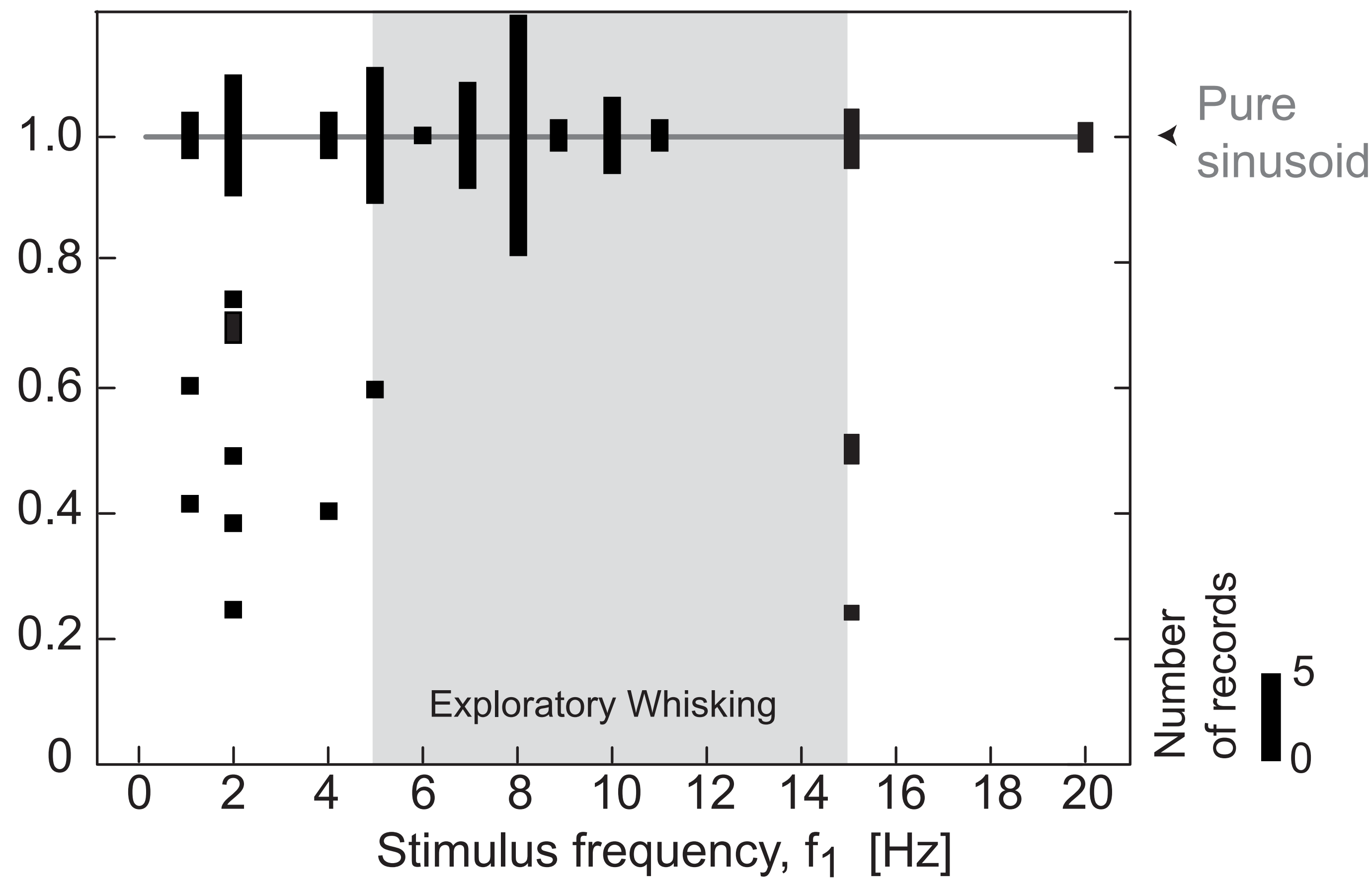
+ Residual Density [Spikes ^{2}/ Hz]

Kleinfeld, Sachdev, Merchant, Jarvis and Ebner - 2002

Response of Units in M1 Vibrissa Cortex is Sinusoidal
(Fundamental Frequency of a Harmonic Spectrum)
for a Broad Range of Stimulation Frequencies

Fraction of response at stimulus frequency

$$\hat{C}\left(f_1\right) = \frac{\left|\hat{B}\left(f_1\right)\right|^2}{\sum_{m=1}^{M}\left|\hat{B}\left(mf_1\right)\right|^2}$$



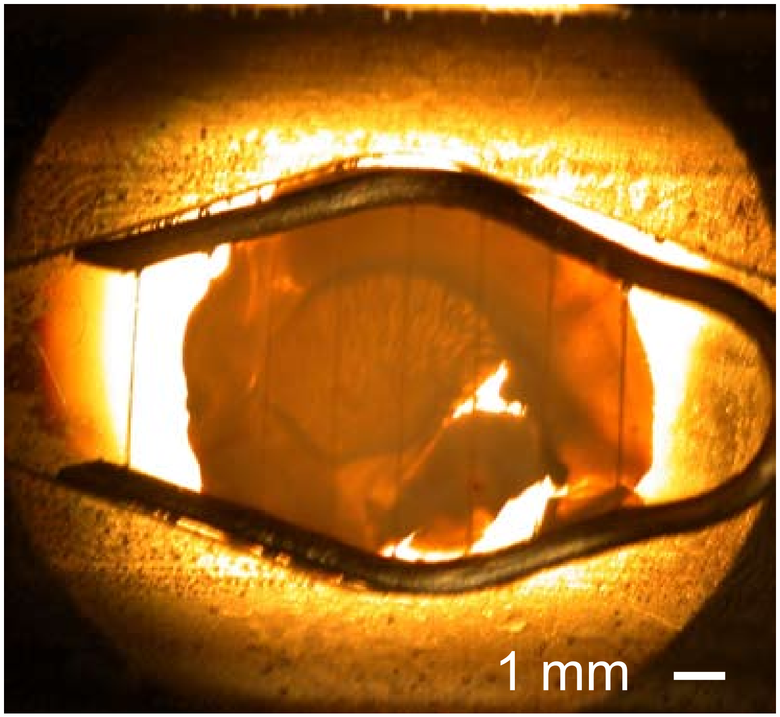
Kleinfeld, Sachdev, Merchant, Jarvis and Ebner - 2002

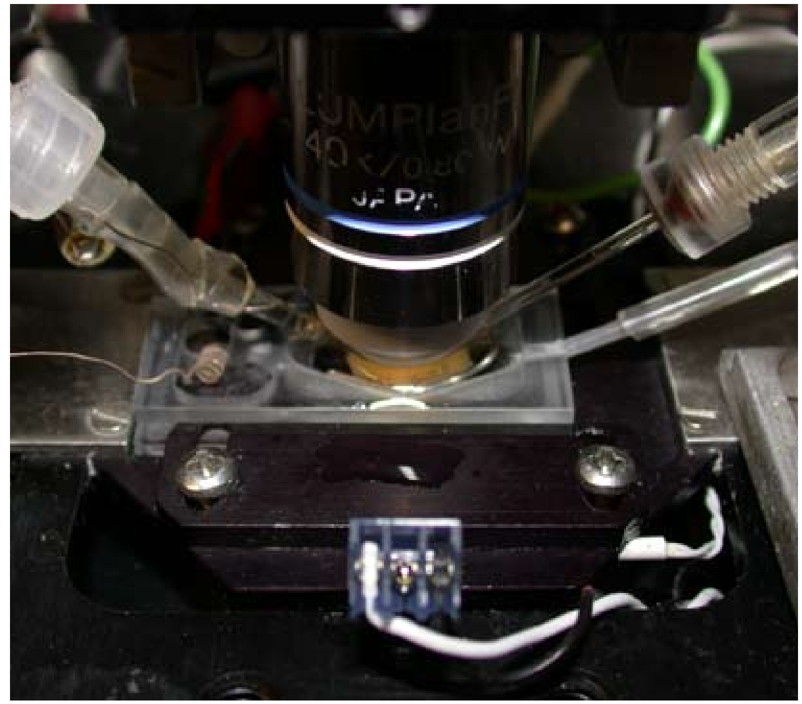
How to denoise confocal imaging data in the study of calcium waves

4

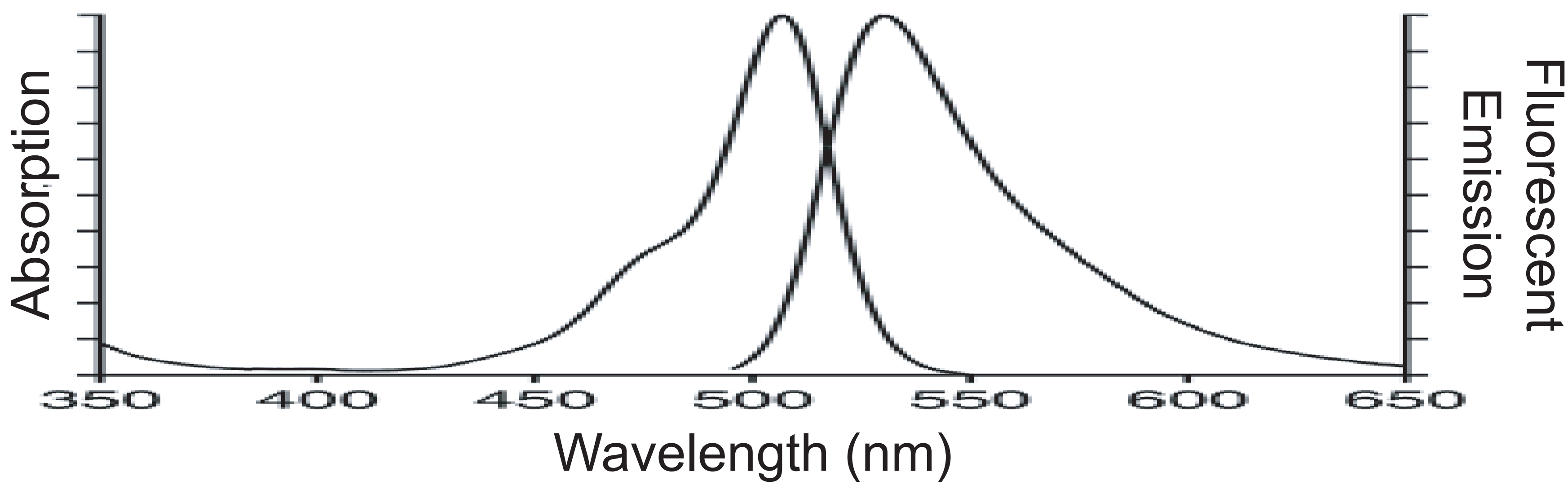
Think singular value decomposition (SVD) to represent space-time correlations in multi-site measurements

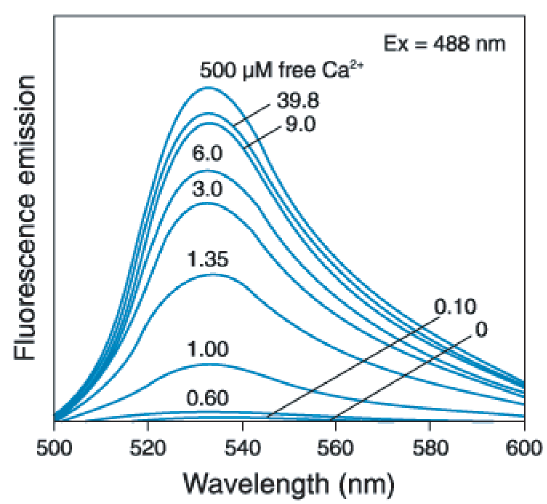
In Vitro Neocortical Slice Preparation





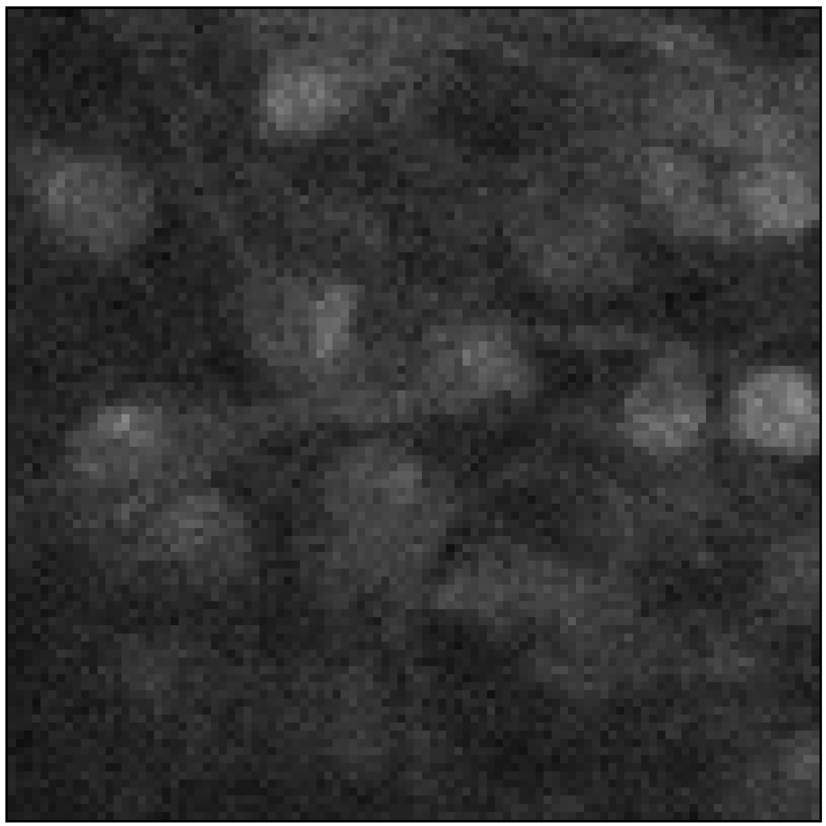
Optical Properties of Ca-Green 2





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.*,

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

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

Temporal functions satisfy the eigenvalue equation

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

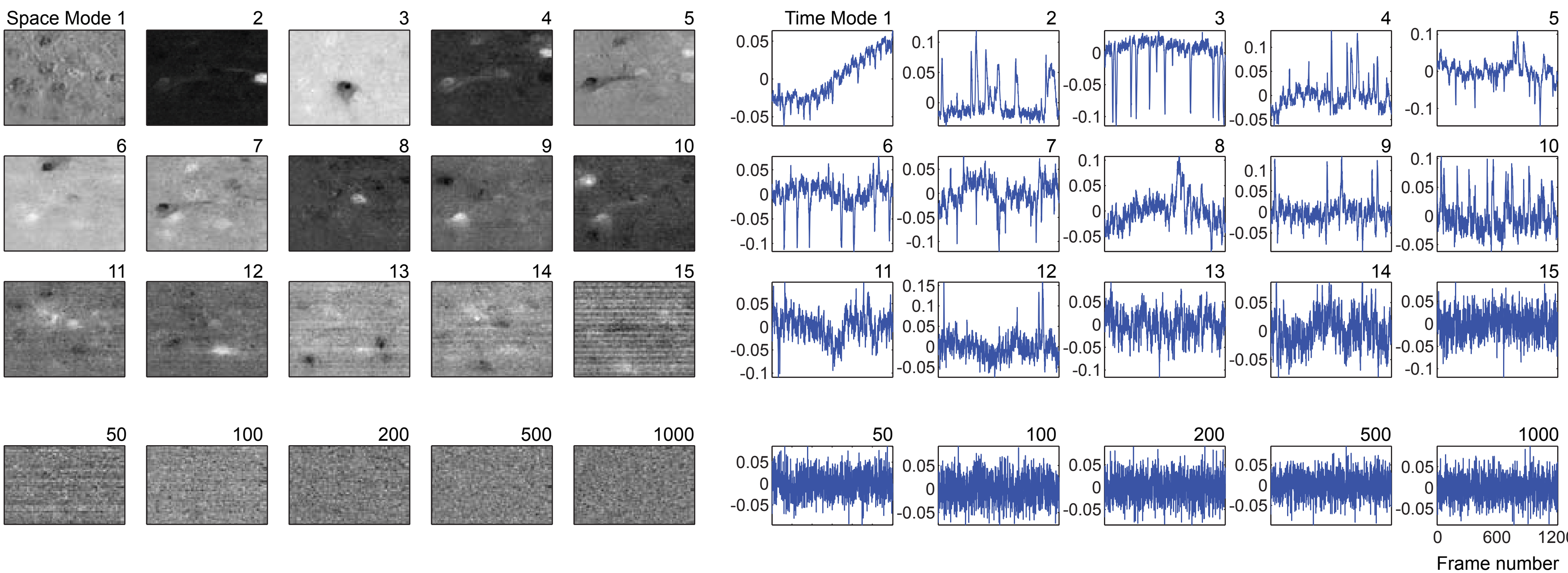
where

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

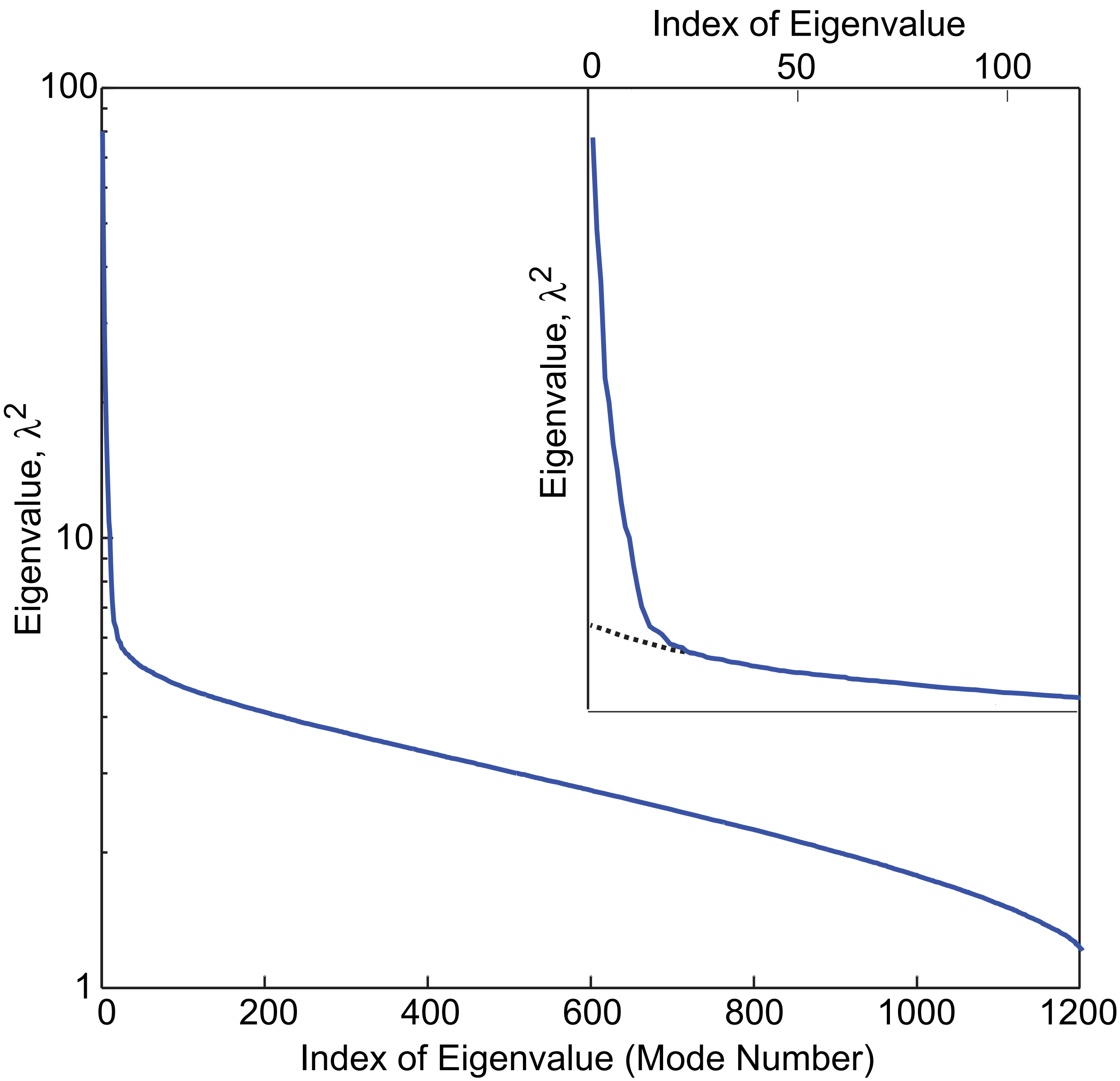
The spatial function that accompanies each temporal function are

$$F_n(s) = \frac{1}{\lambda_n} \sum_{t=1}^{N_t} V(s, t) \, G_n(t) \; .$$

Spatial and Temporal Modes for Ca^{2+} Imaging Data



Spatial and Temporal Modes for Ca^{2+} Imaging Data



How do we denoise data?

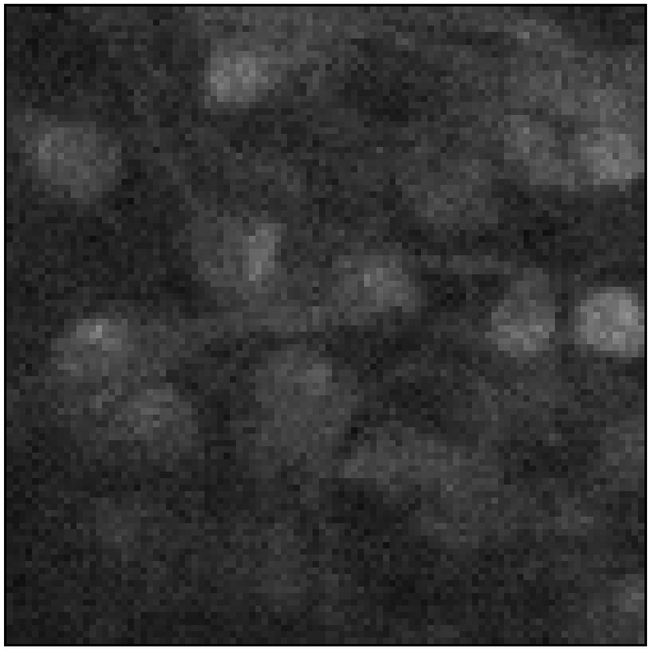
Utility of SVD is that only the lower-order modes carry information.

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

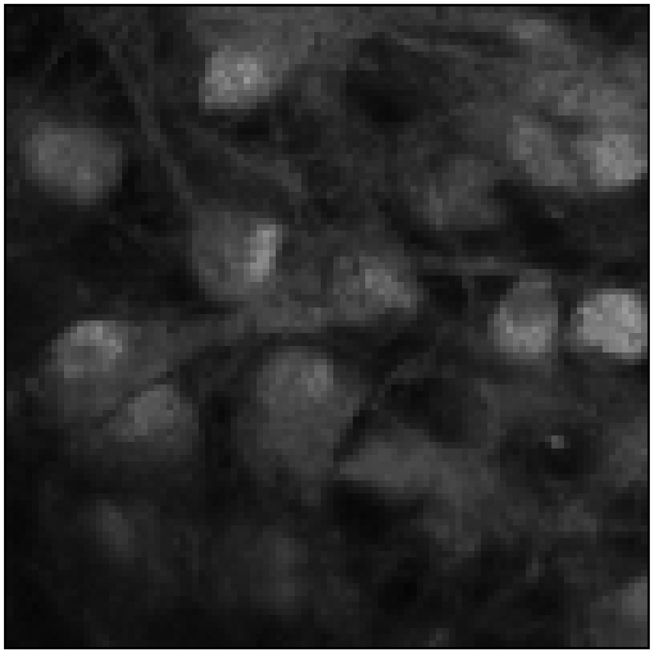
$$V^{\text{reconstructed}}\left(s, t\right) = \sum_{n=1}^{\text{largest signficant mode}} \lambda_n \, F_n(s) \, G_n(t)$$

Intracellular Calcium in Acute Hippocampal Slice

The Raw



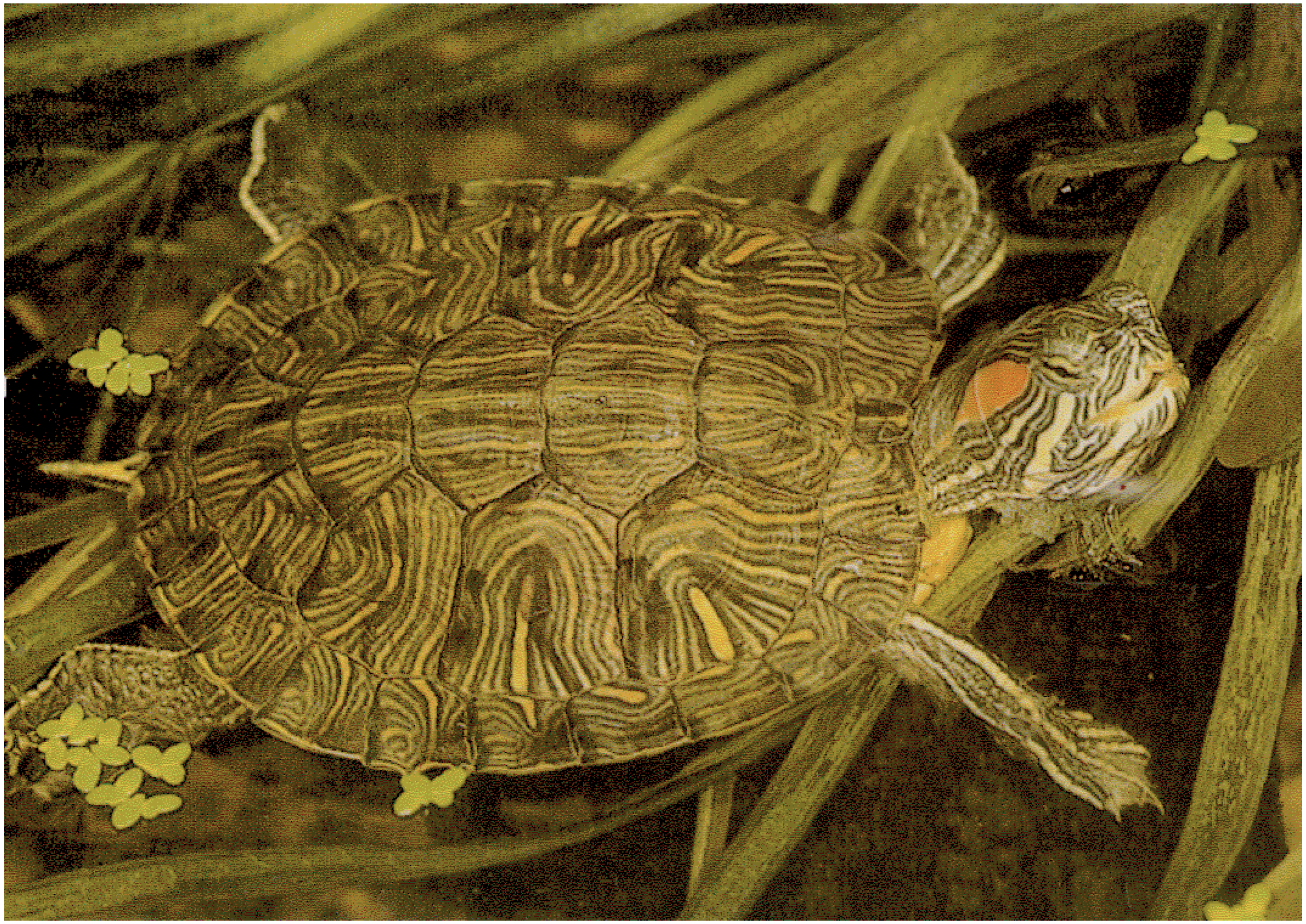
The Cooked



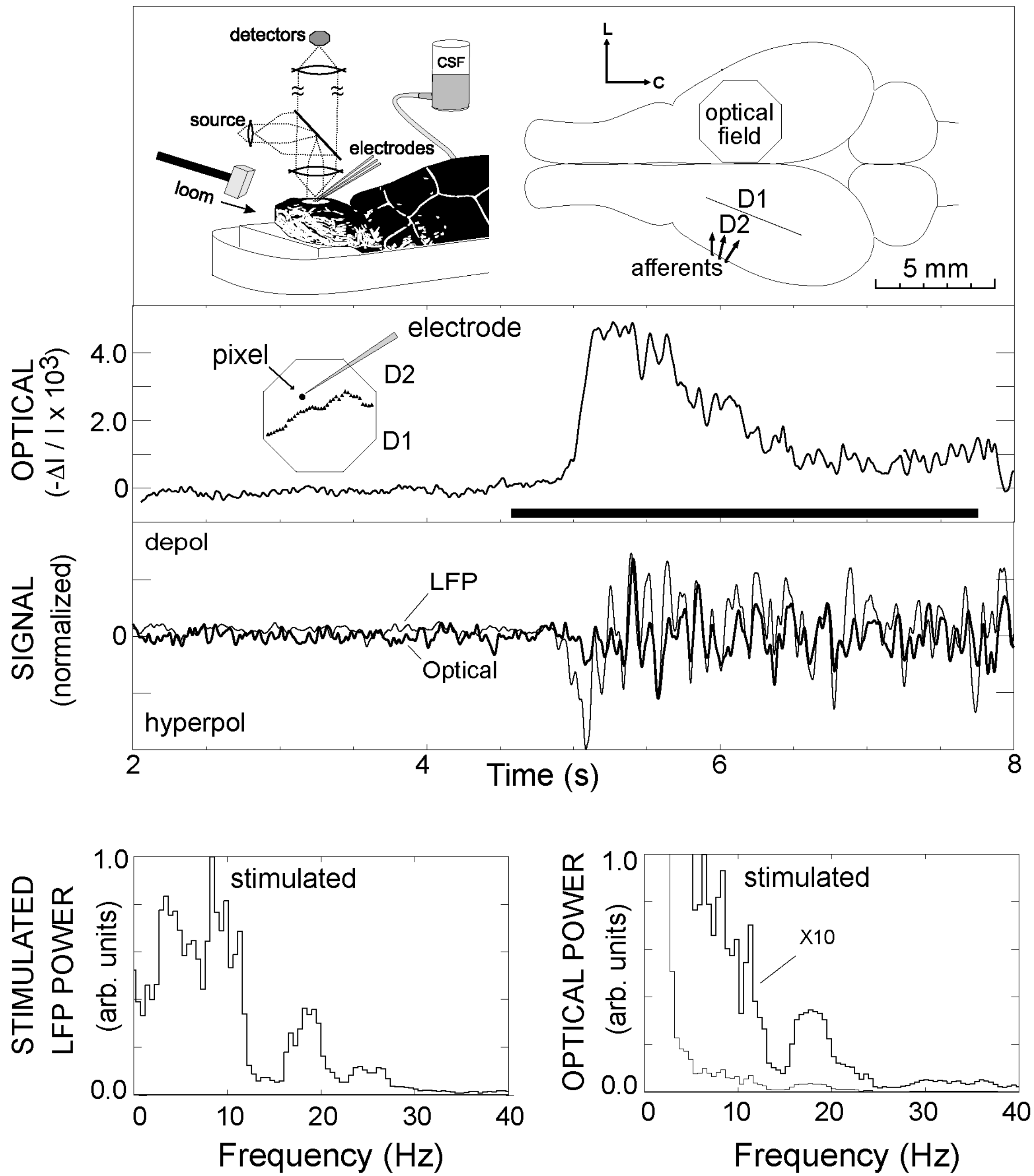
How to delineate electrical wave phenomena in turtle visual cortex

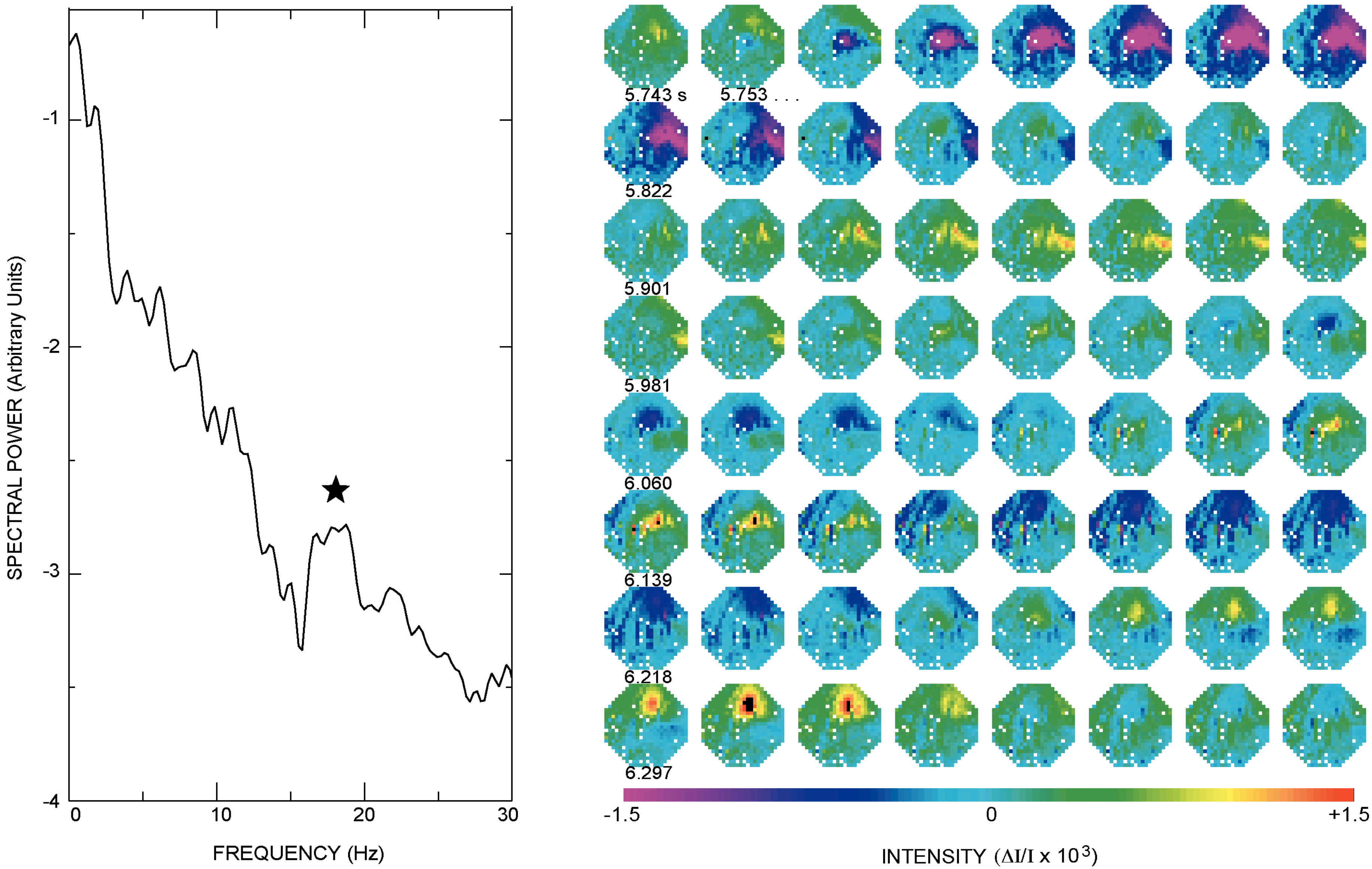
5

Think SVD to represent space-frequency correlations across multi-site measurements



Voltage Sensitive Dye Imaging of Turtle Visual Cortex





SPECTRAL POWER (Arbitrary Units)
-1
-2
-3
-4
0
10
20
30
FREQUENCY (Hz)
5.743 s
5.753 . . .
5.822
5.901
5.981
6.060
6.139
6.218
6.297
-1.5
0
+1.5
INTENSITY (ΔI/I x 10³)

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.*,

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

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:

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

This yields

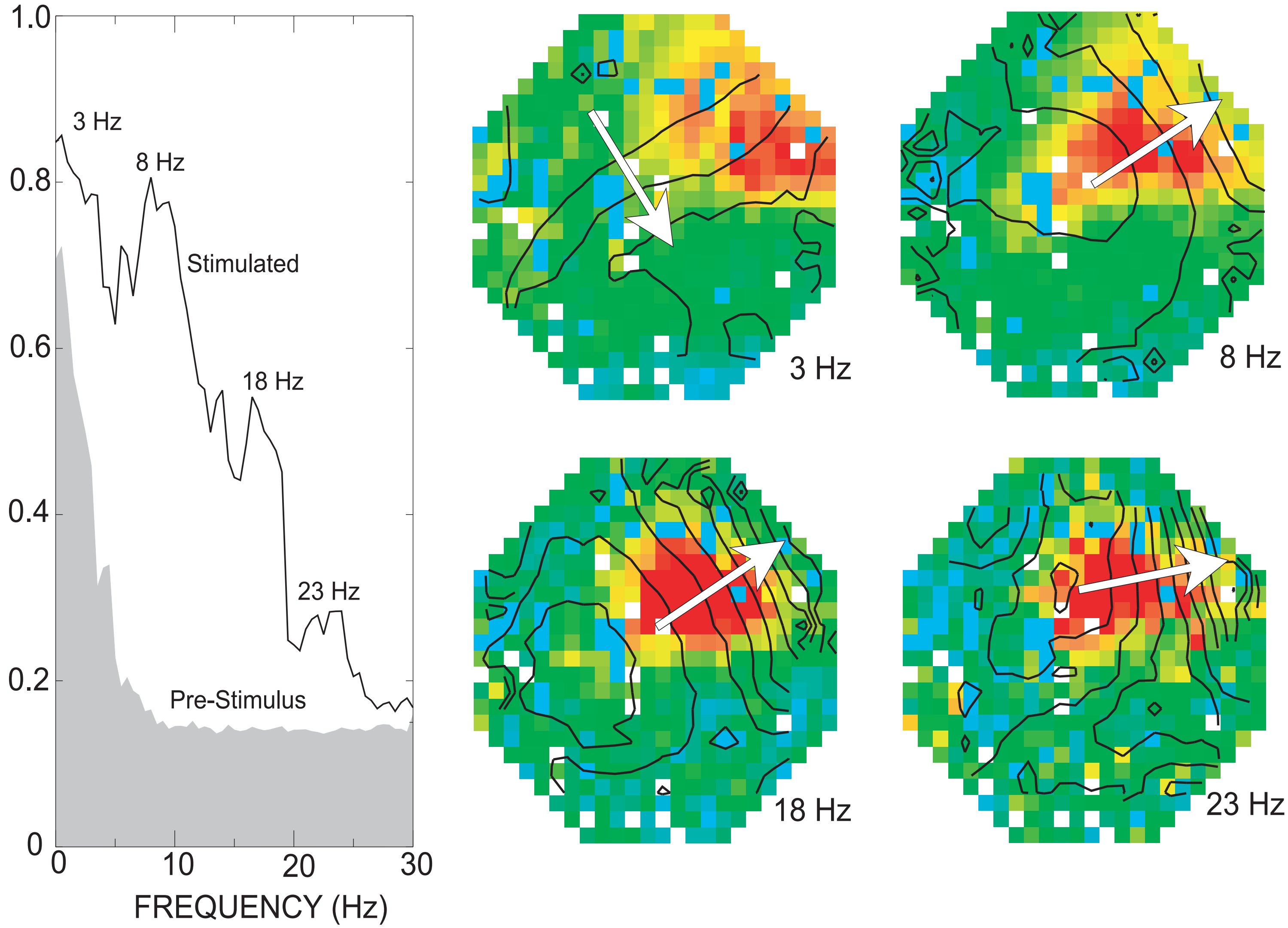
$$\tilde{V}\left(s, k; f_0\right) = \sum_{n=1}^{\mathrm{rank}\{\tilde{V}\}} \lambda_n\, \tilde{F}_n(s)\, \tilde{G}_n(k)$$

where the rank is invariably set by K.

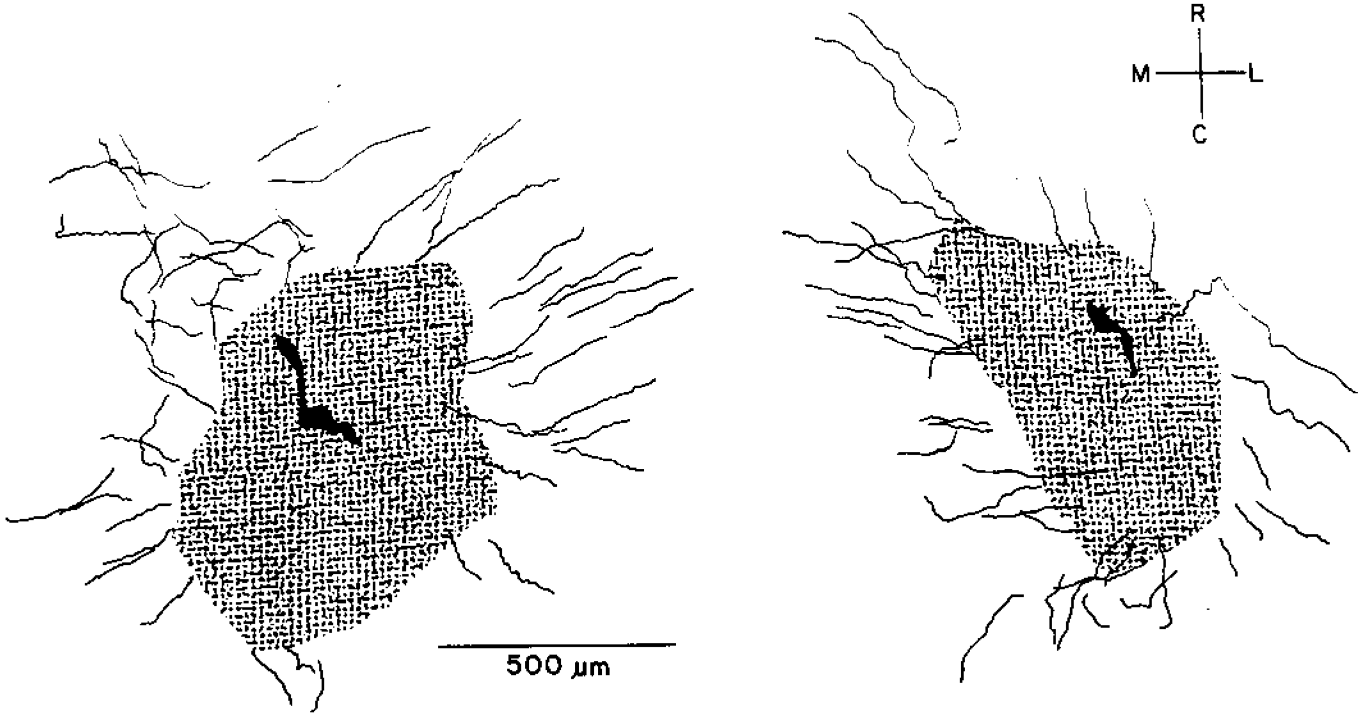
Dominant Modes from a SVD in Space and Temporal Frequency

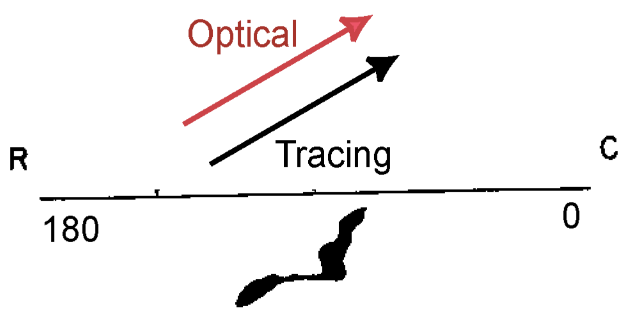
SPATIAL COHERENCE

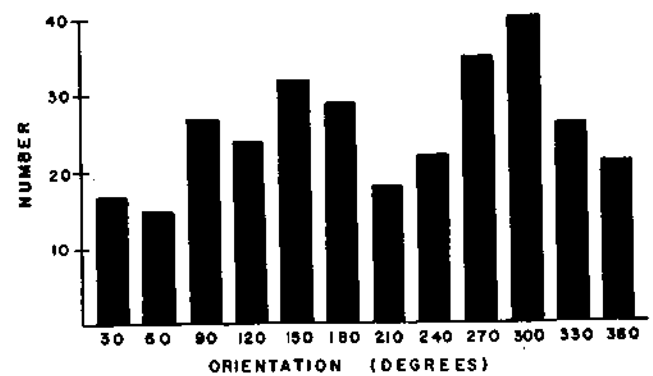
$$\hat{C}(f_0) = \frac{\lambda_1^2(f_0)}{\sum_{k=1}^{K} \lambda_k^2(f_0)}$$



Prechtl, Cohen, Mitra, Pesaran and Kleinfeld (1997)


R
M
L
C
500 µm


Optical
Tracing
R
C
180
0


NUMBER
40
30
20
10
30
60
90
120
150
180
210
240
270
300
330
360
ORIENTATION (DEGREES)

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

Thank you for your attention!