Microelectrodes recordings in the seizure onset zone

Andrei Barborica[1,2]

Cristian Donos[1], Ioana Mindruta[3], Jean Ciurea[4]

[1] University of Bucharest, Physics Department, Electricity and Biophysics, Romania

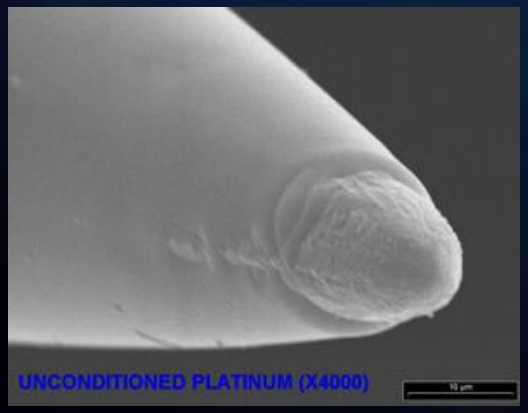
[2] FHC Inc, Bowdoin, Maine, United States

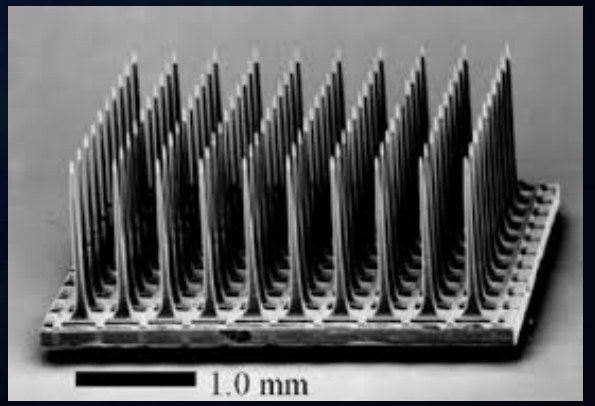
[3] University Emergency Hospital, Bucharest, Romania

[4] Bagdasar-Arseni Hospital, Bucharest, Romania

Why single-unit activity?

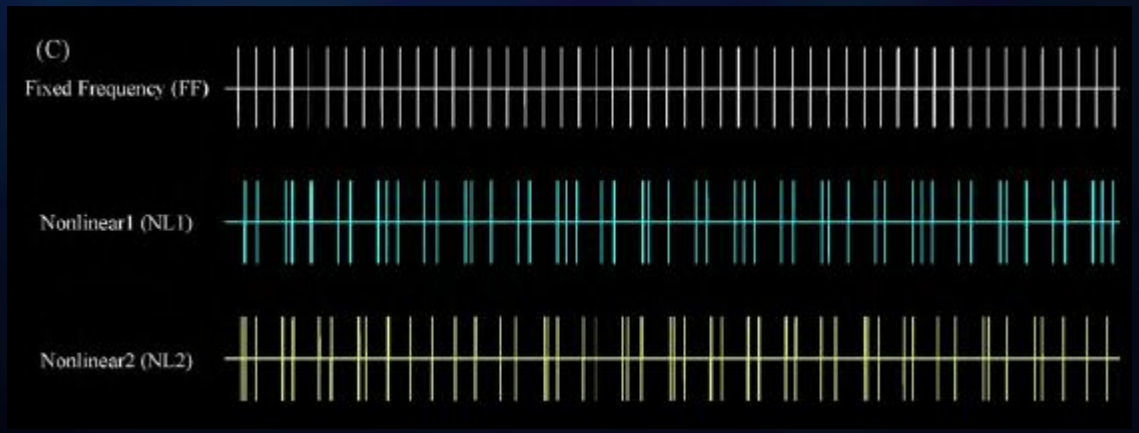
- The single-unit activity is the underlying source of the EEG signals
- Understanding single-unit activity allows us to explain EEG signal features
- Fine details of SUA patterns may represent a better correlate of tissue epileptogenicity





Potential Clinical Applications

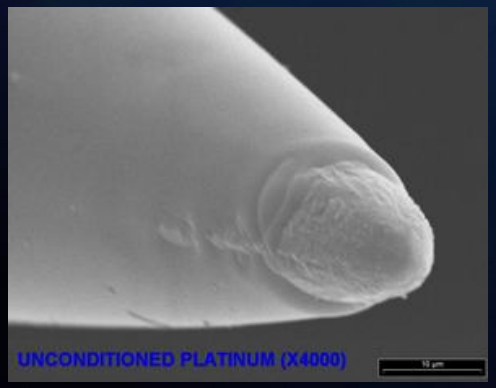
- More accurate localization of seizure onset zone and propagation relays
- Development of advanced open- and closed-loop stimulation protocols for electrical control of seizures

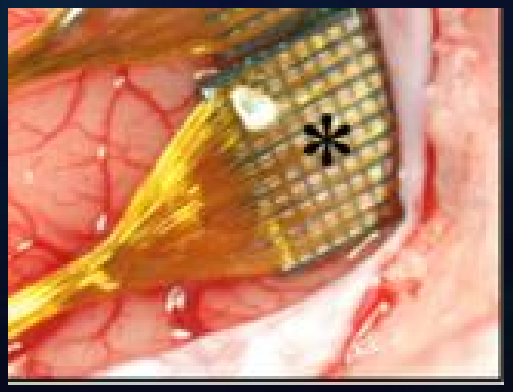


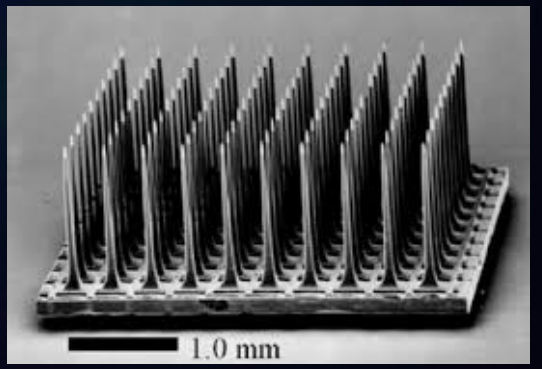
Single-unit correlates of ictal and inter-ictal EEG

- What is a better correlate:
  - Firing rate?

    or
  - Synchrony?

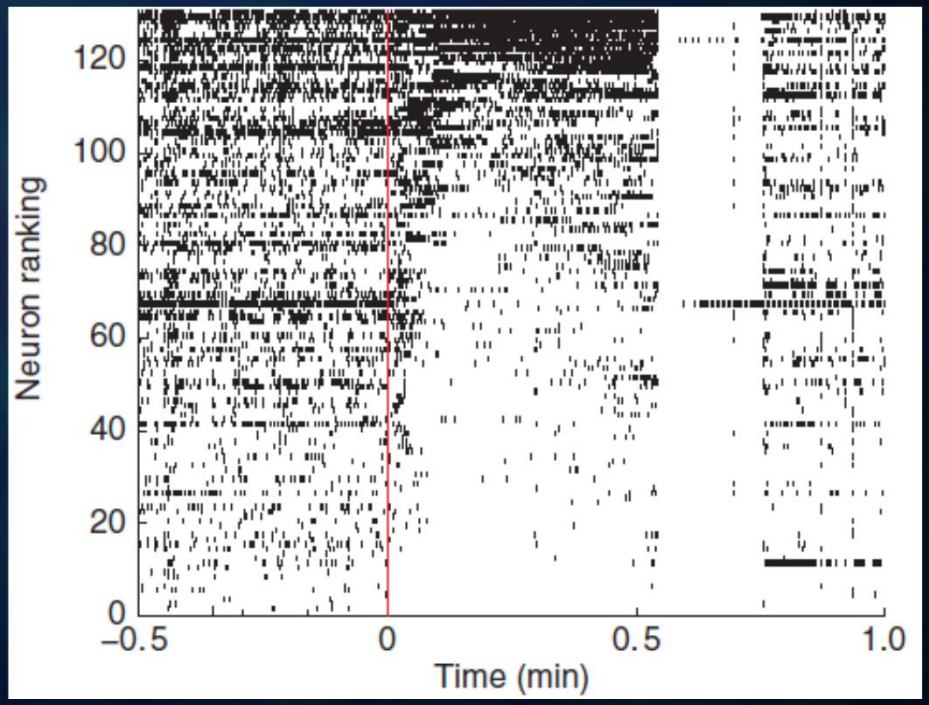


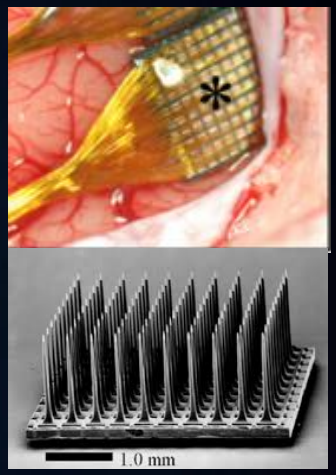




Firing rate or Synchrony?

Firing rate - some neurons increase firing during seizures, some do the opposite



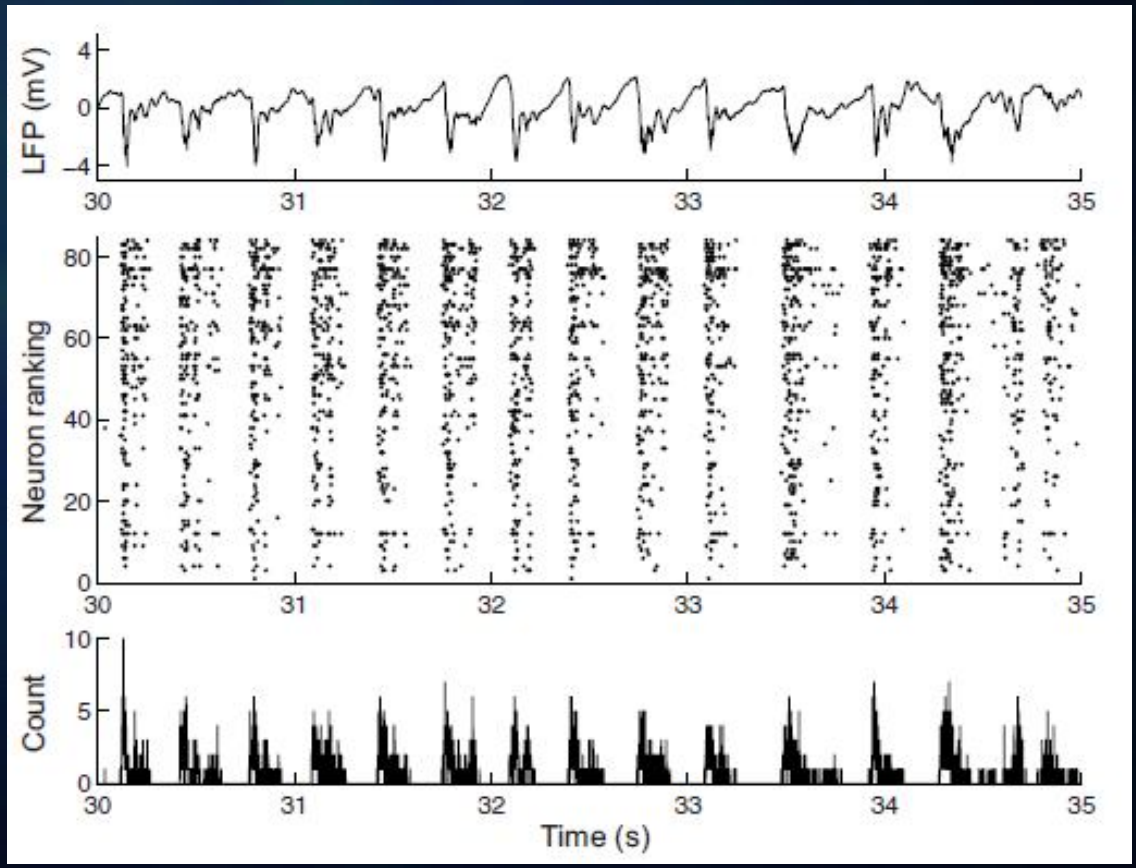


Single unit rasters for 131 neurons simultaneously recorded during an ictal episode. One has to note the heterogeneity of the firing in the initial phase of the seizure (most active neurons are shown on top, while least active at bottom), as well as the common feature of a nearly complete firing suppression towards the end of the seizure.

Truccolo W, Donoghue JA, Hochberg LR, Eskandar EN, Madsen JR, Anderson WS, Brown EN, Halgren E, Cash SS. Nat Neurosci. 2011 May;14(5):635-41.

Firing Rate or Synchrony?

- Synchrony with ictal discharges



Truccolo W, Ahmed OJ, Harrison MT, Eskandar EN, Cosgrove GR, Madsen JR, Blum AS, Potter NS, Hochberg LR, Cash SS. Neuronal ensemble synchrony during human focal seizures. J Neurosci. 2014 Jul 23;34(30):9927-44

Firing Rate or Synchrony?

- SUA synchrony with inter-ictal spikes
- Simultaneous **ECoG** and **μE**

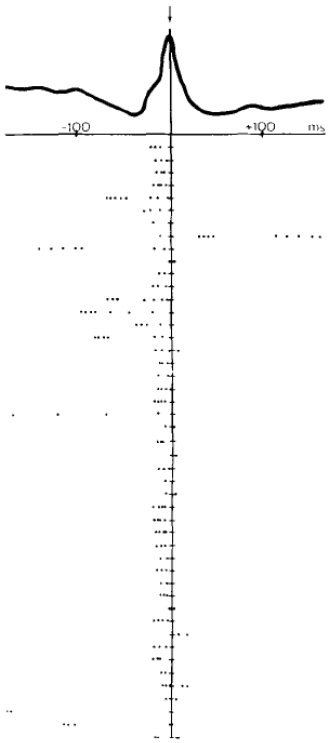


Fig 3. Dot raster of a unit's activity in which the unit fired most commonly during the rising phase of the electrocorticographically recorded spike.

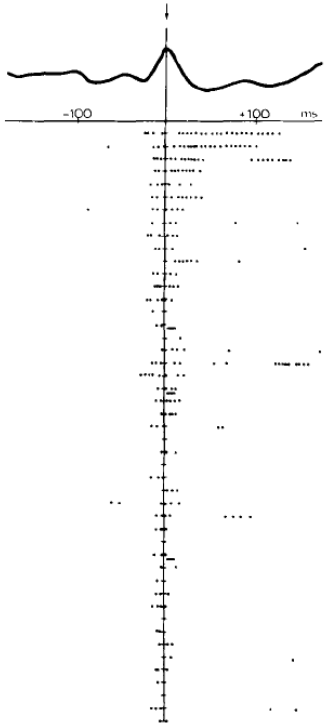
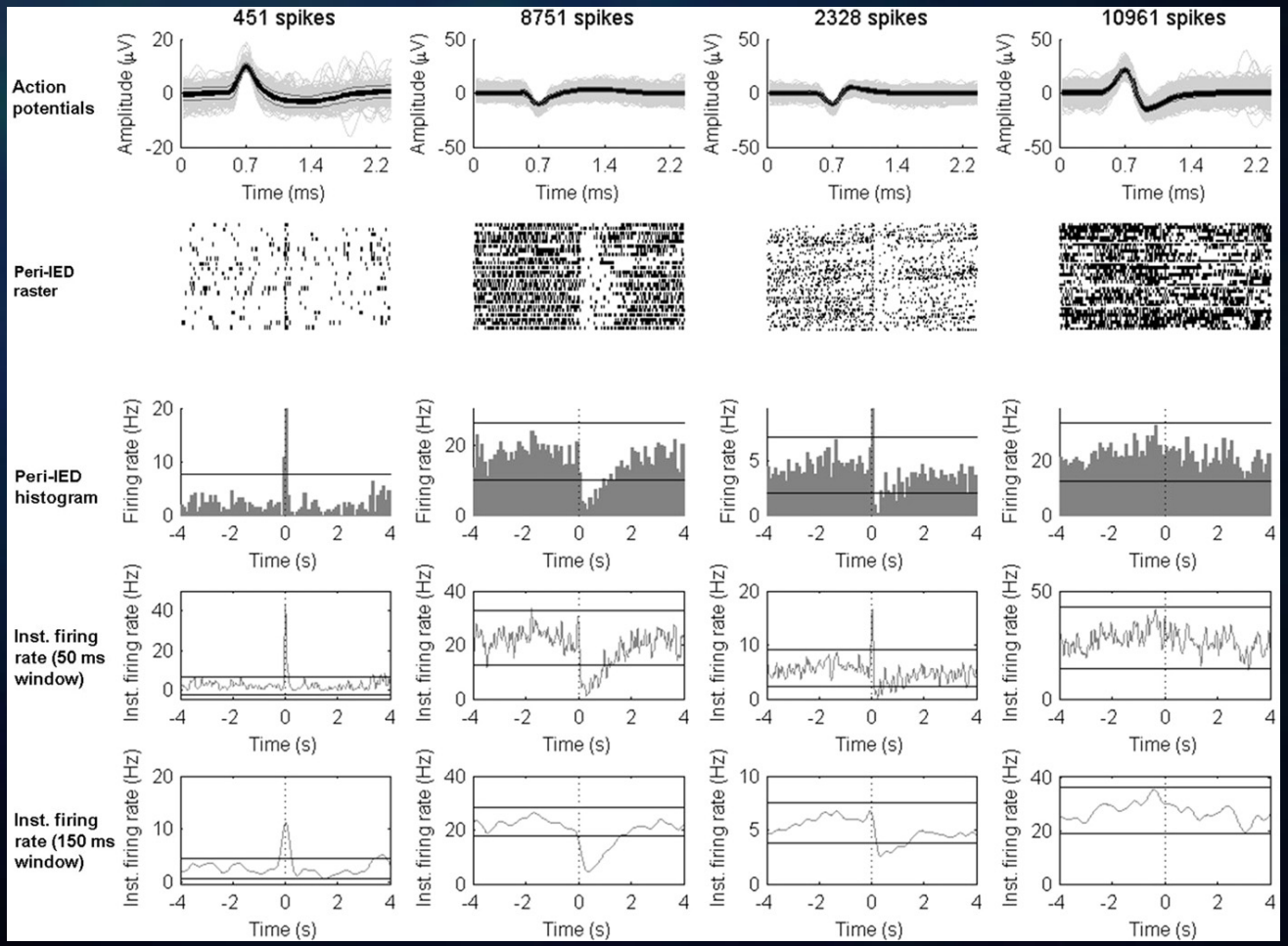


Fig 4. Example of a unit that fired predominantly during the falling phase of the electrocorticographic spike.

Wyler, A.R., Ojemann, G.A. & Ward, A.A. Jr. *Neurons in human epileptic cortex: correlation between unit and EEG activity.* Ann. Neurol. 11, 301–308 (1982)

Firing Rate or Synchrony?

- SUA synchrony with inter-ictal spikes
- Simultaneous depth electrodes and µE



Alarcón G, Martinez J, Kerai SV, Lacruz ME, Quiroga RQ, Selway RP, Richardson MP, García Seoane JJ, Valentín A. *In vivo neuronal firing patterns during human epileptiform discharges replicated by electrical stimulation*. Clin Neurophysiol. 2012 Sep;123(9):1736-44. doi: 10.1016/j.clinph.2012.02.062.

Clinical Neurophysiology 123 (2012) 1736–1744

Contents lists available at SciVerse ScienceDirect

Clinical Neurophysiology

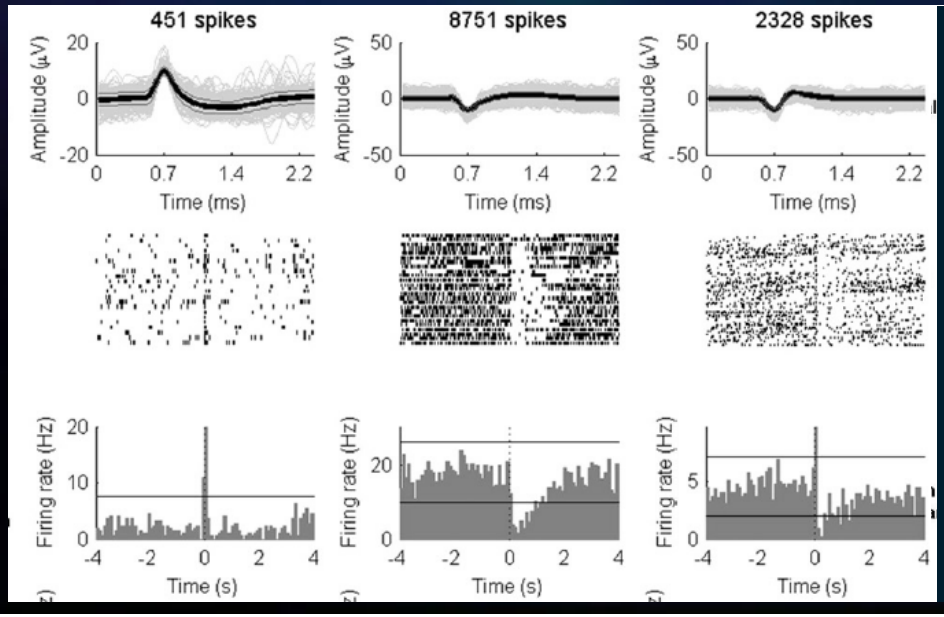
journal homepage: www.elsevier.com/locate/clinph

In vivo neuronal firing patterns during human epileptiform discharges replicated by electrical stimulation

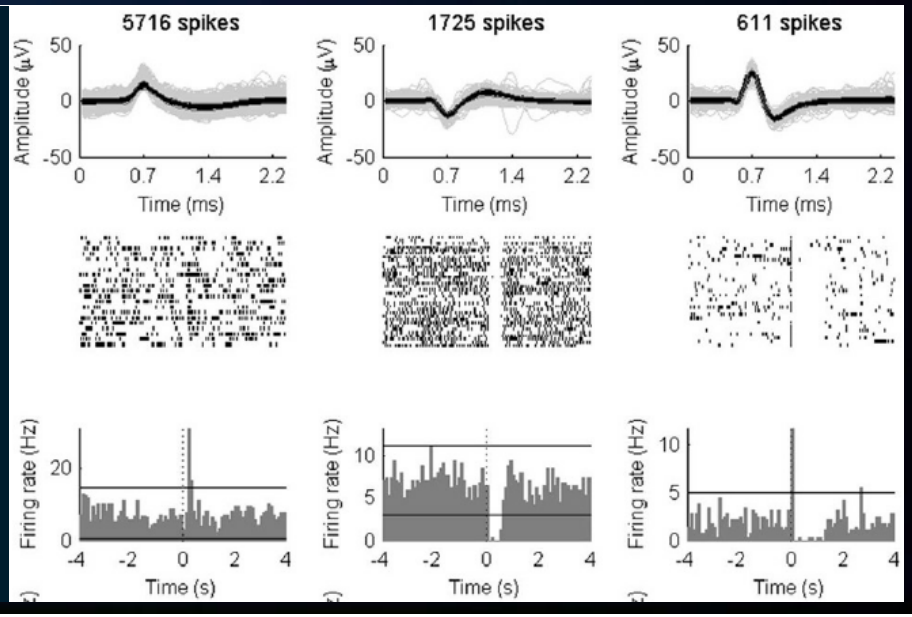
Gonzalo Alarcón [a,b,1,*], Juan Martinez [c,1], Shashivadan V. Kerai [a], Maria E. Lacruz [a], Rodrigo Quian Quiroga [c,d], Richard P. Selway [e], Mark P. Richardson [a], Jorge J. García Seoane [b], Antonio Valentín [a]

- The neuronal firing patterns during interictal epileptiform discharges (IEDs) and after single pulse electrical stimulation (SPES) can be described as burst-only, suppression-only, burst–suppression or no-change.
- Similar neuronal firing patterns can be observed during IEDs and after SPES.
- IEDs and responses to SPES appear to activate similar and generic cortical mechanisms, which may explain transient cognitive impairment.

Inter-Ictal Spikes



Electrical Stimulation



Implications of the synchrony /time-locking

Systems/Circuits

The Journal of Neuroscience, July 23, 2014 • 34(30):9927–9944 • 9927

Neuronal Ensemble Synchrony during Human Focal Seizures

Wilson Truccolo,[1,6,8*] Omar J. Ahmed,[9] Matthew T. Harrison,[3] Emad N. Eskandar,[10,11] G. Rees Cosgrove,[5,7] Joseph R. Madsen,[12,13] Andrew S. Blum,[4] N. Stevenson Potter,[4] Leigh R. Hochberg,[2,6,8,9,14] and Sydney S. Cash[9*]

Time-locking - a measure of the susceptibility of the neuron to synchronization. Truccolo et al 2014:

- Fine temporal synchrony (<10 ms) might affect neuron's efficacy in driving downstream targets
- Temporal synchrony can lead to the formation of large-scale networks (Hipp et al, 2011, Singer 2011)
- Fine temporal synchrony can induce changes in synaptic efficacy / effective network connectivity (Hebb's rule).

al., 2012; Jiruska et al., 2013). Furthermore, the temporal precision of synchrony at the level of single-neuron spiking (action potentials) has not been examined during human seizures, and is a critical issue for understanding the nature and mechanisms of epileptic seizures. Fine temporal (<10 ms) spike synchrony in a group of neurons might substantially affect their efficacy in driving downstream targets (Abeles, 1991; Kumar et al., 2010). In addition, temporal synchrony resulting from the entrainment of neuronal spiking into oscillatory activity can lead to the formation of dynamic large scale networks (Singer, 2011). Fine temporal synchrony can also induce changes in synaptic efficacy (effective network connectivity) via neuronal spike timing-dependent plasticity (Dan and Poo, 2006). Challenges in single-neuron ensemble recordings during human seizures and in the statistical assessment of synchrony have posed difficult obstacles

Single-unit Activity

- Our working hypothesis (EPIDYN Study):

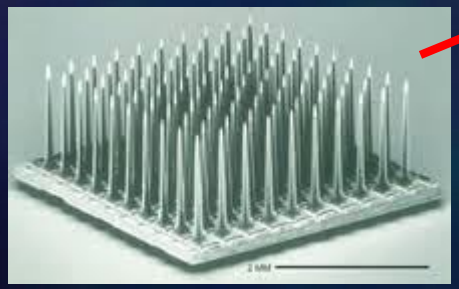
  Neural synchrony or time locking to a spontaneous or stimulation event may be a correlate of epileptogenicity

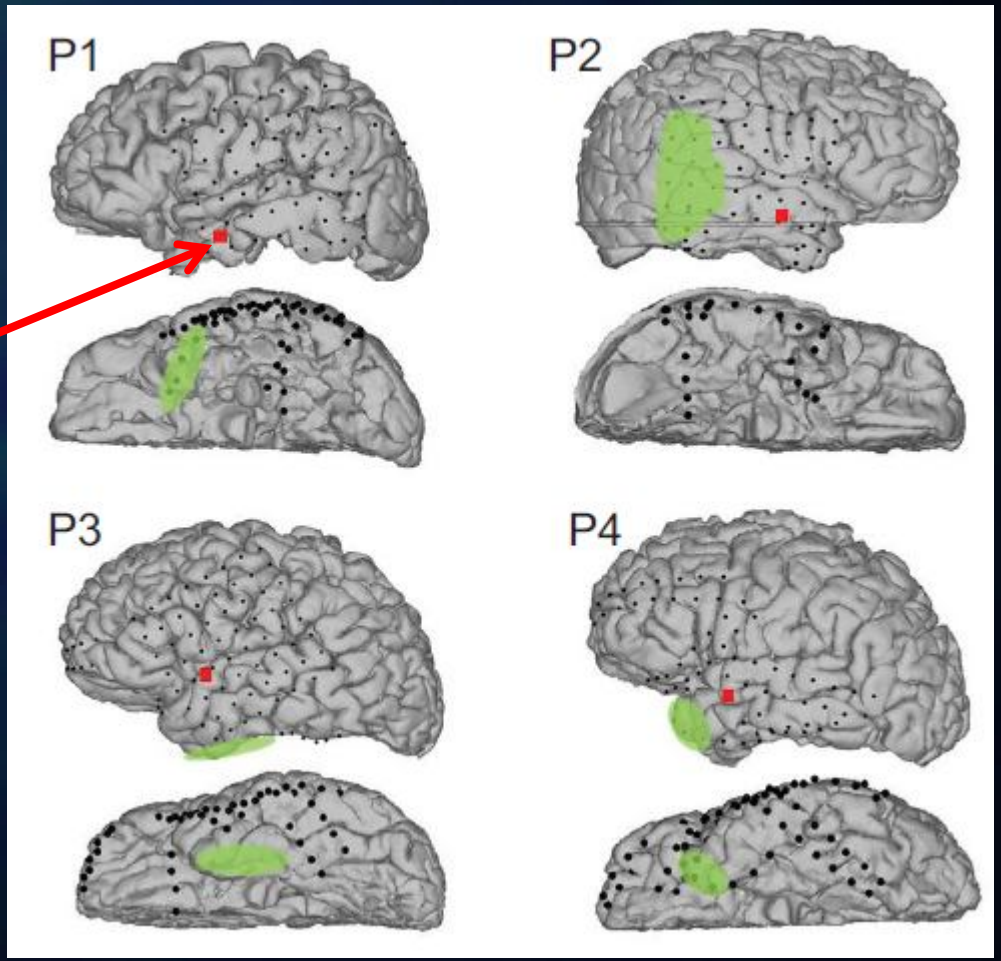
Spontaneous or stimulation-evoked SUA?

- Spontaneous activity – long term monitoring
  - Requires placement of microelectrode array or bundle of microwires during the same procedure as the intracranial electrodes, when SOZ/EZ is not known
- Stimulation-evoked activity
  - Can be performed intraoperatively, just before the resective surgery
  - SOZ/EZ location is known

LTM - Experimental limitations

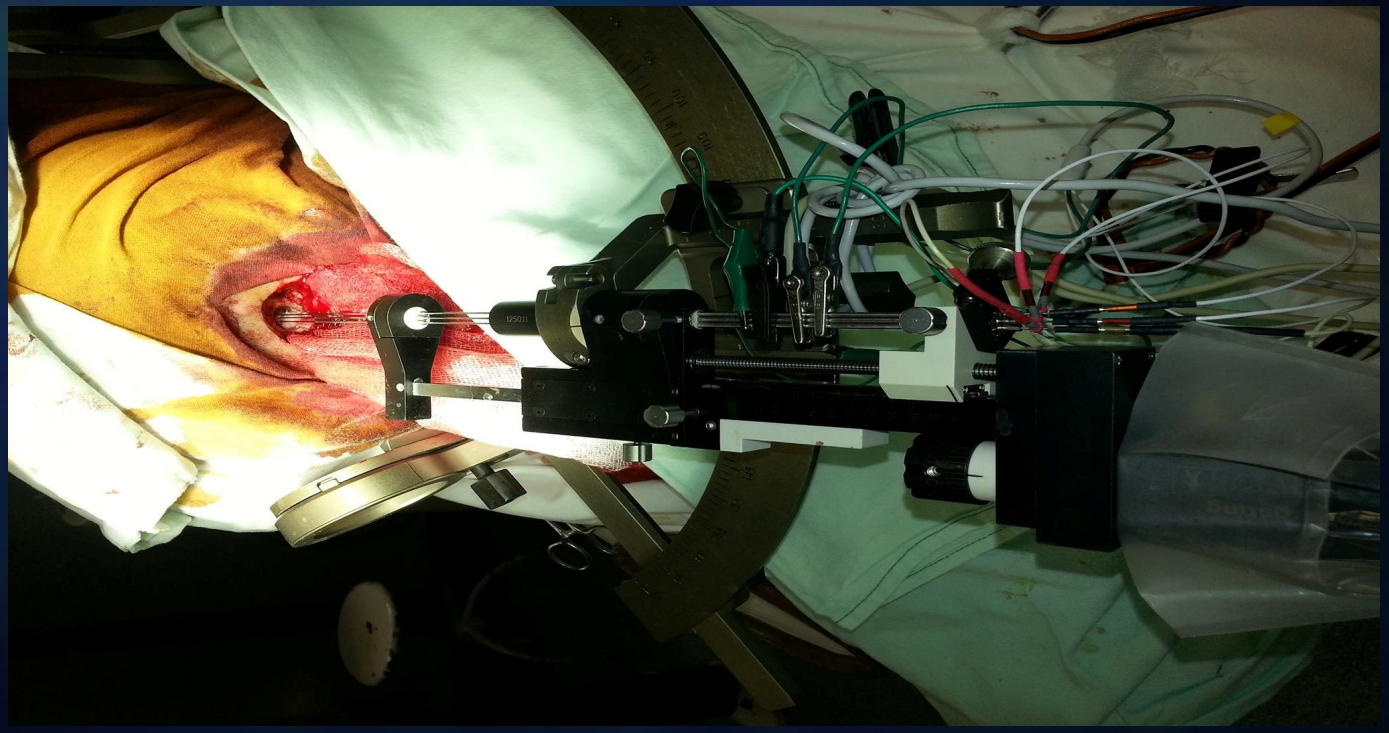
- μE Array location
- Electrode contacts
- SOZ





Intra-operative µE recordings

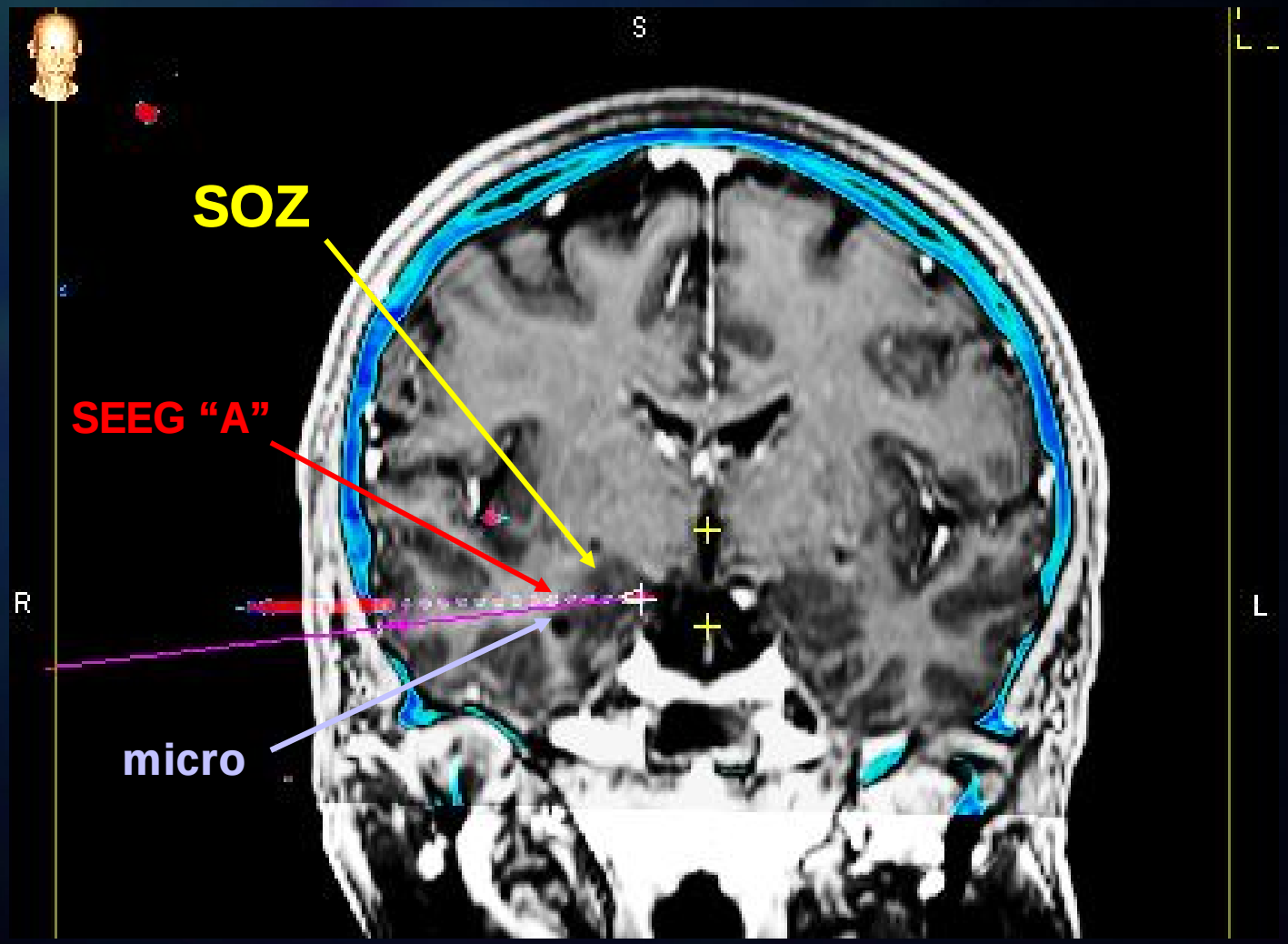
- Allow accurate targeting of epileptogenic tissue with microelectrodes



- Due to limited time window, we have to rely on SU responses to electrical stimulation

Intraoperative µE recordings

- Microelectrode targeting SOZ - Amygdala



EPIDYN Study

- Intraoperative recordings of single-unit activity in SOZ
- SOZ was assessed based on detailed SEEG investigations
- Responses to repetitive electrical stimulation with different frequencies (1, 10, 30, 60 and 130 Hz) and amplitudes

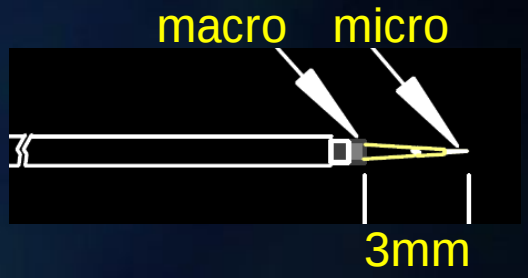
Patients

- 11 patients with drug-resistant focal epilepsy

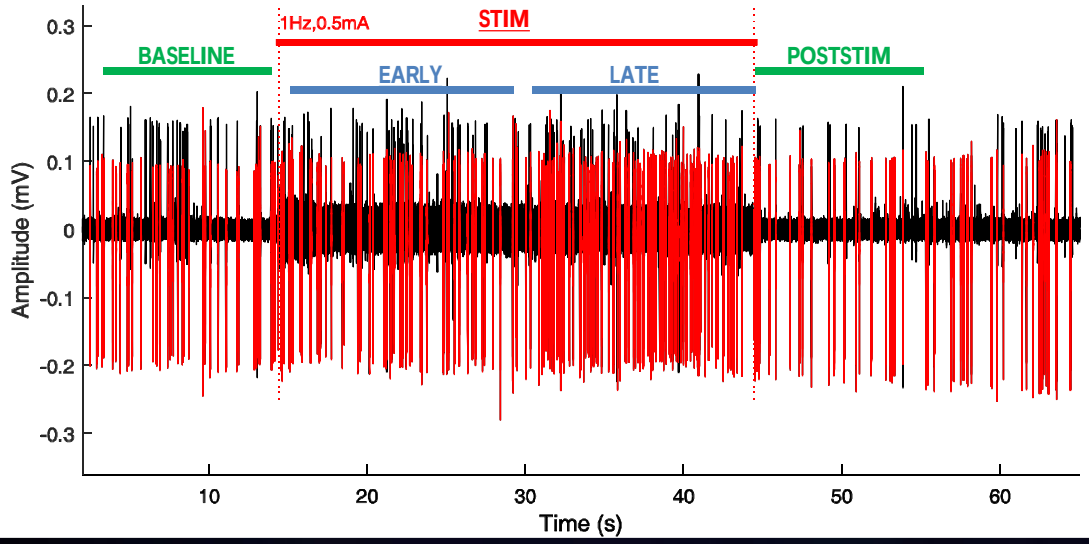
Patient	Sex	Age	Pathology	Epilepsy	SOZ
1	F	32	Type I cortical dysplasia	Temporal	Mesial structures
2	M	46	Hippocampal sclerosis	Mesio-temporal	Amygdala
3	M	39	MCD temporo-occipital basal	Occipital	Basal
4	M	47	DNET	Temporal	Middle temporal gyrus
5	F	40	Type II B cortical dysplsia	Prefrontal	DLPFC
6	F	35	Gliosis	Mesio-temporal	Amygdala
7	F	25	Type II cortical dysplasia	Temporal	Temporal pole
8	F	46	Type II cortical dysplasia	Temporal	Temporal pole
9	M	33	Type I cortical dysplasia	Frontal	Anterior cingulate cortex
10	M	28	Type I cortical dysplasia	Temporal	Hippocampus
11	F	25	N/A	Temporal	Entorhinal cortex

Methods

- Three microelectrodes w/ macro contacts in a linear configuration, 2 mm spacing



- Macro contacts located 3 mm from μE tip
- Record SUA while stimulating on the macro contacts

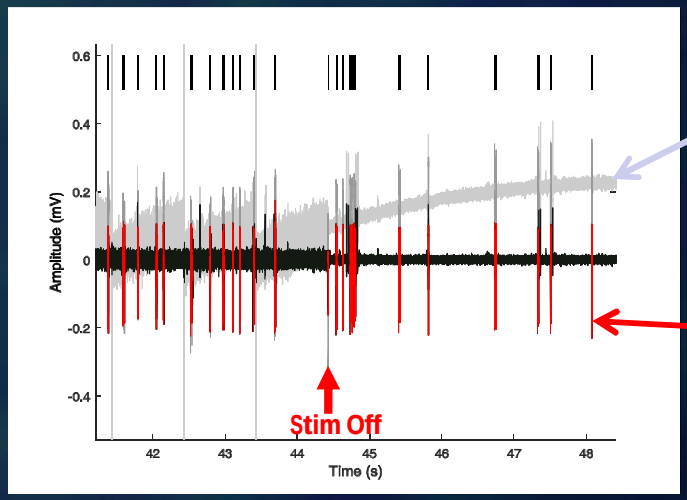


$$MI_{STIM} = \frac{R_{STIM} - R_{BASELINE}}{R_{STIM} + R_{BASELINE}}$$

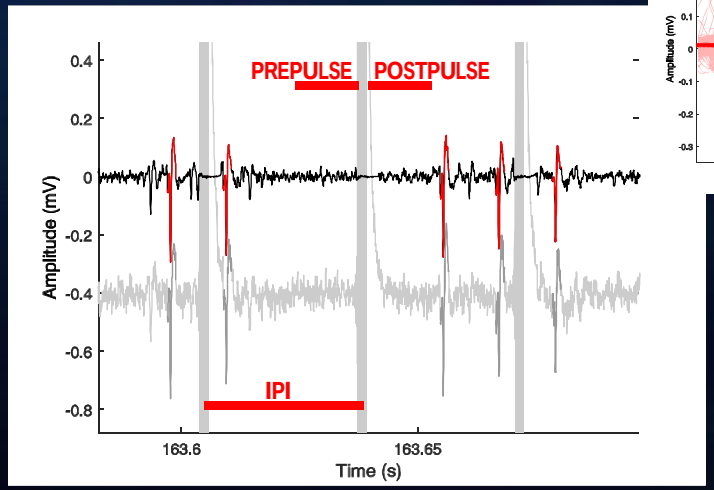
$$MI_{BUILDUP} = \frac{R_{LATE} - R_{EARLY}}{R_{LATE} + R_{EARLY}}$$

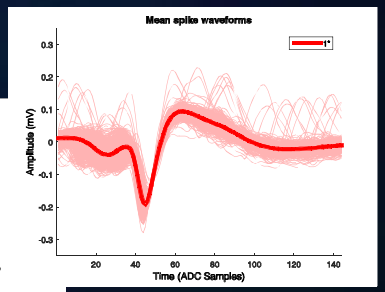
Methods

- Stimulus artifact subtraction: SALPA + LMS



- Inter-pulse interval activity analysis





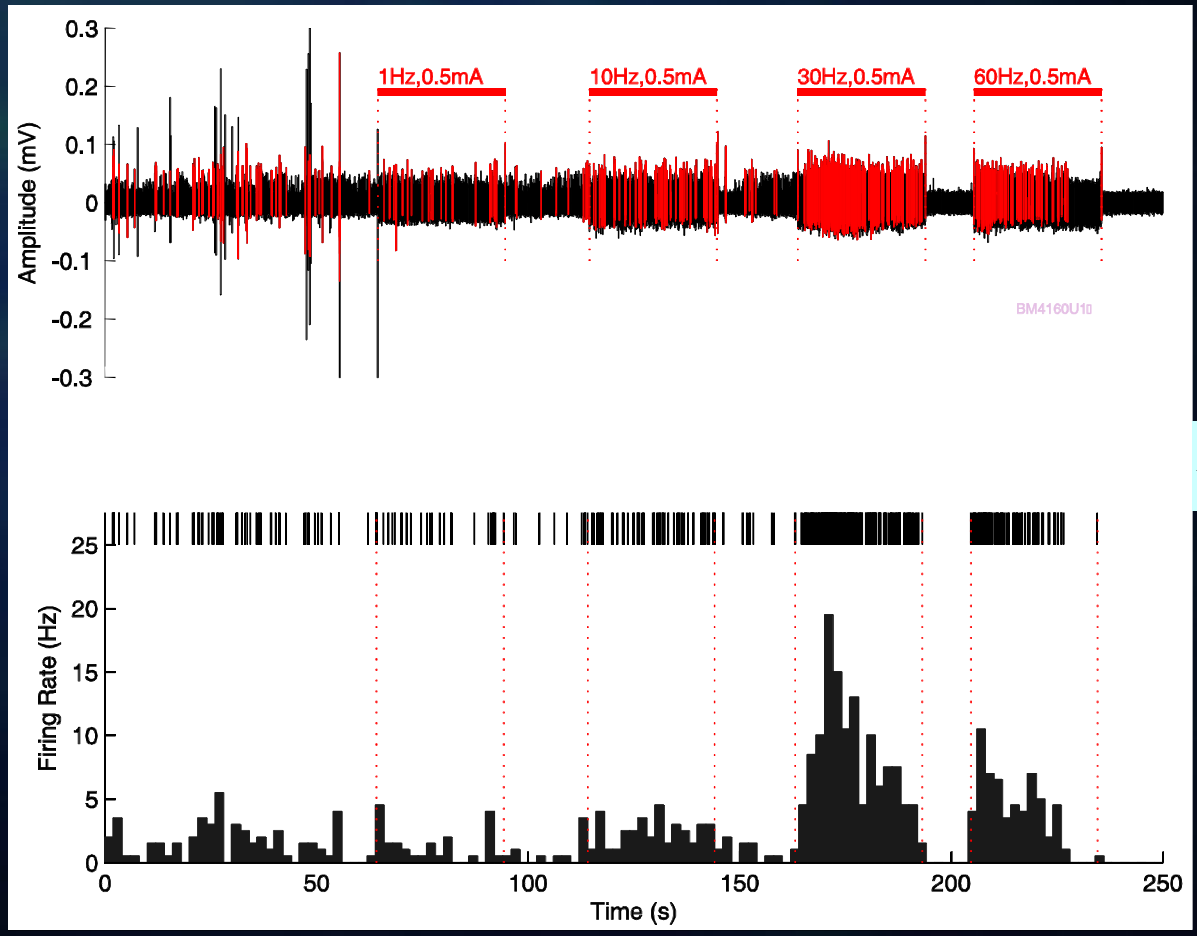
$$TLI = \frac{R_{POSTPULSE} - R_{PREPULSE}}{R_{POSTPULSE} + R_{PREPULSE}}$$

Main Results

- Frequency-dependent firing suppression or enhancement
- Activity buildup/modulation during stimulation epoch (30s)
- Time-locking to the stimulus

Results

- Suppression/enhancement depending on stimulation frequency
- Activity modulation during stimulation epoch



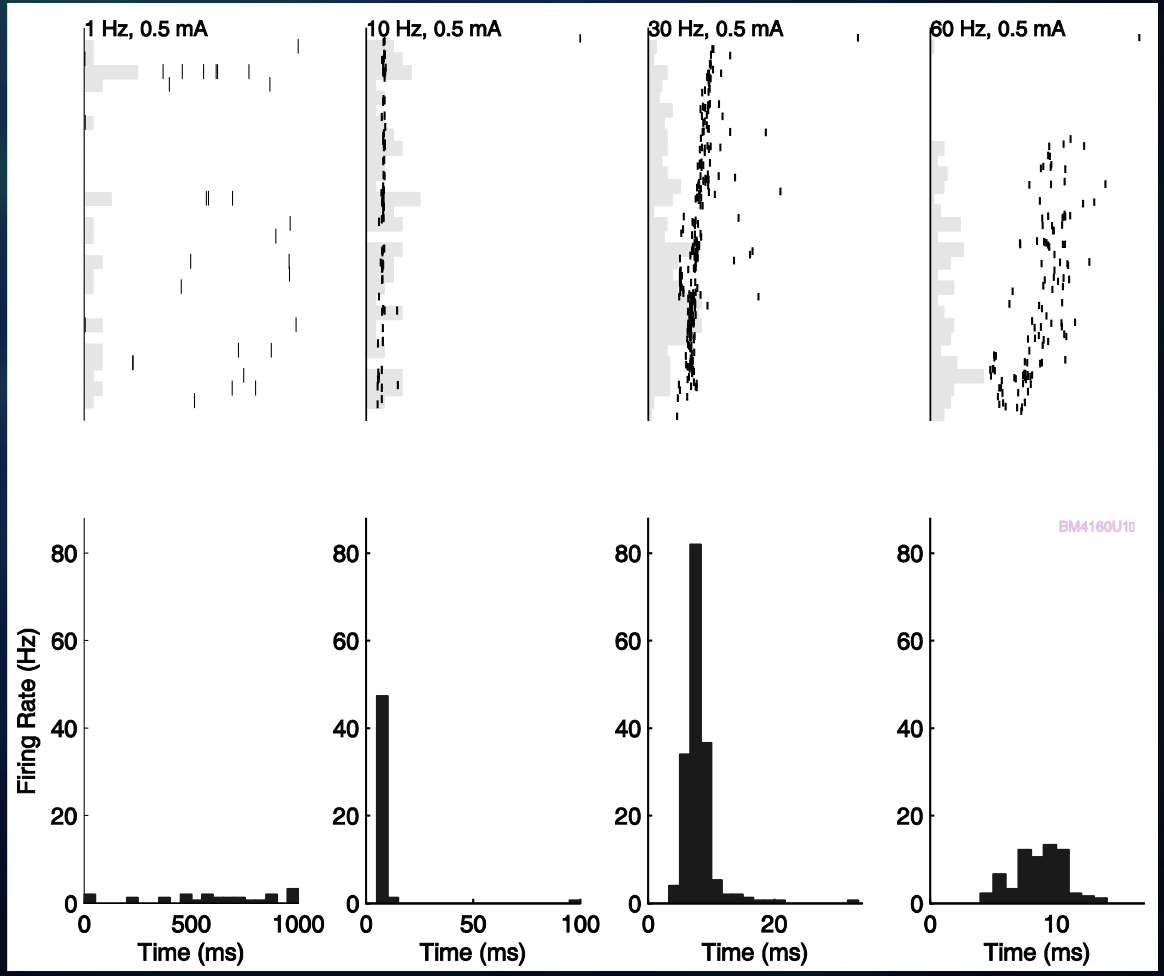
$$MI_{STIM} = \frac{R_{STIM} - R_{BASELINE}}{R_{STIM} + R_{BASELINE}}$$

$$MI_{BUILDUP} = \frac{R_{LATE} - R_{EARLY}}{R_{LATE} + R_{EARLY}}$$

SOZ neuron highly modulated by the application of stimulation pulses, in patient #5 (prefrontal cortical dysplasia). The mean firing rate is little modified by the 1Hz stimulation (1.00 vs 1.70Hz), whereas at higher frequencies, it increases significantly to 2.57, 9.71 and 5.29 Hz for 10, 30 and 60 Hz, respectively.

Results

- Time-locking



$$TLI = \frac{R_{POSTPULSE} - R_{PREPULSE}}{R_{POSTPULSE} + R_{PREPULSE}}$$

SOZ neuron highly modulated by the application of stimulation pulses, in patient #5 (prefrontal cortical dysplasia). The higher firing rate is associated with increased time-locking index of -0.25, 0.47, 0.93, 0.93 for the four stimulation frequencies.

Results

- Entire population (20 neurons, 11 patients)

Stim epoch enhancement / suppression index					
	All frequencies	1 Hz	10 Hz	30 Hz	60 Hz
All neurons	0.08±0.49, n=78	0.09±0.47, n=20	-0.03±0.39, n=20	0.20±0.55, n=20	0.07±0.55, n=18
SOZ	0.08±0.51, n=55	0.06±0.46, n=14	-0.09±0.36, n=14	0.20±0.59, n=14	0.15±0.61, n=13
non-SOZ	0.09±0.46, n=23	0.16±0.54, n=6	0.11±0.46, n=6	0.19±0.50, n=6	-0.14±0.33, n=5
n-way anova analysis					
Factor	p				
Patient	0.0107				
Pathology	0.1058				
Frequency	0.4707				
Timelocking index					
	All frequencies	1 Hz	10 Hz	30 Hz	60 Hz
All neurons	0.16±0.42, n=78	-0.09±0.25, n=20	0.26±0.53, n=20	0.27±0.46, n=20	0.20±0.29, n=18
SOZ	0.22±0.48, n=55	-0.12±0.29, n=14	0.34±0.61, n=14	0.38±0.51, n=14	0.28±0.29, n=13
non-SOZ	0.01±0.11, n=23	-0.02±0.11, n=6	0.05±0.05, n=6	0.03±0.13, n=6	-0.02±0.15, n=5
n-way anova analysis					
Factor	p				
Patient	0.0001				
Pathology	0.0168				
Frequency	0.0024				
Stim epoch buildup index					
	All frequencies	1 Hz	10 Hz	30 Hz	60 Hz
All neurons	-0.09±0.38, n=78	0.02±0.38, n=20	-0.07±0.29, n=20	-0.16±0.26, n=20	-0.18±0.54, n=18
SOZ	-0.14±0.40, n=55	-0.03±0.33, n=14	-0.13±0.31, n=14	-0.16±0.28, n=14	-0.25±0.62, n=13
non-SOZ	0.02±0.30, n=23	0.15±0.47, n=6	0.05±0.21, n=6	-0.15±0.22, n=6	0.01±0.18, n=5
n-way anova analysis					
Factor	p				
Patient	0.2023				
Pathology	0.1038				
Frequency	0.3016				

Results

- Responses in pathological vs normal tissue
- Epileptogenic tissue exhibits higher time-locking (TLI 62%-75% @30 Hz) vs normal (TLI -5.2% to 14% @30Hz)
- The effect is stronger at high frequencies (>=30 Hz)

Pathology	Stim Epoch Pattern	Inter-Pulse Pattern	Frequency (Hz)														
			1					10					30				
			n	Baseline (Hz)	Stim Epoch (Hz)	Enhancement (+) / Suppression (-)	Time-locking index	n	Baseline (Hz)	Stim Epoch (Hz)	Enhancement (+) / Suppression (-)	Time-locking index	n	Baseline (Hz)	Stim Epoch (Hz)	Enhancement(+) / Suppression (-)	Time-locking index
SOZ	No-change	No-change	3	4.6	4.5	0.7%	1.2%	1	13.6	11.9	-6.5%	-5.6%	0				
		Time-locked	1	6.3	5.0	-12.0%	-17.2%	0					1	6.6	7.4	5.6%	62.2%
	Enhancement	No-change	2	0.2	4.5	66.7%	-2.4%	1	2.1	2.9	15.8%	-41.7%	3	1.2	5.0	61.5%	5.0%
		Time-locked	3	9.6	13.4	42.9%	-16.8%	4	2.9	5.3	35.1%	65.5%	6	3.8	9.3	54.7%	65.1%
	Suppression	No-change	5	8.8	4.0	-33.3%	-18.6%	3	11.6	4.9	-31.2%	11.4%	2	6.4	0.9	-75.8%	-46.2%
		Time-locked	0					5	7.7	3.5	-35.8%	46.7%	2	8.7	3.5	-43.0%	74.9%
	Buildup	No-change	7	6.3	5.0	8.1%	-4.7%	2	15.5	6.1	-36.8%	18.2%	5	3.2	3.3	6.6%	-15.5%
		Time-locked	0					5	4.7	2.9	-6.0%	47.2%	7	4.3	6.4	29.5%	72.9%
Normal	No-change	No-change	1	1.3	1.2	-5.0%	-2.5%	3	6.3	5.5	-5.5%	2.7%	0				
		Time-locked	0					0					2	7.4	8.1	4.7%	-5.2%
	Enhancement	No-change	4	3.6	8.1	41.8%	-4.4%	2	0.6	3.7	61.6%	5.8%	3	1.1	3.7	54.1%	13.9%
		Time-locked	0					0					0				
	Suppression	No-change	1	1.6	0.3	-66.0%	8.0%	1	5.1	2.1	-41.1%	8.2%	1	3.4	0.9	-57.6%	-14.0%
		Time-locked	0					0					0				
	Buildup	No-change	5	2.2	5.1	16.0%	-4.1%	3	3.2	3.4	8.1%	7.1%	3	1.5	1.5	16.8%	6.6%
		Time-locked	0					0					1	7.6	8.1	3.3%	-5.5%

Conclusions

- There is a single-unit activity signature of the pathological cortex
- Time-locking appears to be the main feature of the firing patterns in epileptogenic cortex
- Only frequencies of 10 Hz and above result in significant time-locking.
- Higher frequencies (30 Hz) have an excitatory effect, particularly in pathological tissue.
- These findings contribute to the understanding the basic mechanisms underlying epileptogenic networks and in modulating the neuronal activity through electrical stimulation.

Potential Clinical Applications

- More accurate localization of seizure onset zone and propagation relays
- Development of advanced open- and closed-loop stimulation protocols for electrical control of seizures

Neuromodulation

- Single-unit responses to DES may allow in the future the design of stimulation protocols deconstructing hypersynchronous networks

Behavioural Brain Research 214 (2010) 377–385

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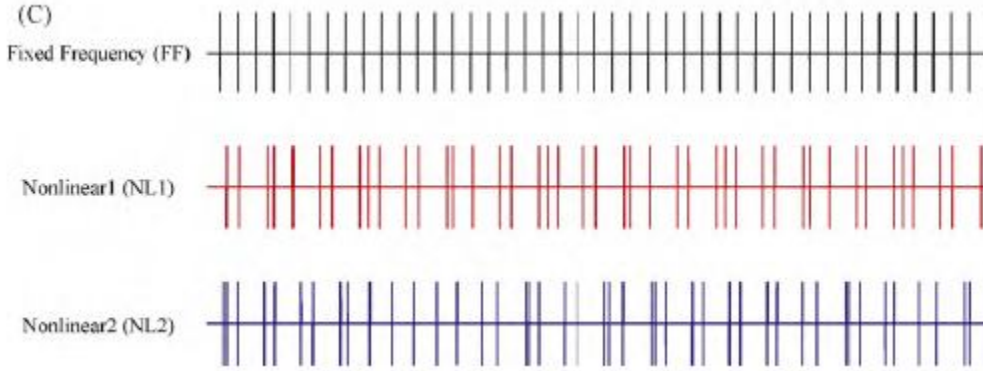
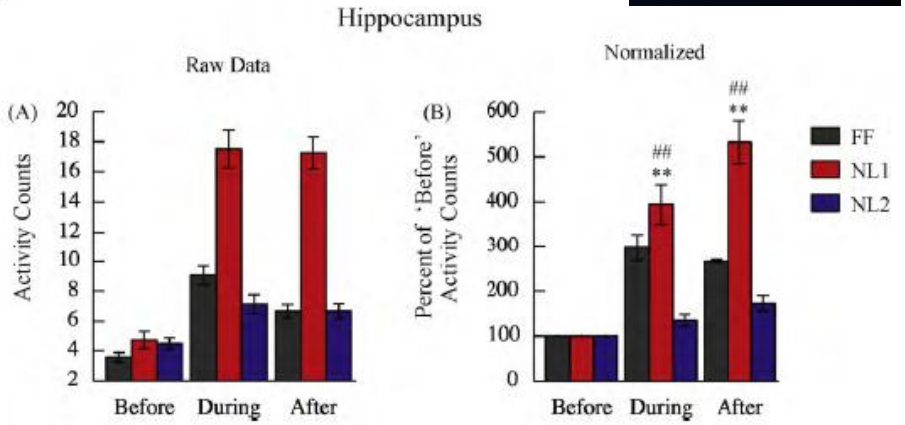
Research report

Temporal patterning of pulses during deep brain stimulation affects central nervous system arousal

Amy Wells Quinkert[a,*], Nicholas D. Schiff[b], Donald W. Pfaff[a]





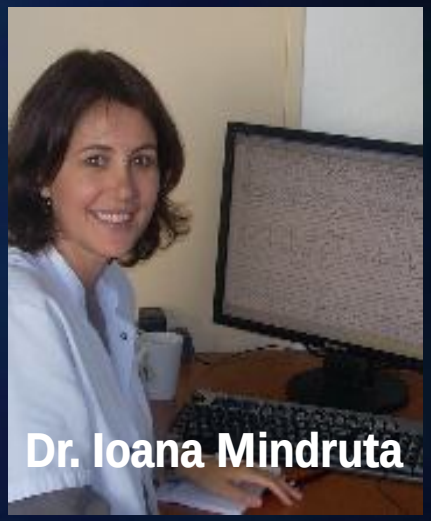
The Research Team

Biophysics


Dr. Andrei Barborica


Dr. Cristian Donos

Neurology


Dr. Ioana Mindruta


Mihai Maliia

Neurosurgery


Dr. Alin Rasina Dr. Jan Ciurea

EEG Technicians


Mariana Popa


Victorita Raiciu

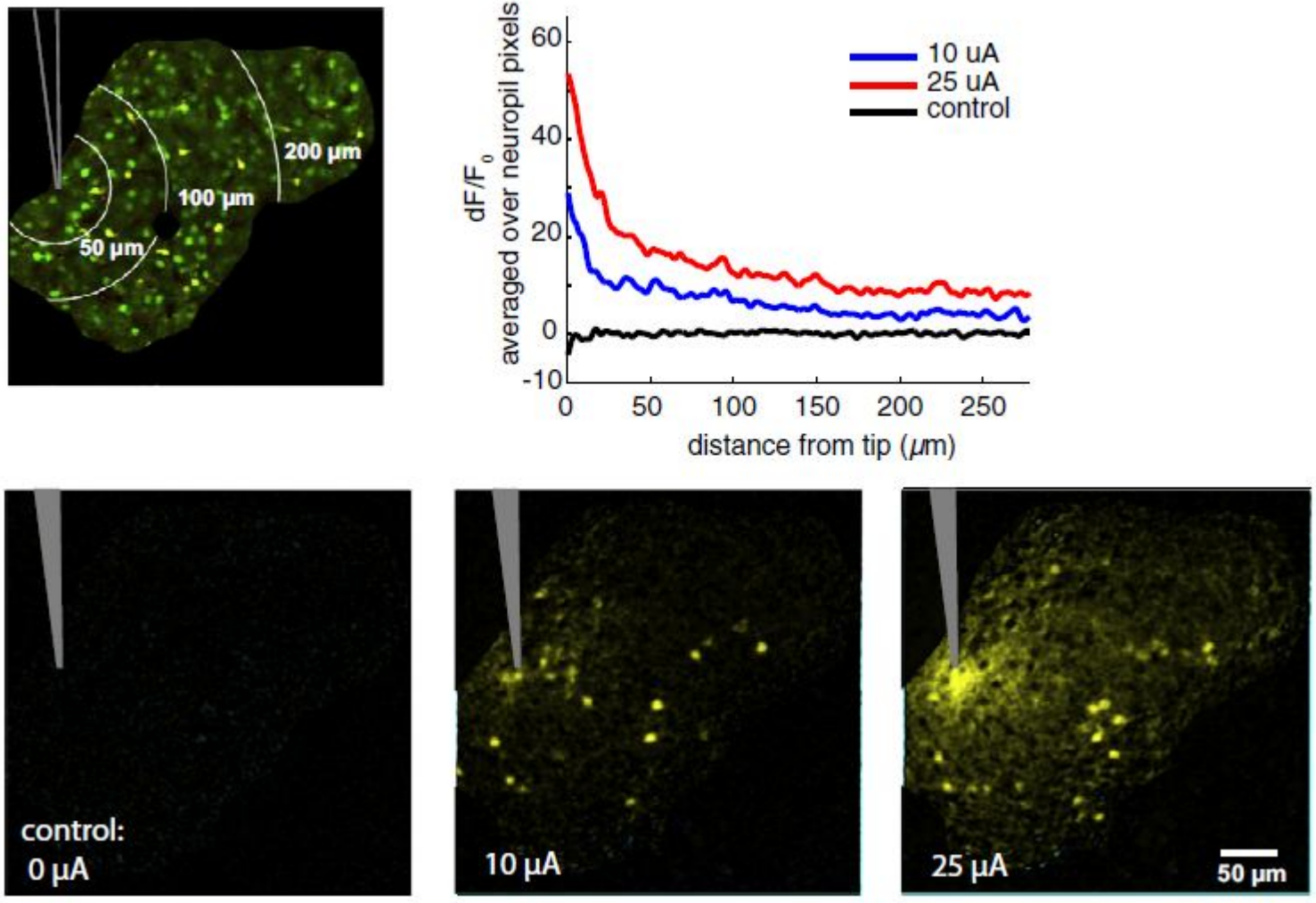
Supplementary Information

Neuron
Article

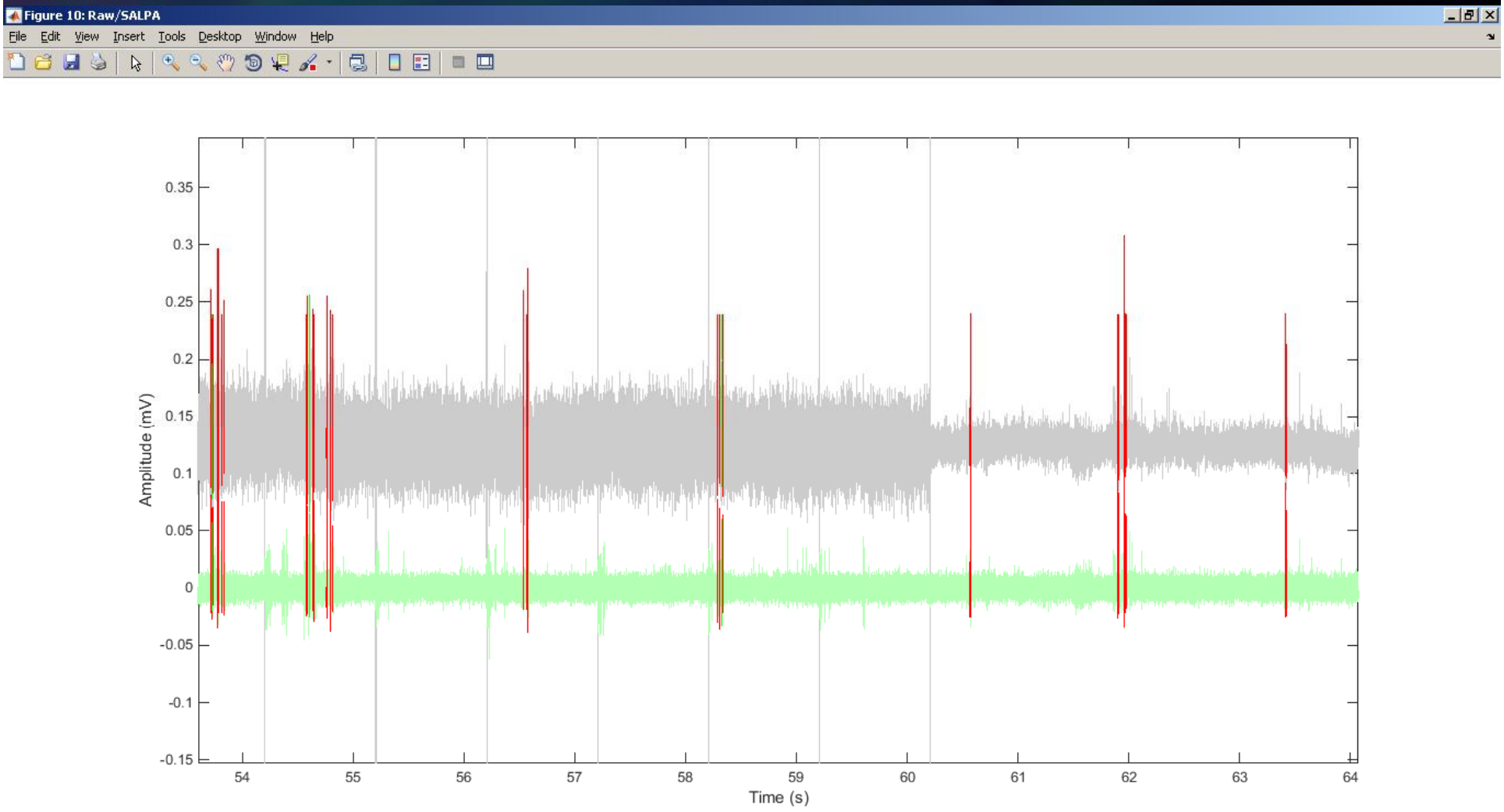
Direct Activation of Sparse, Distributed Populations of Cortical Neurons by Electrical Microstimulation

Mark H. Histed,[1,*] Vincent Bonin,[1] and R. Clay Reid[1,*]

What do we stimulate?



stimulus artifact and stimulator noise

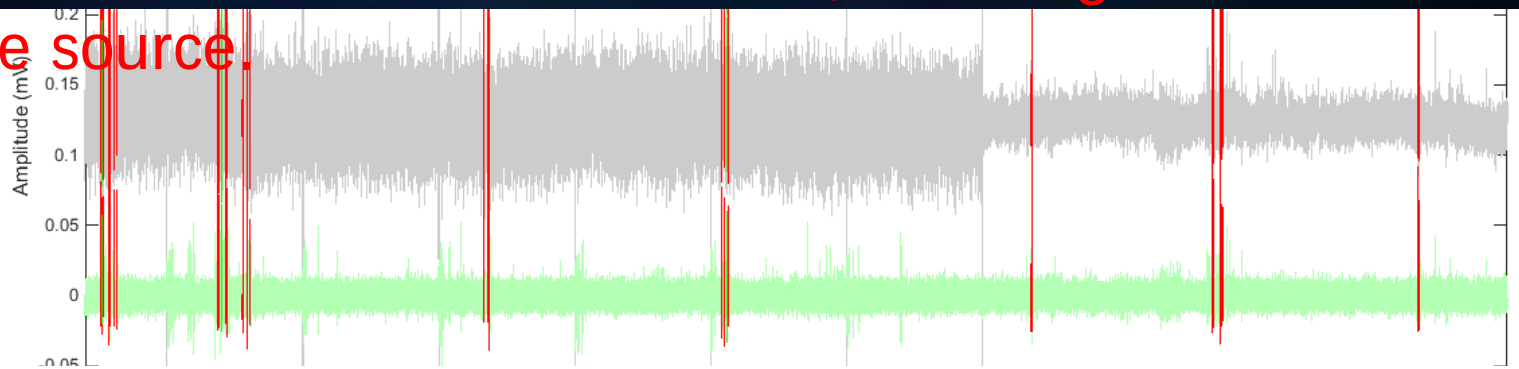


Adaptive Noise Cancelling: Principles and Applications

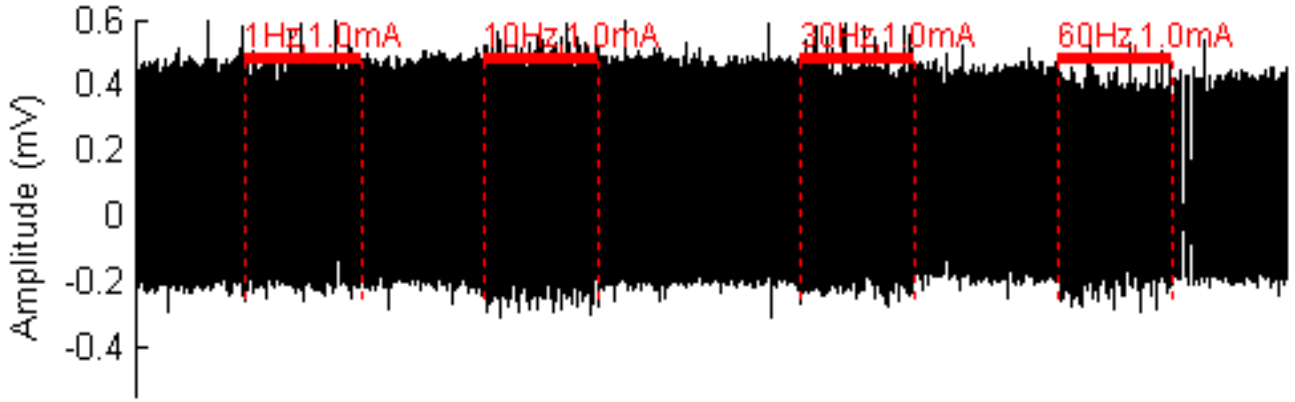
BERNARD WIDROW, SENIOR MEMBER, IEEE, JOHN R. GLOVER, JR., MEMBER, IEEE,
JOHN M. McCOOL, SENIOR MEMBER, IEEE, JOHN KAUNITZ, MEMBER, IEEE,
CHARLES S. WILLIAMS, STUDENT MEMBER, IEEE, ROBERT H. HEARN,
JAMES R. ZEIDLER, EUGENE DONG, JR., AND ROBERT C. GOODLIN

Abstract—This paper describes the concept of adaptive noise cancelling, an alternative method of estimating signals corrupted by additive noise or interference. The method uses a "primary" input containing the corrupted signal and a "reference" input containing noise correlated in some unknown way with the primary noise. The reference input is adaptively filtered and subtracted from the primary input to obtain the signal estimate. Adaptive filtering before subtraction allows the treatment of inputs that are deterministic or stochastic, stationary or time variable. Wiener solutions are developed to describe asymptotic adaptive performance and output signal-to-noise ratio for stationary stochastic inputs, including single and multiple reference inputs. These solutions show that when the reference input is free of signal and certain other conditions are met noise in the primary input can be essentially eliminated without signal distortion. It is further shown that in treating periodic interference the adaptive noise canceller acts as a notch filter with narrow bandwidth, infinite null, and the capability of tracking the exact frequency of the interference; in this case the canceller behaves as a linear, time-invariant system, with the adaptive filter converging on a dynamic rather than a static solution. Experimental results are presented that illustrate the usefulness of the adaptive noise cancelling technique in a variety of practical applications. These applications include the cancelling of various forms of periodic interference in electrocardiography, the cancelling of periodic interference in

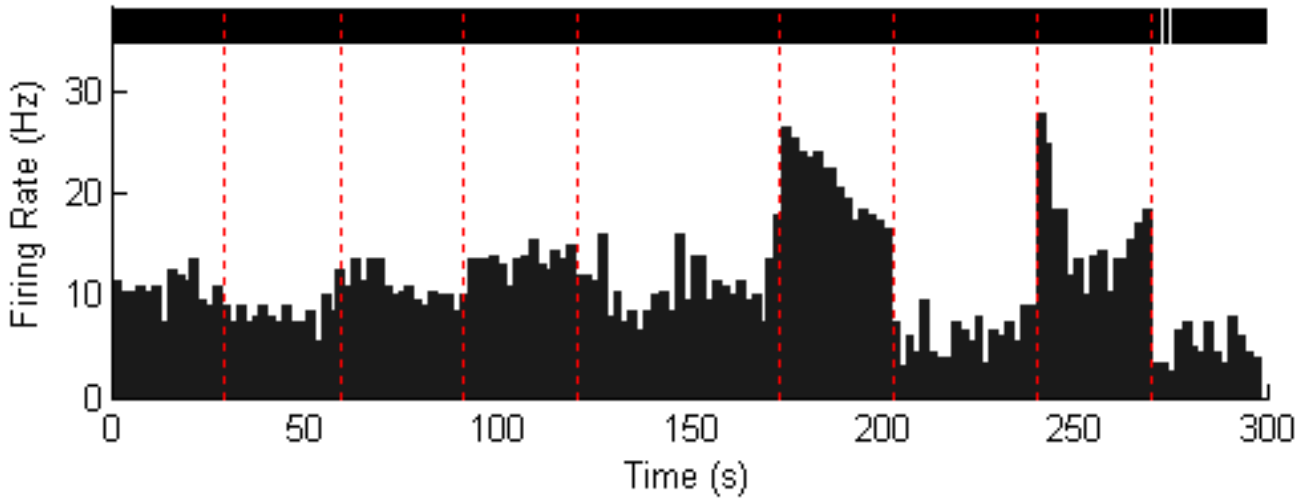
We cancel the stimulator noise (not the stimulation artifact) that is correlated across channels, as it originates from the same source.



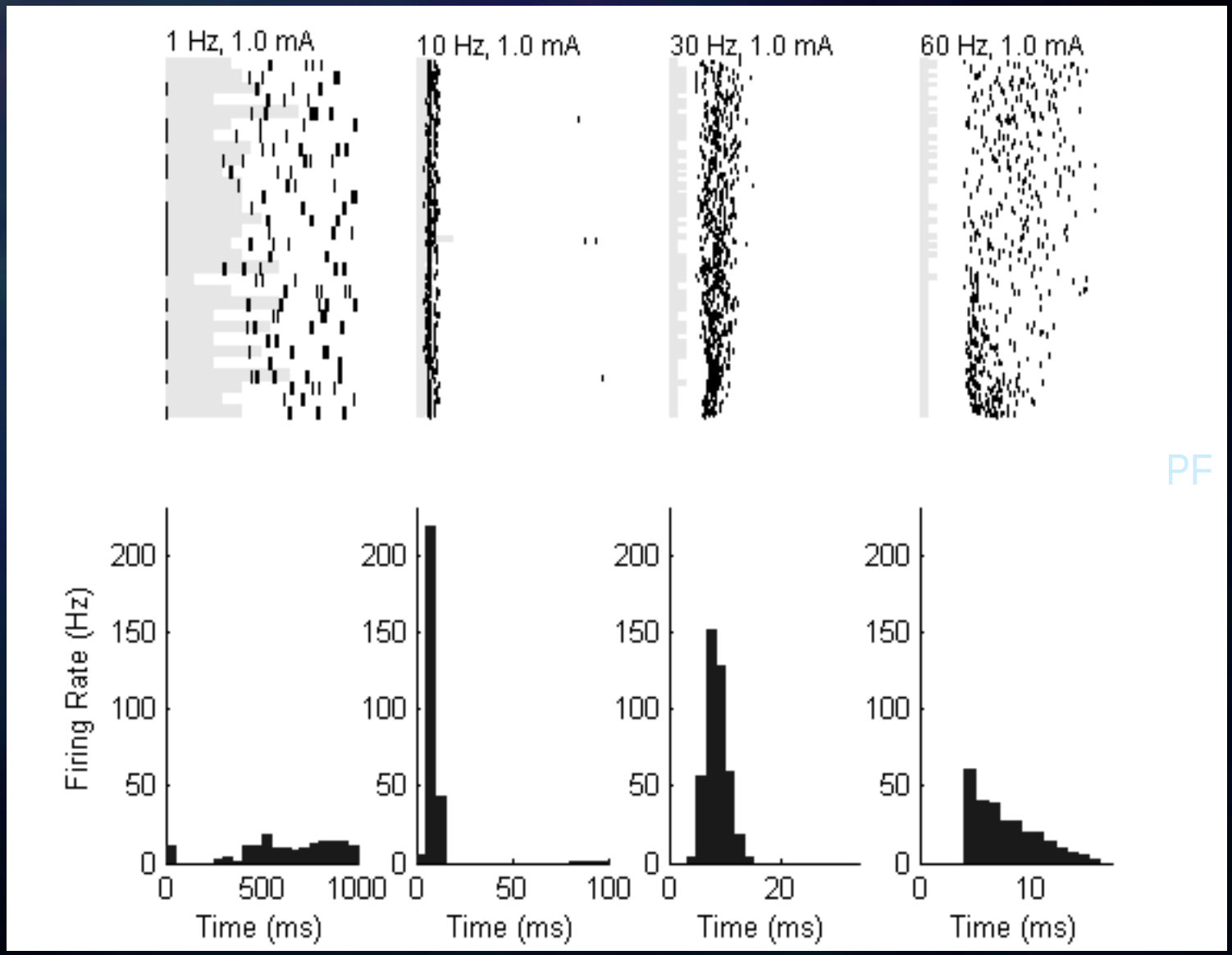
Additional Examples

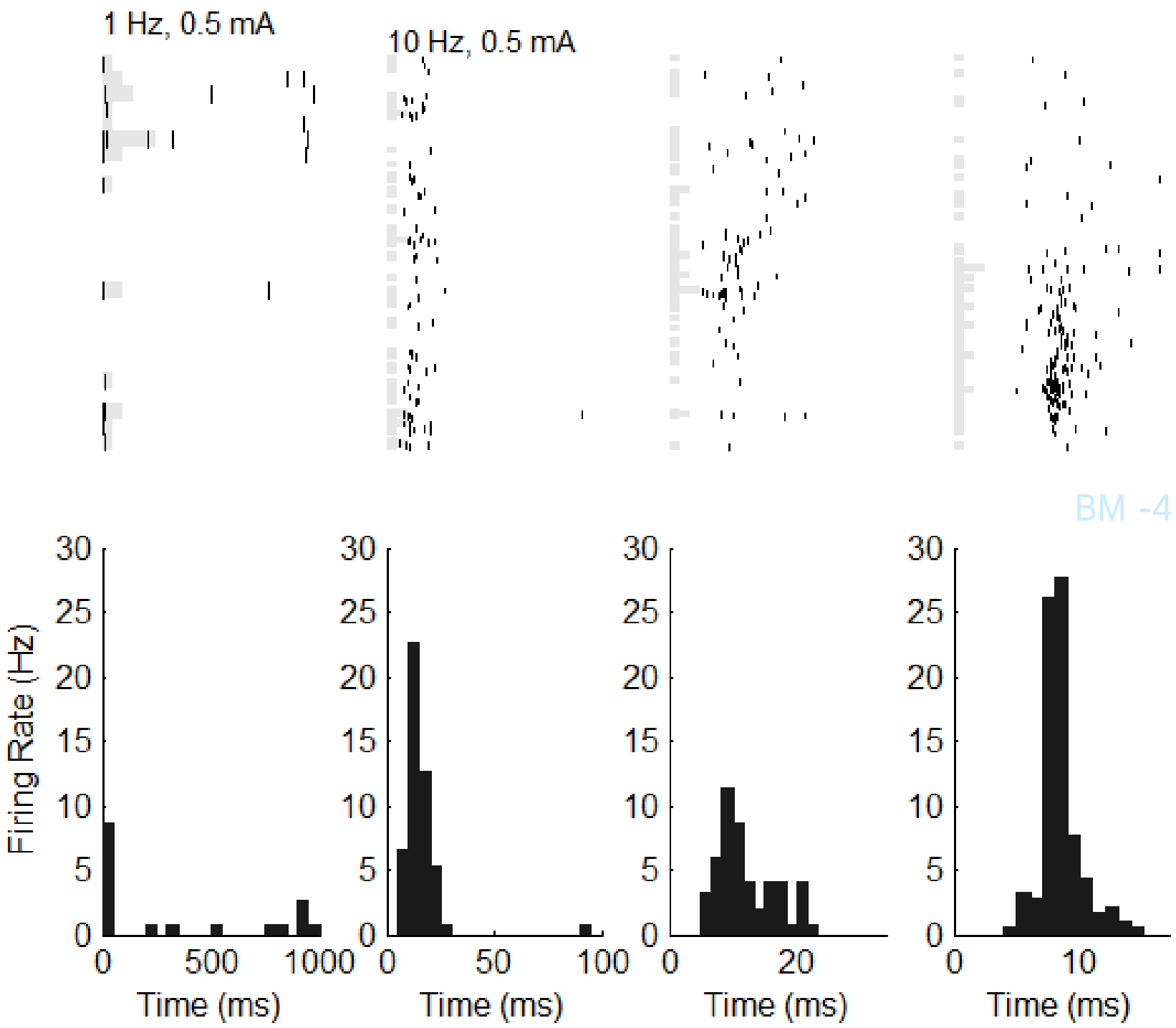


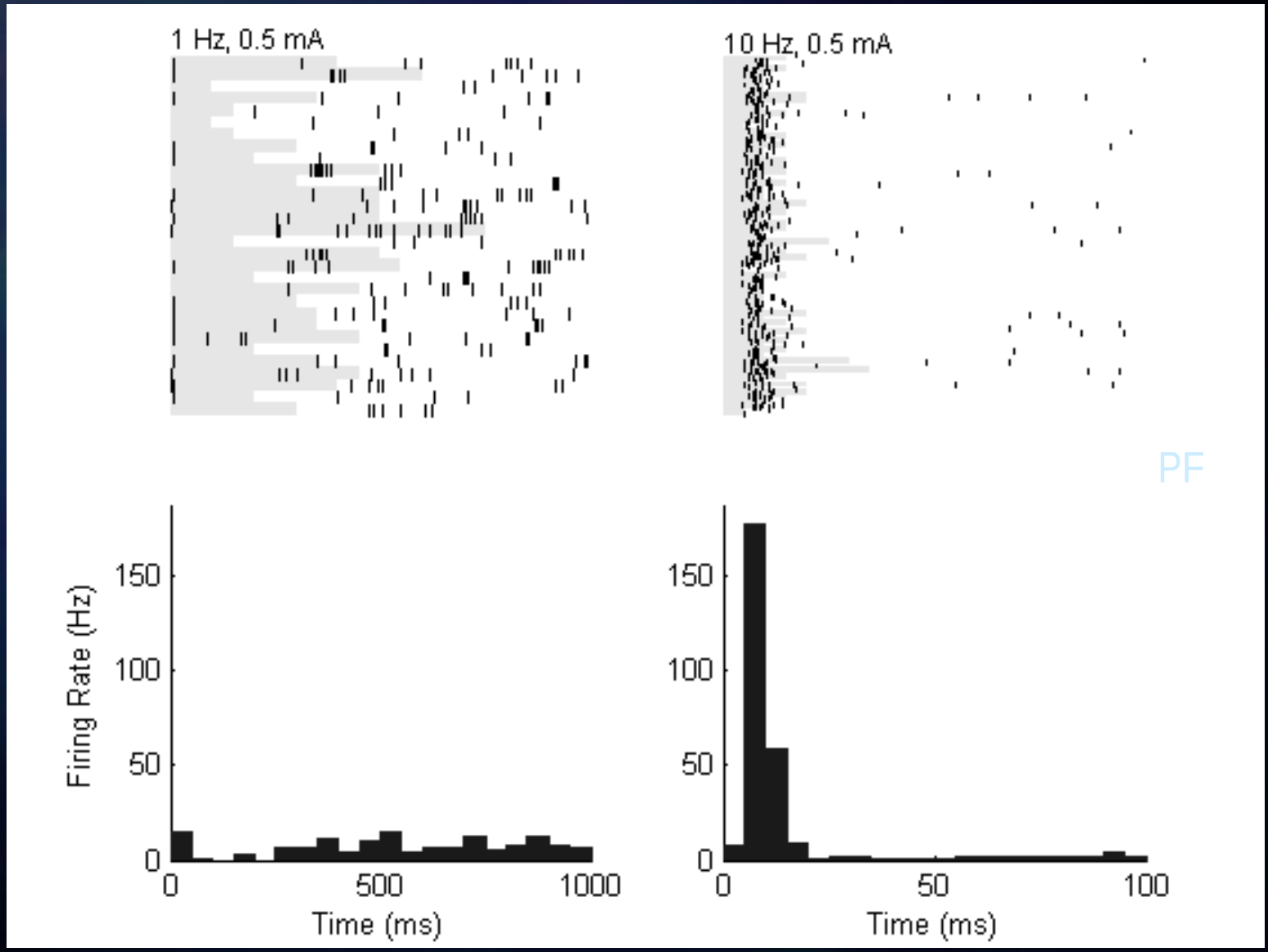
PF



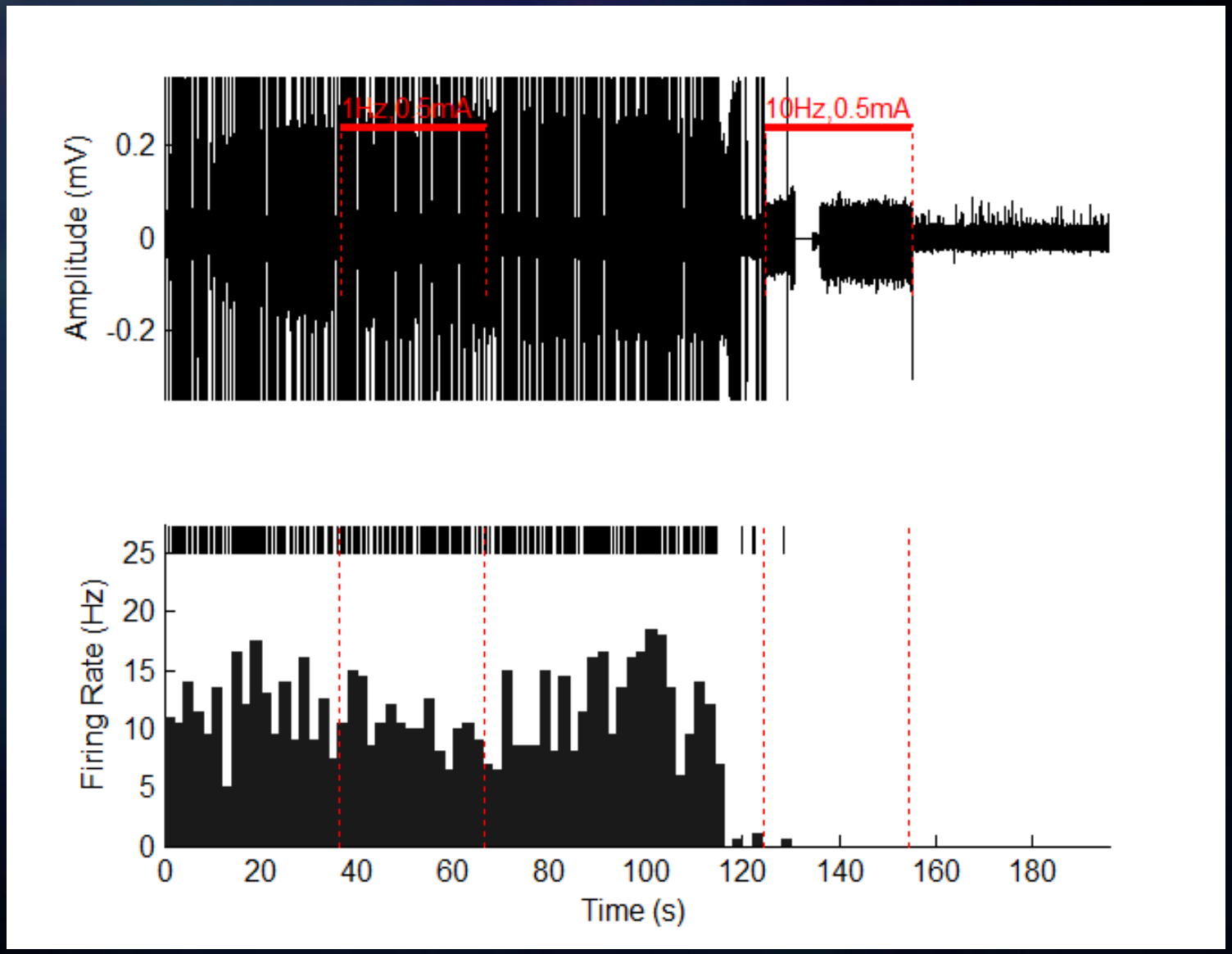
unit 1


1 Hz, 1.0 mA
10 Hz, 1.0 mA
30 Hz, 1.0 mA
60 Hz, 1.0 mA
PF
Firing Rate (Hz)
200
150
100
50
0
0
500
1000
Time (ms)
0
50
100
Time (ms)
0
20
Time (ms)
0
10
Time (ms)

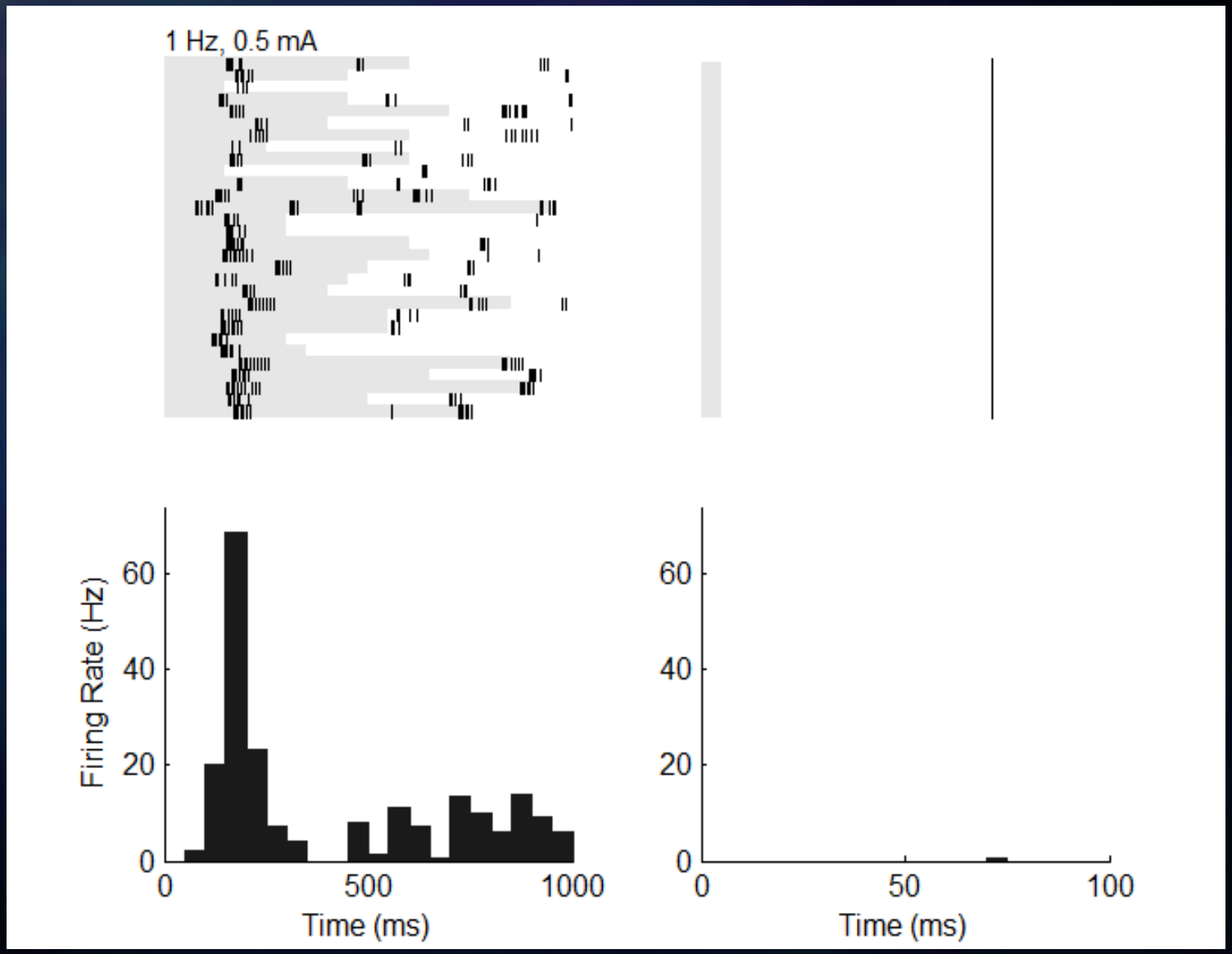

1 Hz, 0.5 mA
10 Hz, 0.5 mA
BM -4.22
Firing Rate (Hz)
0
5
10
15
20
25
30
0
500
1000
50
100
20
10
Time (ms)


1 Hz, 0.5 mA
10 Hz, 0.5 mA
PF
Firing Rate (Hz)
150
100
50
0
0
500
1000
Time (ms)
150
100
50
0
0
50
100
Time (ms)

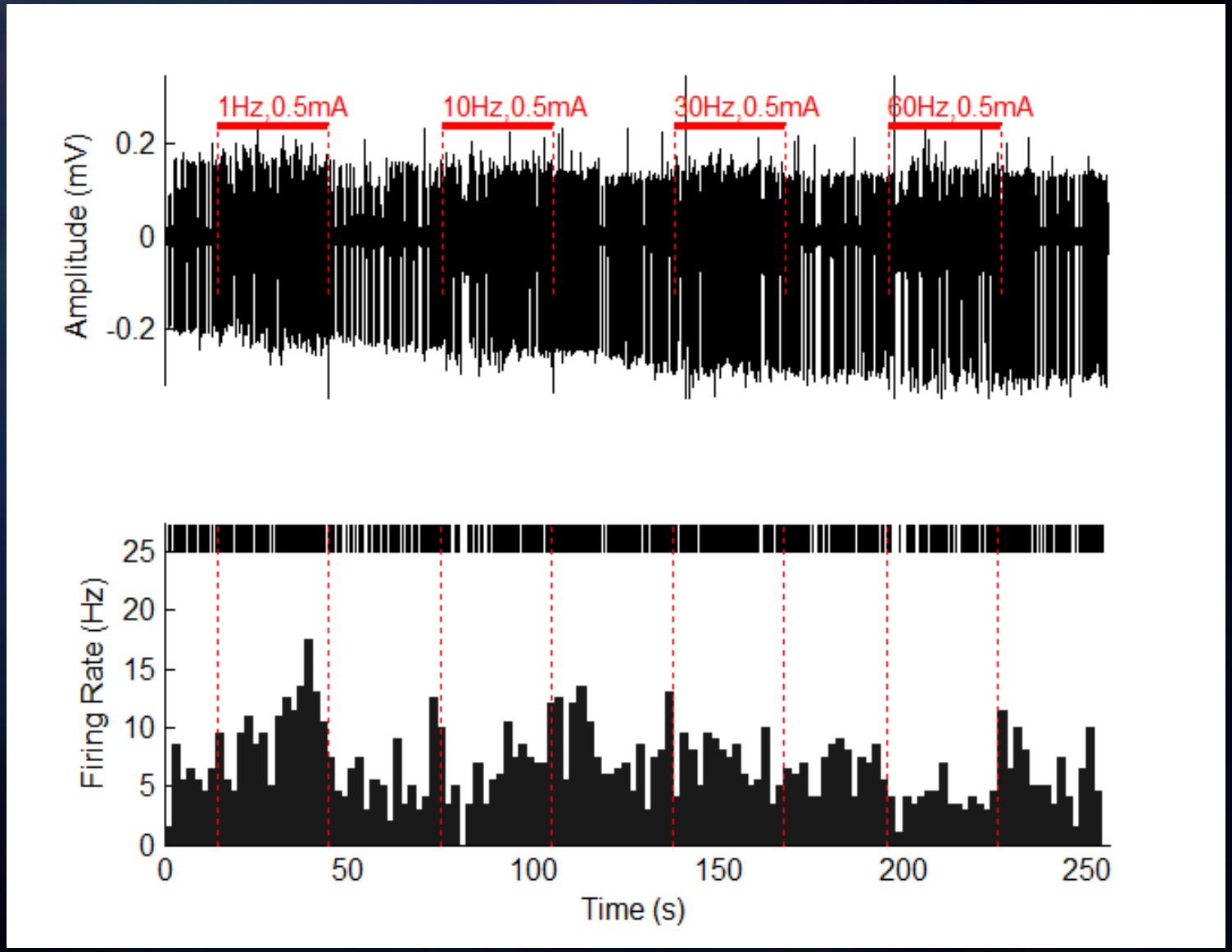
unit 1


1Hz,0.5mA
10Hz,0.5mA
Amplitude (mV)
0.2
0
-0.2
Firing Rate (Hz)
25
20
15
10
5
0
0
20
40
60
80
100
120
140
160
180
Time (s)

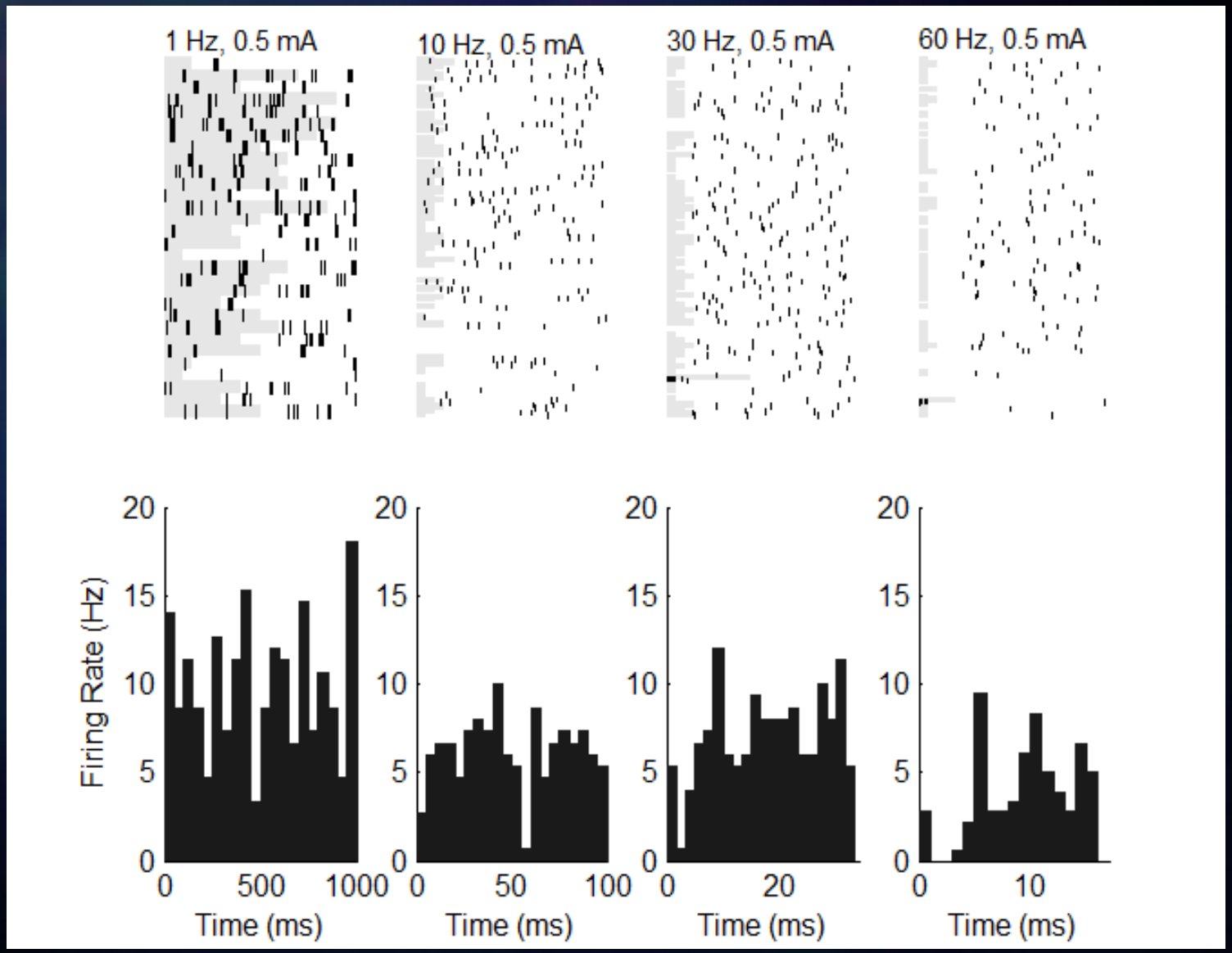
unit 1


1 Hz, 0.5 mA
Firing Rate (Hz)
60
40
20
0
0
500
1000
Time (ms)
60
40
20
0
0
50
100
Time (ms)

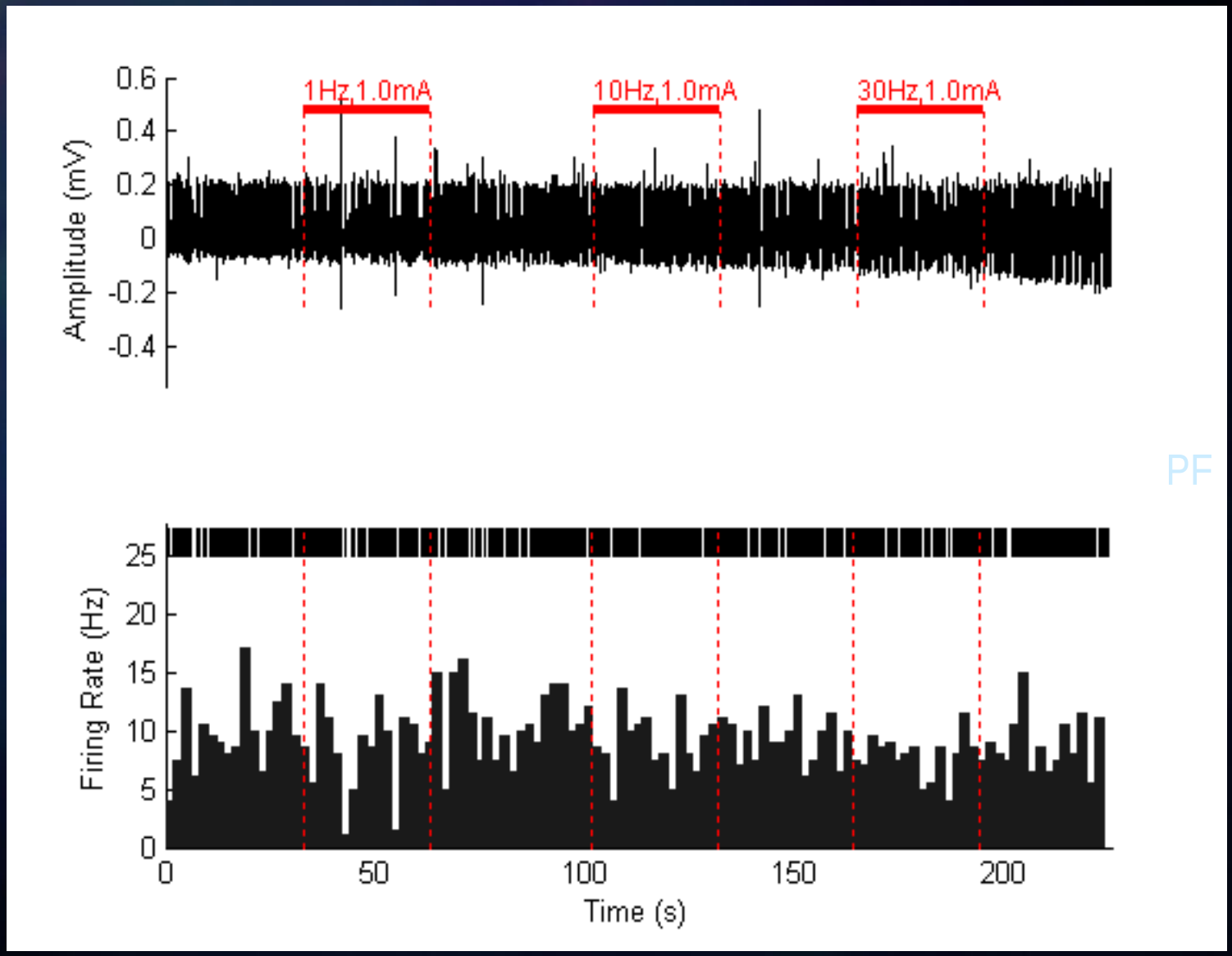
unit 1


1Hz,0.5mA
10Hz,0.5mA
30Hz,0.5mA
60Hz,0.5mA
Amplitude (mV)
0.2
0
-0.2
Firing Rate (Hz)
25
20
15
10
5
0
0
50
100
150
200
250
Time (s)

unit 1

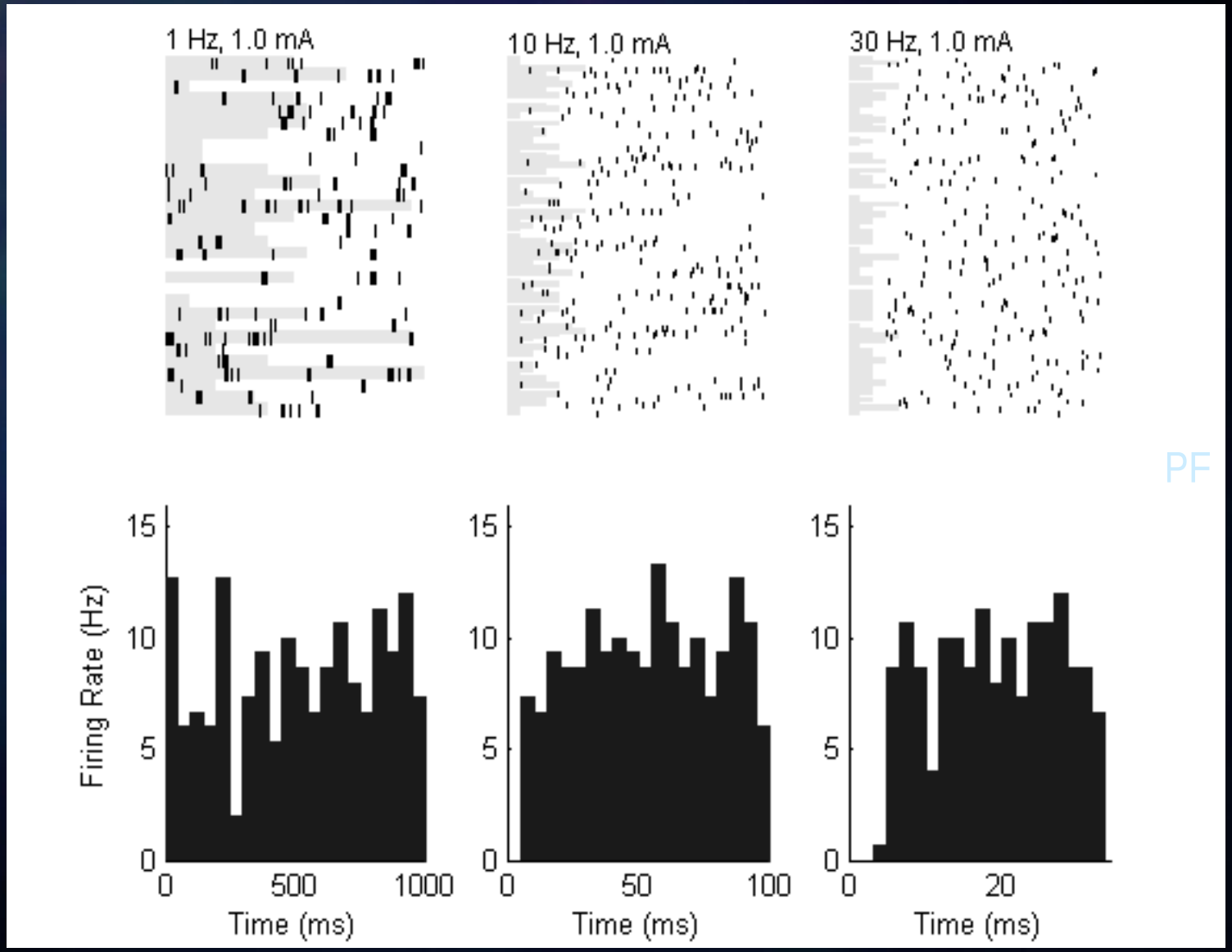

1 Hz, 0.5 mA
10 Hz, 0.5 mA
30 Hz, 0.5 mA
60 Hz, 0.5 mA
Firing Rate (Hz)
0
5
10
15
20
0
500
1000
50
100
20
10
Time (ms)

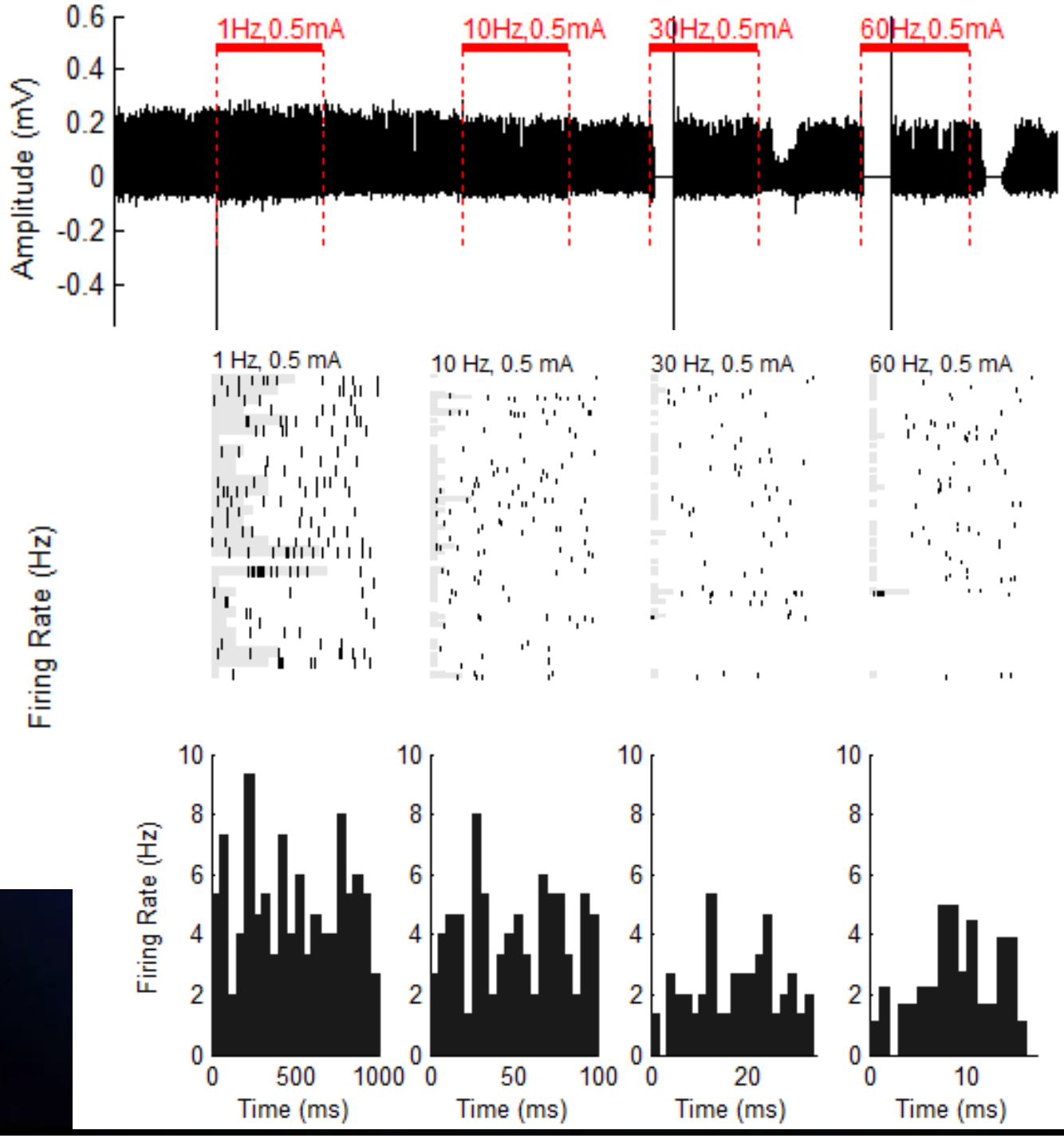
unit 1

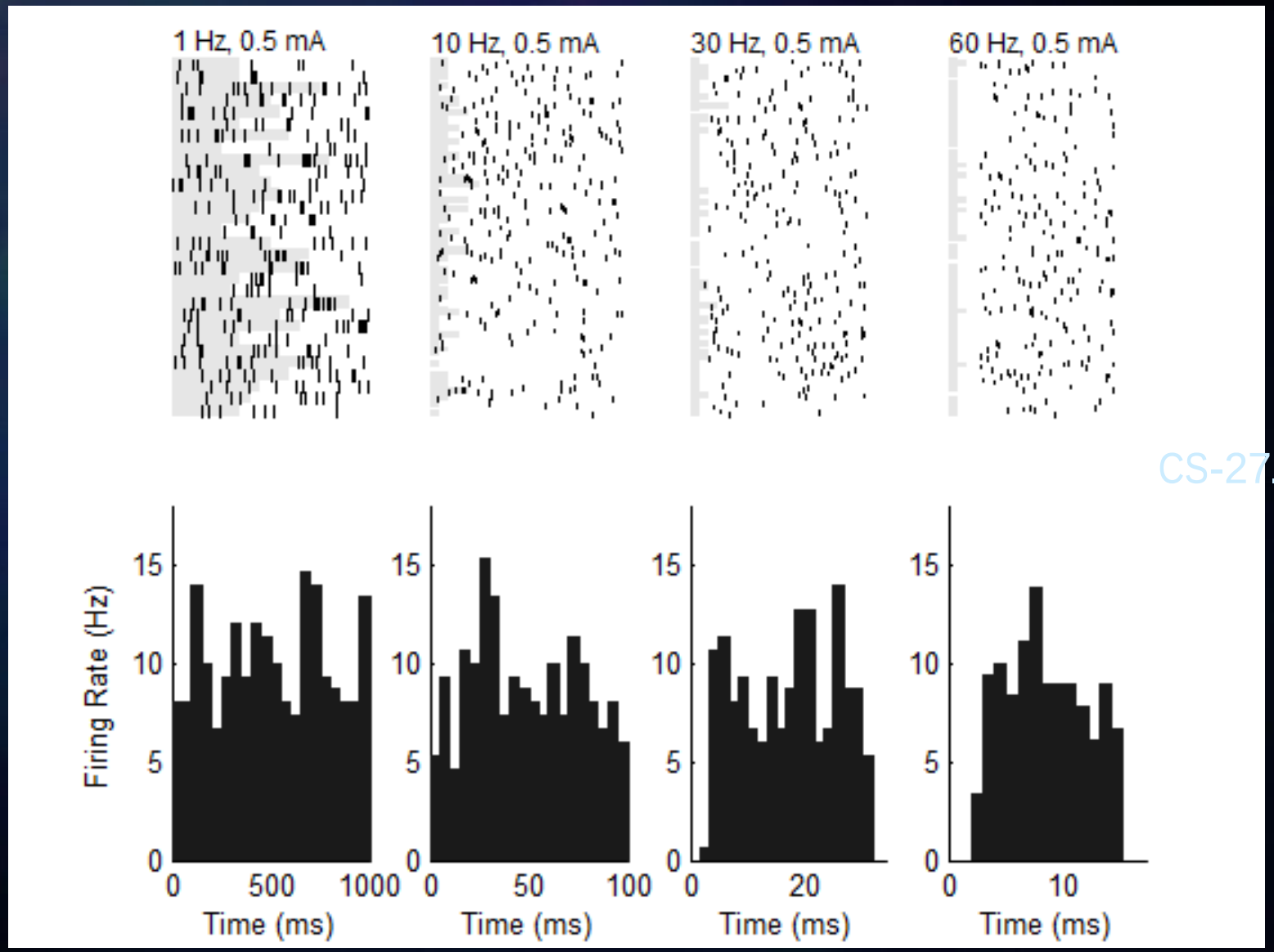

1Hz,1.0mA
10Hz,1.0mA
30Hz,1.0mA
Amplitude (mV)
0.6
0.4
0.2
0
-0.2
-0.4
Firing Rate (Hz)
25
20
15
10
5
0
0
50
100
150
200
Time (s)

PF

unit 1


1 Hz, 1.0 mA
10 Hz, 1.0 mA
30 Hz, 1.0 mA
PF
Firing Rate (Hz)
15
10
5
0
0
500
1000
Time (ms)
15
10
5
0
0
50
100
Time (ms)
15
10
5
0
0
20
Time (ms)


1Hz,0.5mA
10Hz,0.5mA
30Hz,0.5mA
60Hz,0.5mA
Amplitude (mV)
0.6
0.4
0.2
0
-0.2
-0.4
1 Hz, 0.5 mA
10 Hz, 0.5 mA
30 Hz, 0.5 mA
60 Hz, 0.5 mA
Firing Rate (Hz)
Firing Rate (Hz)
Time (ms)
Time (ms)
Time (ms)
Time (ms)


1 Hz, 0.5 mA
10 Hz, 0.5 mA
30 Hz, 0.5 mA
60 Hz, 0.5 mA
Firing Rate (Hz)
0
5
10
15
0
500
1000
Time (ms)
0
50
100
Time (ms)
0
20
Time (ms)
0
10
Time (ms)

CS-27.82