Connectivity Induced Synchronization in Cortical Neuronal Cultures

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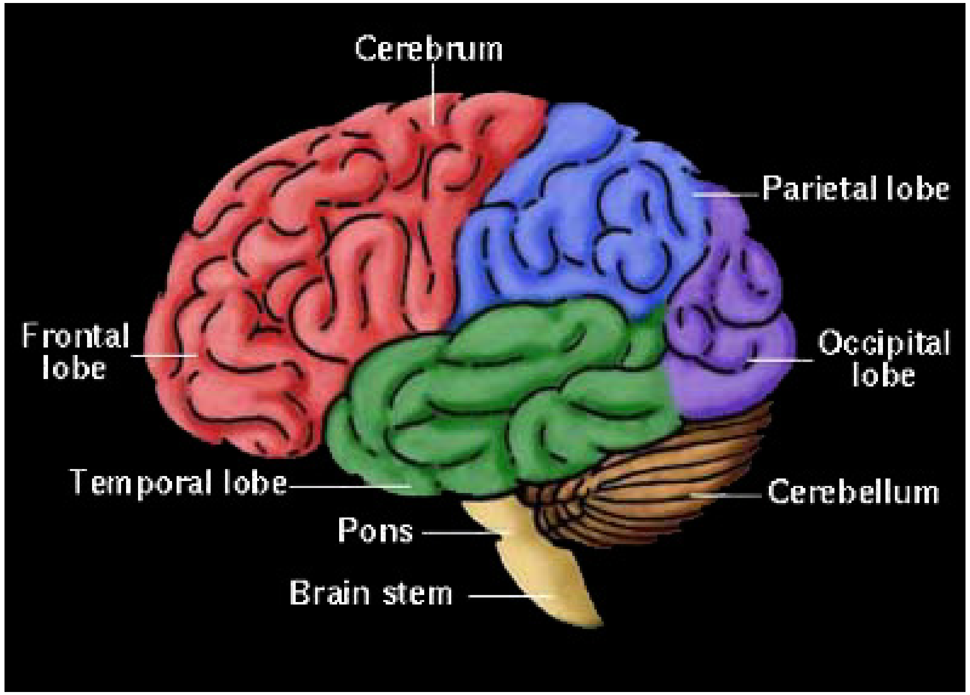
1. Synchronized Bursting (SB) in Cultures
   Ca image experiments

2. A Possible Mechanism of SB
   Electrophysiological experiments

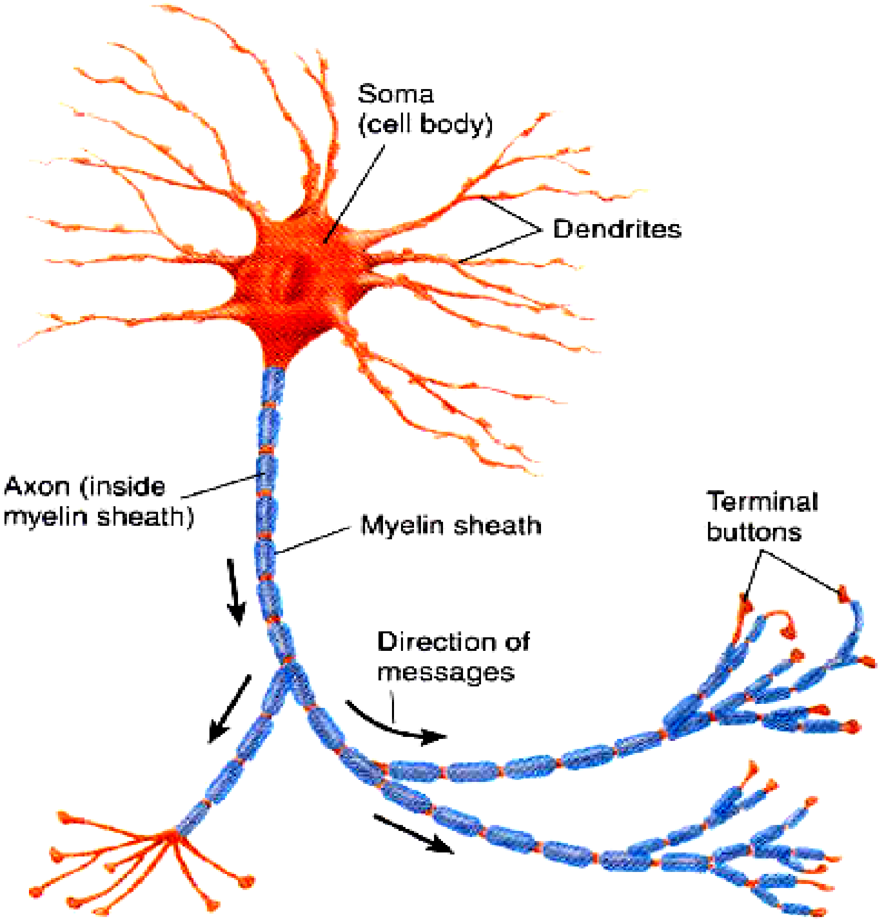
3. Role of Glia
   Culture staining and Ca image experiments

Neuron→ Network → Brain



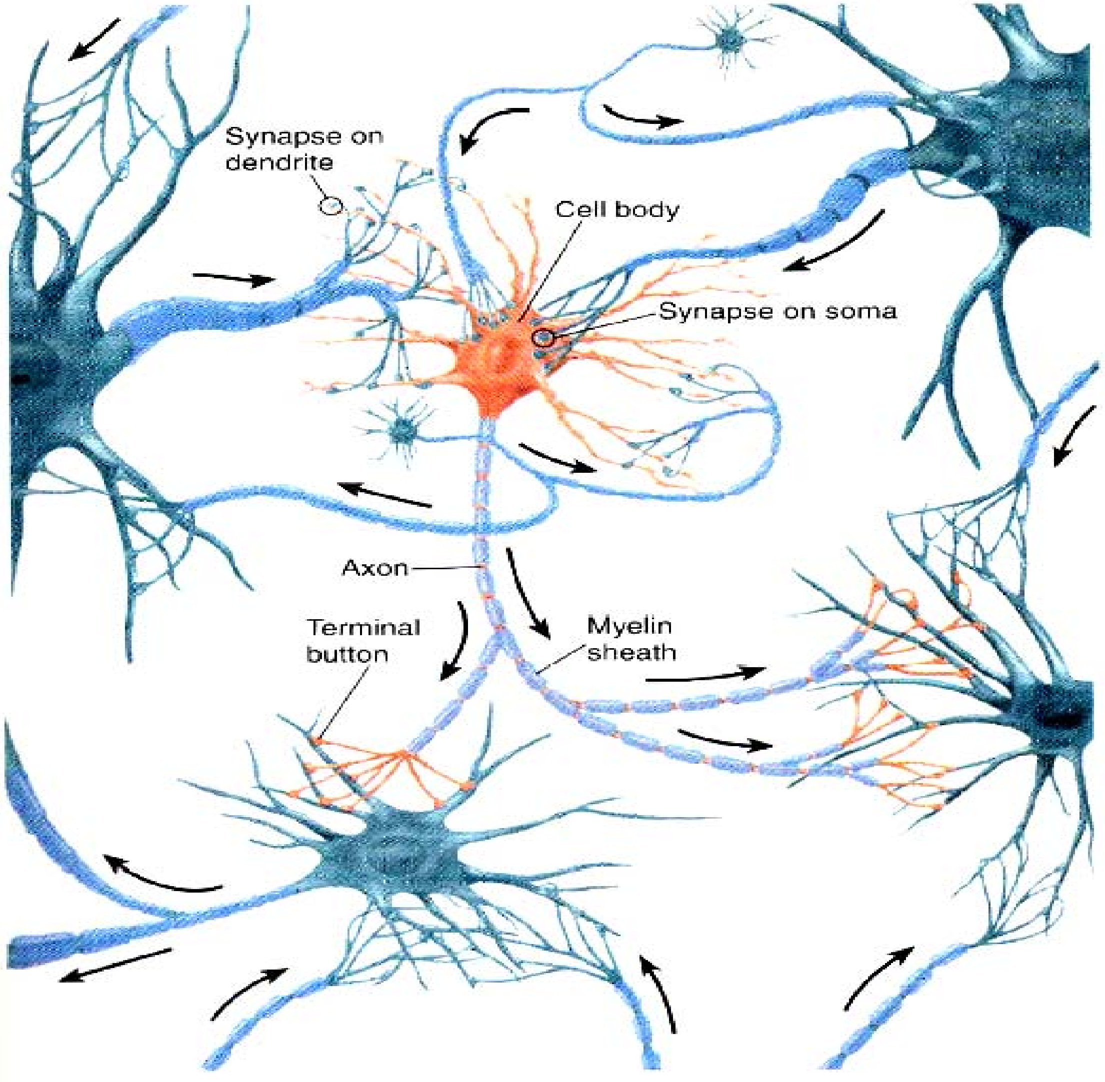
Simple Behavior of node →
complex behavior of the system !

Neuron – an excitable element



From: The physiology of behavior

Connection between neurons: Synapses



From: The physiology of behavior

Different Approaches

Top Down

- fMRI, MEG
- Brain Waves

Bottom Up

- Neuronal Cultures

Important Issues for Neuroscience

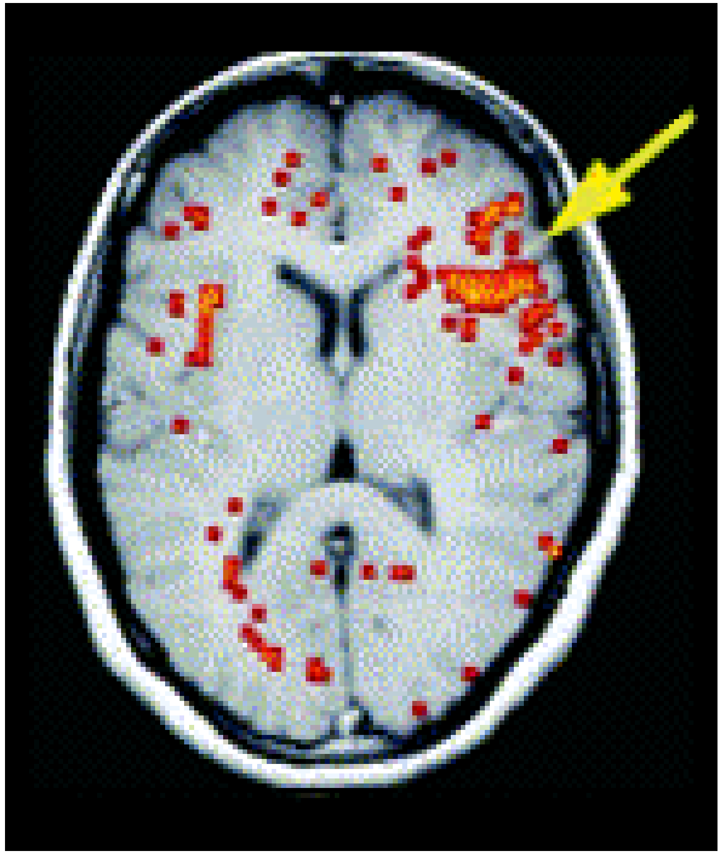
Good to understand:

- Dynamics of Synapses
- Topology of Neural Networks
- Dynamics of Neural Networks

  → Brain functions?

But we do not even understand Epilepsy!

(synchronization?)



Brain scan of a person with frontal lobe epilepsy. Arrow points to the focus of seizure activity. [Image reproduced with permission from Seeck et al. (1998) Electroenceph. Clin. Neurophys. 106, 508-512.]

European Journal of Neuroscience, Vol. 9, pp. 990–999, 1997

Synchronization of Neuronal Activity Promotes Survival of Individual Rat Neocortical Neurons in Early Development

Thomas Voigt[1,2], Herwig Baier[3] and Ana Dolabela de Lima[1,2]
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[2]Present address: Otto-von-Guericke Universität Magdeburg, Medizinische Fakultät, Institut für Physiologie, Leipziger Str. 44, 39120 Magdeburg, Germany
[3]Present address: University of California, San Diego, Department of Biology, CA 92093-0366, USA

Our Goals

- Synchronization in neural networks seems to be generic and robust.
- Generate synchronization in neuronal networks and try to understand it

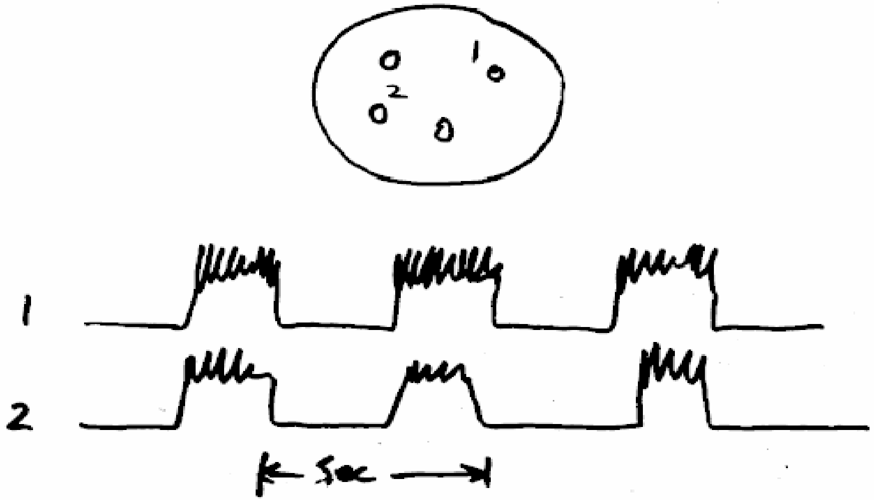
Primary Neuronal Cultures in the view of a Physicist

- Growing (random?) Networks

- Self-organized assembly of identical nonlinear elements

- Generic Synaptic dynamics + Topology ←→ (Network Synchronization) ?

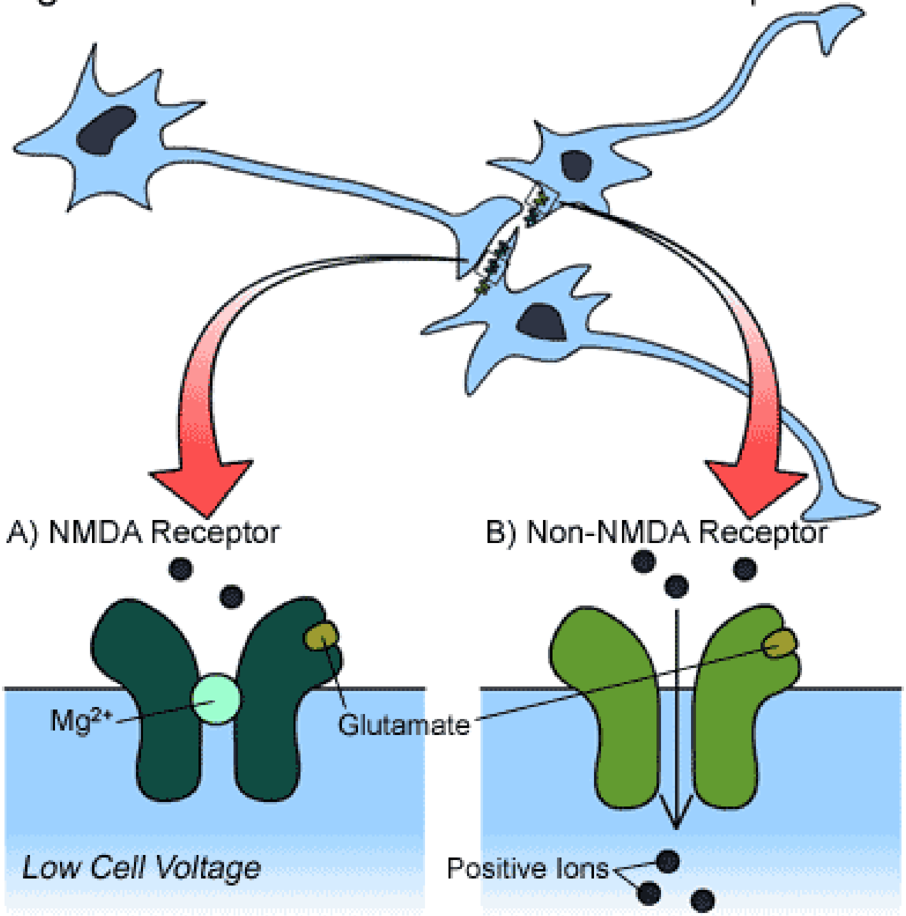
Synchronous Bursting induced by low [Mg^{++}] (Muramoto 1988)



→ Synchronized firing of spatially distributed neurons with $f \lesssim 1.0$ Hz

↳ Brain waves ~ 40 Hz

Figure L-1: NMDA and Non-NMDA Receptors

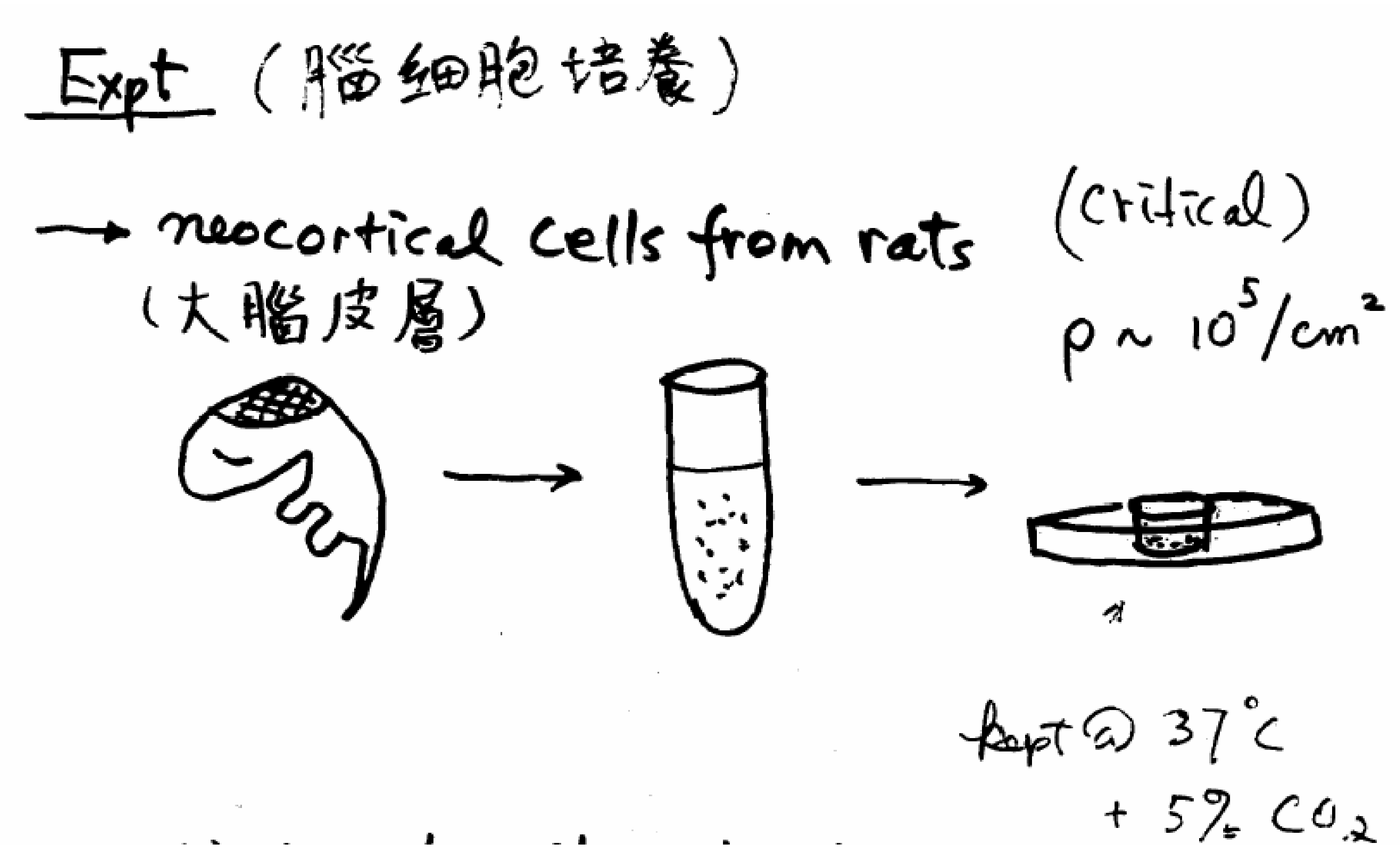


A) The NMDA receptor is usually blocked by the Mg^{2+} ion. Positive ions are unable to rush in even if glutamate binds to NMDA unless the Mg^{2+} ion is removed by an increase in the cell voltage.

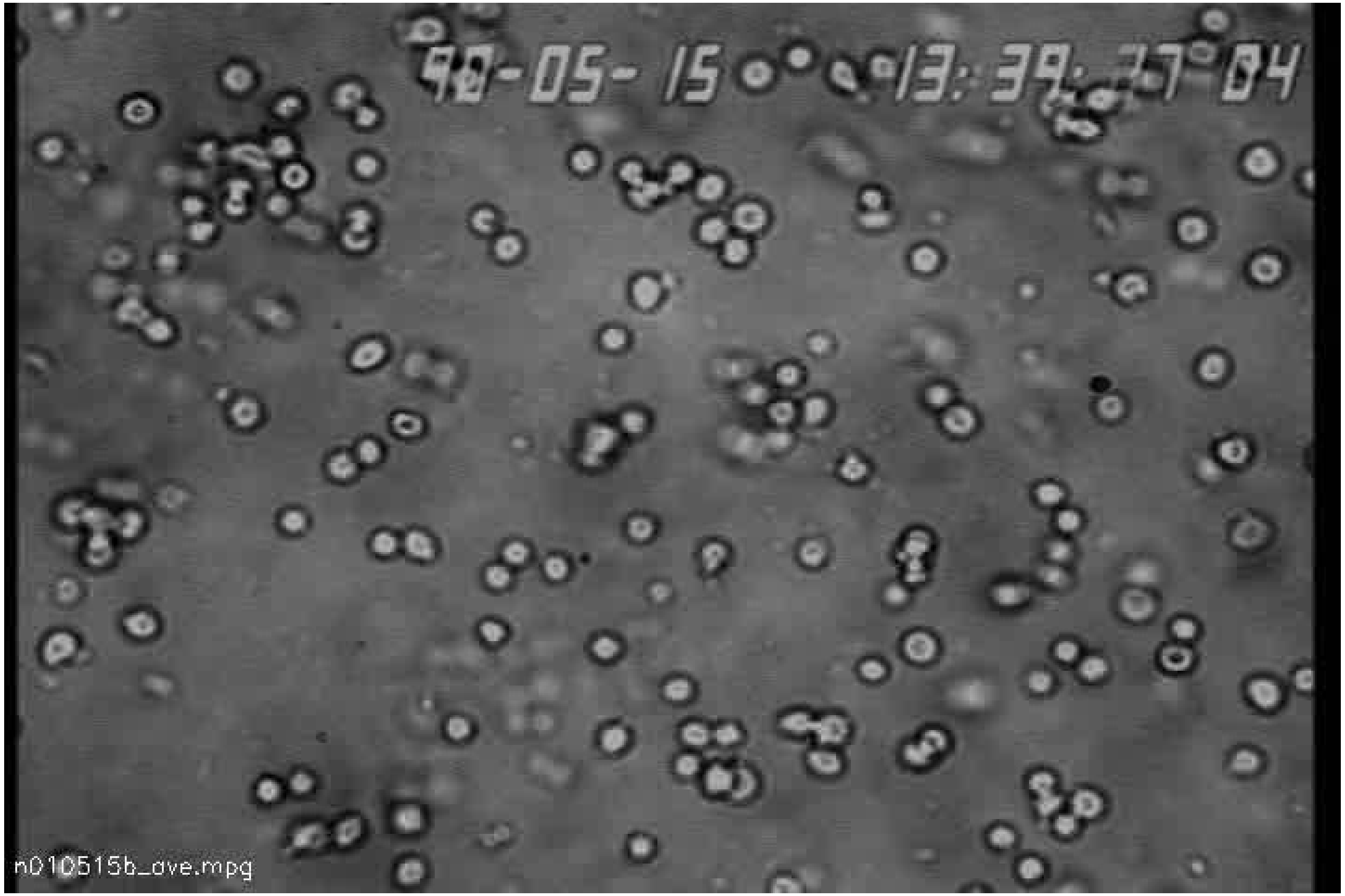
B) The non-NMDA receptor opens as soon as glutamate binds to it. Opening of the non-NMDA receptor allows the entry of positive ions into the cell.

http://www.stanford.edu/group/hopes/treatmts/antiglut/f_l01nmdarcptr.gif

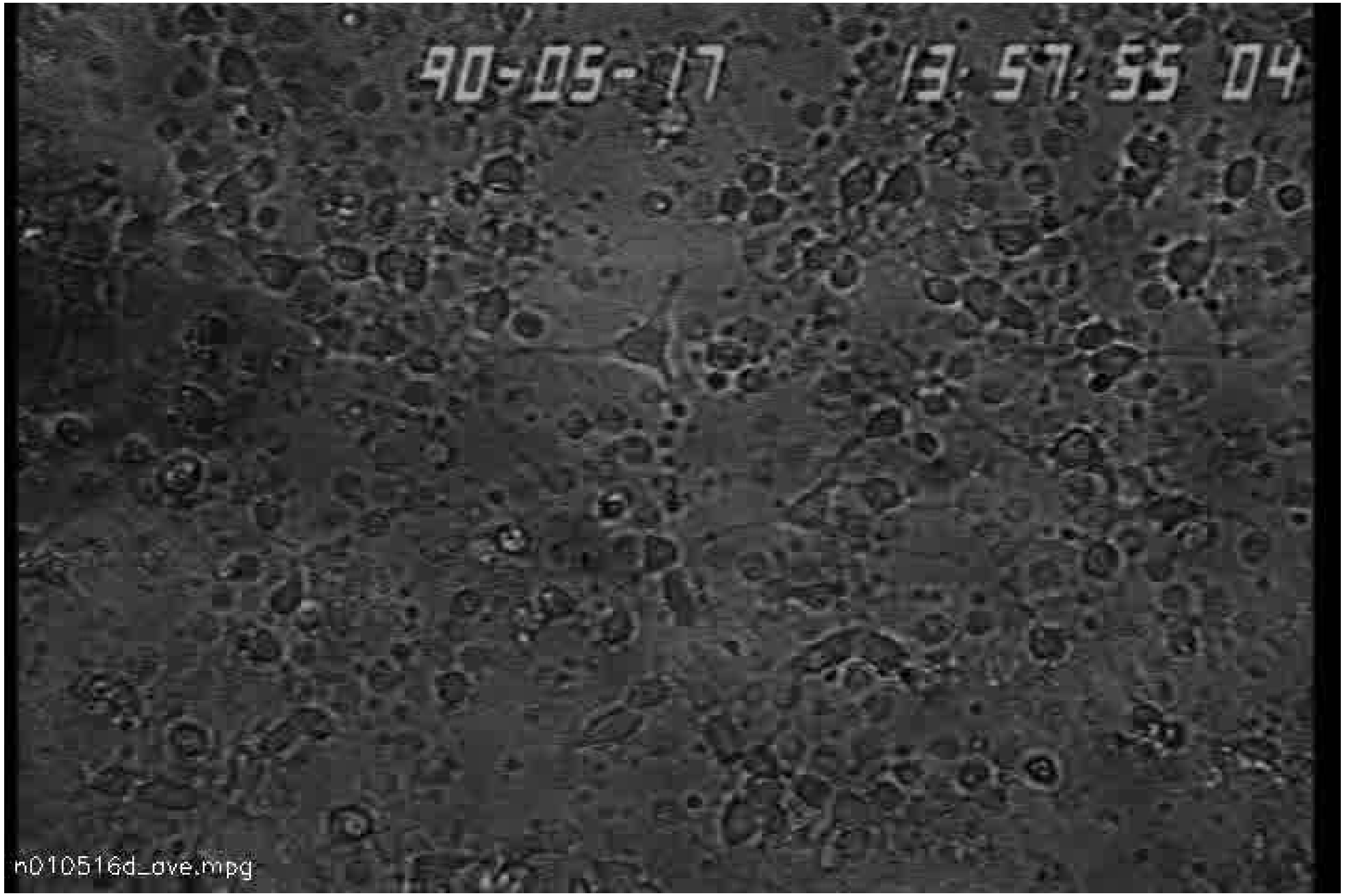
Cell Culture



Plating



Growth of Network



Control parameters

- Age of culture → physical connections
- $[Mg^{++}]$ → synaptic (signal) connections
- No. photolysis → Number of nodes

What have we done?

- Prepare cortical neuronal culture

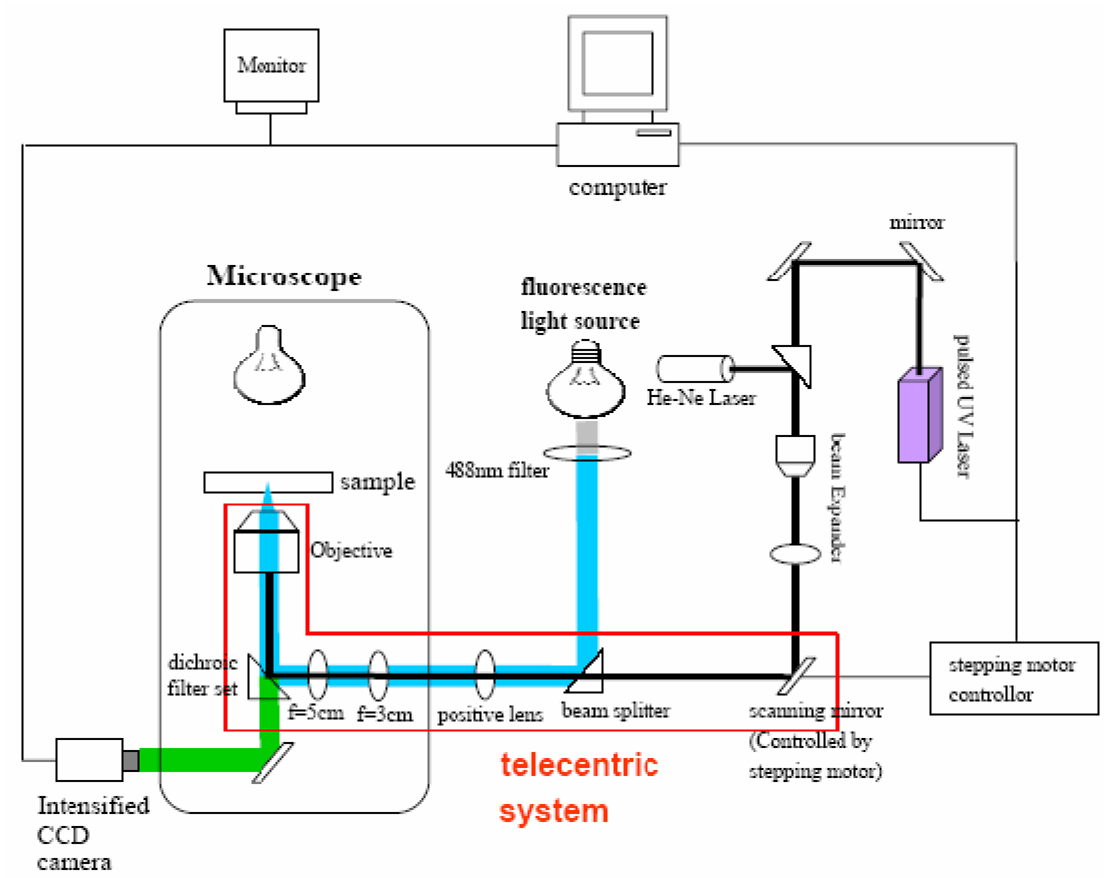
- Produce SF by low Mg condition

- Monitor of network behavior
  - Ca imaging
  - electrophysiology measurement

Control of network connections:

- Mg concentration
- growth condition
- physically removing connections by UV laser

Experimental Setup

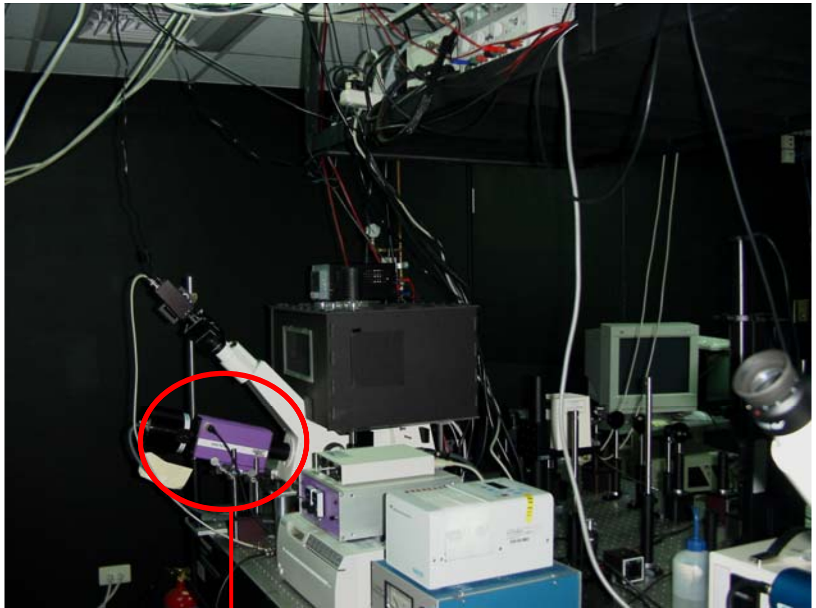


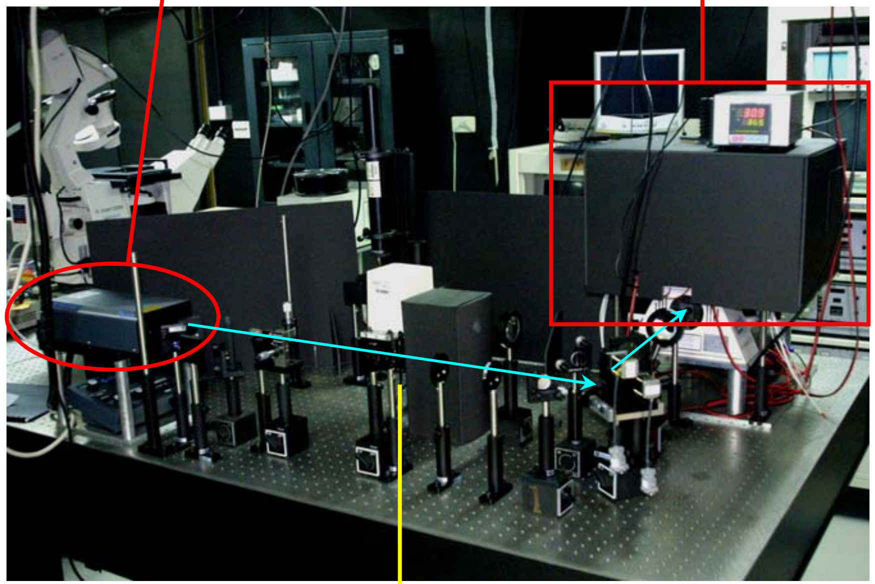
Fluorescence Imaging
(Calcium fluorescence dye – Oregon Green 488)

&

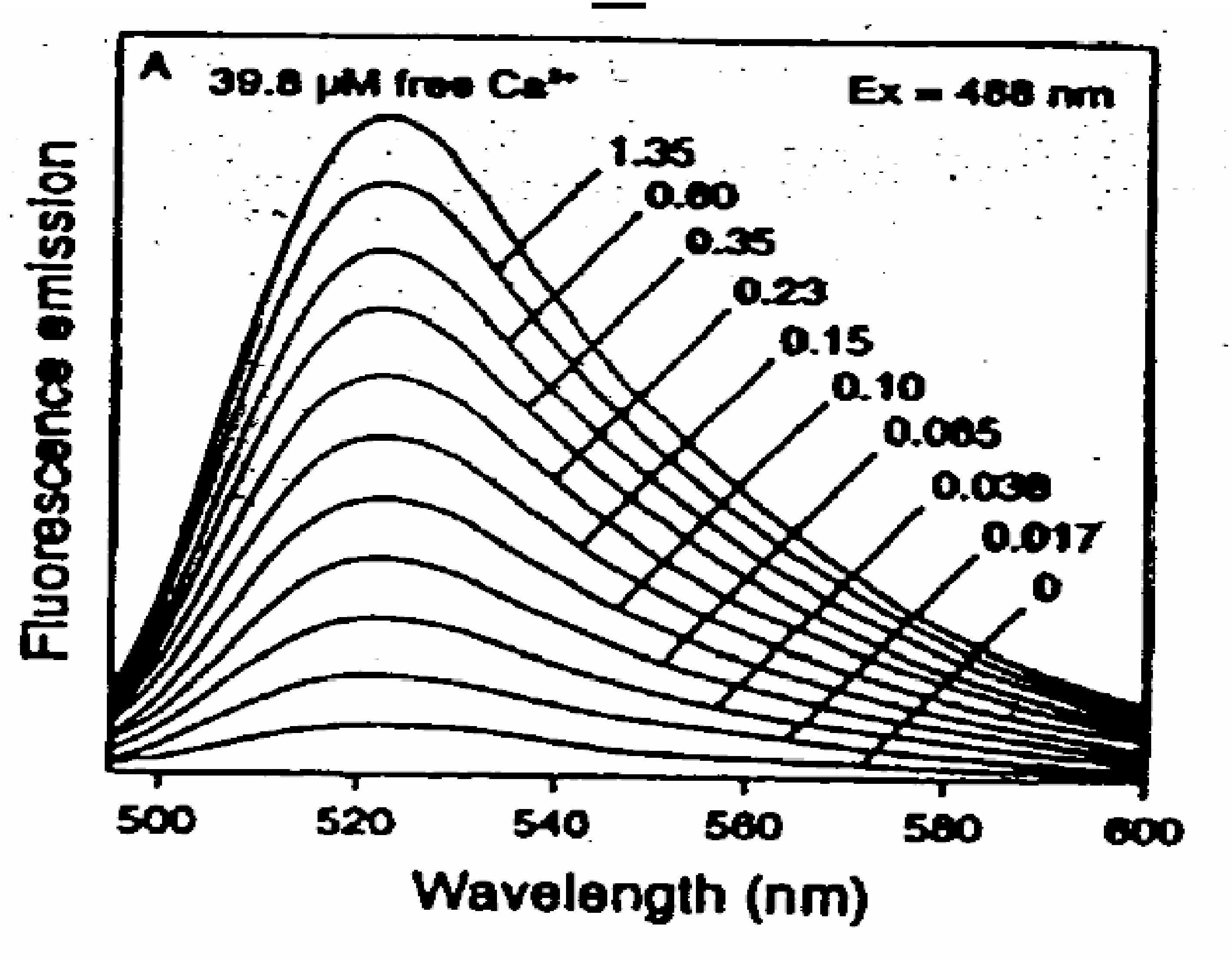
UV Laser Photolysis

The set-up of experiments

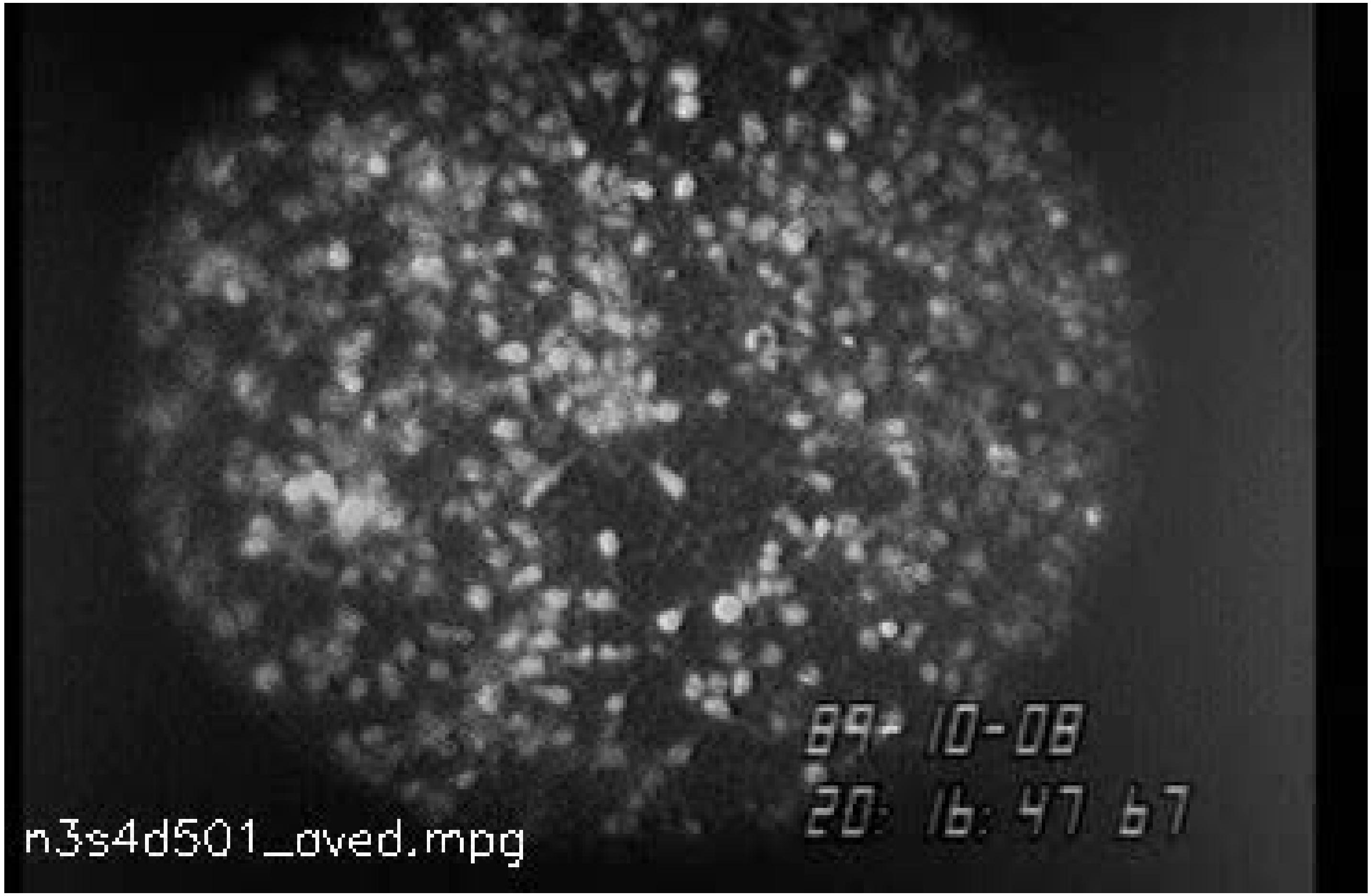


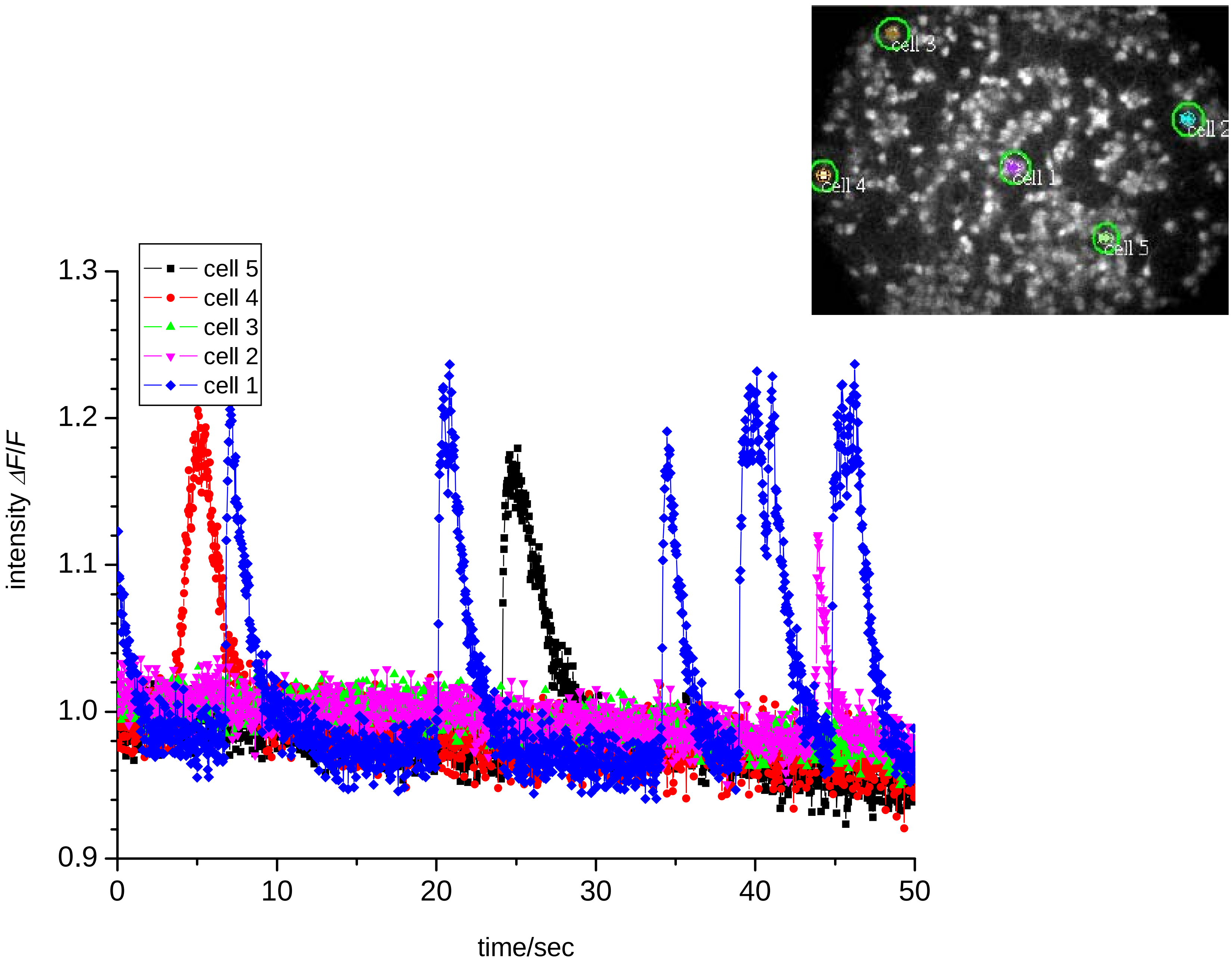


Calcium Measurement with OG_488

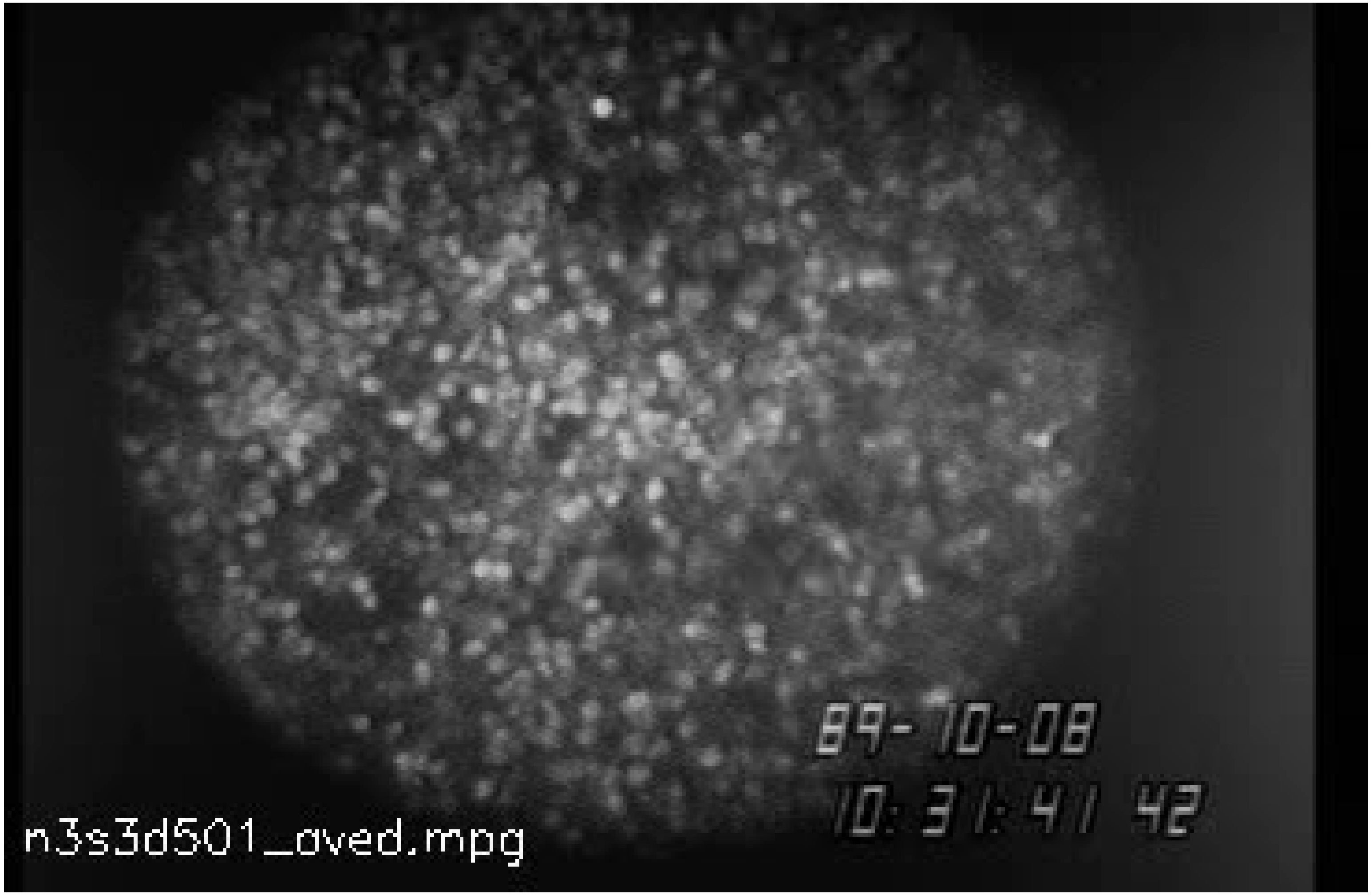


Random Firing

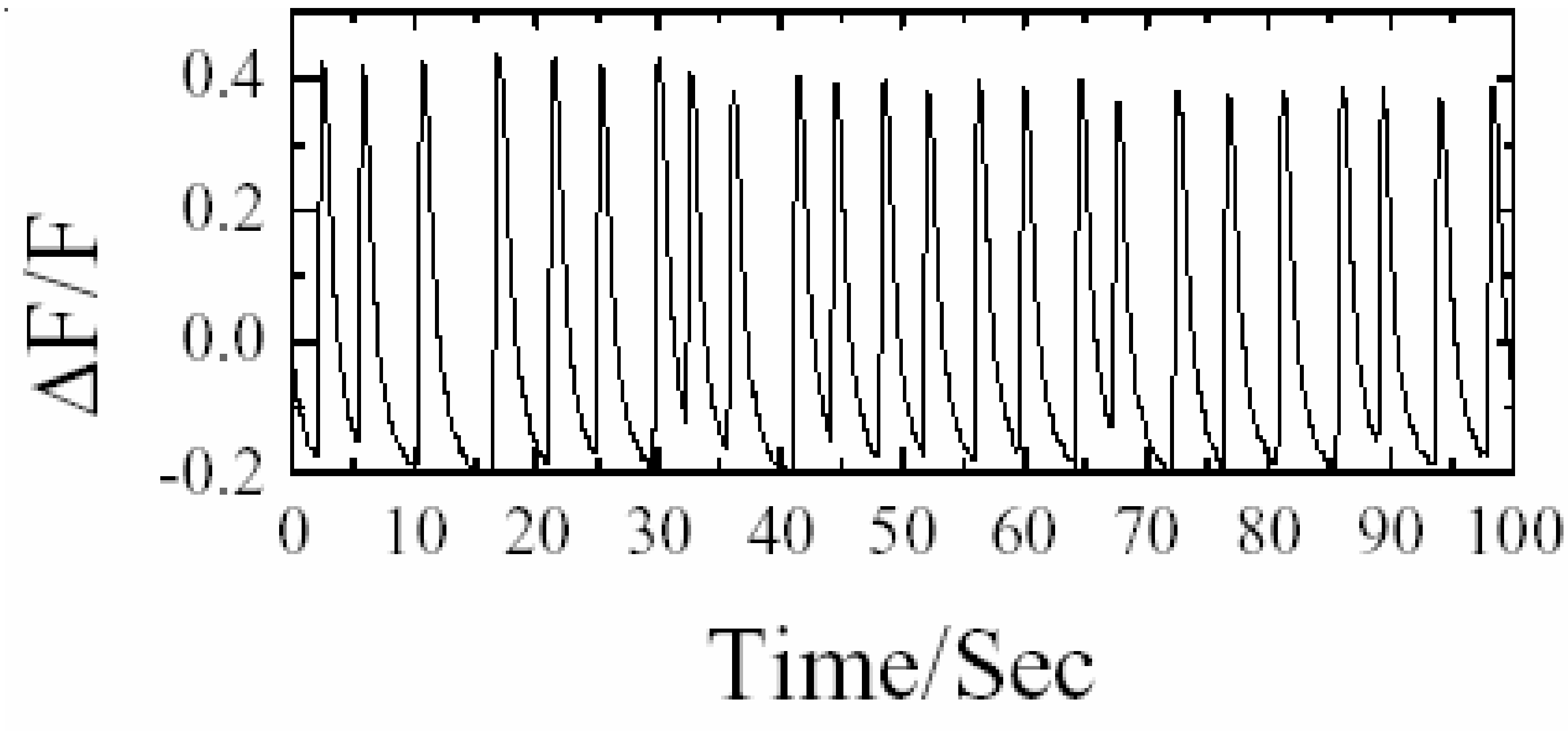



cell 5
cell 4
cell 3
cell 2
cell 1
intensity ΔF/F
time/sec
0.9
1.0
1.1
1.2
1.3
0
10
20
30
40
50
cell 3
cell 2
cell 1
cell 4
cell 5

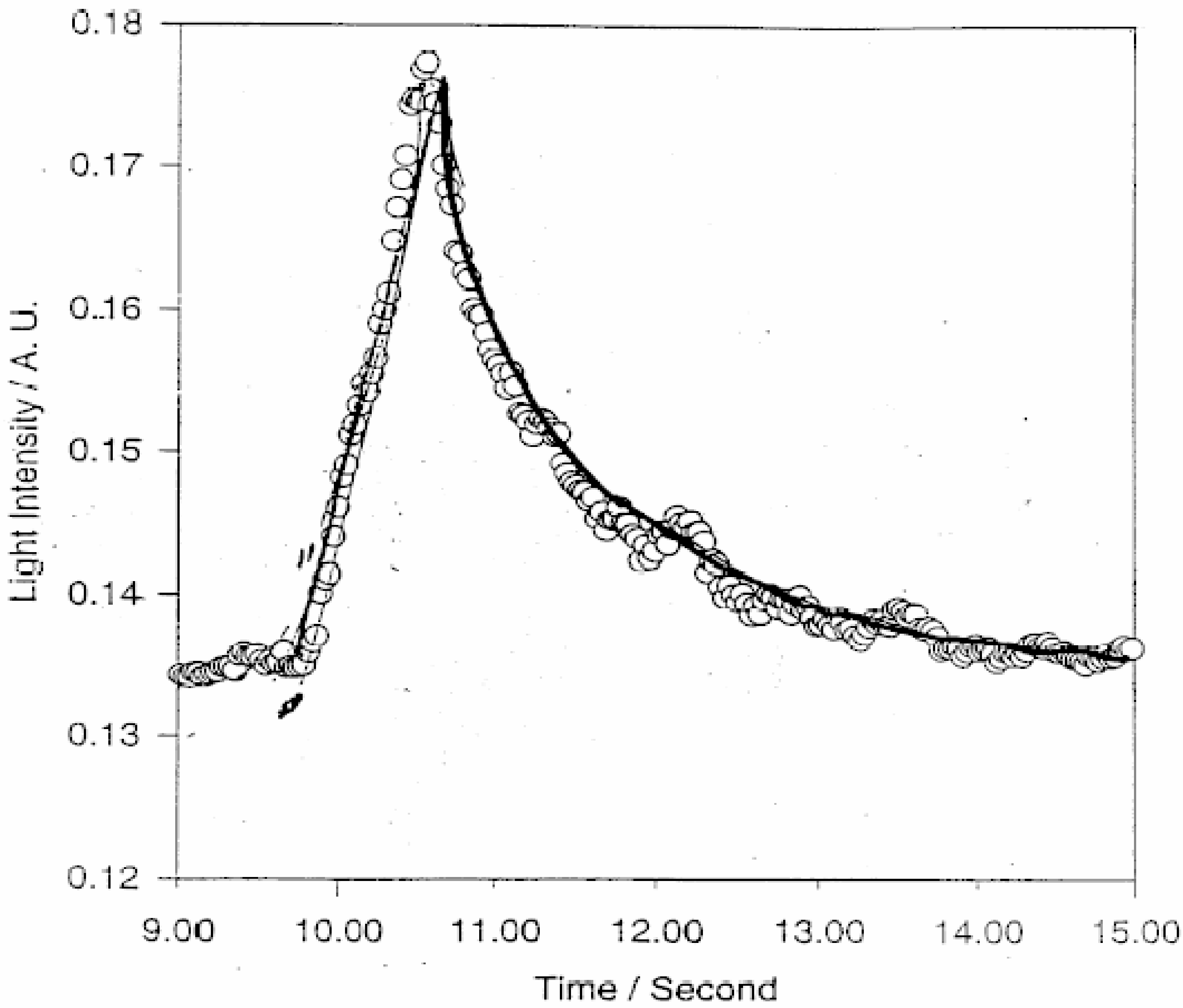
Synchronized Firing



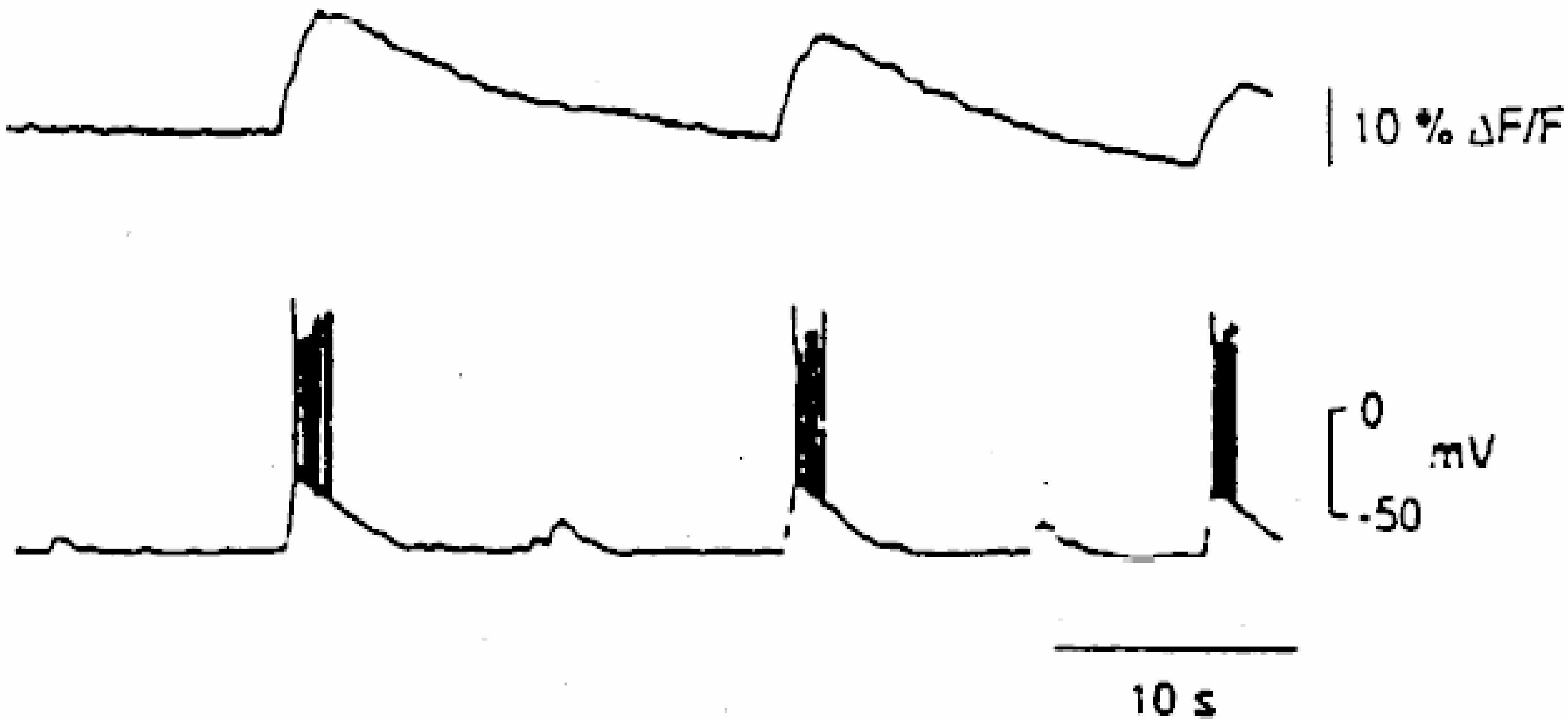
Sample fluorescence intensity data of the synchronized firing of a neuronal network.



Bursting Pulse (Universal)

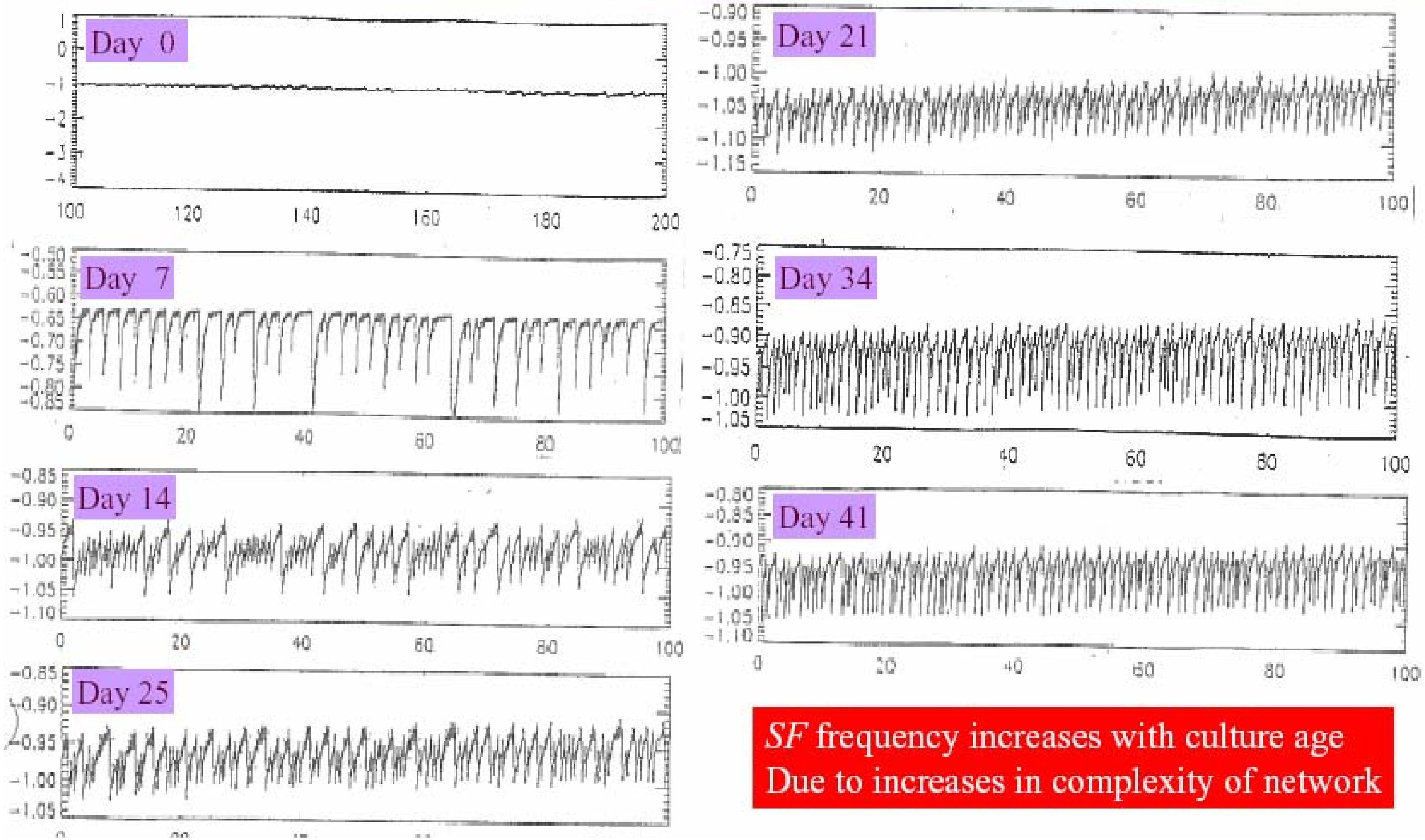


Many Spikes in one pulse



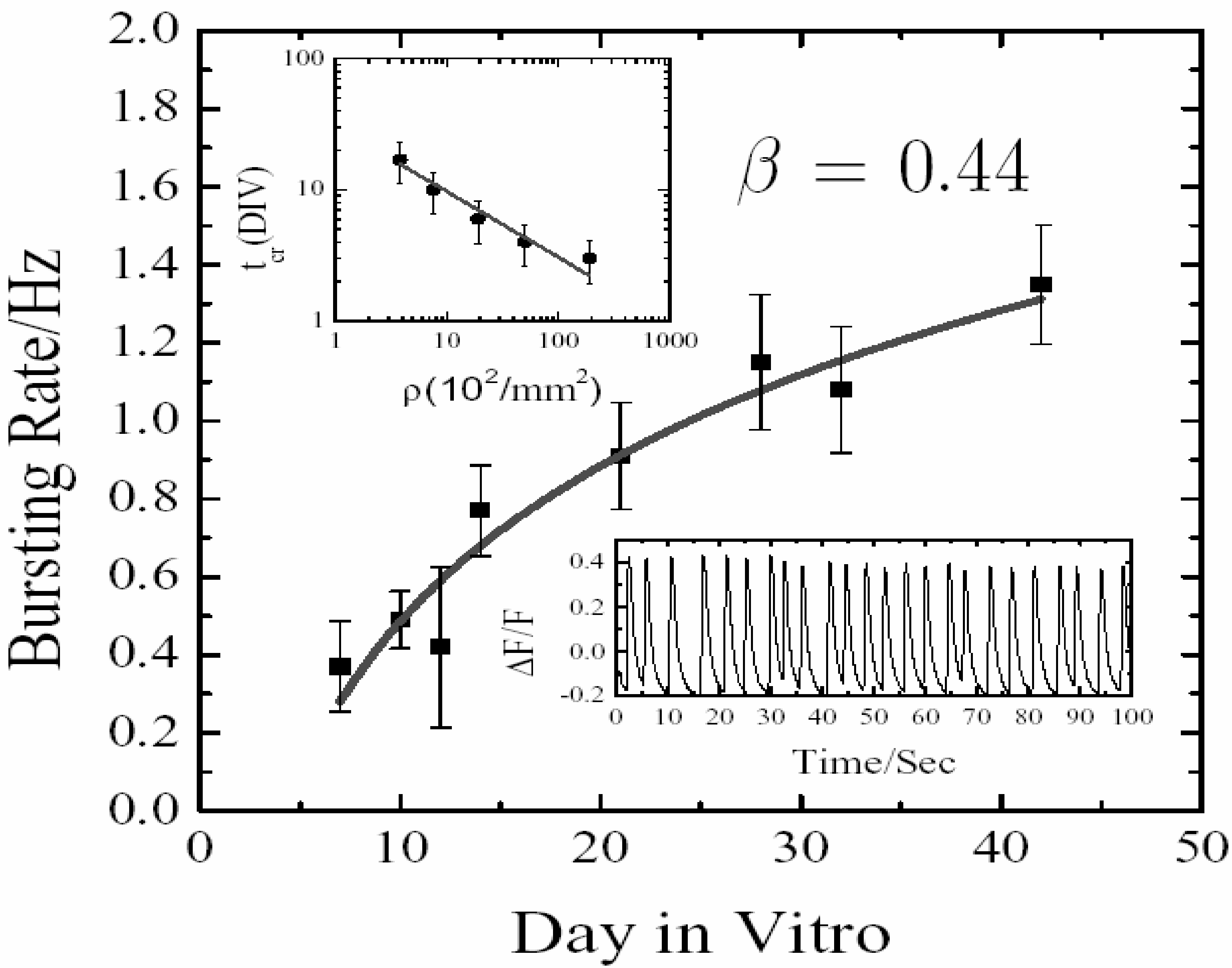
Synchronized Firing (SF) in neural networks

Light emitted measured by phototube

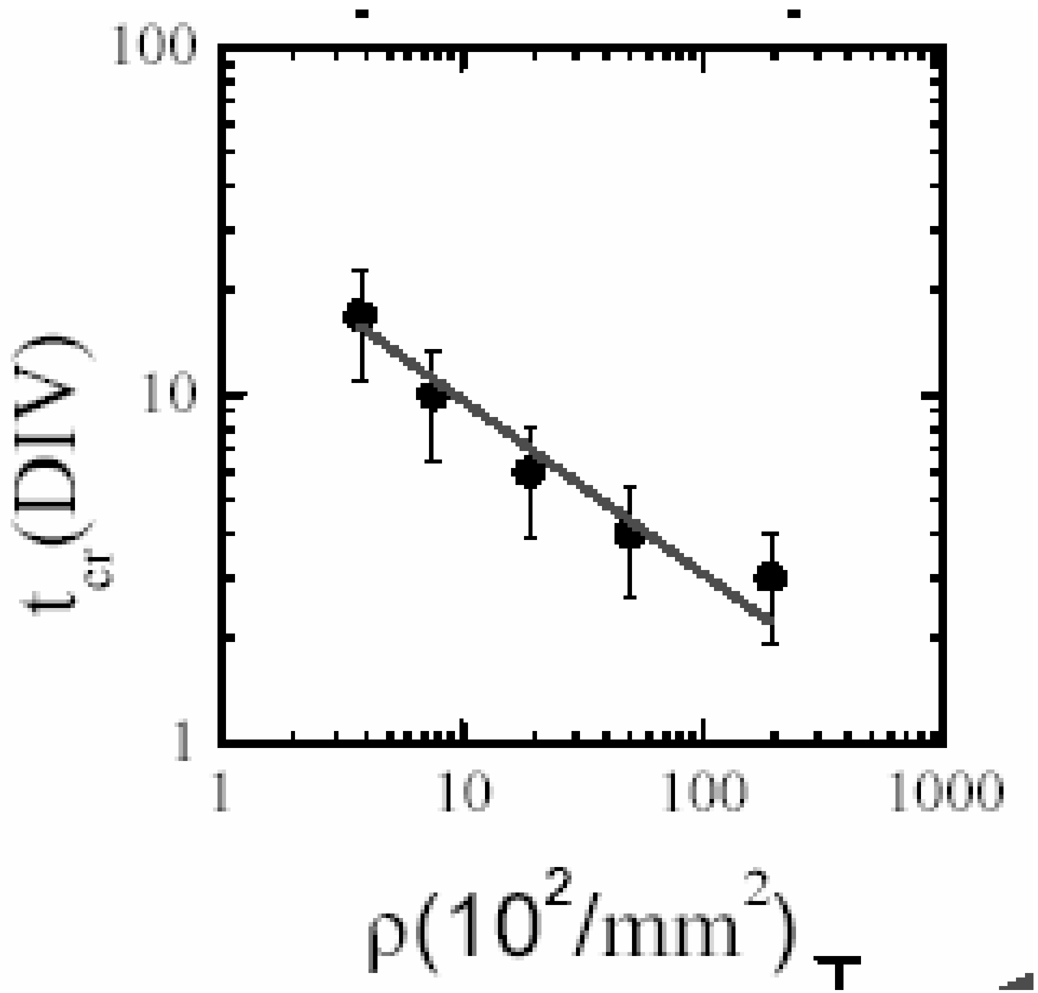


SF frequency increases with culture age
Due to increases in complexity of network

Result $f = f_c + f_0 log(t/t_c)$ $t_c \sim \rho^{-\beta}$



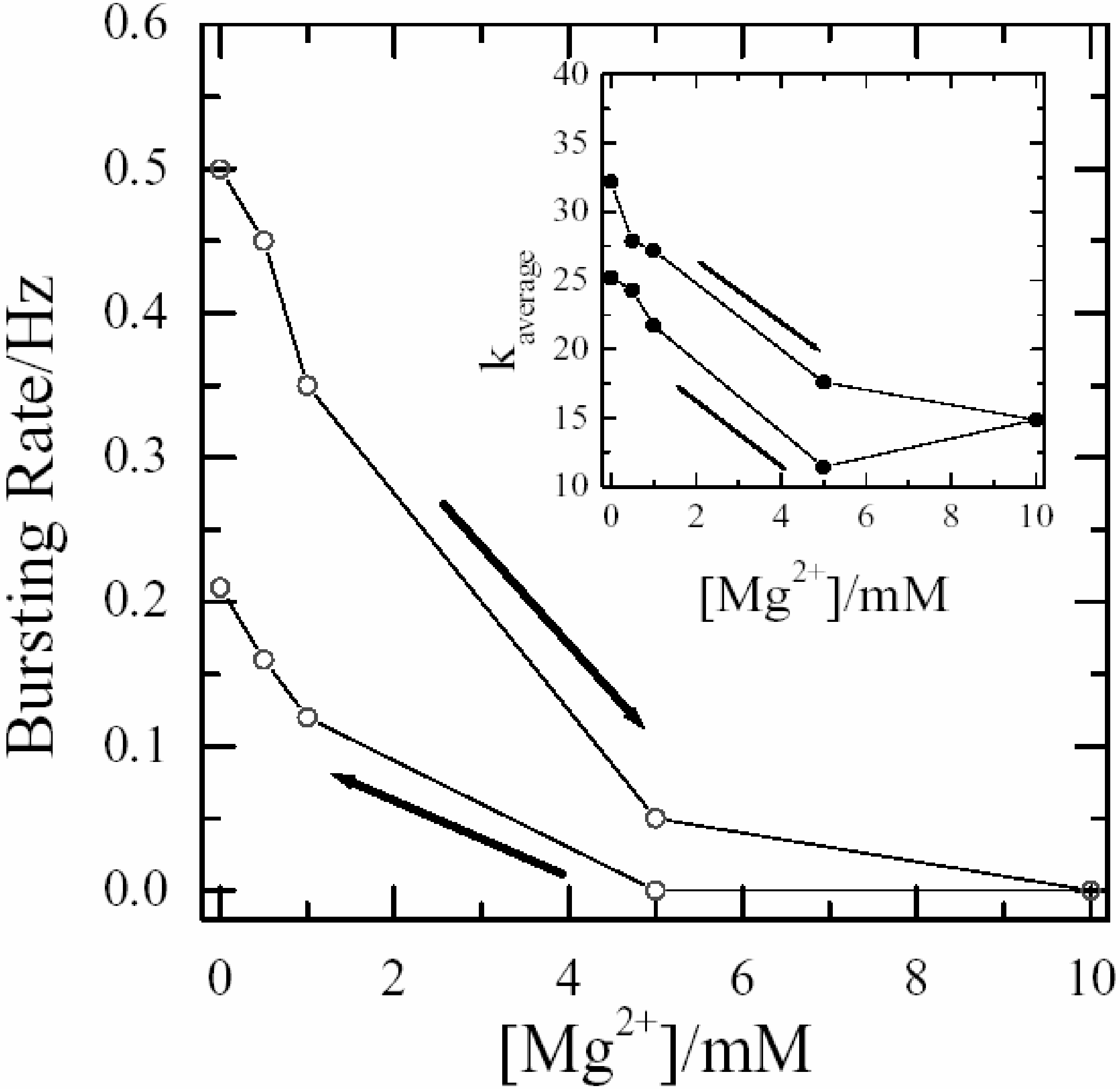
Critical Firing Density and time



$$t_c \sim \rho^{-\beta}$$

$$\beta = 0.44$$

Mg Experiment



Network Reconstruction

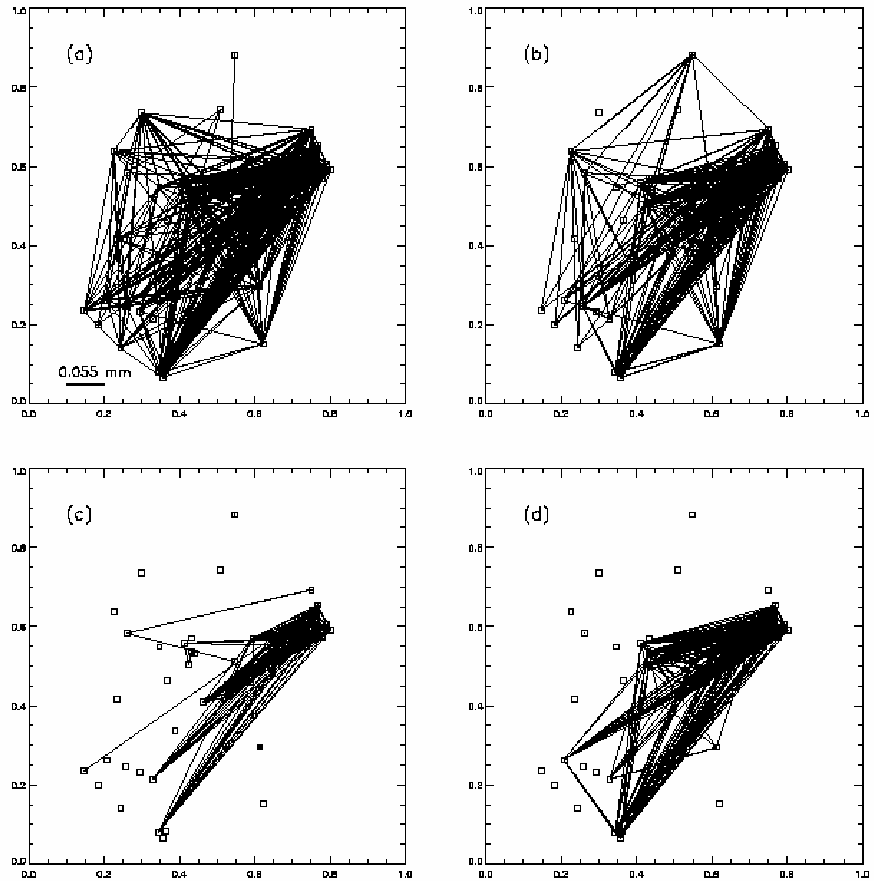
$$\Delta I_i(t) \equiv I_i(t) - < I_i(t) >$$

$$c_{ij} = \frac{1}{N_{ij}} \int \Delta I_i(t) \Delta I_j(t) dt$$

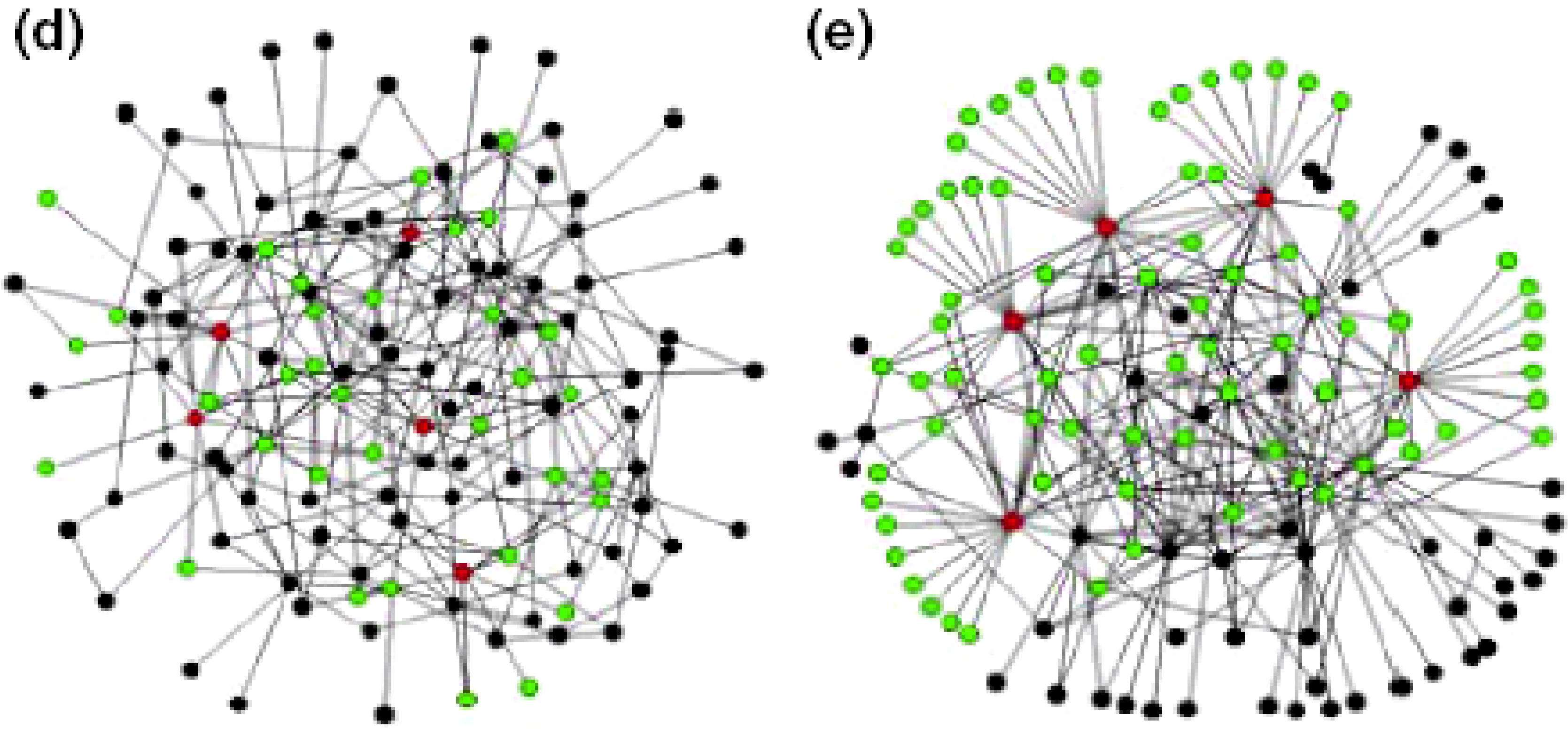
$$N_{ij} \equiv \sqrt{\int \Delta I_i{}^2(t) dt \int \Delta I_j{}^2(t) dt}$$

$$-1 \leq c_{ij} \leq 1$$

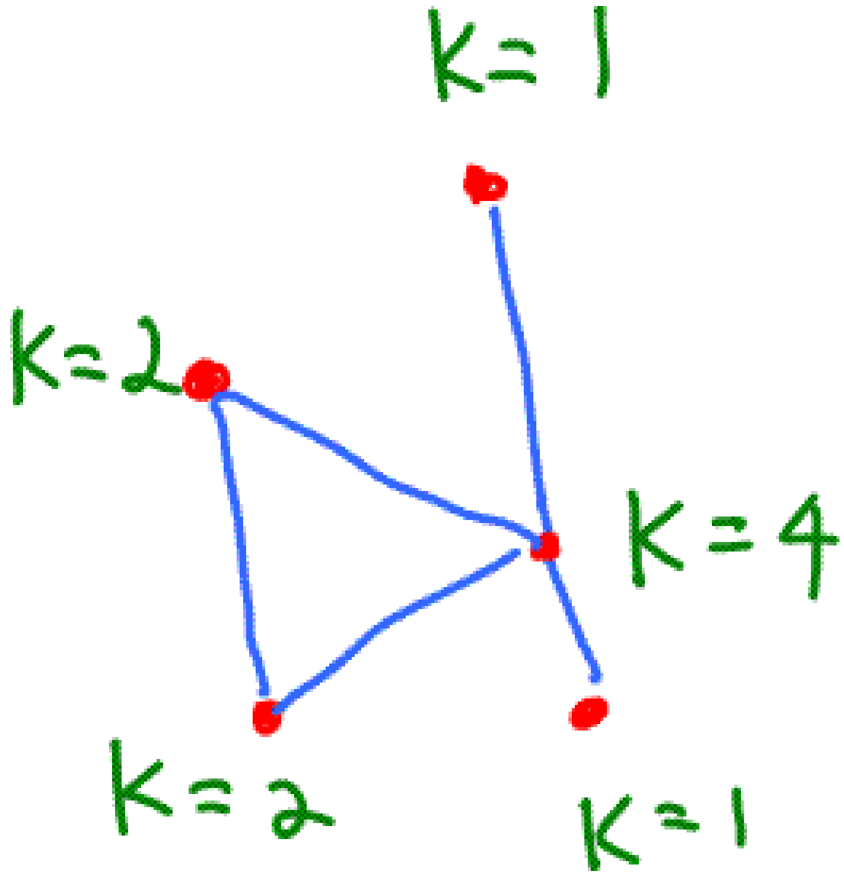
$$|c_{ij}| > 0.5$$



Network Topology



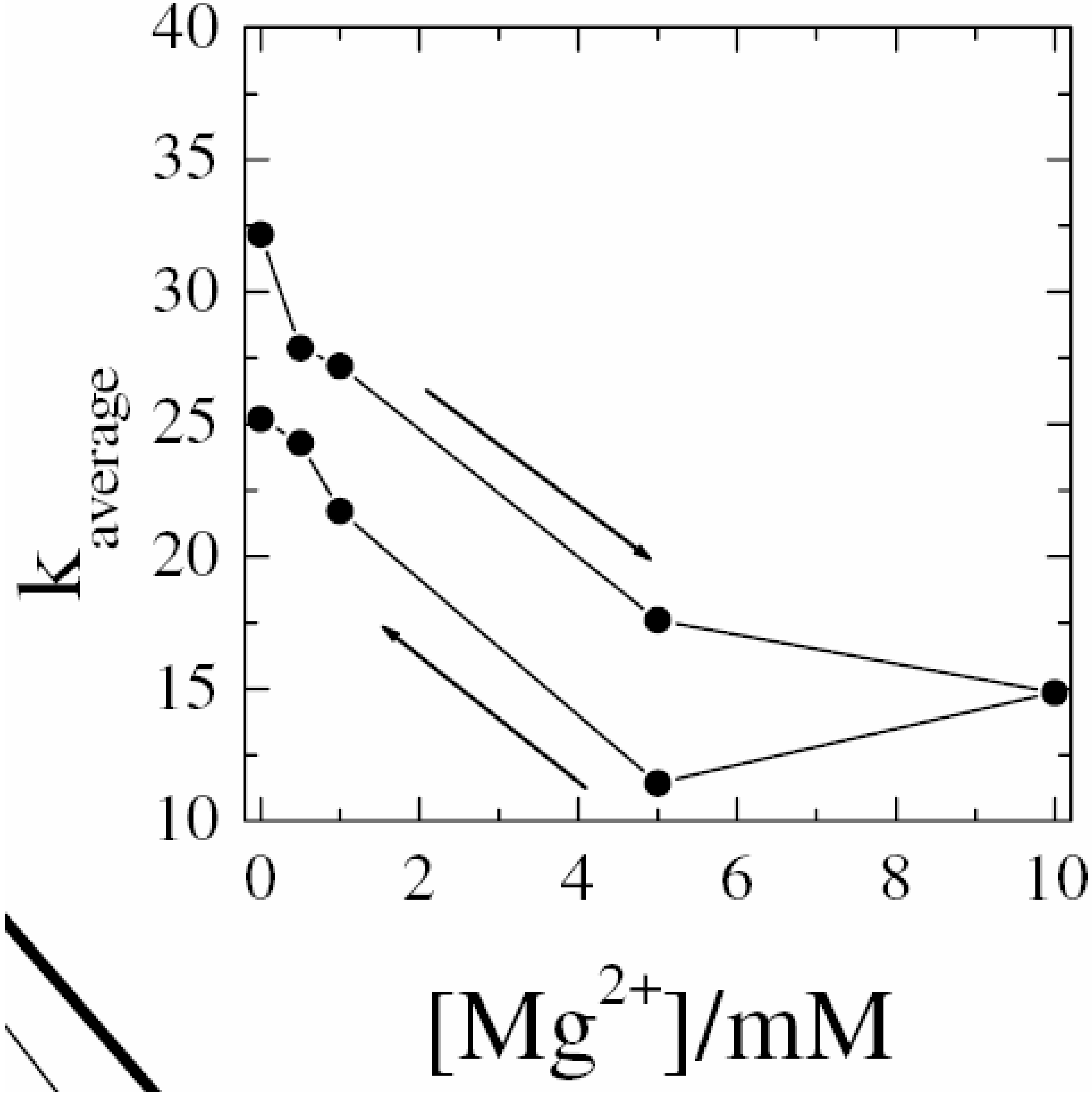
Connectivity and Topology



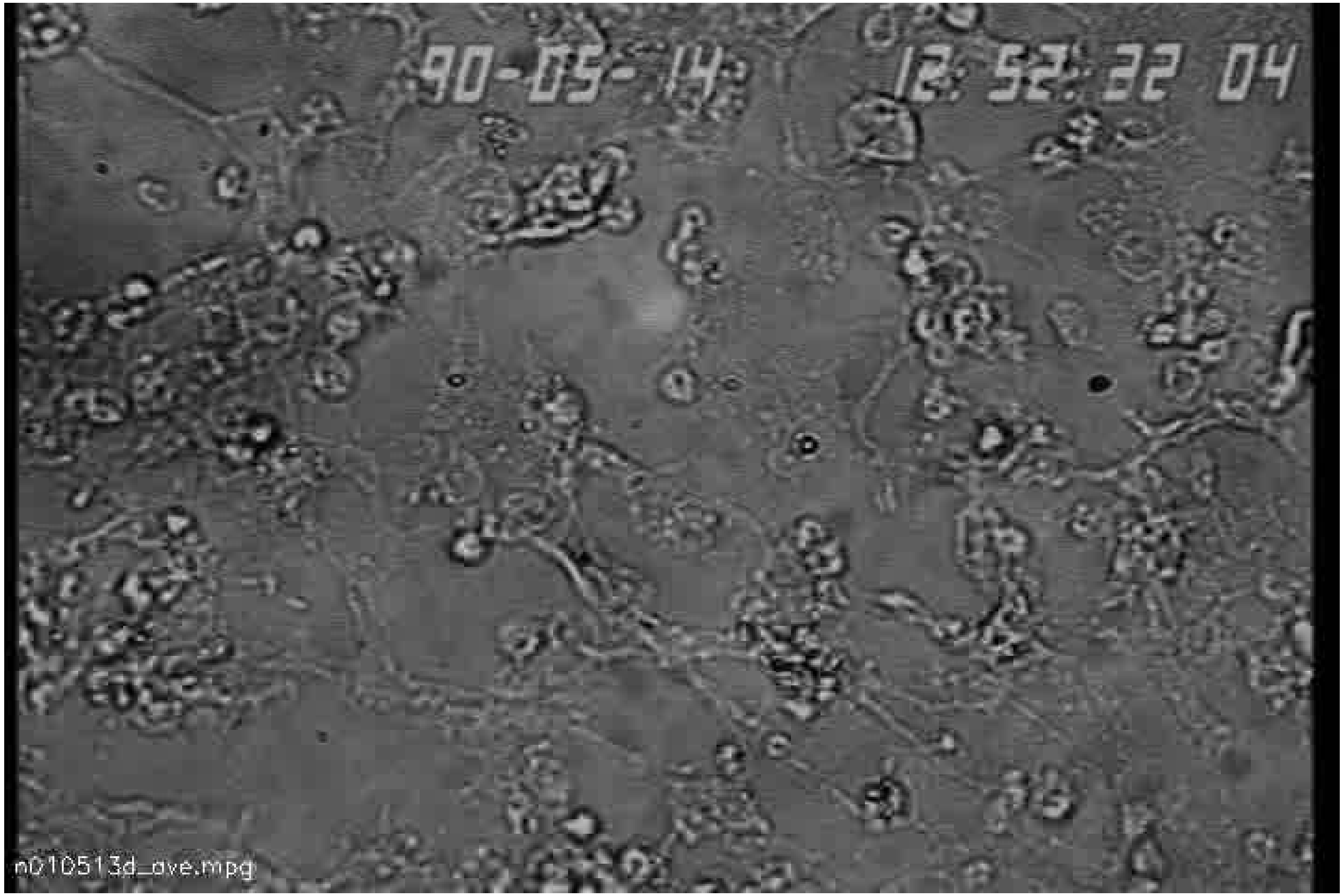
$\bar{k}$ - mean connectivity

$P(k)$ - degree distribution

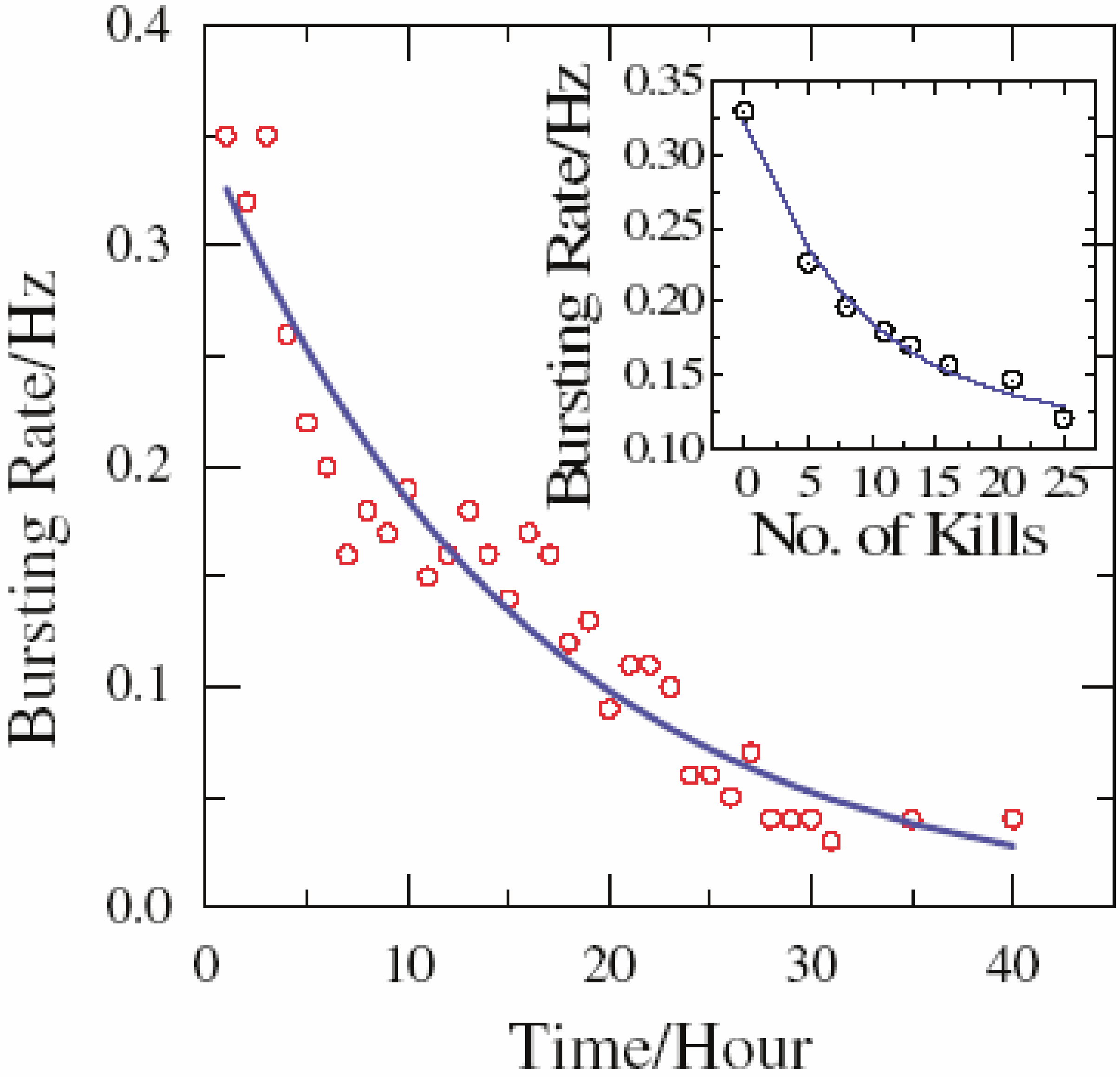
Reconstructed Connectivity



Dying Network

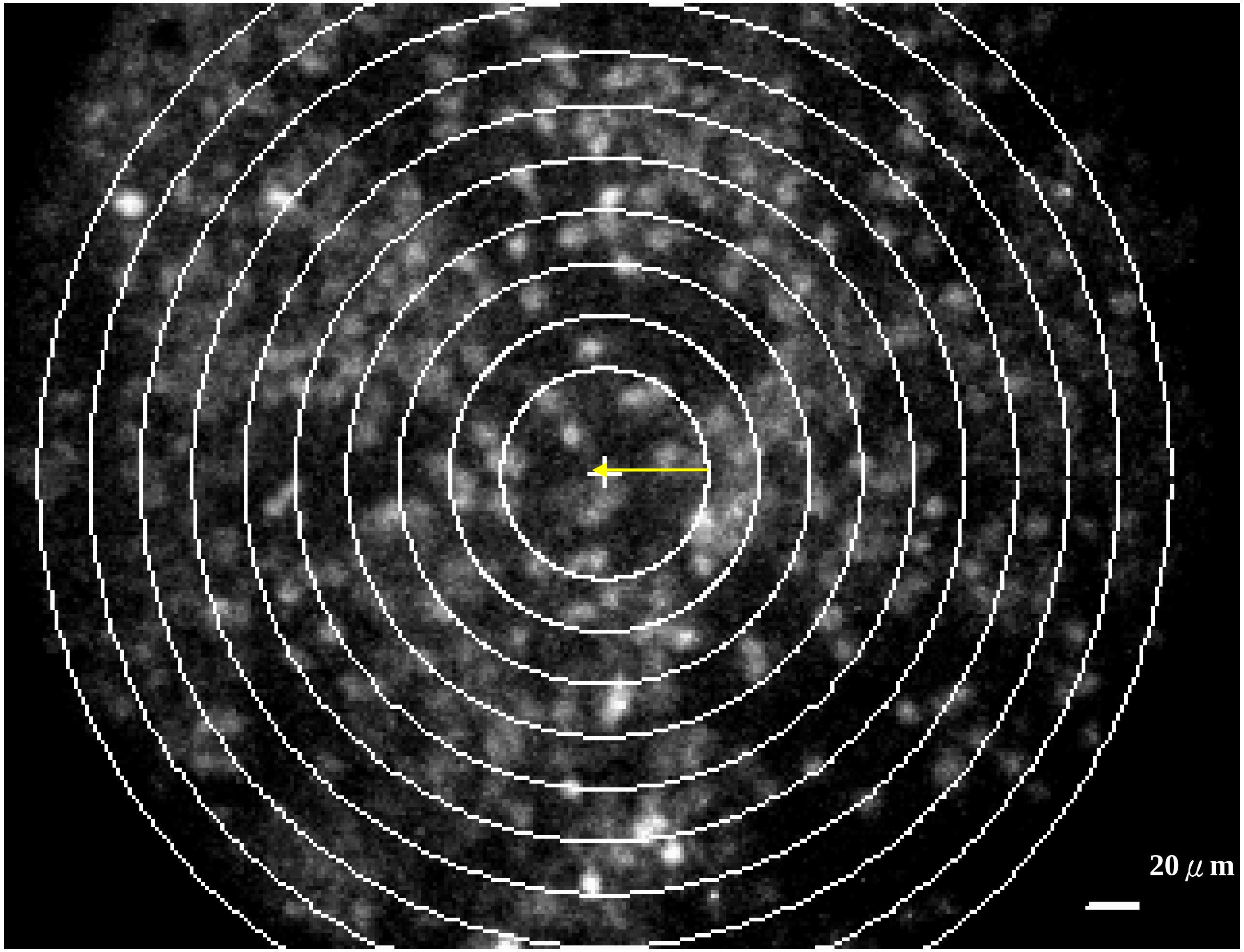


Death


Bursting Rate/Hz
Time/Hour
0.0
0.1
0.2
0.3
0.4
0
10
20
30
40
Bursting Rate/Hz
No. of Kills
0.10
0.15
0.20
0.25
0.30
0.35
0
5
10
15
20
25

Experiments of critical range of Synchronous Firing

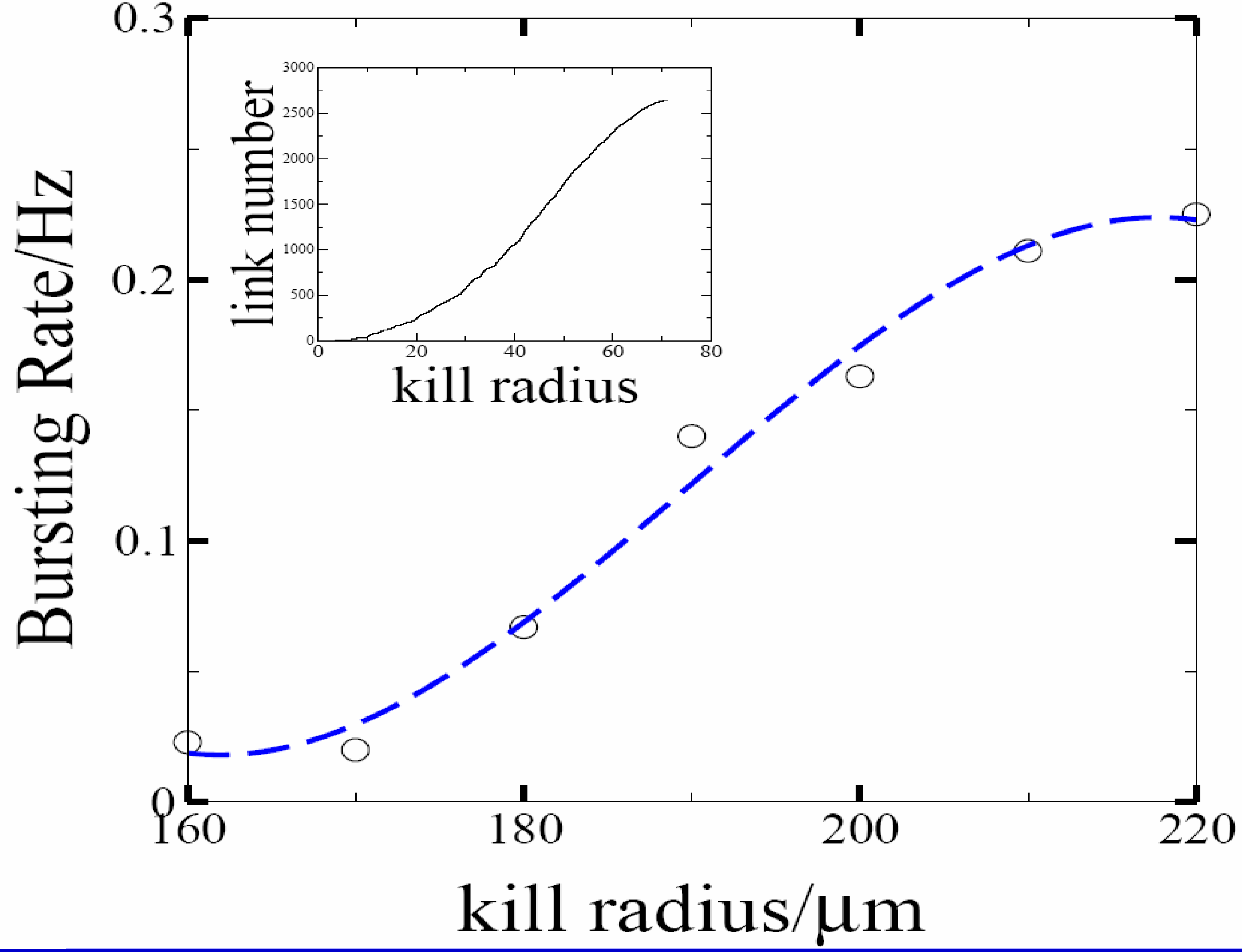
UV Killing process



Experiments of critical range of Synchronous Firing

UV Killing process

Cell Density (cells/ml) / SF frequency pattern	5.0×10^5	1.0×10^6	1.9×10^6	2.6×10^6
SF frequency decrease with kill process	4	22	2	0
SF frequency does not change with kill process	2	7	2	2
SF frequency increase with kill process	1	0	1	2



Bursting Rate/Hz
0.3
0.2
0.1
0
160
180
200
220
kill radius/μm
link number
3000
2500
2000
1500
1000
500
0
0
20
40
60
80
kill radius

Summary I

- Bursting frequency increases with DIV
- Bursting frequency decreases with [Mg^{++}]
- Physical Connection increases with DIV
- Signal Connection decreases with [Mg^{++}]

- Connectivity induced synchronization

Mechanism of SF?

Coherence Resonance in a Noise-Driven Excitable System

Arkady S. Pikovsky* and Jürgen Kurths*

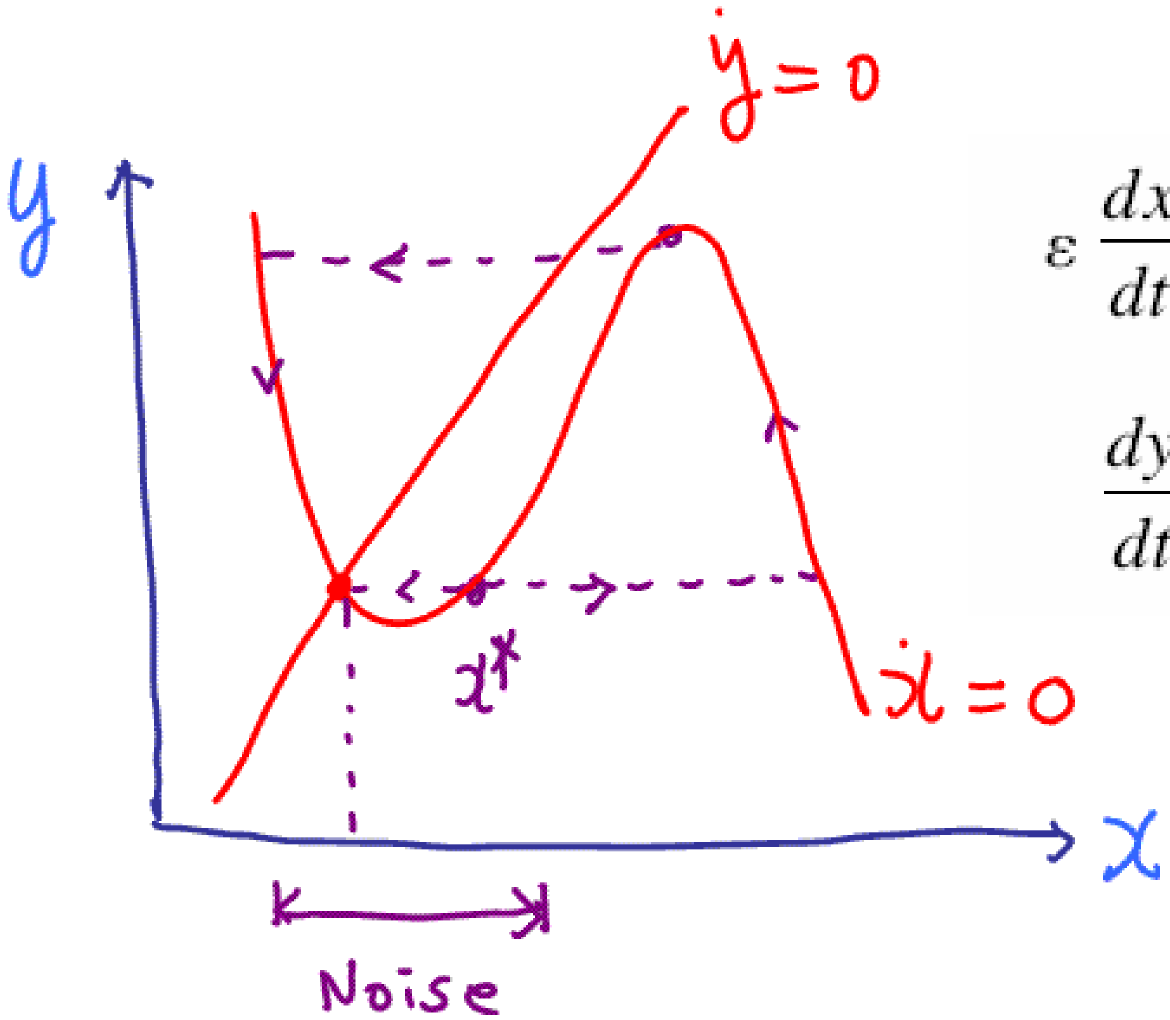
Max–Planck–Arbeitsgruppe "Nichtlineare Dynamik" an der Universität Potsdam Am Neuen Palais 19, PF 601553, D-14415, Potsdam, Germany

(Received 9 August 1996)

We study the dynamics of the excitable Fitz Hugh–Nagumo system under external noisy driving. Noise activates the system producing a sequence of pulses. The coherence of these noise-induced oscillations is shown to be maximal for a certain noise amplitude. This new effect of coherence resonance is explained by different noise dependencies of the activation and the excursion times. A simple one-dimensional model based on the Langevin dynamics is proposed for the quantitative description of this phenomenon. [S0031-9007(97)02349-1]

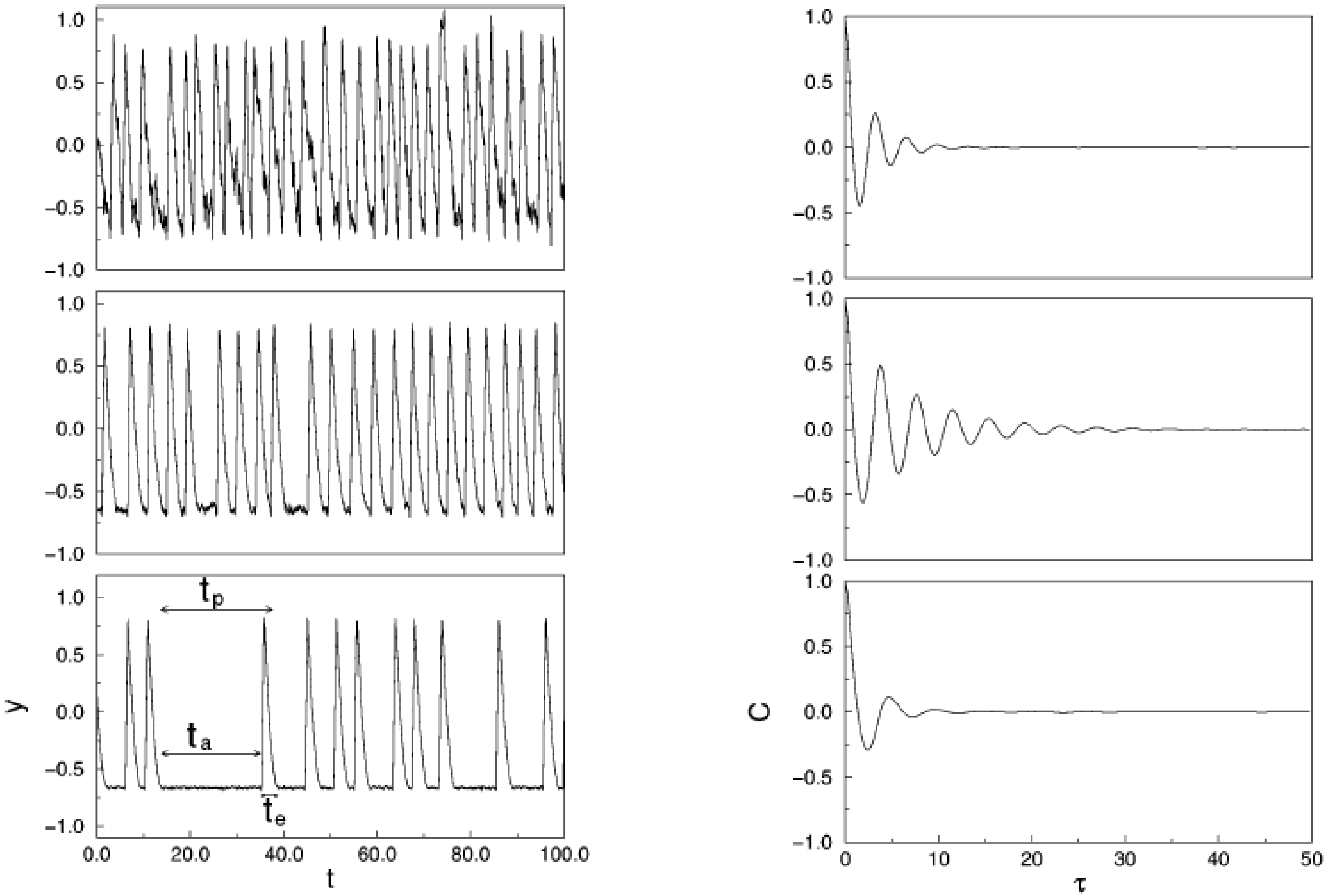
PACS numbers: 05.40.+j, 05.20.–y

Coherence Resonance In Excitable systems



$$\varepsilon \frac{dx}{dt} = x - \frac{x^3}{3} - y\,,$$

$$\frac{dy}{dt} = x + a + D\xi(t)\,.$$


y
t
t_p
t_a
t_e
C
τ

Phase synchronization in coupled nonidentical excitable systems and array-enhanced coherence resonance

Bambi Hu[1,2] and Changsong Zhou[1]

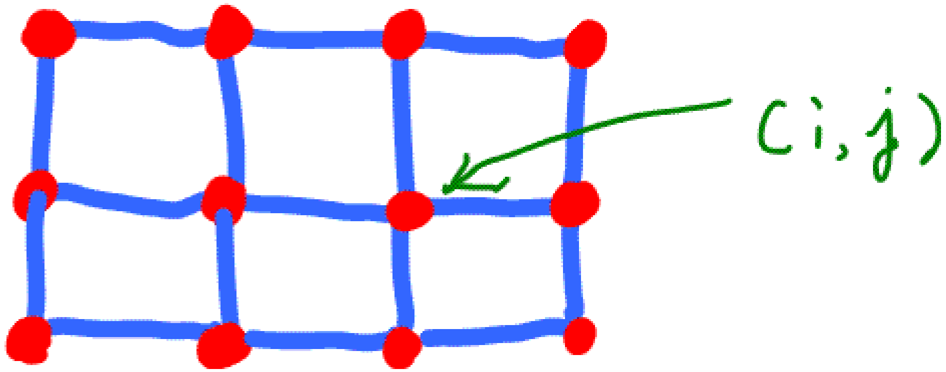
[1]*Department of Physics and Centre for Nonlinear Studies, Hong Kong Baptist University, Hong Kong, China*

[2]*Department of Physics, University of Houston, Houston, Texas 77204*

(Received 28 September 1999)

We study the dynamics of a lattice of coupled nonidentical Fitz Hugh-Nagumo system subject to independent external noise. It is shown that these stochastic oscillators can lead to global synchronization behavior *without an external signal*. With the increase of the noise intensity, the system exhibits coherence resonance behavior. Coupling can enhance greatly the noise-induced coherence in the system.

PHYSICAL REVIEW E VOLUME 61, NUMBER 2 FEBRUARY 2000



FitzHugh-Nagumo neurons in a $M \times N$ lattice is represented as follows:

$$\epsilon \dot{x}_{ij} = x_{ij} - \frac{x_{ij}^3}{3} - y_{ij} + \xi_{ij}(t) + g(x_{i+1,j} + x_{i-1,j} + x_{i,j+1} + x_{i,j-1} - 4x_{ij}), \quad (1)$$

$$\dot{y}_{ij} = x_{ij} + a \quad (i = 1,2, \ldots, M, j = 1,2, \ldots, N),$$

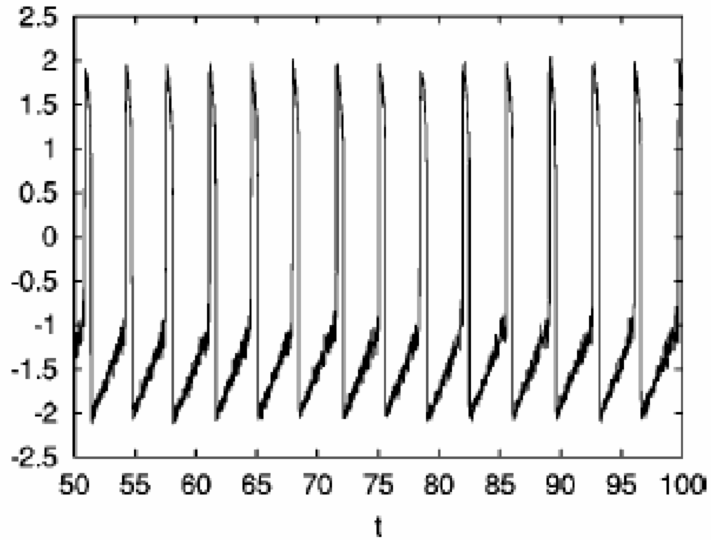
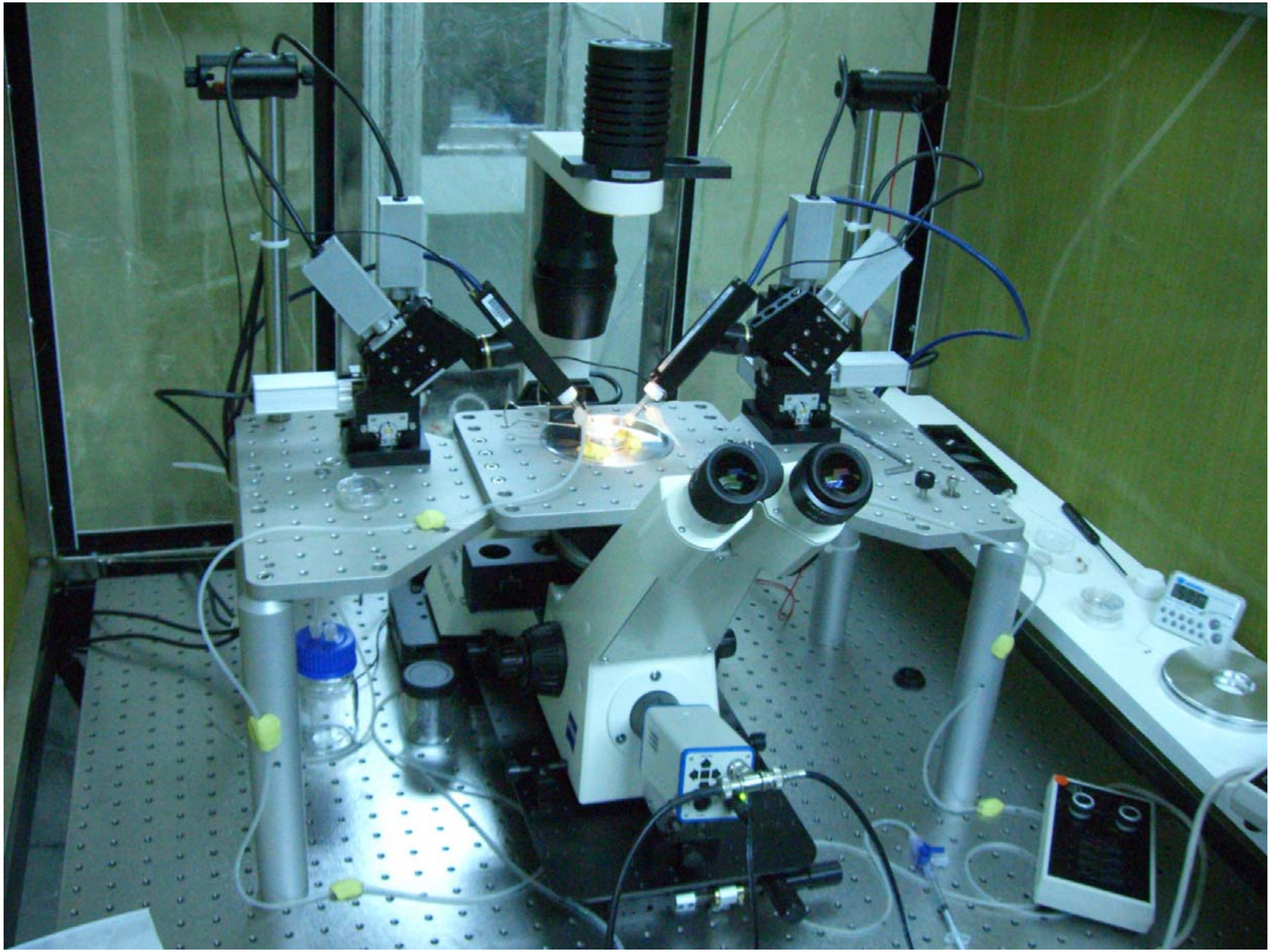


FIG. 4. A time series of x_{11} with $N = M = 10$, $g = 0.06$, and $D = 4.0 \times 10^{-5}$ in a state of a coherence resonance oscillation sustained by noise and coupling.

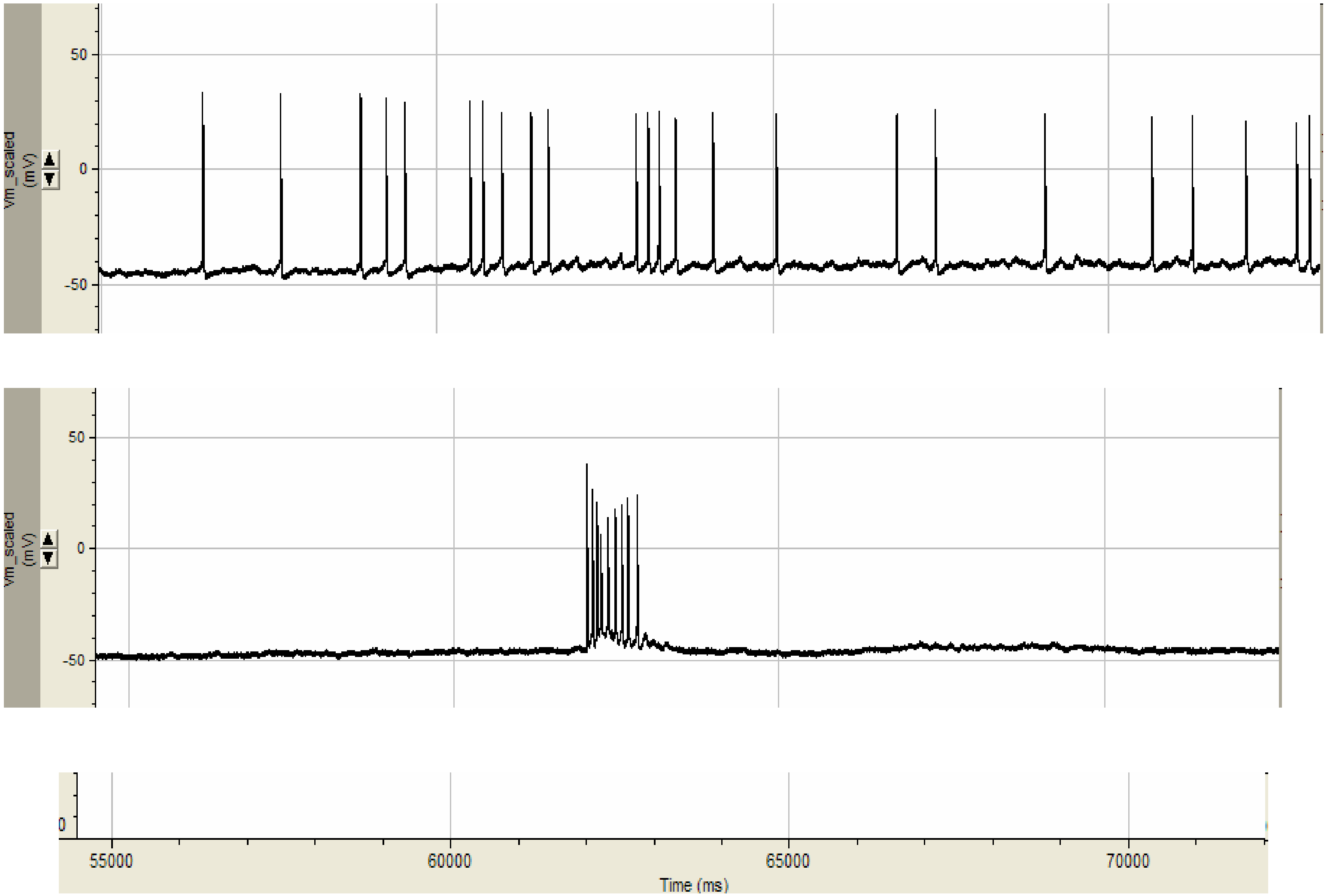
PHYSICAL REVIEW E, VOLUME 65, 051906

Yuji Shinohara,[1] Takashi Kanamaru,[2] Hideyuki Suzuki,[1] Takehiko Horita,[1] and Kazuyuki Aihara[1,3]

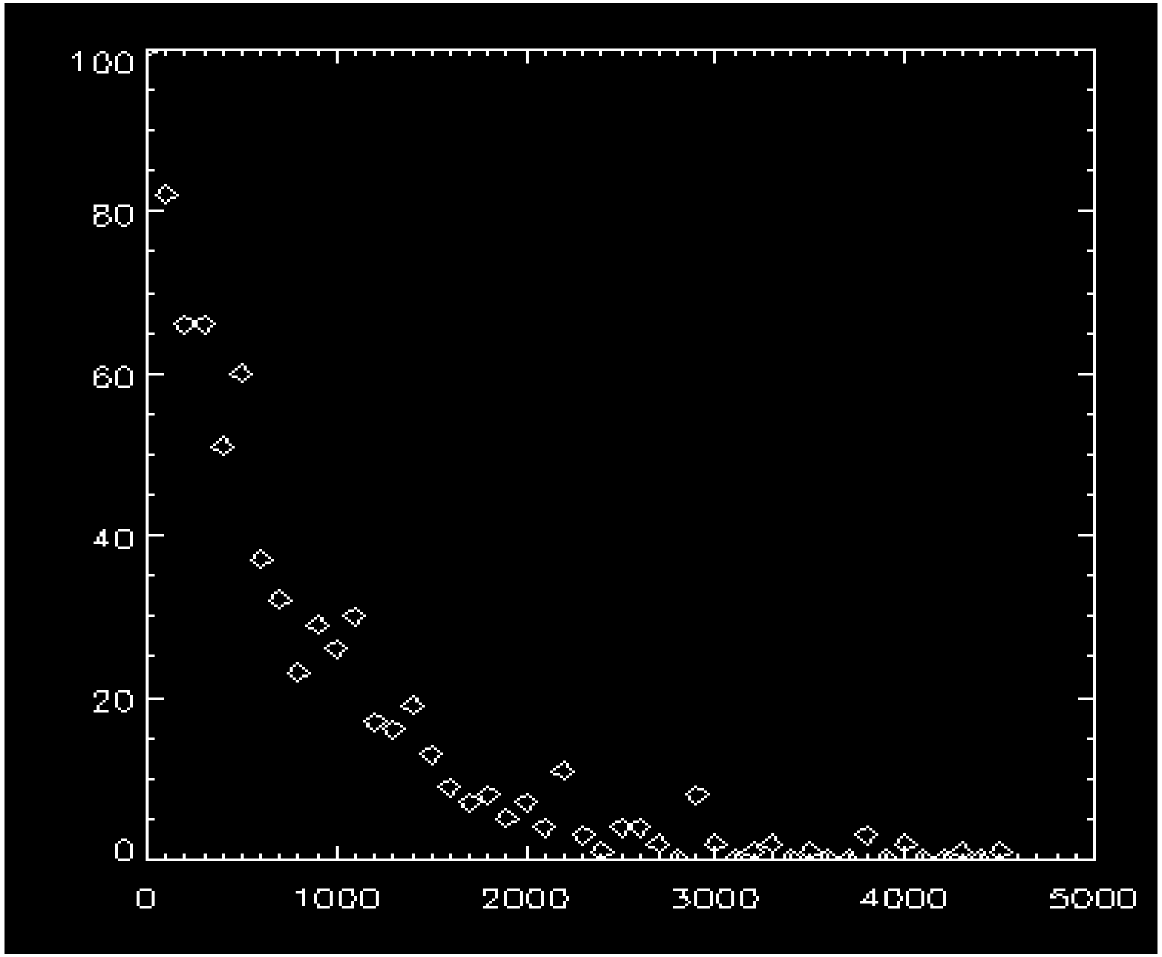


Patch Clamp Experiments

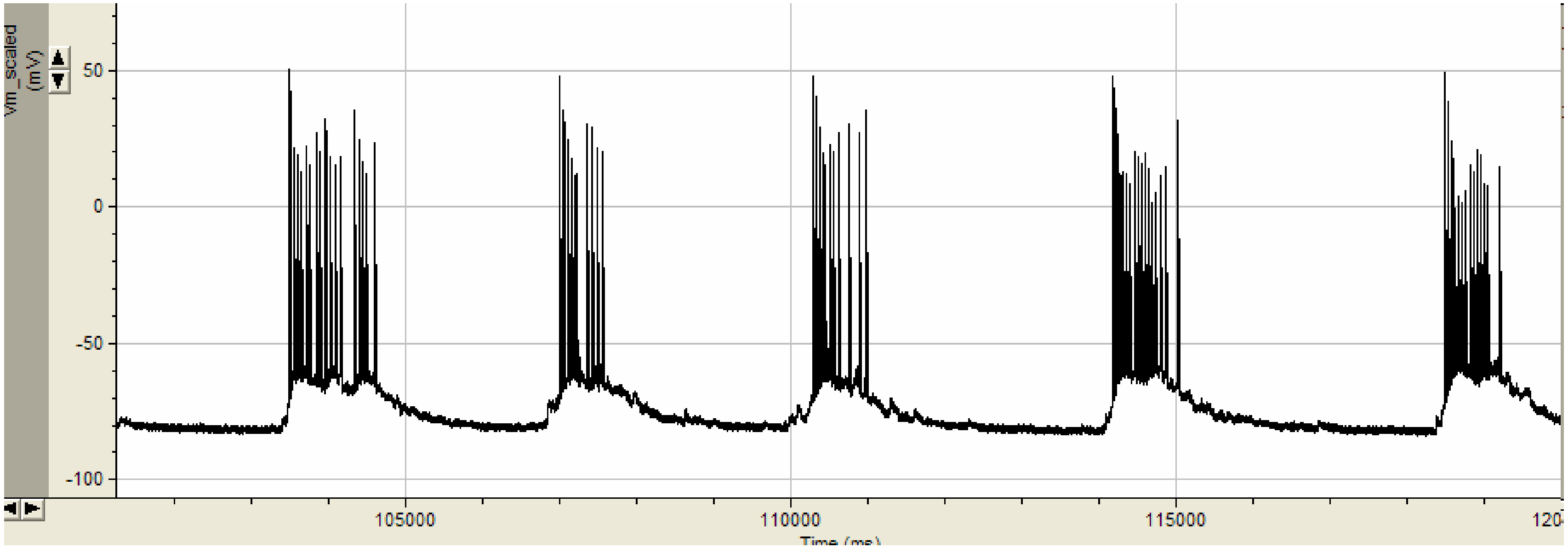
Firings from Non-SB Neurons



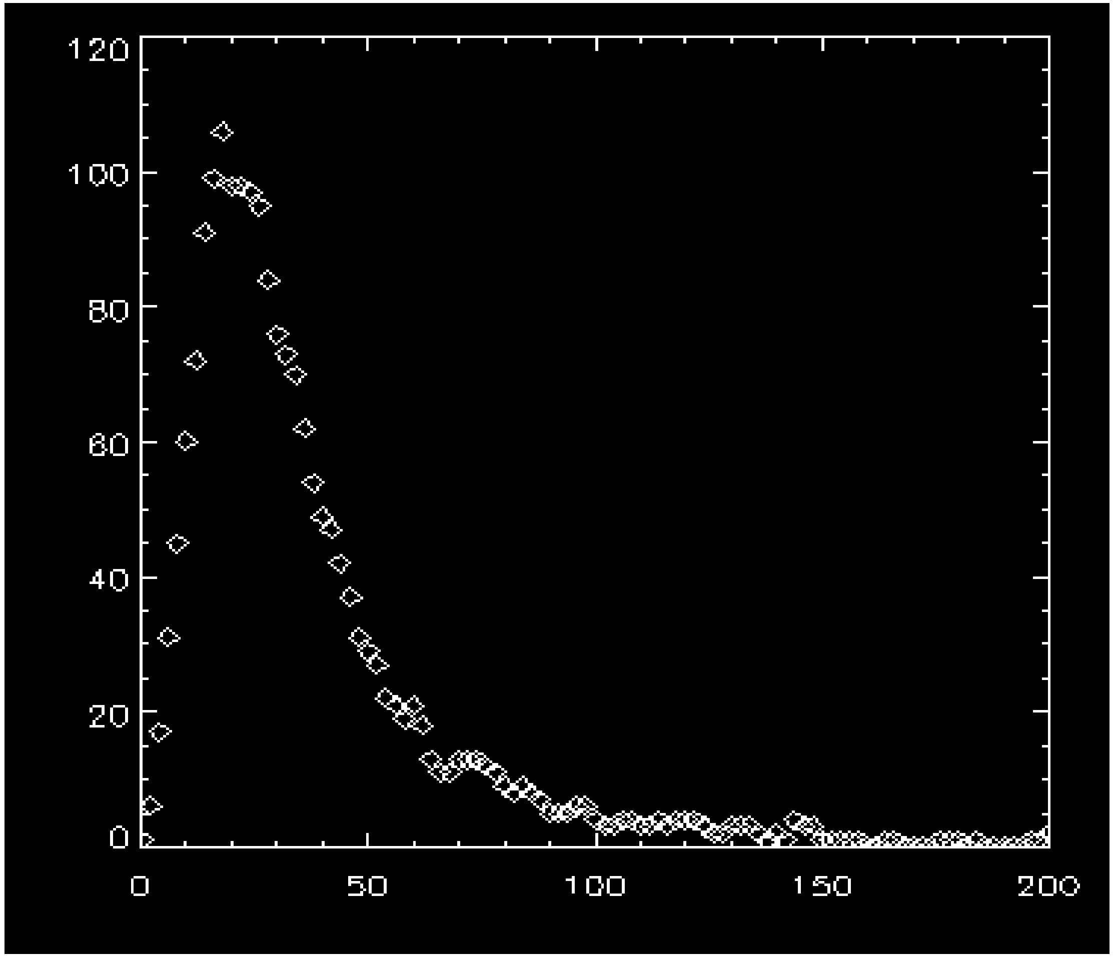
Histogram of ISI



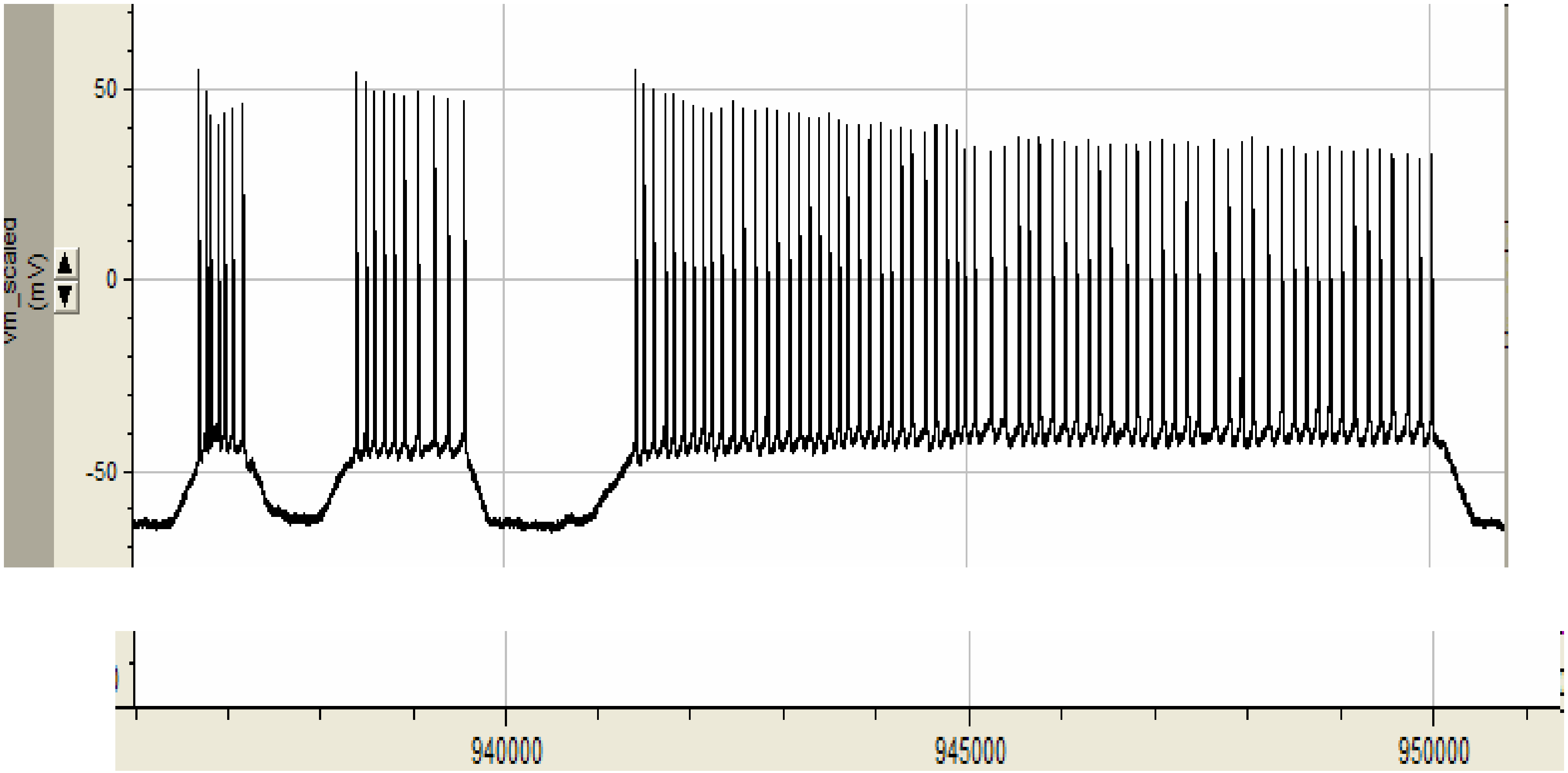
Firings from SB neurons



Histogram of ISI



Artificially generated input



Spiking Statistics

Non-SB neurons

→ random firing (intrinsic noise)

→ random bursting? (network noise?)

SB- Neurons

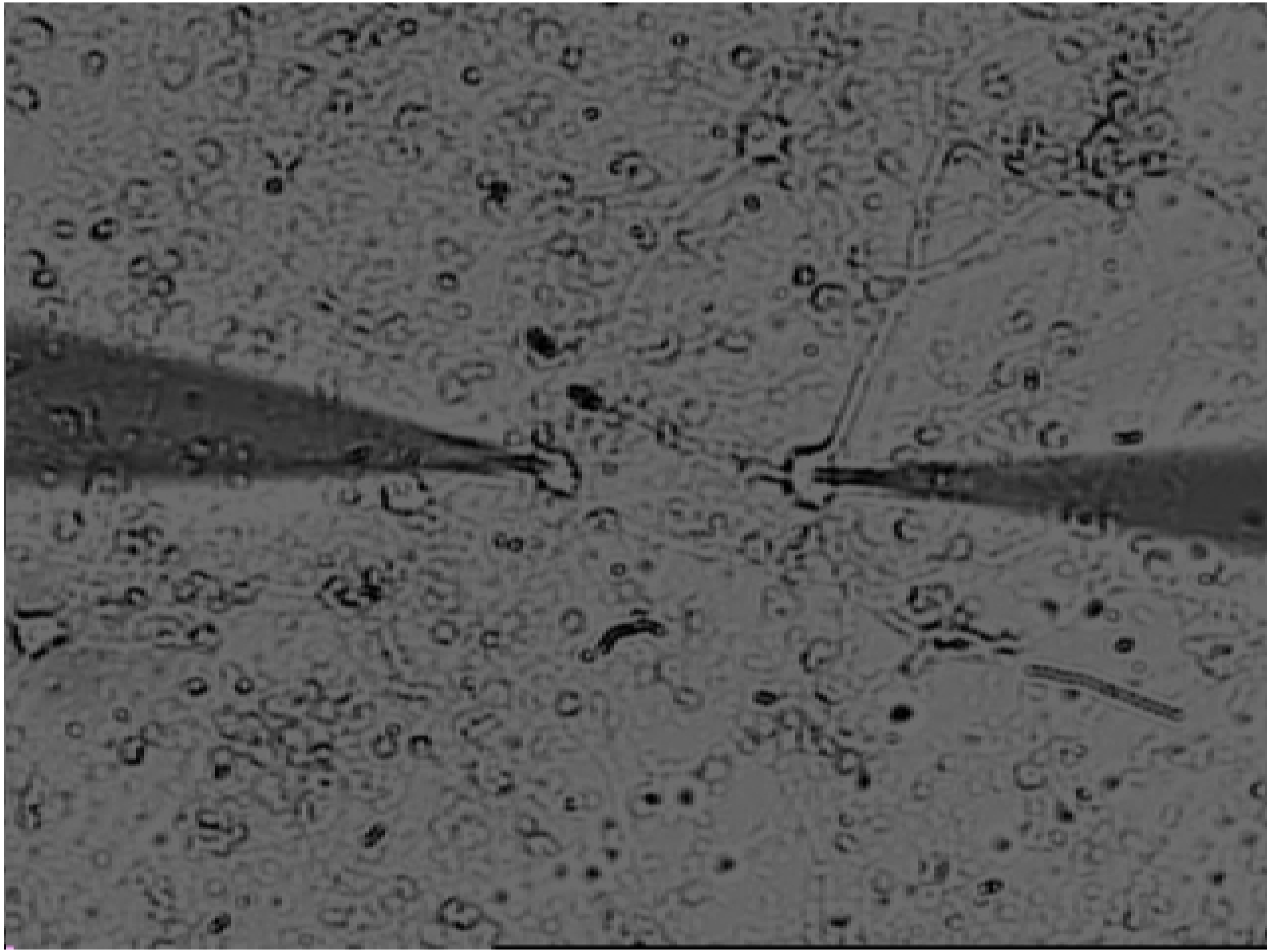
→ two time scales

→ intrinsic action potential time scale

→ Time between bursts

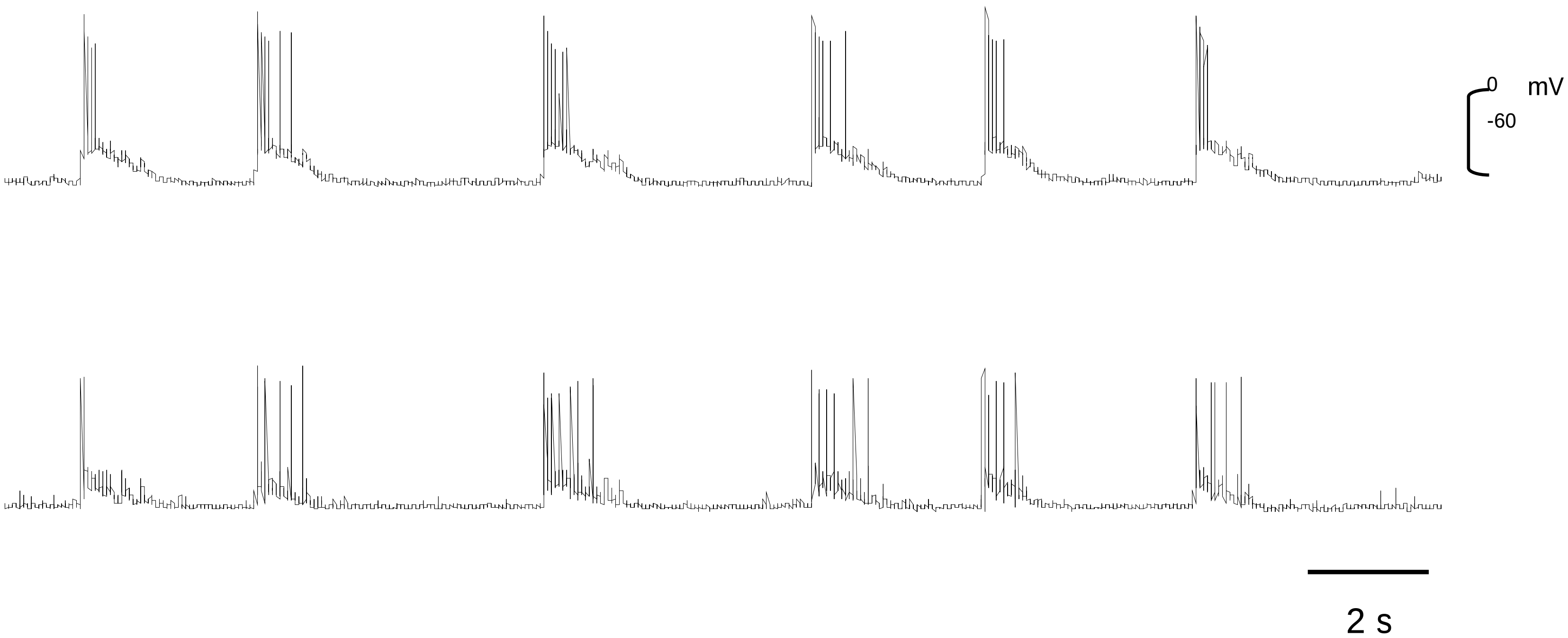
Array-Enhanced Coherent Resonance (AECR)

→ global synchronization, time scale of action potential

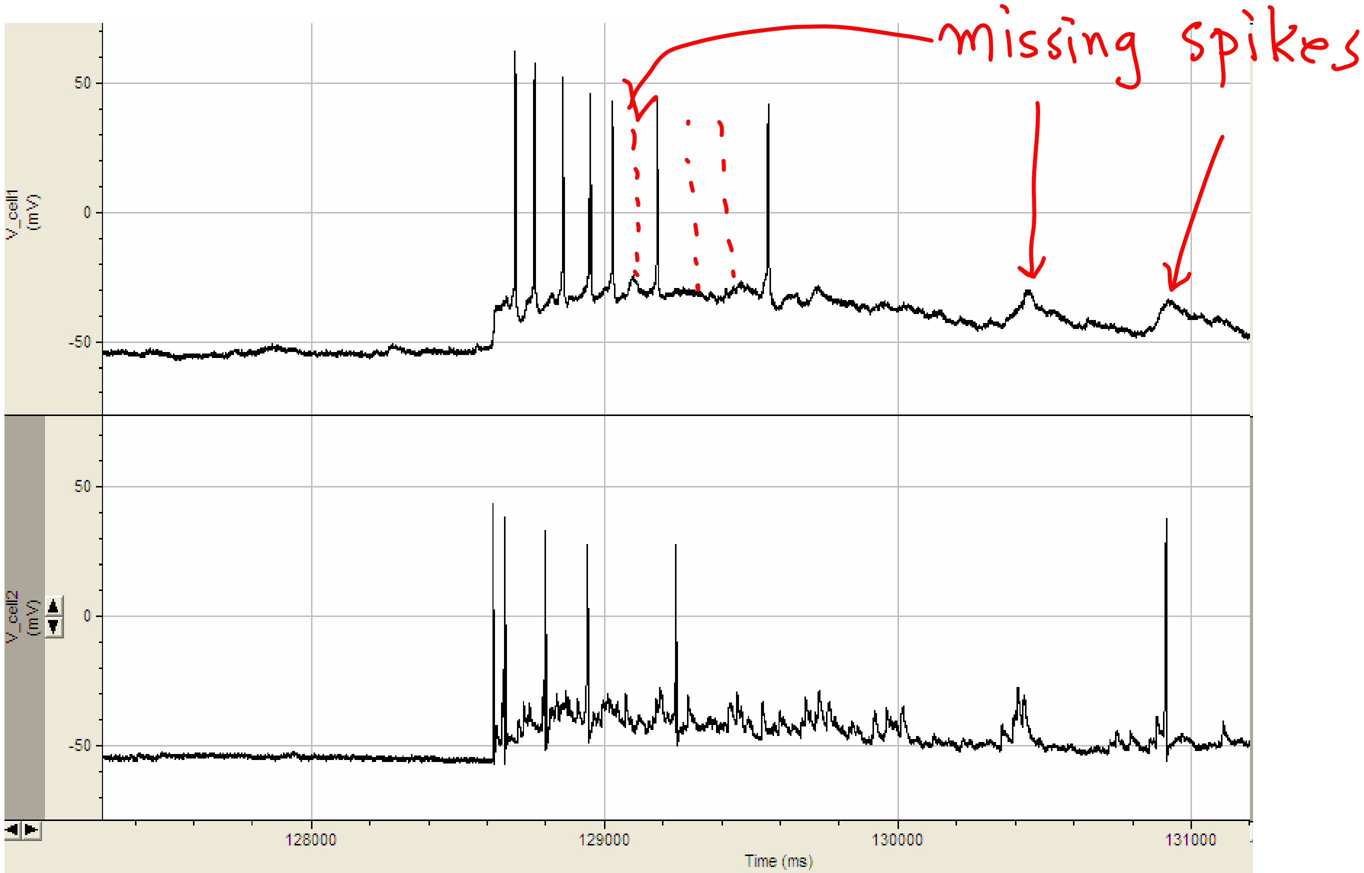


Electrophysiology result
(whole-cell recording, current-clamp)

Glia and neuron mixed culture (8DIV, 5X10^5)



Good synchronization among bursts but no synchronization among spikes



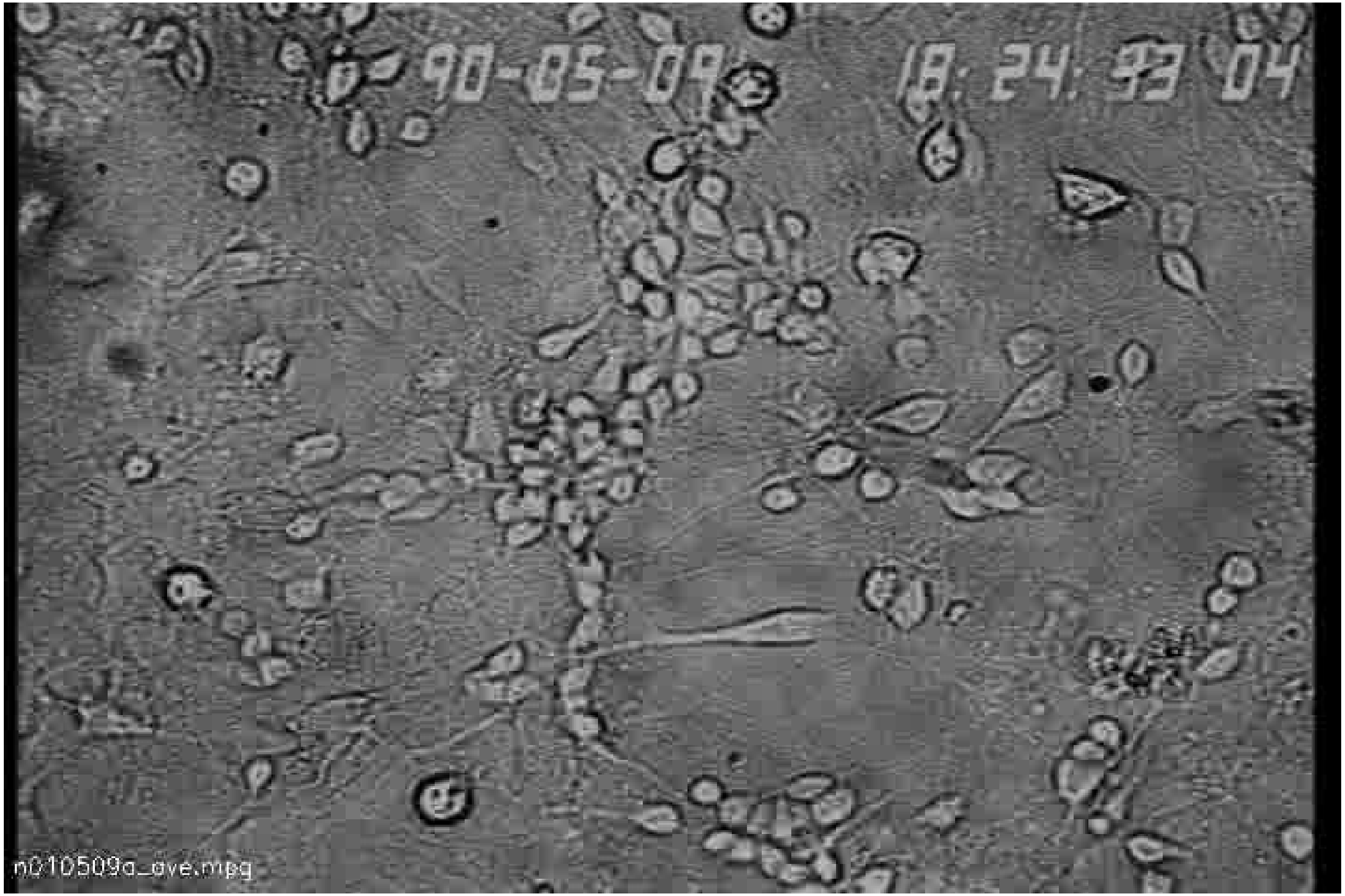
Summary II

- Synchronized burstings are induced by the increase in network connectivity

- There are both noises from the nodes and the network.

- Similar to AECR only in the burst level not in the spikes level

Role of Glia?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Annu. Rev. Physiol. 2001. 63:795–813

DYNAMIC SIGNALING BETWEEN ASTROCYTES AND NEURONS

Alfonso Araque[1], Giorgio Carmignoto[2], and Philip G Haydon[3]

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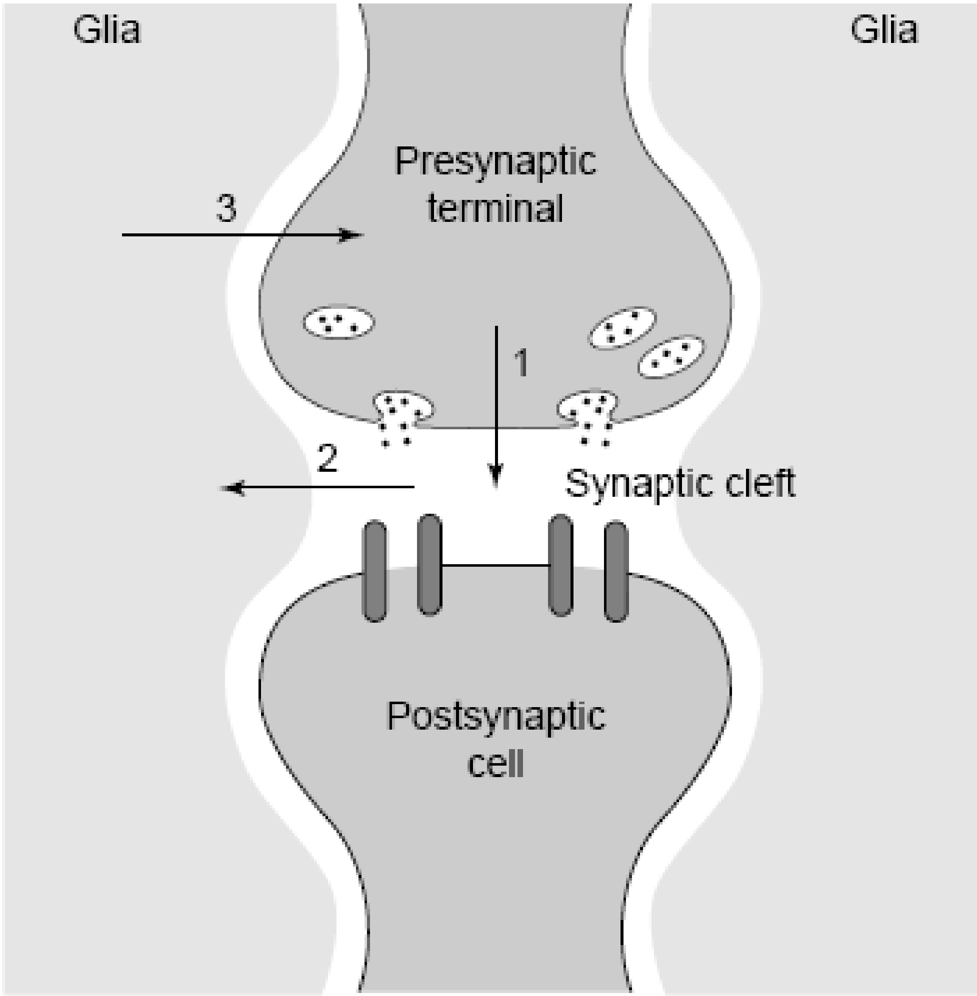
e-mail: araque@cajal.csic.es;
[2]*Department of Experimental Biomedical Sciences, and CNR Center for the Study of Biomembranes, University of Padova, 35121 Padova, Italy;*
e-mail: gcarmi@civ.bio.unipd.it;
[3]*Department of Zoology and Genetics, Roy J. Carver Laboratory for Ultrahigh Resolution Biological Microscopy, Iowa State University, Ames, Iowa 50011;*
e-mail: pghaydon@iastate.edu

Tripartite Synapse



Haydon et al

208 *TINS* Vol. 22, No. 5, 1999

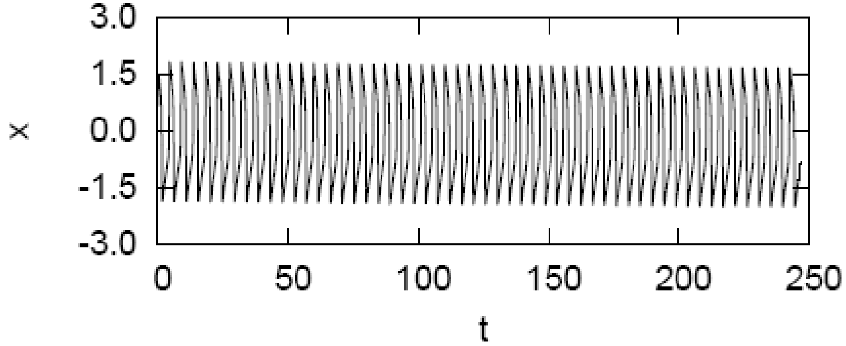
Bursting of neurons induced by inhibitory mechanism

$$\epsilon \frac{dx}{dt} = x - \frac{x^3}{3} - y - zg + \xi(t)$$

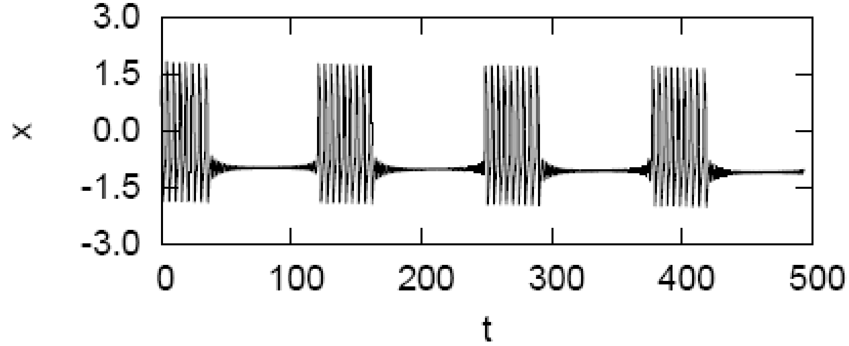
$$\frac{dy}{dt} = a + bx - y$$

$$\frac{dg}{dt} = -\frac{g}{\tau} + \gamma\, \Theta\, (rzx - \theta)$$

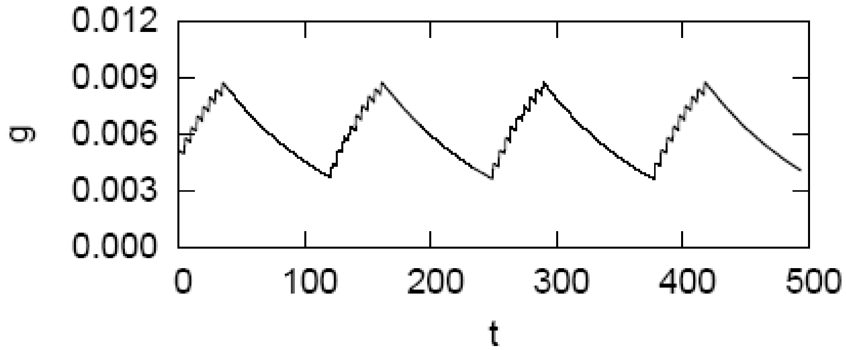
Effect of Connectivity



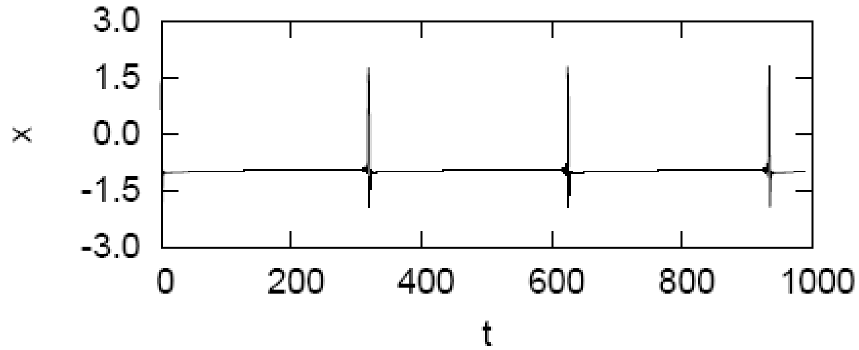
(a) $z = 2.0$



(b) $z = 3.5$

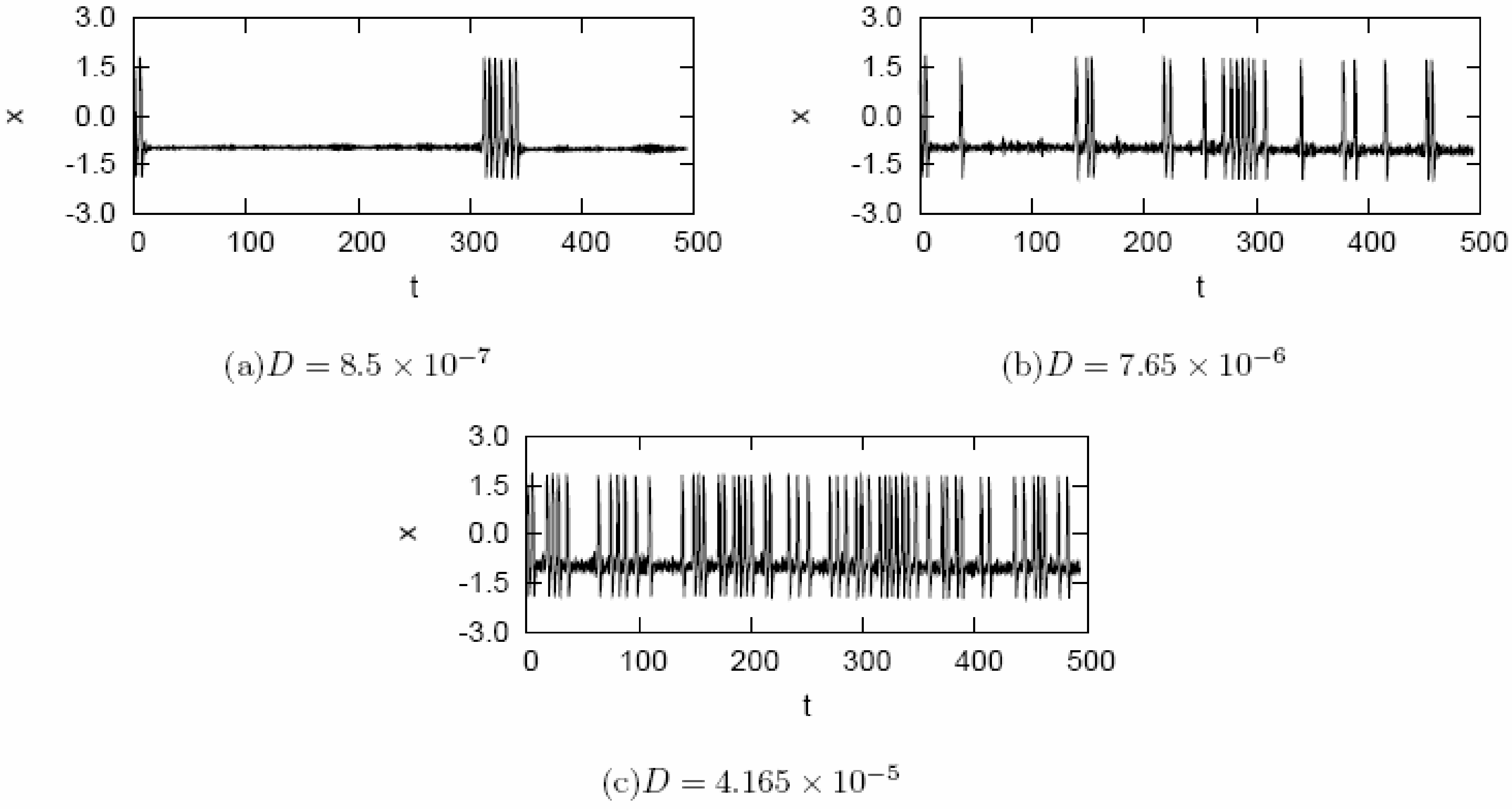


(c) $z = 3.5$; $g(t)$



(d) $z = 7.0$

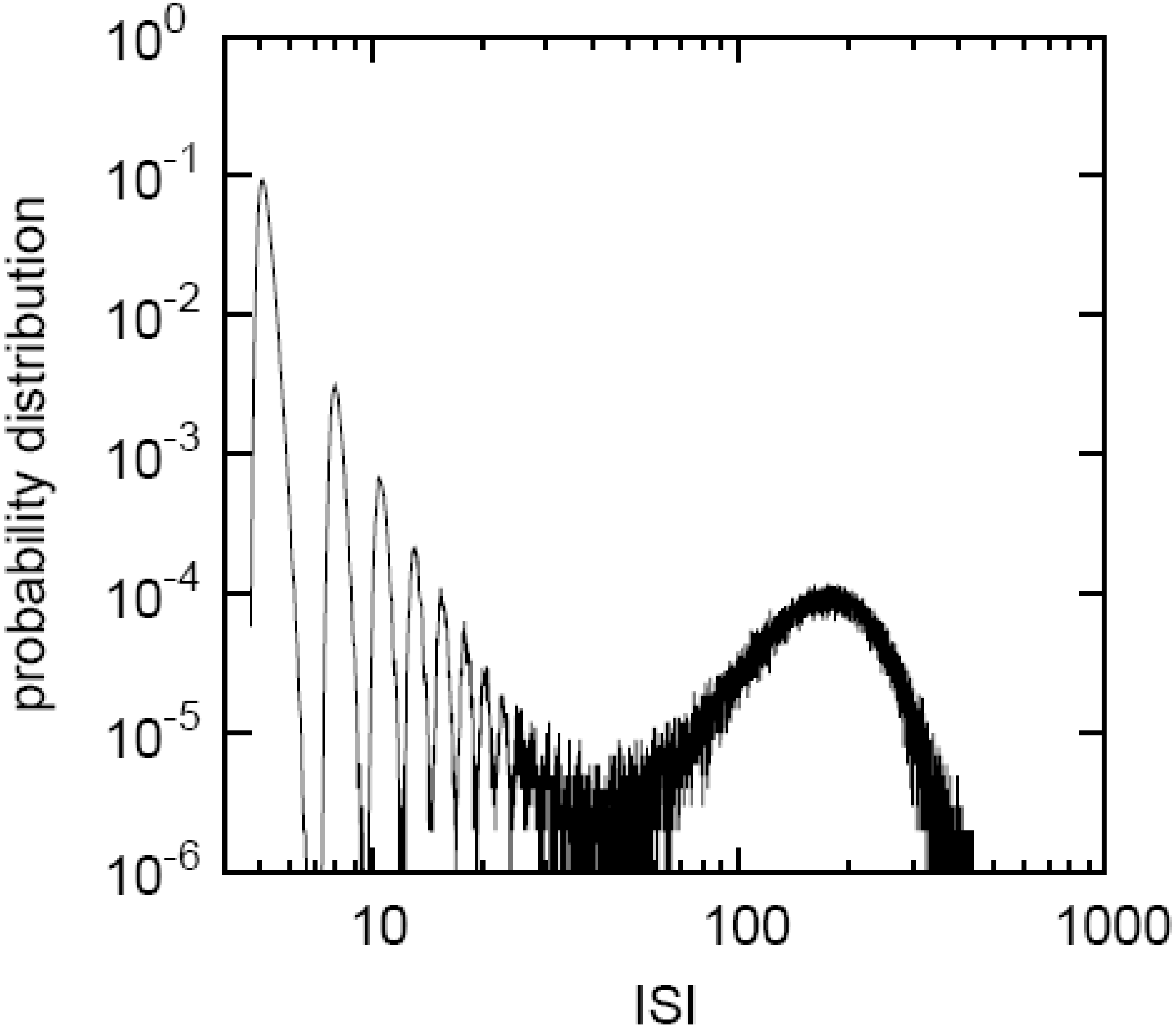
Effects of Noise-missing spikes



(a) $D = 8.5 \times 10^{-7}$

(b) $D = 7.65 \times 10^{-6}$

(c) $D = 4.165 \times 10^{-5}$



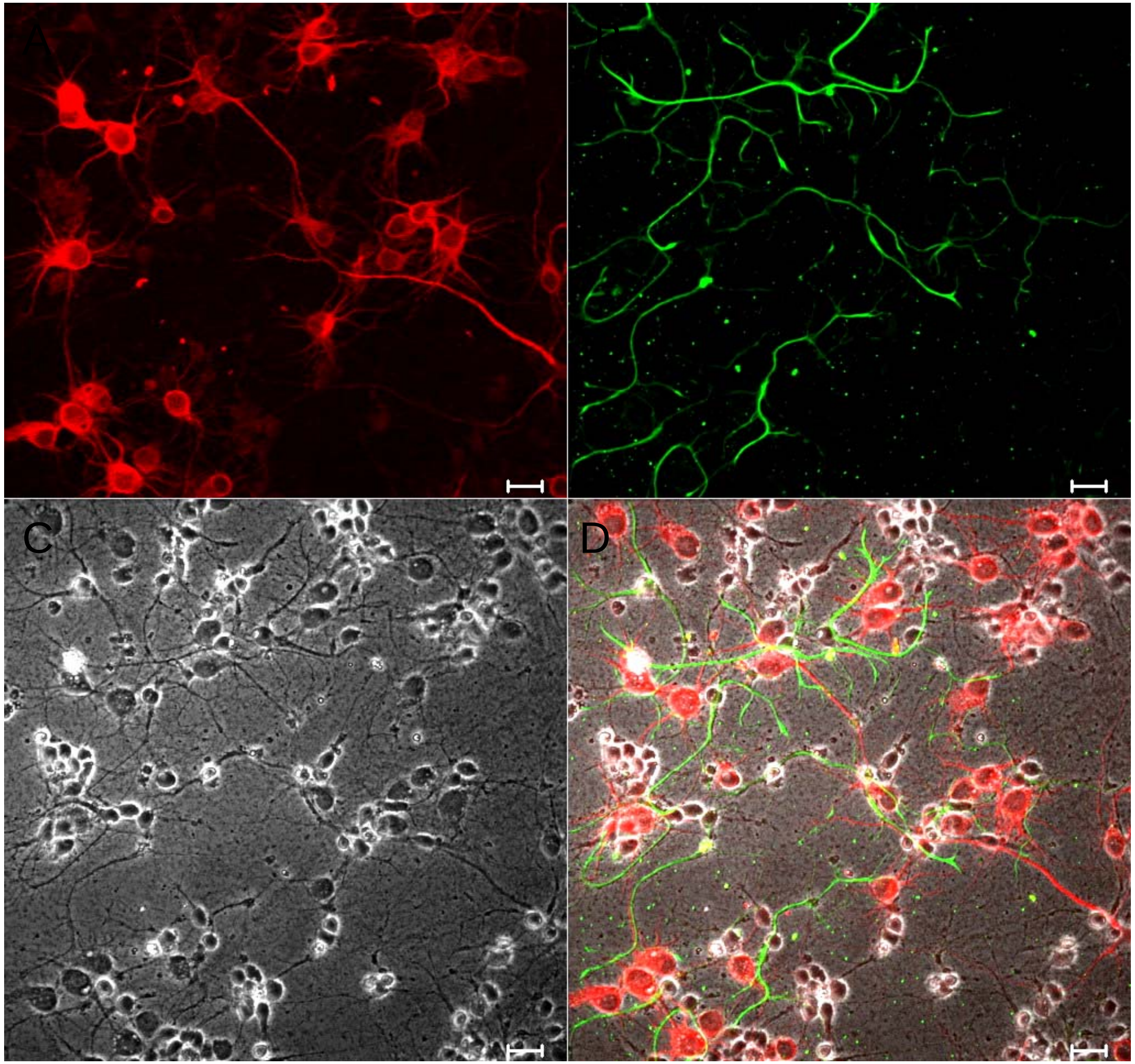
probability distribution
10^0
10^-1
10^-2
10^-3
10^-4
10^-5
10^-6
10
100
1000
ISI

Culture Experiments

	Glia-suppressed cultures (GSCs)		Neuron-glia cocultures (NGCs)	Glia-enhanced cultures (GECs)		
Treatment	NB/B27	GCM	NB/B27	Pre-plate	Post-plate	
					GSCs	NGCs

Table. 1 Summary of the culture preparations

1. Immunostaining results: NGCs



7DIV, plate cell density:

~700 cells/mm^2

(A) red, anti-MAP2 (neuronal marker)

(B) green, anti-GFAP (glia marker)

(C) phase contrast image

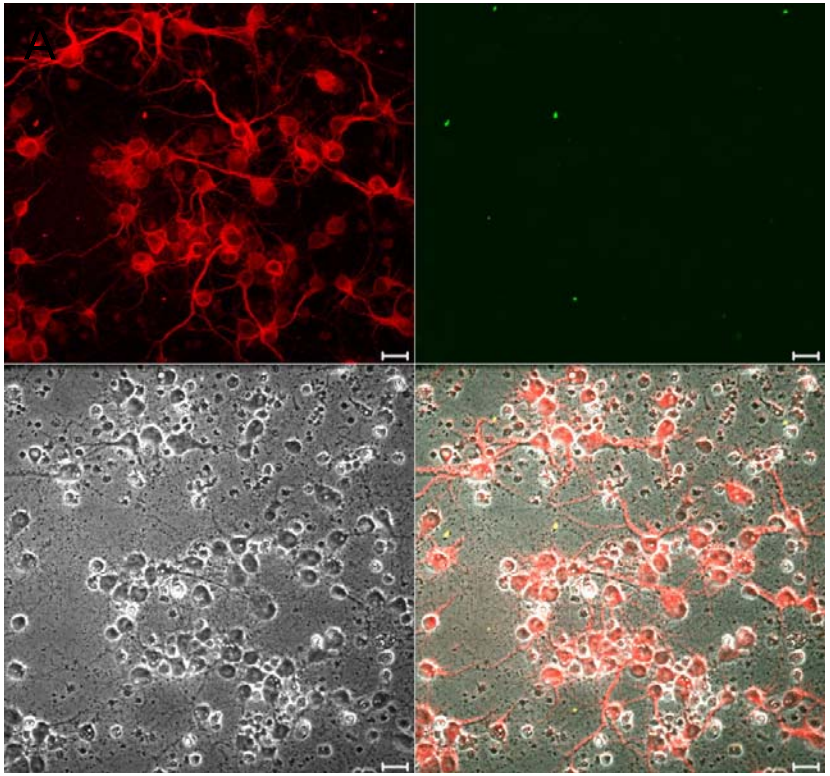
(D) merged (A) (B) (C)

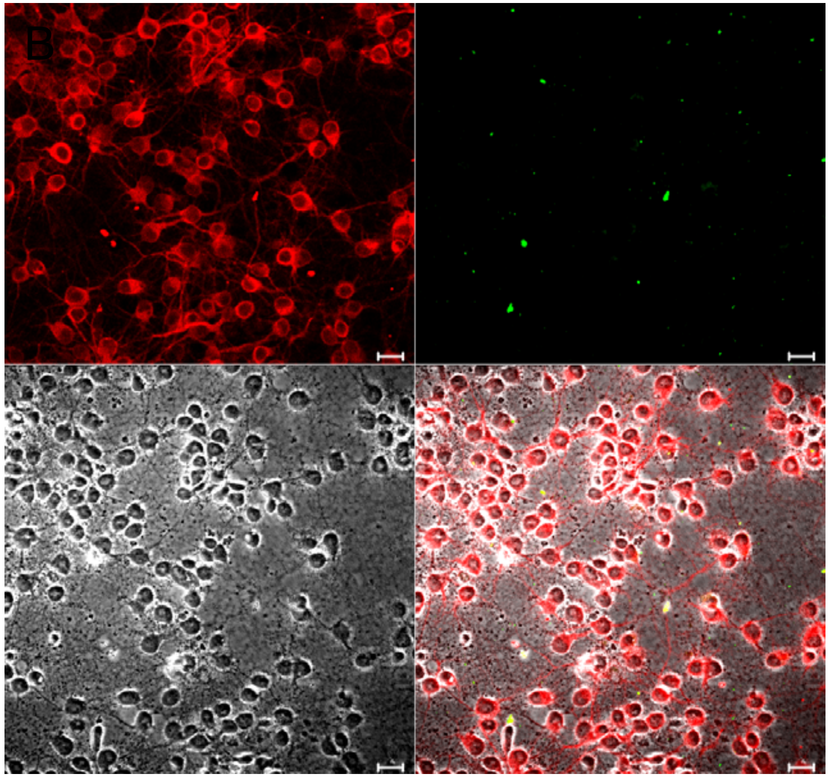
scale bar: 20 μm

7DIV, GSCs

plate cell density: 1000 mm^2

(A) AraC only (B) AraC+GCM



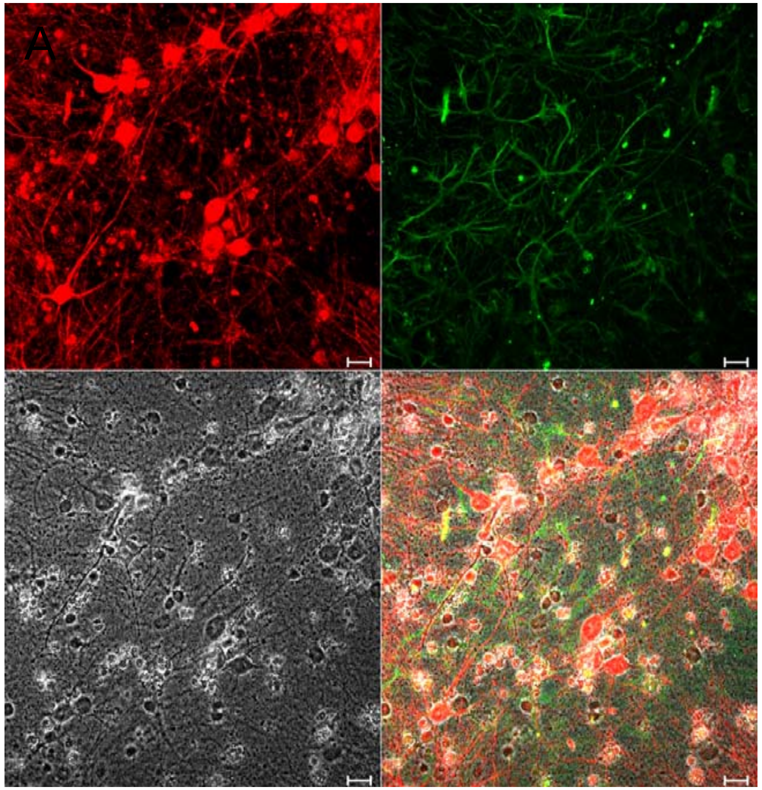


GECs, 7DIV

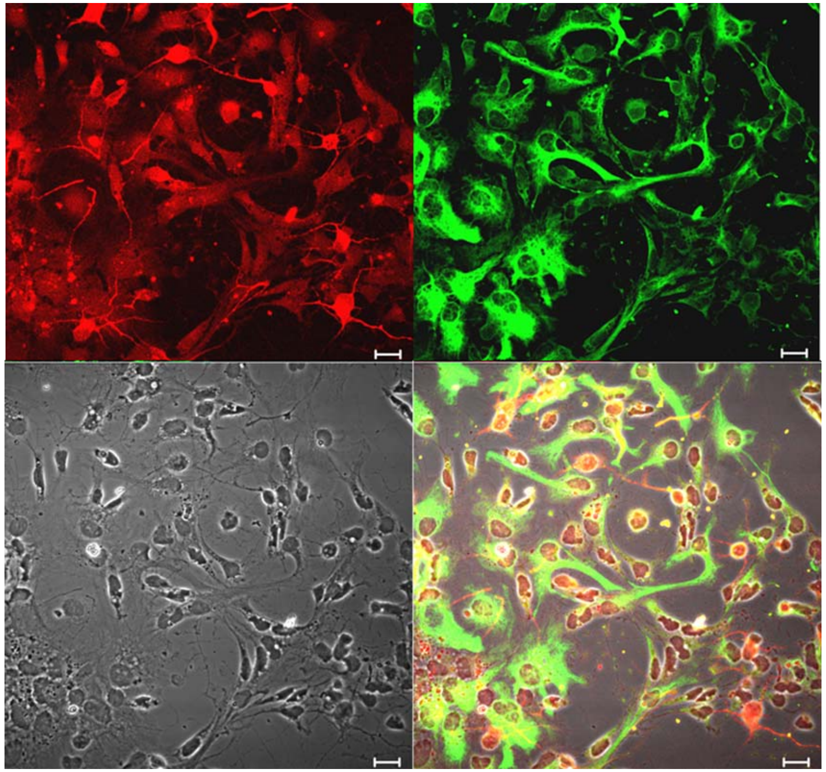
plate cell density: 1000 cells/mm^2

astrocytes density: ~200 cells/mm^2

A



B



Scale bar: 20 μ m

(A) pre-plate glia

(B) post-plate glia (GSCs)

Summary III

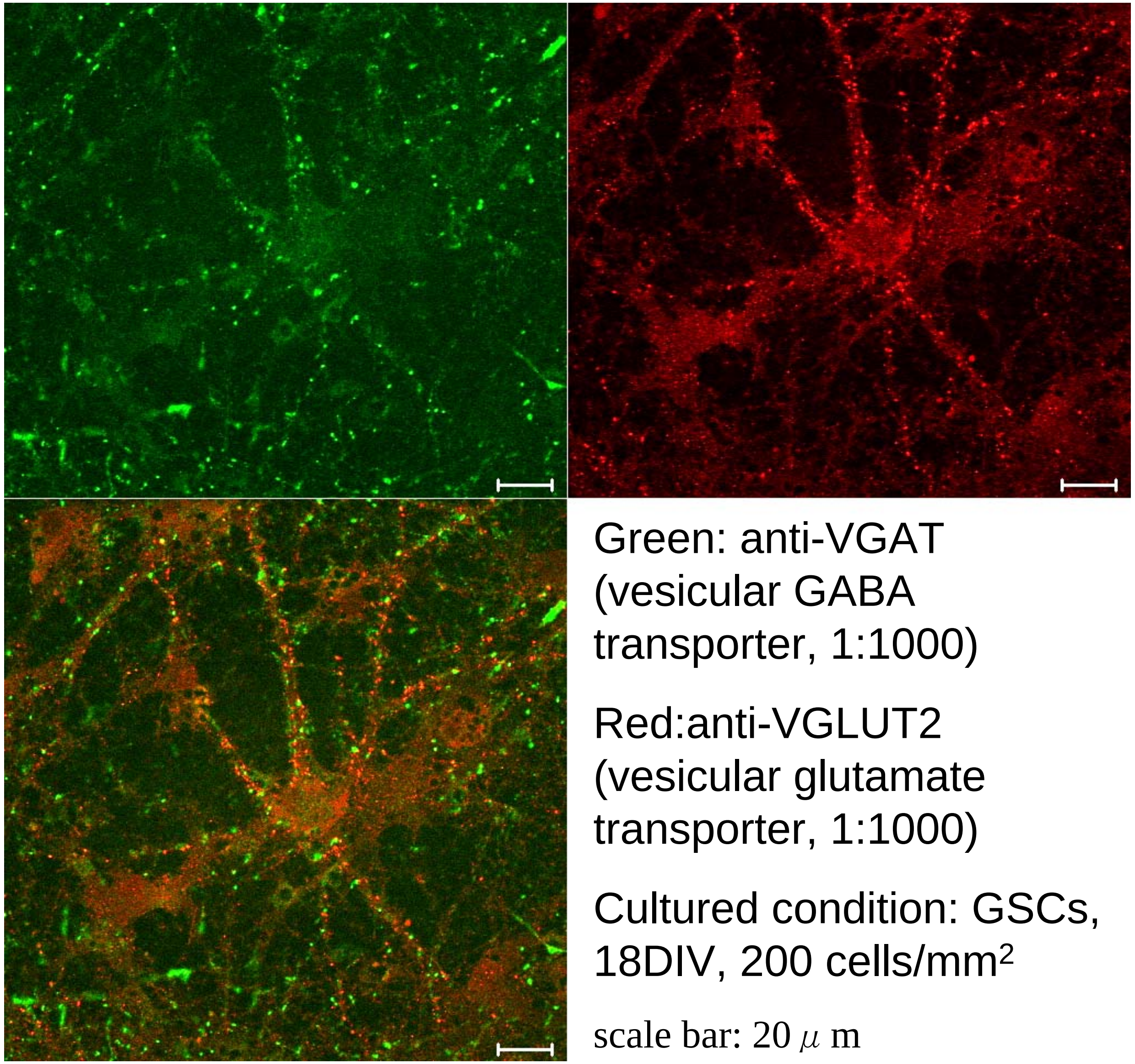
- Glia are NOT needed to generate synchronized bursting → network behaviour? → inhibitory connections?

- Forms of bursting are different with and without glia → change in topology(synaptic connection?)?

- Post-plated glia seem to suppress SB

  → different forms of astrocytes?

$$
\begin{aligned}
\epsilon \frac{dx}{dt} &= x - \frac{x^3}{3} - y - zg + \xi(t) \\
\frac{dy}{dt} &= a + bx - y \\
\frac{dg}{dt} &= -\frac{g}{\tau} + \gamma\, \Theta\, (rzx - \theta)
\end{aligned}
$$



Green: anti-VGAT (vesicular GABA transporter, 1:1000)

Red:anti-VGLUT2 (vesicular glutamate transporter, 1:1000)

Cultured condition: GSCs, 18DIV, 200 cells/mm^2

scale bar: 20 μ m

Open Questions

- How to understand the different time scales?
- What is the inhibitory mechanism?
- Role of glia?