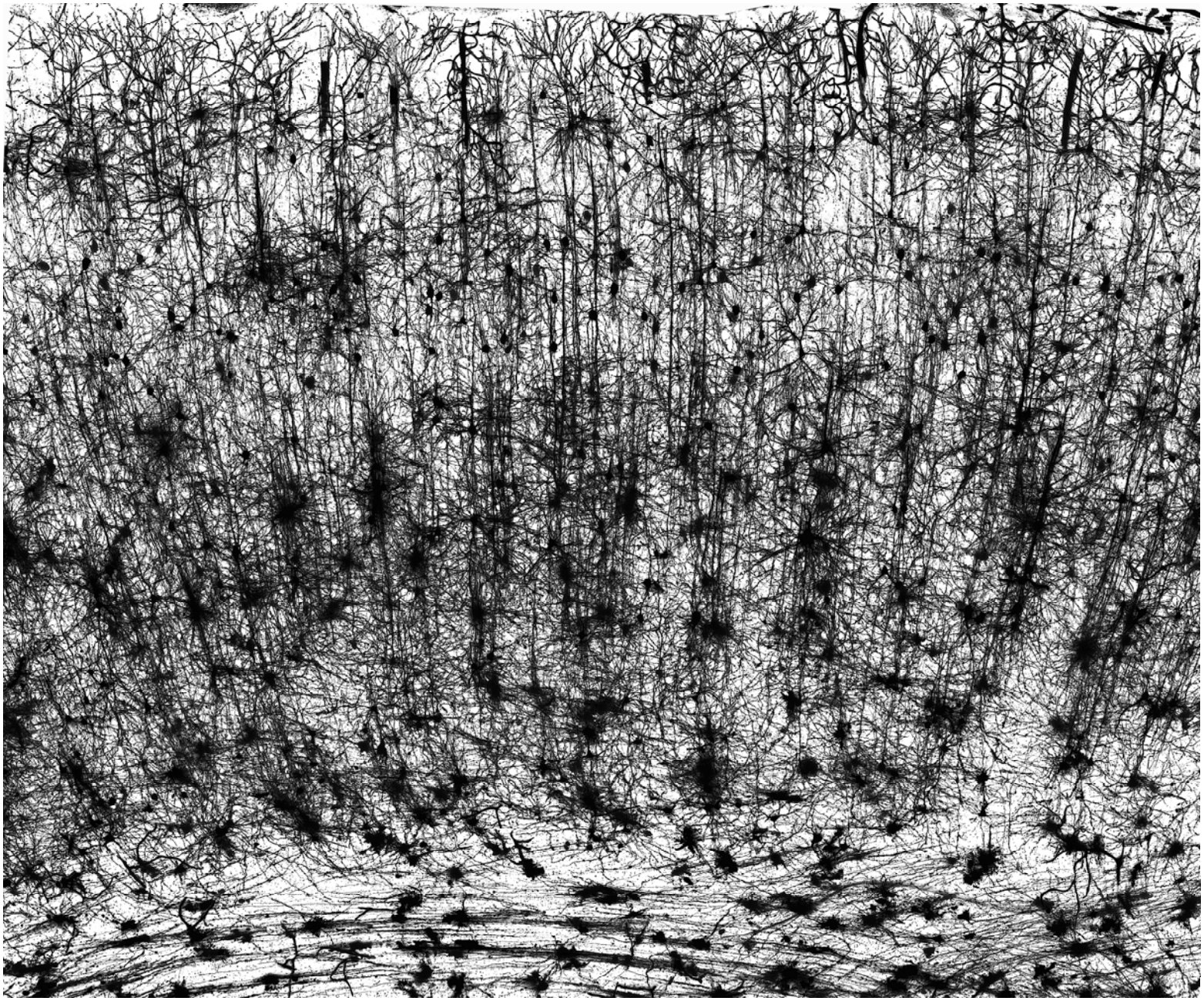
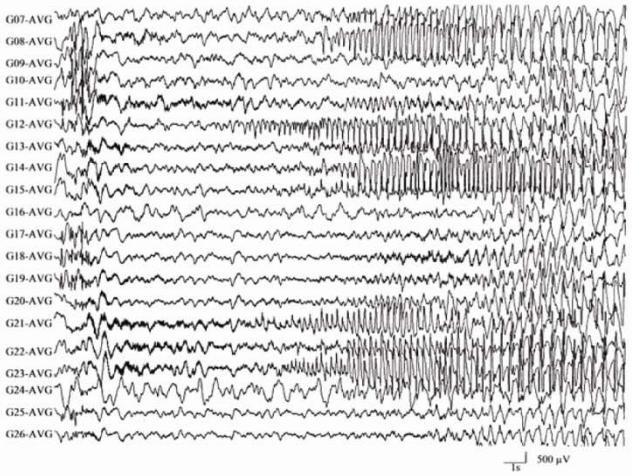
Golgi-Cox, mouse somatosensory cortex, courtesy of Dr. Farid Hamzei-Sichani



Some Cellular Mechanisms of Epilepsy

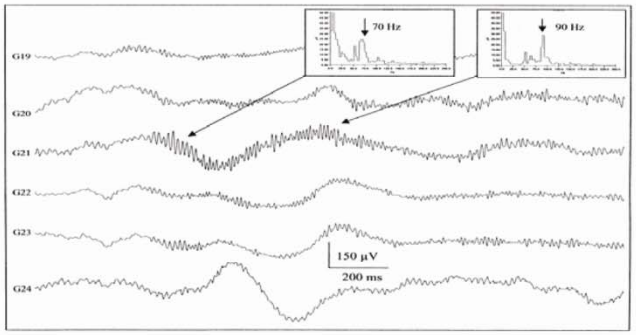
Roger D. Traub, M.D.
Dept. of Physical Sciences, IBM T.J. Watson Research Center
Yorktown Heights, NY
&
Dept. of Neurology
Columbia University, New York, NY

A

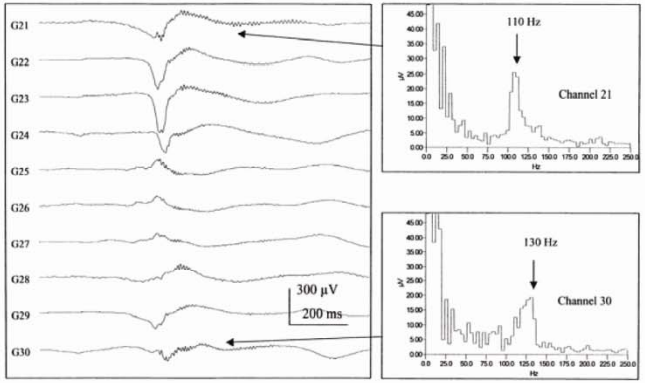


Human ECoG data:
very fast oscillations, followed by electrographic seizure

B

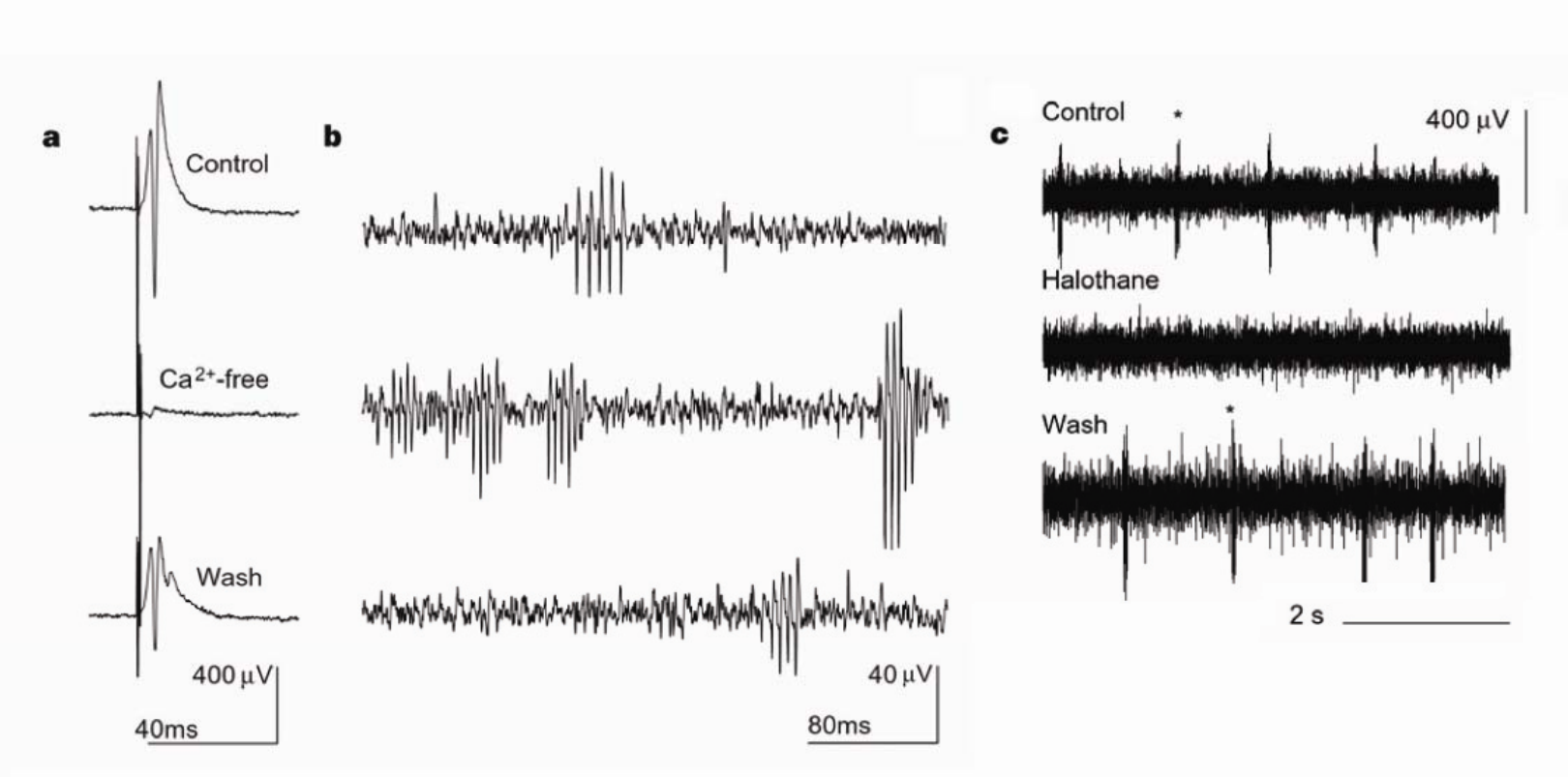


C



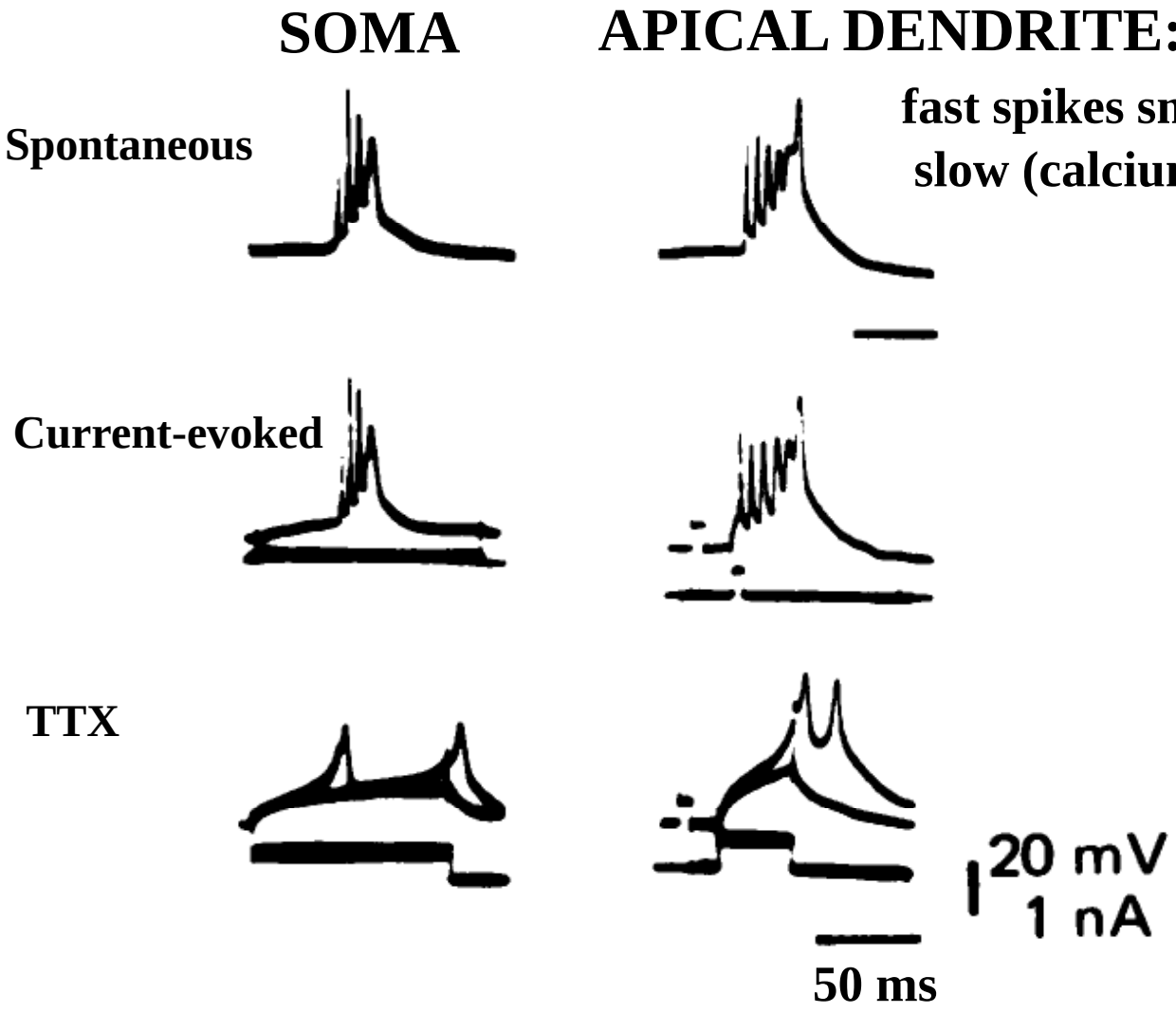
Traub RD., Whittington MA, Buhl EH, LeBeau FEN, Bibbig A, Boyd S, Cross H, Baldeweg T (2001) A possible role for gap junctions in generation of very fast EEG oscillations preceding the onset of, and perhaps initiating, seizures. Epilepsia 42: 153-170.

Non-synaptic ~200 Hz “ripples” in a population of hippocampal CA1 pyramidal neurons



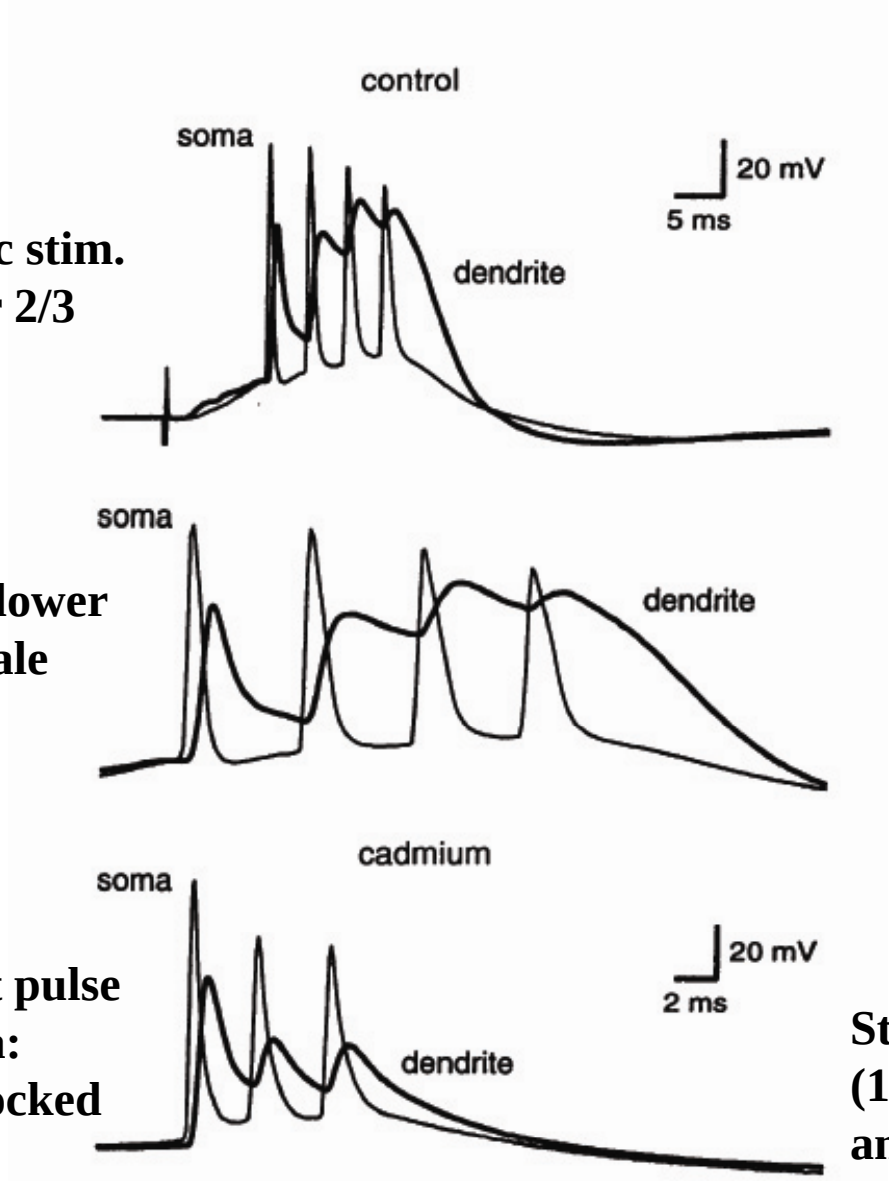
Draguhn A, Traub RD, Schmitz D, Jefferys JGR (1998)
Electrical coupling underlies high-frequency oscillations in the hippocampus *in vitro*. *Nature* 394: 189-192.

Robert K.S. Wong SUNY Downstate Medical Center, Brooklyn, 2006



Wong, R.K.S., Prince, D.A. and Basbaum, A.I. (1979) Intradendritic recordings from hippocampal neurons. Proc. Nat. Acad. Sci. USA 76: 986-990.

Layer 5: neocortical pyramidal neuron



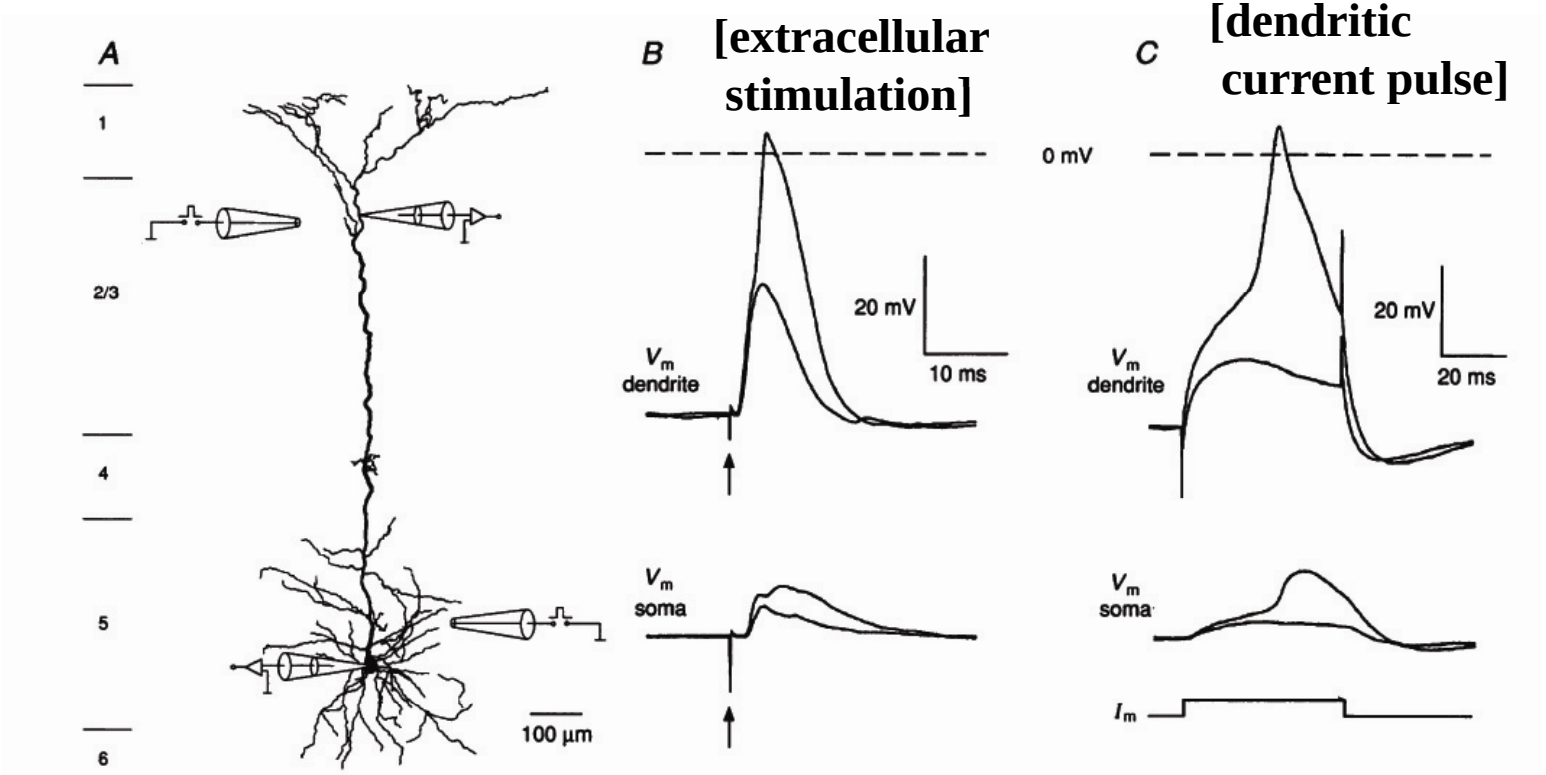
Synaptic stim. to layer 2/3

Same: slower time scale

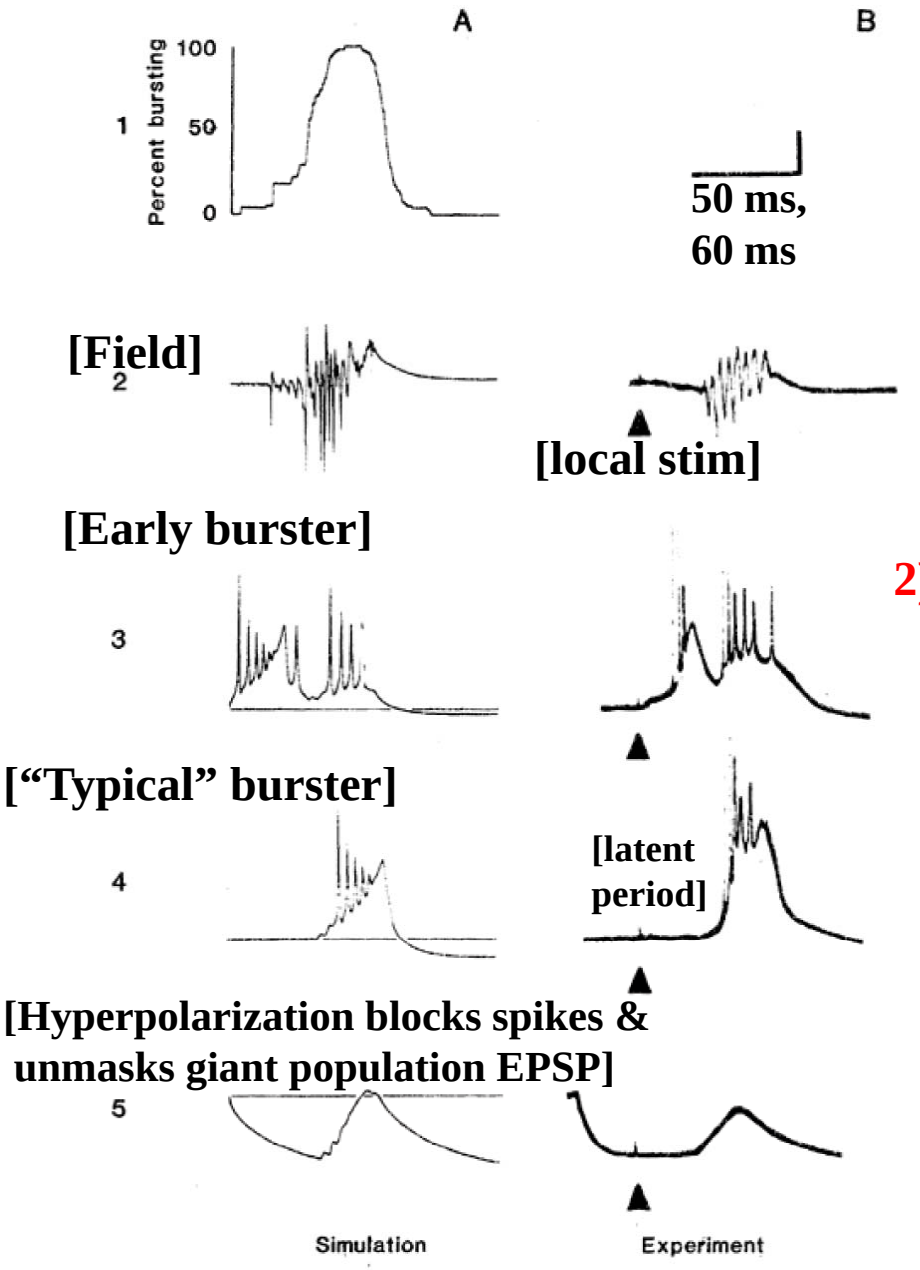
Current pulse to soma: gCa blocked

Stuart G, Schiller J, Sakmann B (1997) Action potential initiation and propagation in rat neocortical pyramidal neurons.
J. Physiol. 505: 617-632.

Layer 5: neocortical pyramidal neuron



Schiller J, Schiller Y, Stuart G, Sakmann B (1997) Calcium action potentials restricted to distal apical dendrites of rat neocortical pyramidal neurons. J. Physiol. 505: 605-616.

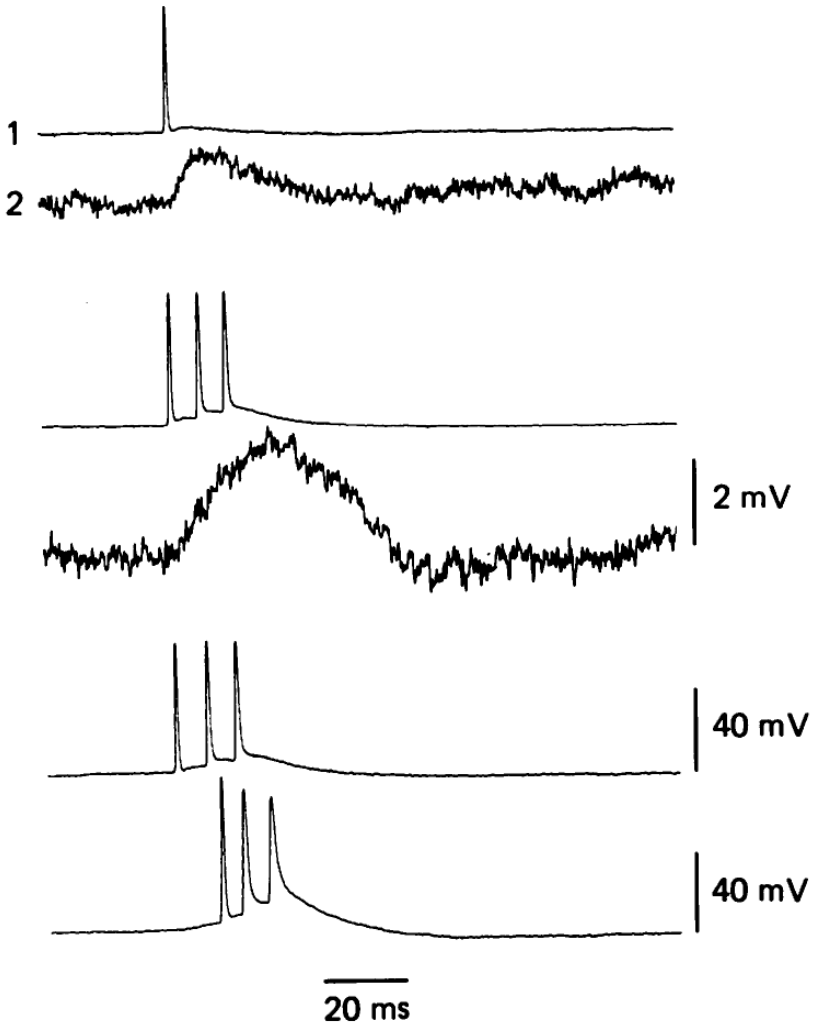


In vitro epileptiform synchronized burst: $GABA_A$ receptors blocked. Hippocampal CA2/CA3.

Basic model properties:

1) **Each neuron connects to >1 other;**
2) **Bursting propagates from neuron to neuron**

Traub RD, Wong RKS (1982) Cellular mechanism of neuronal synchronization in epilepsy. *Science* 216, 745-747.



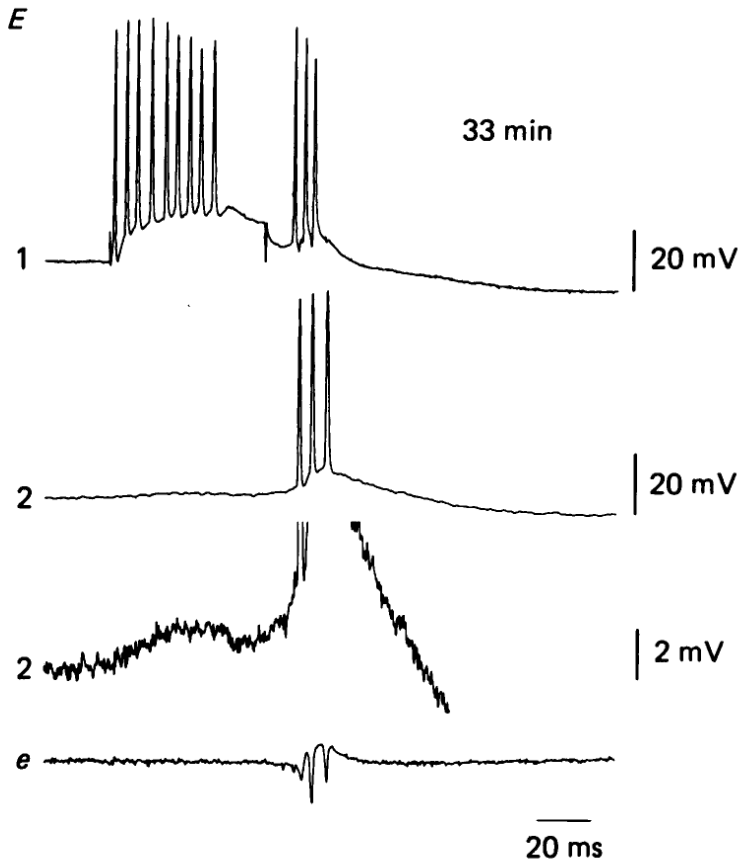
Monosynaptically connected CA3 pyramidal neurons

(Richard Miles)

Burst propagation with latency 11 ms

Miles R, Wong RKS (1987) Inhibitory control of local excitatory circuits in the guinea-pig hippocampus. J. Physiol. 388: 611-629.

Stimulating a single pyramidal neuron can indeed evoke an epileptiform burst, at least if there is disinhibition

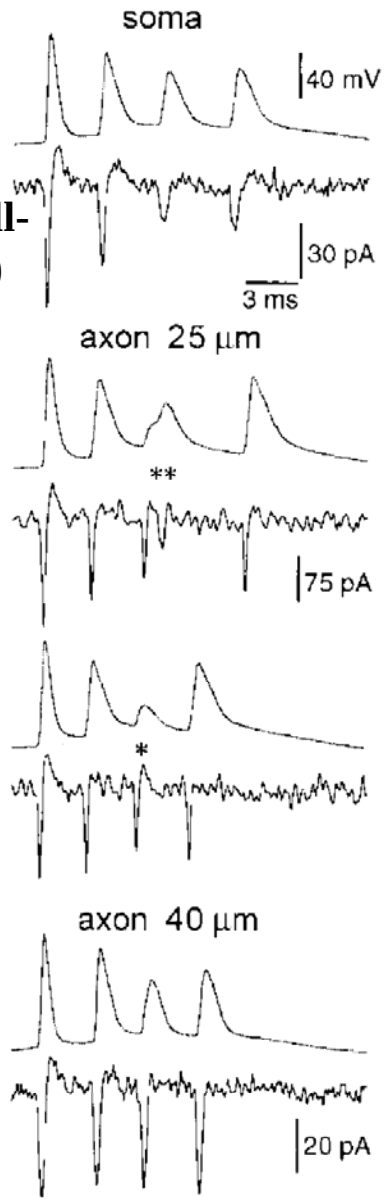


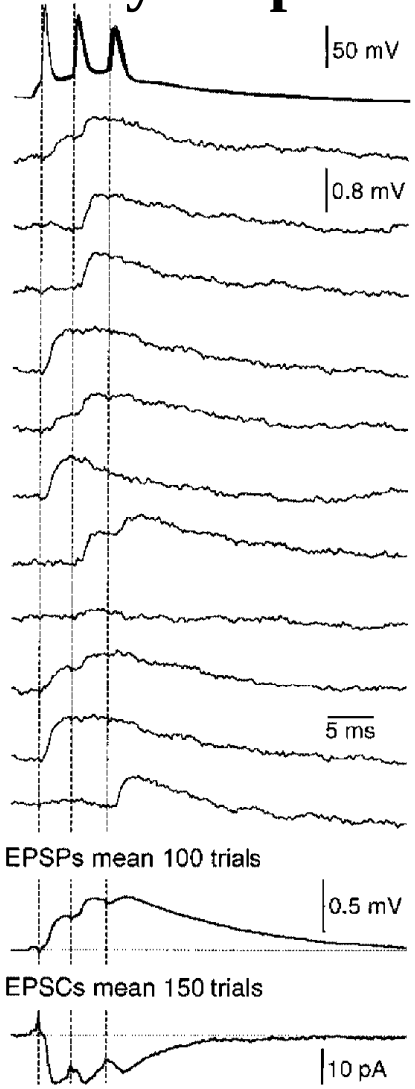
Miles R, Wong RKS (1987) Inhibitory control of local excitatory circuits in the guinea-pig hippocampus. J. Physiol. 388: 611-629.

[Previously shown in Miles & Wong (1983) Single neurones can initiate synchronized population discharge in the hippocampus. Nature 306: 371-373.]

[synaptically coupled layer 5 pyr. neurons]

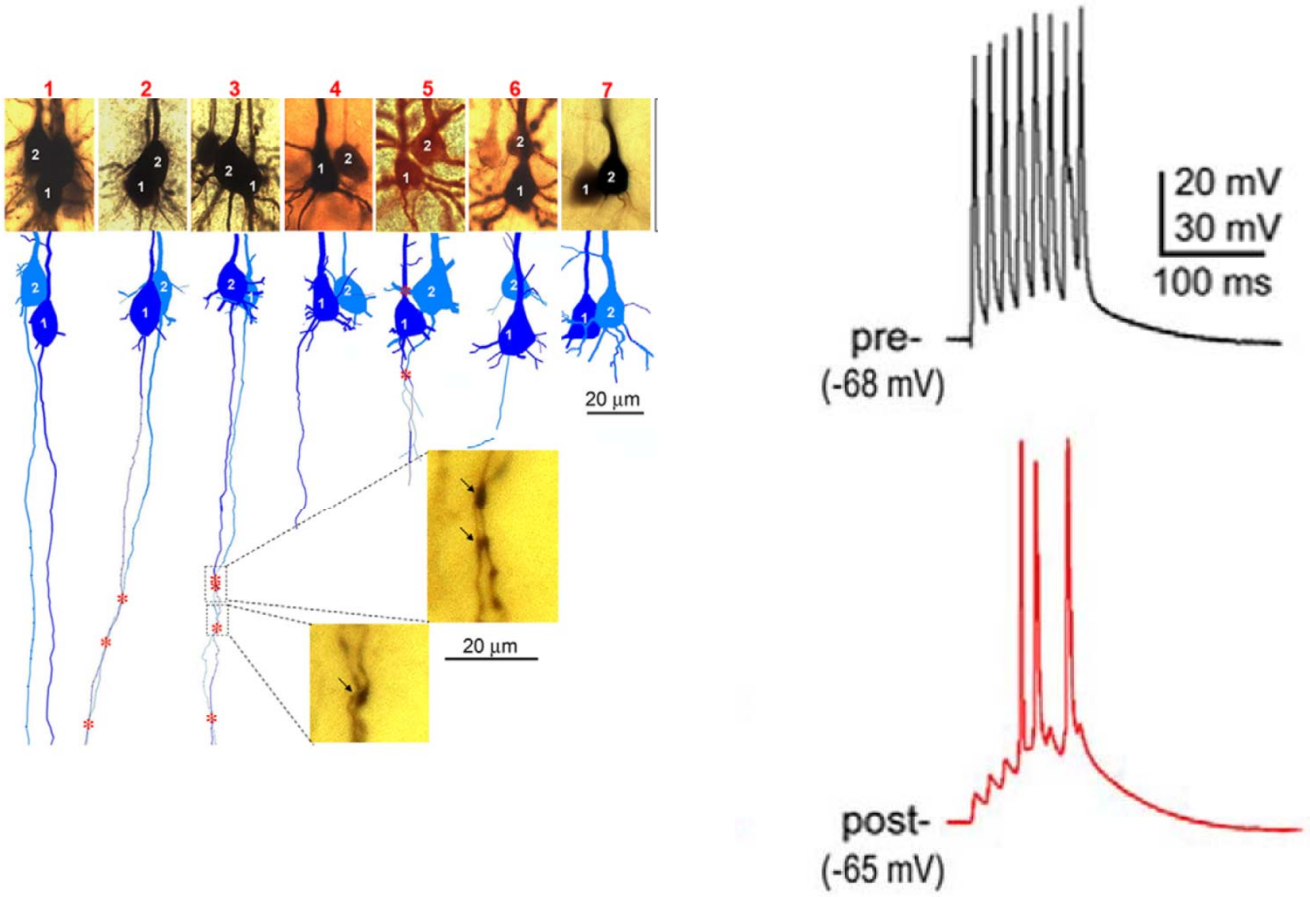
Axon (cell-attached)



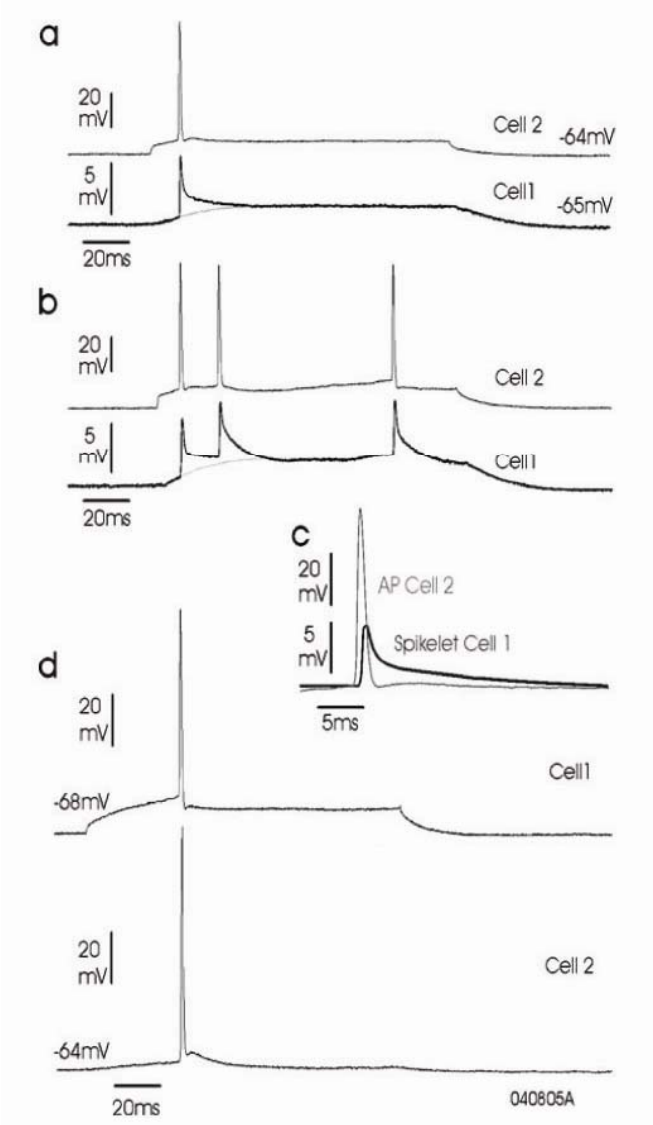


Williams SR, Stuart GJ (1999) Mechanisms and consequences of action potential burst firing in rat neocortical pyramidal neurons. J. Physiol. 521: 467-482.

Burst propagation across a gap junction, 2 coupled neocortical pyramidal cells, P32 rat



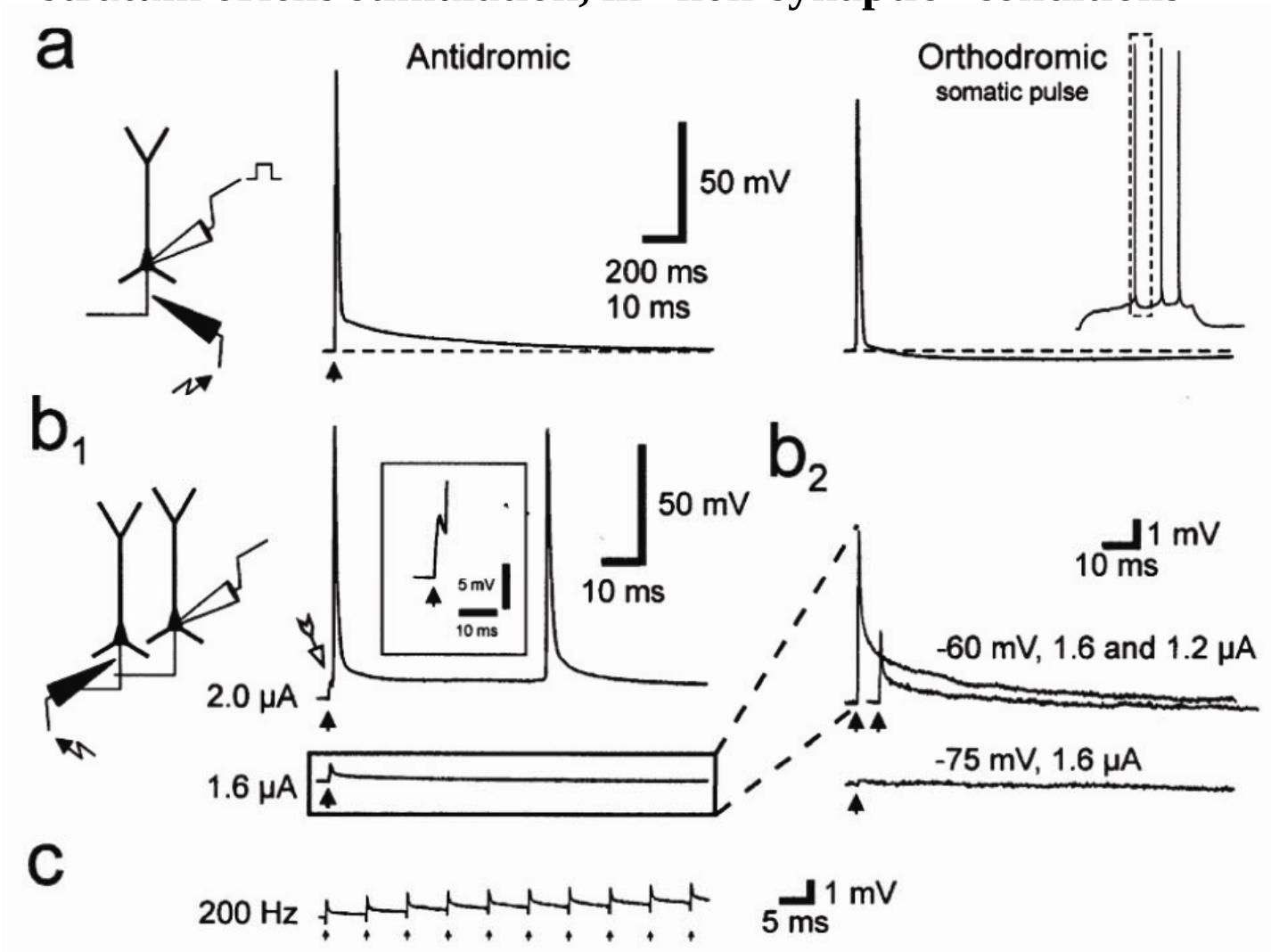
Wang Y, Barakat A, Zhou H (2010) Electrotonic coupling between pyramidal neurons in the neocortex. PLoS ONE 5(4) e10253.



Spike:spikelet & spike:spike transduction between two CA1 pyramidal neurons

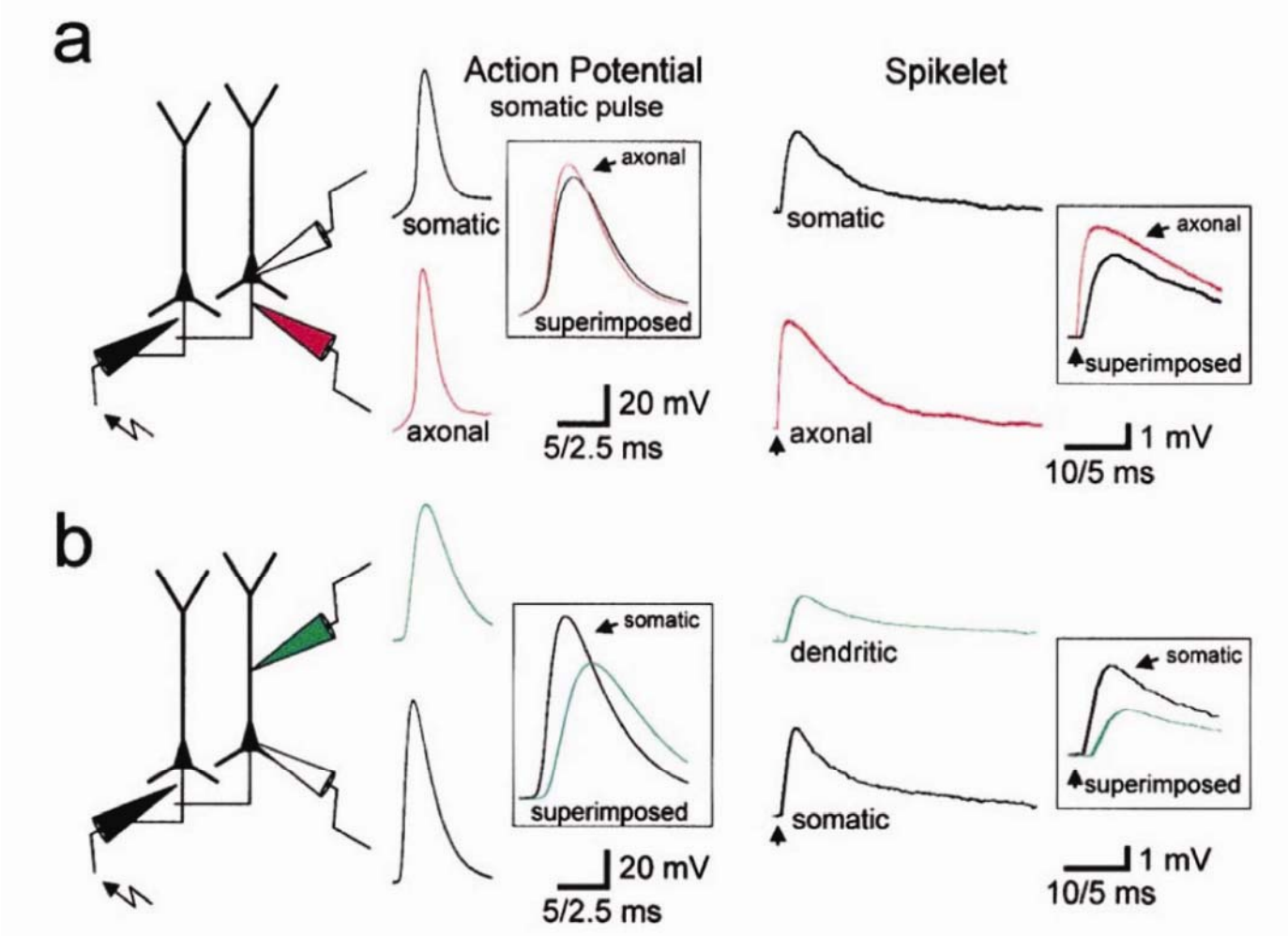
Mercer A, Bannister AP, Thomson AM (2006) Electrical coupling between pyramidal cells in adult cortical regions. Brain Cell Biol. 35: 13-27.

Antidromic spikes and "spikelets" in CA1 pyramidal neurons after stratum oriens stimulation, in "non-synaptic" conditions

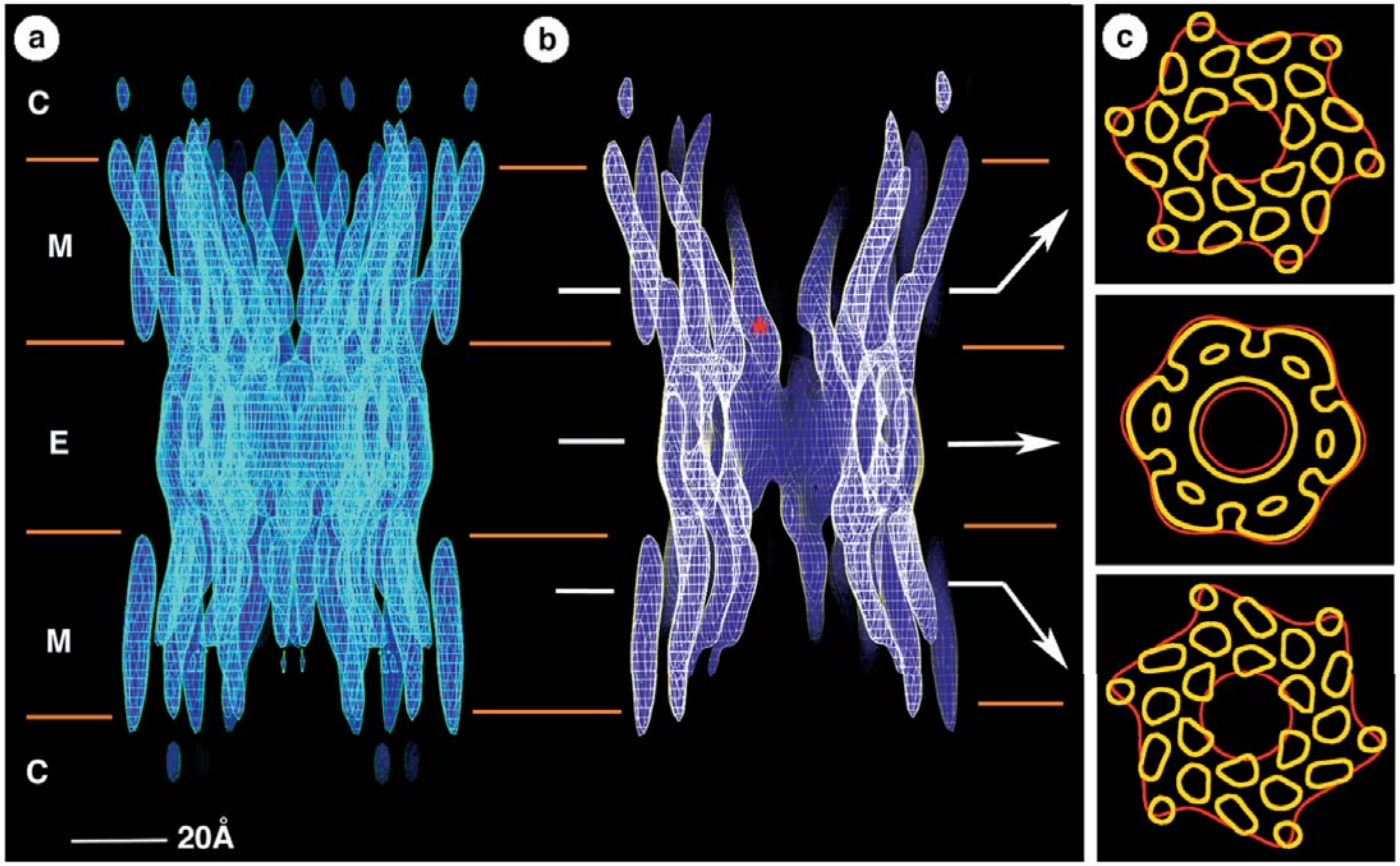


Schmitz D, Schuchmann S, Fisahn A, Draguhn A, Buhl EH, Petrasch-Parwez RE, Dermietzel R, Heinemann U, Traub RD (2001) Axo-axonal coupling: a novel mechanism for ultrafast neuronal communication. *Neuron* 31: 831-840.

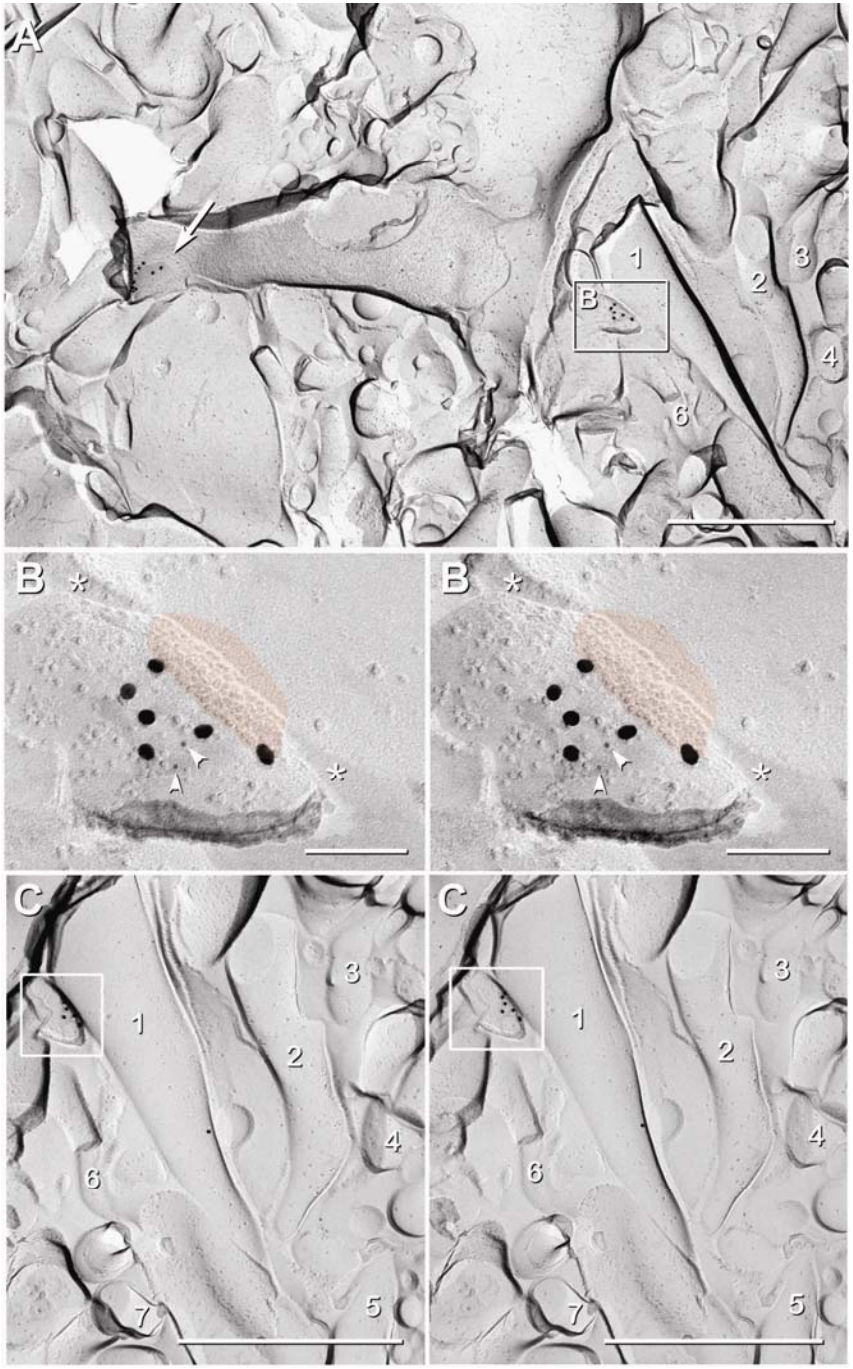
Spikelets are decrementally conducted *axonal* action potentials



Schmitz D, Schuchmann S, Fisahn A, Draguhn A, Buhl EH, Petrasch-Parwez RE, Dermietzel R, Heinemann U, Traub RD (2001) Axo-axonal coupling: a novel mechanism for ultrafast neuronal communication. *Neuron* 31: 831-840.

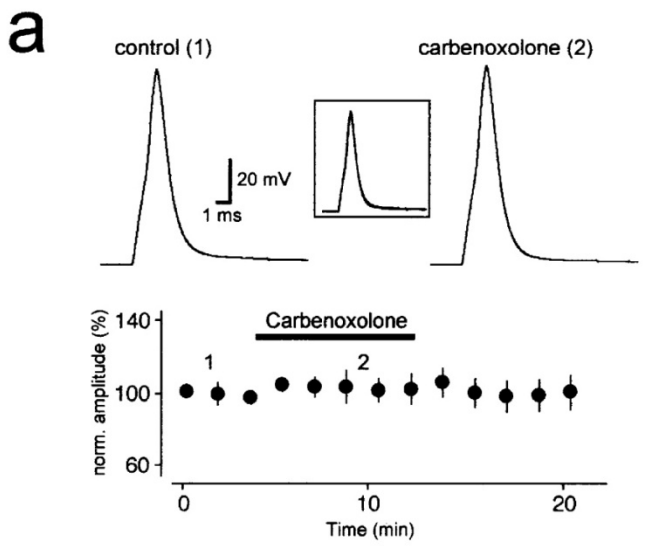


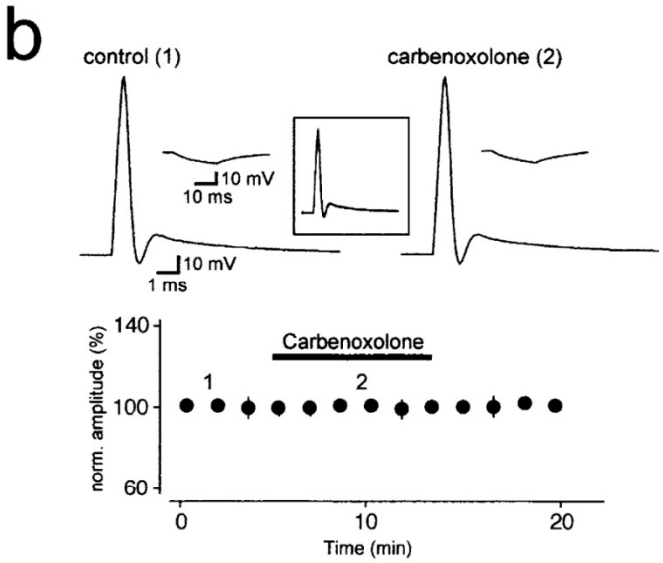
Gap junction structure: recombinant cardiac connexin (lacking COOH-terminal domain), expressed in BHK cells. Electron crystallography, ~7.5 Å resolution in membrane plane, 21 Å in vertical plane. V.M. Unger et al., 1999, Science.



Ultrastructural evidence for gap junctions between mossy fibers, CA3 hippocampus

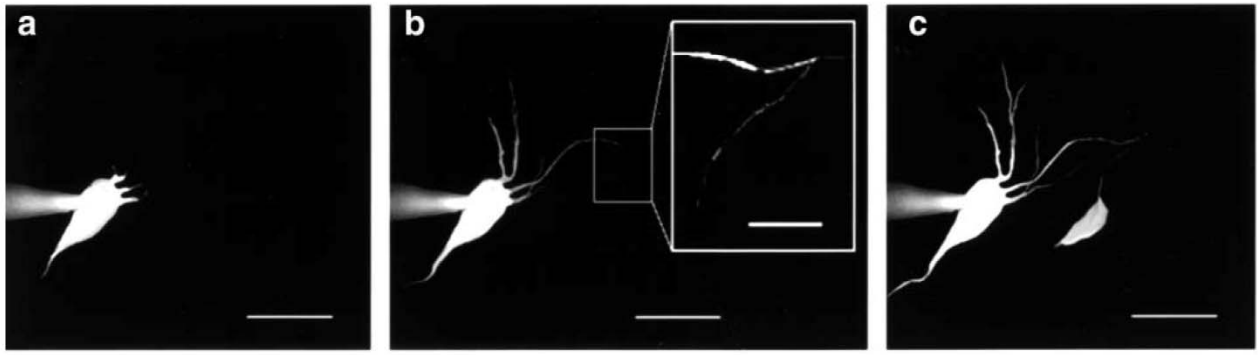
Hamzei-Sichani, F., Kamasawa, N., Janssen, W.G.M., Yasamura, T., Davidson, K.G.V, Hof, P.R., Wearne, S.L., Stewart, M.G., Young, S.R., Whittington, M.A., Rash, J.E. and Traub, R.D. (2007)
Gap junctions on hippocampal mossy fiber axons demonstrated by thin-section electron microscopy and freeze-fracture replica immunogold labeling.
Proc. Natl. Acad. Sci. USA 104: 12548-12553.



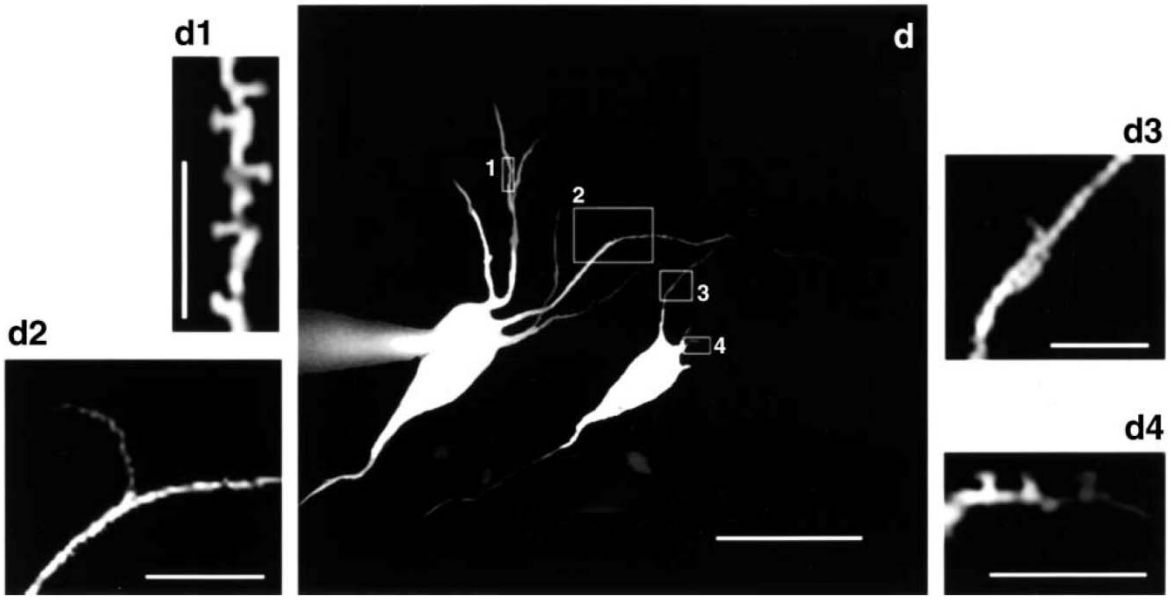


Lack of effect of carbenoxolone on axonal action potentials.

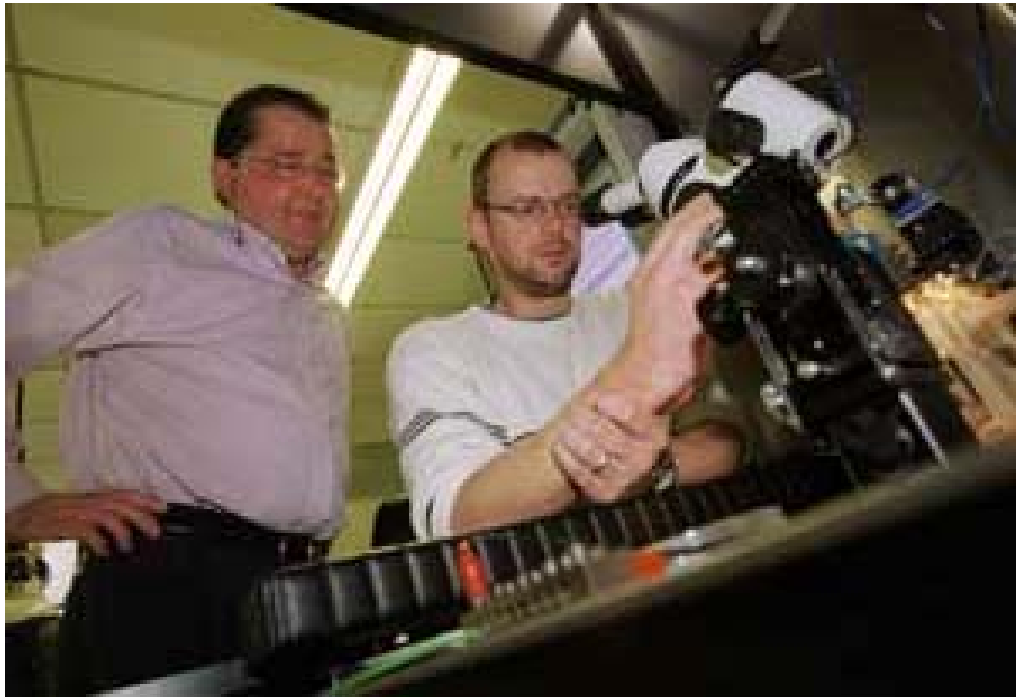
D. Schmitz et al., 2001



CA1 pyramidal cells are dye-coupled through their axons by light microscopic criteria.



Schmitz D, Schuchmann S, Fisahn A, Draguhn A, Buhl EH, Petrasch-Parwez RE, Dermietzel R, Heinemann U, Traub RD (2001) Axo-axonal coupling: a novel mechanism for ultrafast neuronal communication. Neuron 31: 831-840.



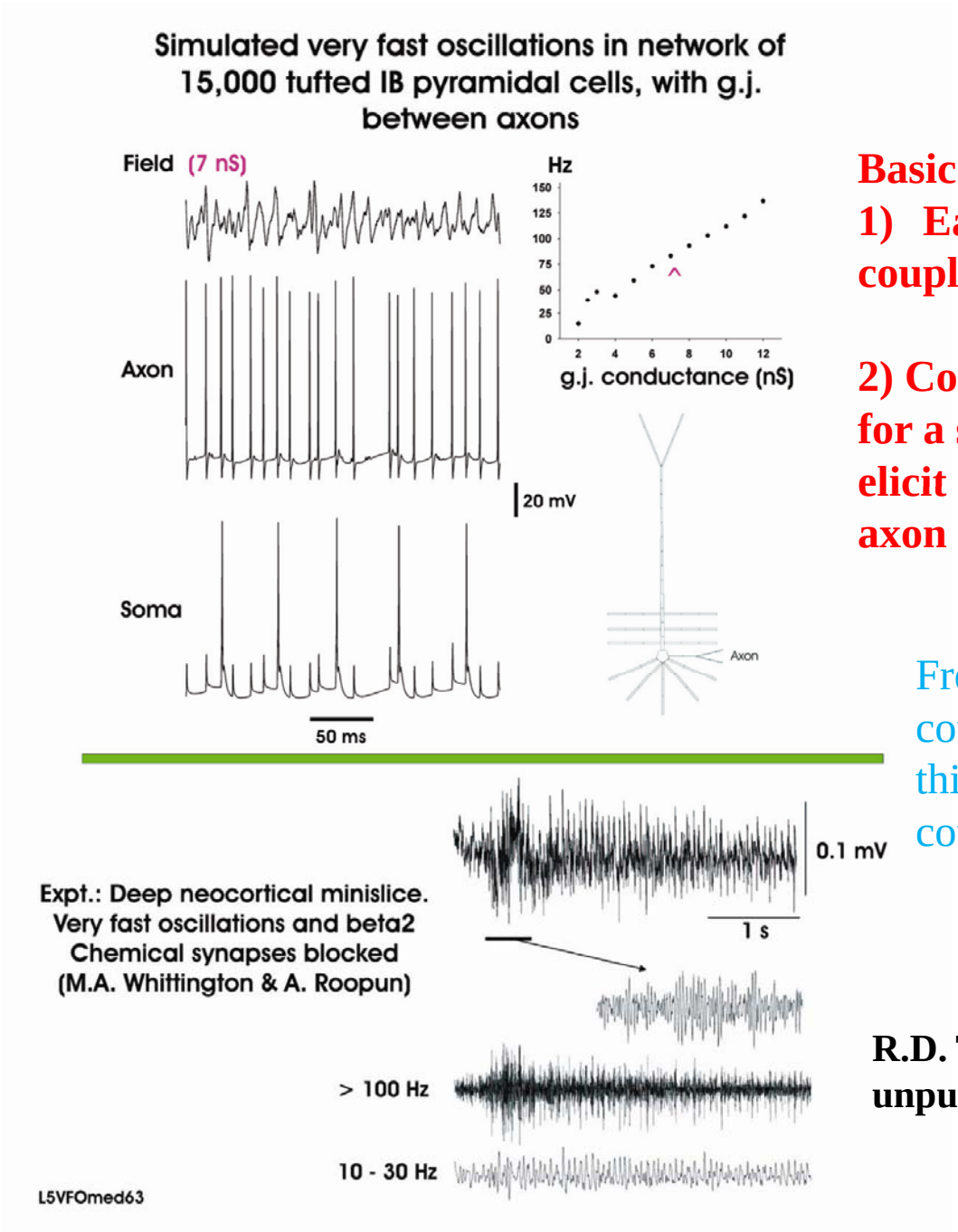
Eberhard Buhl & Miles A. Whittington, Leeds, 2002

German colleagues

Andreas Draguhn

Dietmar Schmitz

Hannah Monyer



Basic model assumptions:

1) Each axon is electrically coupled to just a few others

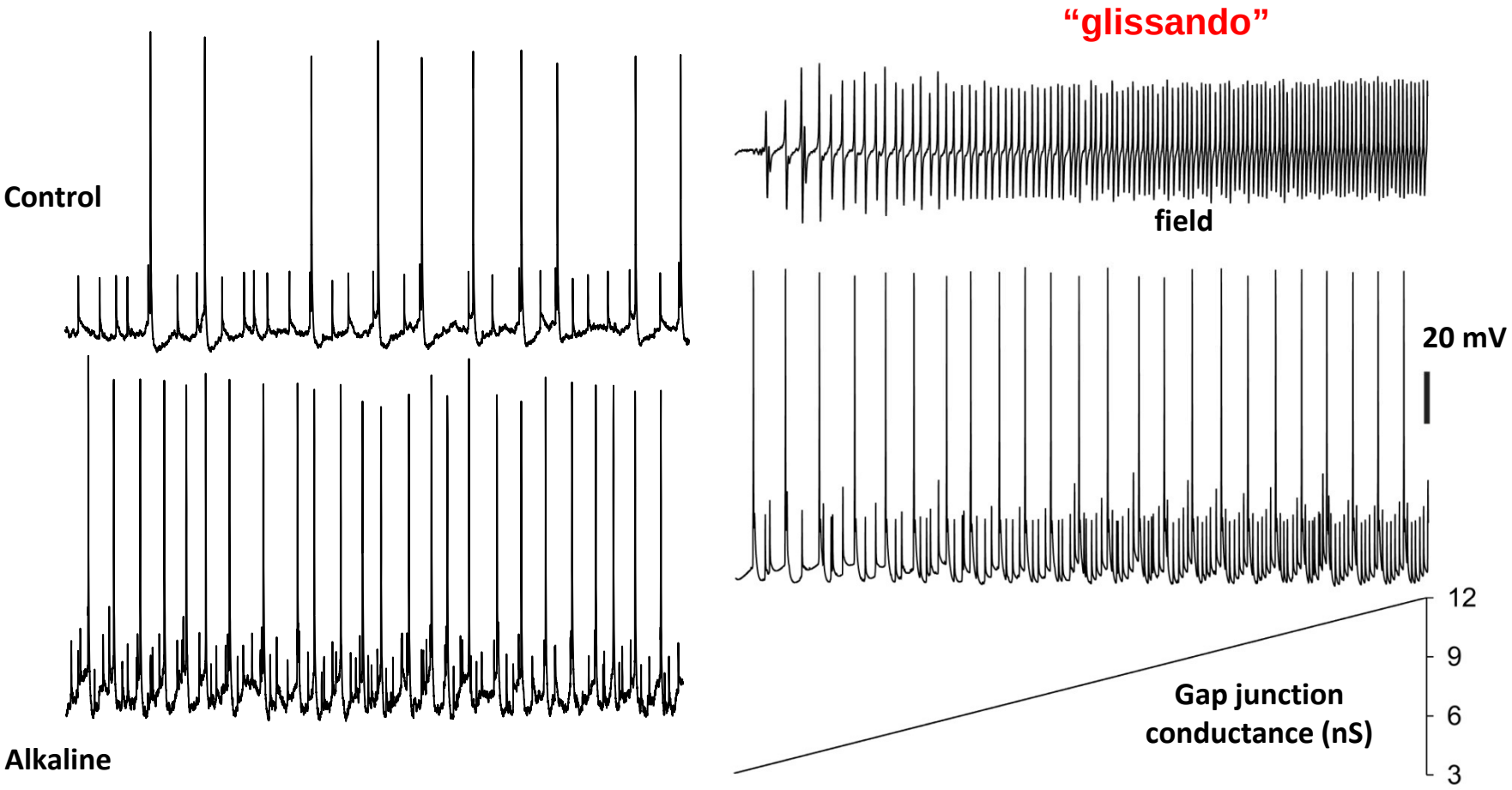
2) Coupling is strong enough for a spike in one axon to elicit a spike in a coupled axon at short latency (< 1 ms)

Frequency variation with coupling strength implies this can not be a system of coupled oscillators

R.D. Traub & Miles A. Whittington, unpublished data

Experiment

Model

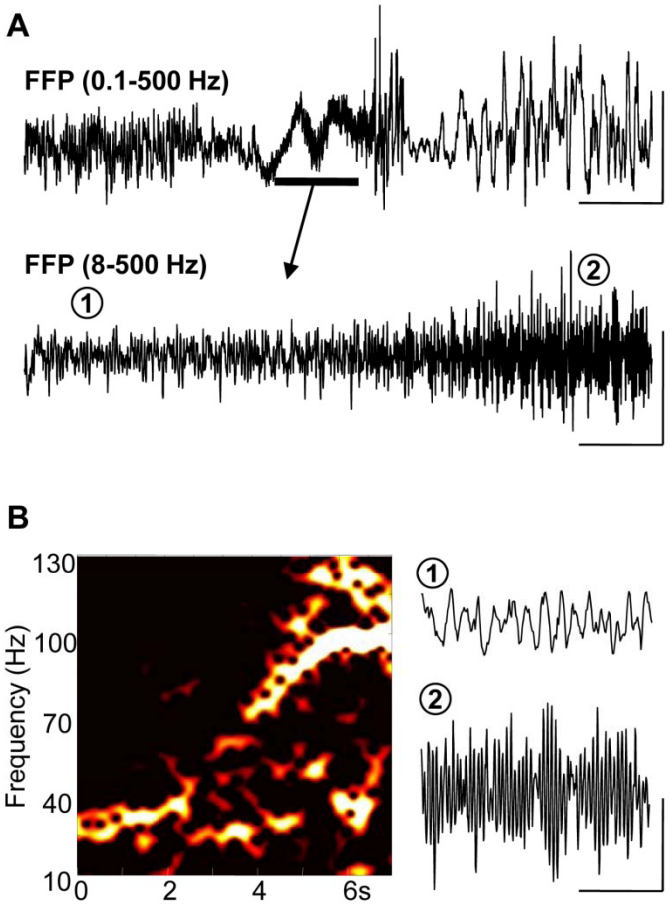


1 second traces, Layer 5 neocortex
M.A. Whittington, R.D. Traub (unpublished)

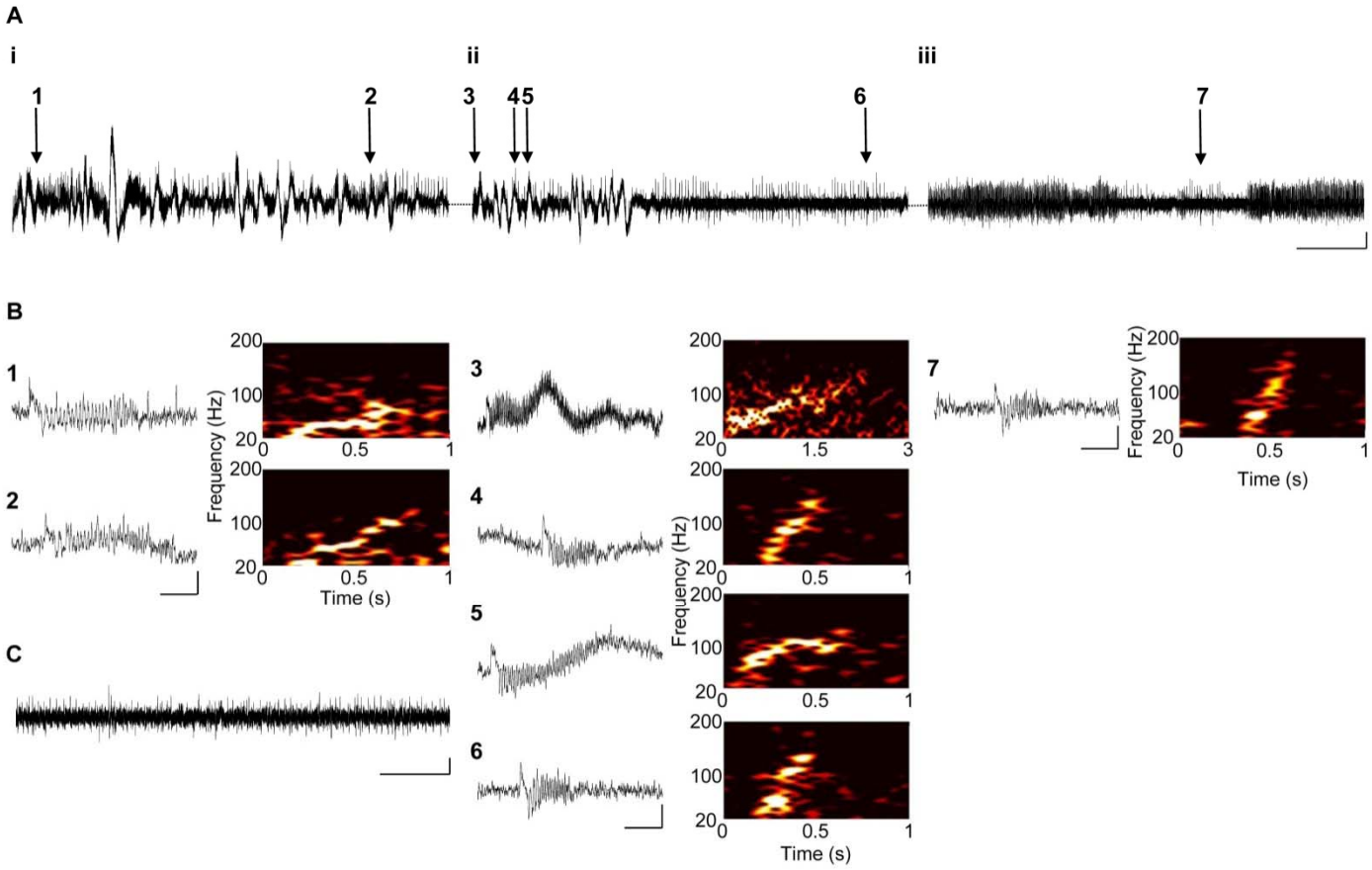
Digression on “glissandi”

Mark Cunningham, Miles Whittington, Roger Traub et al., in prep.

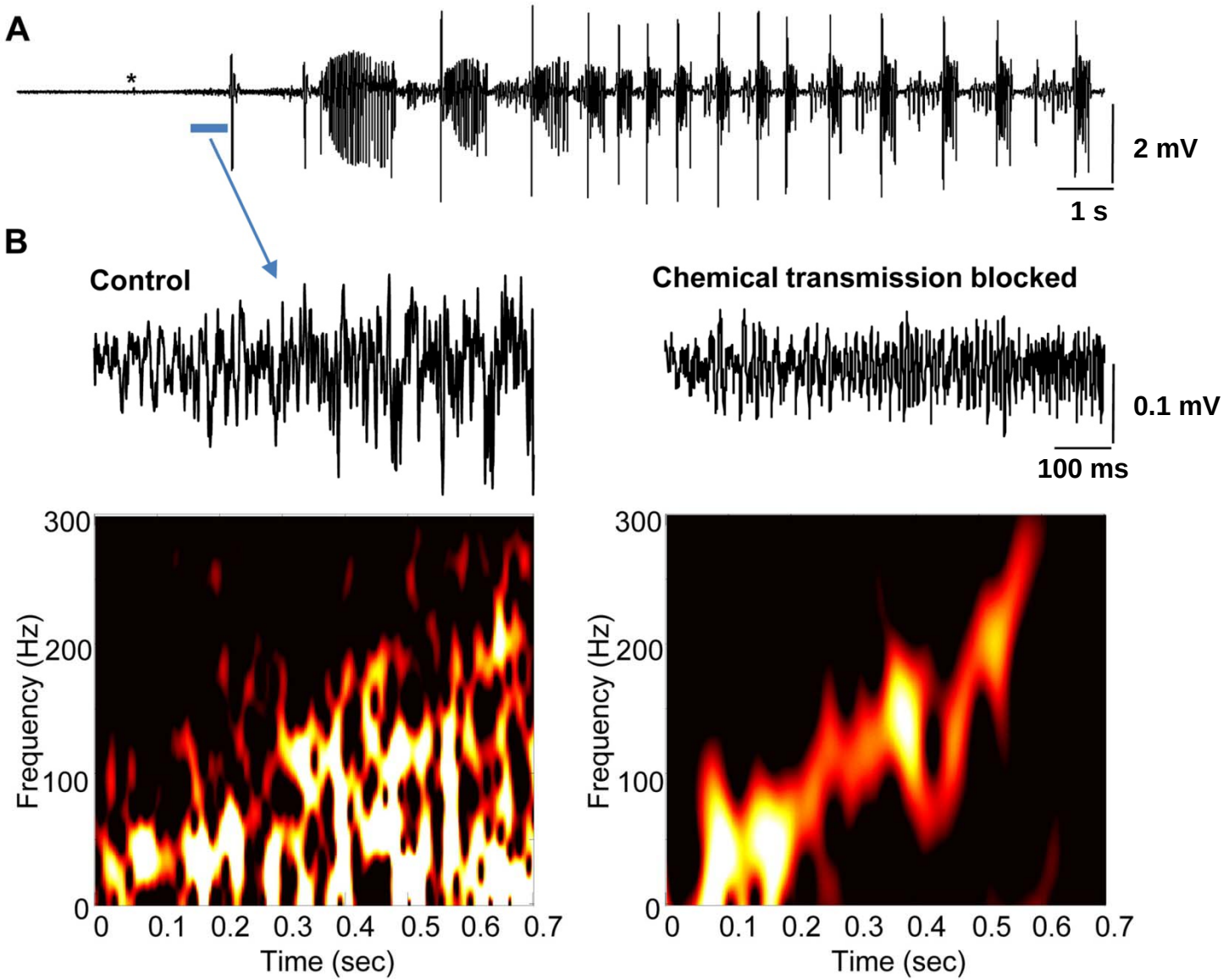
Epilepsy patient, ECoG, prior to electrographic sz



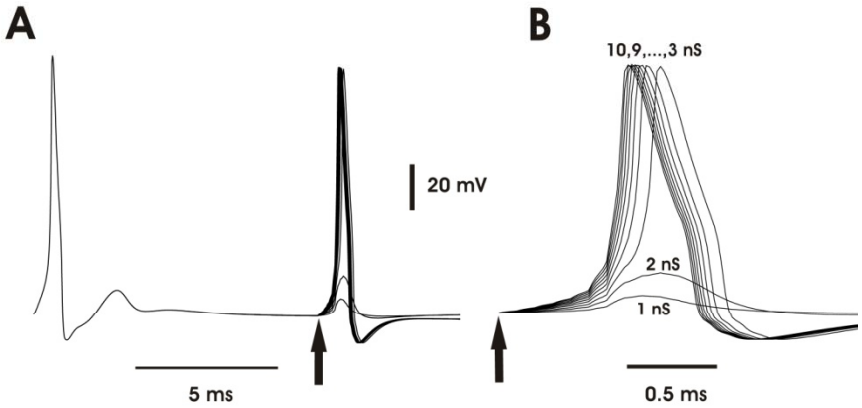
Epilepsy patient: resected neocortex in vitro



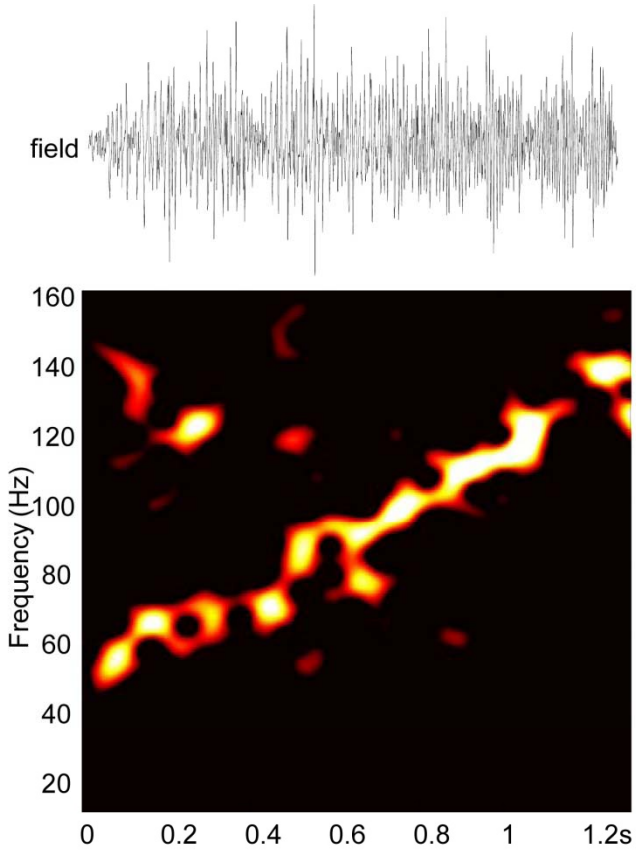
Rat frontal neocortex in vitro: alkaline conditions

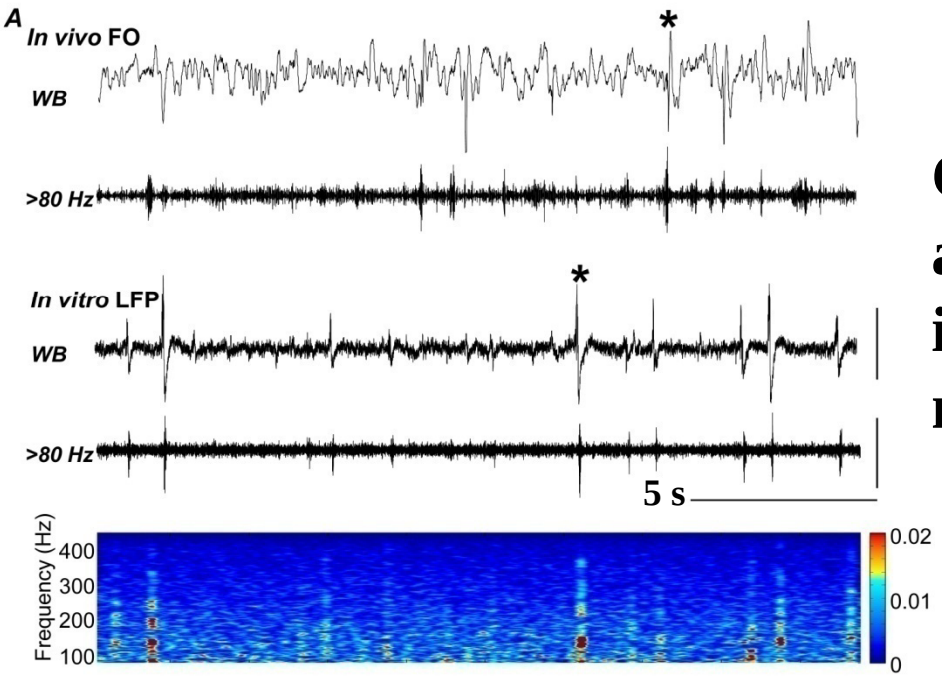


Network model:
2 cells (left); 15,000 cells (right)

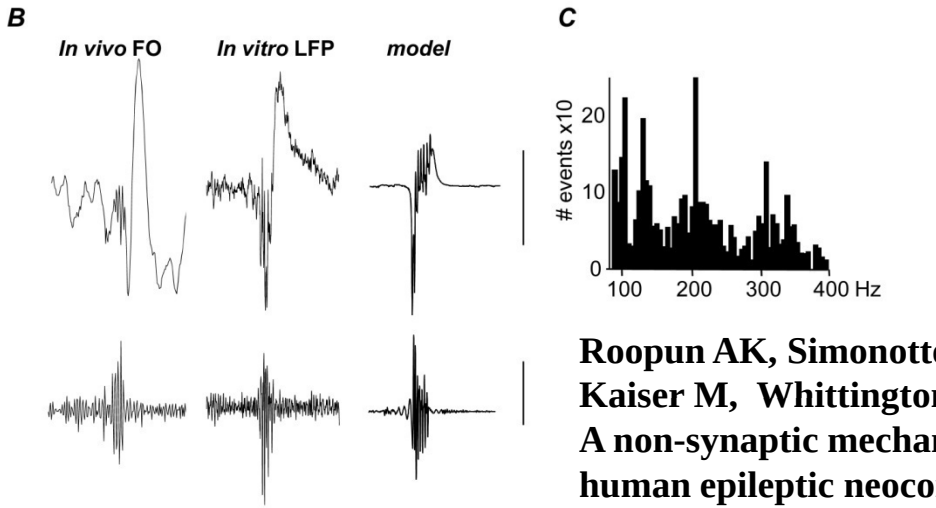


L5VFOpulse7



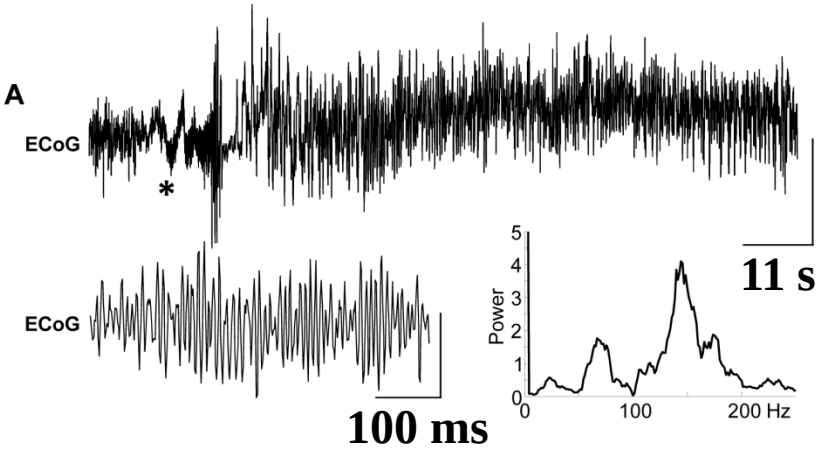


Co-existence of bursts and VFO in human tissue: in situ, in vitro, and network model

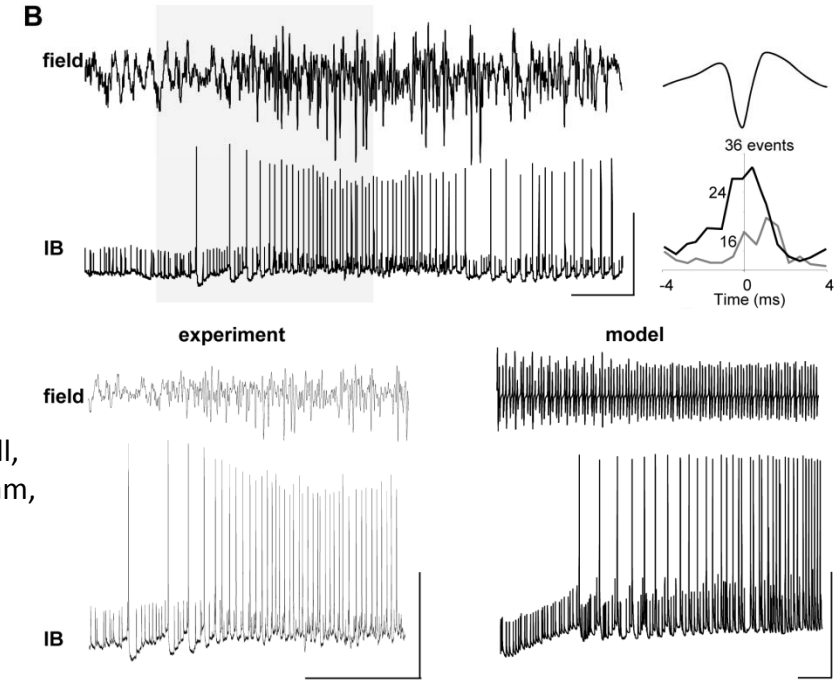


Roopun AK, Simonotto JD, Pierce ML, Jenkins A, Schofield I, Kaiser M, Whittington MA, Traub RD, Cunningham MO (2010) A non-synaptic mechanism underlying interictal discharges in human epileptic neocortex. *Proc. Natl. Acad. Sci. USA* 107: 338-343.

Human



Rat & model



R.D. Traub, R. Duncan, A.J.C. Russell, T. Baldeweg, Y. Tu, M.O. Cunningham, M.A. Whittington: Epilepsia, 2010

Propagation of activity in a *locally random* network of coupled, excitable elements (c.f. Lewis &Rinzel, 2000; Traub et al., 2010)

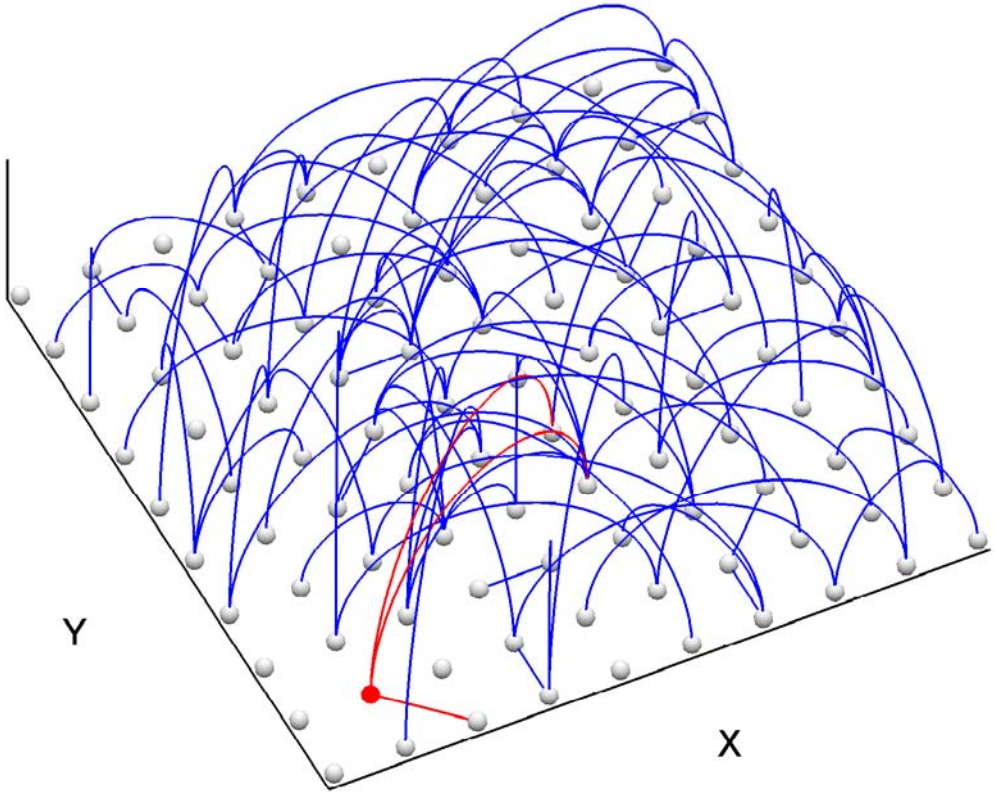
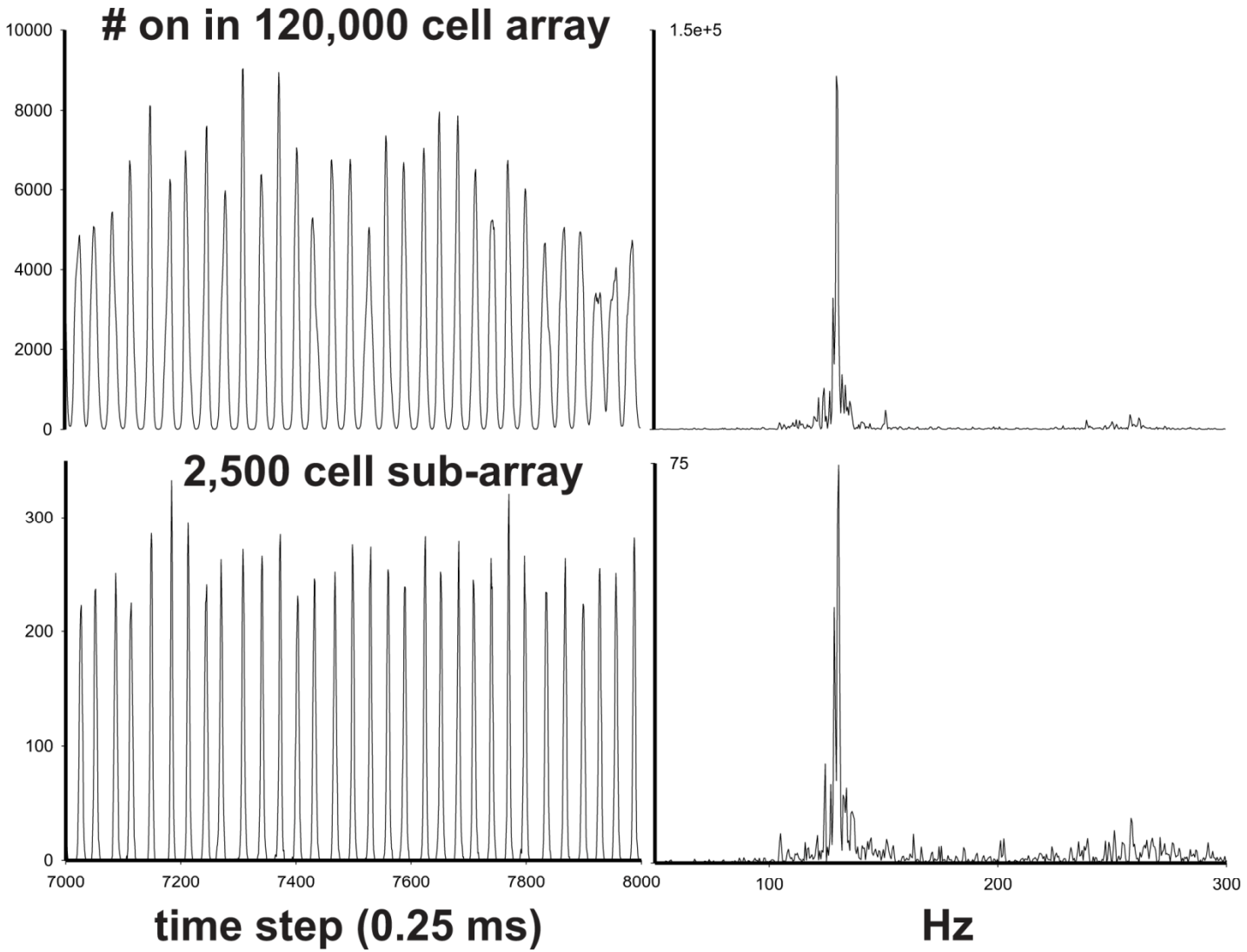
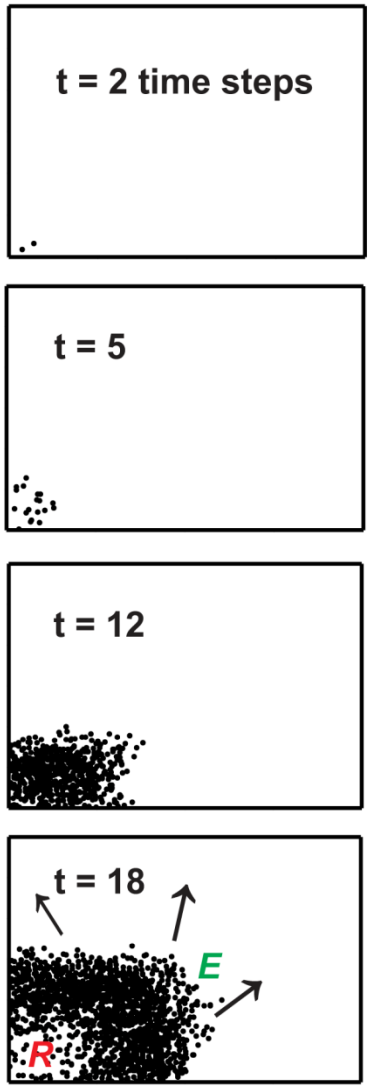


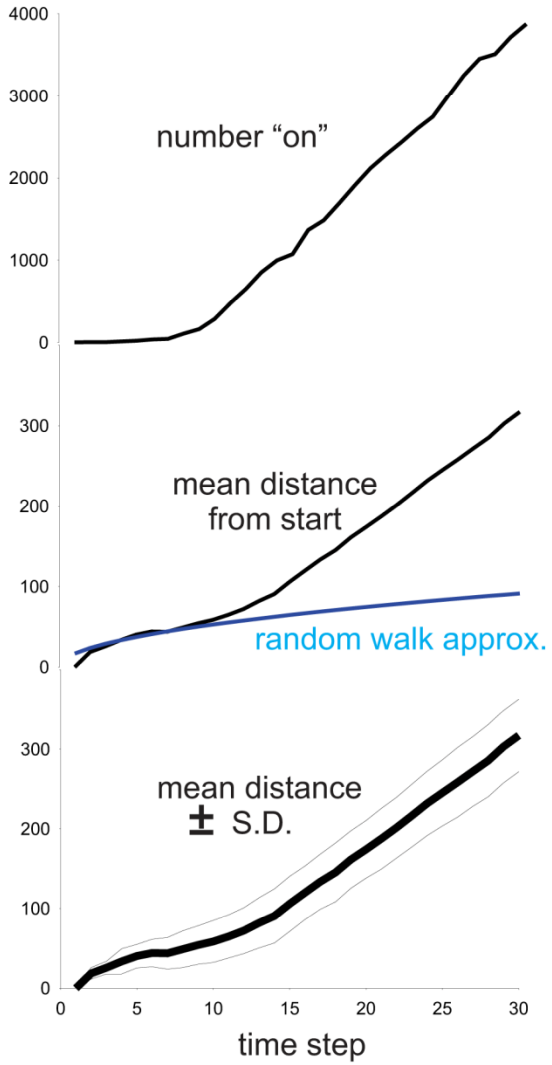
Figure: Nikita Vladimirov

Network frequency in local-random graph is independent of spatial scale (!)

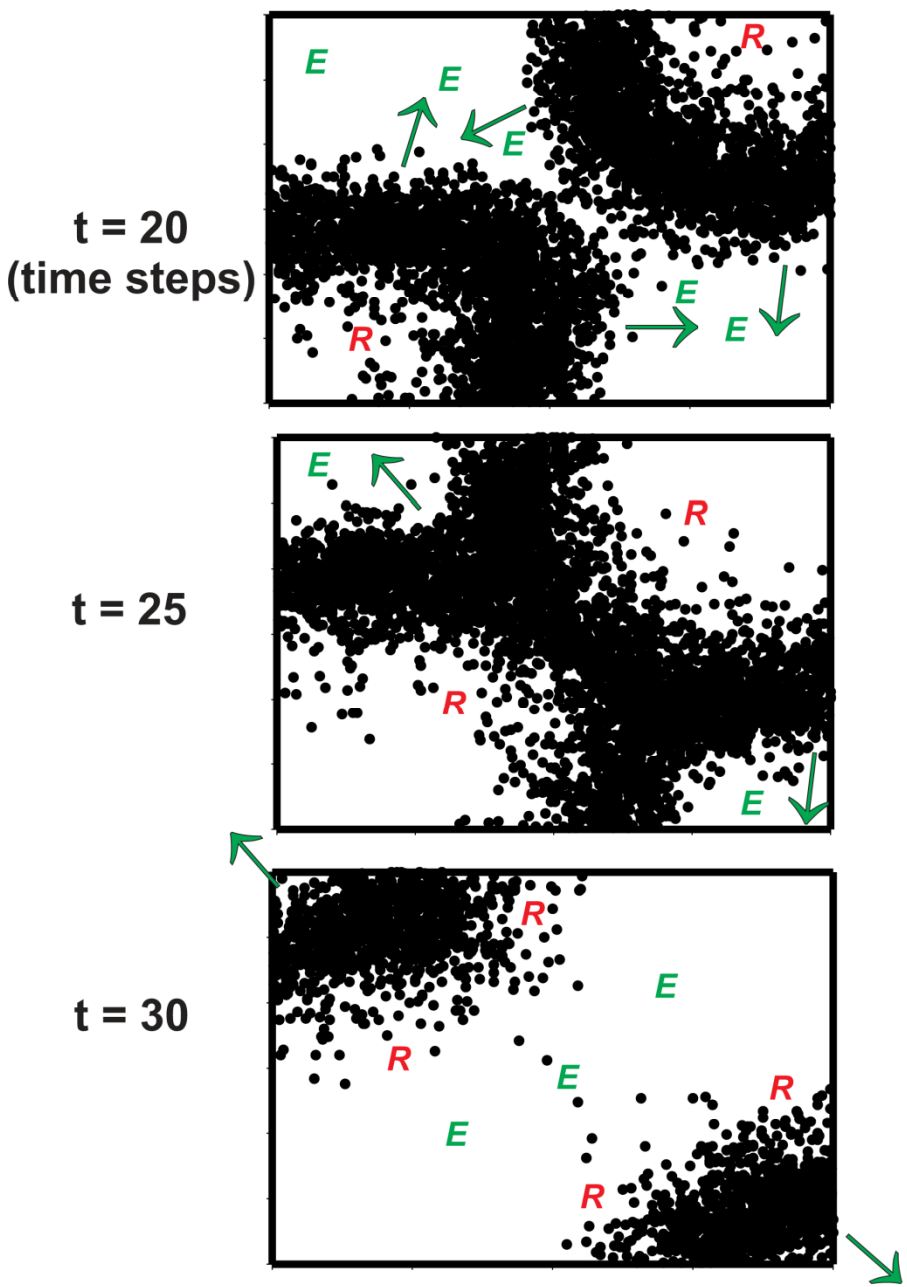


C.A. wave propagation begins as random walk, but becomes linear. Velocity depends on structural parameters (while period depends on structural parameters, noise rate, and refractoriness)



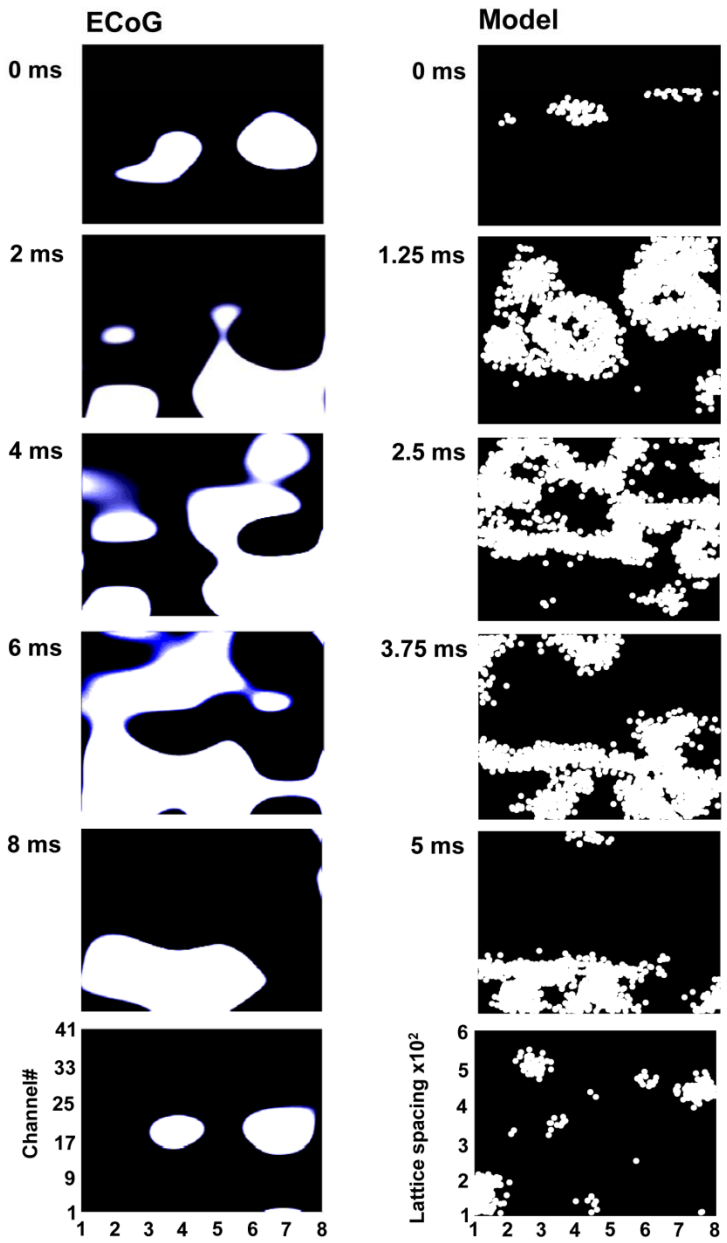


Let “k” be the index of a vertex. Then wave velocity depends on <k x k> / <k>, independent of detailed topology.
(N. Vladimirov, R.D. Traub, Y. Tu, 2011)



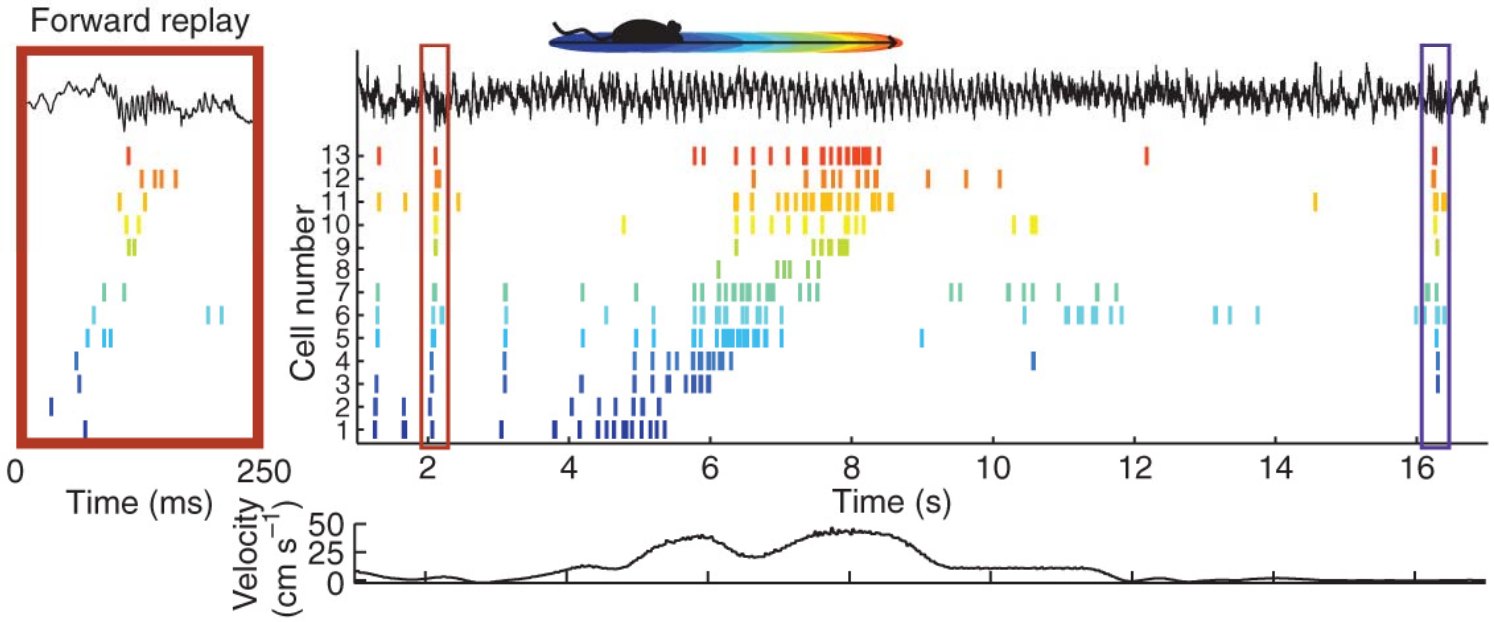
In cellular automaton model, waves coalesce without interpenetration or interference.

(R.D. Traub et al., Epilepsia 2010)



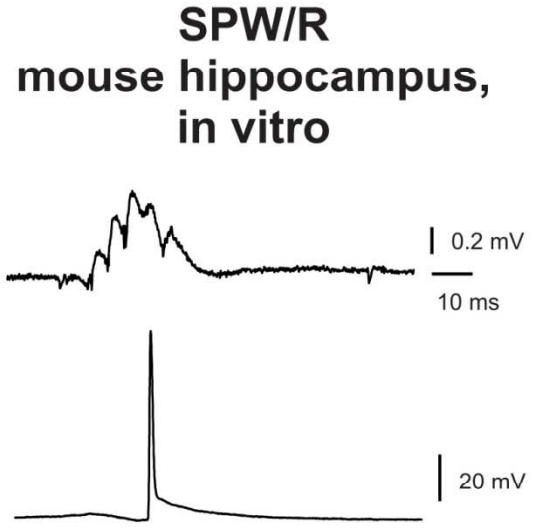
R.D. Traub et al. 2010, Epilepsia

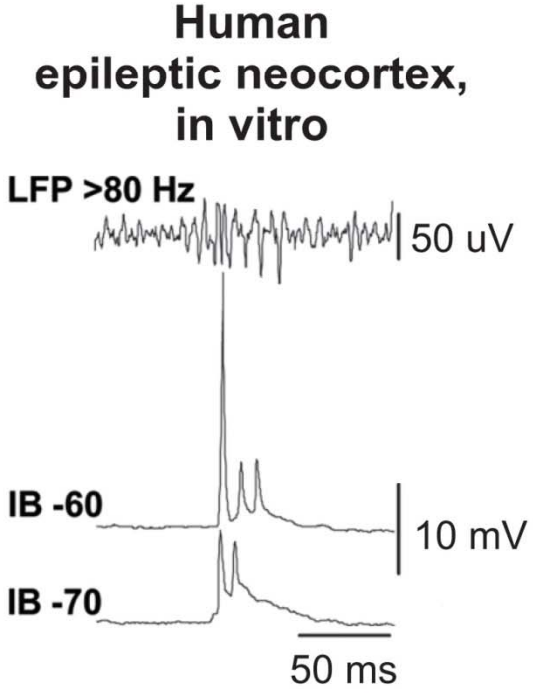
Sharp wave/ripples may have “cognitive” significance



Carr MF, Jadhav SP, Frank LM (2011) Hippocampal replay in the awake state: a potential substrate for memory consolidation and retrieval. *Nature Neurosci*. 14: 147-153.

Very fast oscillations, with putative axonal activity, characterize *both* physiological *and* epileptic ripples

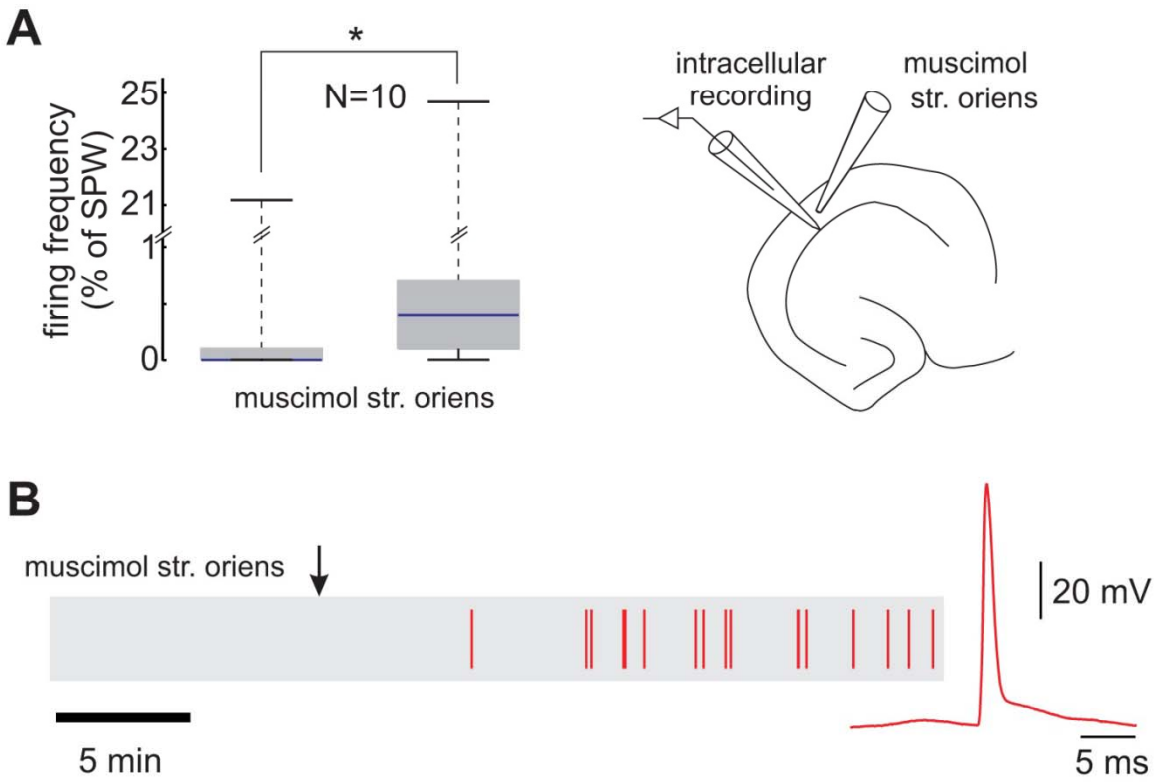




Bähner, F., Weiss, E.K., Birke, G., Maier, N., Schmitz, D., Rudolph, U., Frotscher, M., Traub, R.D., Both, M., Draguhn, A. (2011) Cellular correlate of assembly formation in oscillating hippocampal networks. *Proc. Natl. Acad. Sci. USA;*

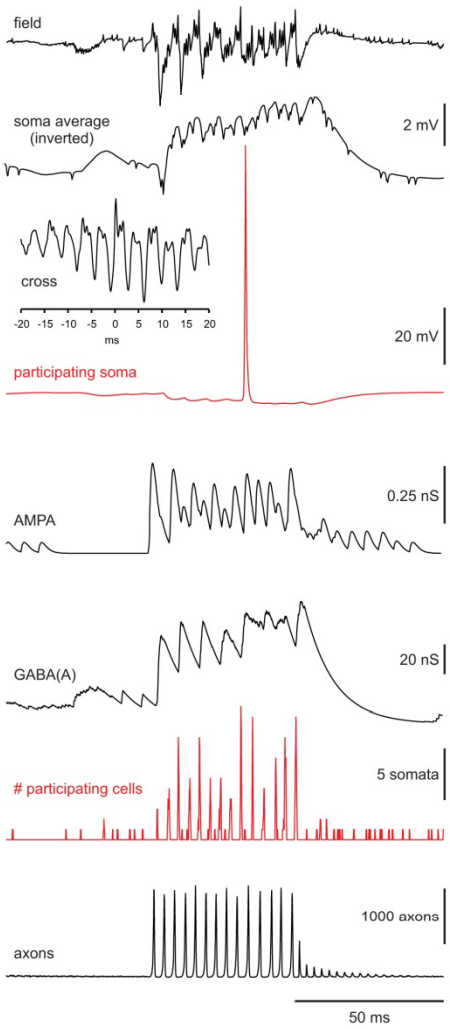
Roopun, A.K., Simonotto, J.D., Pierce, M.L., Jenkins, A., Schofield, I., Kaiser, M., Whittington, M.A., Traub, R.D., Cunningham, M.O. (2010) A non-synaptic mechanism underlying interictal discharges in human epileptic neocortex. *Proc. Natl. Acad. Sci. USA* 107: 338-343.

GABA(A) receptors excite axons, while (in physiological conditions) inhibiting soma & dendrites



Bähner, F., Weiss, E.K., Birke, G., Maier, N., Schmitz, D., Rudolph, U., Frotscher, M., Traub, R.D., Both, M., Draguhn, A. (2011) Cellular correlate of assembly formation in oscillating hippocampal networks. *Proc. Natl. Acad. Sci. USA;*

Simulating sharp wave/ripples: interplay between gap junctions and chemical synapses

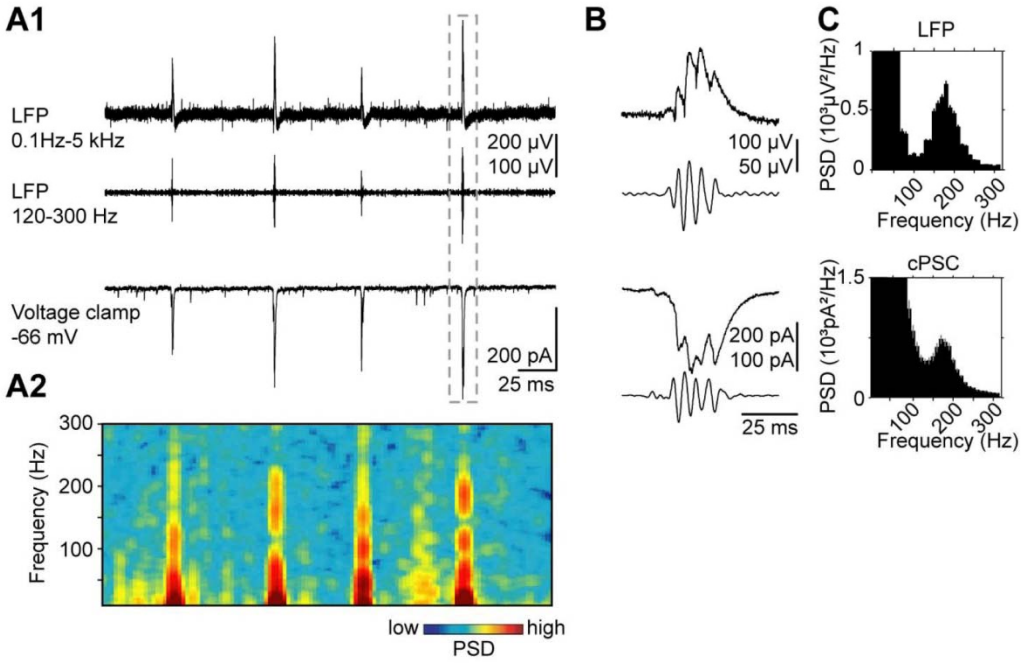


Bähner, F., Weiss, E.K., Birke, G., Maier, N., Schmitz, D., Rudolph, U., Frotscher, M., Traub, R.D., Both, M., Draguhn, A. (2011)
Cellular correlate of assembly formation in oscillating hippocampal networks. *Proc. Natl. Acad. Sci. USA;*

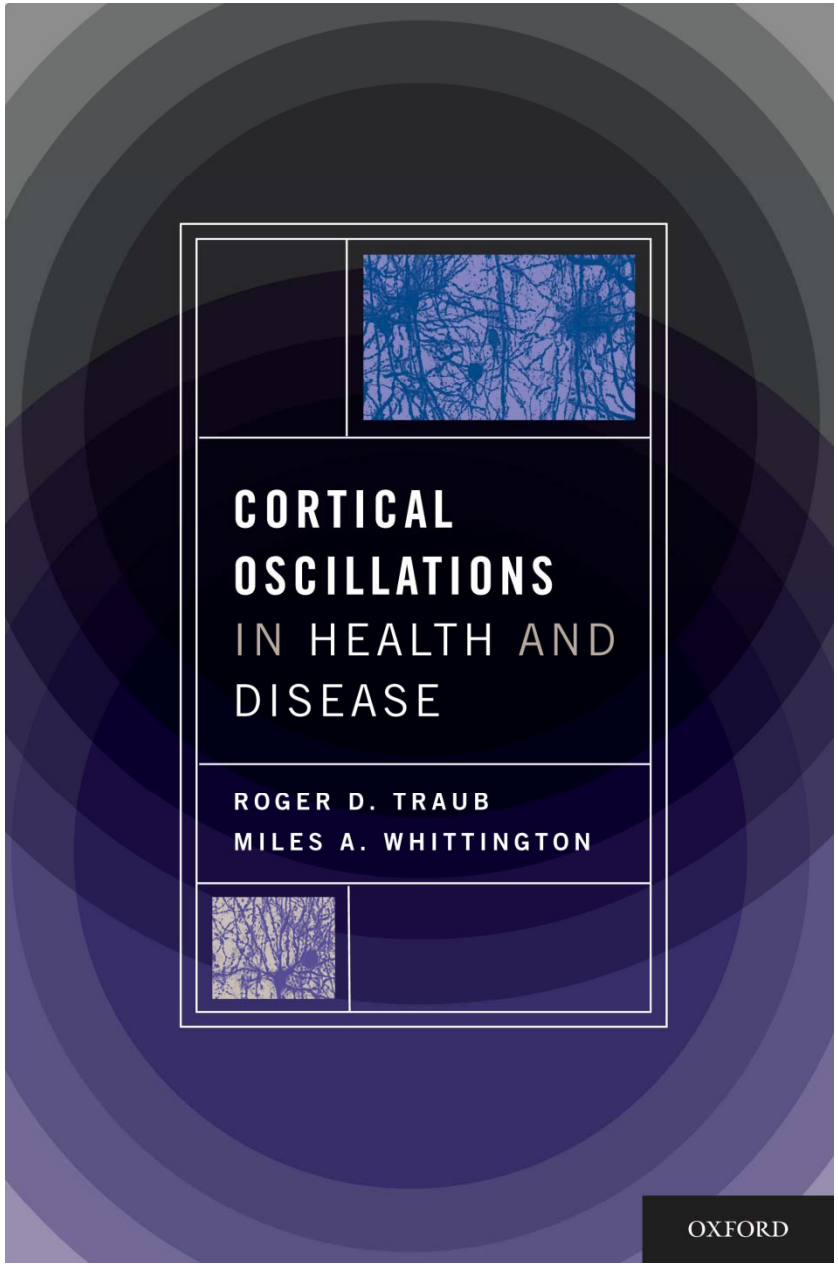
Experimental verification of a SPW/R model prediction: ripple-frequency EPSCs

Fields

Synaptic currents



N. Maier, A. Tejero-Cantero, A.L. Dorn, J. Winterer, P. Beed, G. Morris, R. Kempter, J.F.A. Poulet, C. Leibold, D. Schmitz (2011) Coherent phasic excitation during hippocampal ripples. Neuron 72: 137-152.



SEE ALSO:

Traub RD, Cunningham MO, Whittington MA (in press) Chemical synaptic and gap junctional interactions between principal neurons: partners in epileptogenesis. *Neural Networks*

Oxford University Press, 2010

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- **Andrea Bibbig, *Downstate***
- **Mark Cunningham, *Newcastle***
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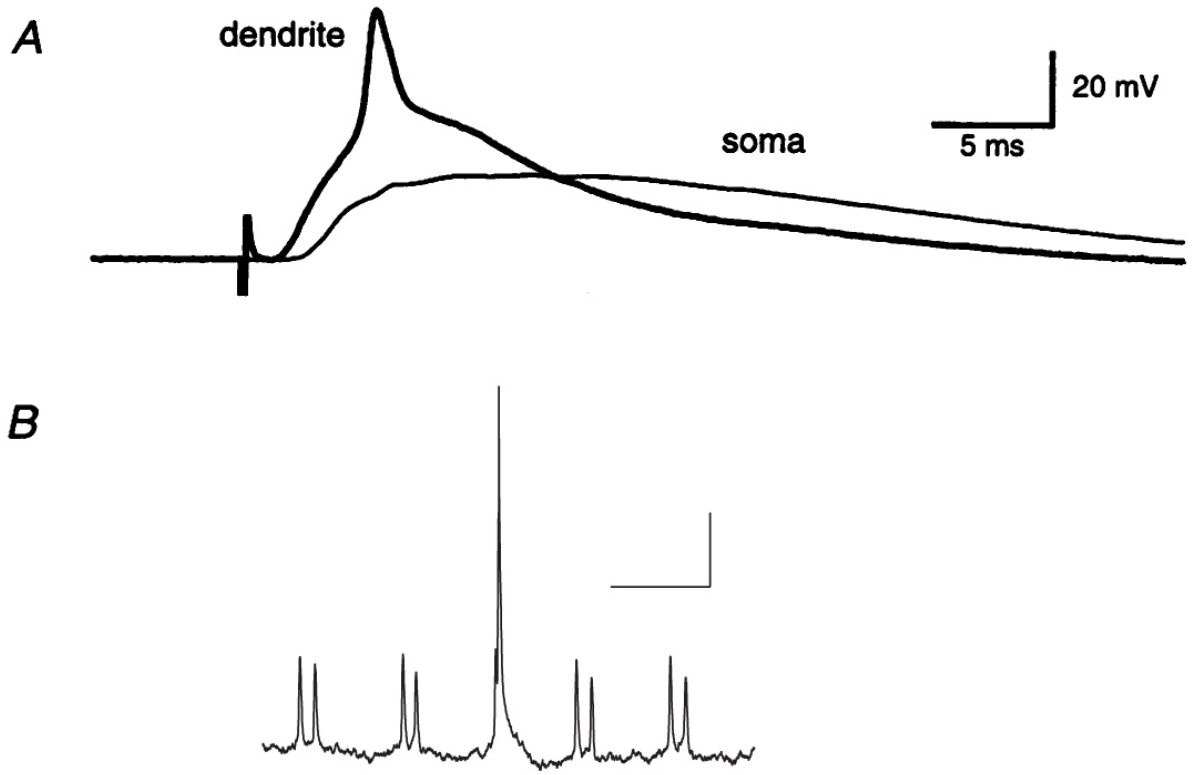
- **Richard Miles, Robert K.S. Wong**



Stuart, Schiller & Sakmann, 1997

Roopun et al., 2006