Networks of neurons: Synchrony and Oscillations

13 Sept, 2016

- Rhythms of the brain
- Weak synapses and synchrony
- Mechanisms of oscillations
- Oscillations in the hippocampus in health and in epilepsy

- **Rhythms of the brain**
- Weak synapses and synchrony
- Mechanisms of oscillations
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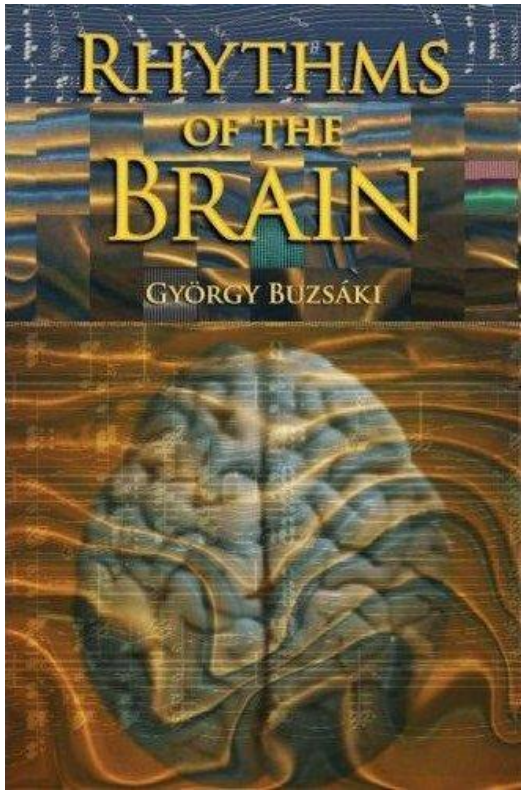
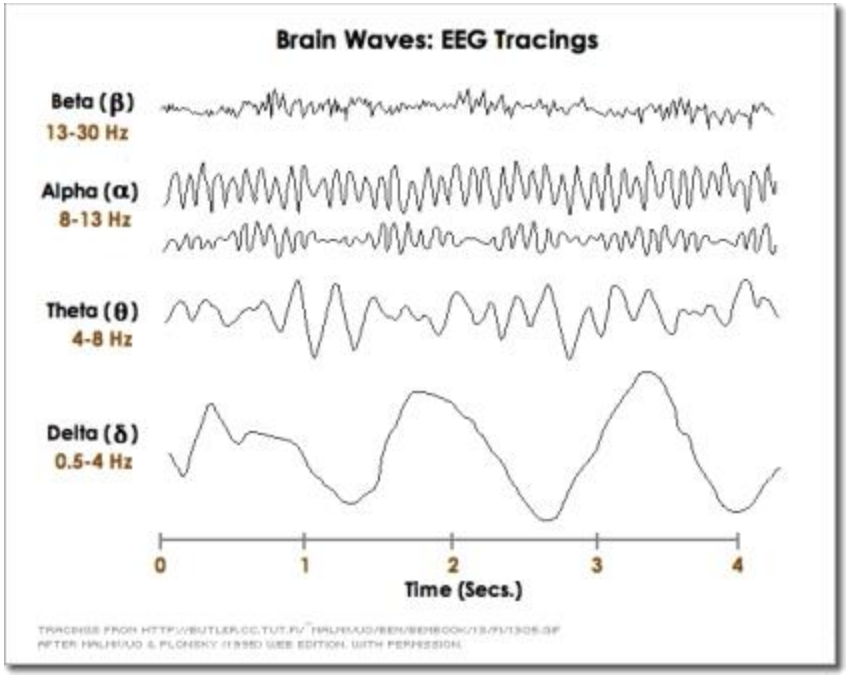
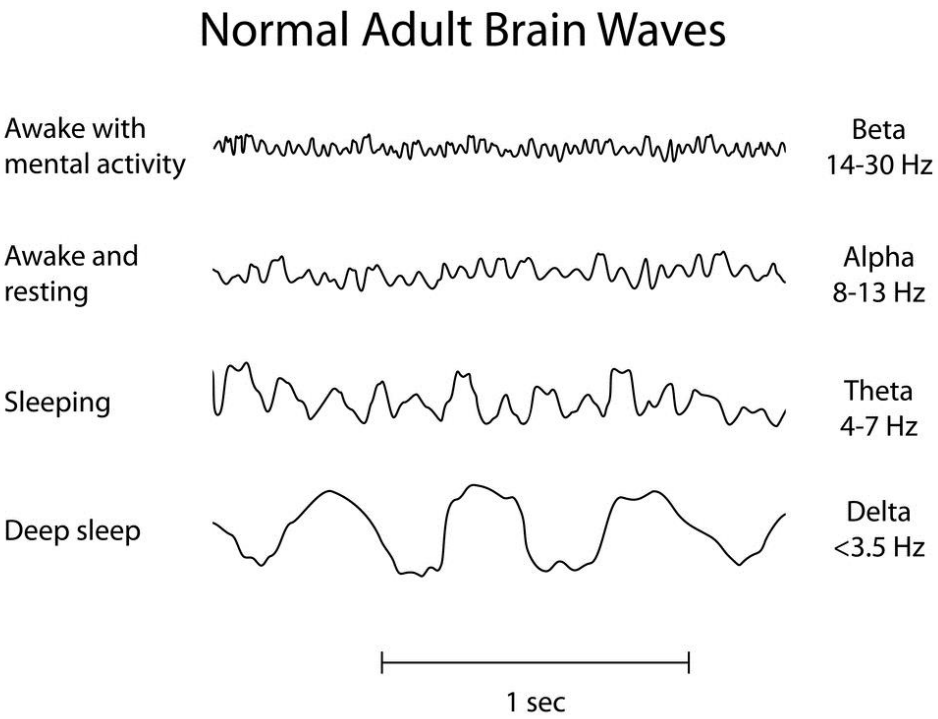
A popular topic



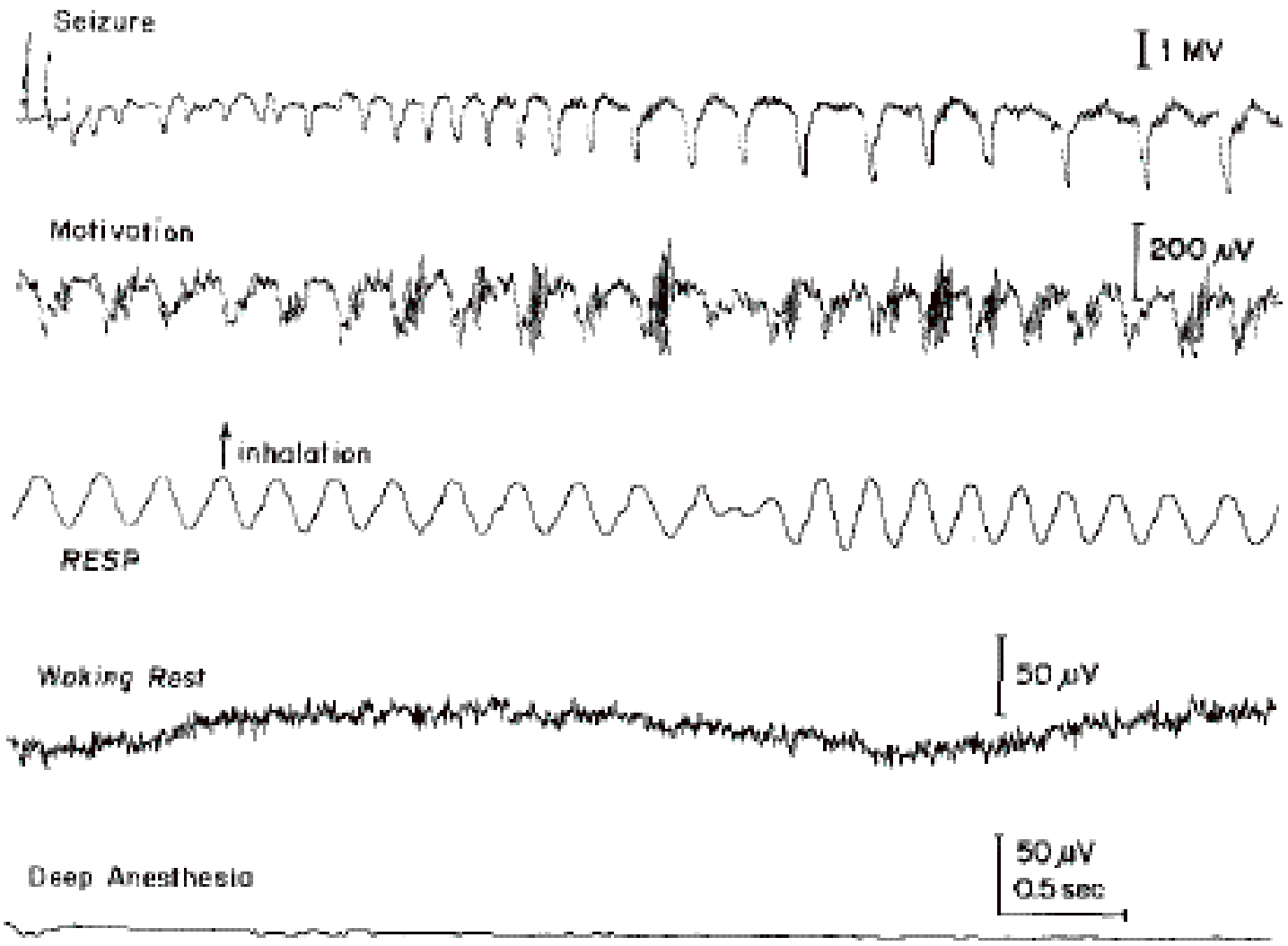
2770 citations since 2006

Many healthy oscillations





Healthy and unhealthy oscillations



Gamma oscillations 30 – 80 Hz

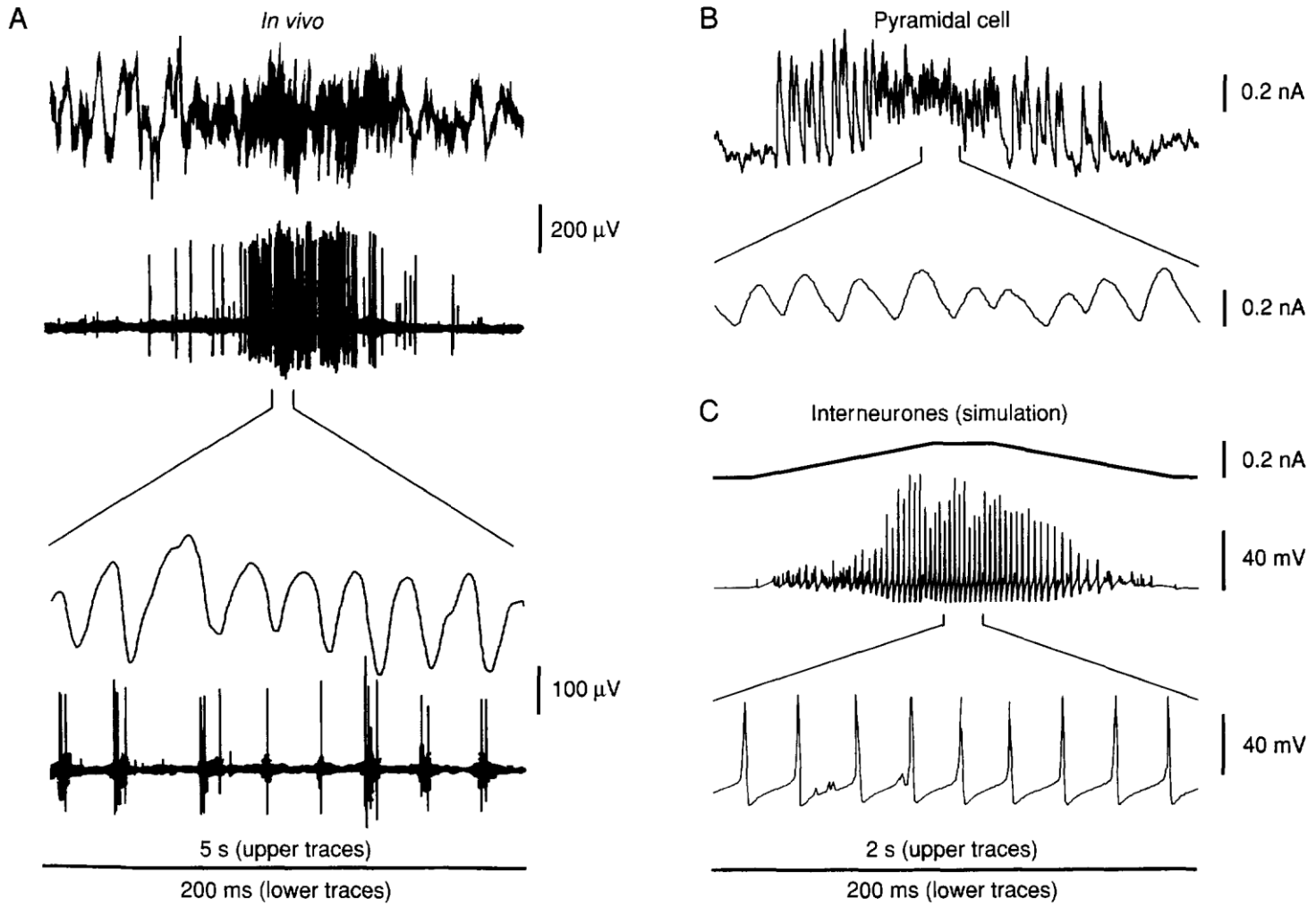
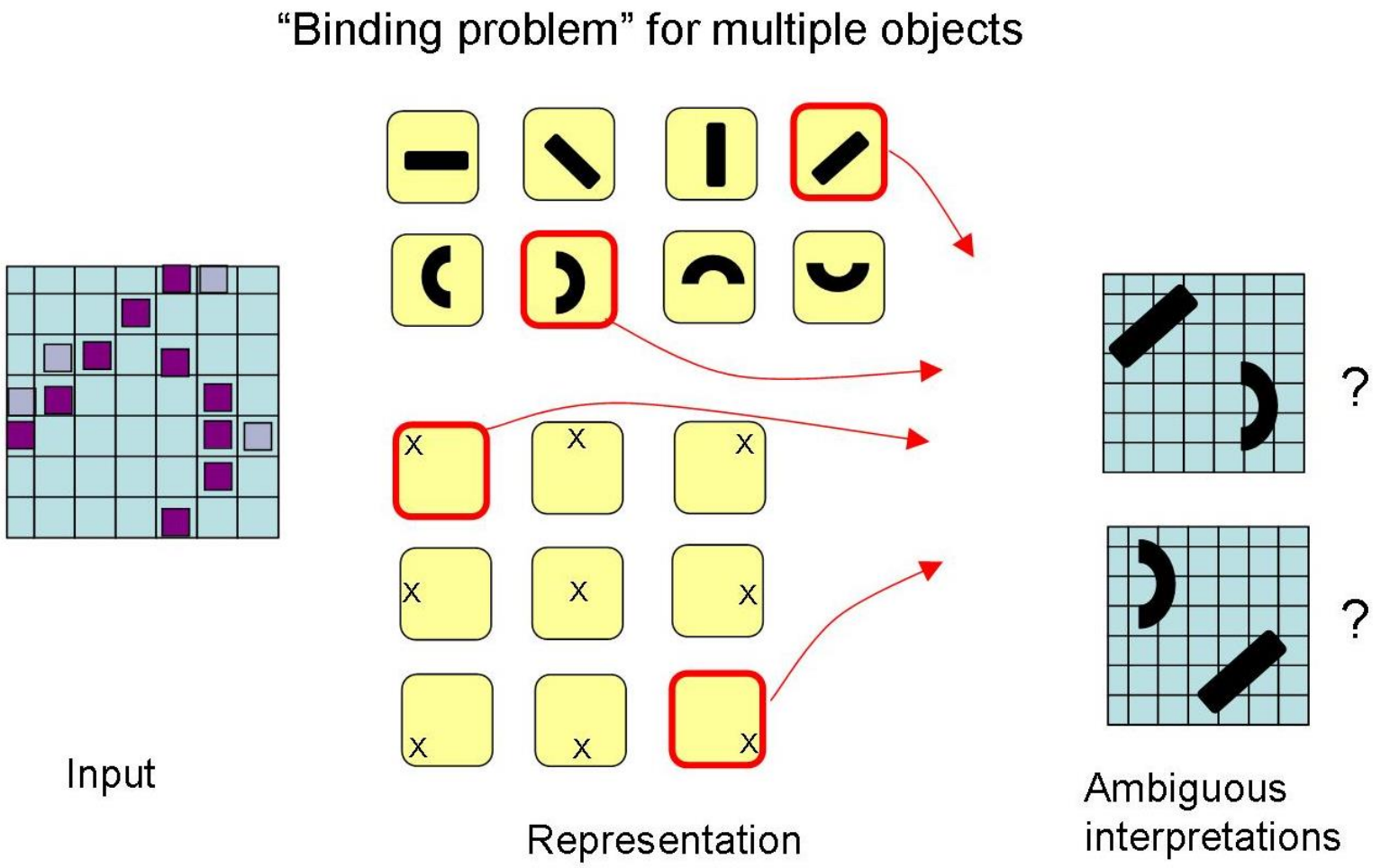
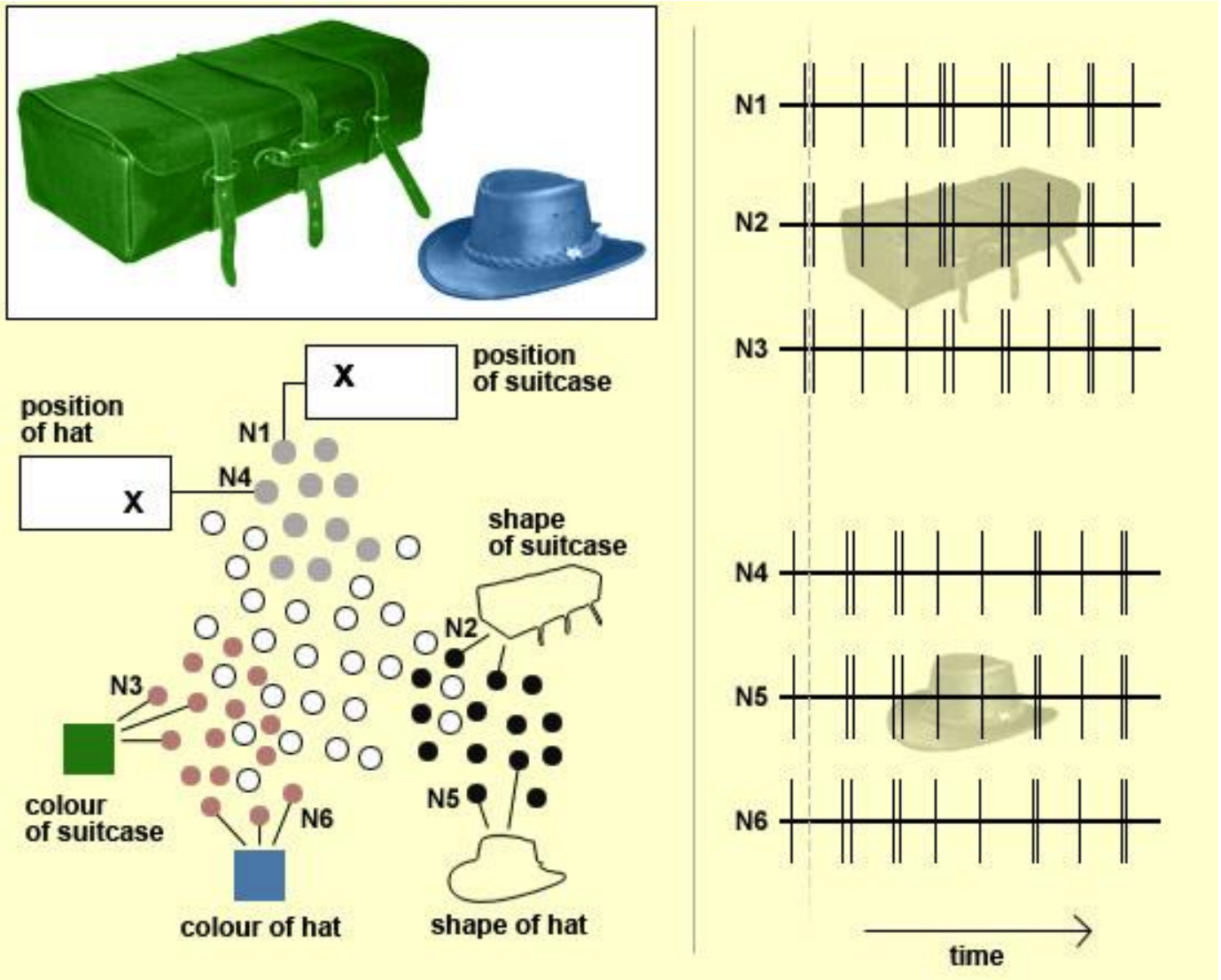


Fig. 1. *40 Hz oscillations.* **(A)** *Recordings from the cat visual cortex show synchronous oscillations in the local-field potential (top trace) and multi-unit recordings (second trace) in response to a moving-bar visual stimulus. These have been expanded below to reveal an oscillation in the local-field potential of 40 Hz and the phase-locked discharge of local neurones.* Adapted, with permission, from Ref. 3. **(B)** *A recording from a CA1 pyramidal cell in a rat hippocampal slice following a pulse of glutamate shows that an oscillation of ~40 Hz can be induced* in vitro. *The expanded portion of the trace represents the same timescale as in* A *(timescales are the same for* B *and* C*).* **(C)** *The hippocampal ~40 Hz oscillation is driven by the network of inhibitory neurones. Illustrated is a simulation of the application of an inward ('glutamate') current (top trace) to a network of 16 inhibitory neurones which induced a ~40 Hz discharge evident in the mean membrane potential of these neurones.*


"Binding problem" for multiple objects
Input
Representation
Ambiguous interpretations
?
?

A proposed solution with oscillations



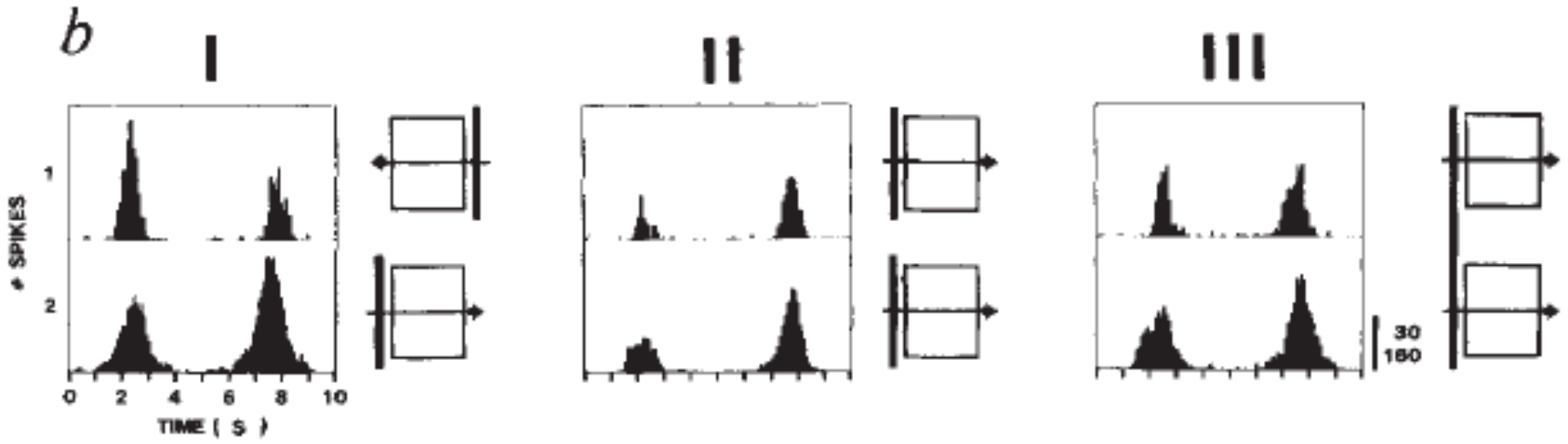
Data consistent with this

Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties

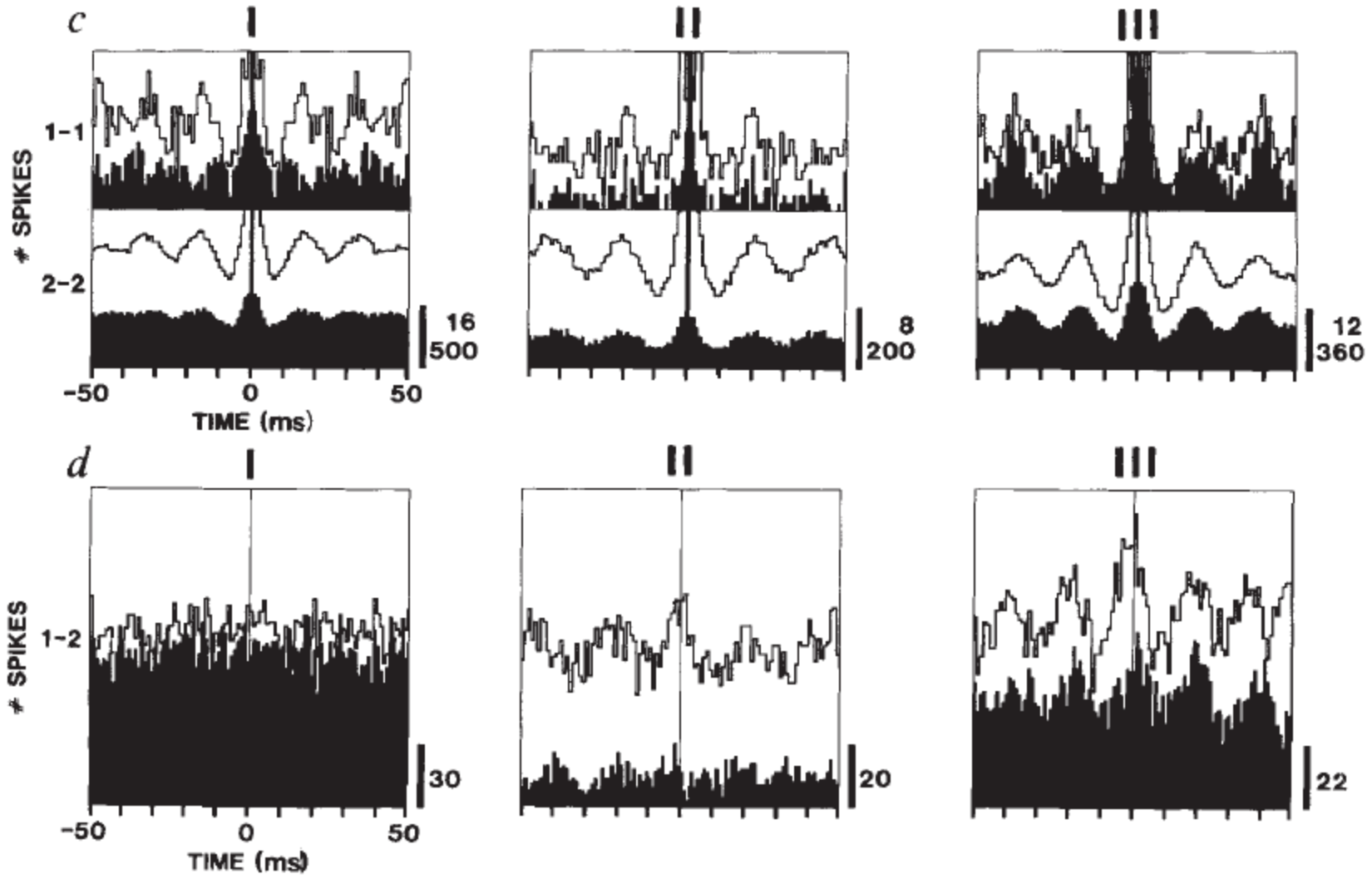
Charles M. Gray, Peter König, Andreas K. Engel & Wolf Singer

A FUNDAMENTAL step in visual pattern recognition is the establishment of relations between spatially separate features. Recently, we have shown that neurons in the cat visual cortex have oscillatory responses in the range 40–60 Hz (refs 1, 2) which occur in synchrony for cells in a functional column and are tightly correlated with a local oscillatory field potential. This led us to hypothesize that the synchronization of oscillatory responses of spatially distributed, feature selective cells might be a way to establish relations between features in different parts of the visual field[2,3]. In support of this hypothesis, we demonstrate here that neurons in spatially separate columns can synchronize their oscillatory responses. The synchronization has, on average, no phase difference, depends on the spatial separation and the orientation preference of the cells and is influenced by global stimulus properties.

Three conditions tested



The correlograms corresponding to these conditions



Note much stronger oscillations in condition III

- Rhythms of the brain
- **Weak synapses and synchrony**
- Mechanisms of oscillations
- Oscillations in the hippocampus in health and in epilepsy

Input synchrony and the irregular firing of cortical neurons

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Cortical neurons in the waking brain fire highly irregular, seemingly random, spike trains in response to constant sensory stimulation, whereas *in vitro* they fire regularly in response to constant current injection. To test whether, as has been suggested, this high *in vivo* variability could be due to the postsynaptic currents generated by independent synaptic inputs, we injected synthetic synaptic current into neocortical neurons in brain slices. We report that independent inputs cannot account for this high variability, but this variability can be explained by a simple alternative model of the synaptic drive in which inputs arrive synchronously. Our results suggest that synchrony may be important in the neural code by providing a means for encoding signals with high temporal fidelity over a population of neurons.

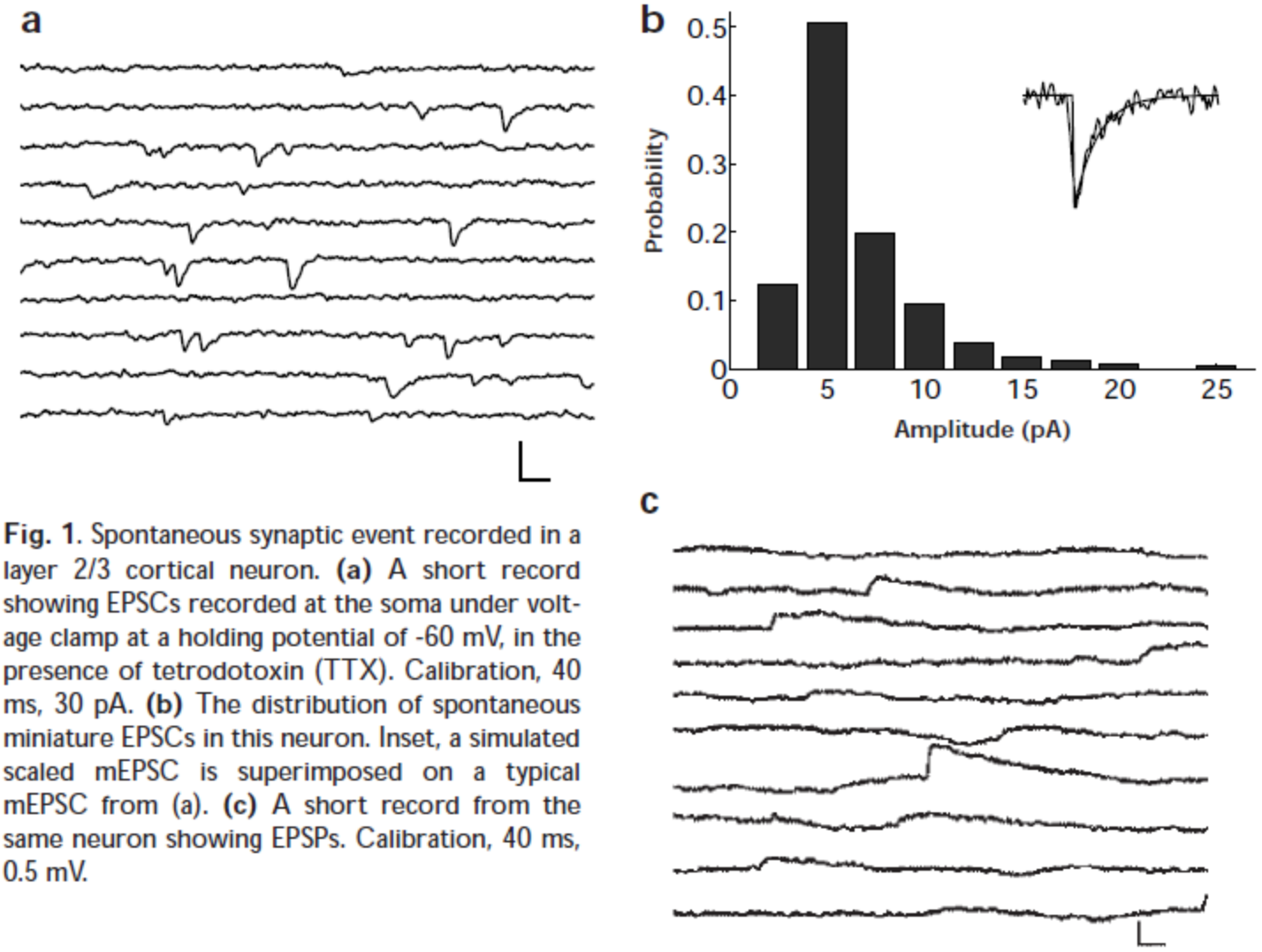


Fig. 1. Spontaneous synaptic event recorded in a layer 2/3 cortical neuron. **(a)** A short record showing EPSCs recorded at the soma under voltage clamp at a holding potential of -60 mV, in the presence of tetrodotoxin (TTX). Calibration, 40 ms, 30 pA. **(b)** The distribution of spontaneous miniature EPSCs in this neuron. Inset, a simulated scaled mEPSC is superimposed on a typical mEPSC from (a). **(c)** A short record from the same neuron showing EPSPs. Calibration, 40 ms, 0.5 mV.

$$CV = \sigma_{isi} / \mu_{isi}$$

$$F = \sigma_N^2 / \mu_N$$

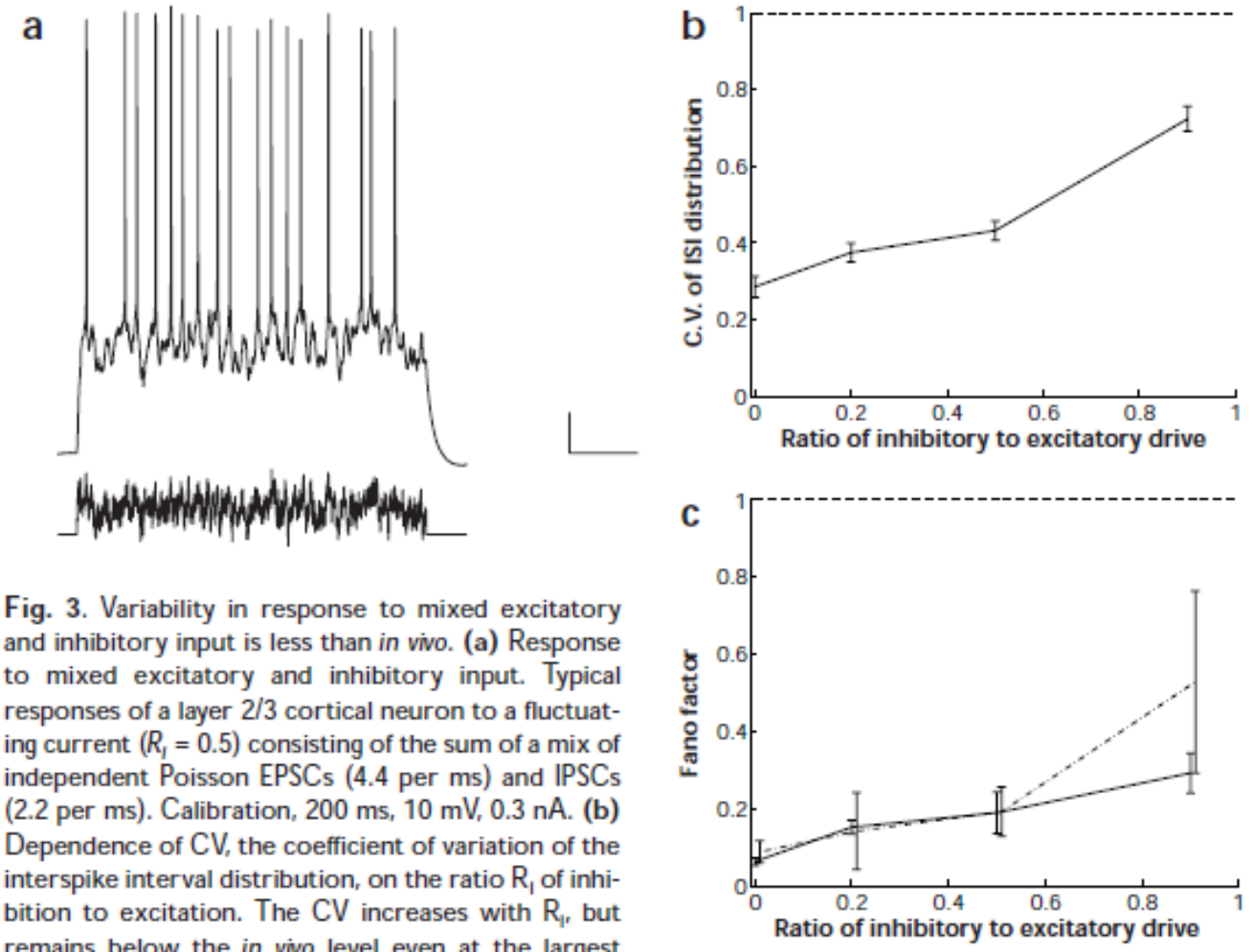
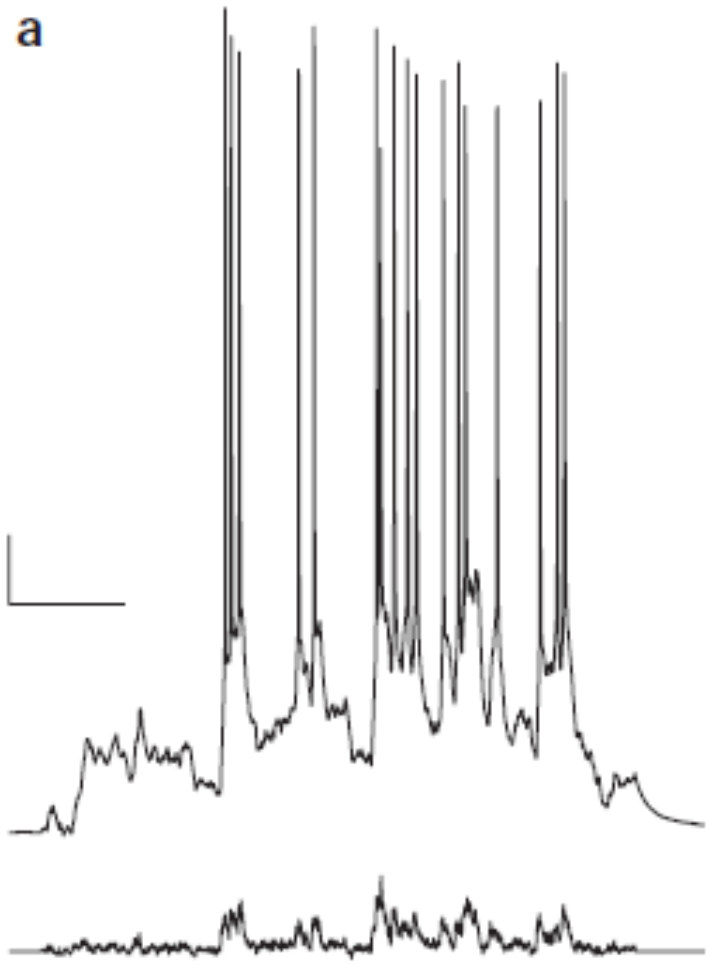


Fig. 3. Variability in response to mixed excitatory and inhibitory input is less than *in vivo*. **(a)** Response to mixed excitatory and inhibitory input. Typical responses of a layer 2/3 cortical neuron to a fluctuating current ($R_I = 0.5$) consisting of the sum of a mix of independent Poisson EPSCs (4.4 per ms) and IPSCs (2.2 per ms). Calibration, 200 ms, 10 mV, 0.3 nA. **(b)** Dependence of CV, the coefficient of variation of the interspike interval distribution, on the ratio R_I of inhibition to excitation. The CV increases with R_I, but remains below the *in vivo* level even at the largest value of R_I tested. The dotted line indicates the CV of a Poisson process. The error bars indicate the standard error. **(c)** Dependence of the Fano factor F (the variance divided by the mean of the spike count) on the ratio R_I. The solid line shows the actual Fano factor, whereas the dashed line shows the Fano factor predicted from $F = CV^2$. Even for high values of R_I, the Fano factor of the response to synthetic synaptic currents remains far below that observed *in vivo*. The dotted line indicates the Fano factor of a Poisson process. The error bars indicate the standard error.



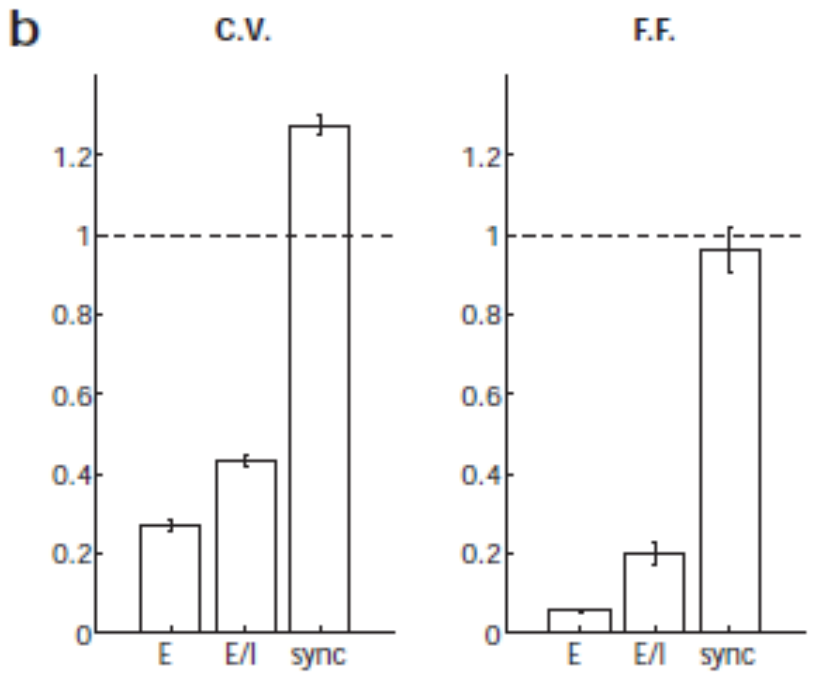
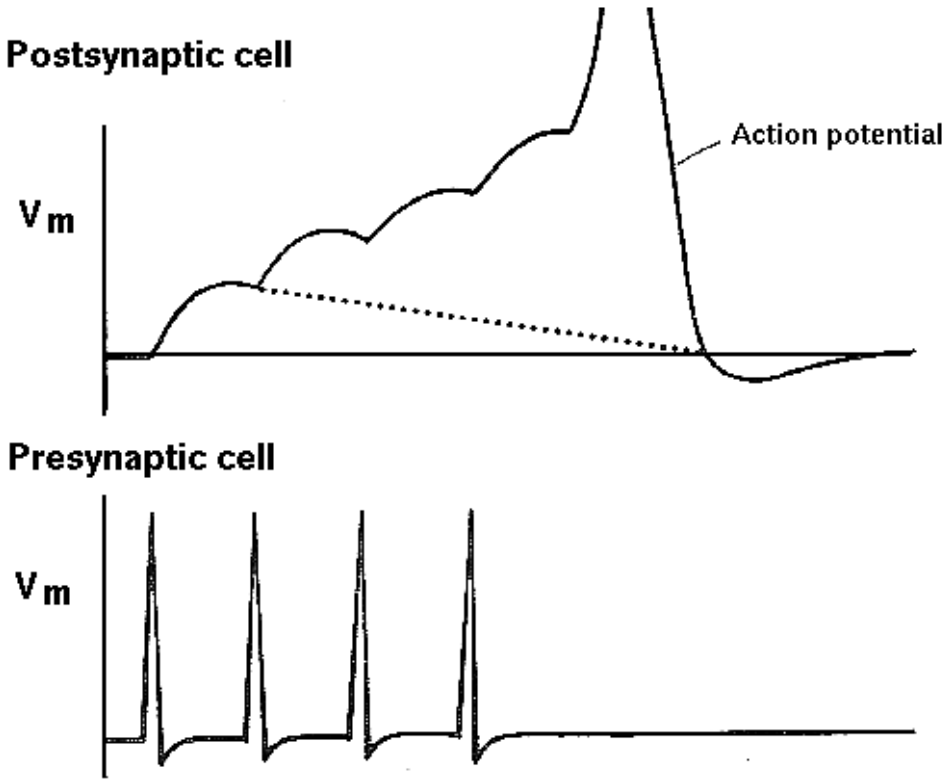
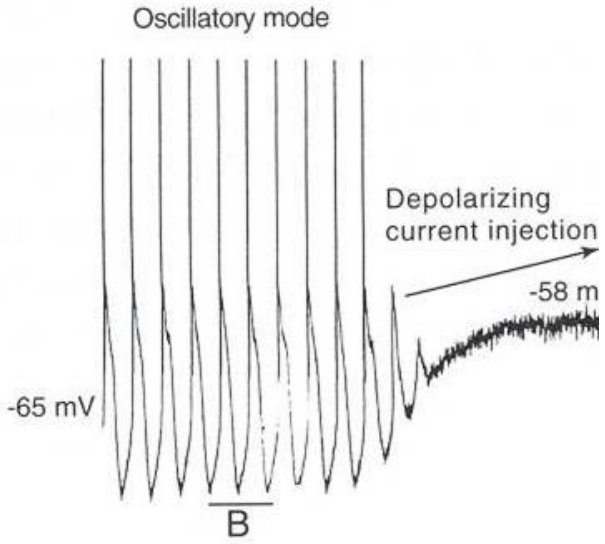


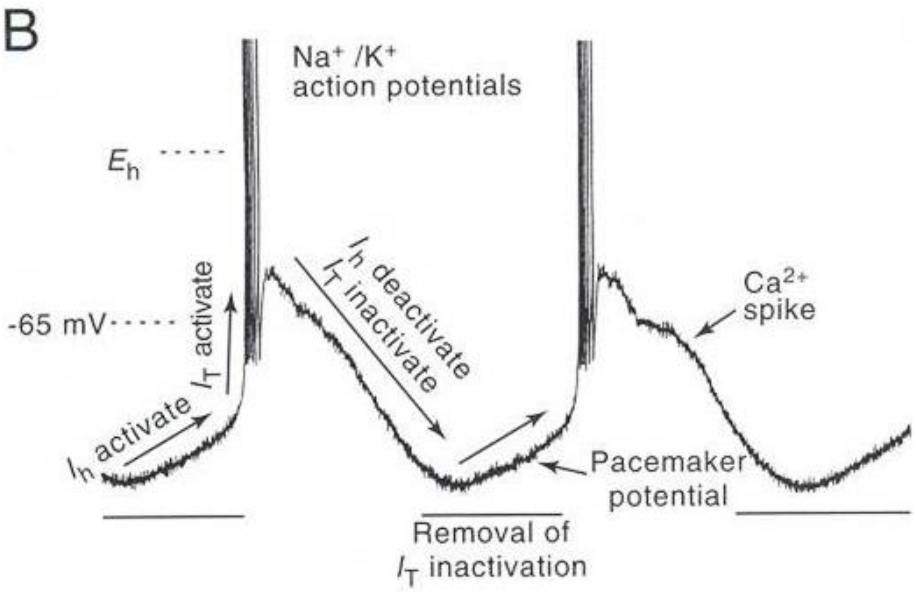
Fig. 5. Input synchrony yields *in vivo* variability. **(a)** Response to an input drive consisting primarily of occasional large brief (30–50 ms) excitatory events, randomly distributed in time, each consisting of the nearly synchronous arrival of on average 100–200 EPSCs, yielding transient peak currents as high as 1 nA or more. Calibration, 200 ms, 10 mV (top), 0.1 nA (bottom). **(b)** Summary of CV and Fano factor. Left, CV for purely excitatory (E), mixed excitatory/inhibitory (E/I), and synchronous (sync), inputs. Right, same statistics for the Fano factor. For both graphs, the error bars indicate standard errors. The dotted lines indicate the value of unity expected for both CV and Fano factor for a perfect Poisson process and are near the values typically observed from cortical spike trains *in vivo*.


Postsynaptic cell
Action potential
Vm
Presynaptic cell
Vm

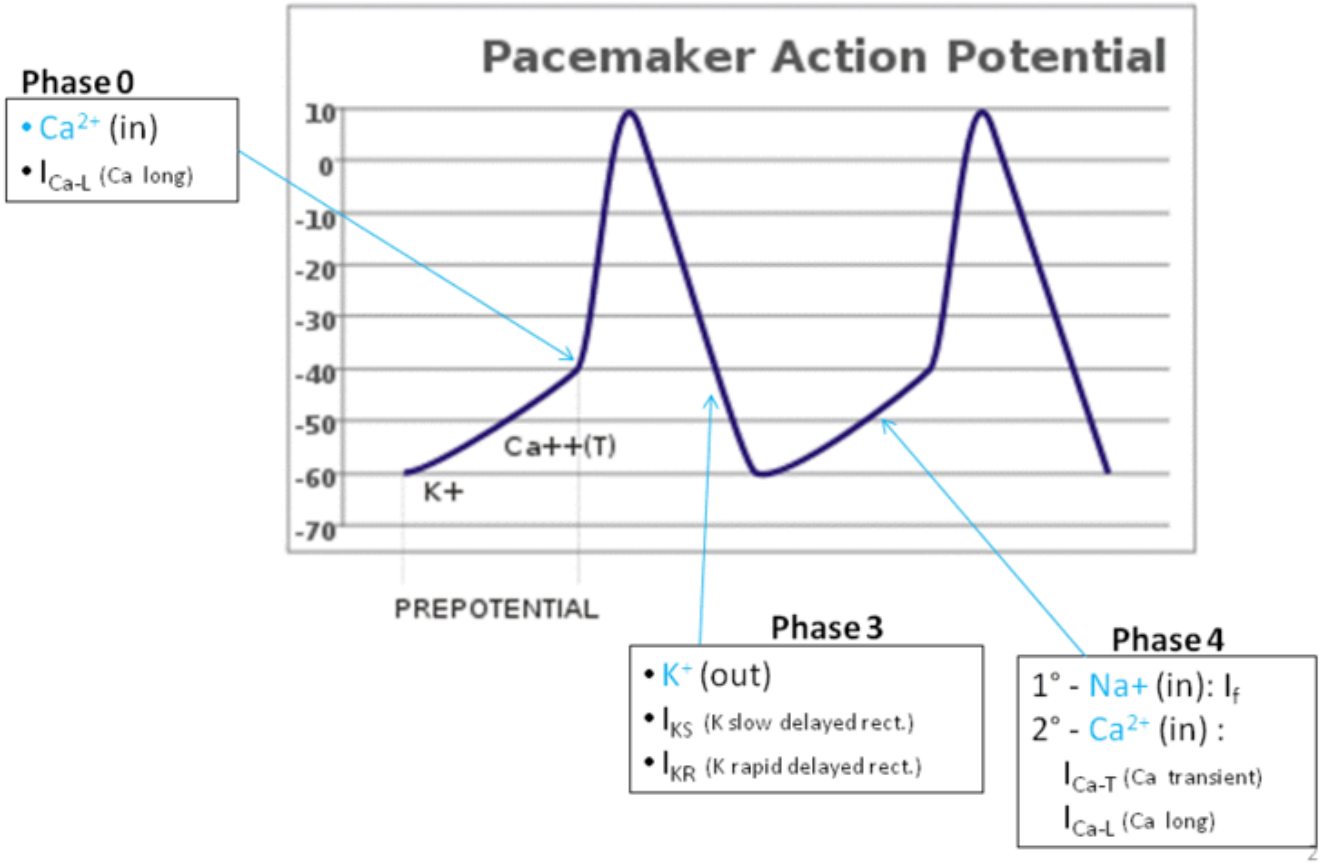
- Rhythms of the brain
- Weak synapses and synchrony
- **Mechanisms of oscillations**
- Oscillations in the hippocampus in health and in epilepsy

One mechanism:
intrinsic pacemaker
Cells (thalamus)
as we saw before

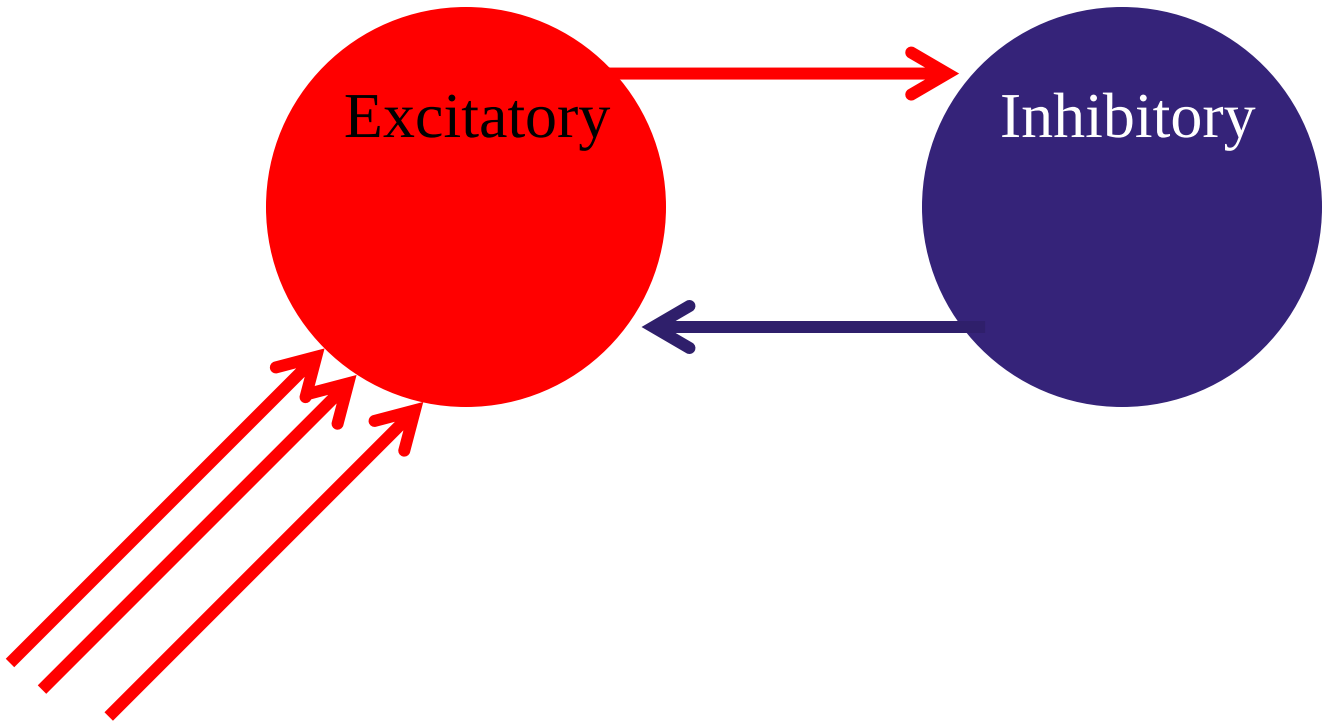




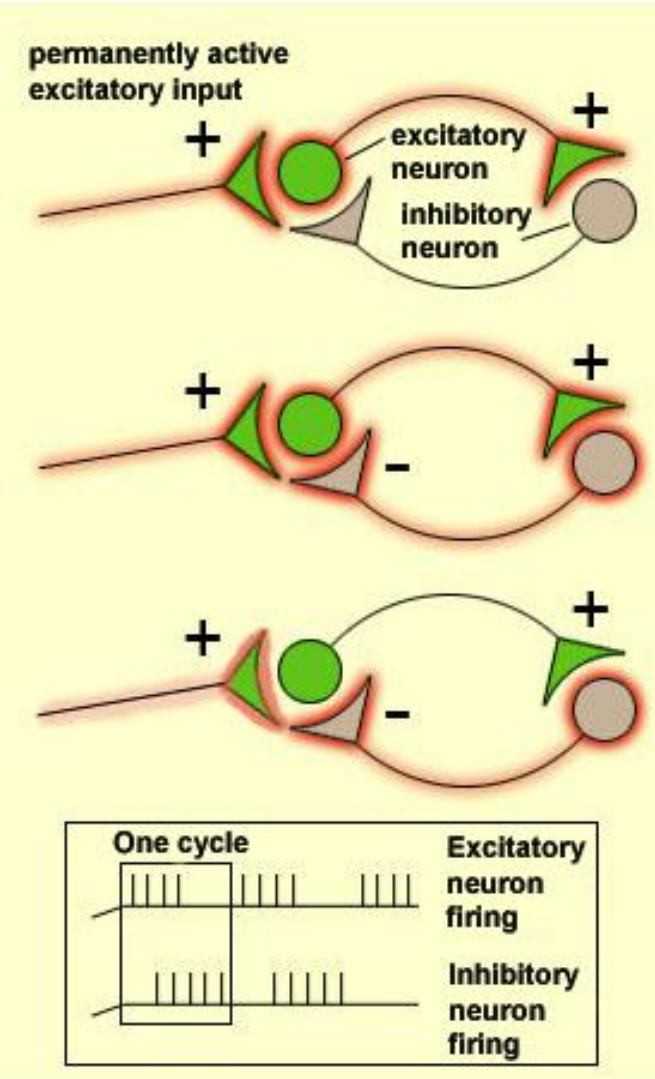
One mechanism:
intrinsic pacemaker
Cells (heart)



A very simple
network model



A very simple network model



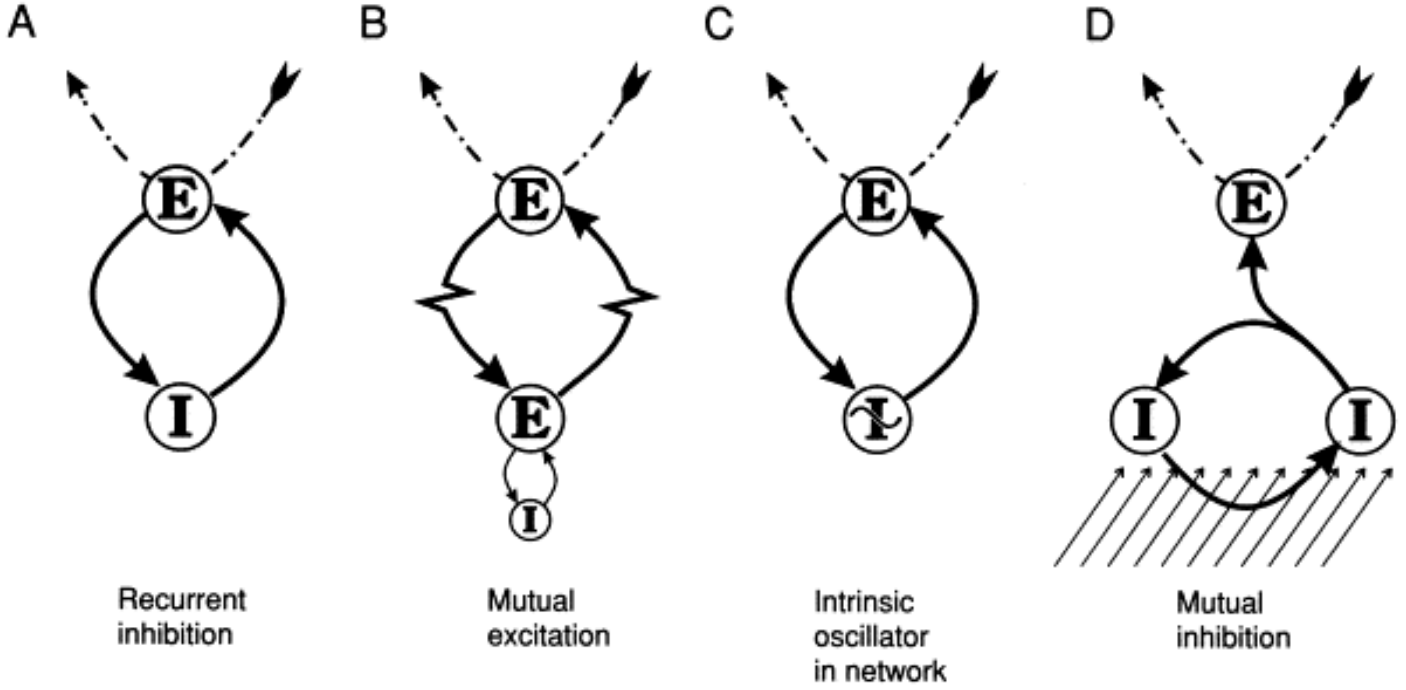
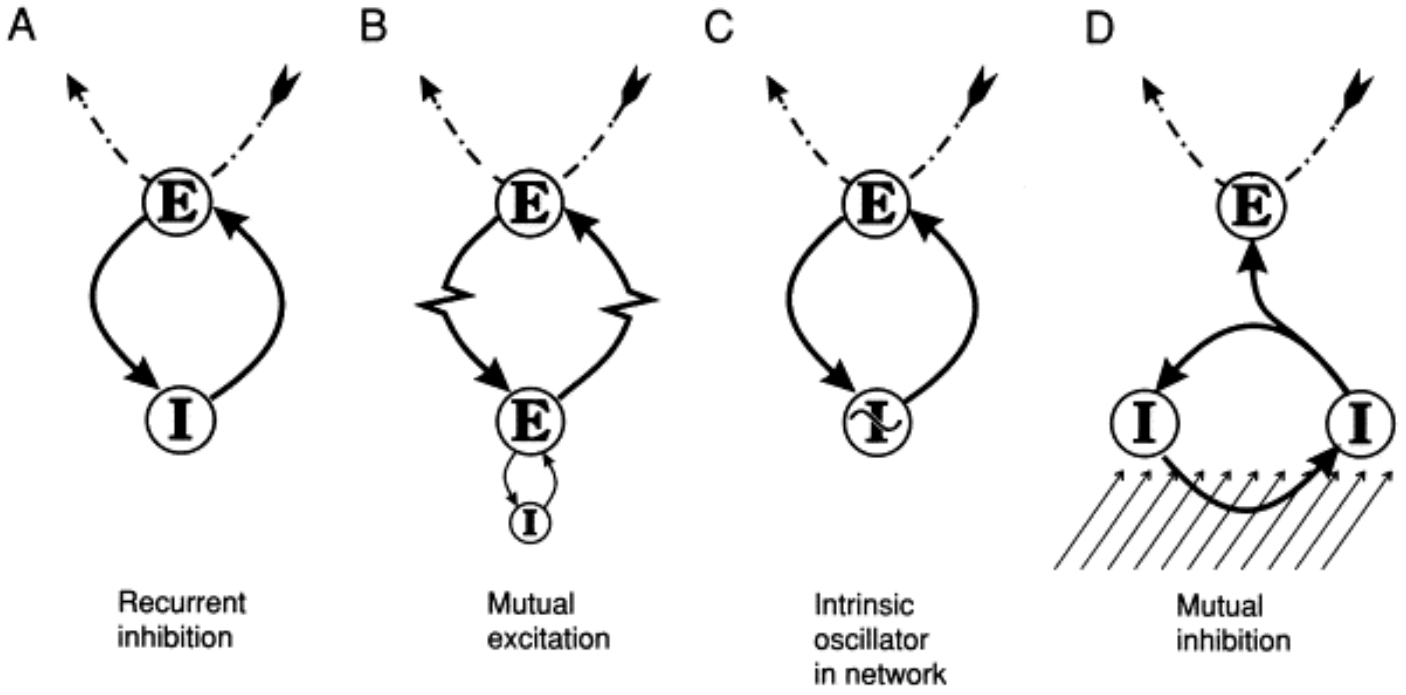


Fig. 2. ***Simplified representations to illustrate the essential features of several mechanisms proposed to be involved in the generation of gamma oscillations.*** *In each case, E (excitatory) and I (inhibitory) represent networks of neurones that are mutually connected, the continuous lines indicate the key connections for their respective mechanisms, and the dot–dash arrow indicates the flow of specific information through the network.* **(A)** *illustrates the recurrent inhibitory loop model proposed by Freeman* **et al.**[5] *Computer theoretical analysis has subsequently shown that mutual excitation is required, but that mutual inhibition is not.* **(B)** *shows a similar model in which the time delays along the axons coupling groups of excitatory neurones play a key role*[33]*, and which also receives contributions from recurrent inhibition.* **(C)** *proposes that neurones with intrinsic-oscillator properties can impose their own rhythm on the synaptic network in which they are embedded*[34–37]*.* **(D)** *represents our own model of gamma oscillations in the hippocampus, in which interneurones are tonically excited (thin arrows) so that they will fire at a rate >40 Hz. The divergent inhibitory connections between these neurones result in synchronized inhibition across the population. When this decays, the neurones will discharge due to the tonic excitation that drives the rhythm*[38] *imposing a rhythm of about 40 Hz. Notice that in its simplest form* (D) *separates the role of the oscillator (or clock) and the processor.*



Under these models, do all cells have to oscillate?

If so, what would be the use of having most of the neurons do the same thing?

- Rhythms of the brain
- Weak synapses and synchrony
- Mechanisms of oscillations
- **Oscillations in the hippocampus in health and in epilepsy**

Biophysically detailed network models to explain:

- Synchronous bursts in the hippocampus seen during epilepsy.

- Rhythmic oscillations in the hippocampus seen during normal behaviors such as sniffing and walking.

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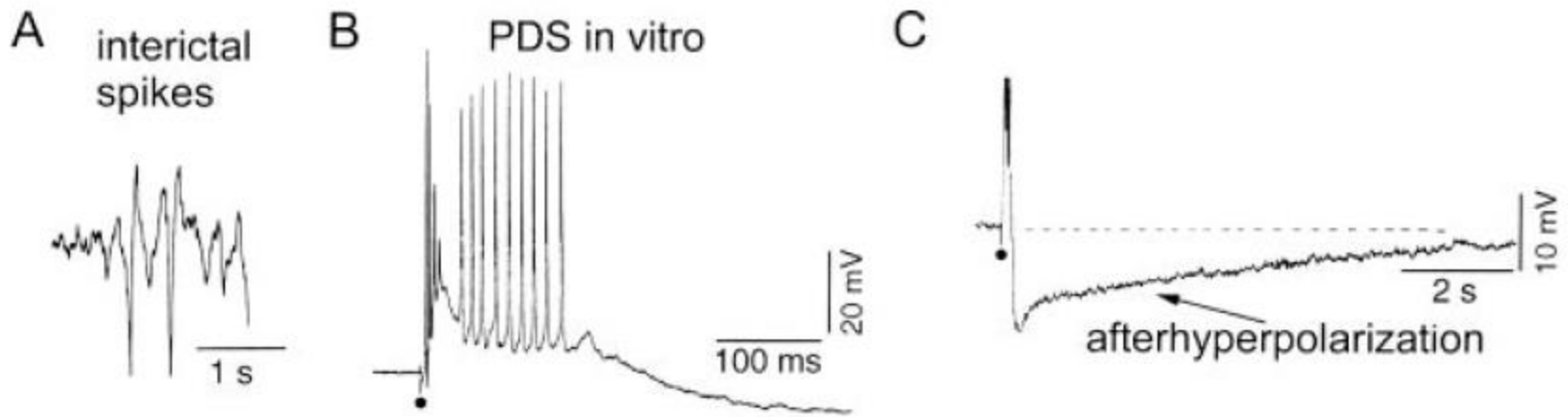

Figure 1 Interictal spike generation in hippocampus and cortex. (*A*) Example of two interictal spikes in the human EEG. Interictal spikes are brief (~0.1 s) events typically localized to a particular region of the forebrain. (*B*) Intracellular recording in a human cortical pyramidal cell maintained in a cortical slice in vitro during the generation of a epileptiform burst similar to that underlying the generation of interictal spikes. The depolarization underlying the epileptiform activity is termed a paroxysmal depolarization shift (PDS) and results in the initiation of a high-frequency burst of action potentials. (*C*) The PDS in the human cortical neuron is followed by a prolonged after-hyperpolarization that is generated by the activation of various K^+ currents.

Cellular Mechanism of Neuronal Synchronization in Epilepsy

Abstract. *Interictal spikes are a simple kind of epileptic neuronal activity. Field potentials and intracellular recordings observed during interictal spikes of penicillin-treated slices of the hippocampus were reproduced by a mathematical model of a network of 100 hippocampal neurons from the region including CA2 and CA3. The model shows that this form of neuronal synchronization arises because of mutual excitation between neurons, each of which is capable of intrinsic bursting in response to a brief input.*

SCIENCE, VOL. 216, 14 MAY 1982

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IBM Watson Research Center, Yorktown Heights, New York 10598, and *Neurological Institute, New York 10032*
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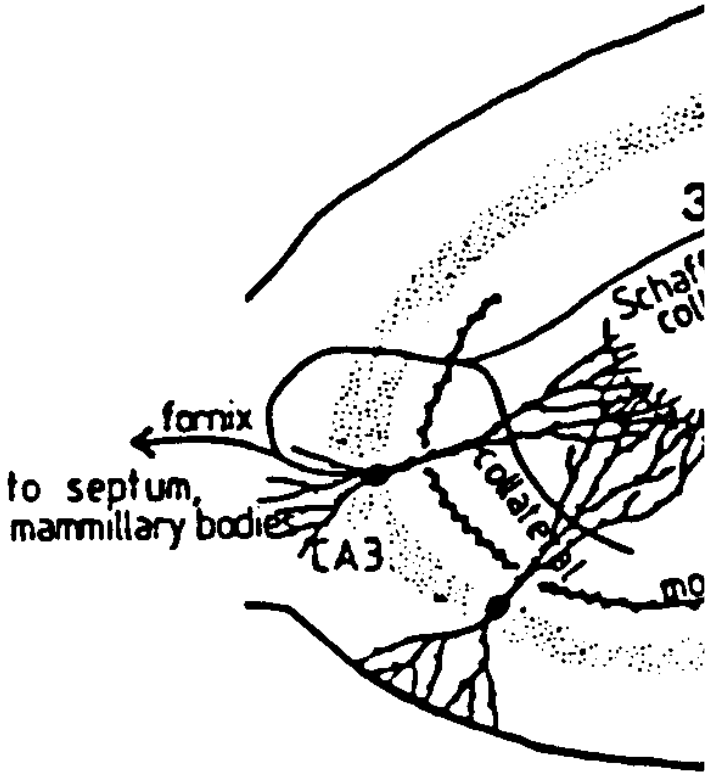
Their questions

- How does synchronization occur during an interictal spike?

- Why is there a long and variable latency between stimulation and the onset of an interictal spike?


fornix
to septum,
mammillary bodies
CA3
Schaf
Col
Collateral
mo

(a)

- Individual cells can intrinsically burst

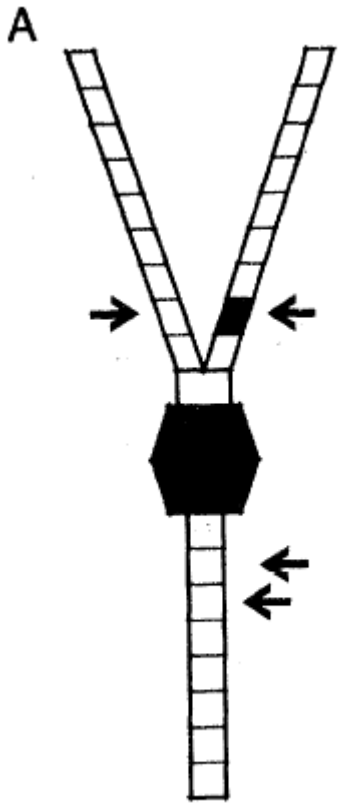
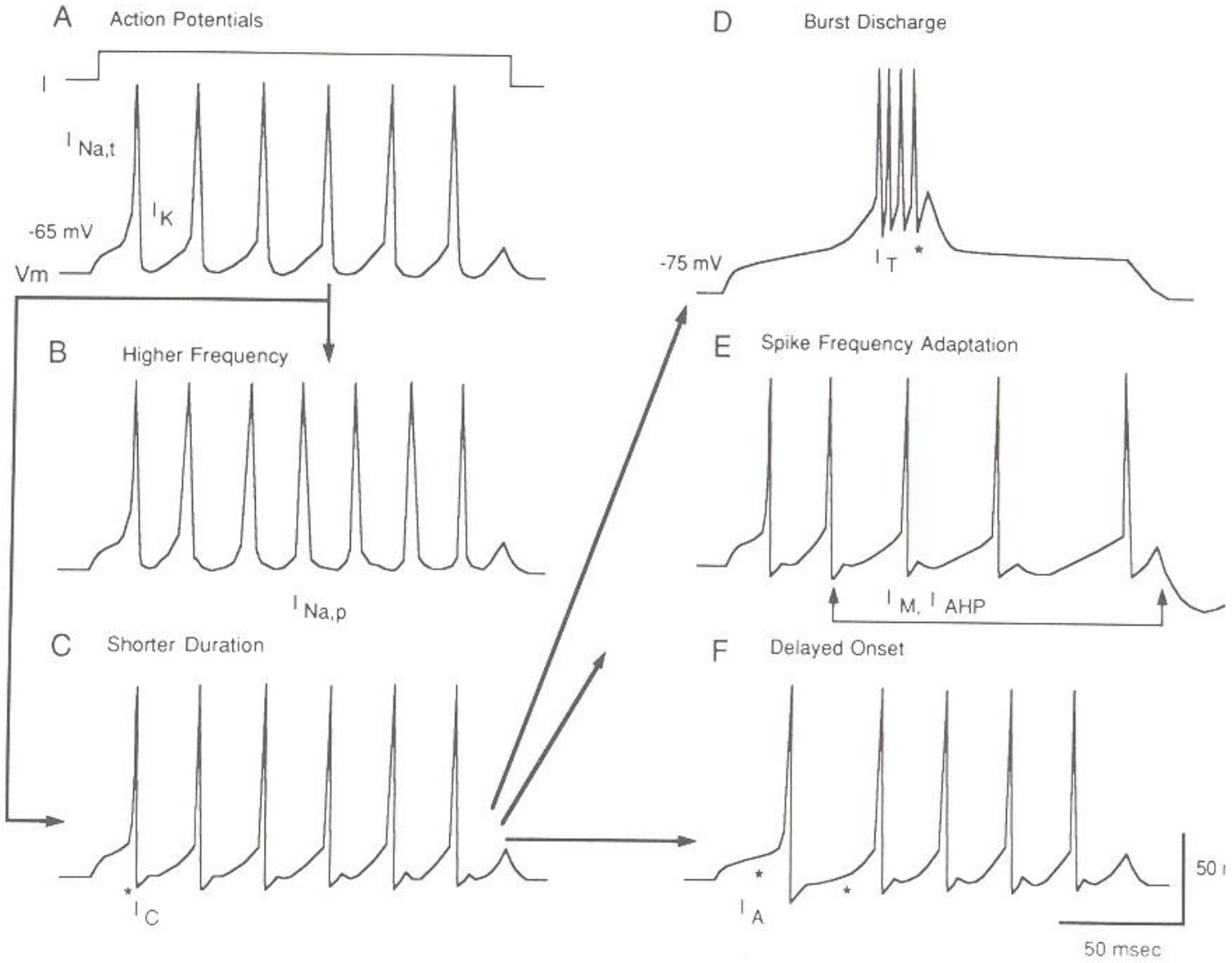
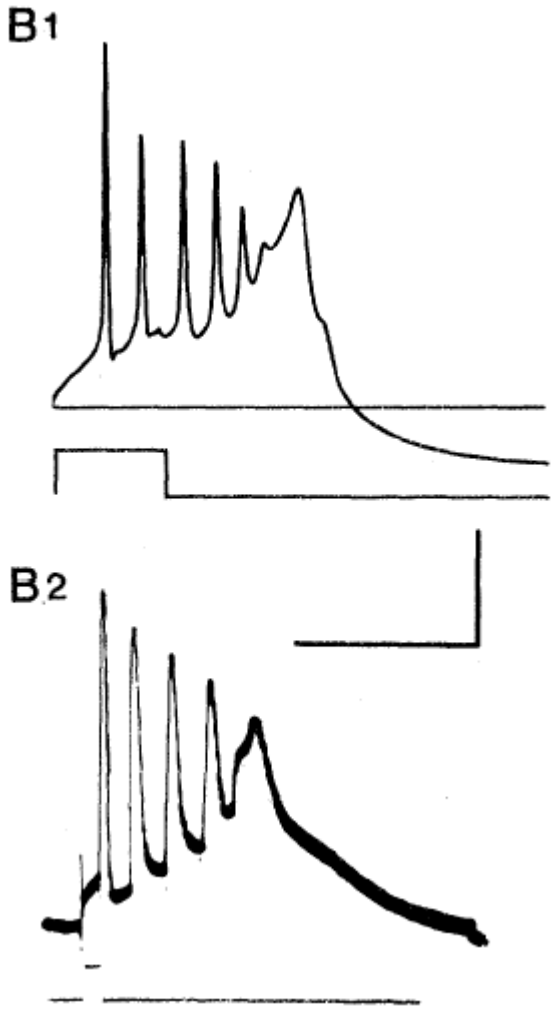


Fig. 1. Structural features of the model. (A) Electrotonic structure of single cell showing division into compartments, soma (central hexagon), basal dendritic cylinder extending below, and branching apical dendrite extending above. Compartments containing active ionic conductances (Na^+, K^+, Ca^{2+}, and Ca^{2+}-mediated slow K^+) are shaded. Locations of excitatory synaptic input are shown by arrows. Each dendritic compartment is 0.1 space constant in electrotonic length.


A
Action Potentials
I
I Na,t
I K
-65 mV
Vm
B
Higher Frequency
I Na,p
C
Shorter Duration
I C
D
Burst Discharge
-75 mV
I T
E
Spike Frequency Adaptation
I M, I AHP
F
Delayed Onset
I A
50 mV
50 msec

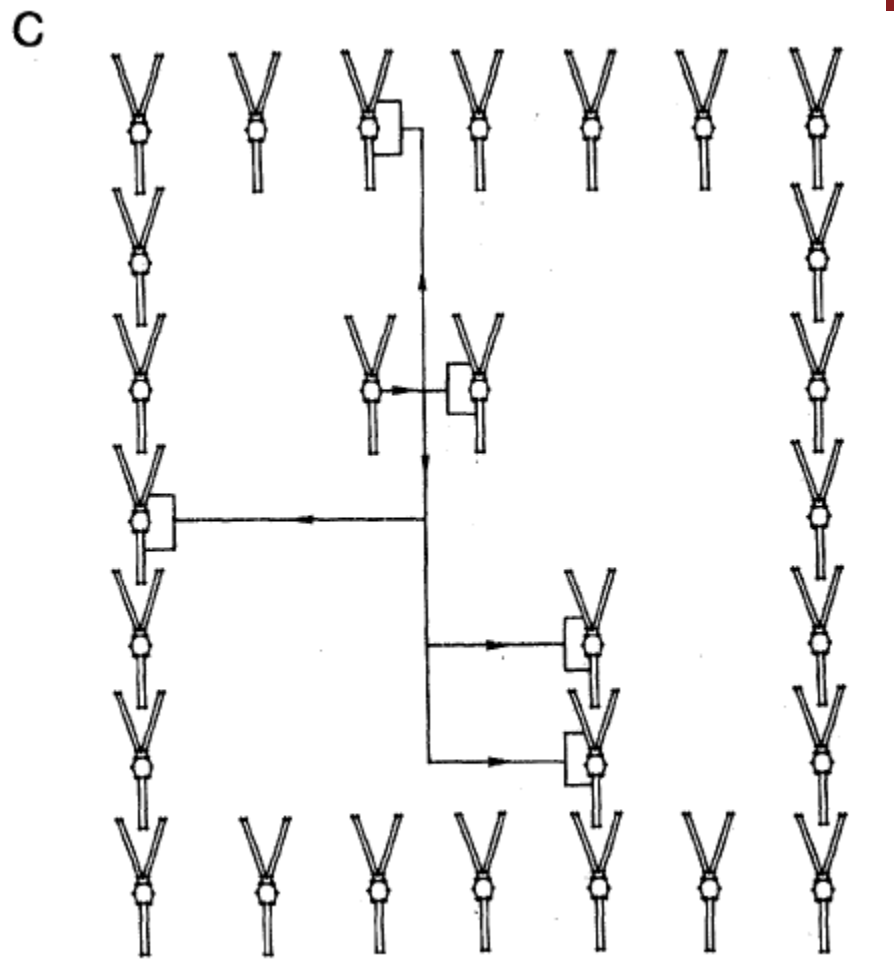


Note afterhyperpolarization

(B1) Intrinsic burst elicited in isolated model neuron by injected depolarizing current (1 nA for 15 msec; lower trace). Calibration: horizontal, 25 msec; vertical, 25 mV, 2.5 nA. (B2) CA3 cell burst evoked by injected current (lower trace). Calibration: horizontal, 40 msec; vertical, 25 mV, 1 nA.

- Individual cells can intrinsically burst

- A burst in one cell will lead to a burst in another cell that is synaptically connected



Note that connections are random

(C) Schematic structure of the model neuronal network. For clarity, a 7 by 7 array is shown, although a 10 by 10 array is used in the simulations. Each cell has the structure shown in (A). Every cell sends an output to an average of five other cells, the spatial location of which is random and not related to distance from the original cell. An example of one possible set of outputs for a cell is shown. There are no inhibitory synaptic inputs, and electrotonic junctions do not occur in this model.

- Individual cells can intrinsically burst
- A burst in one cell will lead to a burst in another cell that is synaptically connected
- There are no inhibitory connections, since bicuculline or penicillin have disabled them

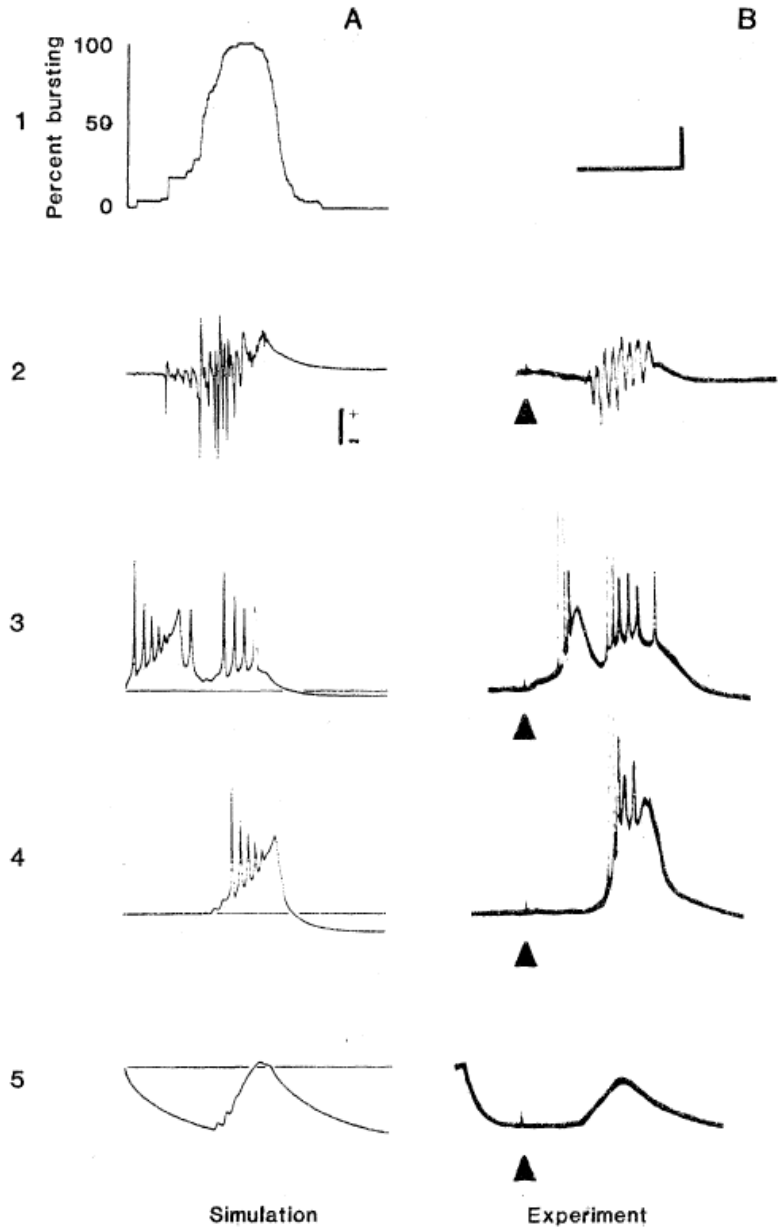
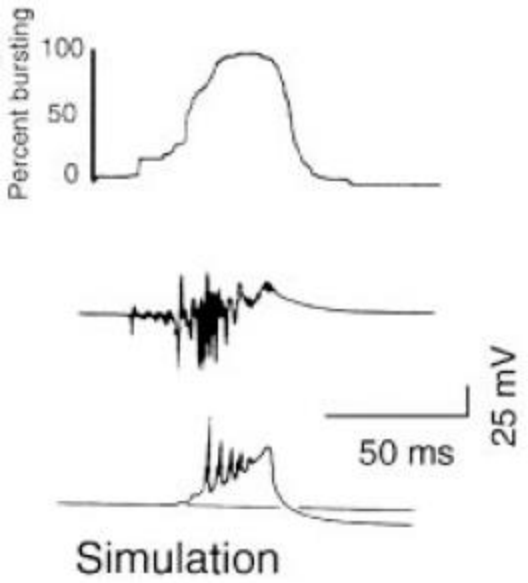


Fig. 2. Simulated and experimentally recorded epileptiform events. (A) Simulated interictal spike, obtained with steady depolarizing current of 1.5 nA to four cells in one corner of network. (A1) Percentage of total cells in network bursting (that is, have fired at least one action potential, but are not yet hyperpolarized). (A2) Field potential. (A3) Simulated soma membrane potential of cell receiving stimulus. Note double burst resulting from EPSP impinging during major part of interictal spike. (A4) Membrane potential of another, more typical, cell. (A5) Membrane potential of same cell as in (A4), with simulation as above, but with 1.5 nA of hyperpolarizing current injected into this cell, revealing underlying EPSP. (B) Experimental interictal spikes, evoked by brief shocks to fimbria and recorded in CA2 region of the pencillin-treated hippocampal slice. (B2) Field potential, isolated CA2. (B3) to (B5) Intracellular records during interictal spikes in intact slice. (B4) and (B5) are from same cell but (B5) is shown during injection of hyperpolarizing current. Triangles mark stimulus artifacts. Calibration: 50 msec in (A) and 60 msec in (B); 25 mV for intracellular records in (A), 4 mV in (B2), and 20 mV in (B3) to (B5).



- How does synchronization occur?

- Why the long and variable latencies?

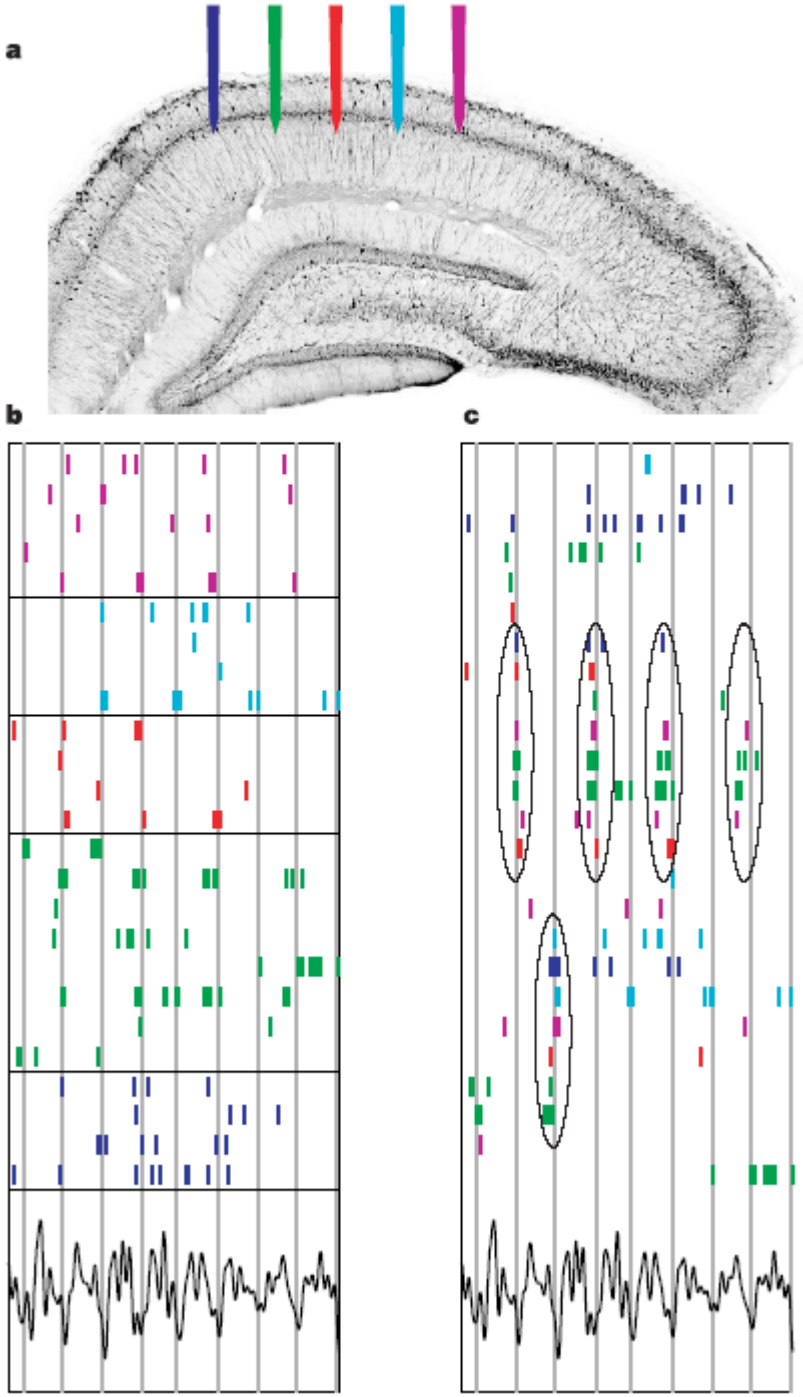
- How does synchronization occur? Because activity spreads from a few stimulated cells to many others, so that all cells are eventually recruited.

- Why the long and variable latencies? The connections between cells are random, and all connections have conduction and synaptic delays. Different connections have different lengths, leading to different latencies.

Biophysically detailed network models to explain:

- Synchronous bursts in the hippocampus seen during epilepsy.

- Rhythmic oscillations in the hippocampus seen during normal behaviors such as sniffing and walking.



Organization of cell assemblies in the hippocampus

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Figure 1 Cell assembly activity in a population. **a**, Location of the recording electrodes. **b**, **c**, Raster plots of 25 pyramidal cells that were active during a 1-s period of spatial exploration out of 68 simultaneously recorded neurons. **b**, Neurons are arranged in order of physical position in the CA1 pyramidal layer (colour-code refers to locations in **a**). Vertical lines indicate troughs of theta waves (bottom trace). Location-specific synchrony is not apparent in the population activity. **c**, The same spike rasters shown in **b**, reordered by stochastic search over all possible orderings to highlight synchrony between anatomically distributed populations. 'Cell assembly' organization is now visible, with repeatedly synchronous firing of some subpopulations (circled).

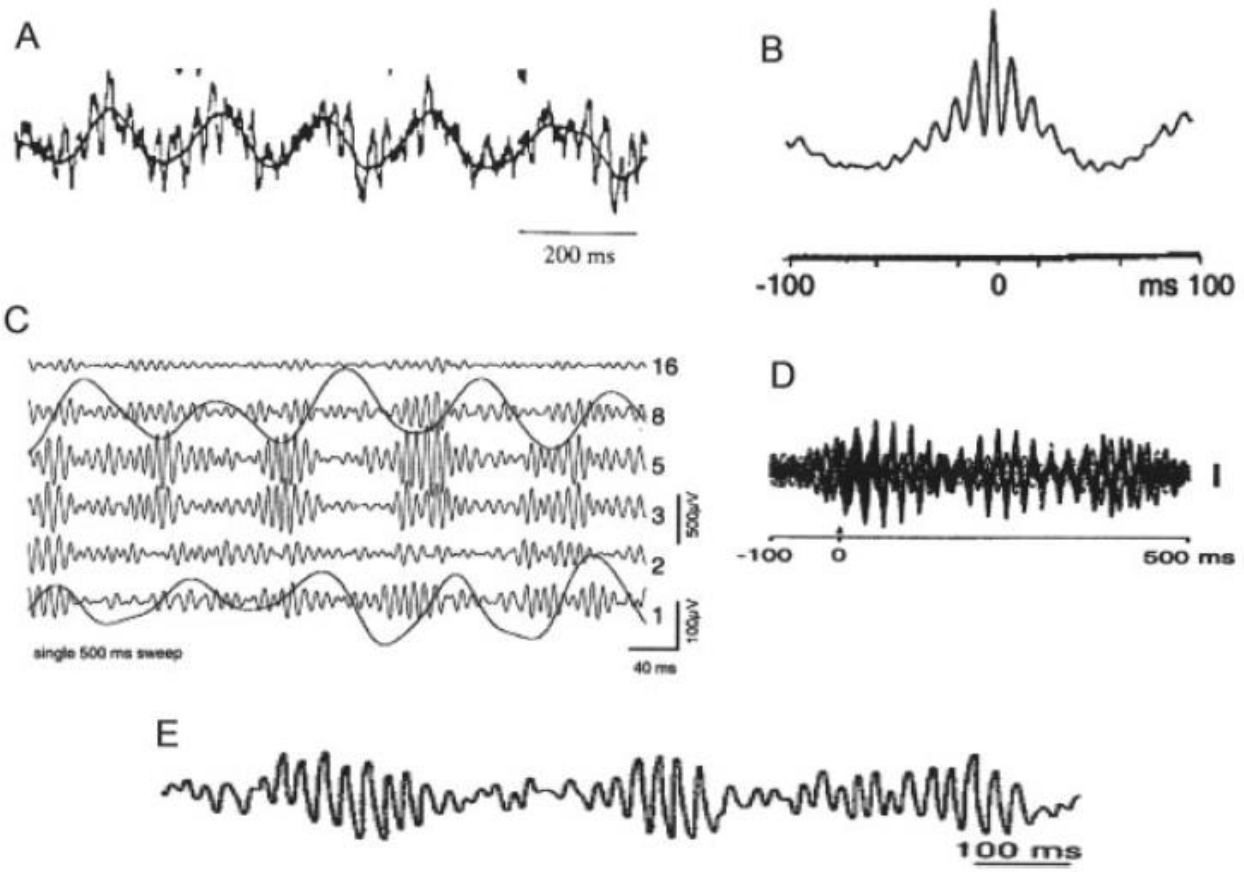

FIGURE 2. Recordings of dual theta/gamma oscillations in the hippocampus and various cortical regions. A: Intracellular recording from hippocampal neuron. Reproduced with permission from Soltesz and Deschenes (1993). B: Field recordings from hippocampus; average triggered on peak of the gamma frequency field potential oscillation. Reproduced with permission from Bragin et al. (1995). C: Field recordings from EC. Highly filtered records show the theta component in isolation. Reproduced with permission from Chrobak and Buzsaki (1998). D: MEG from human midline cortex. Reproduced with permission from Llinas and Ribary (1993). E: Field recording from olfactory cortex. Reproduced with permission from Woolley and Timiras (1965).

Theta oscillations are also seen in slices if carbachol is added

Model of the Origin of Rhythmic Population Oscillations in the Hippocampal Slice

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One goal of mammalian neurobiology is to understand the generation of neuronal activity in large networks. Conceptual schemes have been based on either the properties of single cells or of individual synapses. For instance, the intrinsic oscillatory properties of individual thalamic neurons are thought to underlie thalamic spindle rhythms. This issue has been pursued with a computer model of the CA3 region of the hippocampus that is based on known cellular and synaptic properties. Over a wide range of parameters, this model generates a rhythmic activity at a frequency faster than the firing of individual cells. During each rhythmic event, a few cells fire while most other cells receive synchronous synaptic inputs. This activity resembles the hippocampal theta rhythm as well as synchronized synaptic events observed in vitro. The amplitude and frequency of this emergent rhythmic activity depend on intrinsic cellular properties and the connectivity and strength of both excitatory and inhibitory synapses.

Possible causes of oscillation:

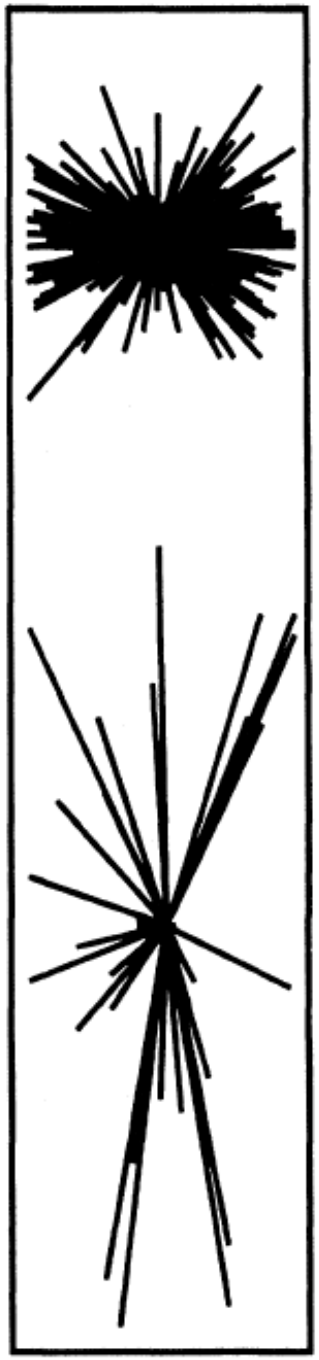
- Intrinsically oscillating cells, or “pacemakers” that fire at 4-8 Hz.
- Time course of synaptic currents. Ex: recurrent inhibition that comes every 1/6 second.
- It is an emergent network phenomenon.

- Individual neurons oscillate at a frequency much slower than the frequency seen in the network: no pacemakers.

- The strength of synaptic potentials affects the frequency of bursting: so the time course of synaptic potentials is not enough when strengths are variable.

- Therefore oscillations are a network phenomenon? If so, we need to model it…

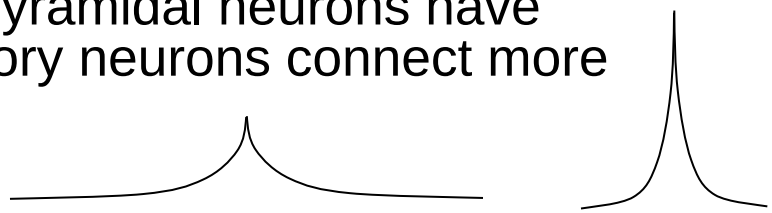
- How are such oscillations generated by the network, if not by single cells or by synaptic potentials?



The model

Fig. 2. Structure of the model. The 9000 pyramidal cells lie in a 40 by 225 array. A 4 by 225 array of inhibitory cells lies superimposed. The output connections of a single inhibitory cell (**above**) and a pyramidal cell (**below**) are shown, illustrating the different spatial distributions and axonal divergences. Each pyramidal cell has an average of 22 outputs. Each inhibitory cell has an average of 220 outputs (*30*).

- 9000 excitatory pyramidal neurons (neurons with currents similar to before)
- 900 inhibitory neurons
- Randomly connected, but with connection probability falling off exponentially with distance. Pyramidal neurons have more distant connections; inhibitory neurons connect more locally



- Strong afterhyperpolarizations in excitatory cells

100 ms long

- One burst can lead to another burst in a connected cell
- Both fast and slow inhibition are included

- How would activity propagate in such a system?

- How would activity propagation be different from in the first model?

- Some pyramidal cells randomly burst
- These cells in turn activate others
- But not all cells can be activated, since some are refractory (afterhyperpolarizations)
- Not all cells can be activated because of inhibition also

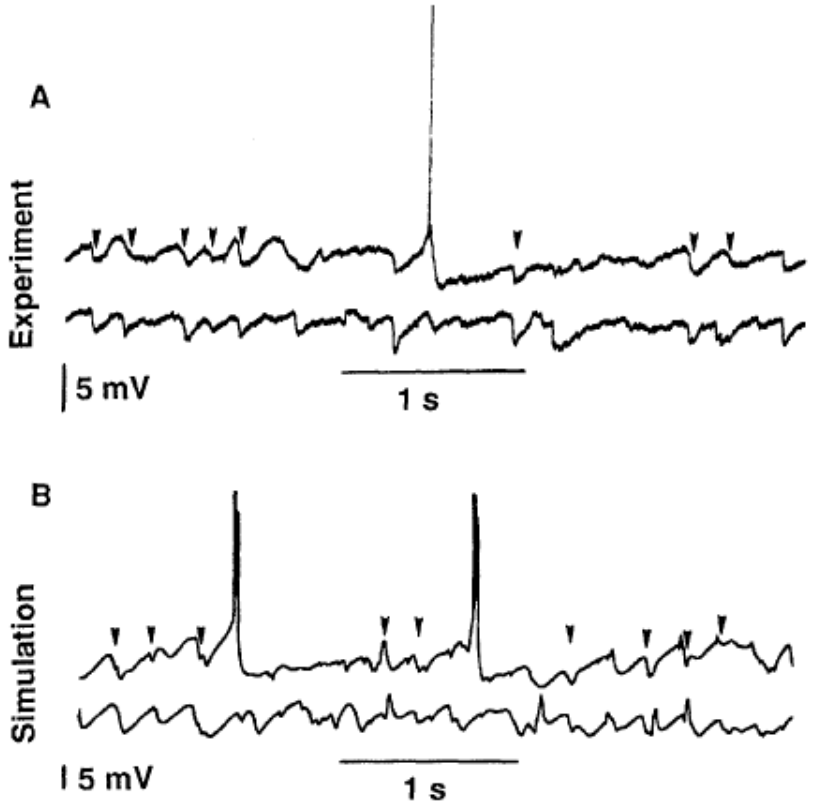


Fig. 1. Synchronized synaptic potentials. (**A**) Simultaneous intracellular potentials from two pyramidal neurons, about 200 μm apart, recorded in stratum pyramidale of the CA3 region of a transverse guinea pig hippocampal slice bathed in normal medium (that is, without blockade of synaptic inhibition). Slice preparation and recording techniques are described in (*28*). The repeating synaptic events, usually inhibitory, are often phase-locked between the two cells. Firing is infrequent. These two cells were not electrotonically coupled. (**B**) Two simultaneous pyramidal cell potentials from a simulation of a network of 9000 model pyramidal cells and 900 inhibitory cells. Portions of these records are clearly rhythmical, whereas in other portions rhythmicity is less clear. Examination of the population as a whole is necessary to see the underlying rhythmicity (Fig. 3). Action potentials are truncated for both experiment and simulation.

Rhythmicity at the network level: oscillations

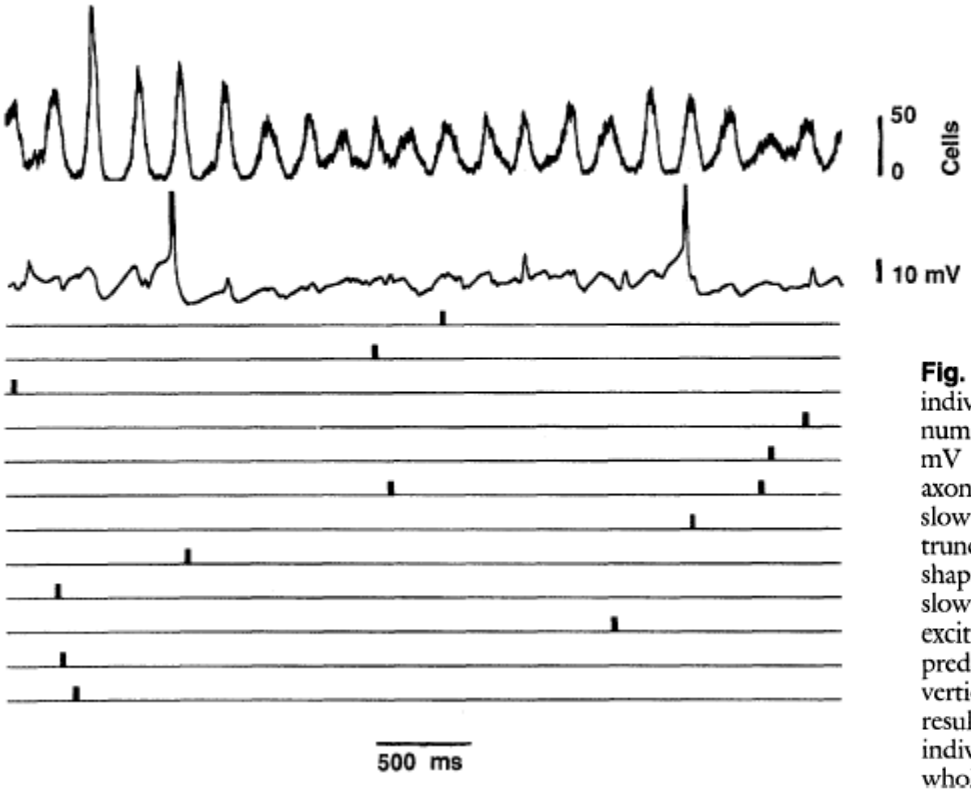


Fig. 3. Rhythmic population activity with nonrhythmical bursting in individual cells. The simulation is the same as in Fig. 1B. (**Upper trace**) The number of pyramidal cells (9000 in all) that are depolarized more than 20 mV (the potential at which they are capable in the model of generating axonal output). (**Middle trace**) Potential of a single cell. It bursts at a much slower rate than the population oscillatory rate. (Action potentials are truncated.) The cell demonstrates repeating synaptic potentials in which the shape changes with the relative admixture of excitatory, fast inhibitory, or slow inhibitory inputs. (With different parameters, for example, larger excitatory strength and lower cellular excitability, synaptic potentials are predominantly excitatory.) (**Lower section**) For 12 different neurons a vertical bar is inscribed at times when the respective neuron fires a burst. The resulting "musical score" emphasizes the irregular firing patterns of the individual cells, in contrast to the global oscillation of the population as a whole. When the cells are synaptically isolated from each other, any cell bursting repeatedly will burst rhythmically (not shown).

The model captures the network oscillation frequency

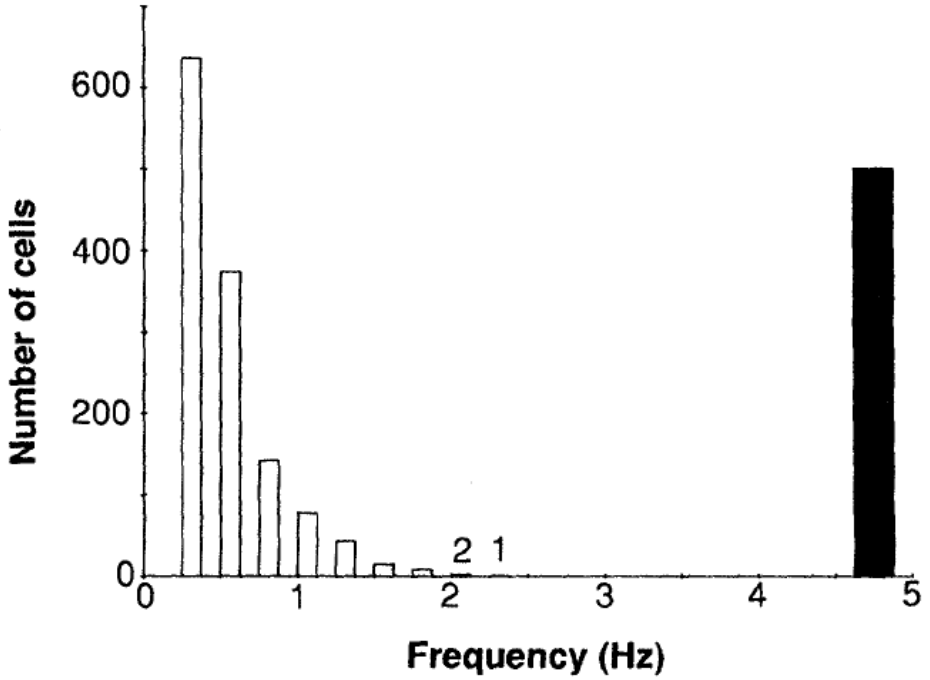


Fig. 4. The frequency of population rhythmicity is much faster than the frequency of any individual cell in isolation. The open bars are a histogram of the bursting rates of the pyramidal cells in isolation with the excitability parameters as in Figs. 1 and 3, but with no synaptic interactions. The bin size is 0.25 Hz. The solid bar is the frequency of the population oscillation (that is, the mean frequency of the oscillation in the top trace of Fig. 3) when synapses are functional. The population frequency for this simulation (4.75 Hz) is related to the time course of slow IPSPs in the model (the time constant for relaxation of the slow IPSP current is 100 ms).

- Fast inhibition: reducing this causes bigger events, but at lower frequency
- Recurrent excitation: increasing this also causes bigger events and lowers the frequency
- Cellular excitability: reducing this decreases the frequency (to intervals longer than the 100 ms slow inhibition)

Changing cellular excitability

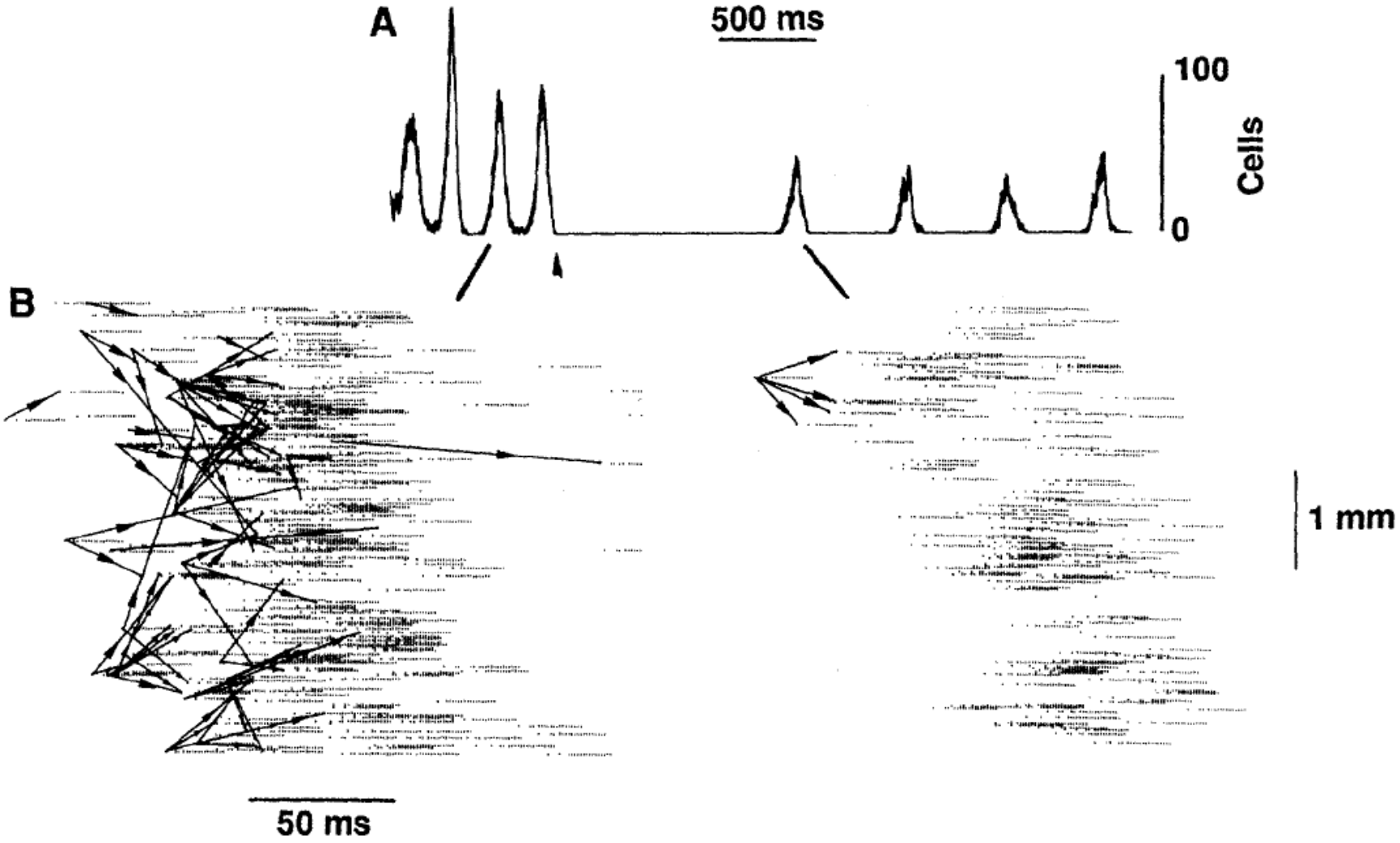


Fig. 5. Effect of cellular excitability on frequency and structure of simulated rhythmical activity. (**A**) Number of cells depolarized beyond 20 mV (above resting potential) as a function of time. Mean cellular excitability begins at a high level, but at the time marked by the arrowhead it is abruptly dropped (4.8-fold). Both frequency and amplitude then decrease. (The amplitude decreases in part because the lower excitability makes it more difficult for bursting to propagate from one cell to another.) (**B**) The structure of individual population waves at two levels of excitability, on an expanded time scale. The horizontal streaks represent bursts in individual cells at various spatial locations. The solid lines with arrows indicate synaptic connections from cells that burst spontaneously ("initiating cells") to those of their followers, which also burst during the event. When excitability is high (left), there are 31 different initiating cells scattered across the array. Other cells are induced to fire by spread of activity along synaptic connections, but (because of cell refractoriness and inhibition) propagation occurs across only certain connections. When excitability is low (right), there are fewer initiating cells. In the example shown, there is only one initiating cell. Arrows are drawn in only for the first generation of synaptic spread of activity.

- Fast inhibition: reducing this causes bigger events, but at lower frequency
- Recurrent excitation: increasing this also causes bigger events and lowers the frequency
- Cellular excitability: reducing this decreases the frequency
- Slow inhibition: reducing this can cause random activity if excitability is high, but slow waves if excitability is low

- All of these factors contribute to the oscillations.
- The oscillations are an emergent network phenomenon.
- The oscillations could not have been predicted by studying one cell in isolation, even in extreme detail.

Supplementary slides

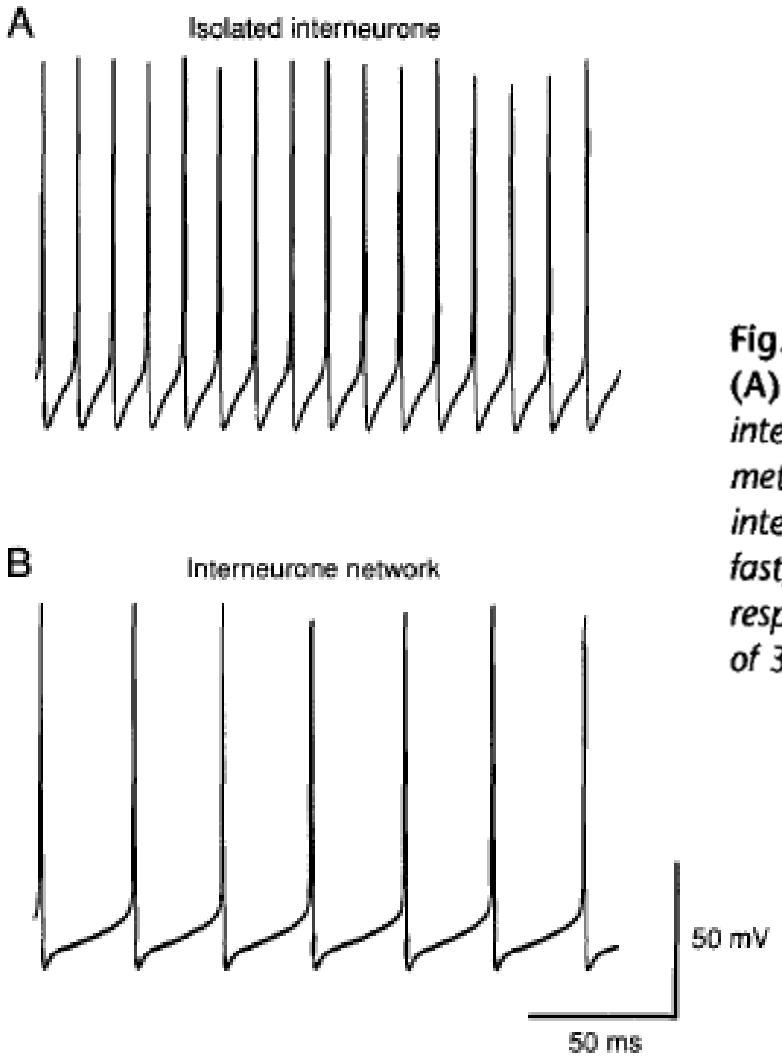


Fig. 3. ***Inhibitory neuronal networks generate gamma oscillations.*** **(A)** *Computer simulation of the brisk excitation of an isolated inhibitory interneurone by an injection of current to mimic the activation of metabotropic glutamate (mGlu) receptors.* **(B)** *The same inhibitory interneurone as part of a network of inhibitory neurones coupled by fast, $GABA_A$-mediated inhibitory postsynaptic potentials (IPSPs). Its response to mGlu receptor activation is now sculpted into an oscillation of 33 Hz by synchronized IPSPs generated by the inhibitory network.*

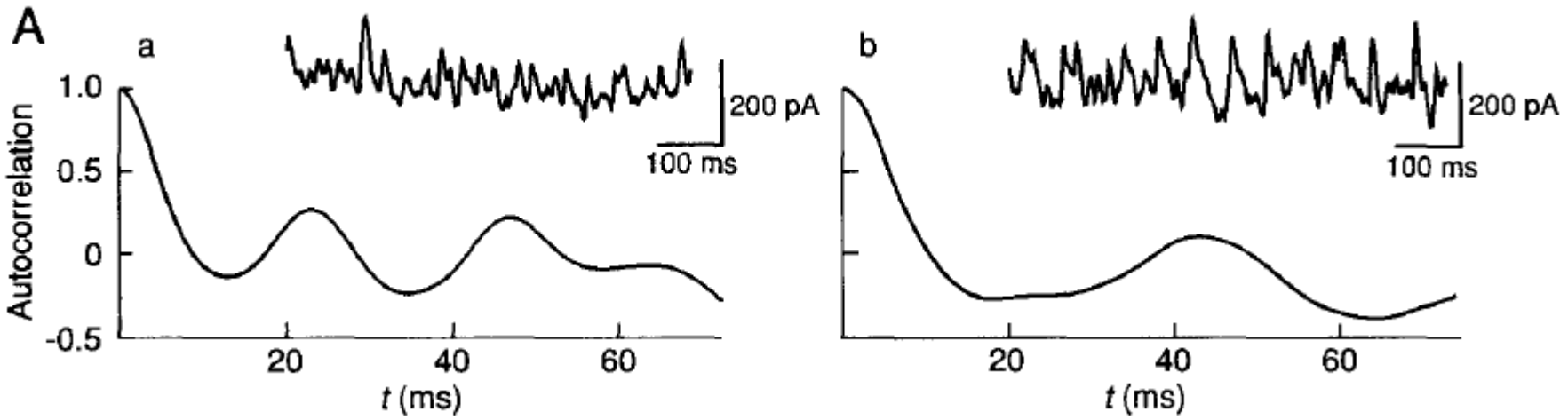
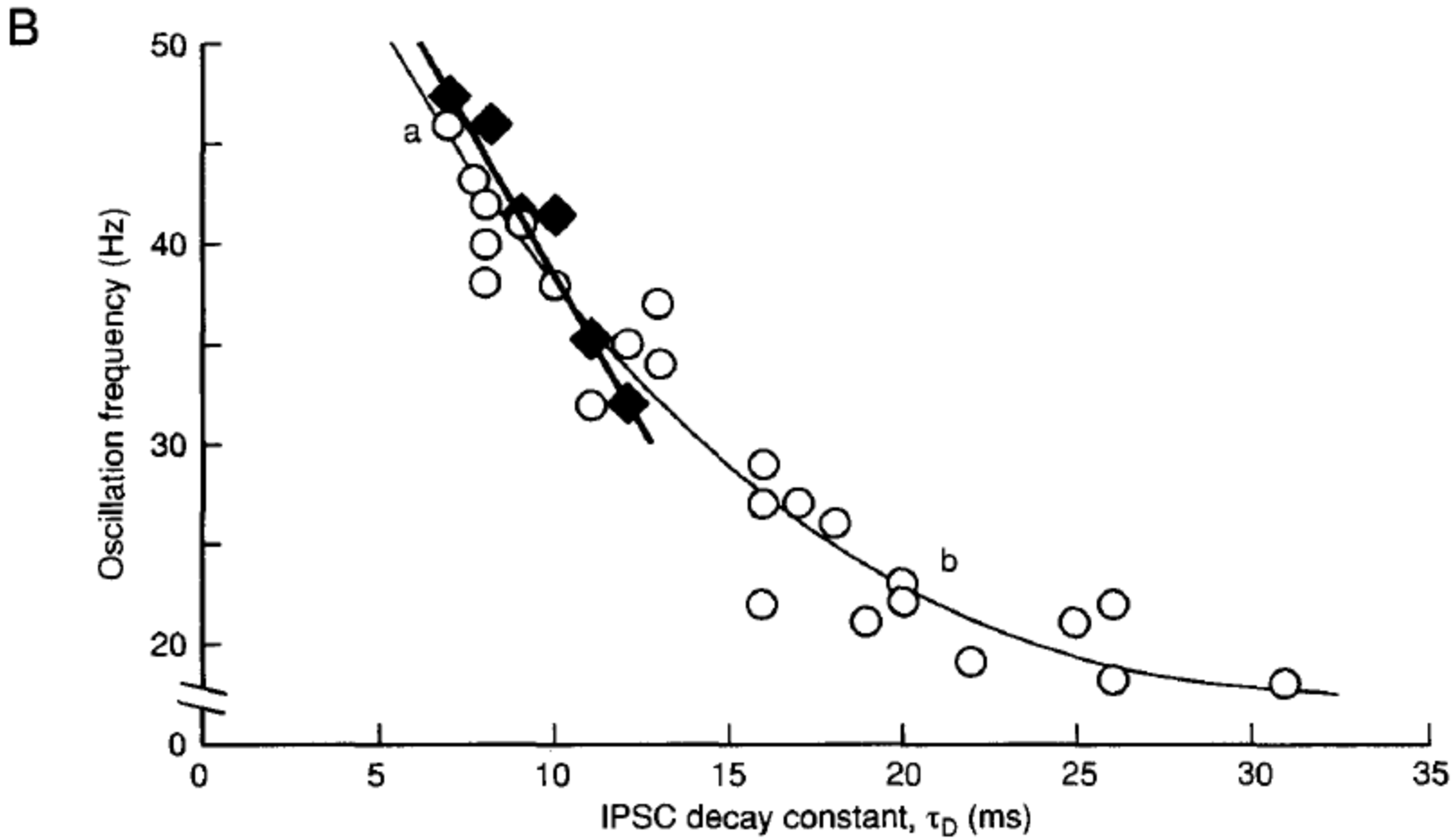


Fig. 4. ***The frequency of oscillation in the inhibitory neuronal network is a function of the decay constant of the inhibitory postsynaptic current (IPSC).*** **(A)** *shows autocorrelations of voltage-clamp recordings from inhibitory interneurones in stratum oriens made during an application of glutamate in the presence of drugs to block ionotropic glutamate receptors.* (a) *Prior to addition of 20 μM pentobarbital, the network oscillated at 22.7 ms [44 Hz; IPSC decay constant (τ_D) was 9.1 ± 0.4 ms], which is faster than pyramidal cells which have a τ_D of 22.4 ± 0.8 ms.* (b) *After equilibration with pentobarbital the period slowed to 44.5 ms (22 Hz; τ_D reached >30 ms).* **(B)** *Measurements made of*



equilibration with pentobarbital the period slowed to 44.5 ms (22 Hz; τ_D reached >30 ms). **(B)** *Measurements made of both network frequency and τ_D (open circles) during the wash-in of 2 μM pentobarbital reveal a close relationship, which matches that predicted by computer simulations (filled diamonds). More recent computer simulations match the non-linearity found at lower frequencies and the upper and lower limits to the synchronous network oscillations, following an increase in the connectivity of the simulated network*[40]. Figure adapted, with permission, from Ref. 38.