Cerebellar oscillations:
- Anesthetized rats
- Transgenic animals
- Recurrent model

Review of literature: γ

Network resonance
- Life simulations
- Resonance frequency

Conclusion

Resonant synchronization of heterogeneous inhibitory networks

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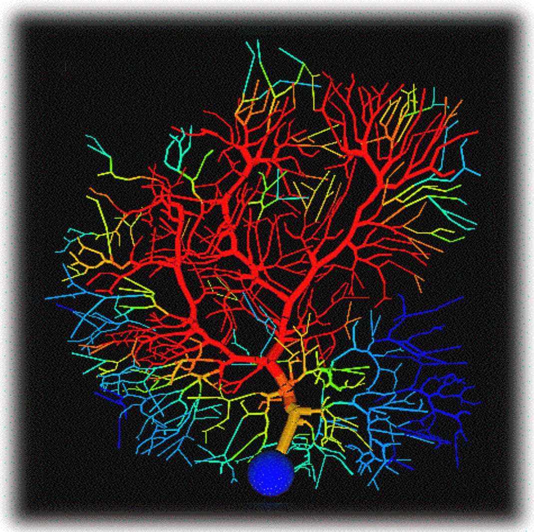
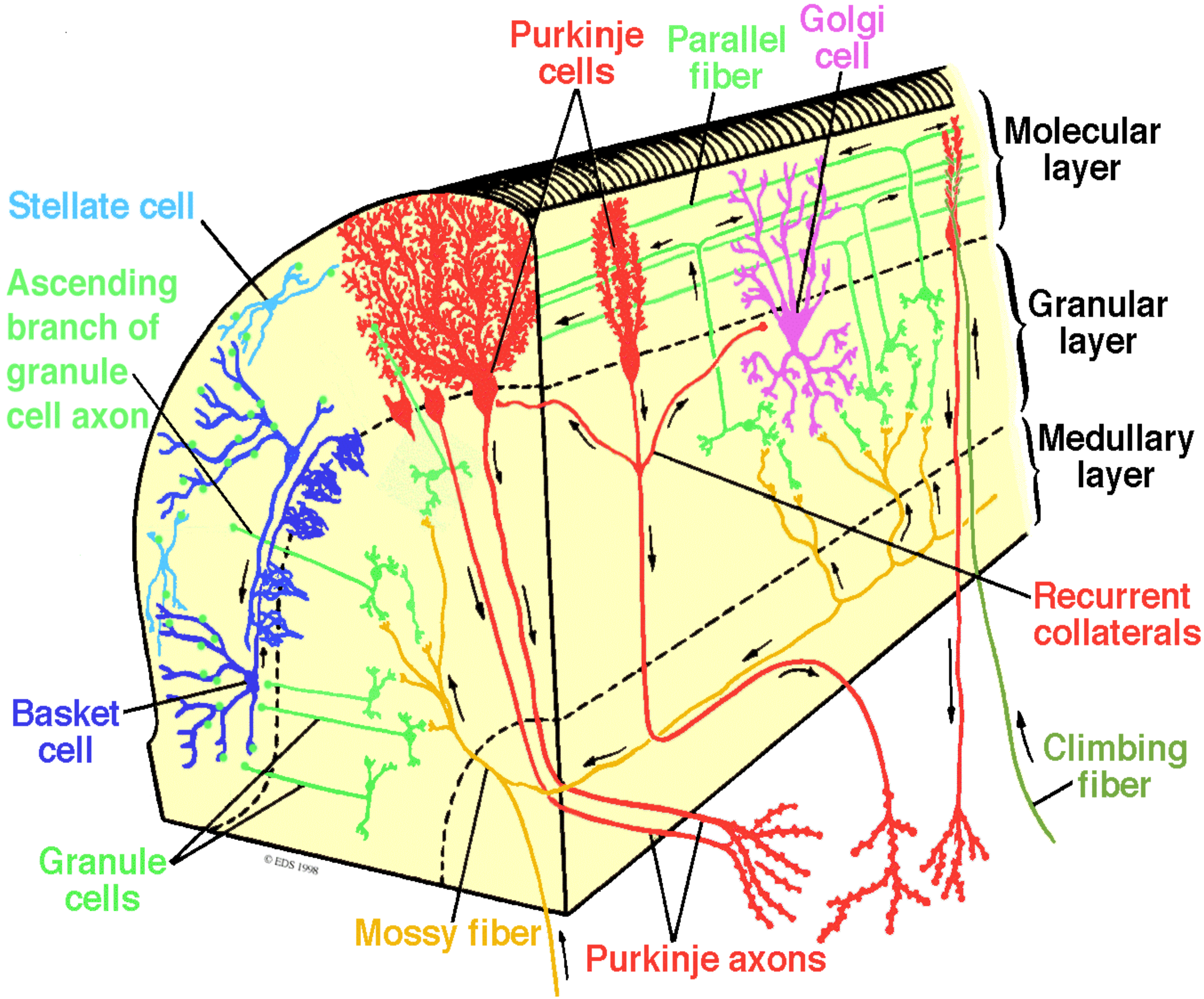
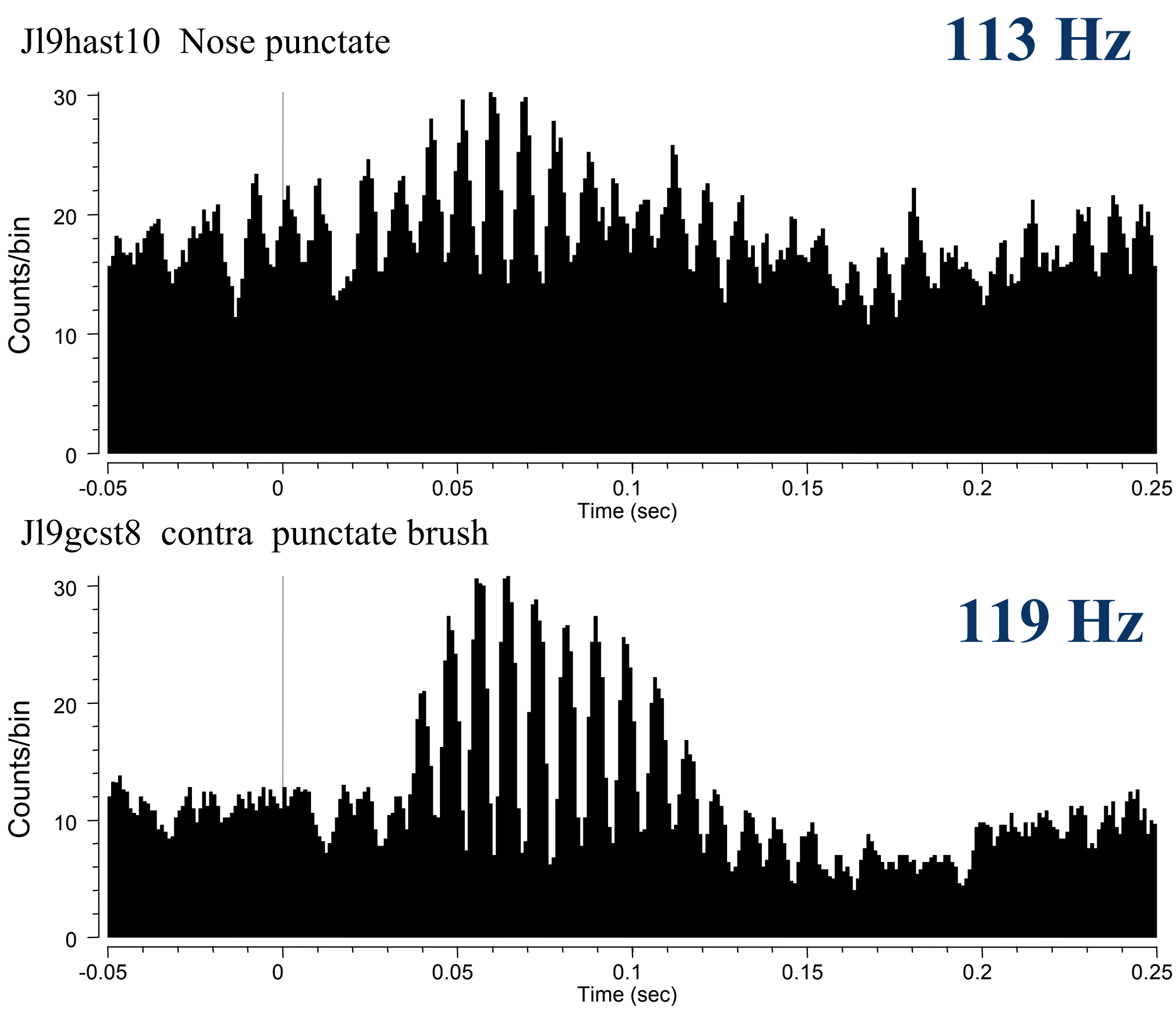



Purkinje cells
Parallel fiber
Golgi cell
Molecular layer
Granular layer
Medullary layer
Stellate cell
Ascending branch of granule cell axon
Basket cell
Granule cells
Mossy fiber
Purkinje axons
Recurrent collaterals
Climbing fiber
© EDS 1998

Oscillations in normal animals: anesthetized rat

Purkinje cell simple spike responses to tactile input: sometimes oscillator

→ Happens rarely (~5% of recordings), always ≥ 100 Hz.



Cerebellum can generate high frequency oscillations

Cortex: **60 Hz**

QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.

Cerebellum: **180 Hz**

Surface recordings from cat brain (chloroform + ether anesthesia)

Adrian *J. Physiol.* 1935

Oscillations in transgenic animals:

Transgenic mice show fast frequency oscillations in cerebellum:

→ recordings in awake transgenic mice lacking calcium binding proteins
→ local field potentials (LFP) show spindle-shaped periods of fast oscillation (167.8 ± 36.0 H
→ LFP oscillation frequency is fairly constant, amplitude is highly variable.
→ LFP oscillations reduced by blocking GABA inhibition or gap junctions.
→ LFP oscillations are synchronized along parallel fiber axis, but not along sagittal axis.

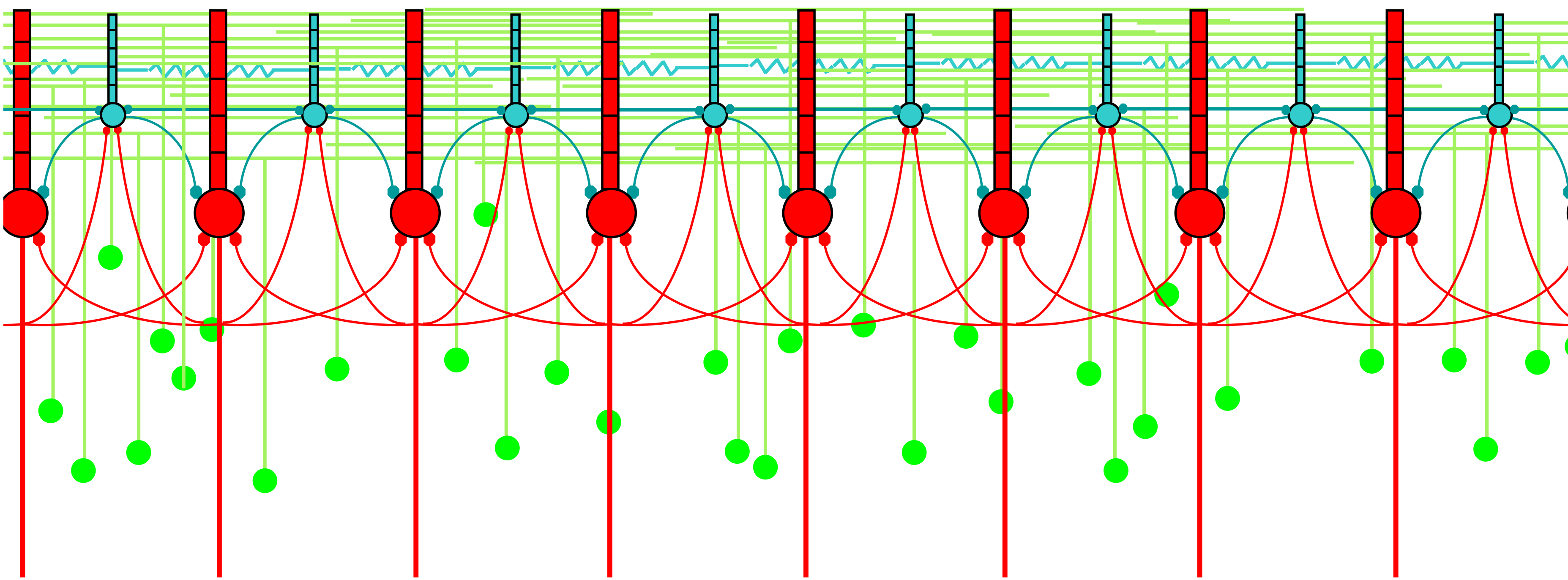
QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.

Cheron et al. *J. Neurosci.* 2004

Oscillations in transgenic animals: model

Recurrent inhibition between molecular layer neurons:

→ Model with 100 spiking inhibitory neurons: Purkinje cells and ML interneurons.
→ Heterogeneous: neurons differ in excitability, synaptic weights randomized.
→ All neurons: 6 voltage gated channels, no spike afterhyperpolarization, no cellular resonanc
→ Feedforward excitation: randomly activated parallel fibers with ≥ 160 synapses on dendrite
→ Nearest neighbor inhibitory coupling: recurrent inhibition. + gap junctions (interneurons on
→ Introduces a resonant frequency in 150-250 Hz range.
→ High inhibitory neuron firing rates are required: neurons must fire in resonance window.



Oscillations in transgenic animals: model

Recurrent inhibition between molecular layer neurons:

→ Spindles are produced continuously and with high power.
→ Explains effects of blocking $GABA_A$ inhibition (= blocks recurrent inhibition).
→ Strong enhancement by gap junctions between interneurons.
→ Oscillations unveil physiological phenomenon of resonance.

Power spectrum:

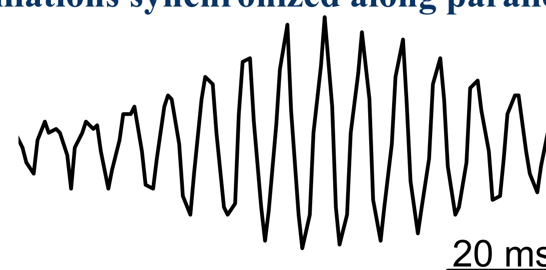
recurrent inhibition
recurrent inhibition + gap junctions
no recurrent inhibition

QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.

Firing Frequency (Hz)

oscillations not synchronized in sagittal axis:

oscillations synchronized along parallel fiber bean



Cerebellar oscillations : conclusions

- **Fast oscillations of Purkinje cell simple spike firing:**
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→ What causes the resonance?

→ What determines the resonance frequency?

Literature: oscillations caused by synchronized firing

Both excitatory and inhibitory neuron populations participate:

QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.

40 Hz oscillation in cortex

Singer & Gray *Ann. Rev. Neurosci* 1995 Jefferys et. al. *TINS* 1996

Literature: oscillations caused by synchronized firing

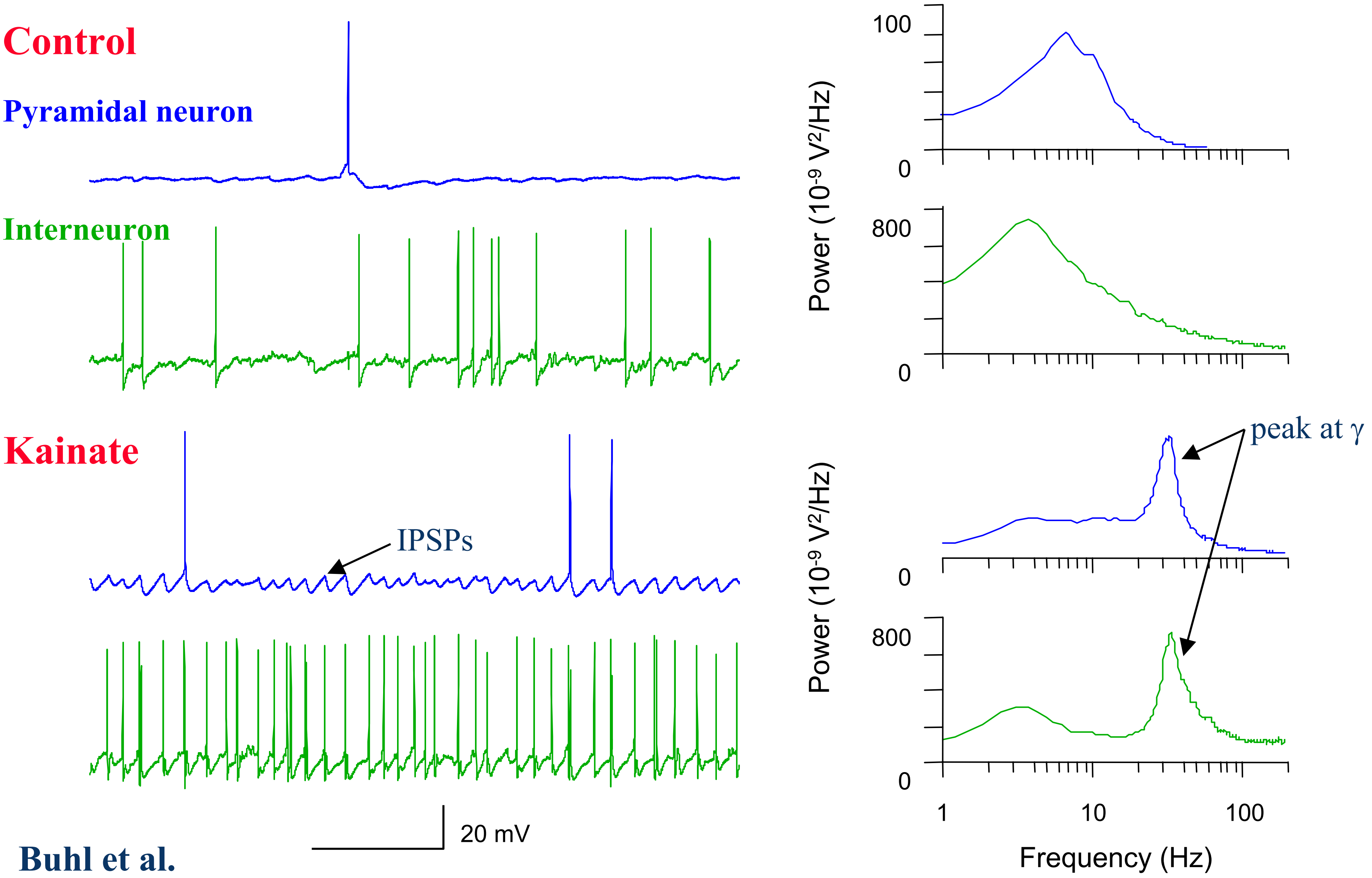
Multiple population mechanisms may be responsible for 40 Hz oscillation

QuickT

Freeman

Jefferys et al. *TINS* 1996

Kainate evokes gamma frequency oscillation in hippocampu



Buhl et al.

How can recurrent inhibition synchronize?

With slow inhibition (small α) only synchronous firing is stable:

Pair of reciprocal inhibitory integrate and fire neurons coupled with α functio

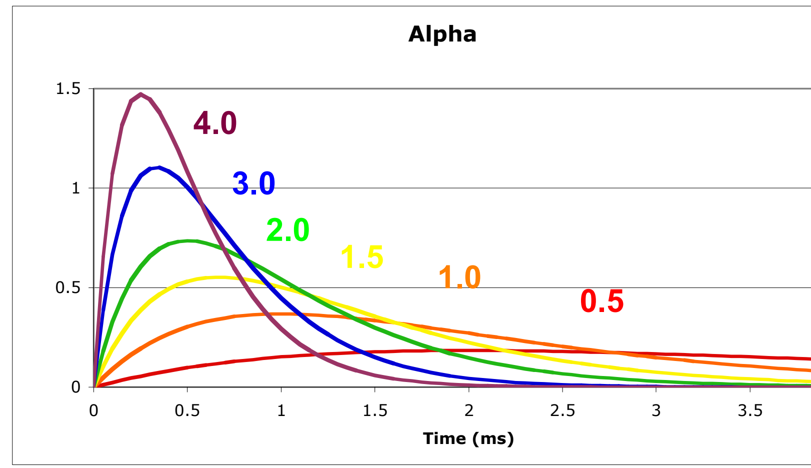
$$g_{syn} = \bar{g}_{syn}\alpha^2 e^{-\alpha t}$$

phase

stable
unstable

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

α



→ focus on shape of synaptic current

Van Vreeswijk, Abbott & Ermentrout *J. Comput. Neurosci.* 1994
(similar results:Ernst, Pawelzik & Geisel *Phys. Rev. Lett.* 1995)

How can recurrent inhibition synchronize?

The decay time constant of inhibition sets oscillation frequency:

Experimental manipulation of decay of $GABA_A$ currents with pentobarbital

Voltage clamp inhibitory currents in interneurons

No barbital: 44 Hz

20 µm barbital: 22 Hz

QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.

- ○ Hippocampal slice with AMPA/NMDA receptors blocked
- ◆ Computer simulation (128 inhibitory interneurons)

QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.

Whittington, Traub & Jefferys *Nature* 1995

How can recurrent inhibition synchronize?

Wang & Buzsáki confirm dependence of oscillation frequency on τ_{syn}:

The synchronization is dependent on firing frequency of neurons:

Network of recurrently coupled inhibitory neurons without axonal delays.

Conductance based models activated by current injection.

QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.

QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.

Wang & Buzsáki *J. Neurosci.* 1996

How can recurrent inhibition synchronize?

The decay time constant of inhibition sets oscillation frequency?

Problem: decay time constant is much shorter!

Whittington measured compound inhibitory currents but Traub simulated this as single synapse

QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.

Bartos, Vida,… & Jonas *PNAS* 2002

How can recurrent inhibition synchronize?

Is the frequency range of recurrent inhibitory networks limited?

Gap junctions between pyramidal neuron axons ‘essential’ for fast oscillations (not blocked by bicuculline in hippocampus).

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autocorrelation e
cross corellation e - i

Traub & Bibbig *J. Neurosci.* 2000

Mechanisms of oscillation with recurrent inhibitio

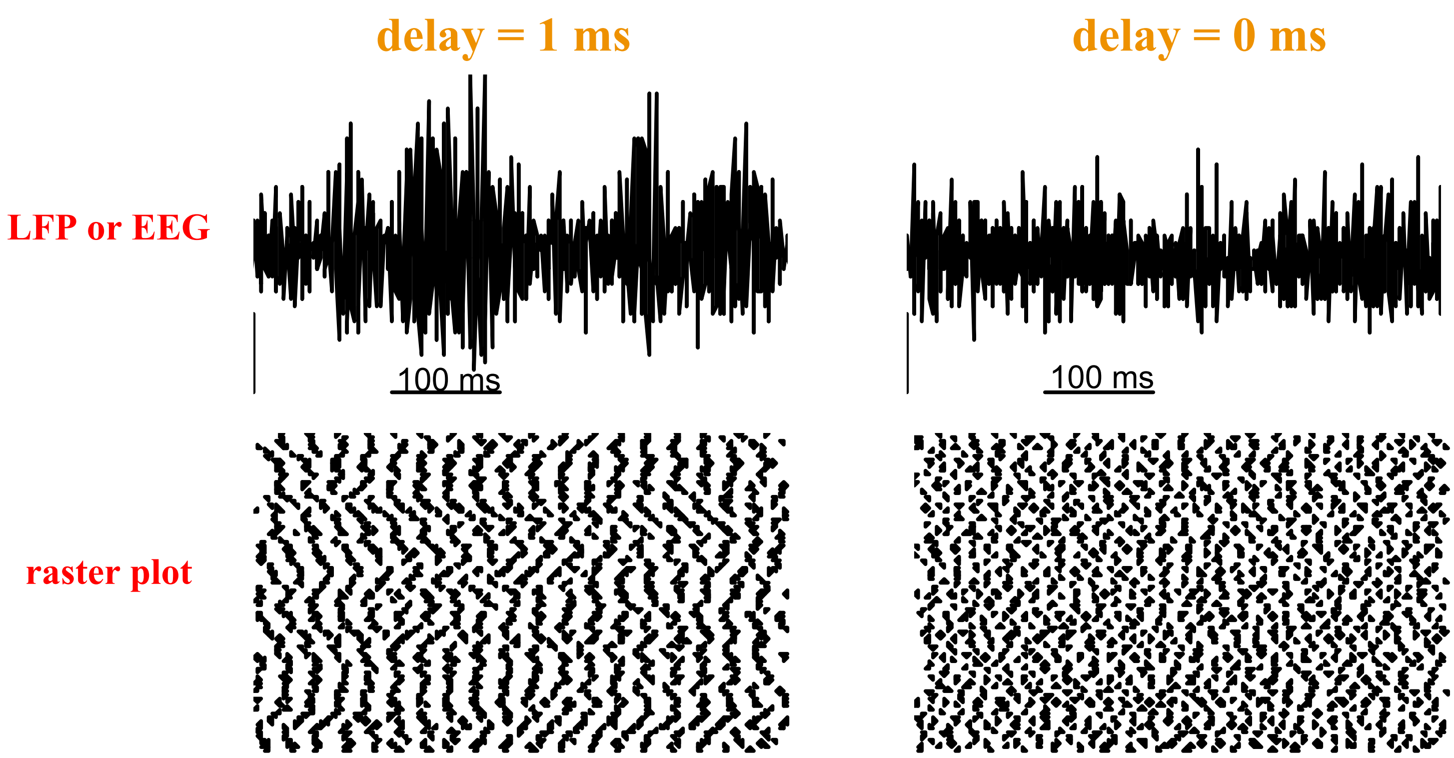
Recurrent inhibition with a delay introduces a resonant frequency:

GENESIS simulations #1

Mechanisms of oscillation with recurrent inhibitio

Recurrent inhibition with a delay introduces a resonant frequency:

→ Delay (axonal + synaptic) is essential.



Maex and De Schutter *J. Neuroscience* 23: 10503-10514 (2003)

Mechanisms of oscillation with recurrent inhibitio

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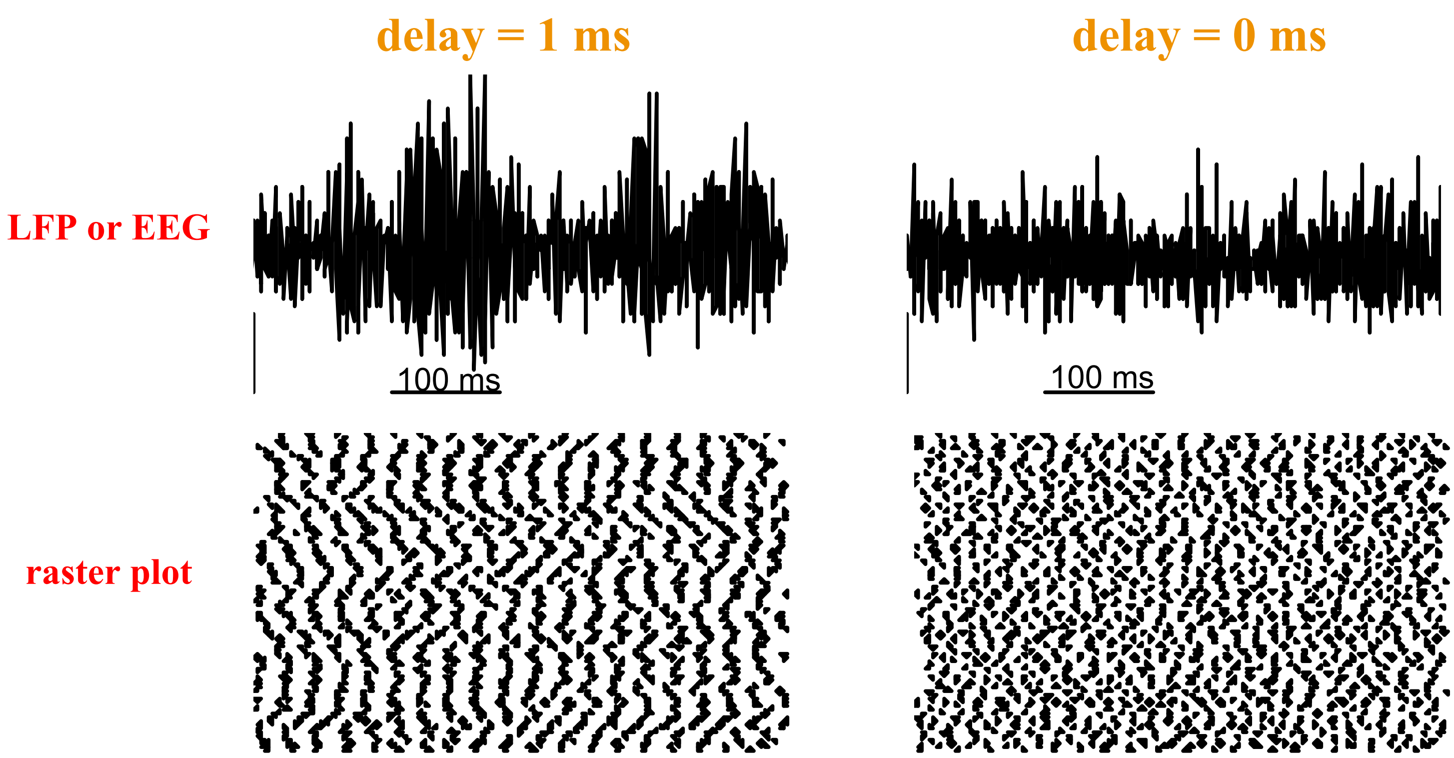


GENESIS simulations #2

Maex and De Schutter *J. Neuroscience* 23: 10503-10514 (2003)

Mechanisms of oscillation with recurrent inhibitio

Recurrent inhibition with a delay introduces a resonant frequency:

→ Delay (axonal + synaptic) is essential (van Vreeswijck et al., 1994; Ernst et al., 1995).

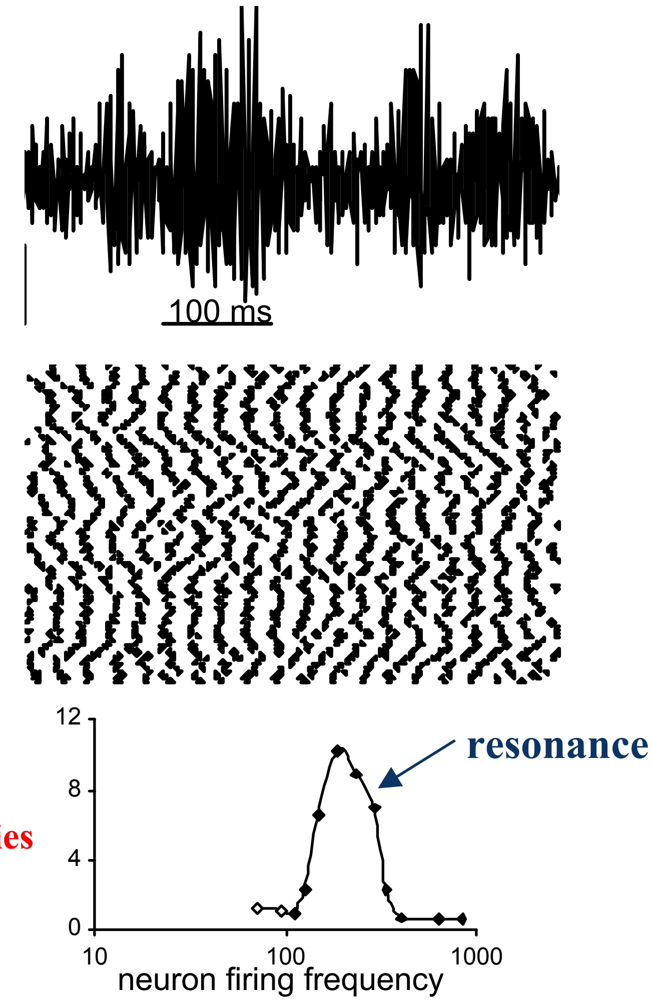
→ Neurons must fire (181 ± 10 Hz) close to frequency of oscillation (187 Hz) = resonance.

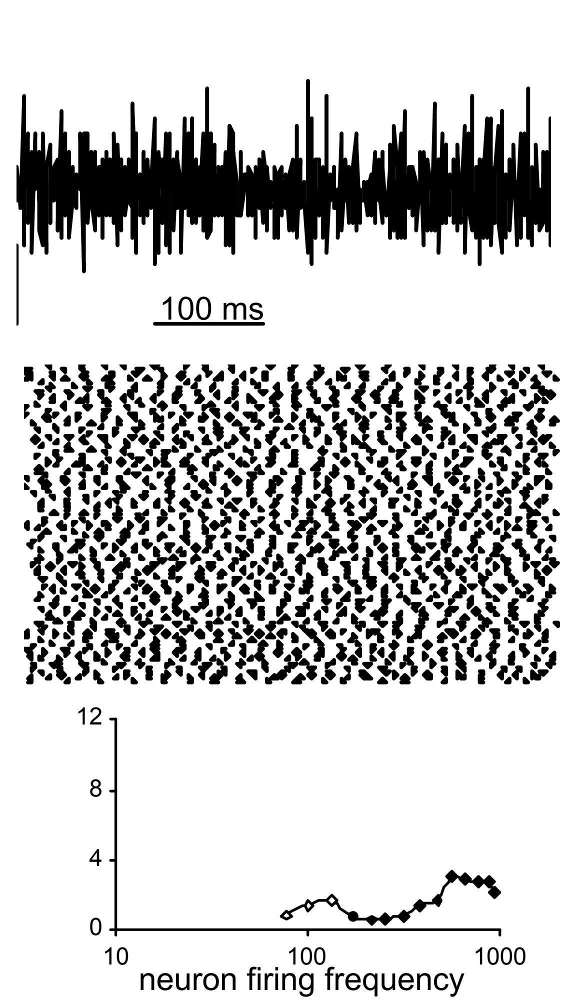
delay = 1 ms **delay = 0 ms**

LFP or EEG

raster plot

LFP power for varying spiking frequencies





Mechanisms of oscillation with recurrent inhibitio

Synaptic delay sets the resonant frequency (1D network):

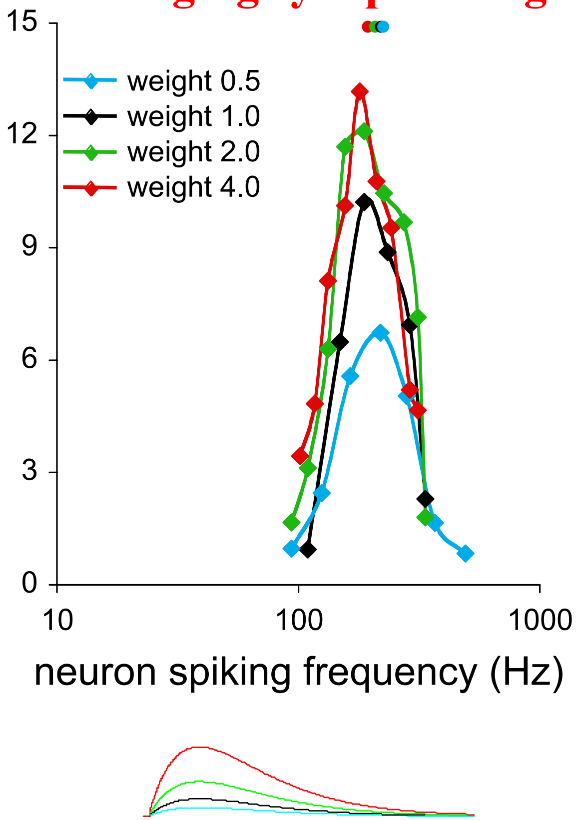
→ Synaptic delay (= axonal delay + latency of synaptic transmission) has strongest effect.

→ Predicted resonance frequency: *f=1/(4d)* (nearest neighbor inhibition).

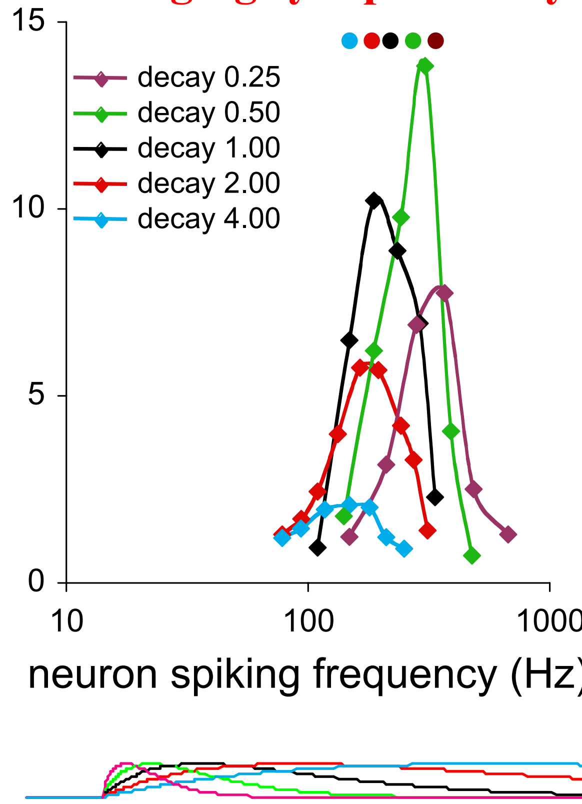
→ Synaptic weights set the power.

→ Synaptic current decay time constant has much weaker effects (⇔ Wittington et al., 1995; Traub et al., 1996; Wang and Buzsáki , 1996).

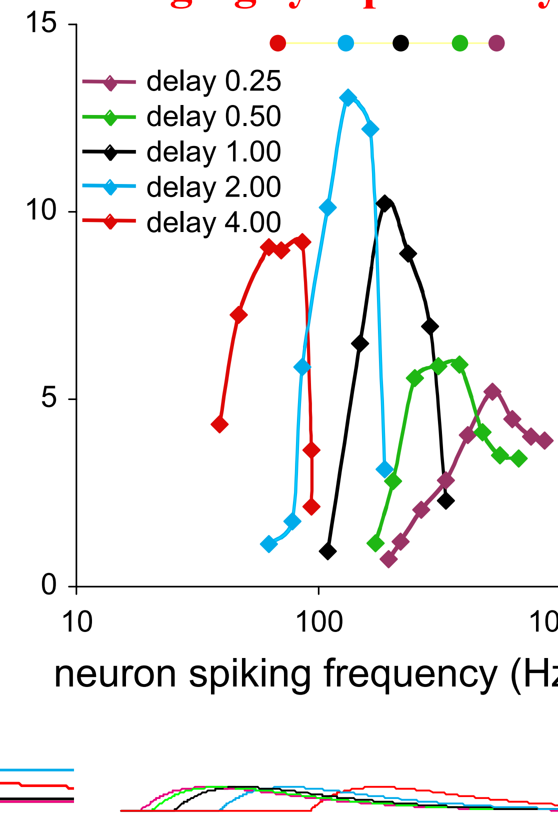
Changing synaptic weight



Changing synaptic decay



Changing synaptic delay



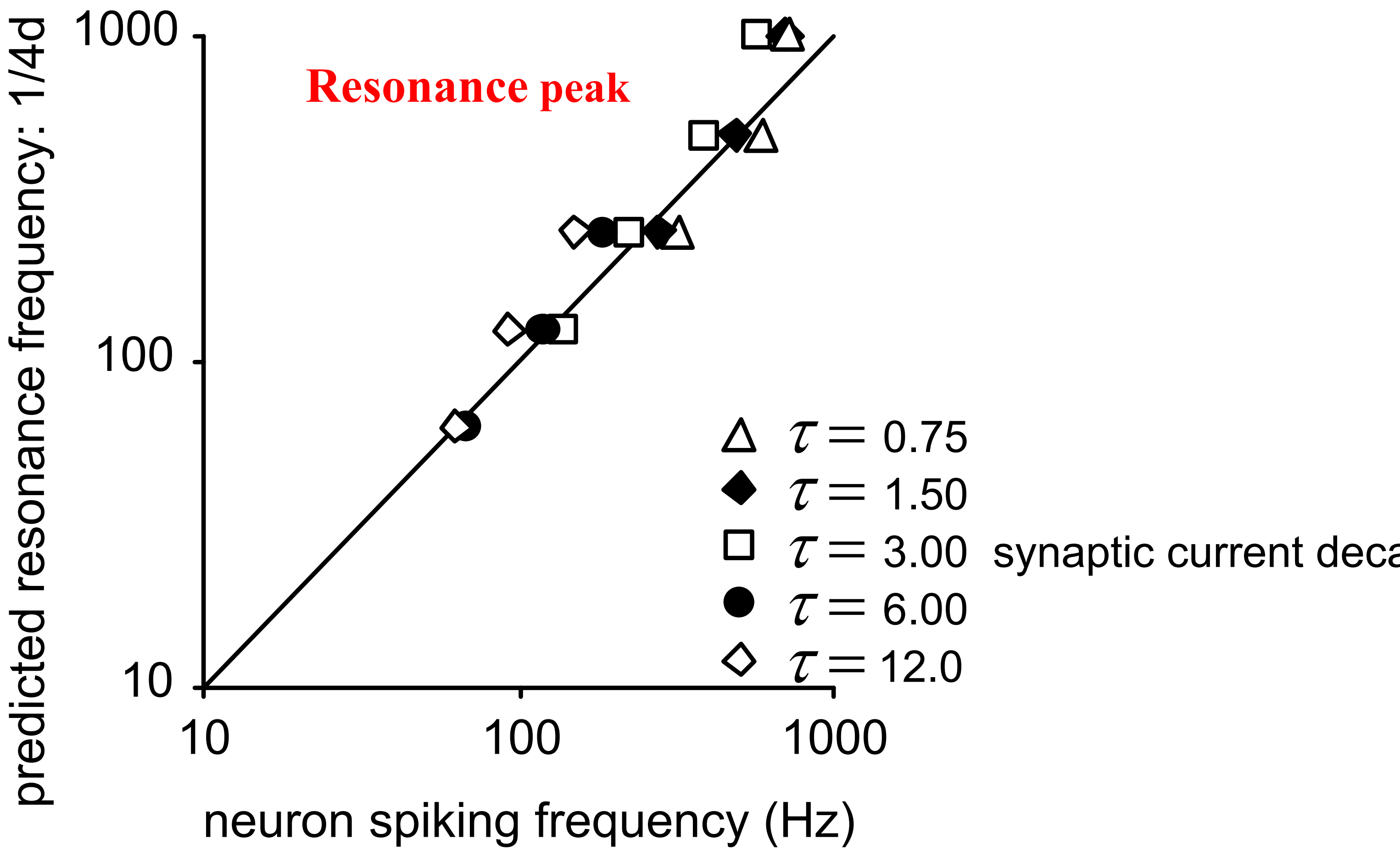
Mechanisms of oscillation with recurrent inhibitio

Synaptic delay sets the resonant frequency (1D network):

→ *f=1/(4d)*

→ Similar relation in networks with slowly firing neurons (Brunel and Wang, 2003).

→ Synaptic current decay has weak effect, but for each delay there is an optimal decay.



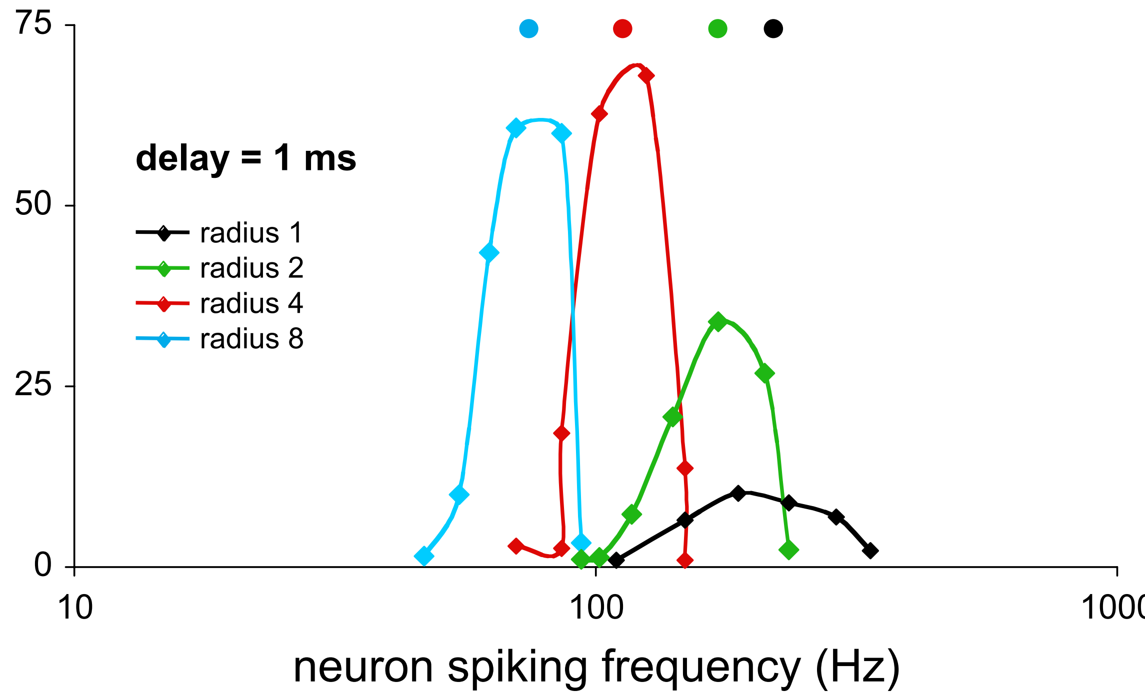
Mechanisms of oscillation with recurrent inhibitio

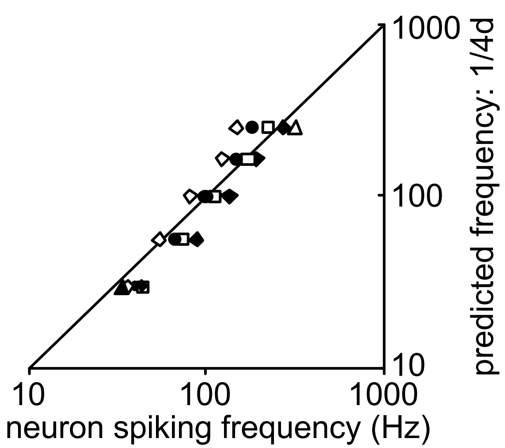
Improved resonance with long range connections (1D network):

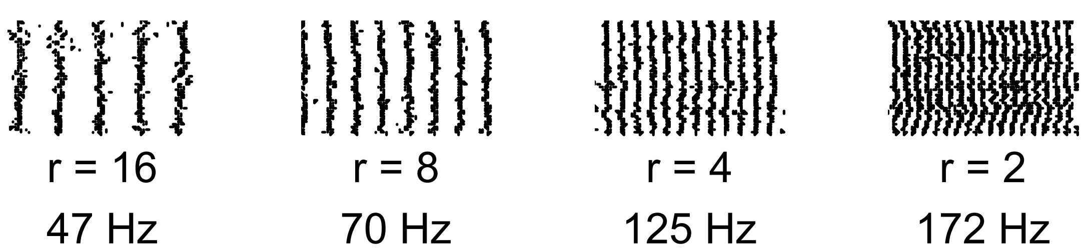
→ Resonance is now determined by mean delay of inhibition for each radius *r*:
gamma oscillation possible for r > 6 with realistic short synaptic decay time constants.

→ Power ↑↑ as *r* ↑.

→ Peak width ↓ as *r* ↑.





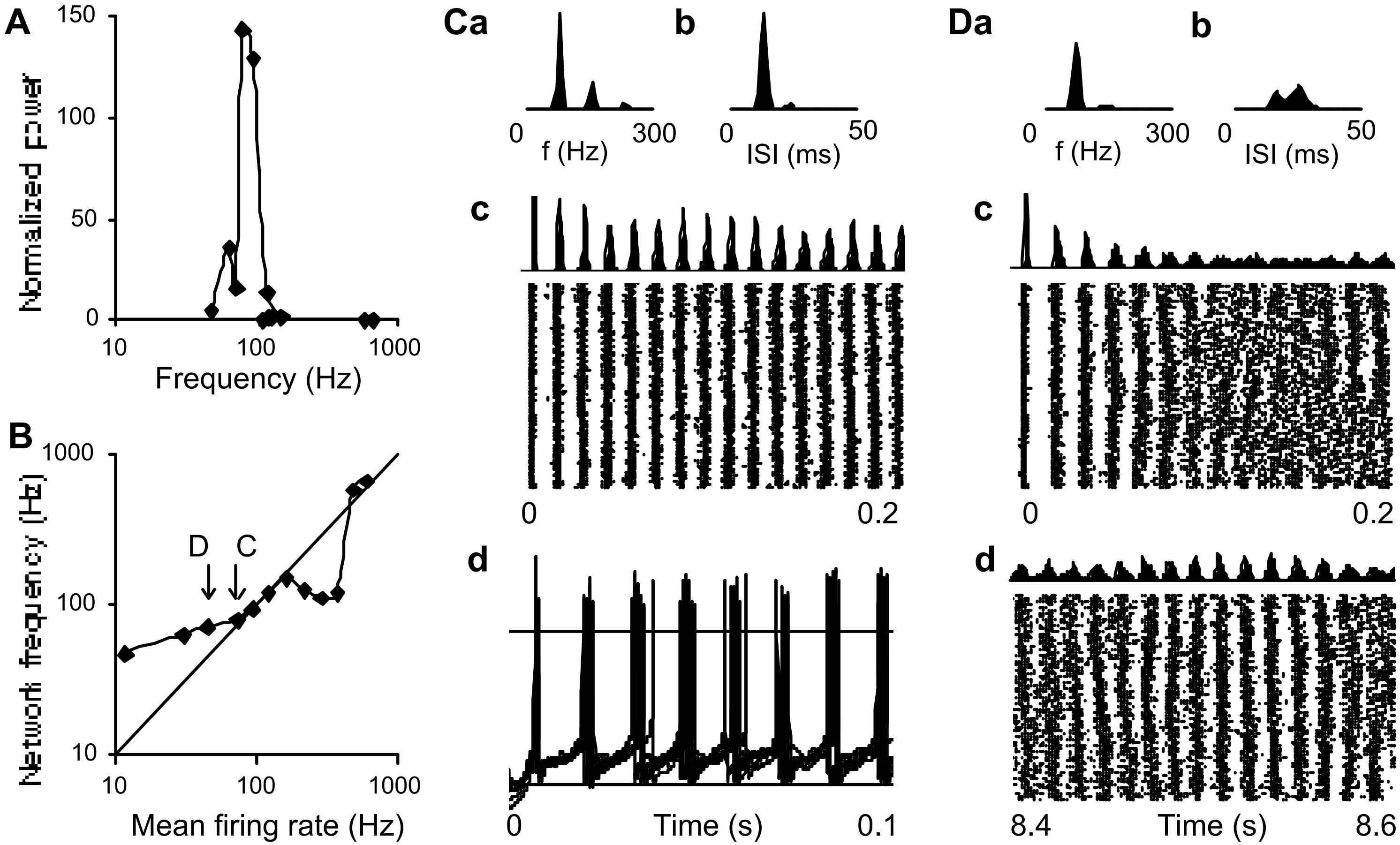


Mechanisms of oscillation with recurrent inhibitio

Resonance in 2D networks:

→ Same relationship between mean delay and resonance provided the connection probability between two neurons, or the connection weight, tapers off with distanc

→ Oscillations at frequencies close to f_R are generated over broad range of firing rate

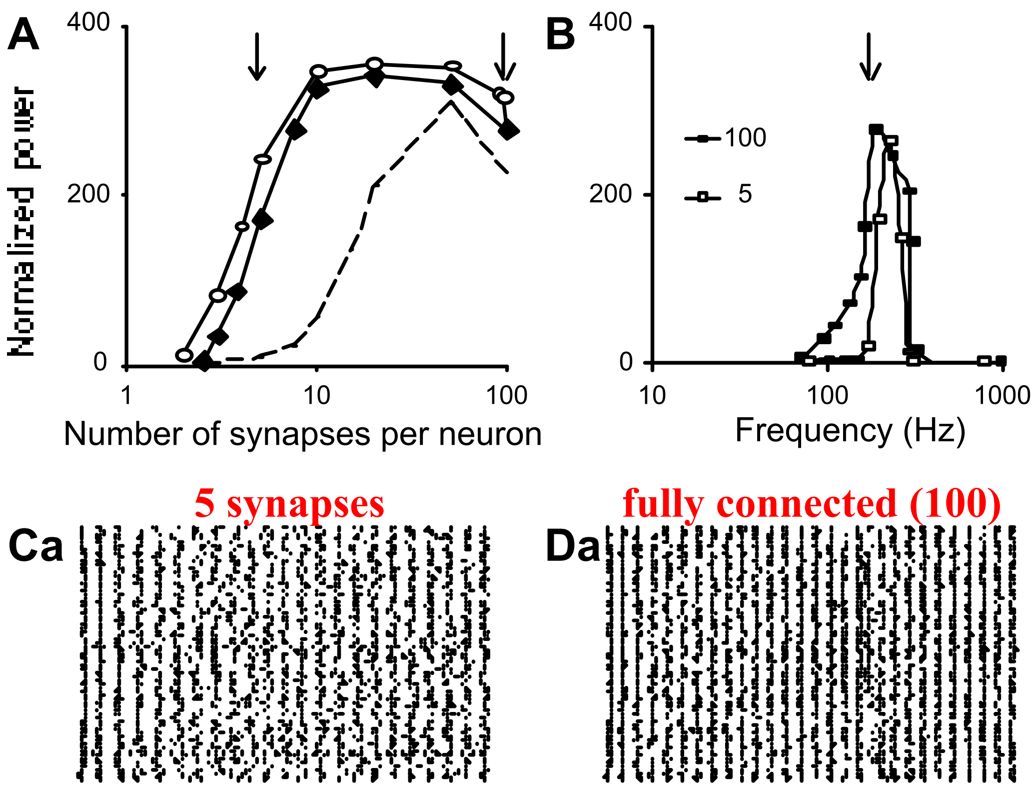


Maex and De Schutter *J. Neuroscience* 23: 10503-10514 (2003)

Mechanisms of oscillation with recurrent inhibitio

Resonance in networks with sparse, asymmetrical connections:

→ A non-topographic network with a mean number of five synapses per neuron produces at resonance a power close to that of the fully connected network.

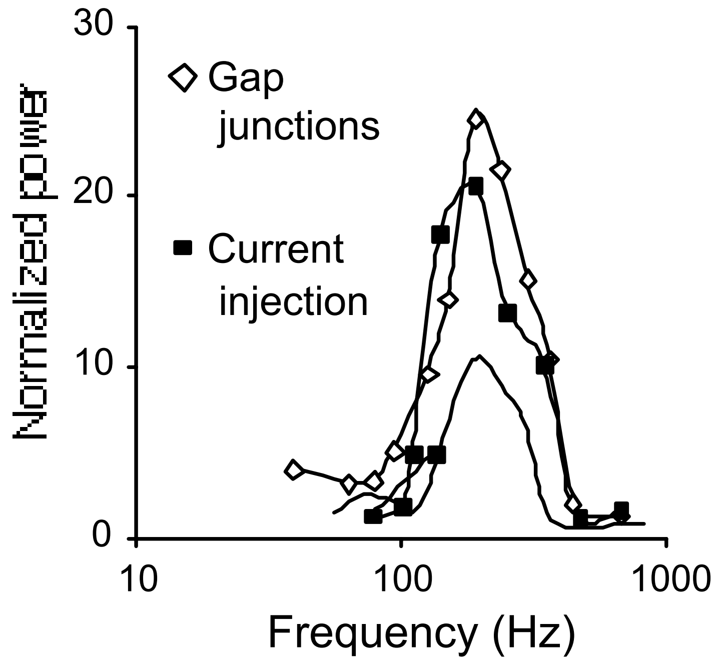


Maex and De Schutter *J. Neuroscience* 23: 10503-10514 (2003)

Mechanisms of oscillation with recurrent inhibitio

Modulating effects:

→ Gap junctions increase oscillation power without changing resonance frequency.
→ Noise and heterogeneity decrease oscillation power.
→ The resonance phenomenon is very robust provided synaptic delays are present (⇔ Wang and Buzsáki , 1996 which did not have delays).



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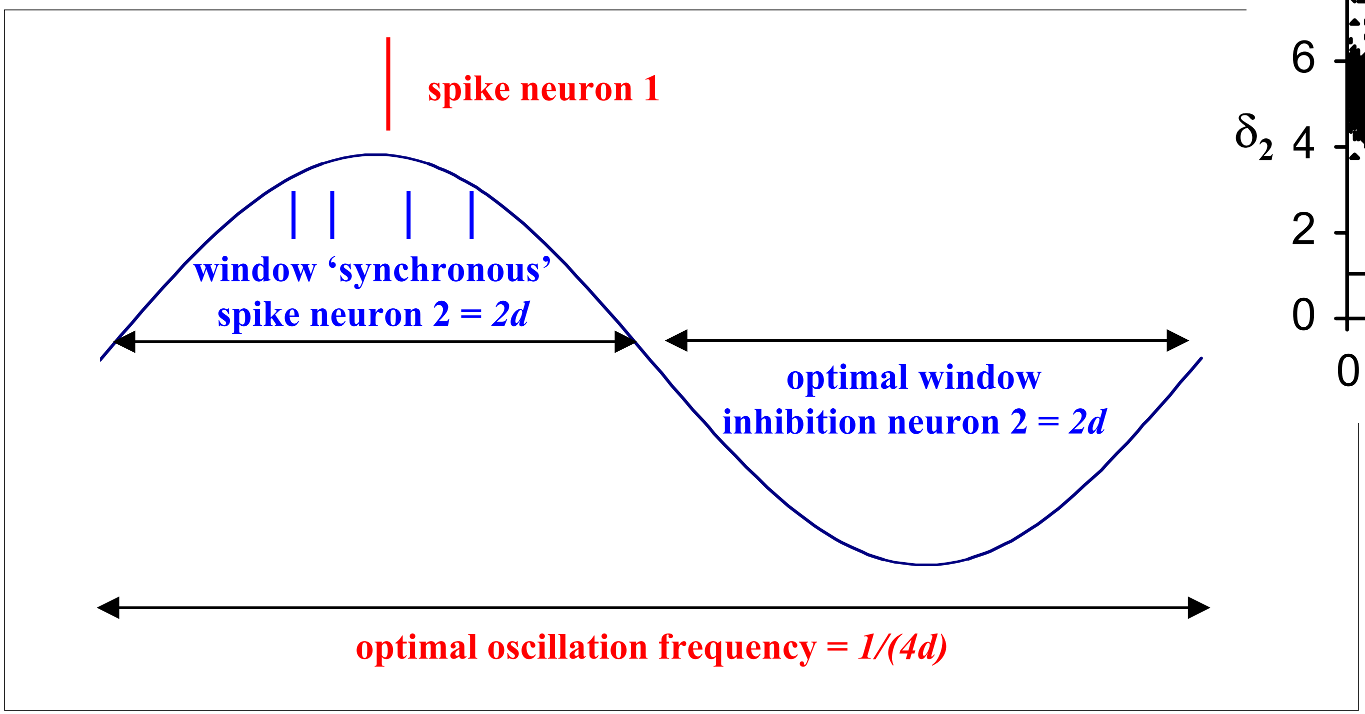
Mechanisms of oscillation with recurrent inhibitio

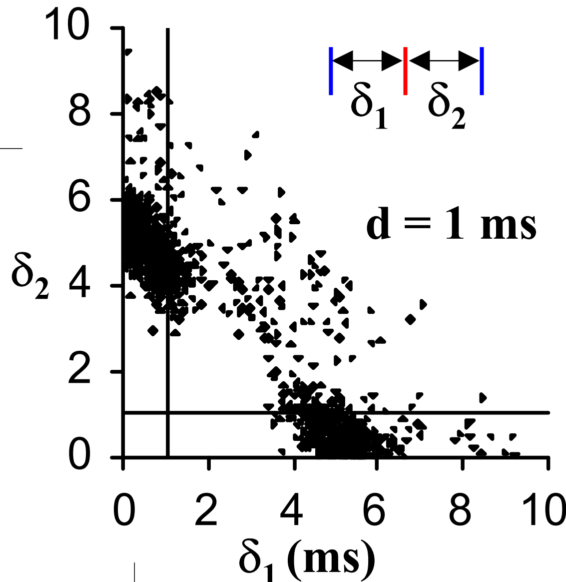
Reason for $f = 1 / (4d)$ relation:

→ Firing of postsynaptic neuron is highest in time window [-*d*, *d*]: otherwise IPSP will coincide with expected spike.

→ The sine wave best covering this *2d* time window has a *4d* period.

→ *f=1/(4d)* is well known property of physical systems (e.g. acoustic resonance).





Resonant oscillations : conclusions

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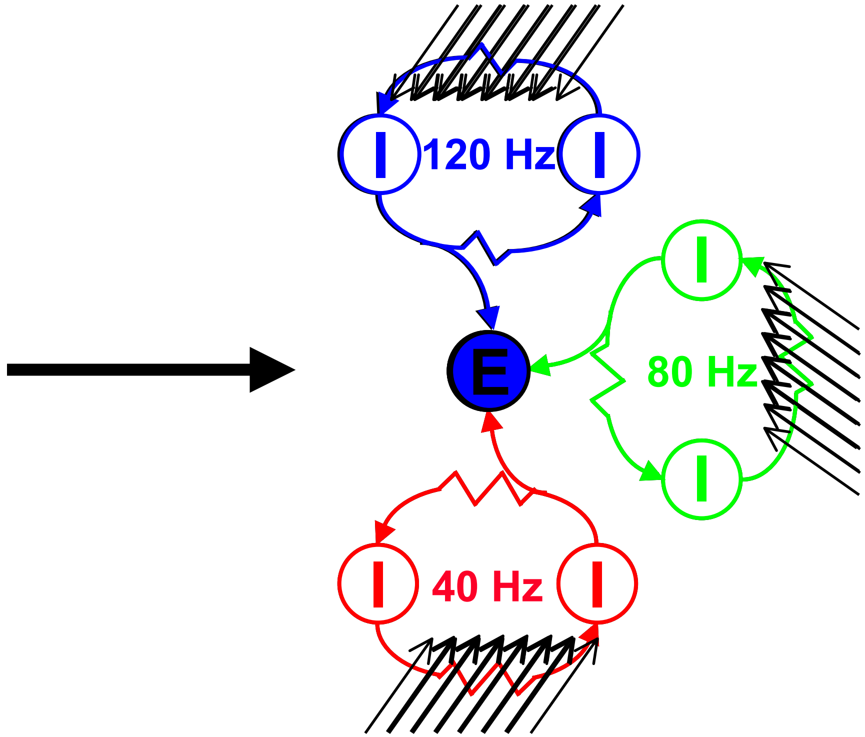
  - → resonance enhanced by long range connections.
  - → may be further enhanced/modulated by intrinsic cellular resonant properties.
  - → this resonance mechanism may operate in normal cerebellum but also during gamma oscillations in cortex and hippocampus.

Resonant synchronization with recurrent inhibitio

Axonal + synaptic delays between interneurons set resonant frequency:

Multiple classes of inhibitory interneurons with typical axonal arbors:

→ Each class has its own resonant frequency based on mean axonal delay (connectivity).
→ Selection by excitatory drive of class with right resonance sets overall network frequency.
→ Not selected inhibitory neurons do not synchronize and provide background inhibition.



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  - → also applies to $I_1 \rightarrow E_1 \rightarrow I_2 \rightarrow E_2 \rightarrow I_1$ instead of $I_1 \rightarrow I_2 \rightarrow I_1$ networks.