

Cerebellar oscillations:

Anesthetized rats

Transgenic animals

Recurrent model

Review of literature: γ

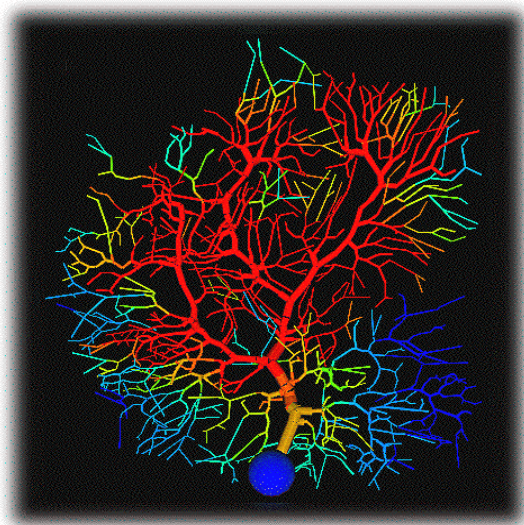
Network resonance

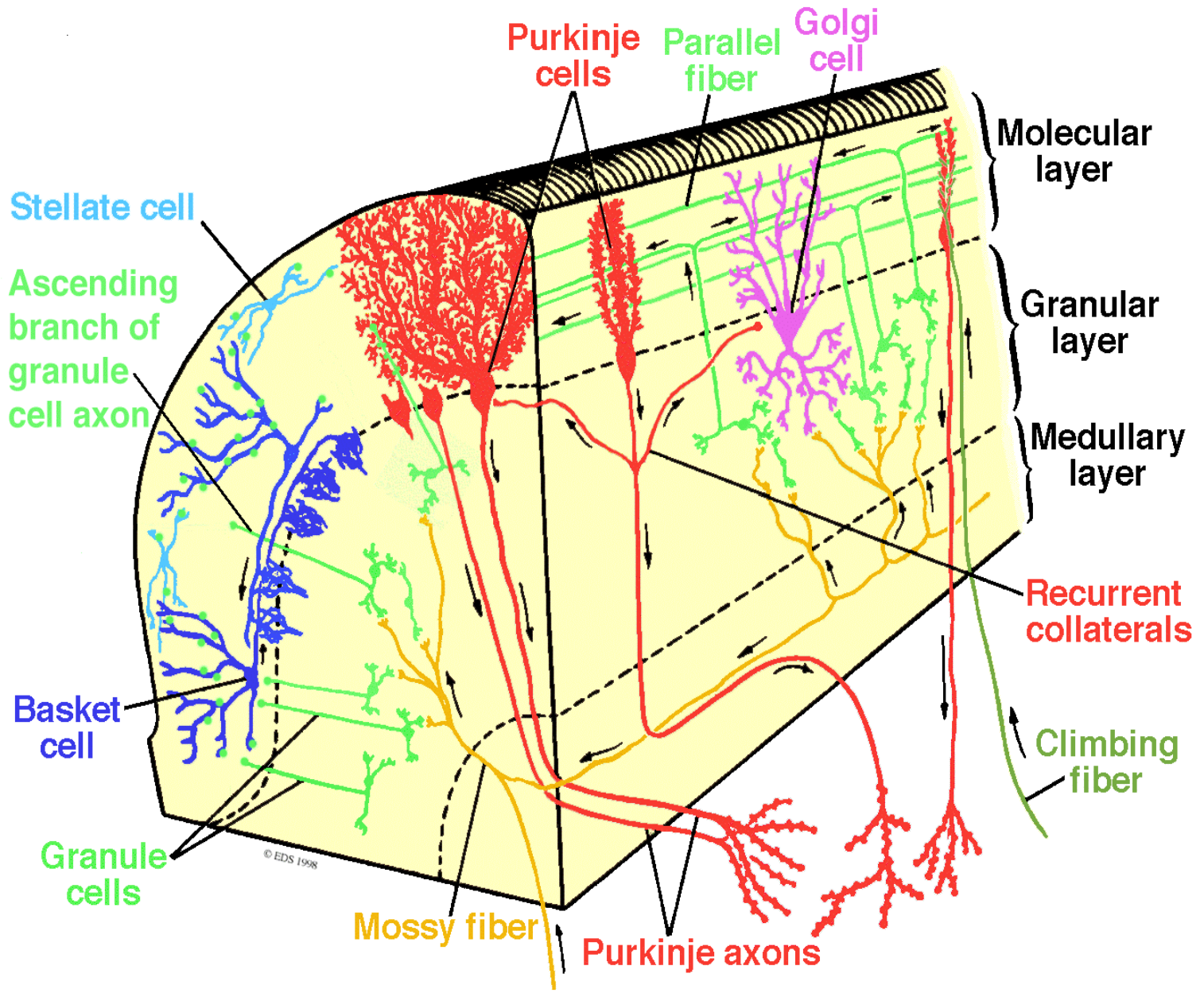
Life simulations

Resonance frequency

Conclusion

Resonant synchronization of heterogeneous inhibitory networks

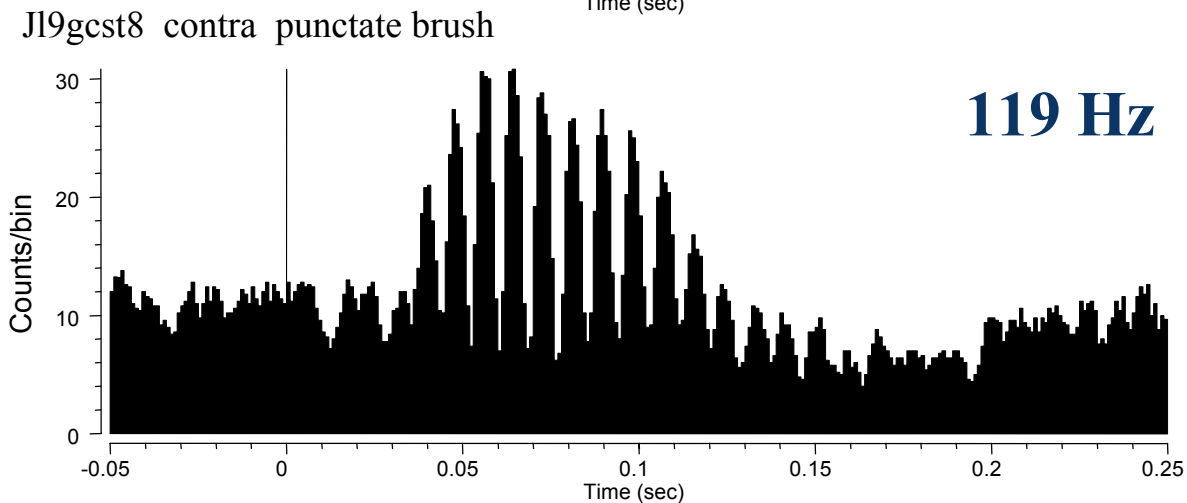
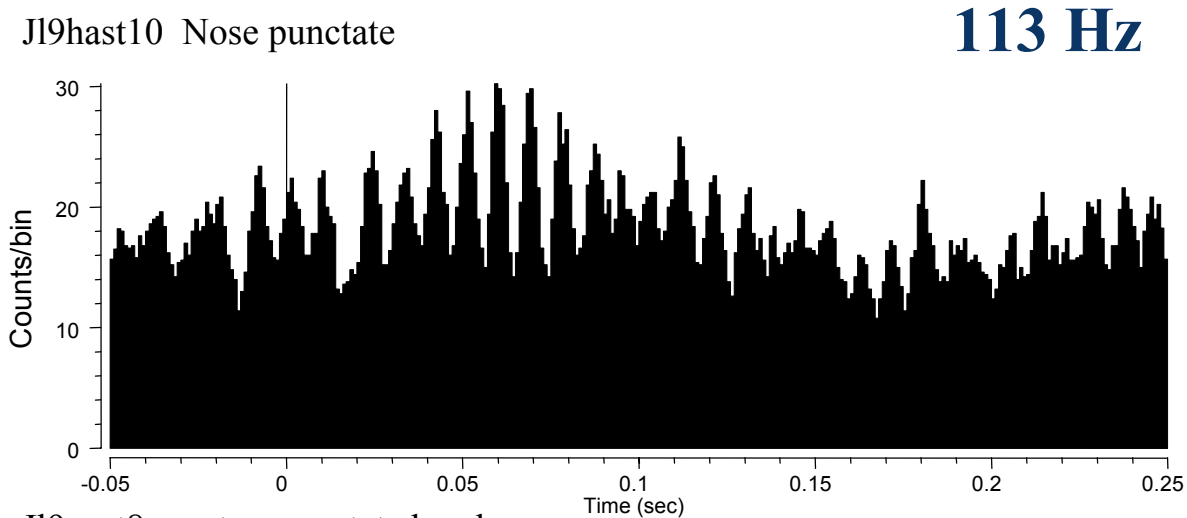
E. De Schutter with:**Reinoud Maex** (modeling)**Antonia Volny-Luraghi** (experiments)**Hugo Cornelis and Mike Wijnants** (software and equipment)**Theoretical Neurobiology, University of Antwerp,
Belgium****<http://www.bbf.uia.ac.be>**



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

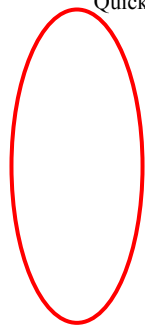
Oscillations in transgenic animals:

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 Hz)
- 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.



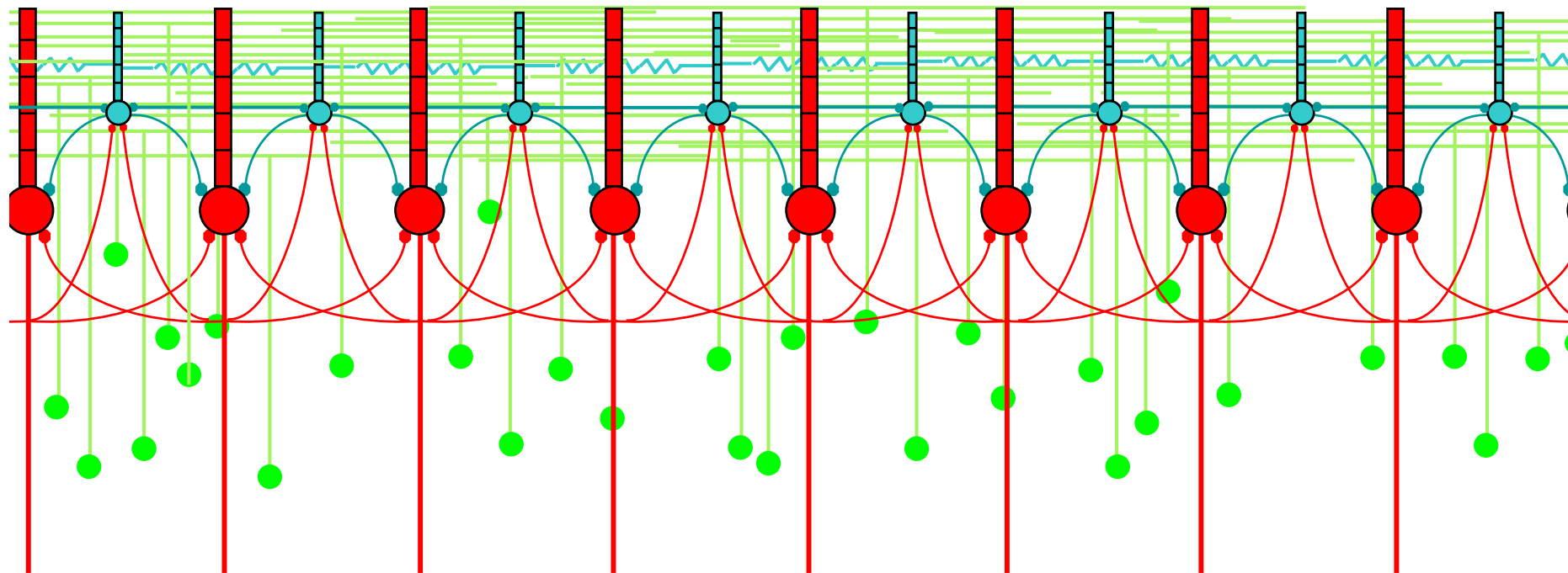
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Oscillations in transgenic animals: model

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 resonance
- 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:

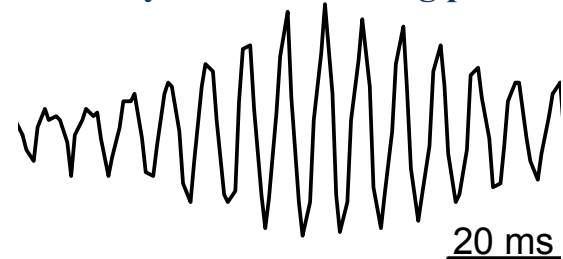


recurrent inhibition
recurrent inhibition + gap junctions
no recurrent inhibition

oscillations not synchronized in sagittal axis:



oscillations synchronized along parallel fiber beam



Firing Frequency (Hz)

Cerebellar oscillations : conclusions

● Fast oscillations of Purkinje cell simple spike firing:

- stimulus evoked in anesthetized rats in ~5% of recordings.
- transgenic animal: spontaneous fast oscillations synchronized along parallel fiber axis.
- LFPO amplitudes vary over time (spindles).
- blockade of inhibition or gap junctions decreases LFPOs.

● Model of fast cerebellar oscillations:

- recurrent inhibitory network of Purkinje cells (recurrent collaterals) + ML interneurons
- or recurrent inhibitory network of ML interneurons driving Purkinje cells.

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- **discovery of resonant frequency.**

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- discovery of resonant frequency.

→ 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

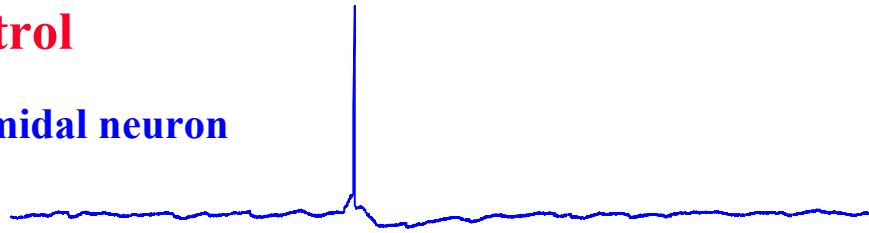
Freeman

Jefferys et al. *TINS* 1996

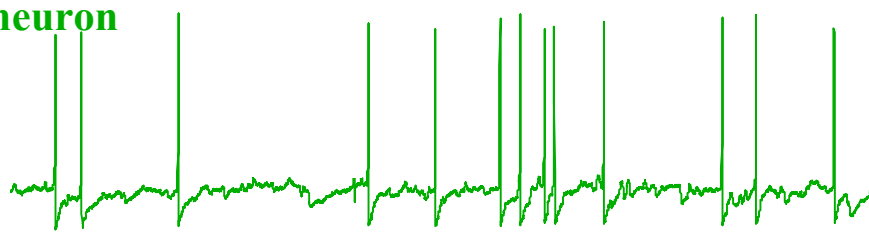
Kainate evokes gamma frequency oscillation in hippocampus

Control

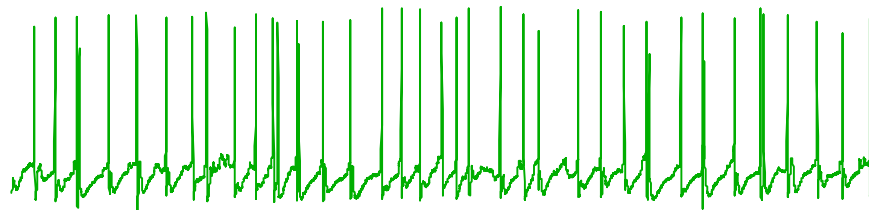
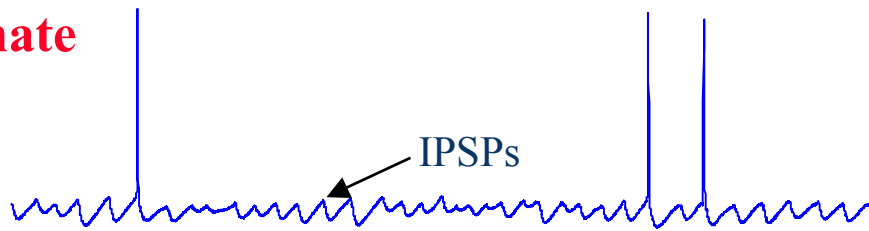
Pyramidal neuron



Interneuron

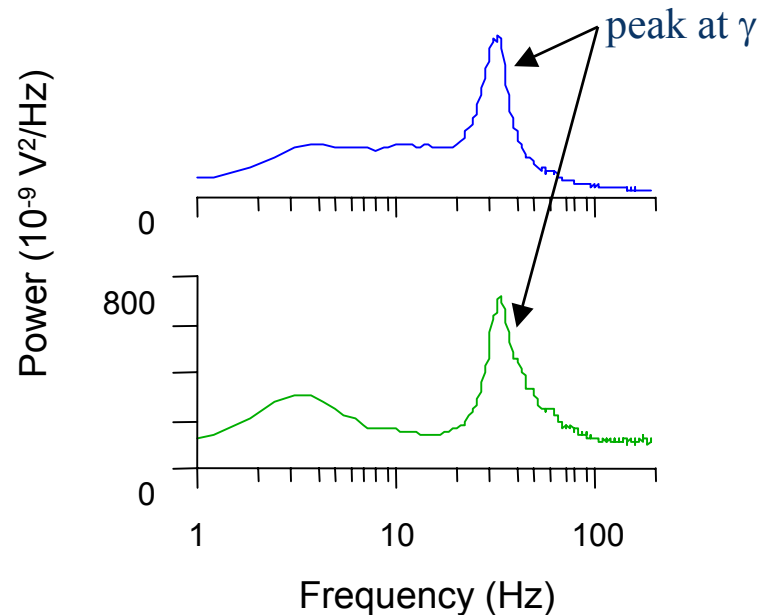
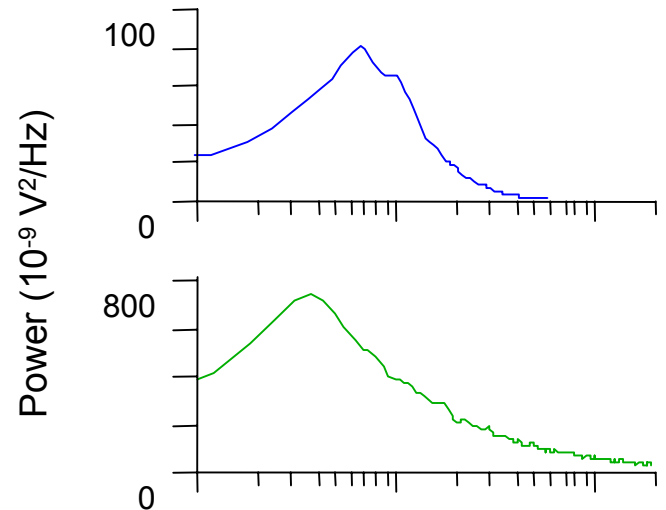


Kainate



20 mV

Buhl et al.



How can recurrent inhibition synchronize?

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

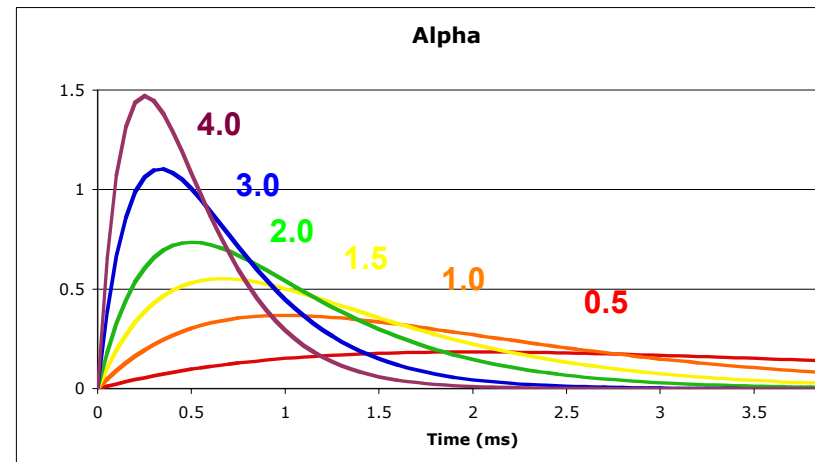
Pair of reciprocal inhibitory integrate and fire neurons coupled with α function

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

phase

— stable
- - - unstable

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



α

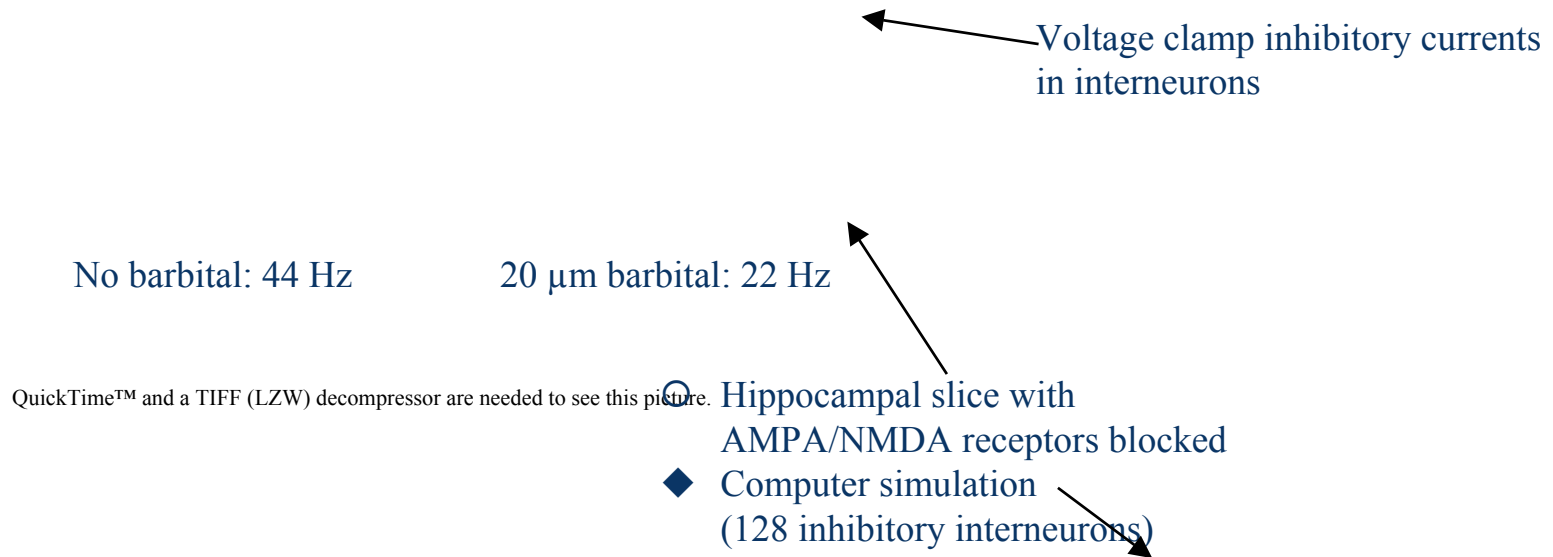
→ focus on shape of synaptic current

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



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.

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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).

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

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— autocorrelation $e - i$
 — cross correlation $e - i$

Traub & Bibbig *J. Neurosci.* 2000

Mechanisms of oscillation with recurrent inhibition

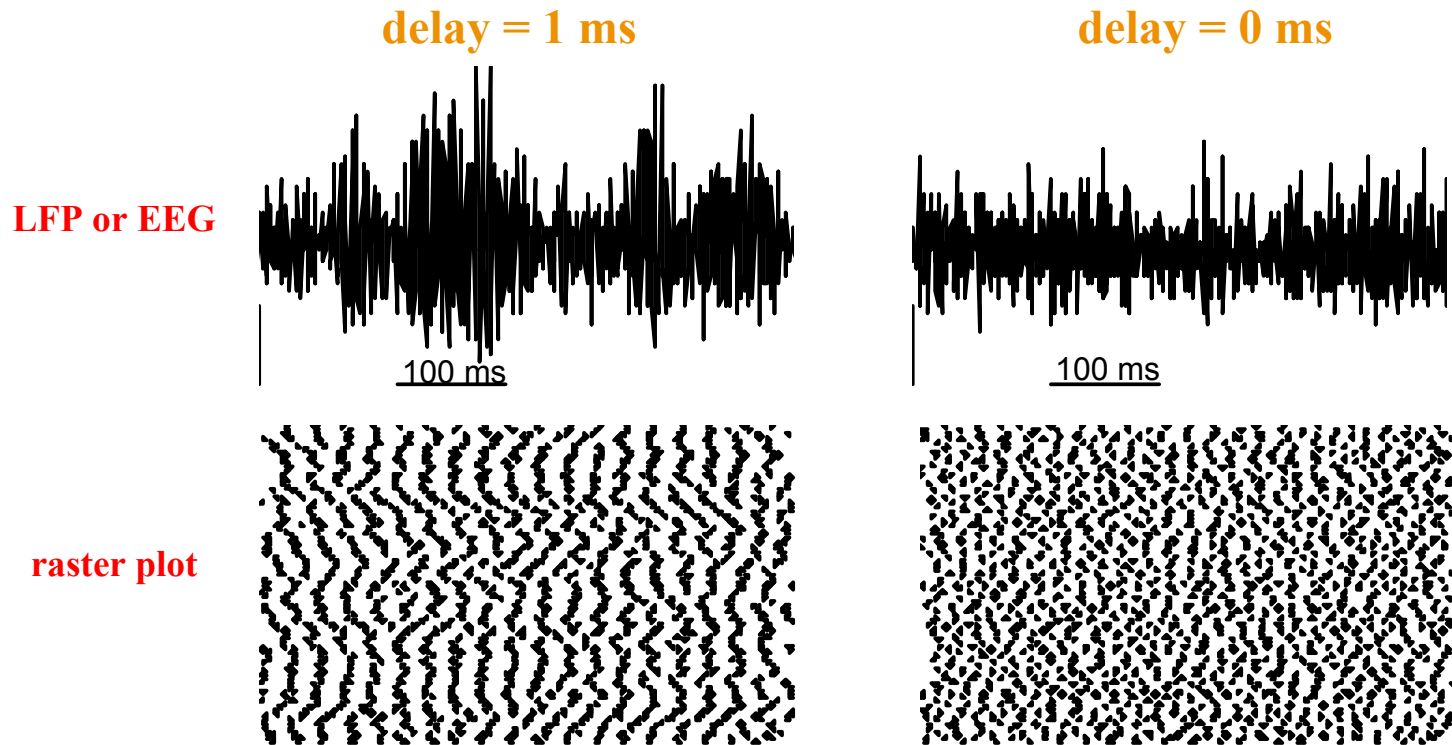
Recurrent inhibition with a delay introduces a resonant frequency:

GENESIS simulations #1

Mechanisms of oscillation with recurrent inhibition

Recurrent inhibition with a delay introduces a resonant frequency:

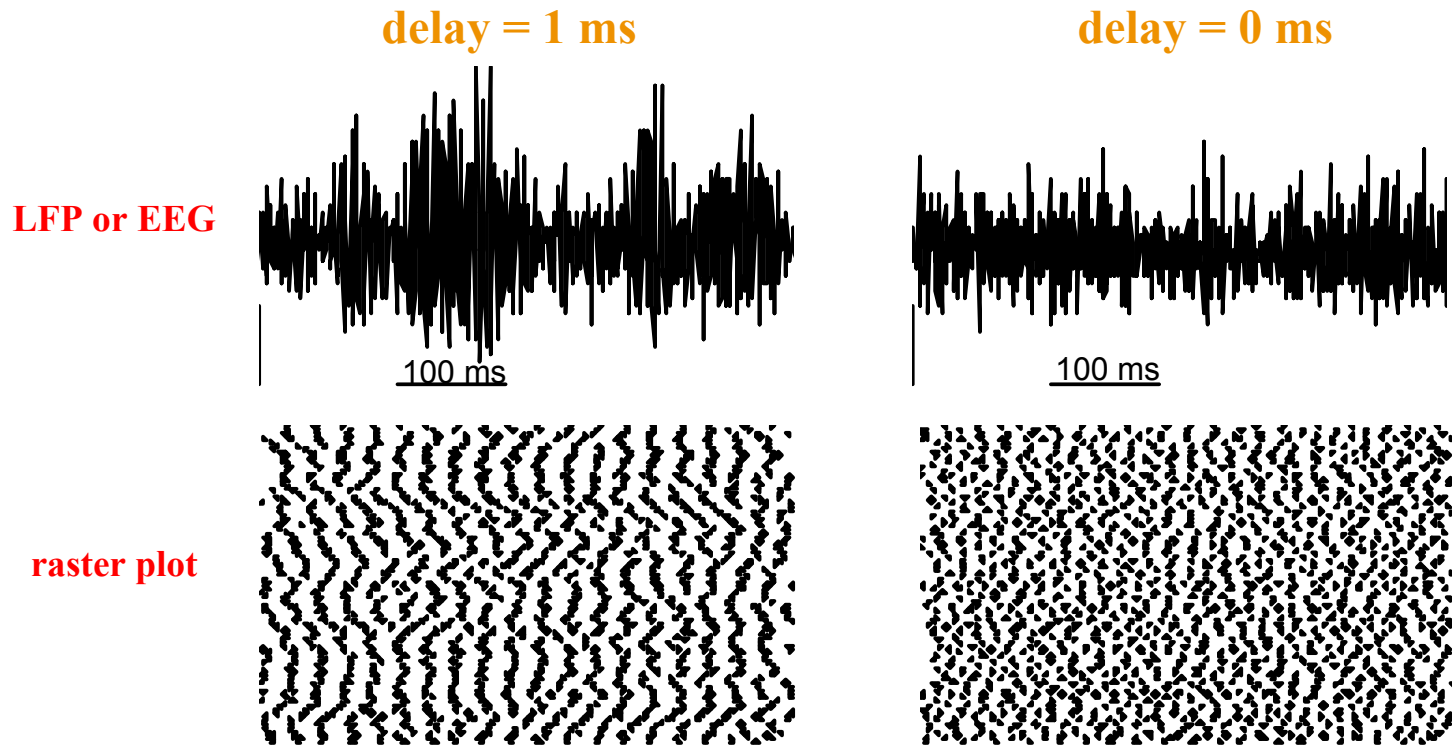
→ Delay (axonal + synaptic) is essential.



Mechanisms of oscillation with recurrent inhibition

Recurrent inhibition with a delay introduces a resonant frequency:

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



GENESIS simulations #2

Mechanisms of oscillation with recurrent inhibition

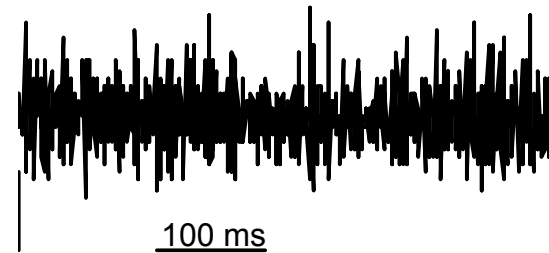
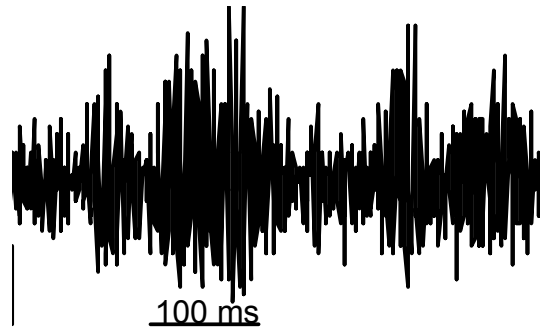
Recurrent inhibition with a delay introduces a resonant frequency:

- Delay (axonal + synaptic) is essential (van Vreeswijk et al., 1994; Ernst et al., 1995).
- Neurons must fire (181 ± 10 Hz) close to frequency of oscillation (187 Hz) = resonance.

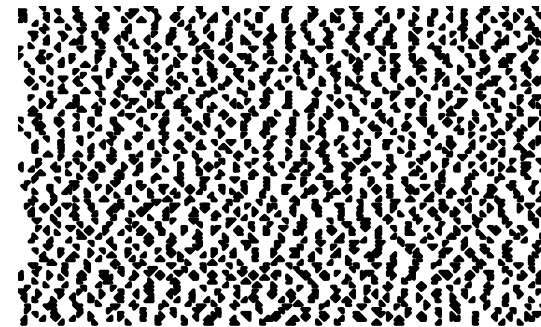
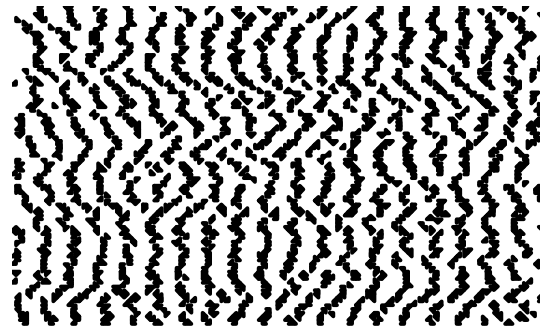
delay = 1 ms

delay = 0 ms

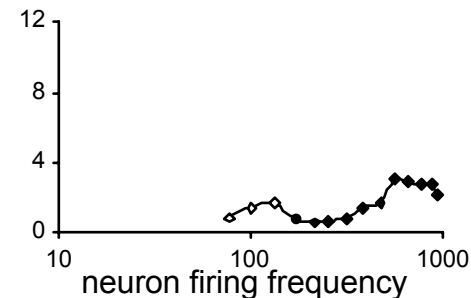
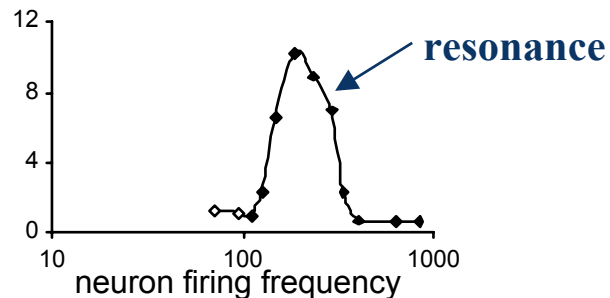
LFP or EEG



raster plot



LFP power
for varying
spiking frequencies

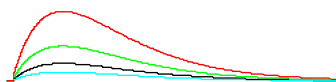
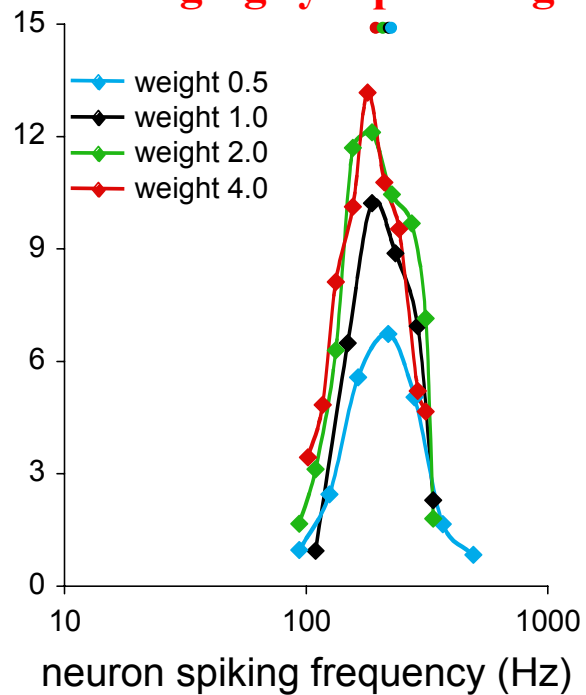


Mechanisms of oscillation with recurrent inhibition

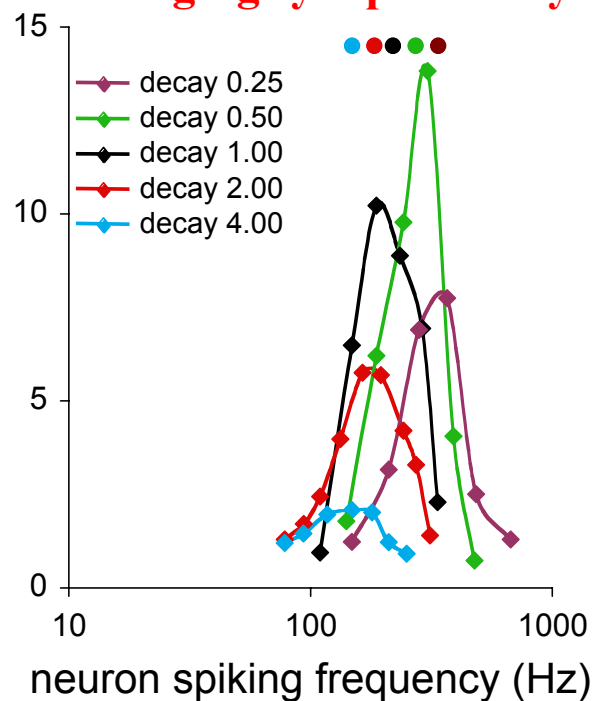
Synaptic delay sets the resonant frequency (1D network):

- 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 (\Leftrightarrow Wittington et al., 1995; Traub et al., 1996; Wang and Buzsáki, 1996).

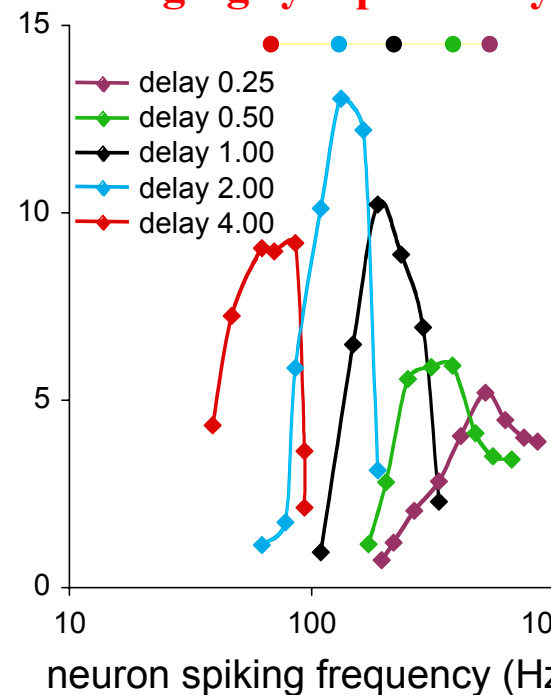
Changing synaptic weight



Changing synaptic decay



Changing synaptic delay



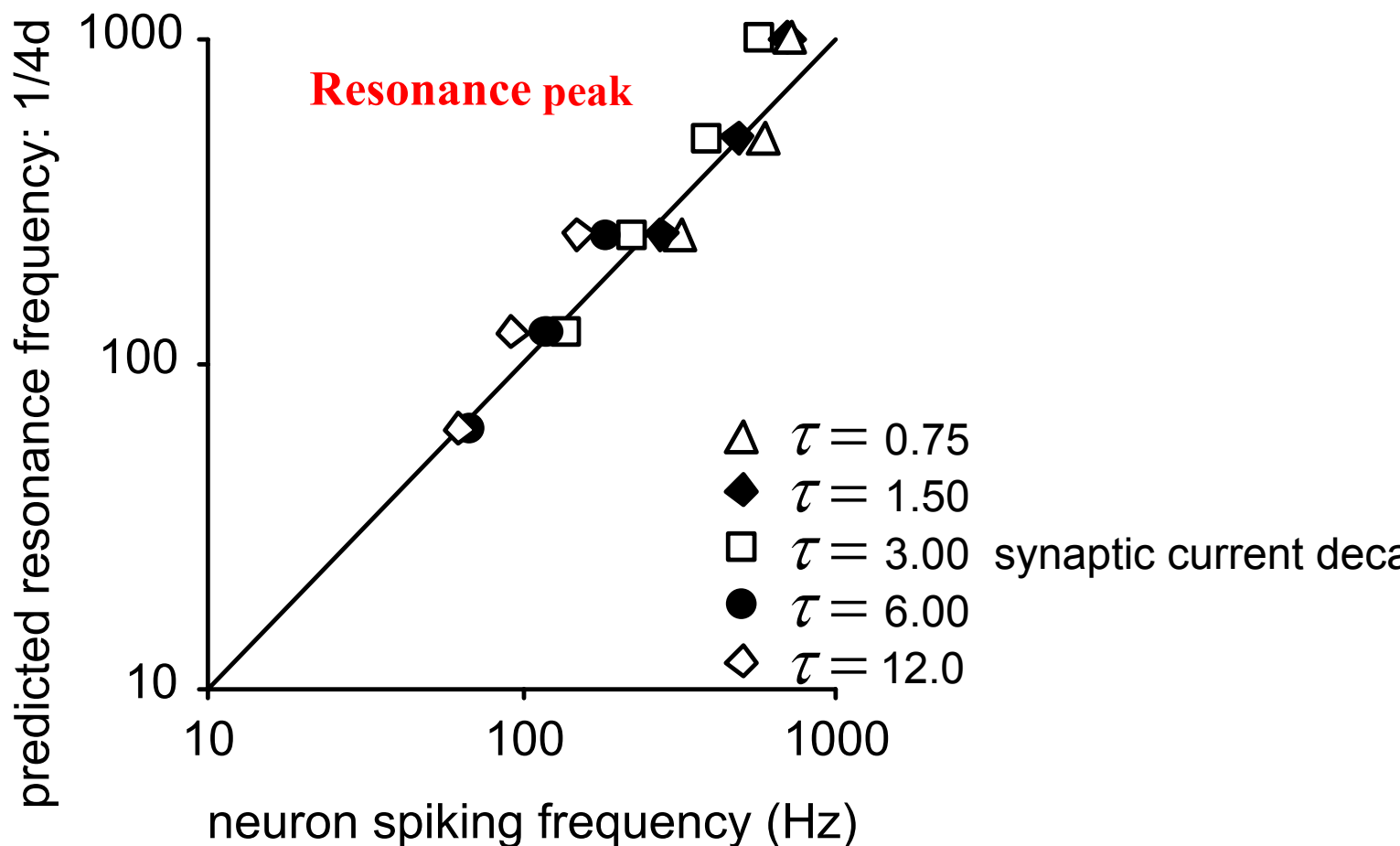
Mechanisms of oscillation with recurrent inhibition

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 inhibition

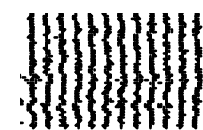
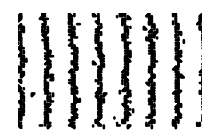
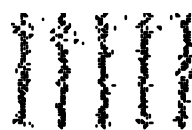
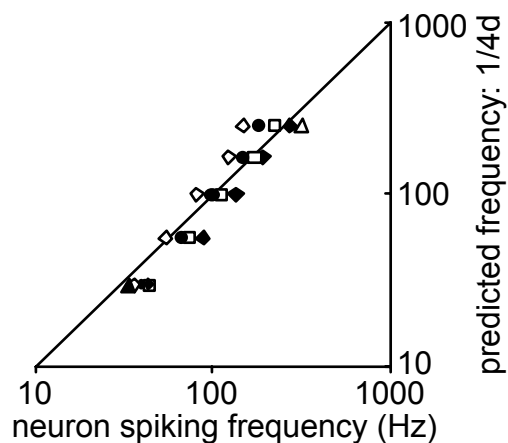
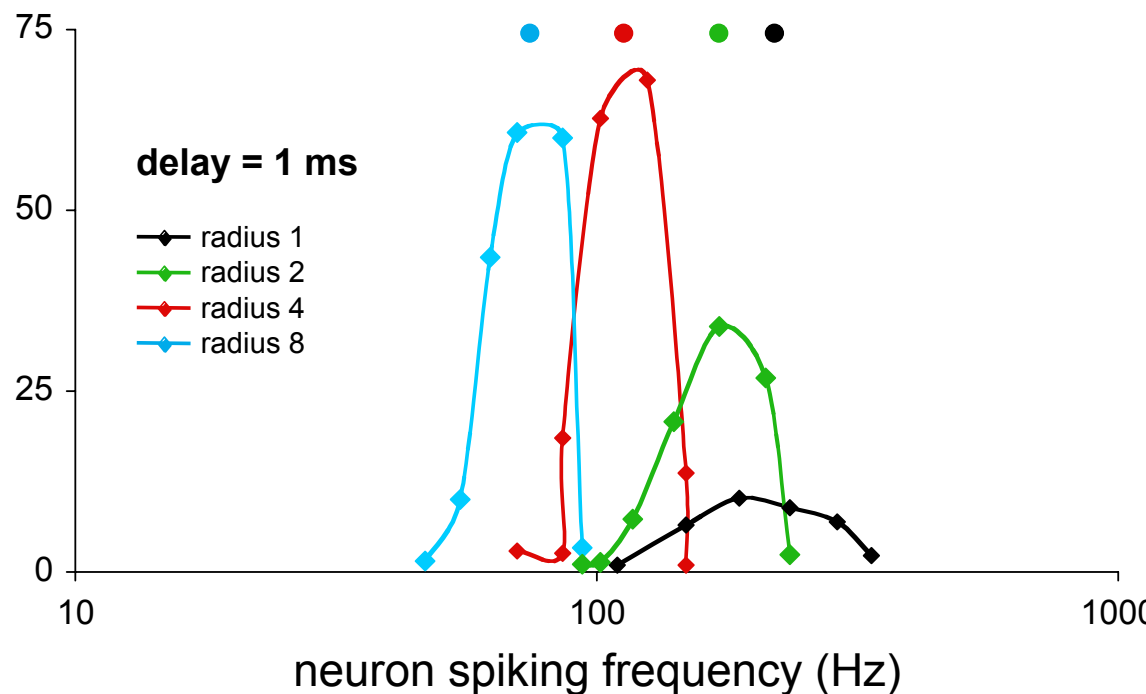
Improved resonance with long range connections (1D network):

→ 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 $\uparrow\uparrow$ as $r \uparrow$.

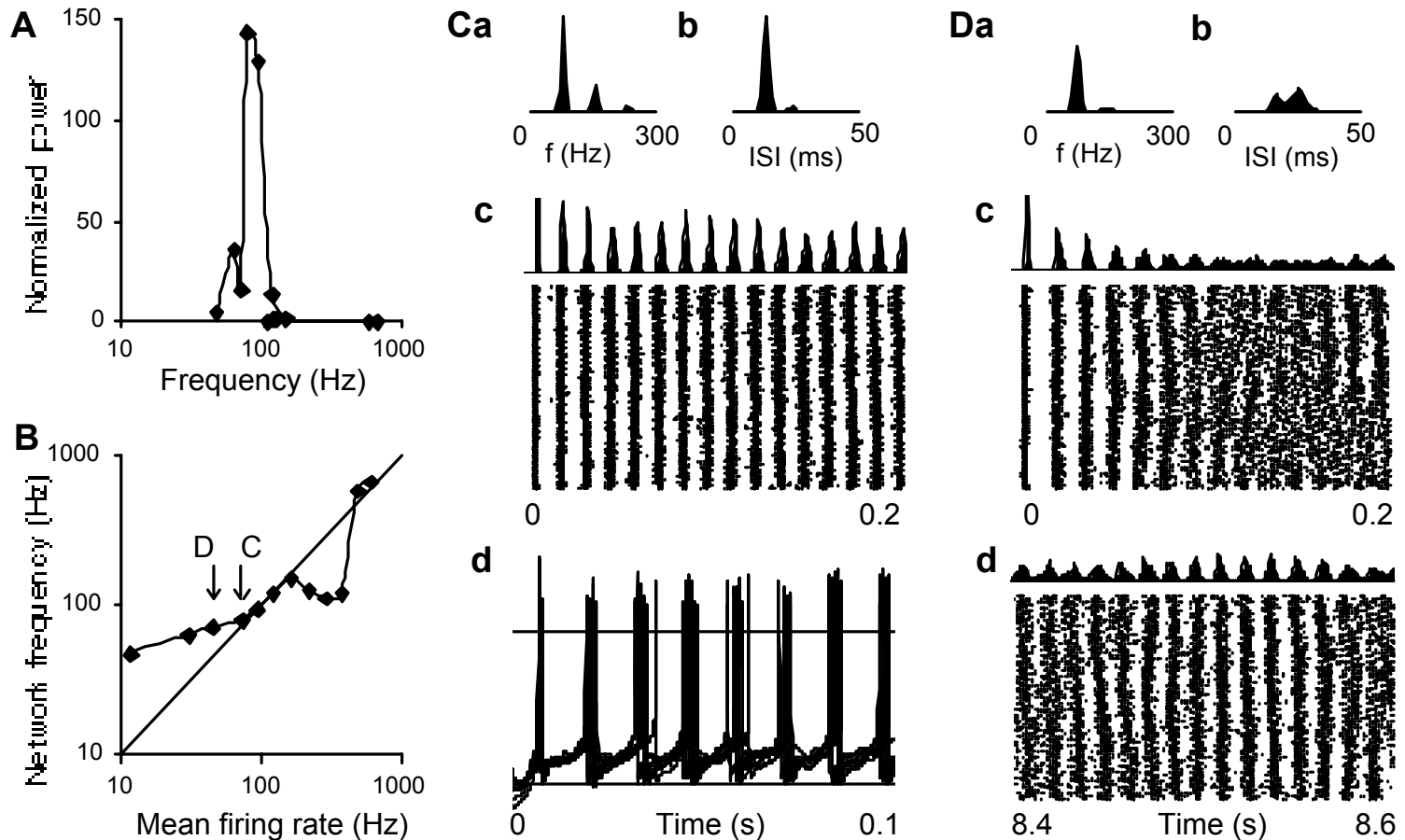
→ Peak width \downarrow as $r \uparrow$.



Mechanisms of oscillation with recurrent inhibition

Resonance in 2D networks:

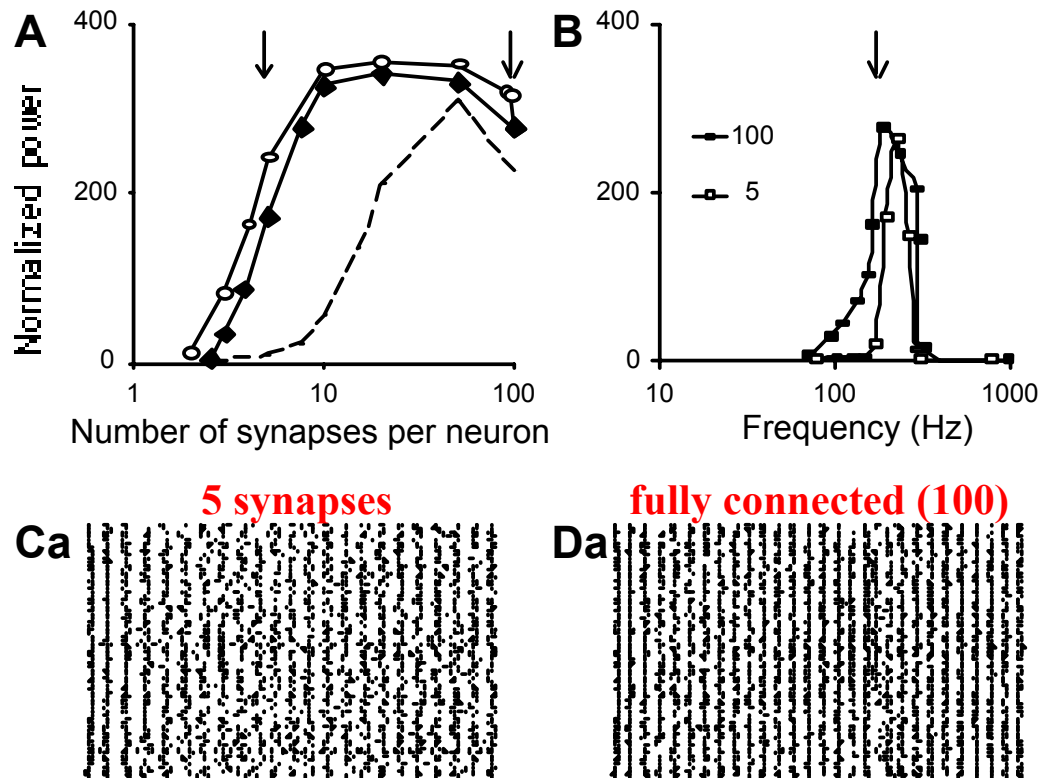
- Same relationship between mean delay and resonance provided the connection probability between two neurons, or the connection weight, tapers off with distance
- Oscillations at frequencies close to f_R are generated over broad range of firing rates



Mechanisms of oscillation with recurrent inhibition

Resonance in networks with sparse, asymmetrical connections:

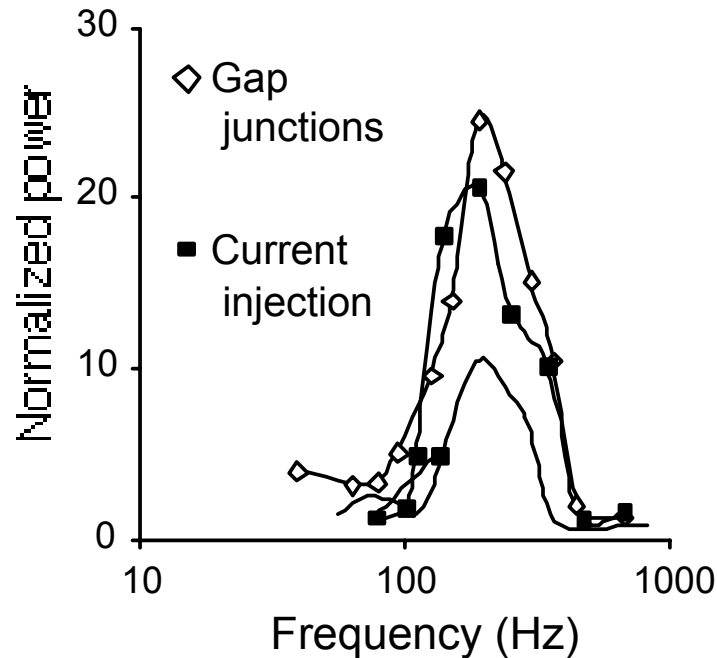
→ A non-topographic network with a mean number of five synapses per neuron produces at resonance a power close to that of the fully connected network.



Mechanisms of oscillation with recurrent inhibition

Modulating effects:

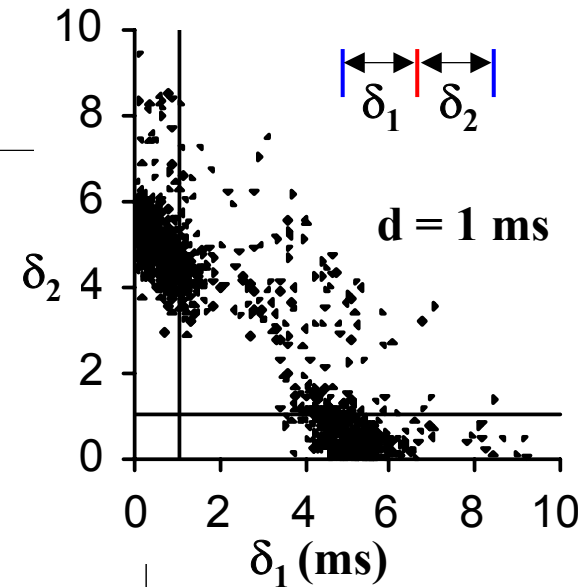
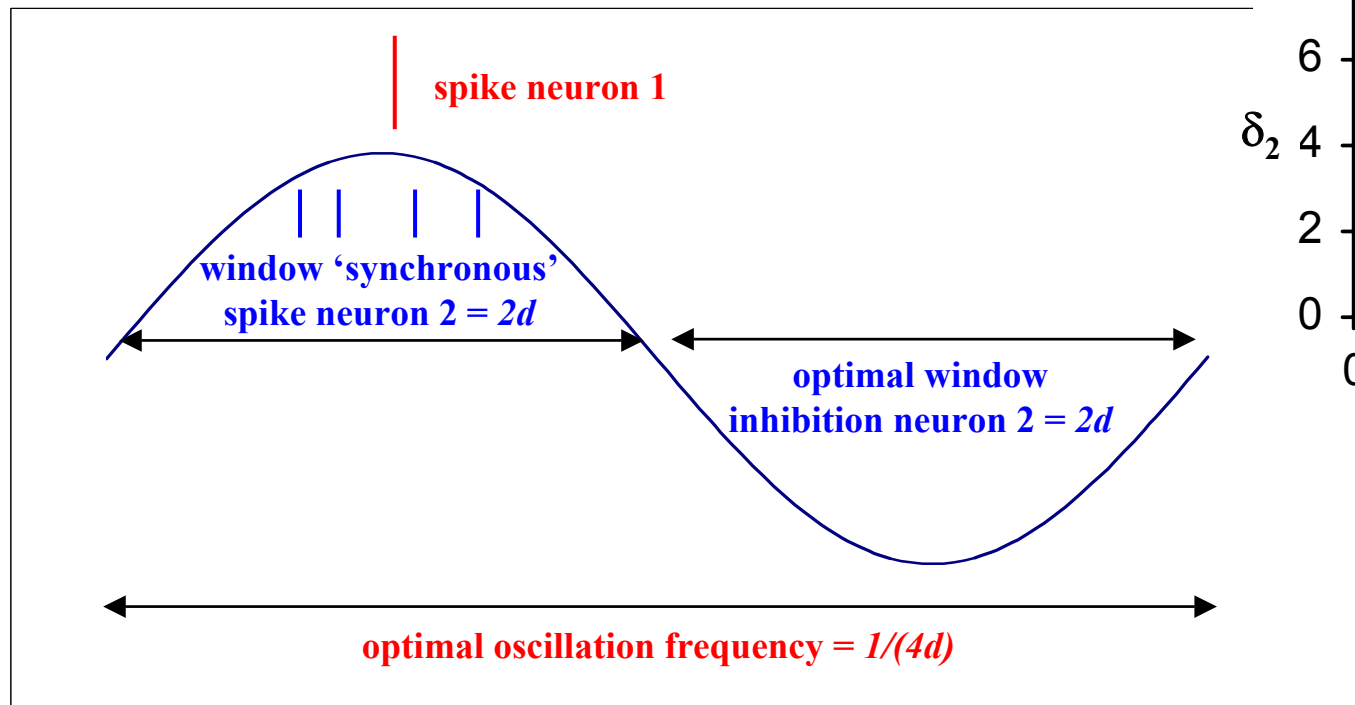
- Gap junctions increase oscillation power without changing resonance frequency.
- Noise and heterogeneity decrease oscillation power.
- The resonance phenomenon is very robust provided synaptic delays are present (⇔ Wang and Buzsáki , 1996 which did not have delays).



Mechanisms of oscillation with recurrent inhibition

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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● Resonant oscillation through recurrent inhibition: **axons are important**

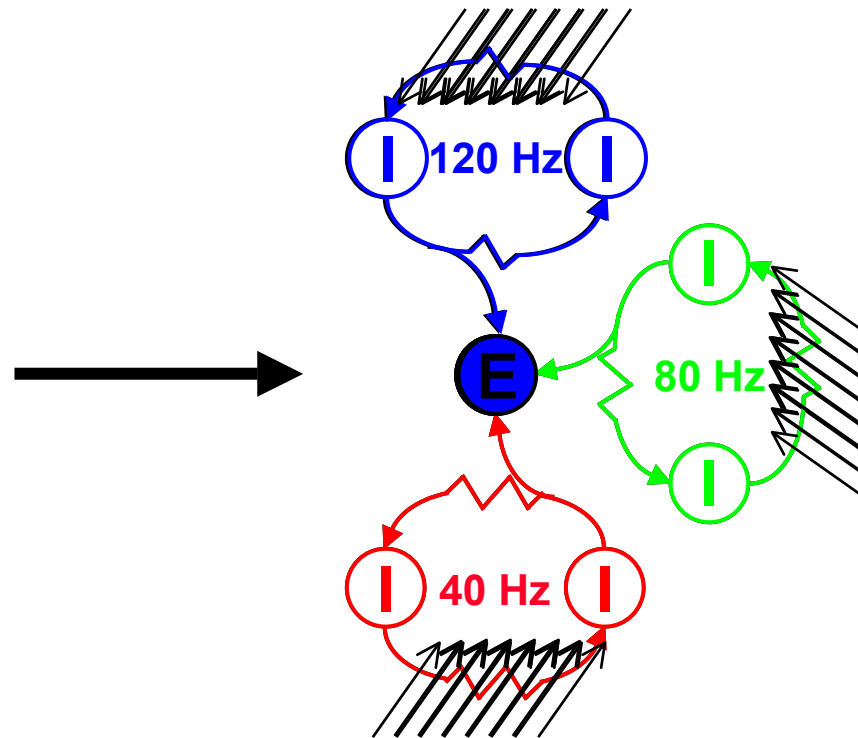
- neurons fire at rates close to the oscillation frequency.
- synaptic delay is necessary: $f=1/(4d)$ → axonal arborization may determine resonance.
- resonance enhanced by long range connections.
- may be further enhanced/modulated by intrinsic cellular resonant properties.
- **this resonance mechanism may operate in normal cerebellum but also during gamma oscillations in cortex and hippocampus.**

Resonant synchronization with recurrent inhibition

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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- **this resonance mechanism may operate in normal cerebellum but also during gamma oscillations in cortex and hippocampus.**
- **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.**