How Very Fast Oscillations may lead to Epilepsy

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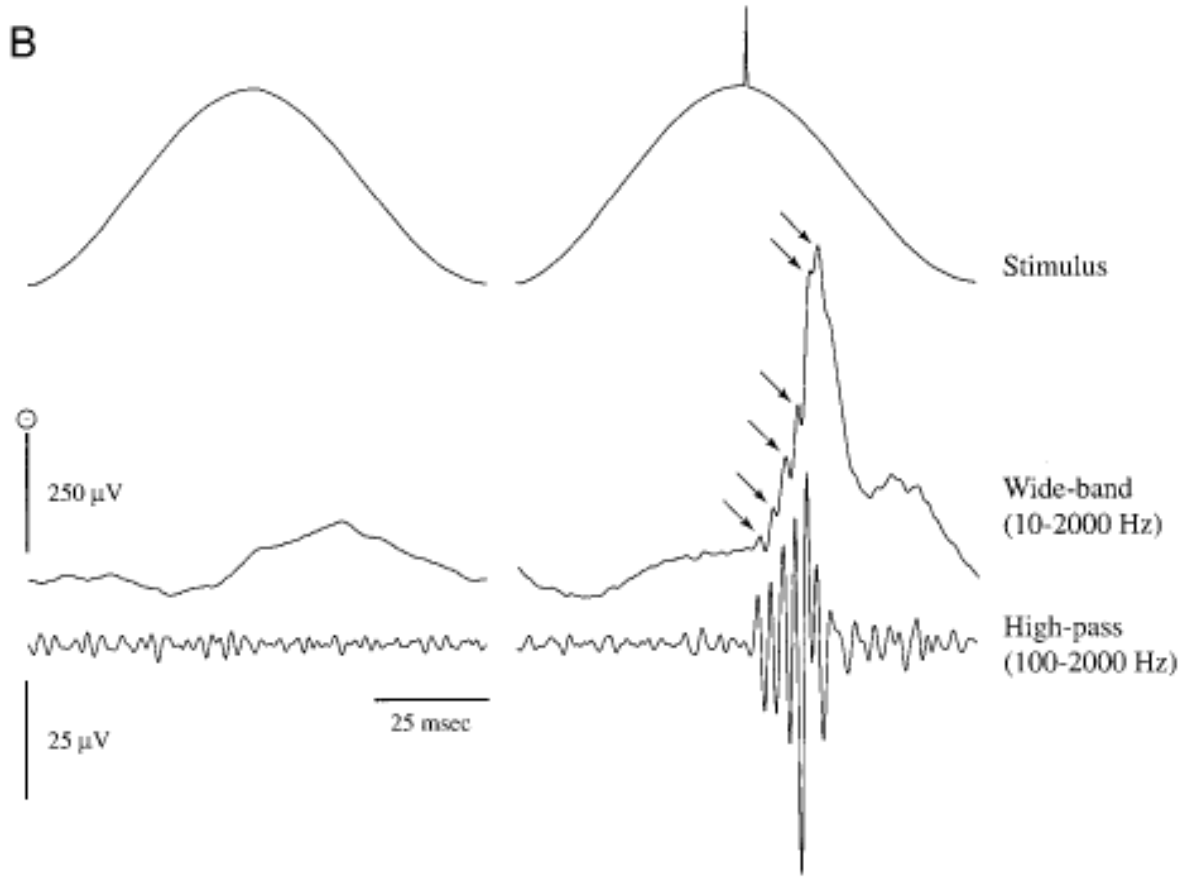
Very Fast Oscillations (VFOs, >80 Hz): normal neocortex

occur during

- cortical activations
- up-state of slow oscillations



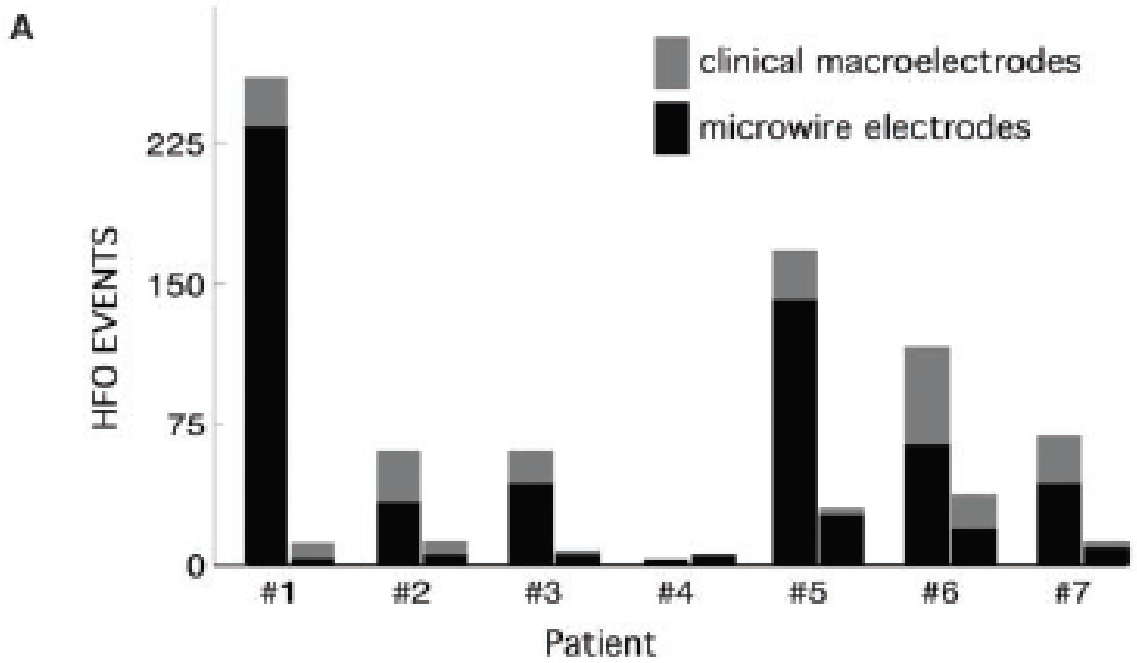
Jones et al. 1999, figure 3B

Temporal Lobe Epilepsy and VFOs

- Most common form of epilepsy
- Almost always linked with a lesion or cortical malformation
- Seizures can start around lesion or in hippocampus.
- Seizures tend to be intractable to medication.
- VFOs more widespread in seizure-onset-zone (SOZ).
- VFOs seen during seizure onset as well as during seizure.

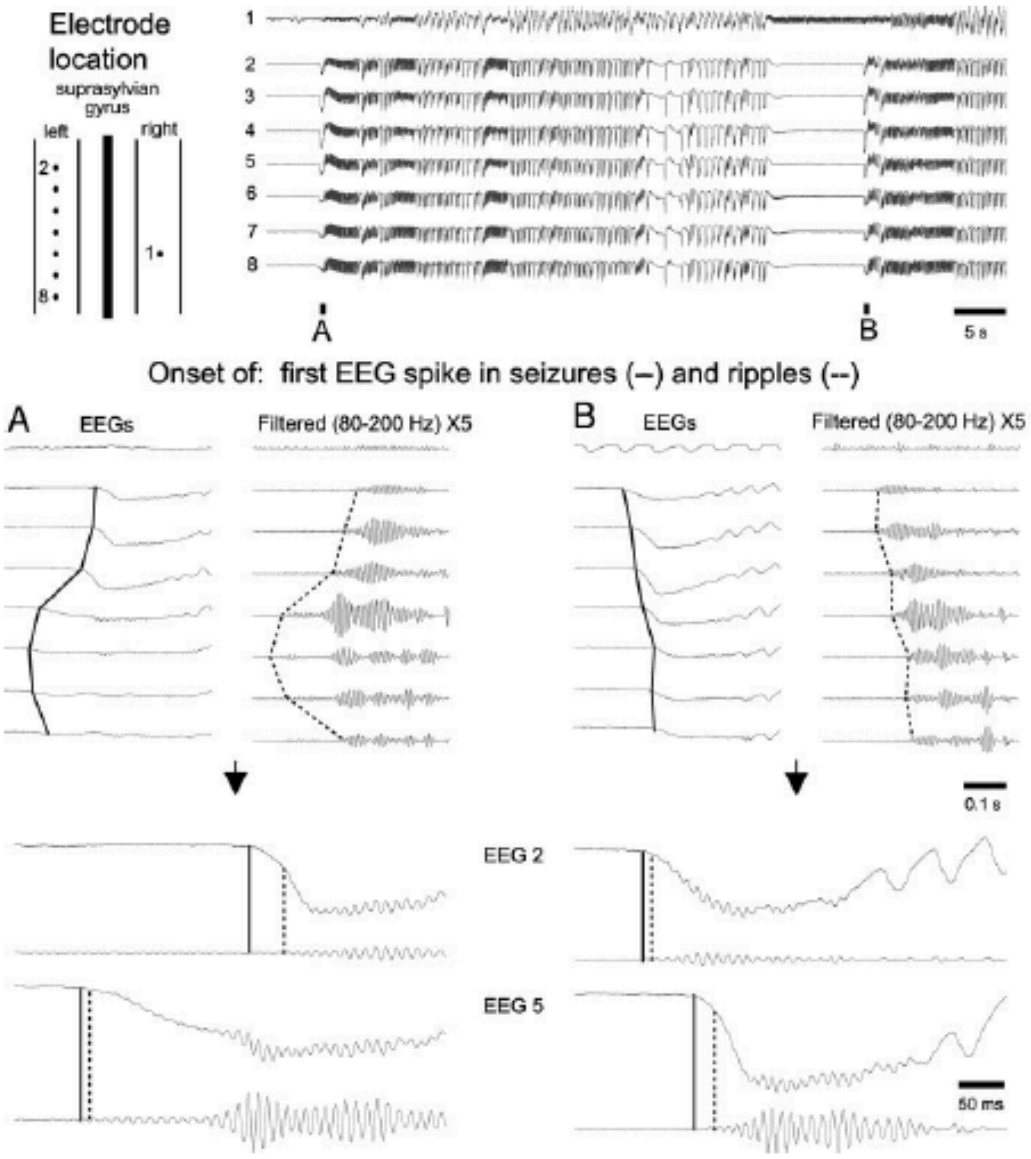
Left bars:
VFOs in SOZ.

Right bars:
VFOs outside SOZ.



Worrell et al. 2008, figure 4A

VFOs at seizure onset



Grenier et al. 2003, figure 3

VFOs start at same:

- place as seizure
- time as seizure

VFOs around a Lesion

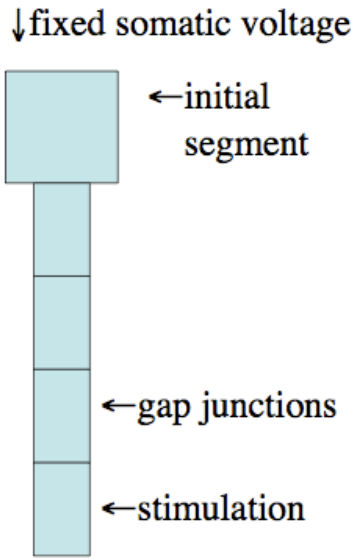
Anatol Bragin and colleagues performed a series of experiments:

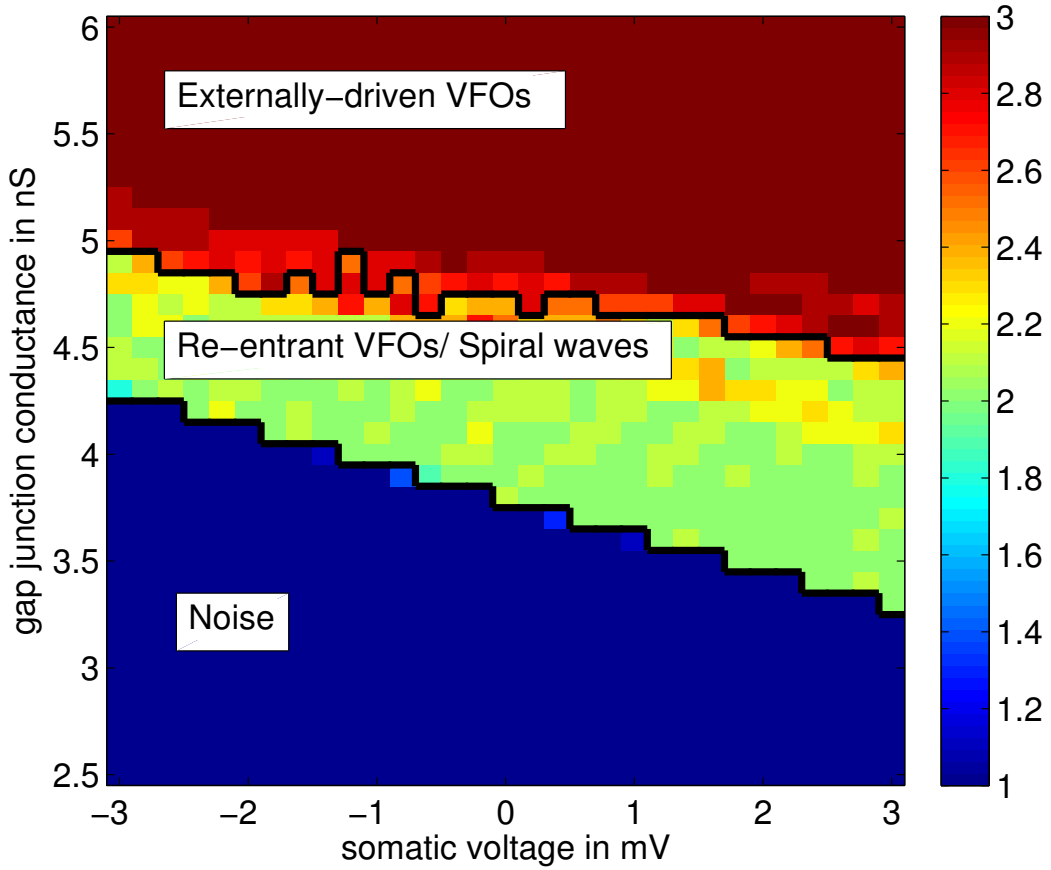
1.
   - Applied kainic acid to rat hippocampus
   - Of 15 rats displaying spontaneous seizures, fast ripples ($>$250 Hz) were found in 9
   - In all 6 rats where electrodes were movable found fast ripples around lesion
2.
   - Applied kainic acid to 26 rats, 19 showed VFOs ($>$ 80 Hz) near lesion
   - All rats that displayed VFOs developed spontaneous seizures.
   - None of the rats that were VFO free developed seizures.
   - The sooner VFOs appeared, the sooner seizures occurred.

Bragin et al. (2002), Bragin et al. (2004)

An axonal plexus can easily produce VFOs

Axonal plexus: a network of axons connected by gap junctions.





Re-entrant VFOs can easily be $>$ 250 Hz.

Gap junctions on pyramidal cell axons

Evidence:

- near somata in 5% of pair recordings in layer 5 of rat neocortex where somata are adjacent (Wang et al. 2010)
- by immuno-gold labeling in hippocampus (Hamzei-Sichani et al. 2007)
- by spikelets seen in the hippocampus and neocortex (Draguhn et al. 1998, Steriade et al. 1993)
- by dye-coupling in the hippocampus and neocortex (Schmitz et al. 2001, Gutnick et al. 1985)

What role could gap junctions on pyramidal cells play in neocortex?

Somatic voltage seems to control VFOs in normal neocortex.

- Perhaps somatic voltage controls VFOs by controlling propagation across gap junctions.

We show that, in neocortical pyramidal cells:

- Somatic voltage can control propagation through gap junctions in the initial segment (IS) and main axon (MA).
- Somatic voltage can't control propagation from gap junctions in collaterals.
- Number of cells connected by uncontrollable gap junctions in normal neocortex is relatively small.

Results imply that:

- Pyramidal cells can control signals to post-synaptic cells by adjusting their somatic voltage.
- Too many collateral gap junctions may lead to epilepsy.

How could the somatic voltage control spike propagation across gap junctions?

We hypothesize that:

Gap junctions may be on any length of unmyelinated axon

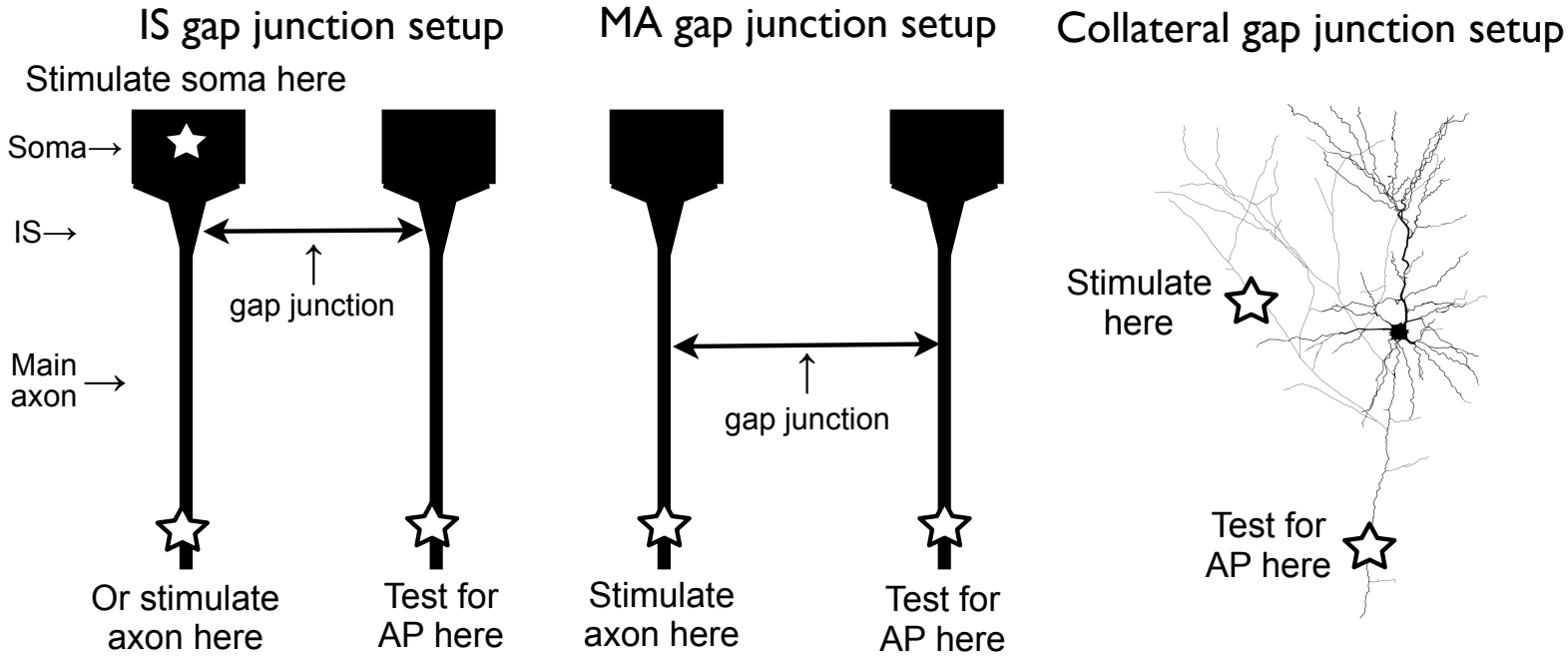
- initial segment (IS), main axon (MA), axon collaterals

So we:

Model the effects of somatic voltage on spike propagation

- across gap junctions in the IS
- across gap junctions in the main axon
- from gap junctions on collaterals

Simulation setup to test AP propagation from gap junctions

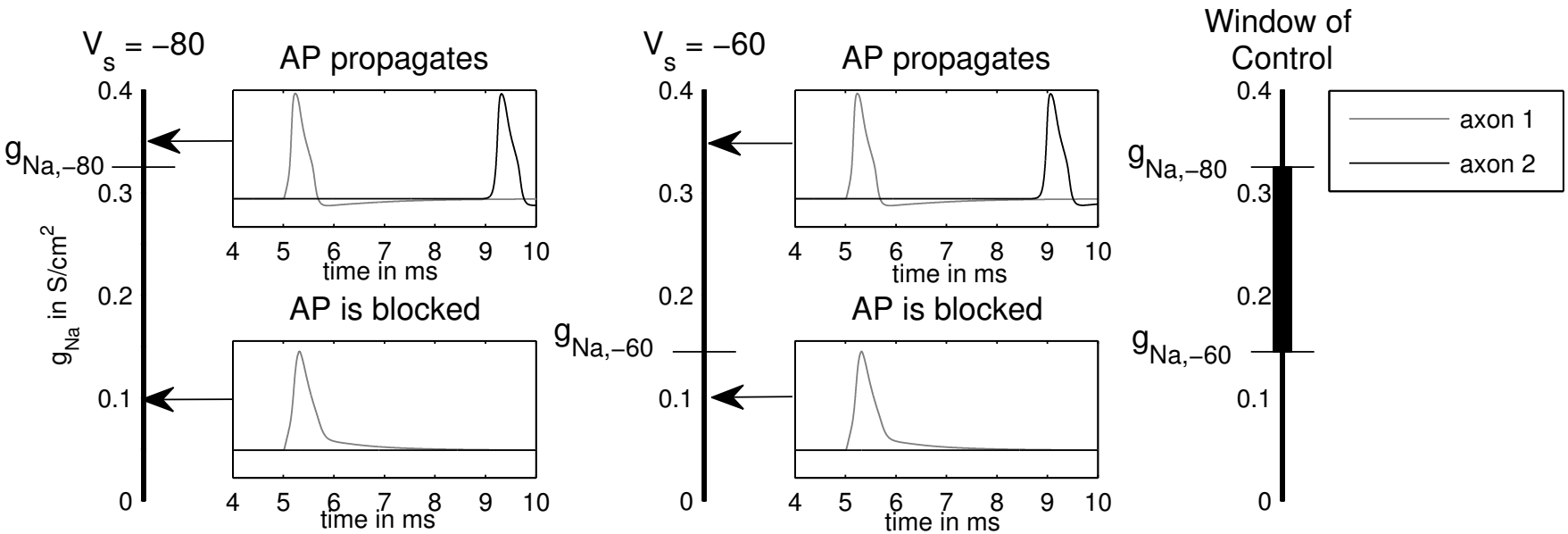


- All models based on 3D cell reconstructions from rat somatosensory cortex.
- Hodgkin-Huxley currents placed throughout axon.
- Vary gap junction conductance, distance from soma, somatic voltage (V_s), and sodium conductance (g_{Na}).

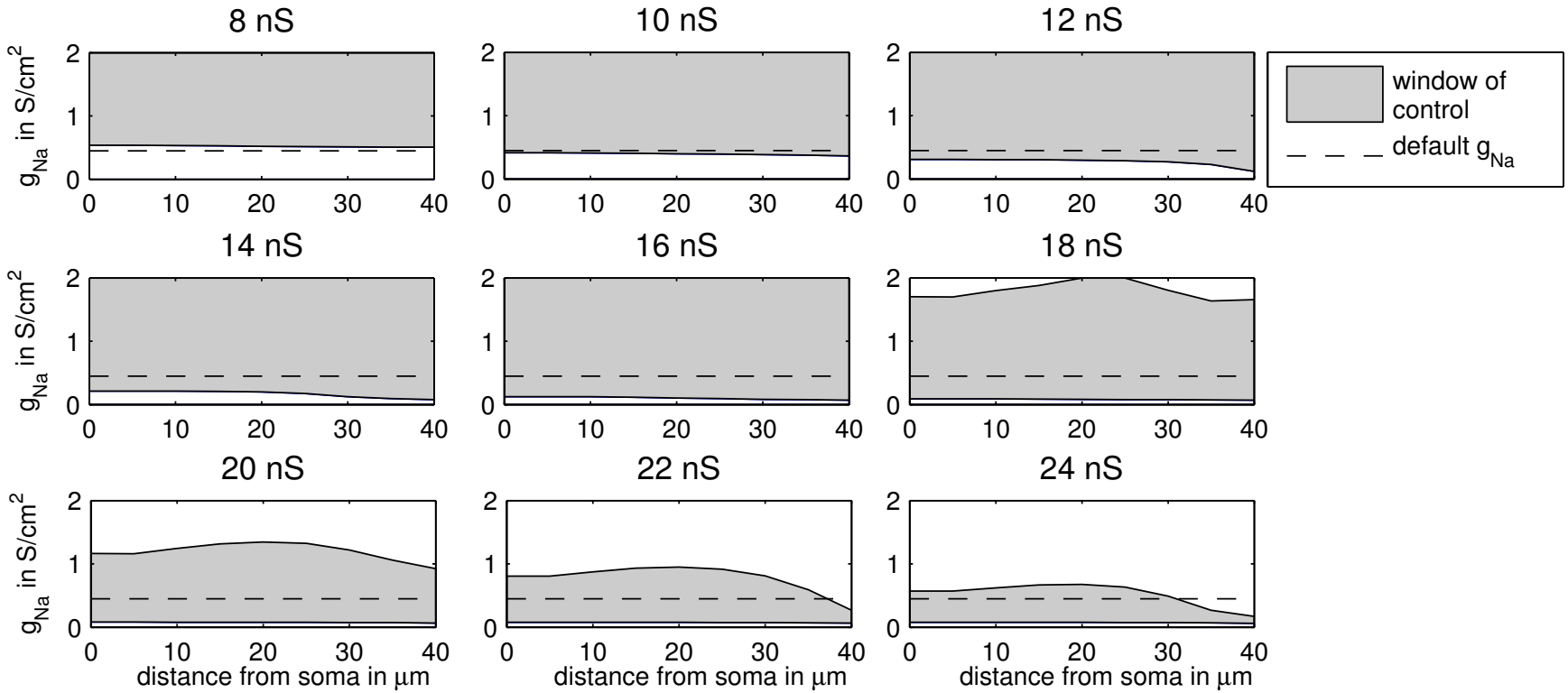
Find *window of control* for every gap junction conductance and distance from soma

Window of control: range of g_{Na} where

- APs don't propagate when $V_s = -80$ mV
- APs propagate when $V_s = -60$ mV

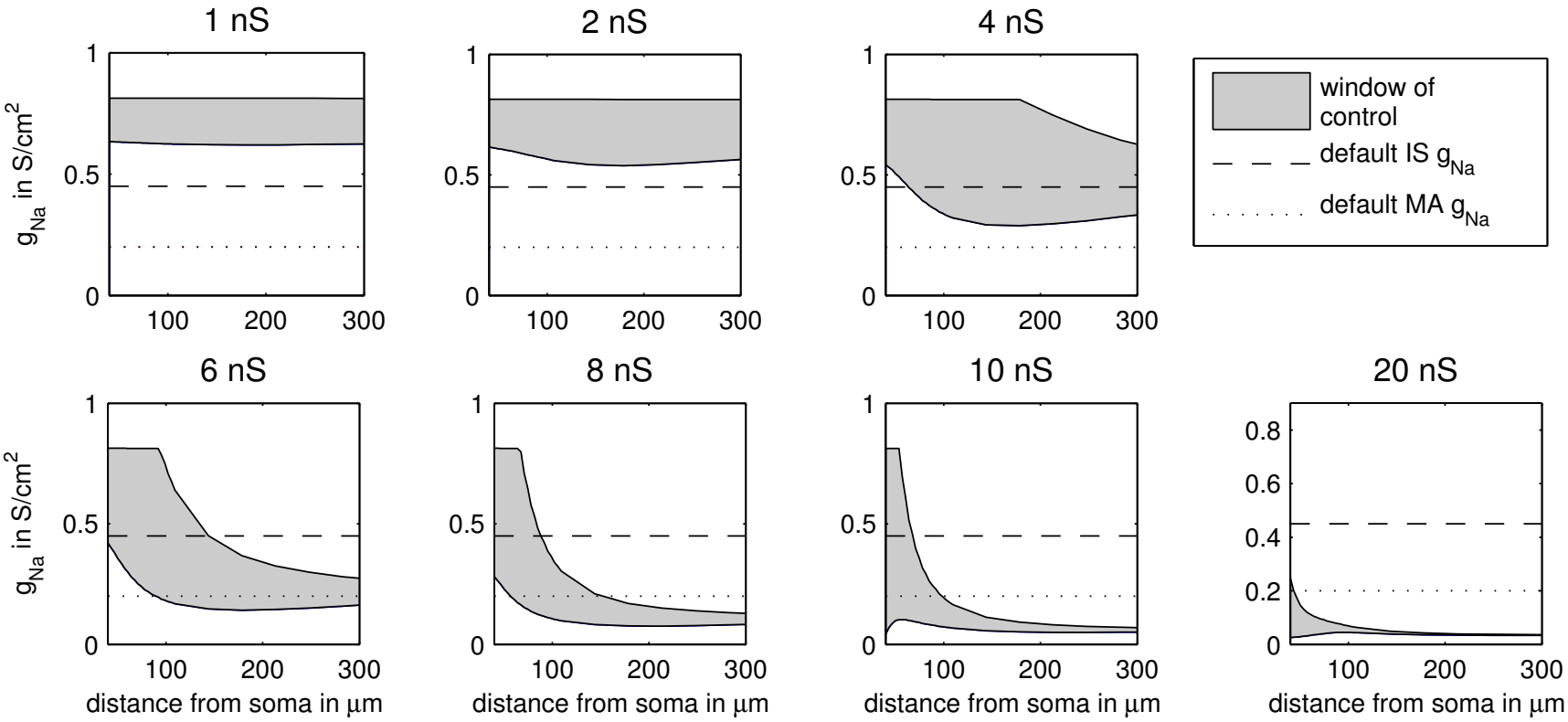


V_s can control gap junctions in the IS



Window of control is wide for a wide range of physiological gap junction conductances.

V_s can control gap junctions in the main axon



Window of control is wide for a wide range of physiological gap junction conductances and distances from the soma.

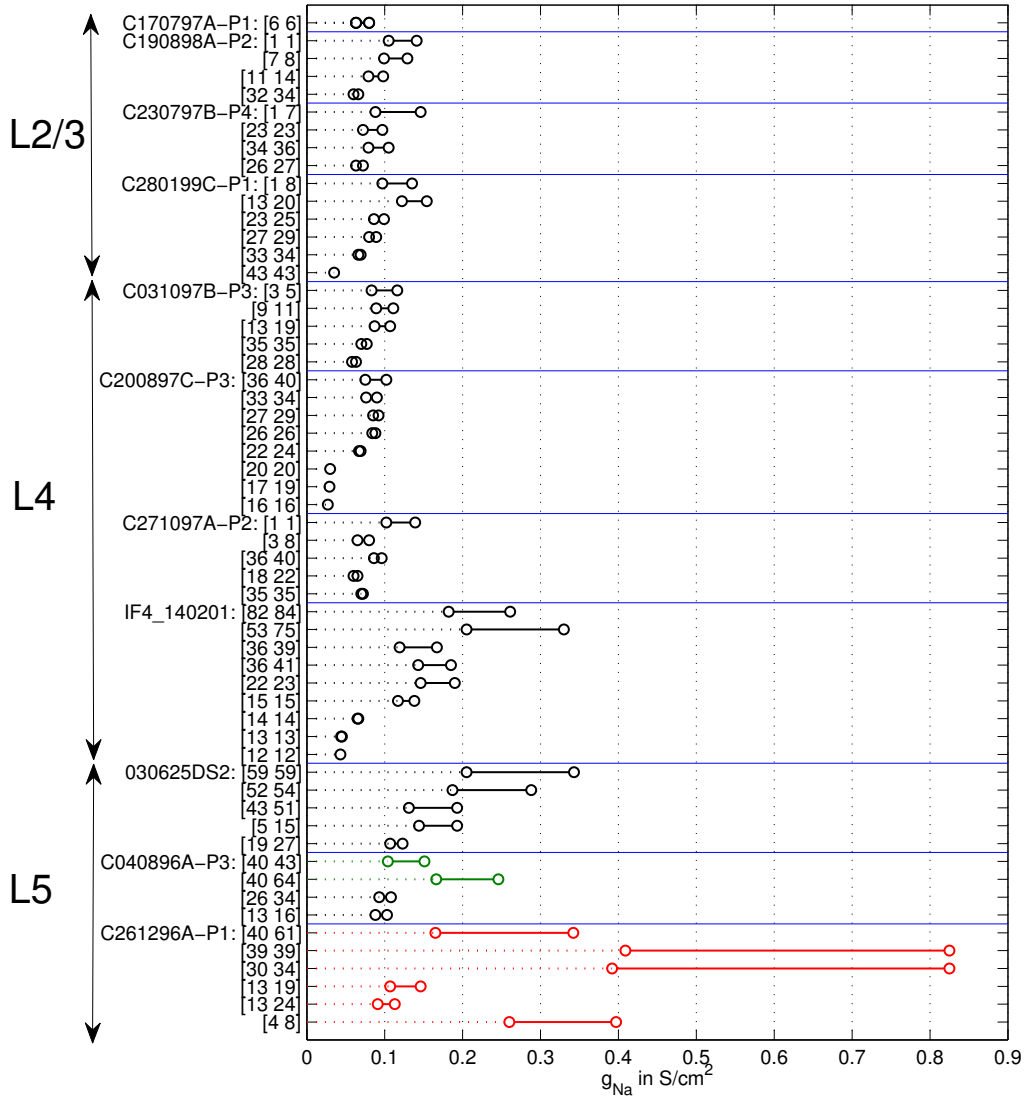
V_s can't control spike propagation from collaterals

Windows of control do not overlap:

- between cells,
- between collaterals in the same cell,
- between stimulation sites on the same collateral.

No g_{Na} where V_s can control all collaterals simultaneously.

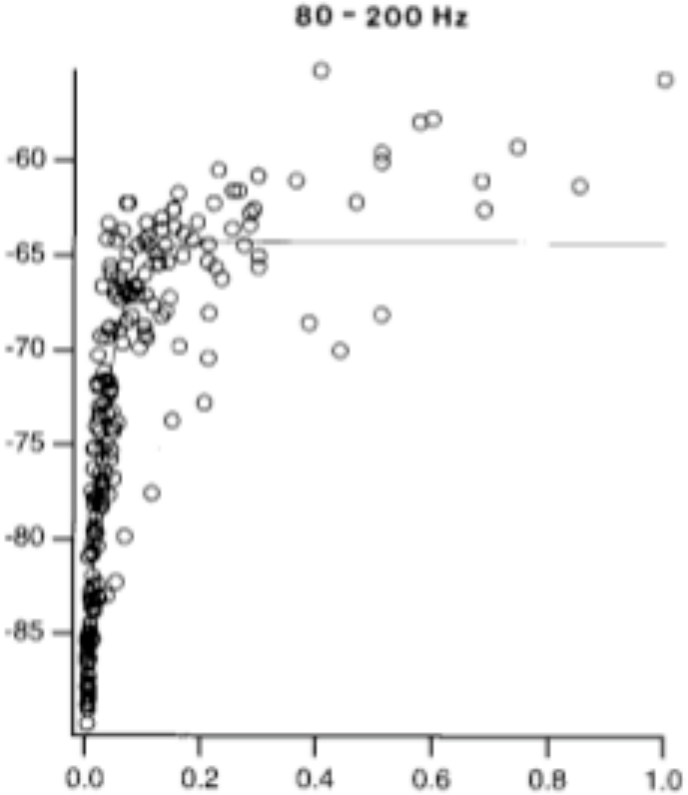
Spikes may propagate from collaterals regardless of V_s.



How many cells may be hard-wired together in normal neocortex?

Hard-wired cells: spikes may propagate between them regardless of somatic voltage.

Relative amplitude of VFO (RA) vs. pyramidal cell voltage (V_s)



Grenier et al. (2001) fig 5

- Data from slow oscillation induced by ketamine-xylazine anesthesia in layer 5
- RA is minimal when $V_s \leq -83$ mV
- How many cells could be firing at VFO frequencies when $V_s \leq -83$ mV?
- How many cells could be connected together without producing VFOs?

Possible number of cells producing VFOs during cell hyperpolarization in normal neocortex

- minimum RA: $\sim$0.01
- number of pyramidal cells in layer 5 within 1 mm^2: 19,550 (Skoglund et al. 1996, Beaulieu 1993)
- maximum fraction of cells in a large connected cluster: 2/3 (Traub et al. 1999)

Number of firing cells: $\sim 0.01 \times 2/3 \times 19,550 \approx 130$

But there could be groups of cells hard-wired together that are not producing VFOs.

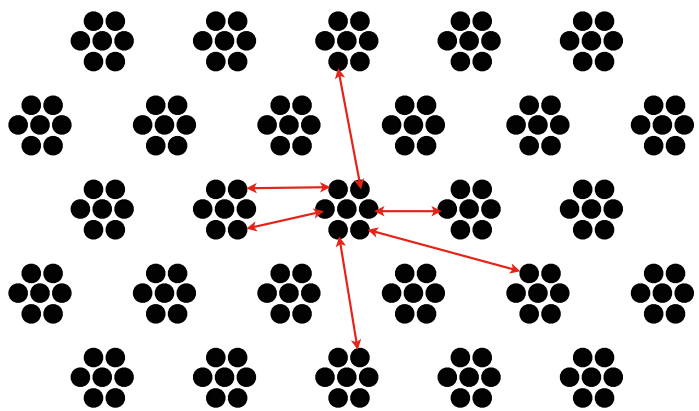
How many cells can be connected together without producing VFOs?

Network model of collateral connections

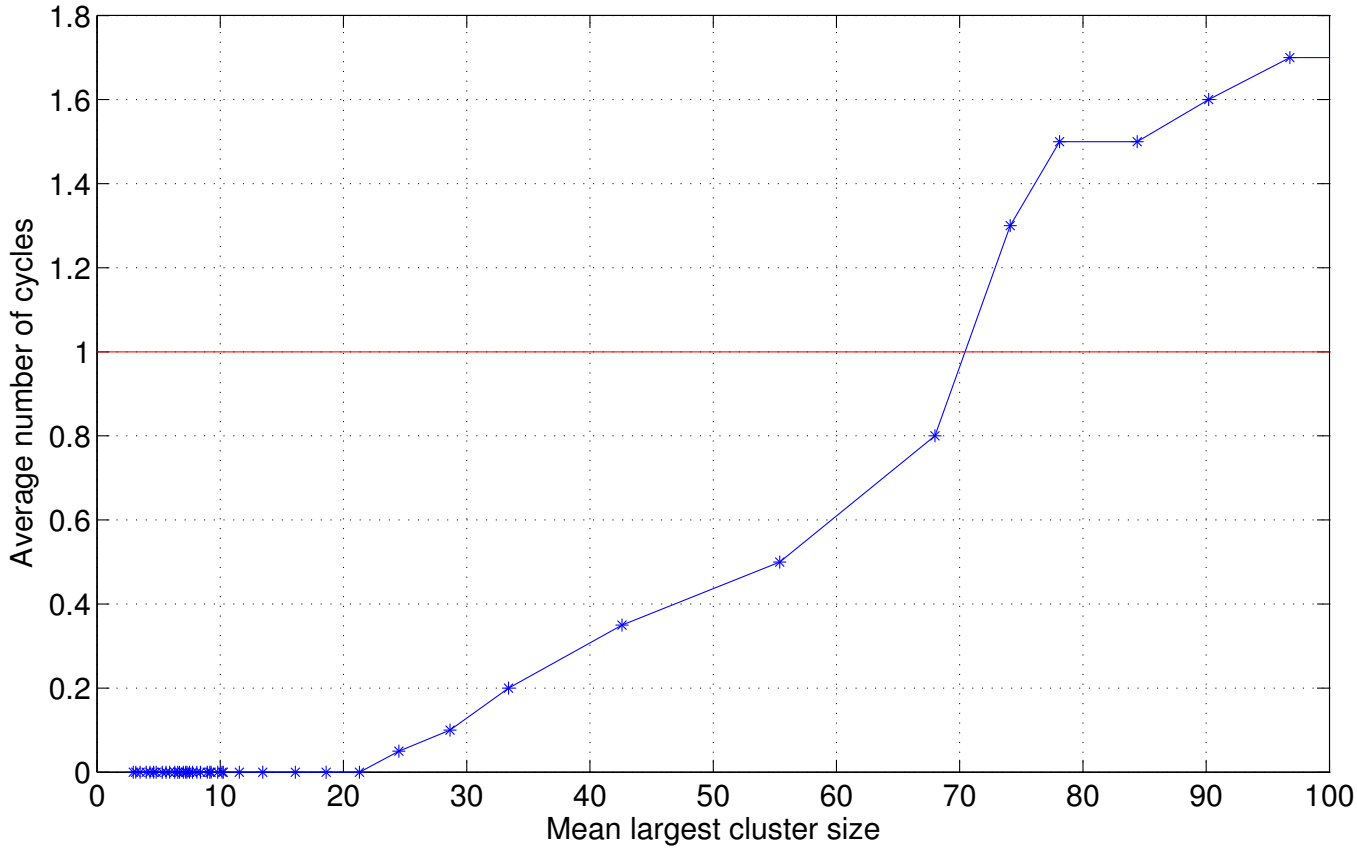
- arrange groups of axons in hexagonal grid
- weigh axons according to total axon lengths of 3D reconstructions
- randomly connect axons
  - within 9 units on grid
  - according to p: probability of connecting per μm^2

Need 1 cycle
for re-entrant VFOs.
As p varies, find:

- average number of cycles (m_{cy})
- size of largest cluster when $m_{cy} = 1$



Cycles form when there are $\sim$70 cells in a cluster

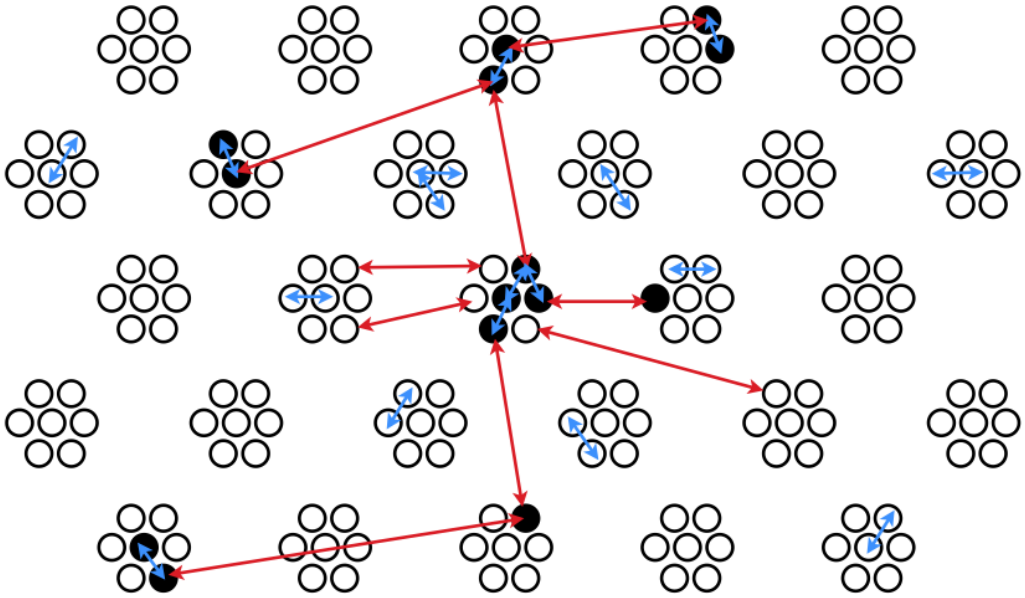


- There can be up to 70 cells hard-wired together without producing VFOs.
- 70<130 $\rightarrow$ maximum number of cells hard-wired together is 130.

What we've learned so far:

- V_s *can* control spike propagation across gap junctions
  - in the IS
  - in the main axon
- V_s *can't* control spike propagation
  - from gap junctions on collaterals
- Cells that are hard-wired together
  - Maximum is $\sim$130 out of 20,000, or 0.65%
  - Can see persistent VFOs if $>$70 cells are hard-wired together.

Implications for neocortical processing



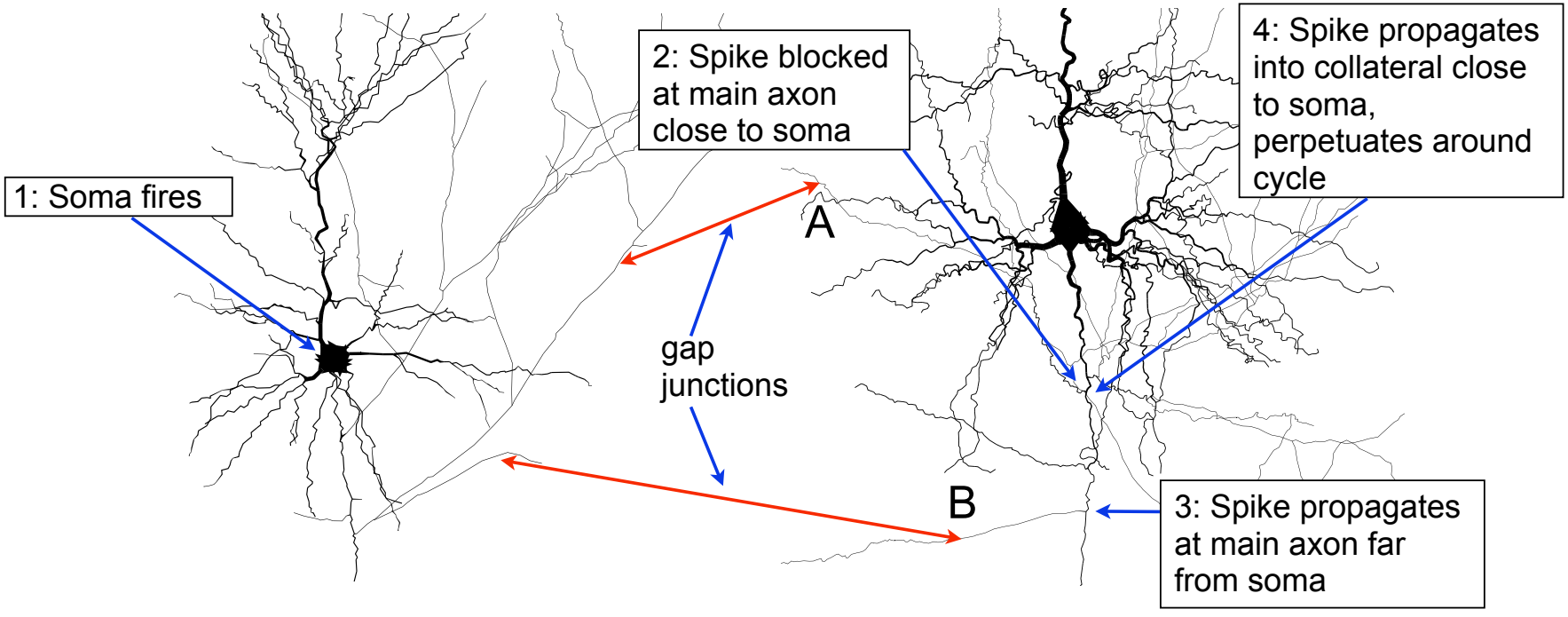
↔ IS/MA connection
↔ collateral connection

If black cells depolarize
and 1 cell fires,
in effect they *all* fire

- cells signal post-synaptic cells by depolarizing,
  not just by firing
- depolarized cells form cell assemblies
- large groups of depolarized cells produce VFOs
  $\rightarrow$ send high-frequency signals to post-synaptic cells
  $\rightarrow$ alter synapses

Implications for temporal lobe epilepsy

What happens when gap junctions form a cycle on collaterals?

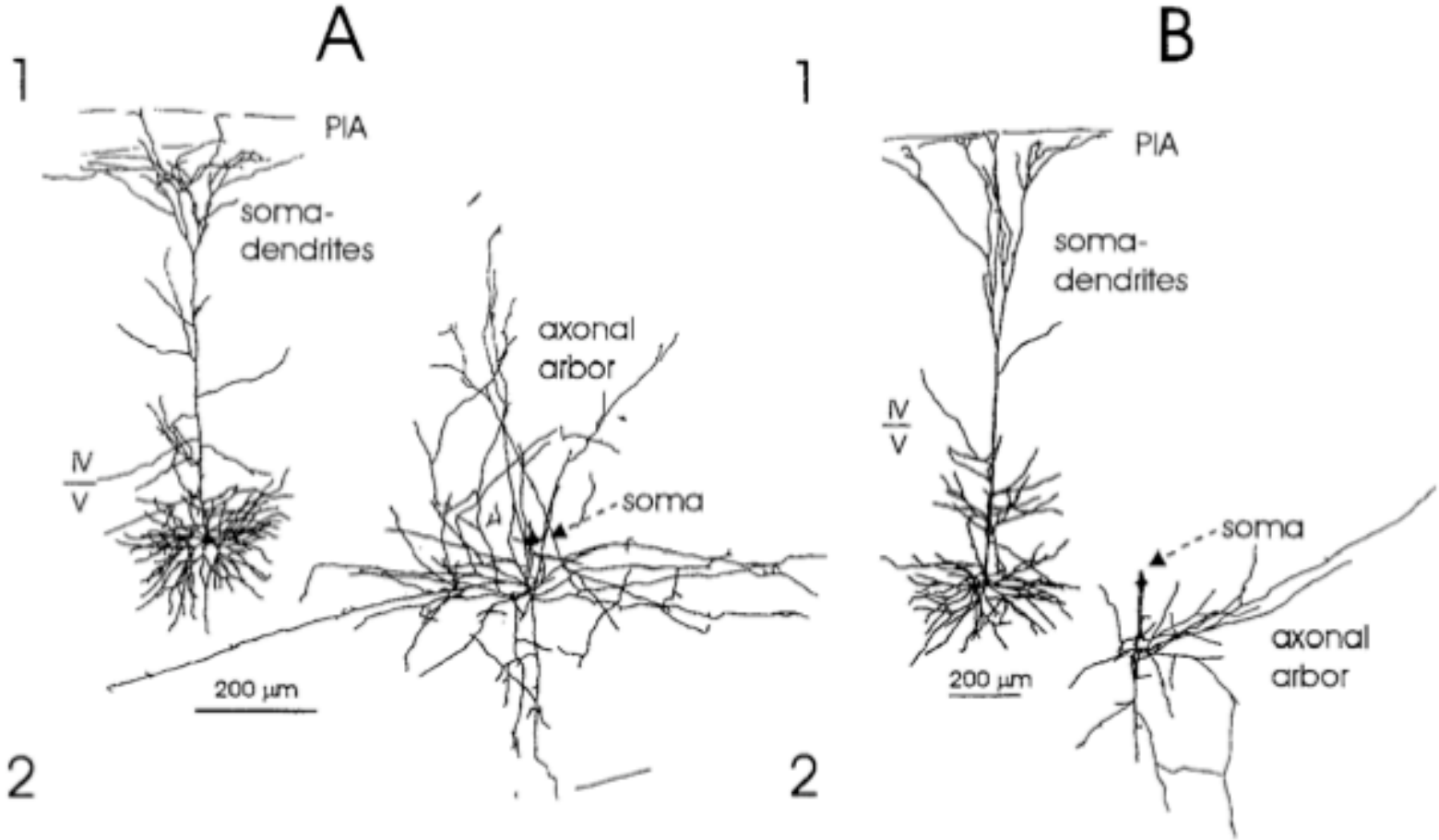


- Easy to get re-entrant VFOs once collaterals form a cycle.
- Small groups of cells may have cycles among collaterals in normal neocortex.
- Axonal sprouting may introduce many more cycles among collaterals.

Axonal Sprouting Near a Lesion

Salin et al. (1995) report:

- 56% increase in total axon length
- 64% increase in number of axon collaterals



Salin et al., 1995, Figure 4

Axonal sprouting, VFOs, and temporal lobe epilepsy

Since somatic voltage can't control spike propagation from collaterals, axonal sprouting may lead to:

- → more gap junctions on collaterals than normal neocortex
- → more cycles formed by gap junctions on collaterals
- → large amplitude re-entrant VFOs that cannot be turned off by somatic hyperpolarization
- → VFOs kindle post-synaptic cells
- → epilepsy

Conclusion and Thanks!

- Gap junctions allow pyramidal cells to send signals by depolarizing in normal neocortex.
- Axonal sprouting can lead to epilepsy because gap junctions on axon collaterals form cycles.

Acknowledgements:

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Thank you for your attention!