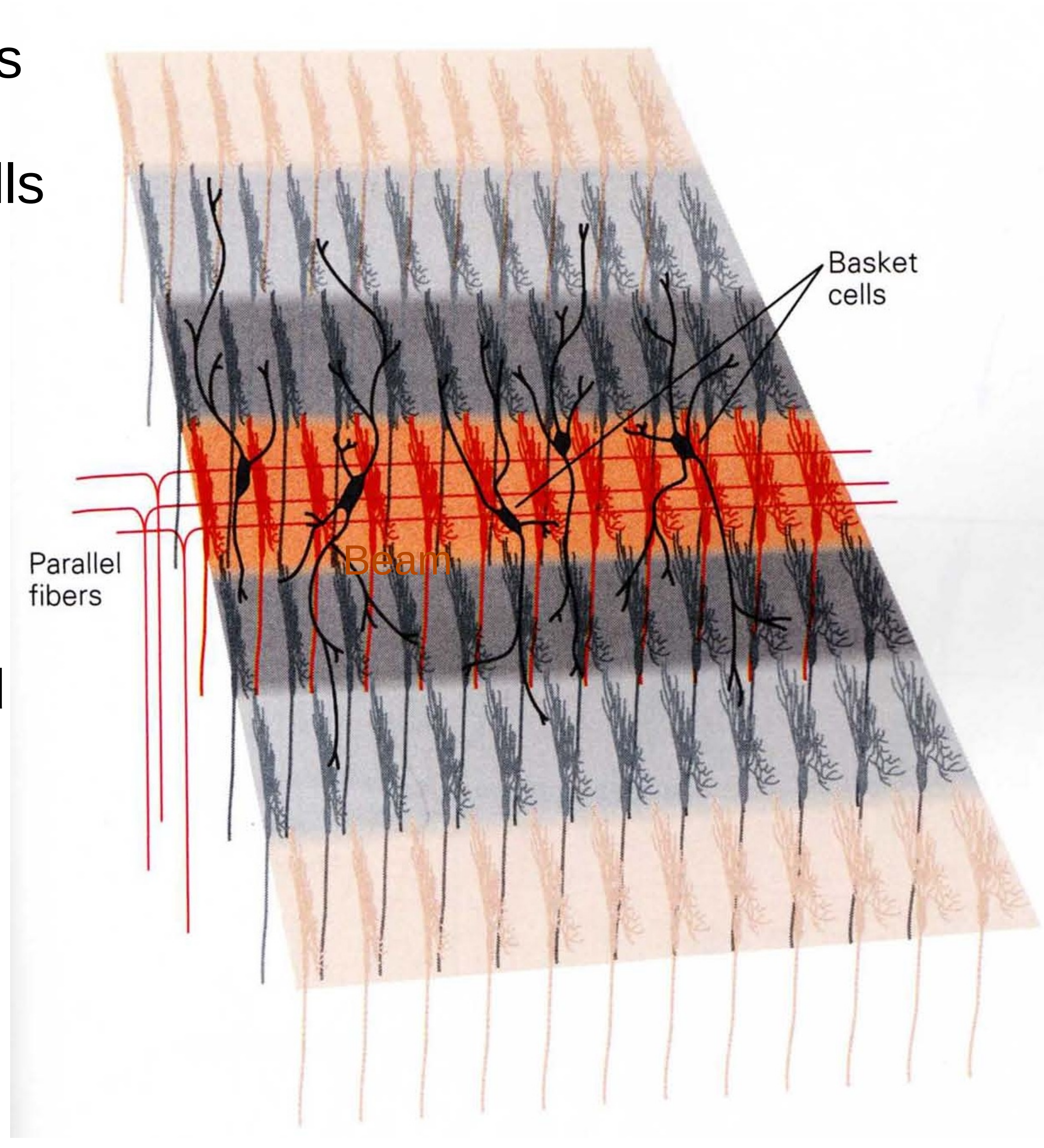
Dynamics of Parallel Fibers and Purkinje Cells

Computational Models of Neural Systems
Lecture 2.5

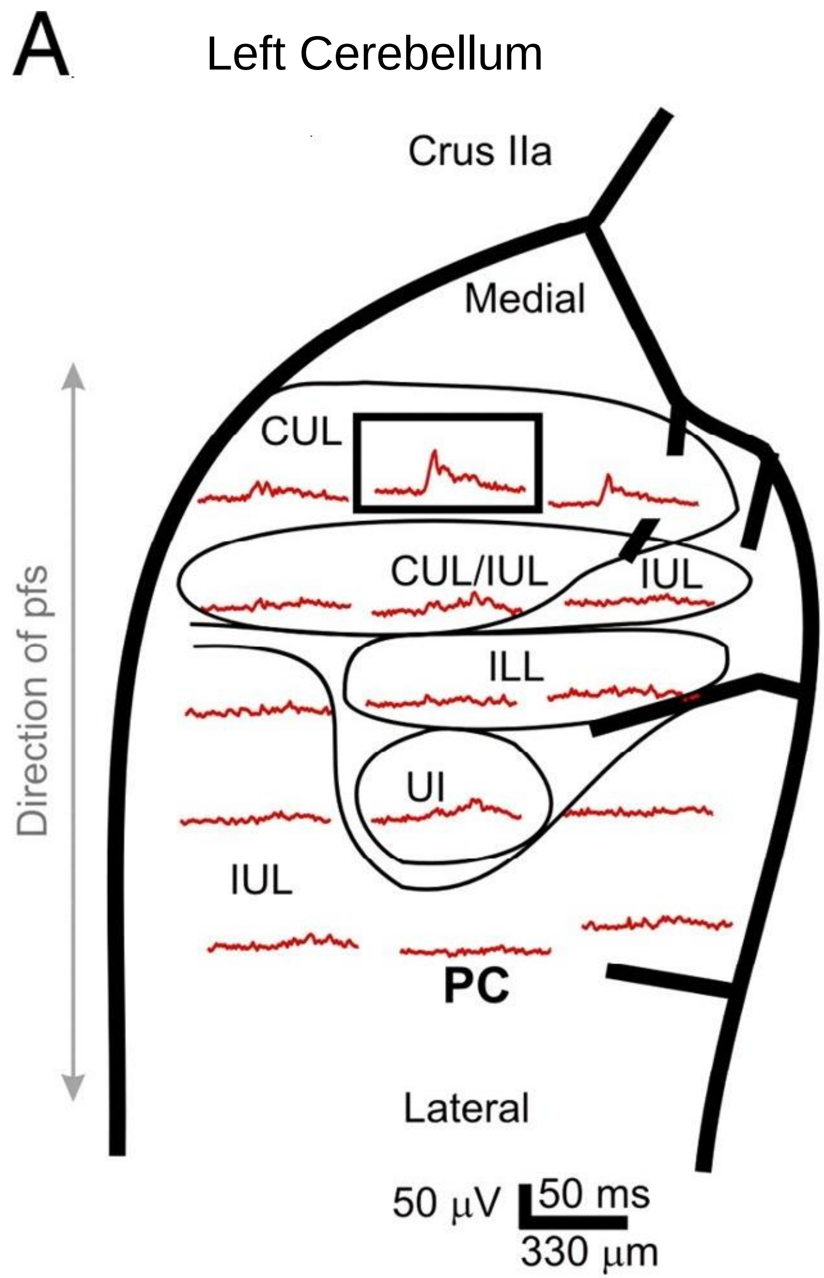
David S. Touretzky
September, 2019

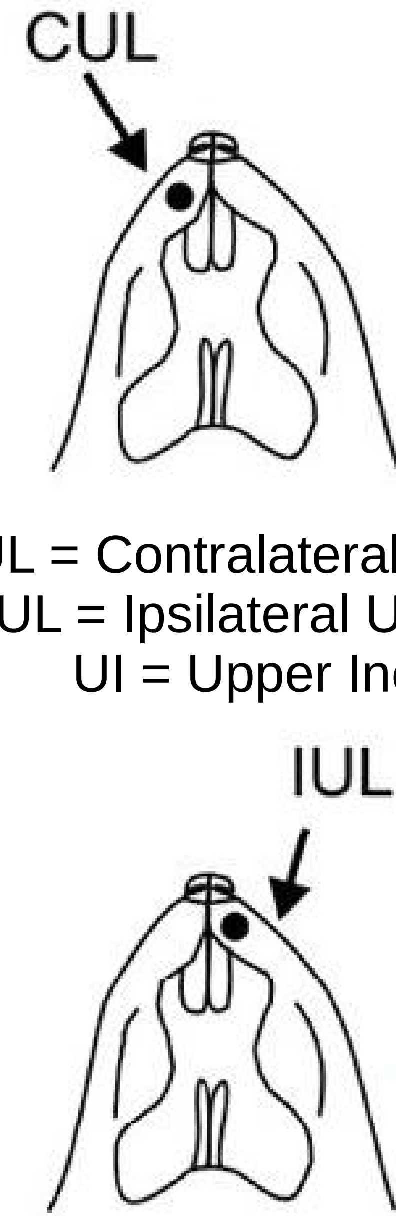
The Beam Hypothesis (Eccles)

- Activation of granule cells should lead to activation of a beam of Purkinje cells along the parallel fiber axis.
- Activity should travel along the beam at the parallel fiber conduction velocity.
- But people haven't found these beams.



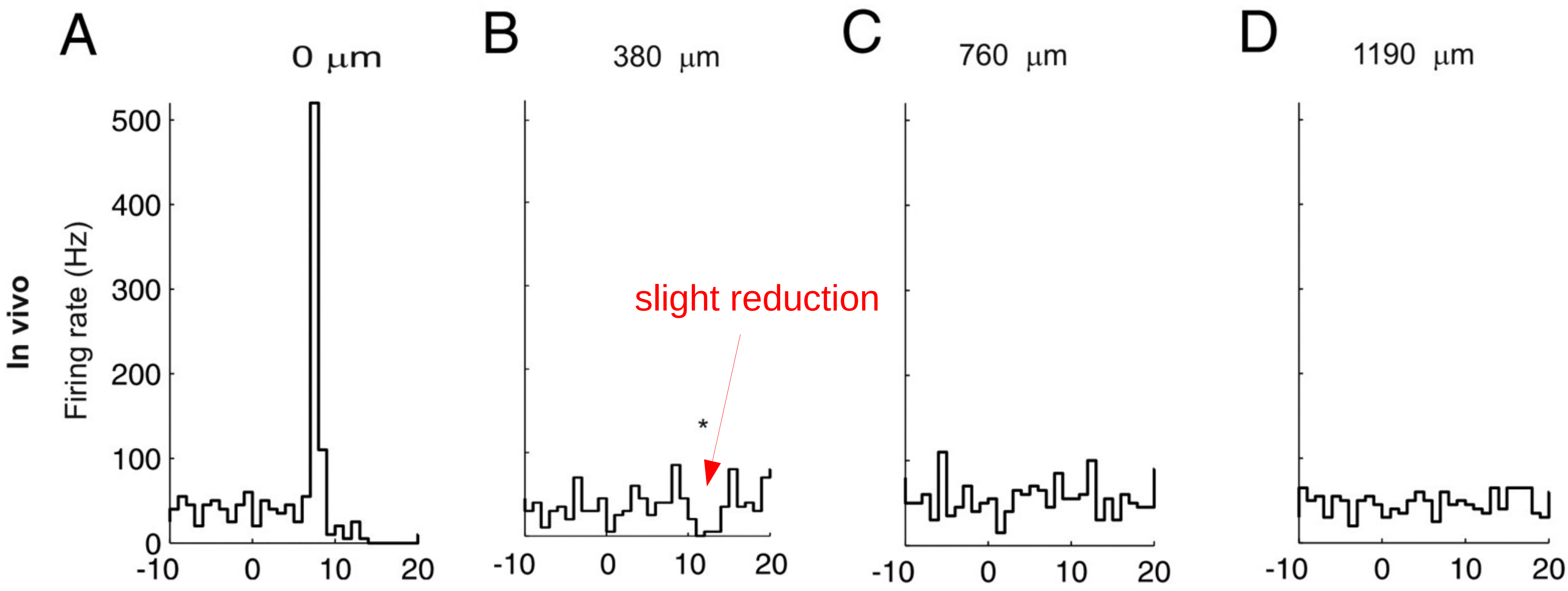
Testing the Beam Hypothesis





CUL = Contralateral Upper Lip
IUL = Ipsilateral Upper Lip
UI = Upper Incisor

Purkinje Cell Response to Lip Stimulation: No Beam



- Activates a 500 × 500 μm patch of granule cells: about 30,000 inputs to each PC.
- Strong PC response immediately above the active granule cells, but no response further along the beam.

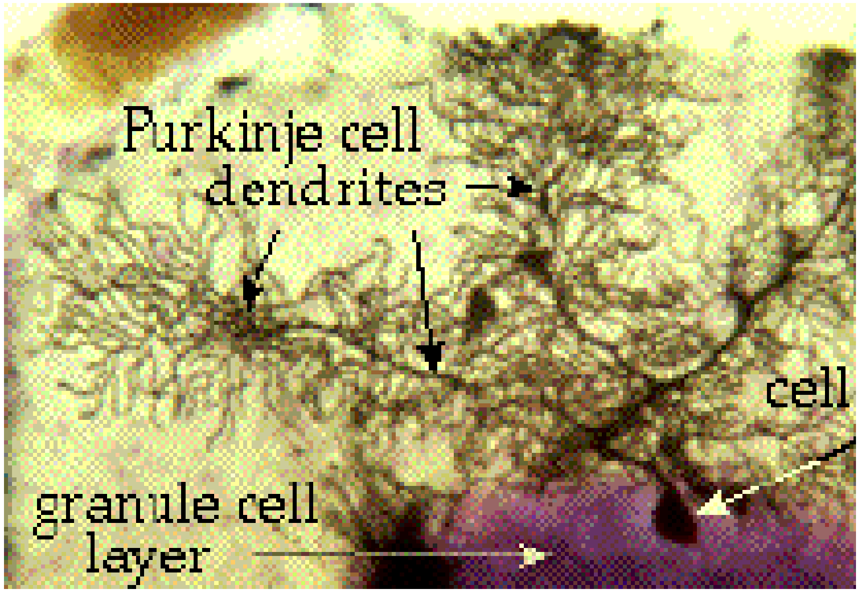
Alternative Explanations for Lack of Beam Response

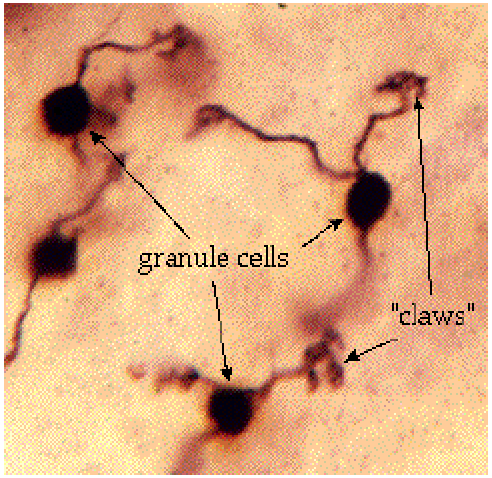
- Desynchronization of parallel fiber activity due to varying conduction velocities? (Llinas 1982)
  - Distal PCs don't get enough *simultaneous* activation to fire.
- Insufficient synaptic input? (Braitenberg et al. 1997)
  - Distal PCs don't get enough *total* activation to fire: not enough granule cells were stimulated.
- Feedforward inhibition! (Santamaria et al., 2007)

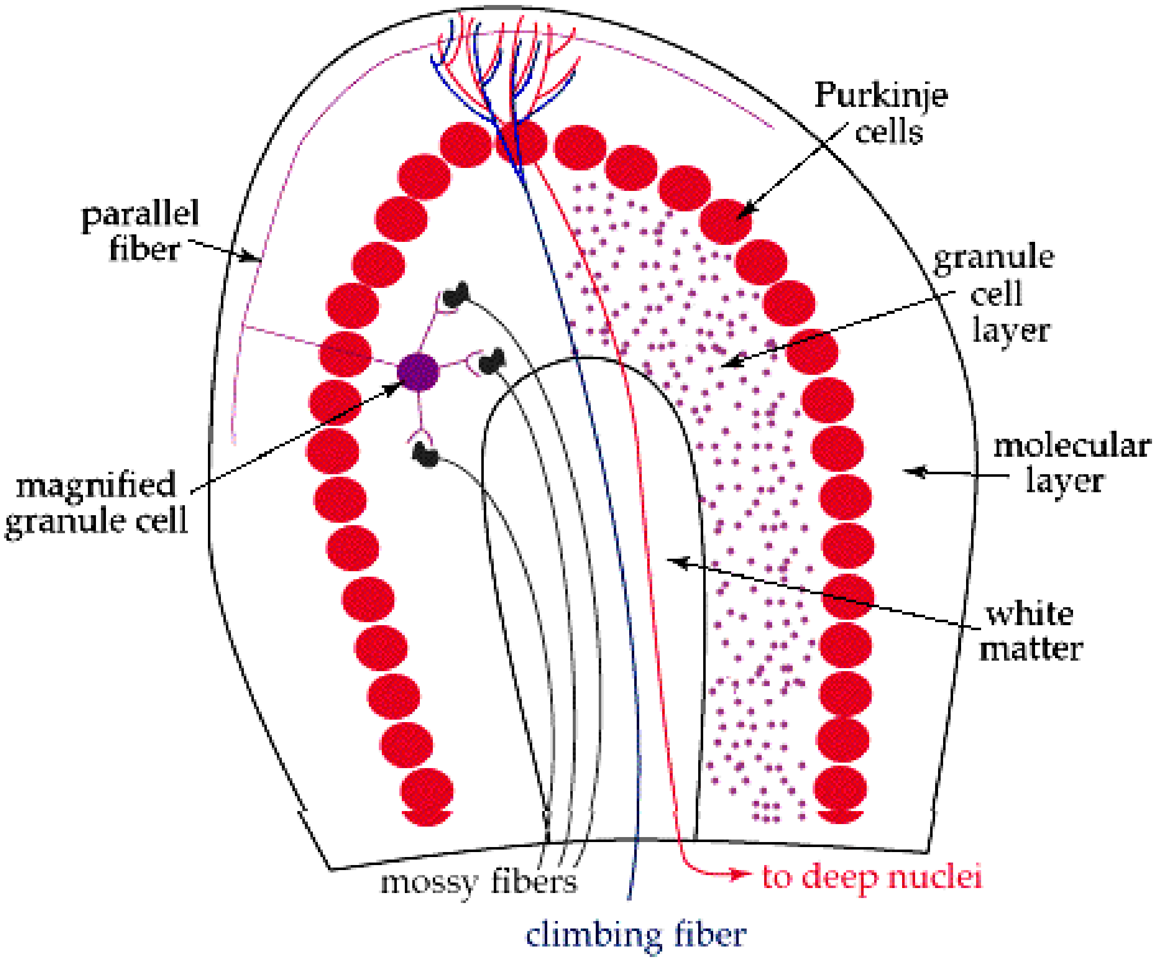
Can FF Inhibition Eliminate the Beam Response?

- Santamaria et al., *J. Neurophys.* 97:248-263, 2007
- Hypothesis: feedforward inhibition from basket and stellate cells suppresses activation of Purkinje cells along the beam.
- Modeling:
  - Use computer simulations to see if they can reproduce the effects the hypothesis purports to explain.
- Experiment:
  - Use $GABA_A$ receptor blockers to remove inhibition and see what happens.

Granule Cell, Purkinje Cell, and Molecular Layers

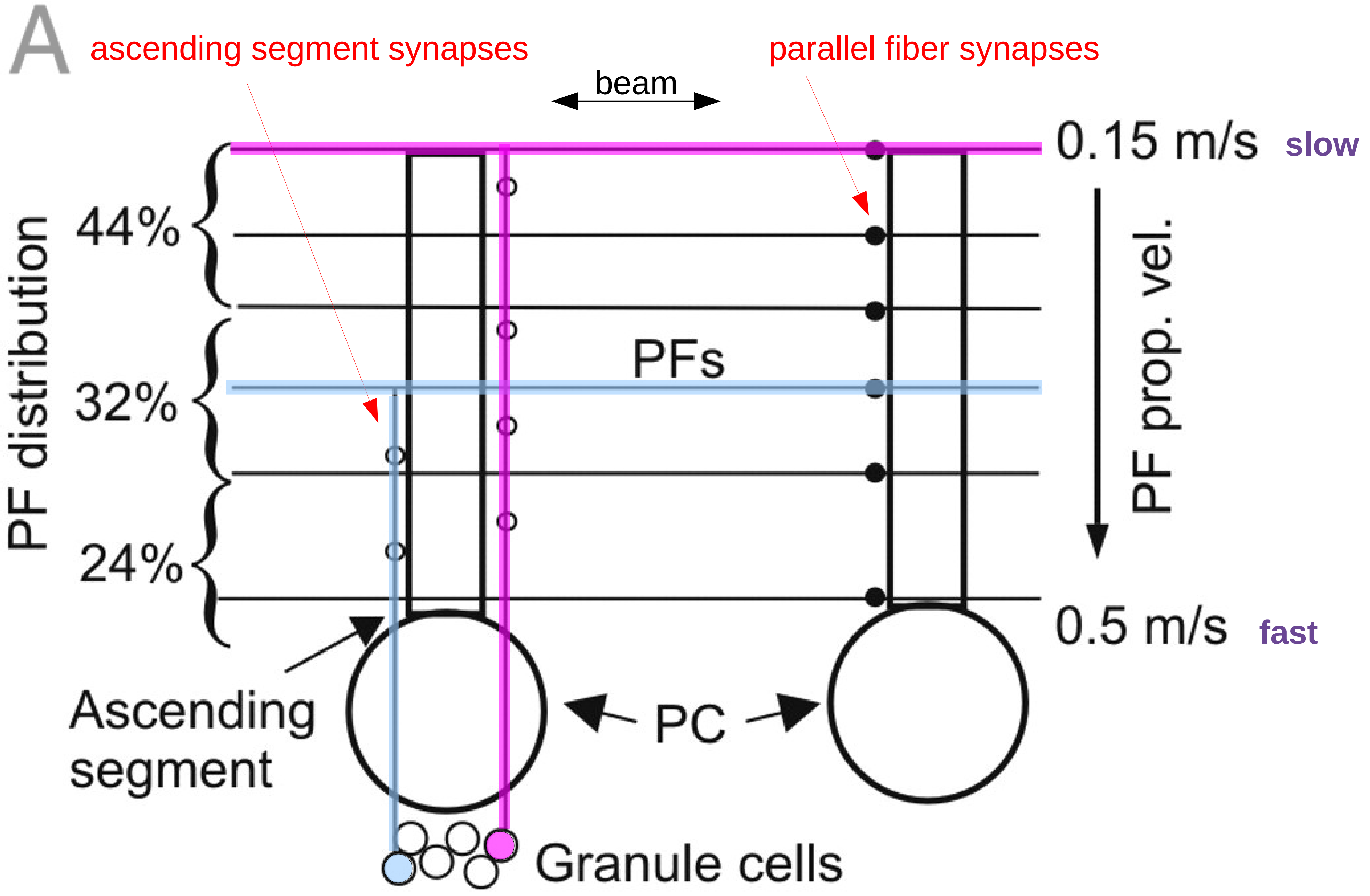






http://thalamus/wustl.edu/course/cerebell.html

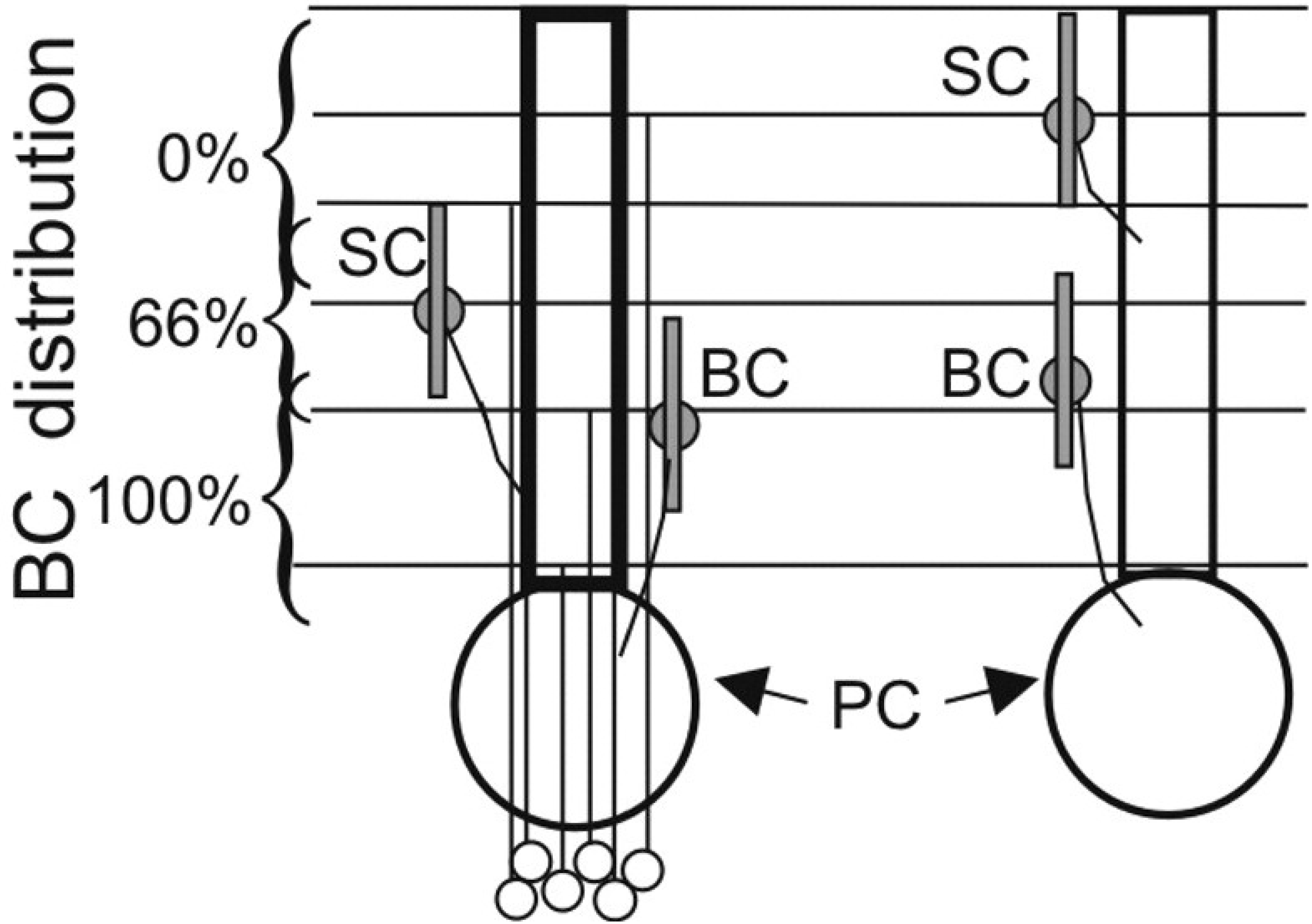
Synapses from Granule Cells Are Present Throughout the Molecular Layer



Scaling Issues

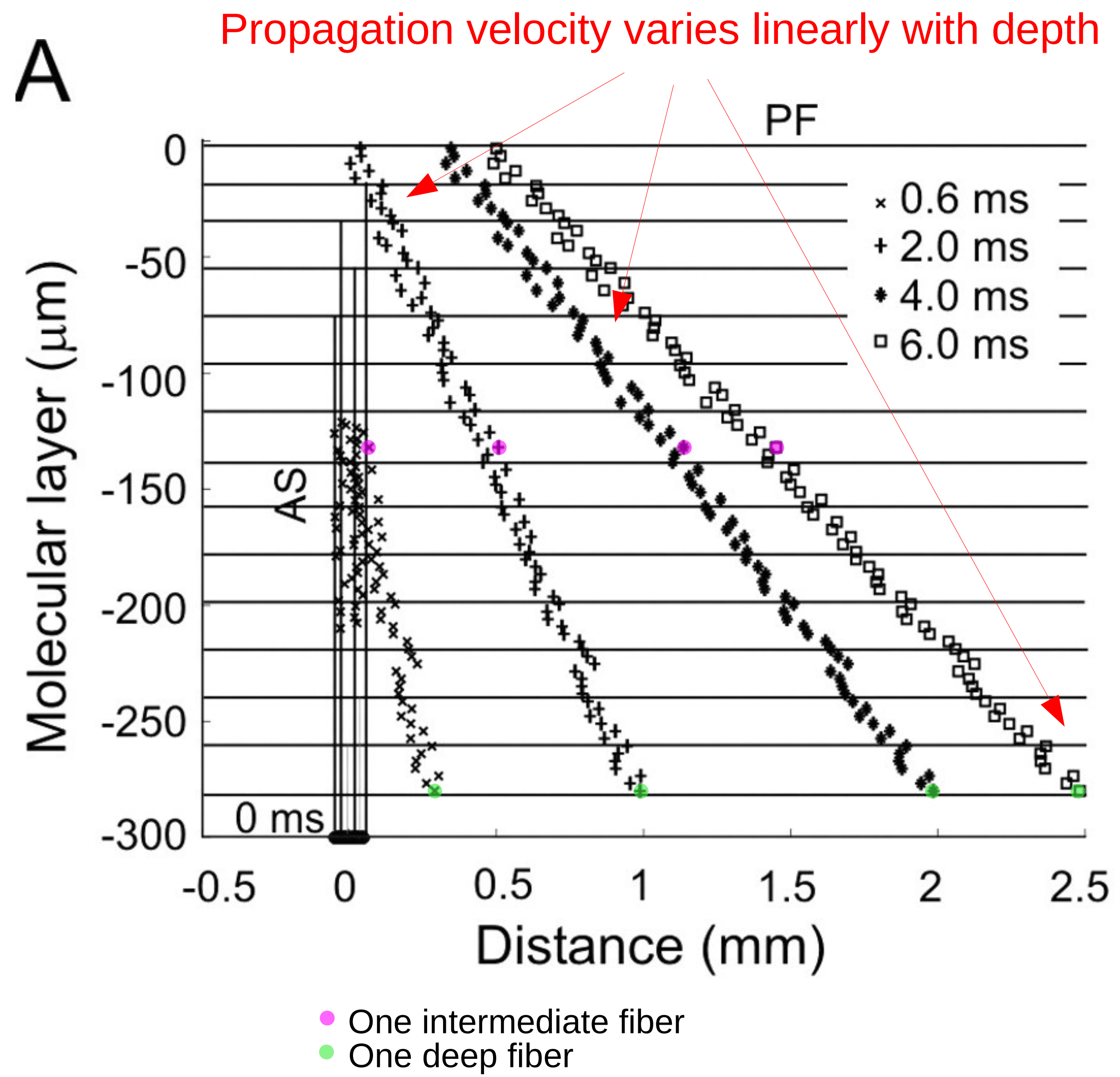
- Real Purkinje cells have around 150,000 synapses.
- The simulation used only 1,600 granule cells / parallel fibers.
- How to maintain realistic Purkinje cell responses?
  - Scale the synaptic input to compensate.
  - In this case, the firing rate of parallel fiber synapses was increased.
- The model also used 1,695 inhibitory interneurons.
  - Close to a realistic value, so no scaling required.

Distribution of Stellate and Basket Cells

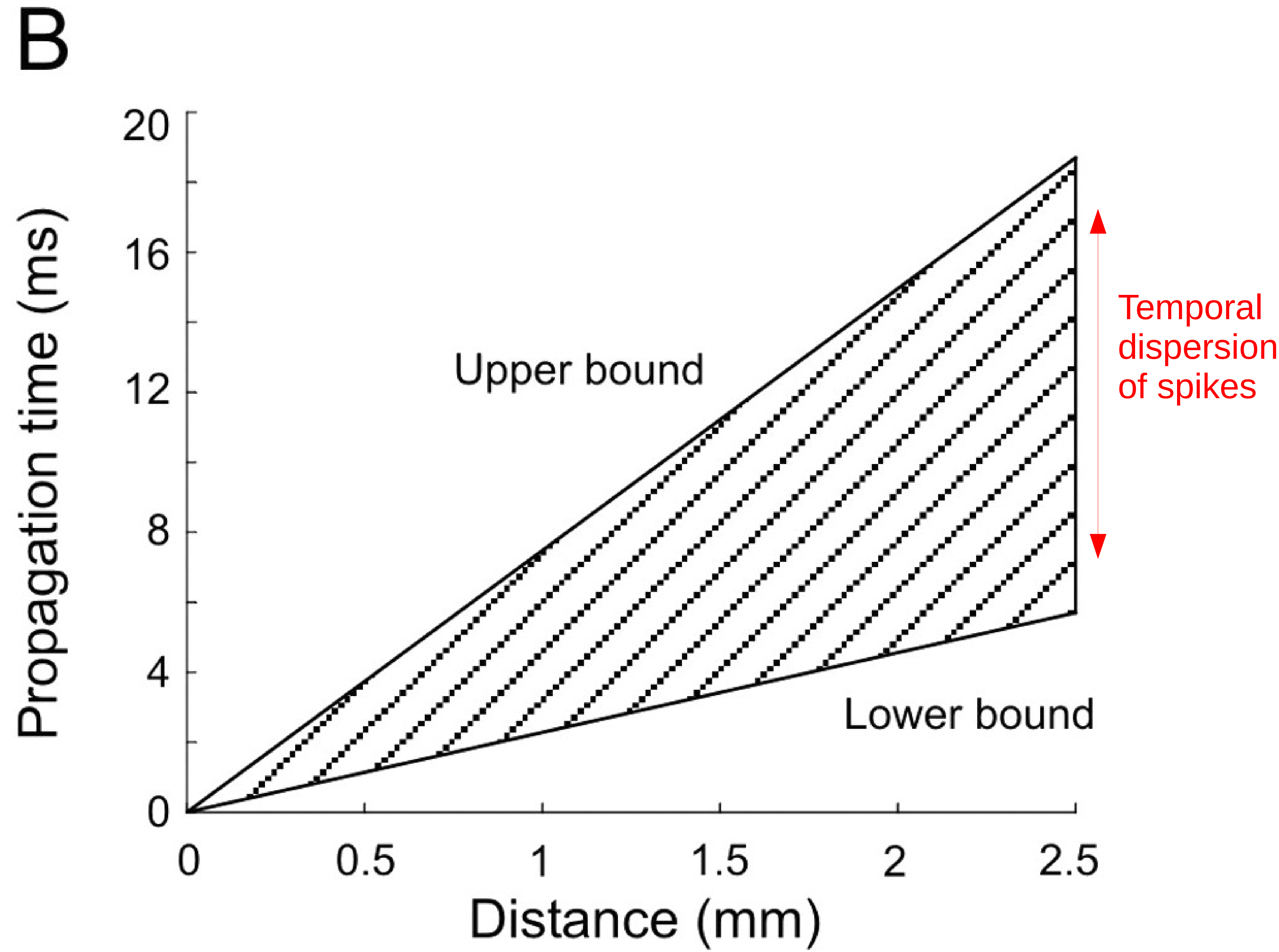


AP Propagation Along Granule Cell Axons

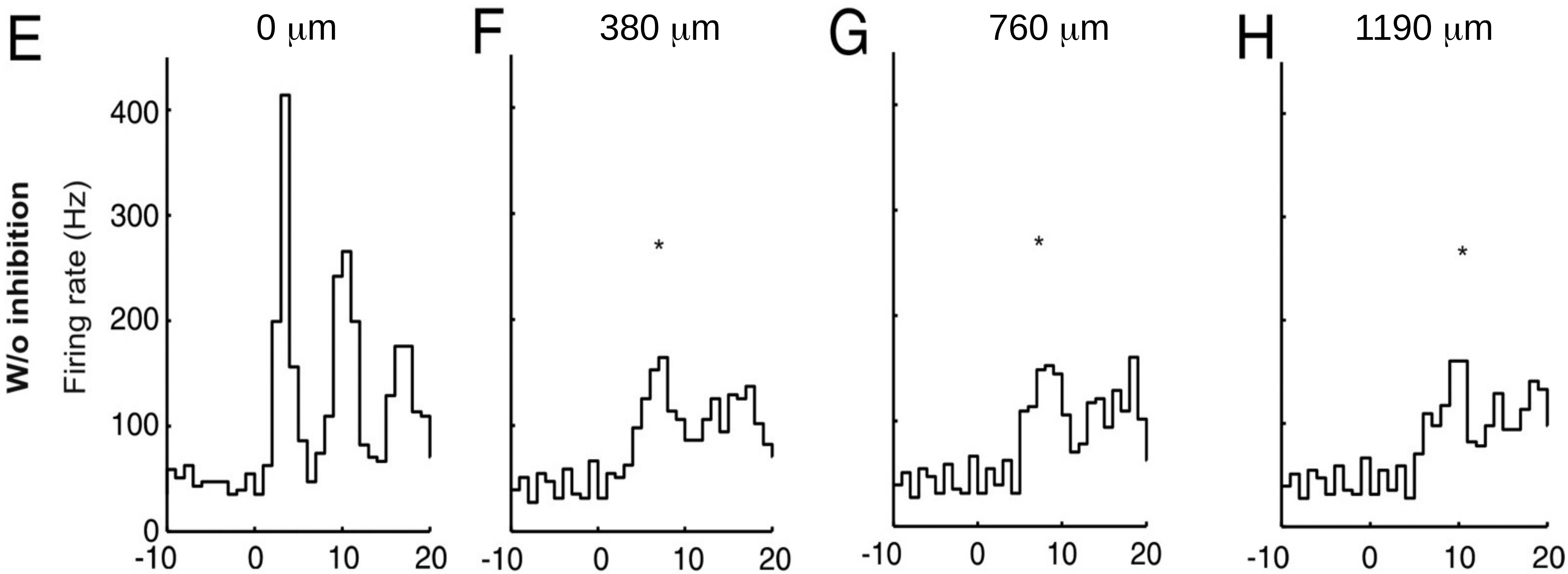
- AS: ascending segment
- 80 cells distributed over 50 μm^2, firing simultaneously
- Volley is increasingly desynchronized as time progresses due to:
  - time to travel along ascending segment to reach bifurcation point
  - parallel fiber propagation velocity varying with depth



Propagation Time vs. Distance Traveled

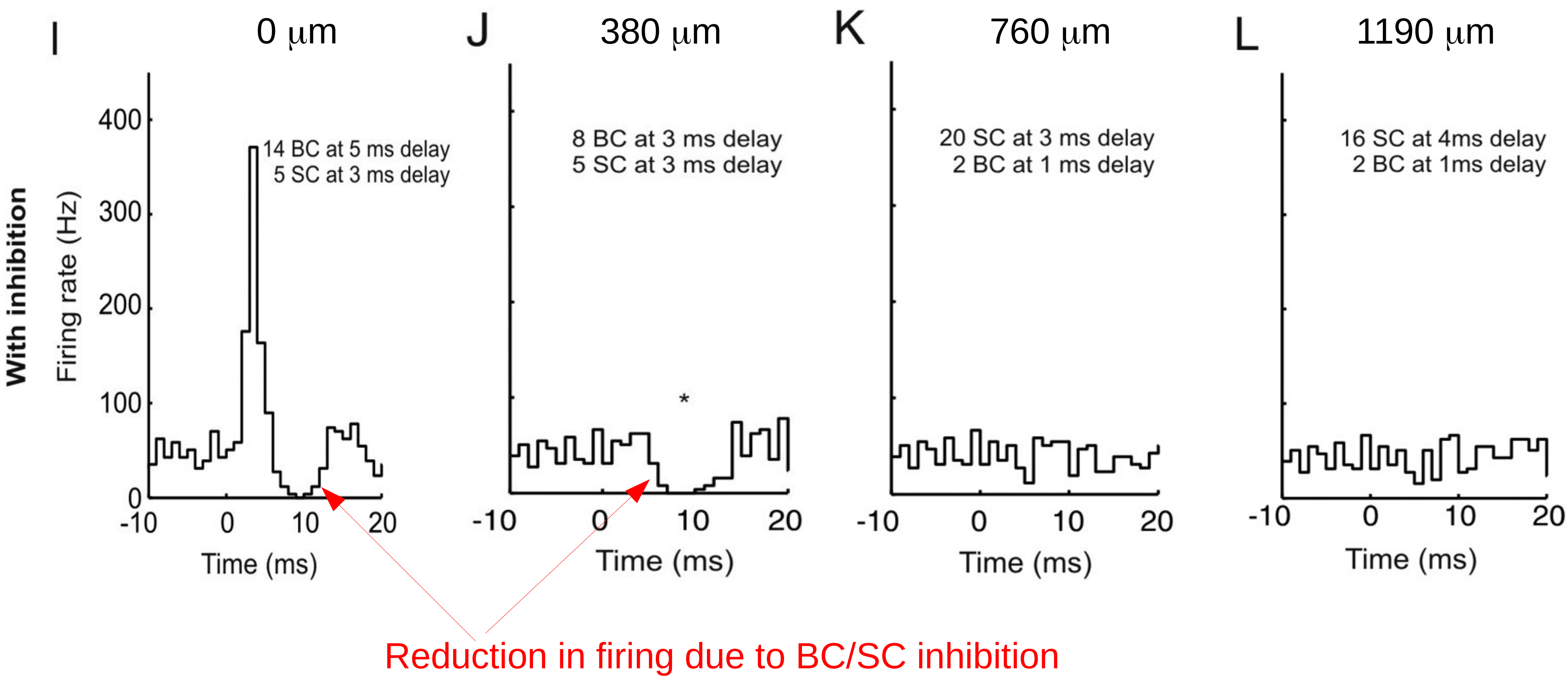


Network Simulation Using Wide Range of Conduction Velocities



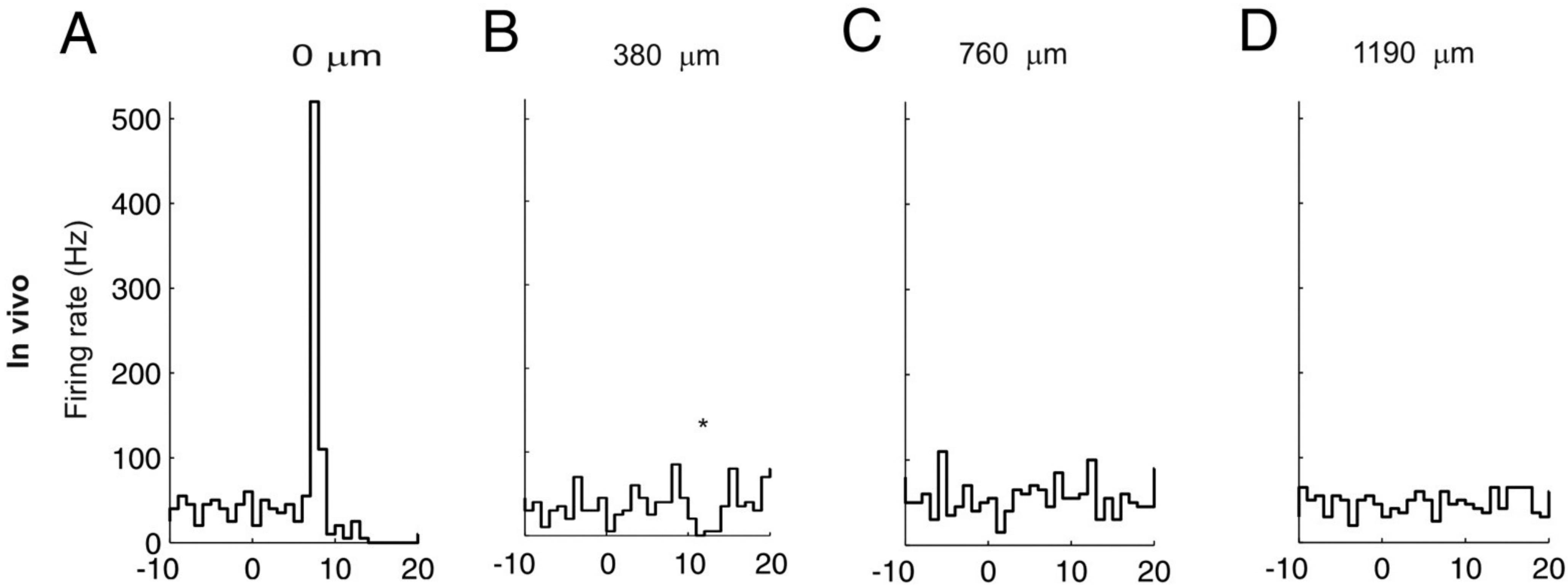
- Strong response immediately above the active granule cells.
- But cells further down the beam do respond. Doesn't fit the experimental data.

Adding Feedforward Inhibition to the Model



Feedforward inhibition eliminates the beam response.

Comparison To Real Data

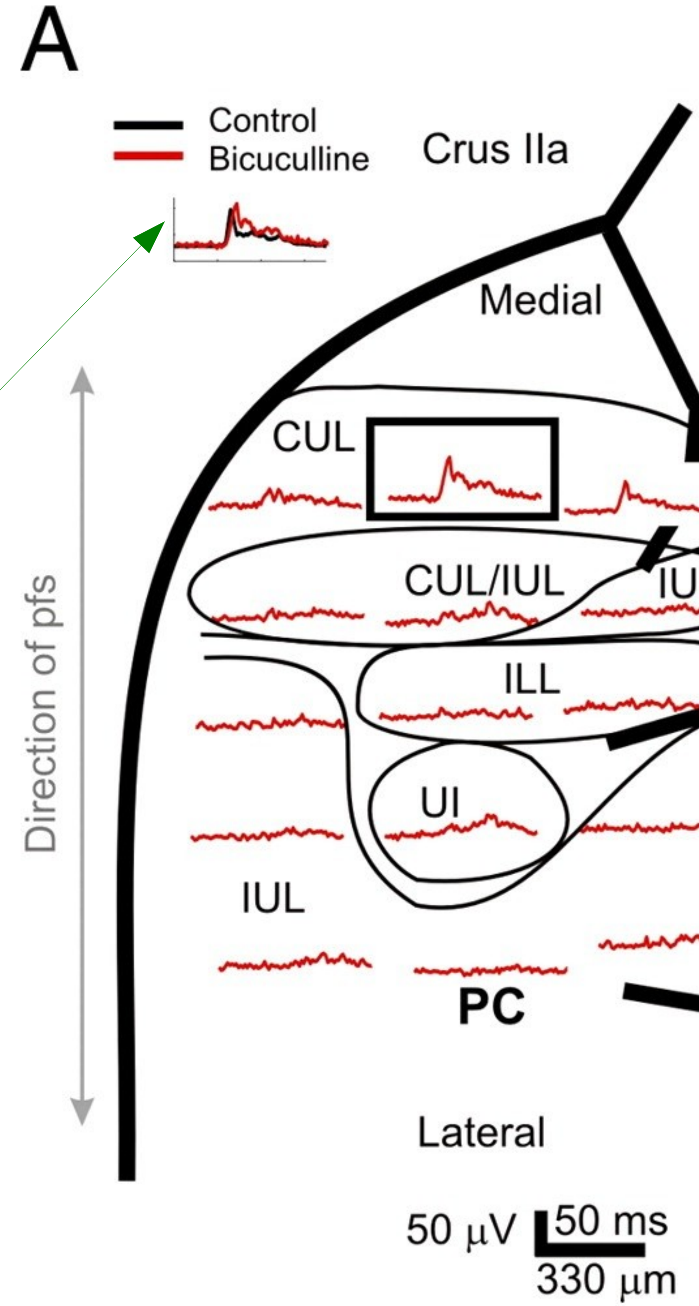


Granule Cell Reponses to Upper Lip Stimulation

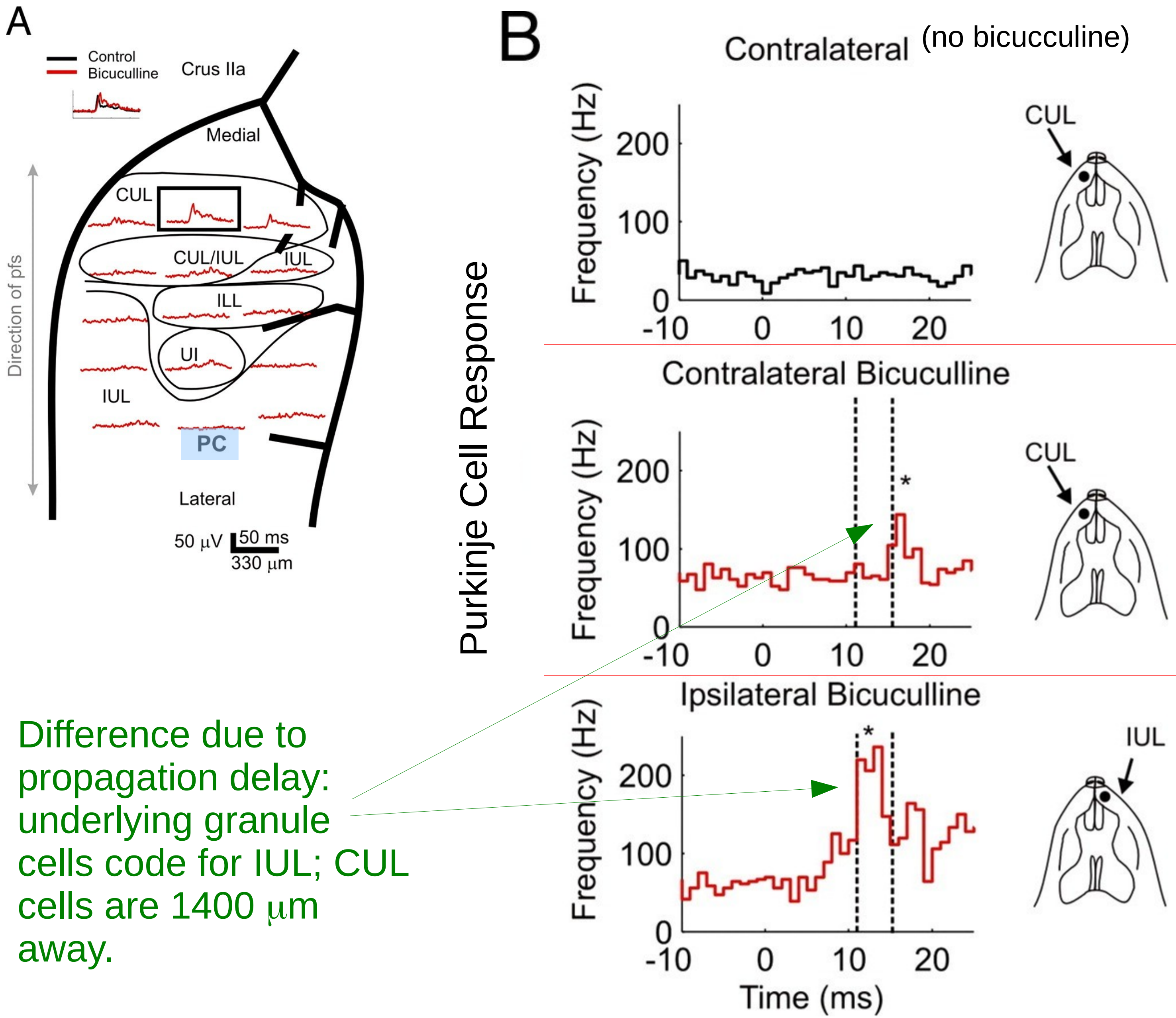
Recordings from Crus IIa

- CUL = Contralateral Upper Lip
- IUL = Ipsilateral Upper Lip
- ILL = Ipsilateral Lower Lip
- UI = Upper Incisor

Granule cells are unaffected by bicucculine (GABA$_A$ blocker).



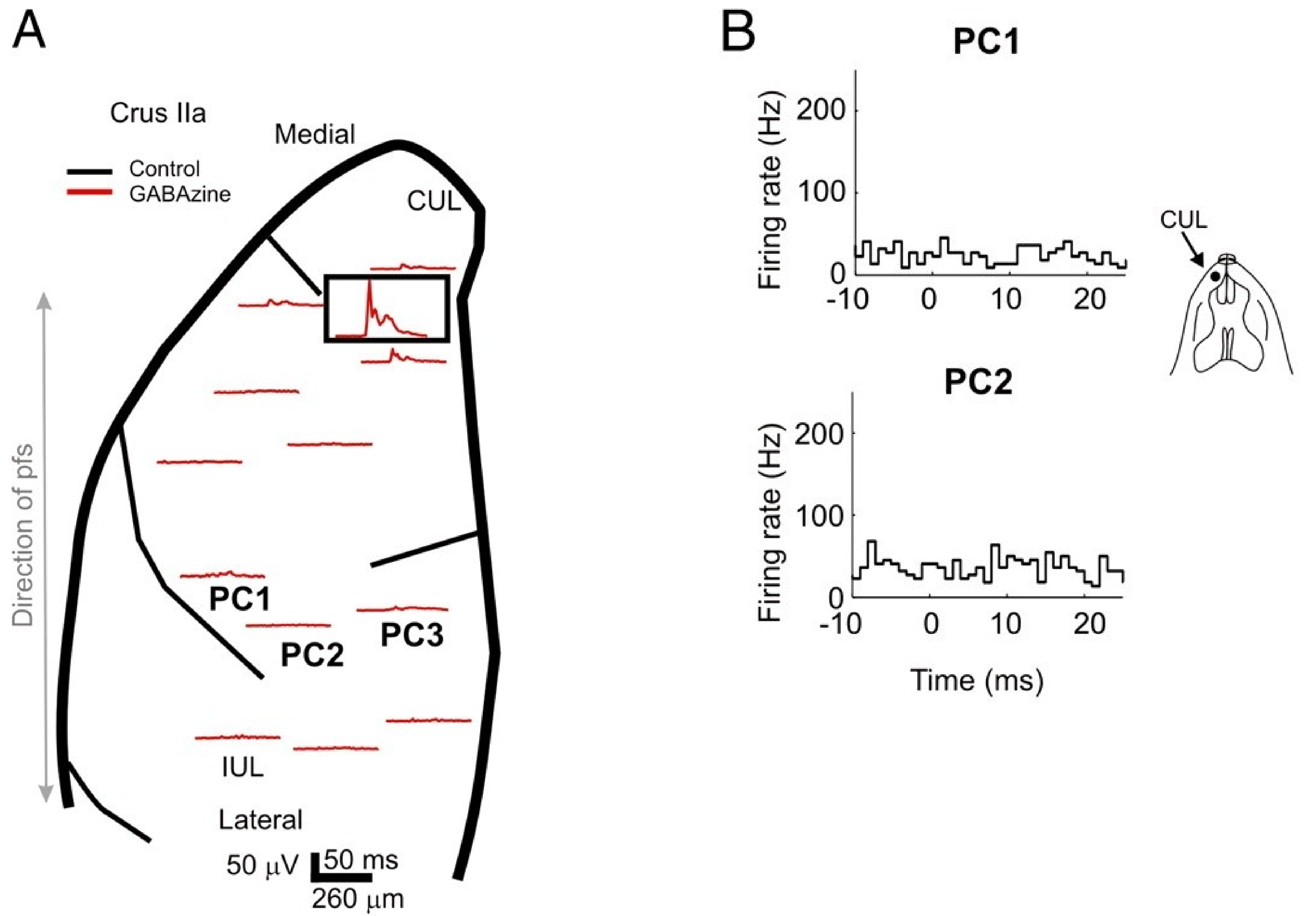
Purkinje Cell Response 1400 μm Away (IUL Stim.)



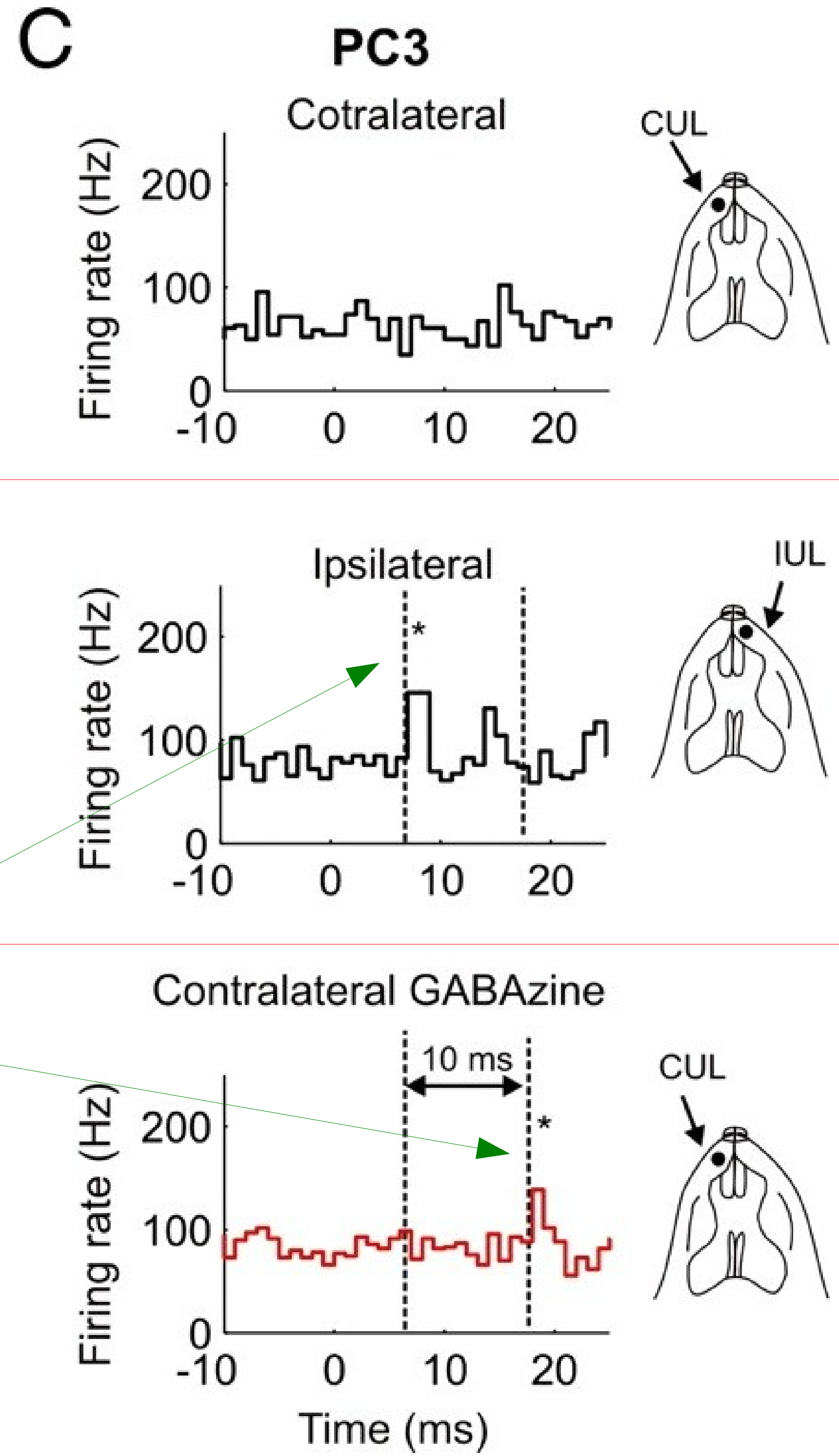
Beam revealed!

Difference due to propagation delay: underlying granule cells code for IUL; CUL cells are 1400 μm away.

Blocking Inhibition By Adding GABAzine

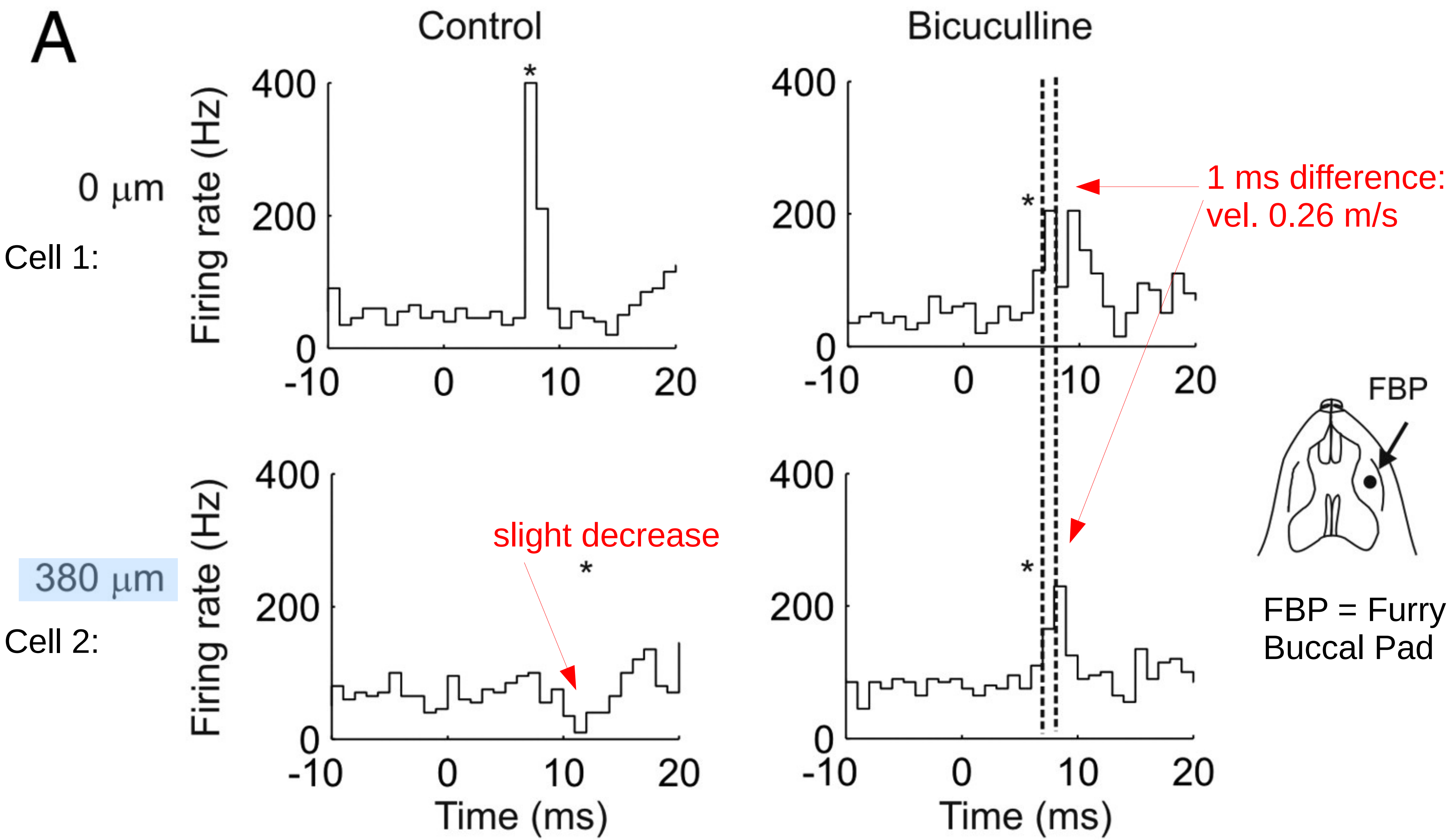


Adding GABAzine

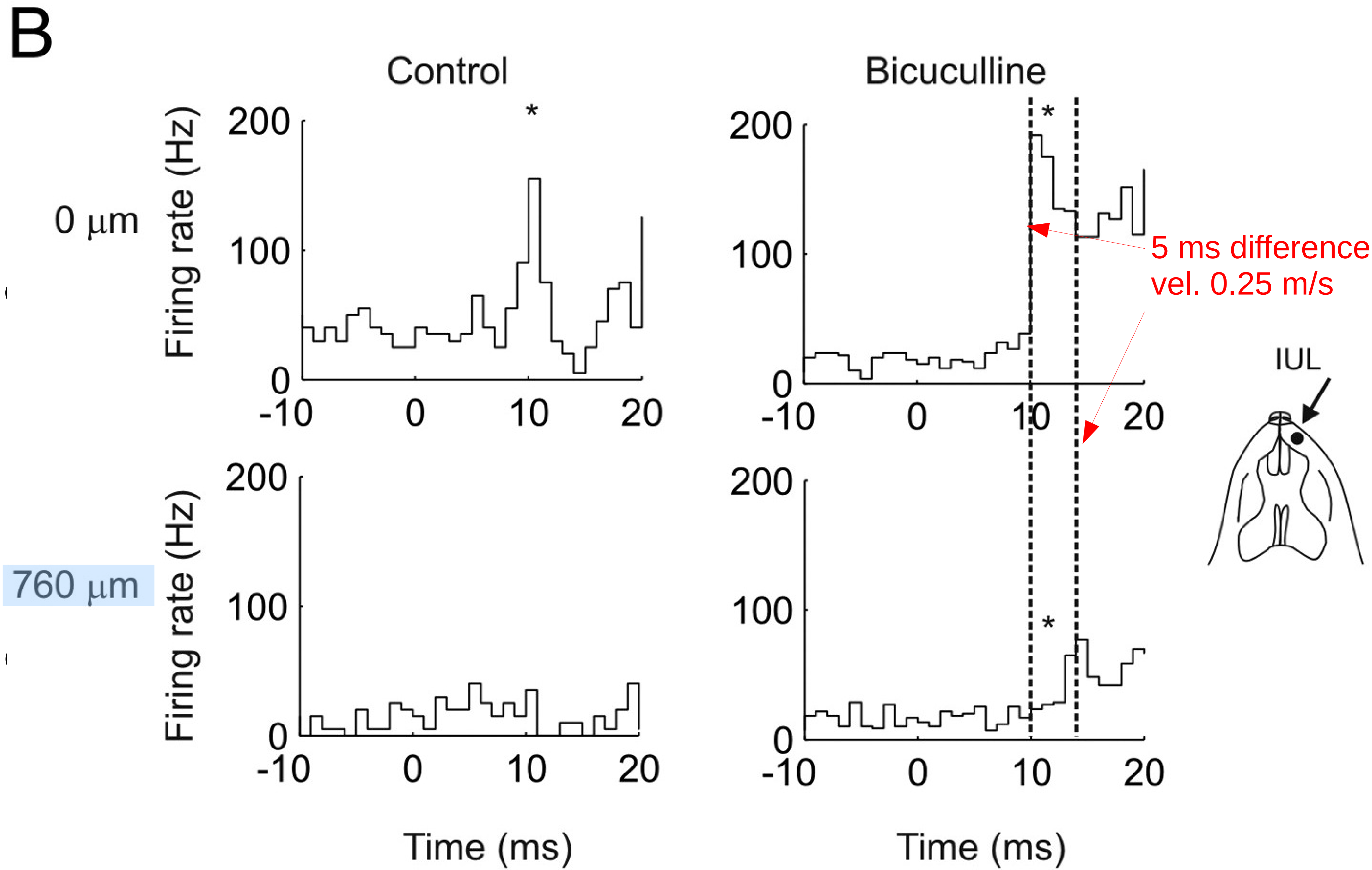


Difference due to propagation delay.

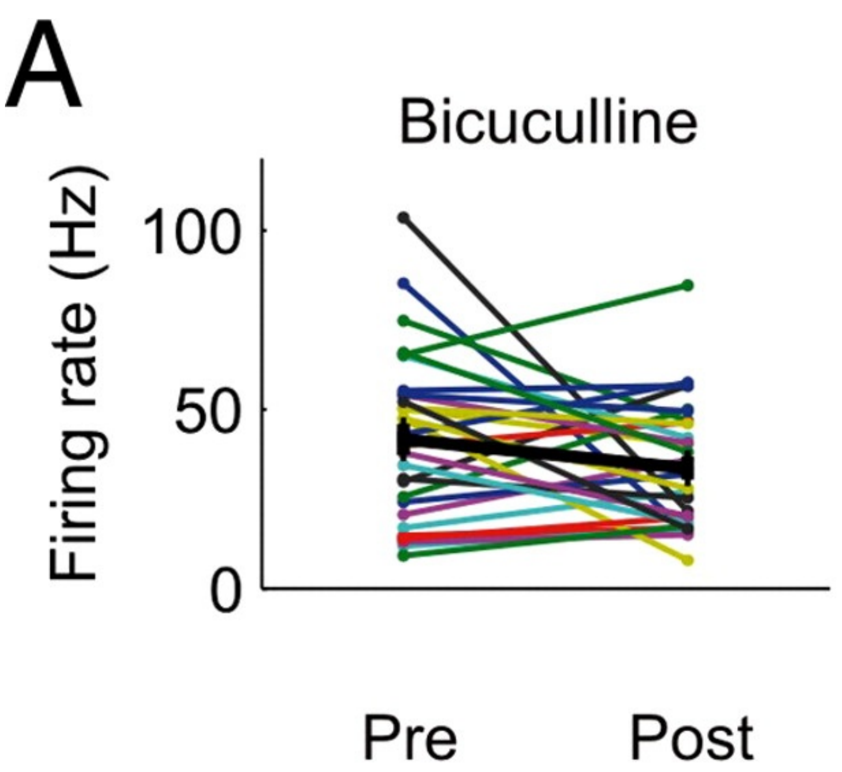
Estimating Propagation Velocities Using Two PCs



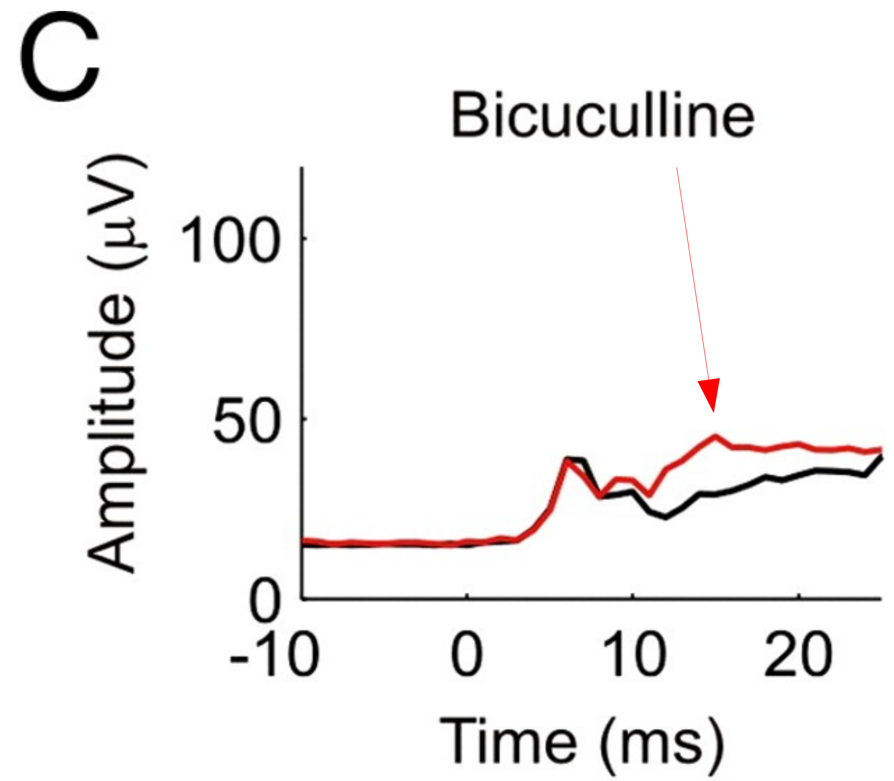
Estimating Propagation Velocities



Blocking $GABA_A$ Receptors Doesn't Increase Purkinje or Granule Cell Excitability: Bicuculline

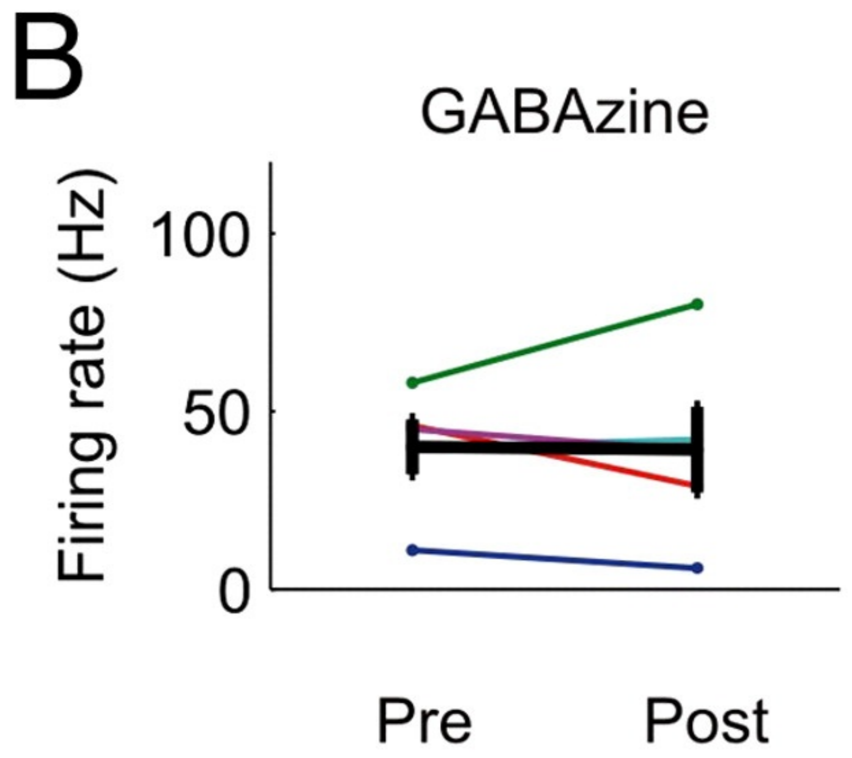


Purkinje cell response to bicuculline

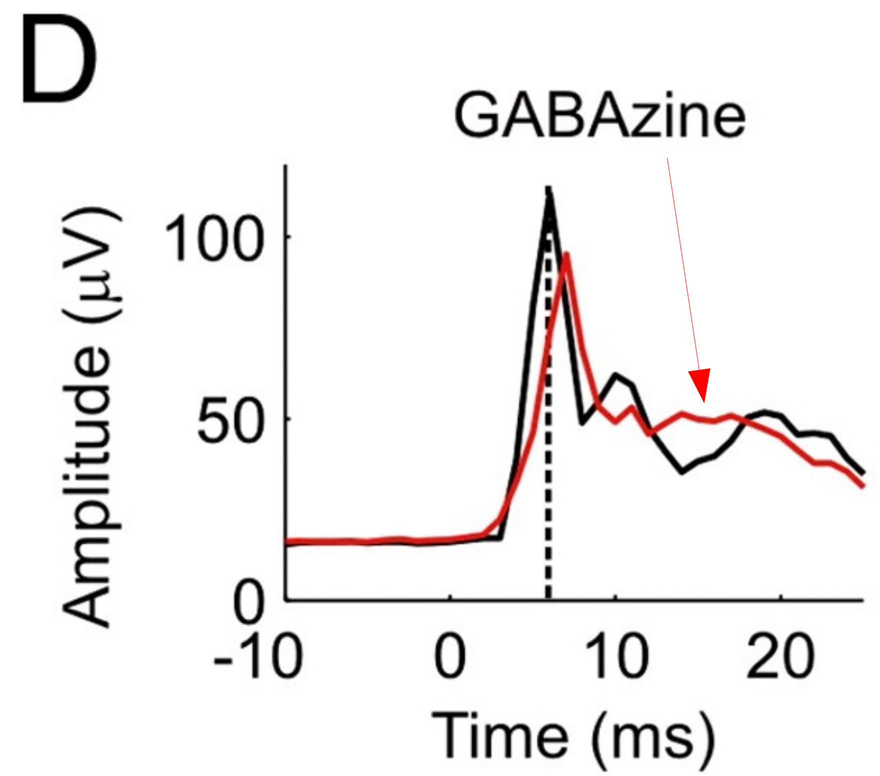


Granule layer response to CUL stimulation

Blocking GABA$_A$ Receptors Doesn't Increase Purkinje or Granule Cell Excitability: Gabazine



Purkinje cell response to GABAzine



Granule layer response to CUL stimulation

Simulation Parameters

- Purkinje cell conductances (from previously published model)
- Range of granule cell axon propagation times (0.15 to 0.5 m/s)
- Number of basket cell synapses as a function of distance from the active granule cells
- Number of stellate cell synapses as a function of distance from the active granule cells
- Temporal delays for basket and stellate cell activation

10 Purkinje Cell Conductances

Table S1

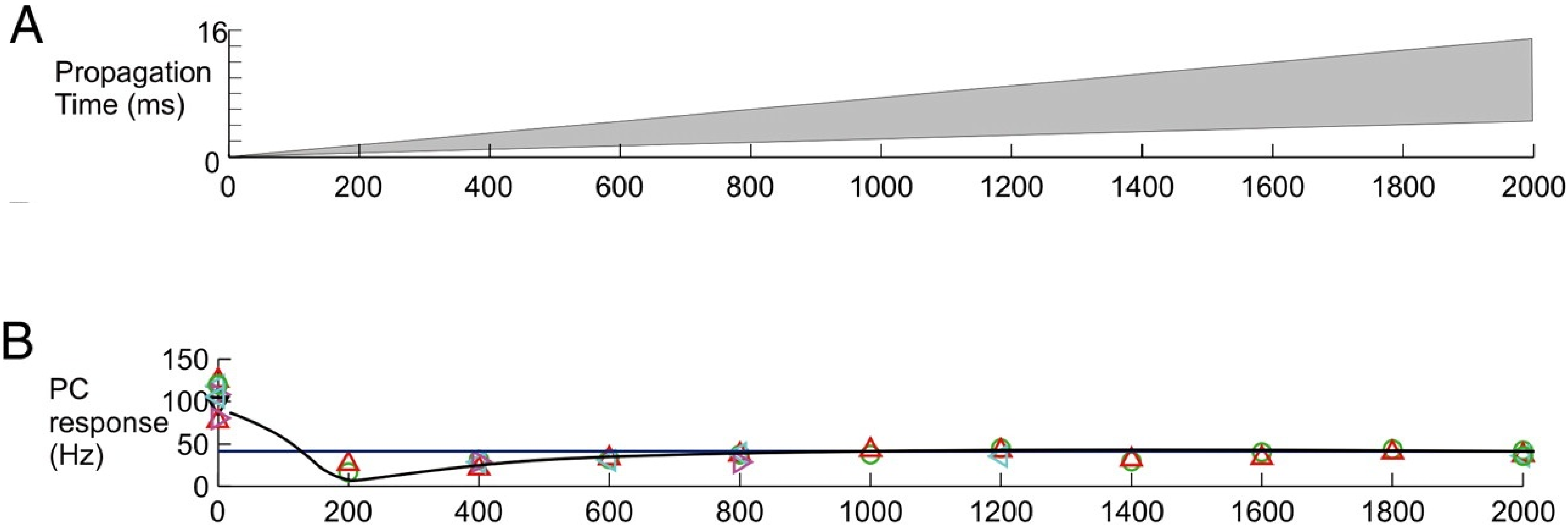
Conductances for the voltage and Ca_{2+} dependent channels in the PC model.

Parameters A, F, and H are in mV. For KC and BK factor **z** is in μM and B in ms.

NAME	Vr	Gate	P	A	B	C	D	E	F	G	H
NaF	45	m	3	35	0	5	-10	7	0	65	20
		h	1	0.23	1	80	10	7.5	0	-3	-18
NaP	45	m	3	200	1	-18	-16	25	1	58	8
CaP	135	m	1	8.5	1	-8	-12.5	35	1	74	14.5
		h	1	1.50×10^{-3}	1	29	8	5.5×10^{-3}	1	23	-8
CaT	135	m	1	2.6	1	21	-8	0.18	1	40	4
		h	1	2.50×10^{-3}	1	40	8	0.19	1	50	-10
Kh	-30										
Kdr	-85										
KM	-85										
KA	-85	m	4	1.4	1	27	-12	0.49	1	30	4
		h	1	1.75×10^{-2}	1	50	8	1.3	1	13	-10
KC	-85	m	1	7.5, α_m is constant				0.11	0	-35	14.9
		z	2	4	10						
K2	-85	m	1	25, α_m is constant				7.5×10^{-2}	0	5	10
		z	2	0.2	10						

Propagation Times, and Purkinje Cell Responses

Fastest pf conduction velocity: 0.5 m/s
Slowest pf conduction velocity: 0.15 m/s



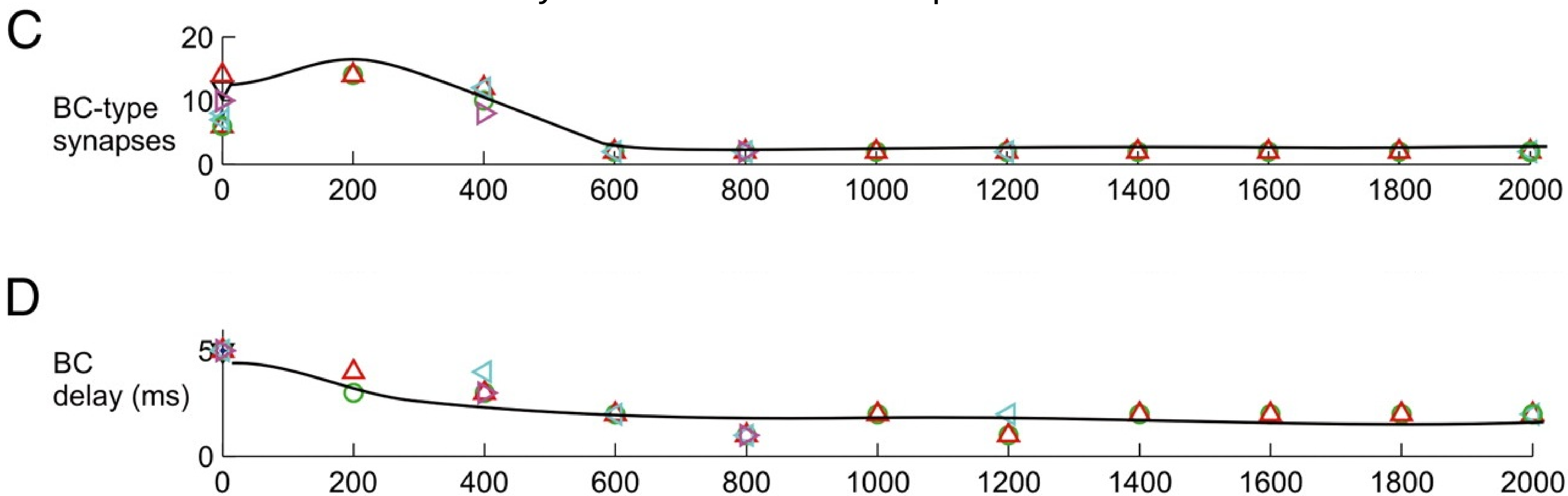
Each symbol denotes a parameter set that was run for 250 trials.

Exploring the Parameter Space

Parameter	***Range***	***Notes***
Minimum granule cell layer activation	2% of total number of granule cells	Activates a PC beam along the full length of parallel fibers if not compensated by feed-forward inhibition. Could be smaller when using higher numbers of parallel fibers in the simulation (Figure S1).
Basket cell synapses	1-16	Fast decay as distance increases from site of stimulation.
Stellate cell synapses	0-30	Increasing as a function of the distance to site of stimulation. Not always required on top of stimulation site.
Basket cell synaptic delay	1-5 ms	Shorter as distance increases from site of stimulation.
Stellate cell synaptic delay	1-5 ms	Wide range outside the areas closest to site of stimulation.

Basket Cell Synapses and Delay

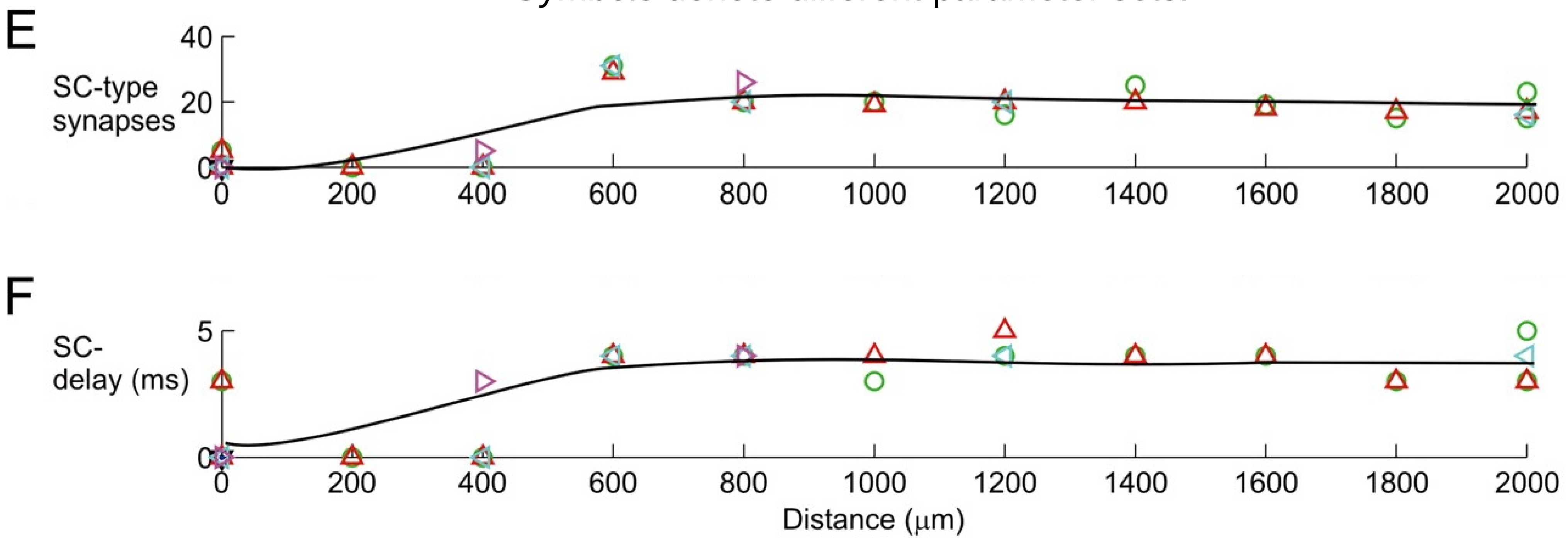
Number of BC synapses needed to replicate physiological data.
Symbols denote different parameter sets.



Range of temporal delays between pf excitation and activation of feedforward basket-type inhibition.

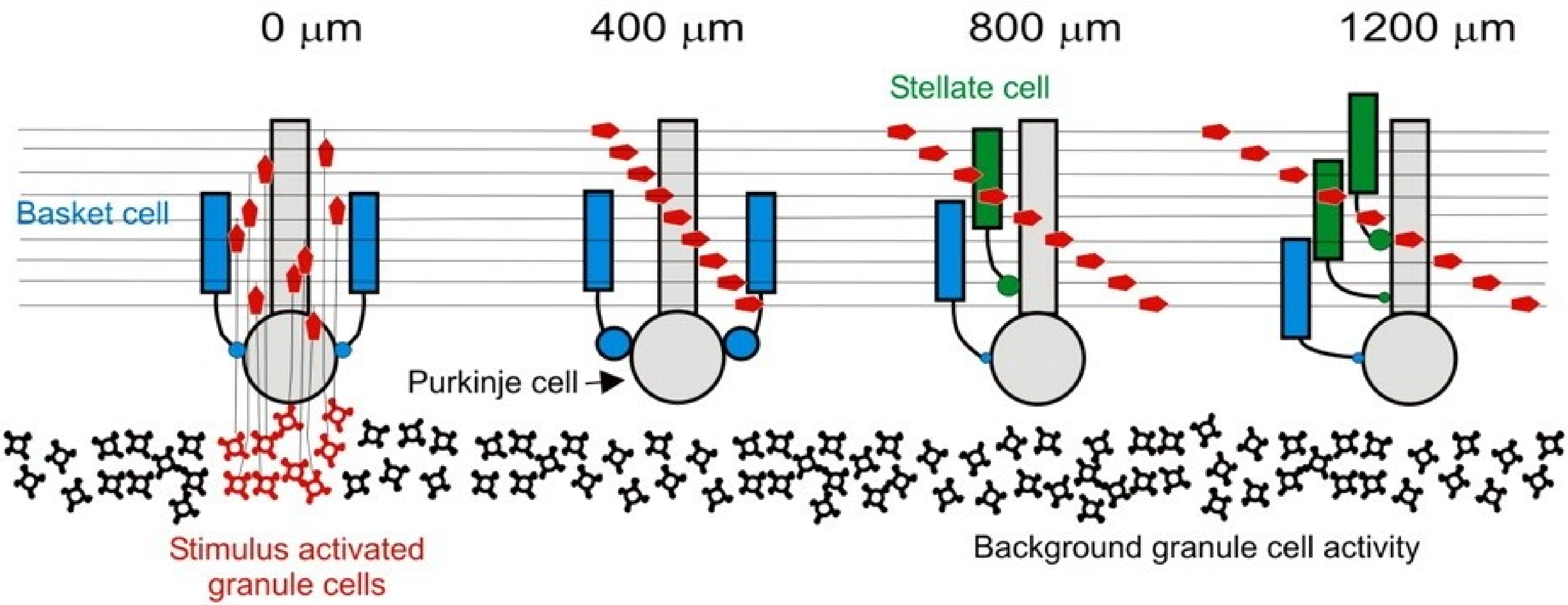
Stellate Cell Synapses and Delay

Number of SC synapses needed to replicate physiological data.
Symbols denote different parameter sets.

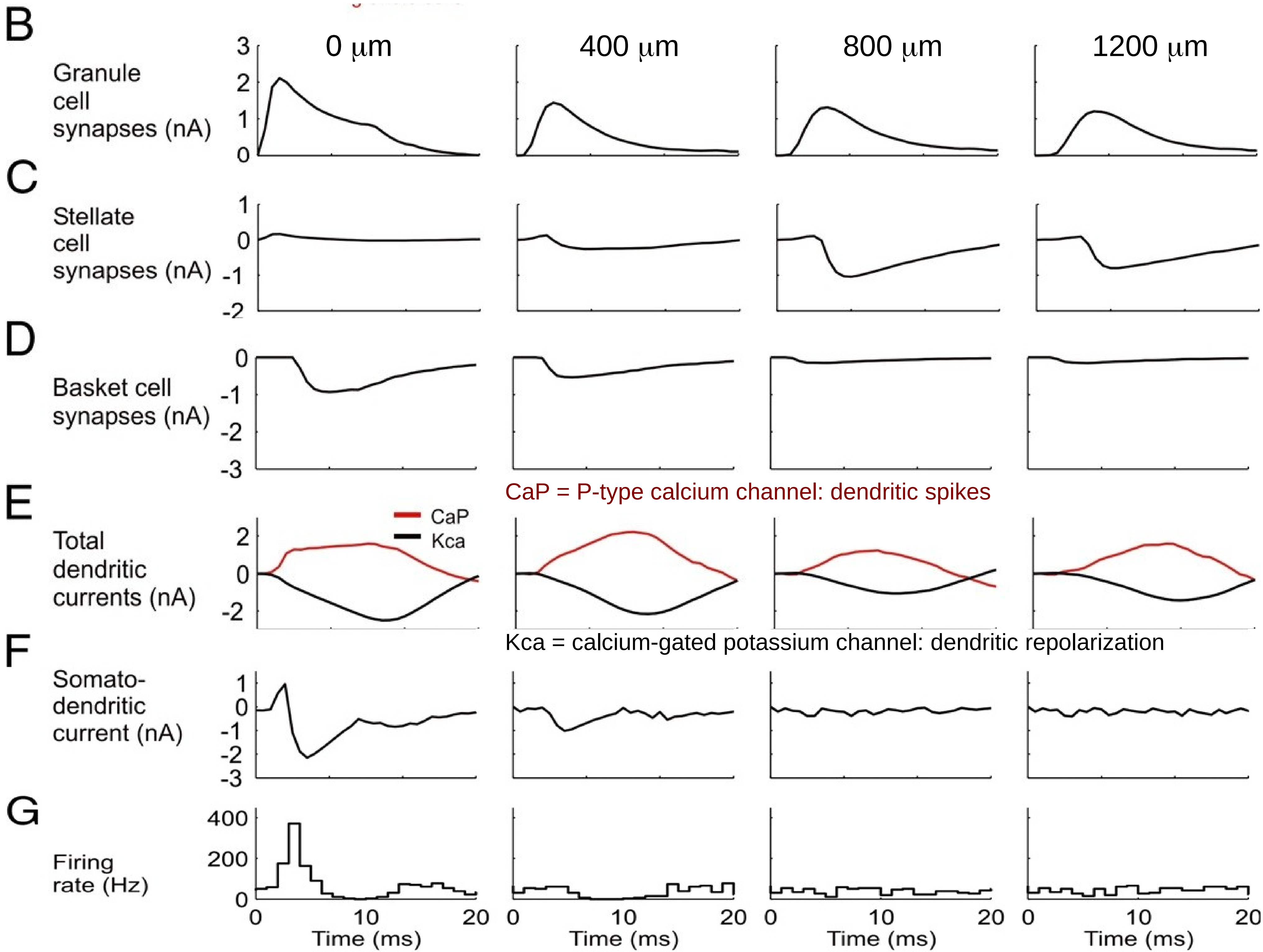


Range of temporal delays between pf excitation and activation of feedforward basket-type inhibition.

Distribution of Synapses Onto Purkinje Cells

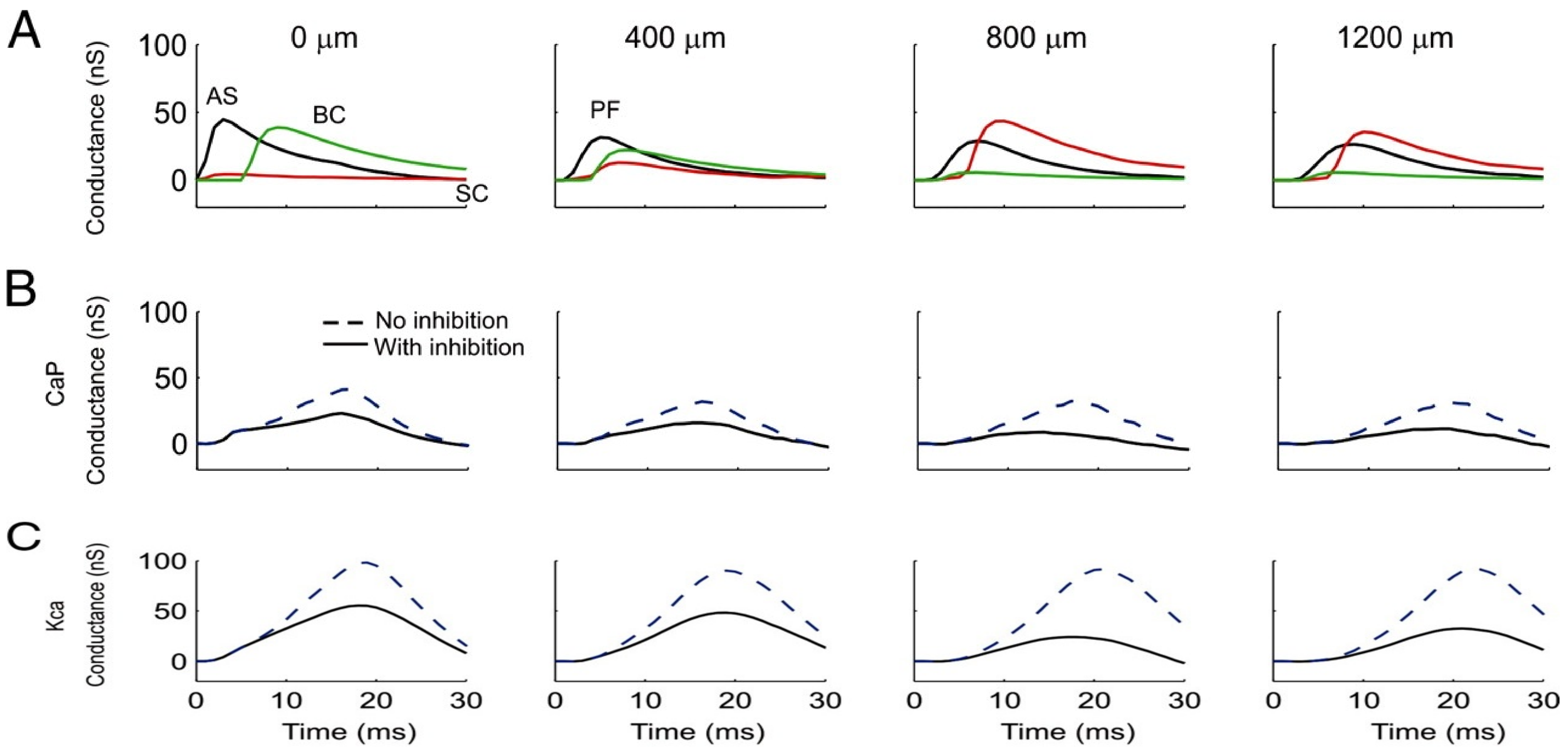


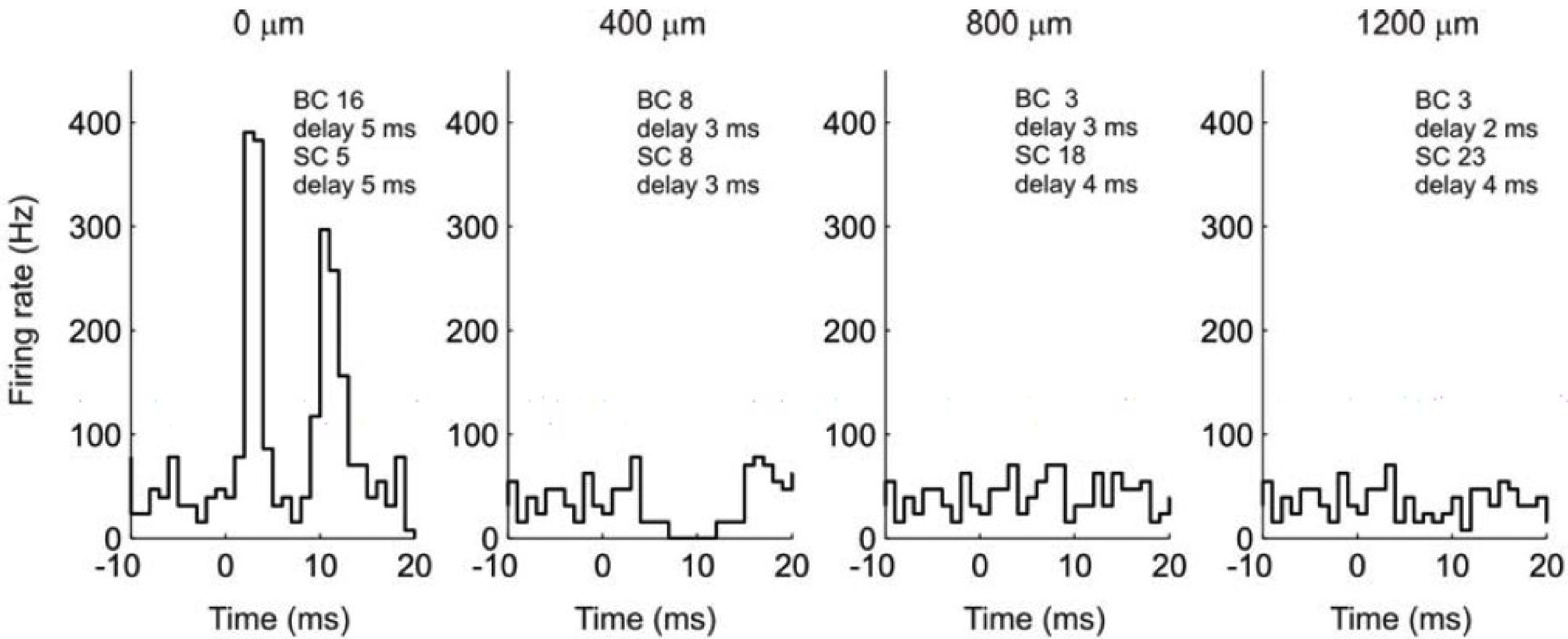
Notice that parallel fiber skew increases with distance.


B
C
D
E
F
G
0 μm
400 μm
800 μm
1200 μm
Granule cell synapses (nA)
Stellate cell synapses (nA)
Basket cell synapses (nA)
Total dendritic currents (nA)
Somato-dendritic current (nA)
Firing rate (Hz)
CaP
Kca
CaP = P-type calcium channel: dendritic spikes
Kca = calcium-gated potassium channel: dendritic repolarization
Time (ms)

PC Dendritic Conductances Along A Beam

granule cell, basket cell (short range inhibition), stellate cell (long range inhibition)



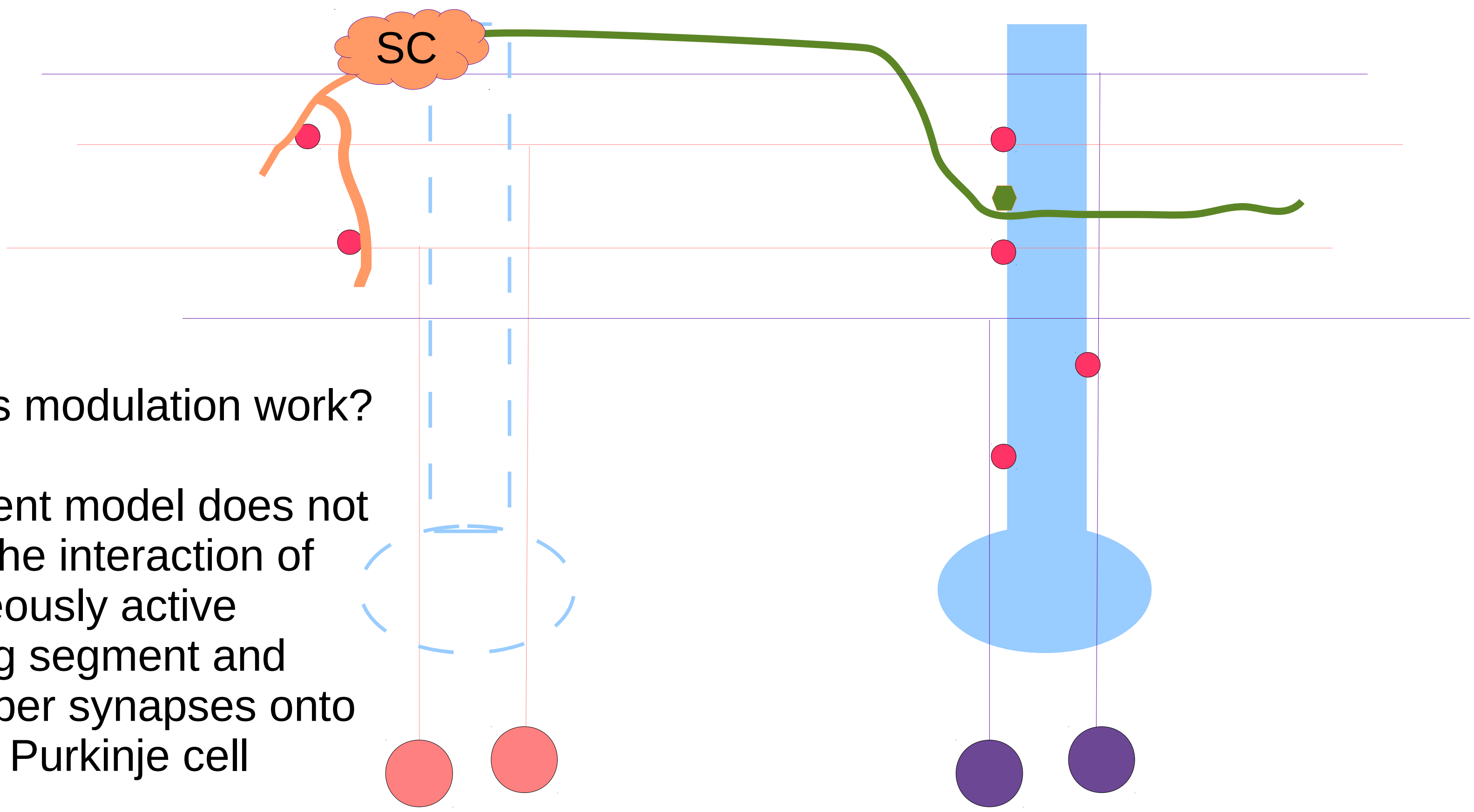


- 15,000 parallel fibers; 0.5% are stimulated
- Used <u>slower conduction velocities</u> for rats: 0.20 to 0.27 m/s
- Random excitation/inhibition to cause 40 Hz spontaneous firing
- Conduction delay and # of BC & SC synapses are shown.
- Same results as for 0.15 m/s to 0.5 m/s conduction velocities.

Conclusions

- Ascending segment excitation arrives too quickly to be blocked by feed-forward inhibition, so PCs directly above the active granule cells will fire due to PF inputs.
- Further along the beam, parallel fiber excitation is blocked by feed-forward inhibition, at 0-400 μm by basket cells, and further out by stellate cells.
  - Aside: although all vertebrates possess a cerebellum, basket-type inhibitory connections are found only in birds and mammals, which have the highest granule cell to Purkinje cell ratios.
- Granule cell synapses made by the ascending segment vs. the parallel fiber segment should be viewed as functionally distinct.

Activation and Modulation



How does modulation work?

The present model does not address the interaction of simultaneously active ascending segment and parallel fiber synapses onto the same Purkinje cell dendrite.

Modulation from stellate cells driven by parallel fibers

Activation from ascending segment and parallel fibers

Santamaria et al.'s Conclusions

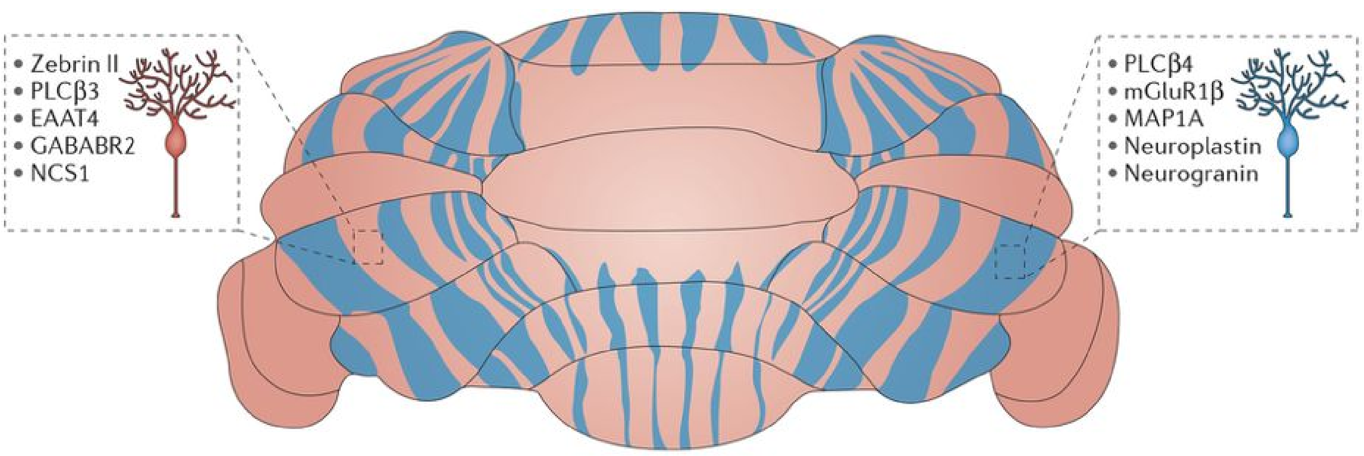
- Why have parallel fibers synapse onto PCs if their effects are blocked by feedforward inhibition?
- Hypothesis:
  - Unlike the ascending segment synapses, parallel fiber synapses are not intended to make the PC fire.
  - Parallel fibers modulate the state of the Purkinje cell dendrite and control its response to excitation from ascending segment synapses.
- A similar hypothesis has been made about cortical pyramidal cells:
  - Perhaps the majority of cortical excitatory synapses serve to modulate dendritic dynamics rather than drive somatic output.
- The paper is a powerful illustration of how modeling and experiments can interact.

D'Angelo et al.: Modeling the Cerebellar Microcircuit

- More realistic models are feasible now, due to:
  - better data about cell types, connectivity, physiology
  - increased computer power
- Zebrin stripes not considered in earlier models:
  - Different types of Purkinje cells, distinguished by molecular markers such as zebrin, form anatomical subregions (striations) and have different response and learning properties
  - Z+ Purkinje cells have slower spontaneous firing (40Hz) than Z- cells (90-100 Hz).
  - Z+ and Z- cells have different pf-PC synaptic plasticity characteristics (response to pf stimulation frequency).
  - Golgi cell somata and dendrites are restricted to the same zebrin stripe of Purkinje cells..

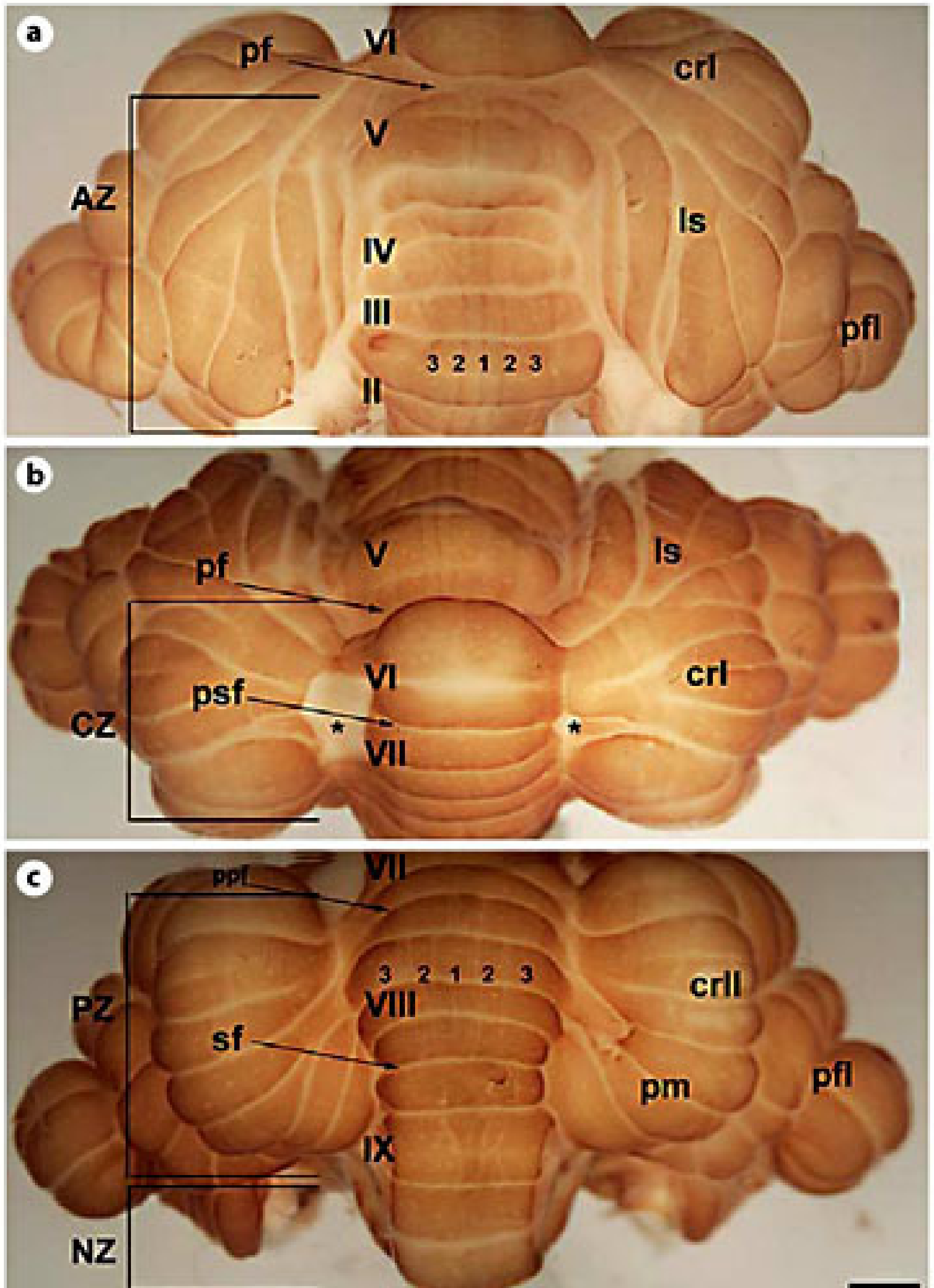
Zebrin Stripes in Mouse Cerebellum

Dasterdji et al. (2012) Frontiers in Neuroanatomy



Cerminara et al. (2015) Nature Reviews Neuroscience.

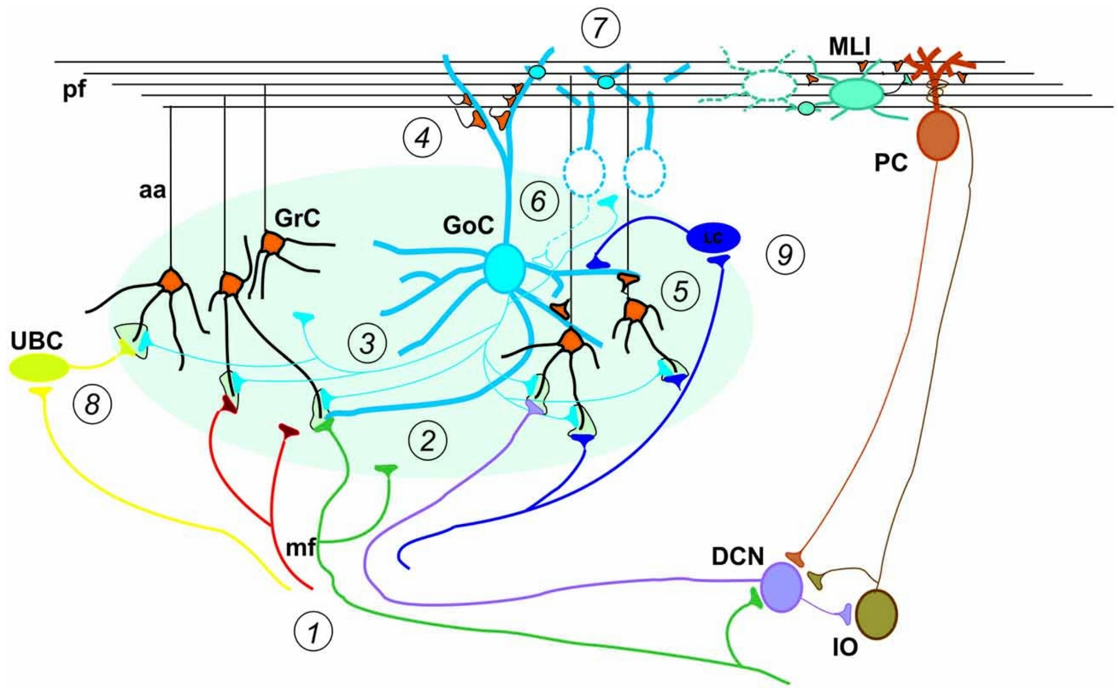
Zebrin Staining in Wallaby Cerebellum



Marzban, Hassan & Hoy, Nathan & R Marotte, Lauren & Hawkes, Richard. (2012). Antigenic Compartmentation of the Cerebellar Cortex in an Australian Marsupial, the Tammar Wallaby Macropus eugenii. Brain, behavior and evolution.

D'Angelo et al.: Modeling the Cerebellar Microcircuit (cont.)

- More than 15 types of plasticity in cerebellum
- Oscillations in inferior olive, granule cell layer
- Waves of activation across Pk cells?
- Gap junctions between nearby Golgi cells, IO cells, stellate cells can lead to synchronization of oscillations
- Recurrent connections DCN<->GrC and DCN<->IO



Conclusions

- Cerebellum anatomy and physiology are more complex than early models assumed.

- The cerebellum's circuitry is not as uniform as originally assumed. There are regional differences:
  - In distribution of cell types.
  - In Purkinje cell learning properties.

- Temporal dynamics (oscillations, frequency response) play an important role that early models don't address.