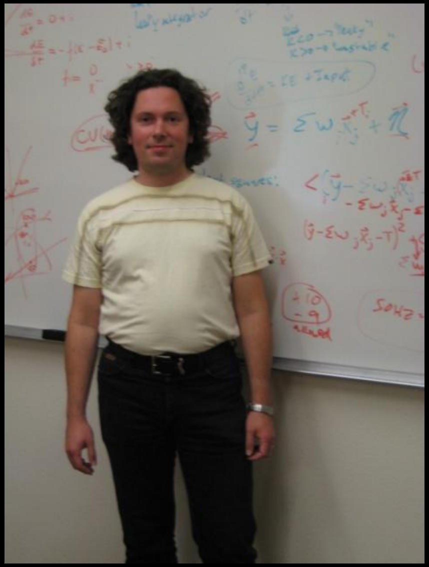
Bridging single-neuron measurements and network function

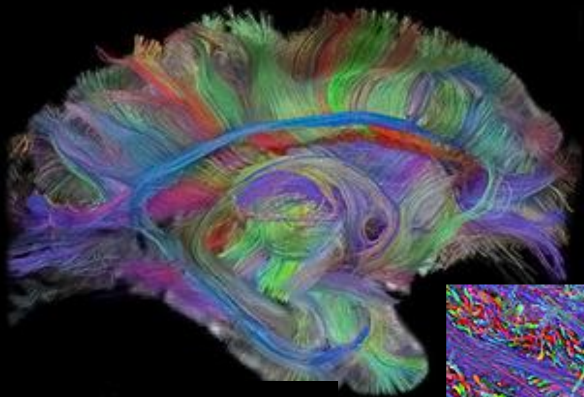


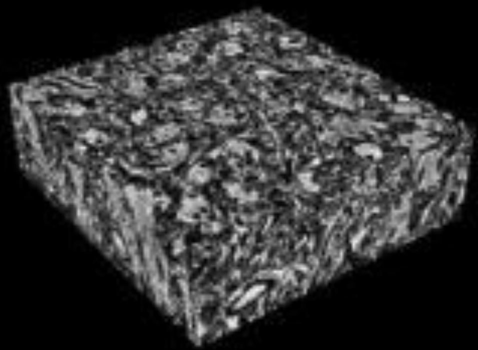
Dimitry Fisher

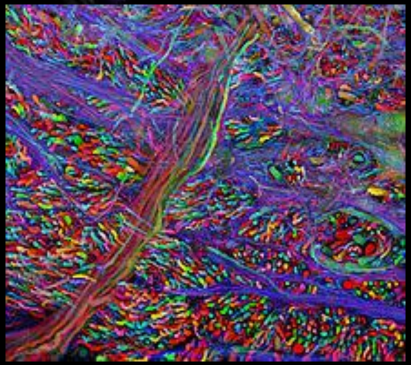
Sukbin Lim

Mark Goldman
Center for Neuroscience
University of California, Davis

Connectomics:
Panacea or Self-Delusion?



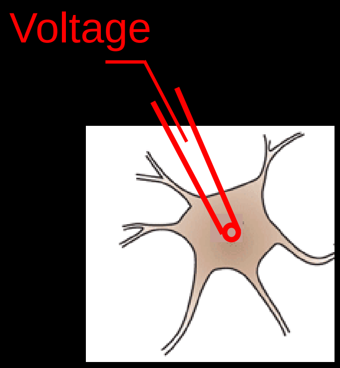




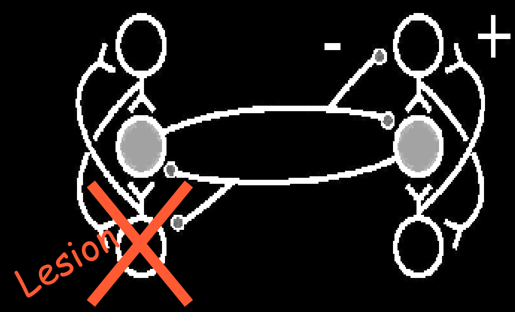
(How much)
insight?

How can we Connect Cells to Behavior?

Complex behavior: Involves mechanisms occurring across multiple scales, from molecules→cells→networks→behavior



Cellular properties (intracellular recordings)



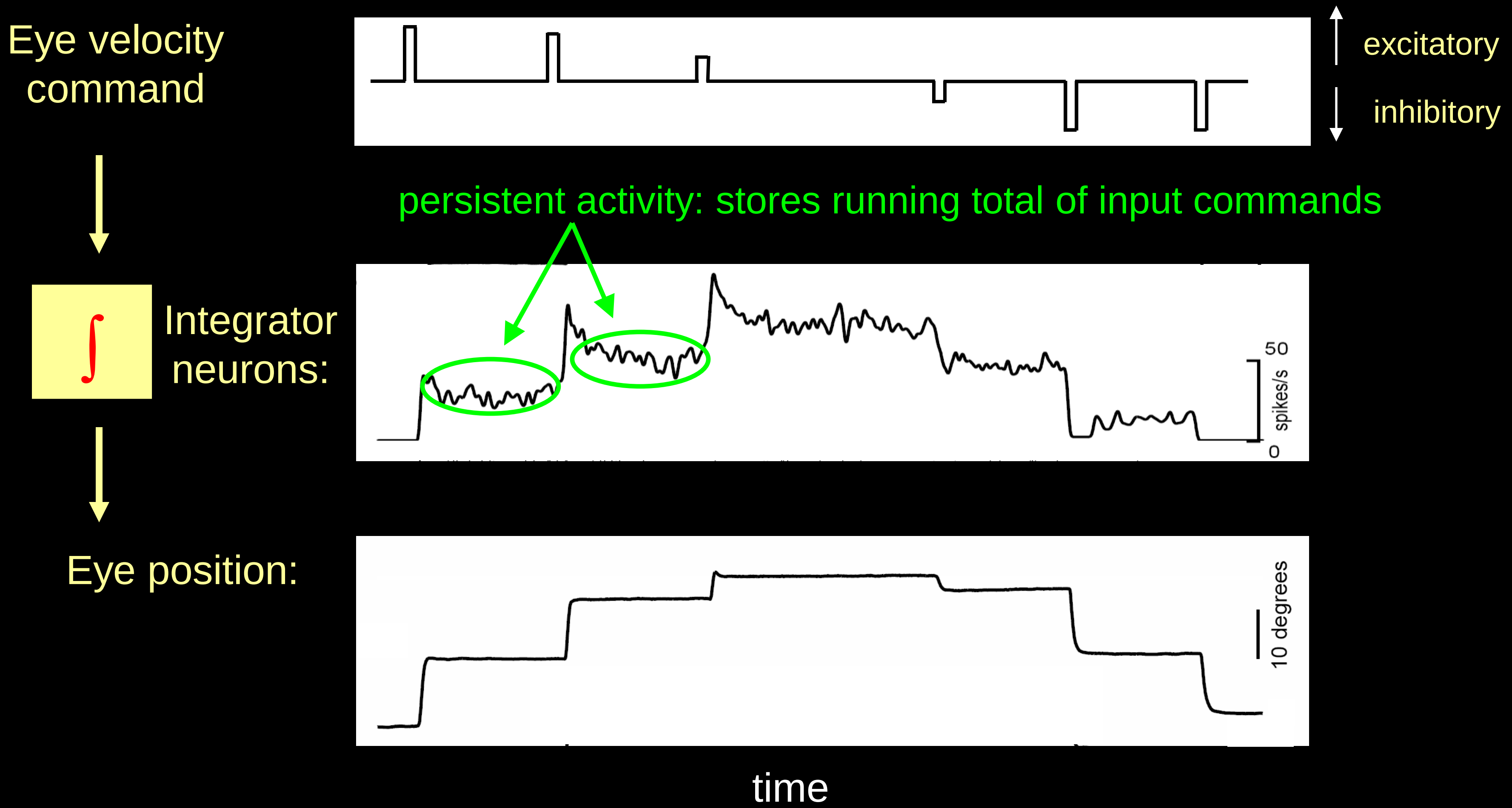
Circuit interactions (anatomy, lesion studies)

Behavioral measures (neuronal response during behavior)

Computational modeling provides a means to connect data at each of these scales

Goldfish Eye Movement System

The Oculomotor Neural Integrator



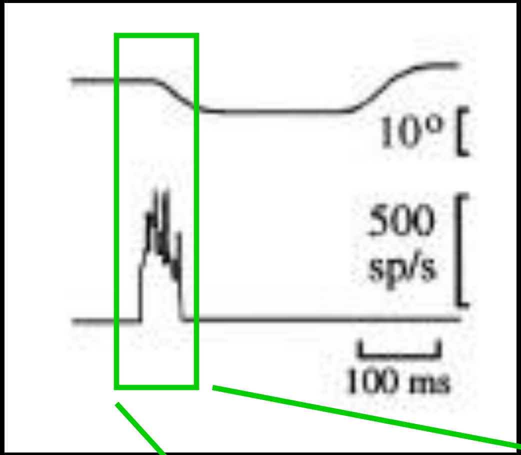
(data from Aksay et al., *Nature Neuroscience*, 2001)

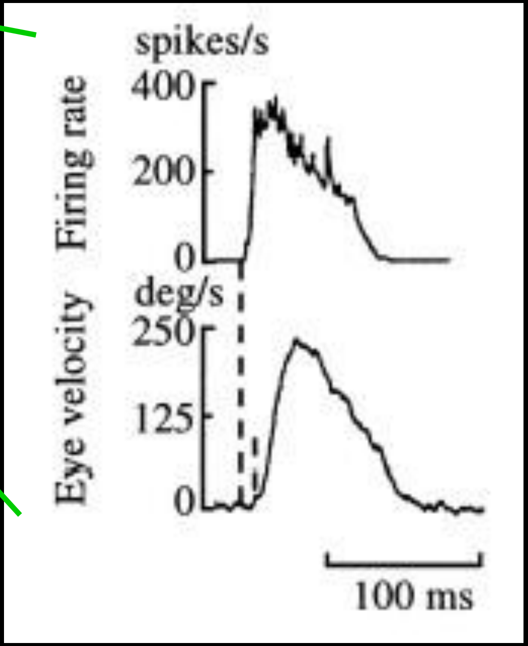
Input to Integrator: Eye Movement Burst Neurons

(adapted from Yoshida et al., 1982)

Eye Position (degrees)

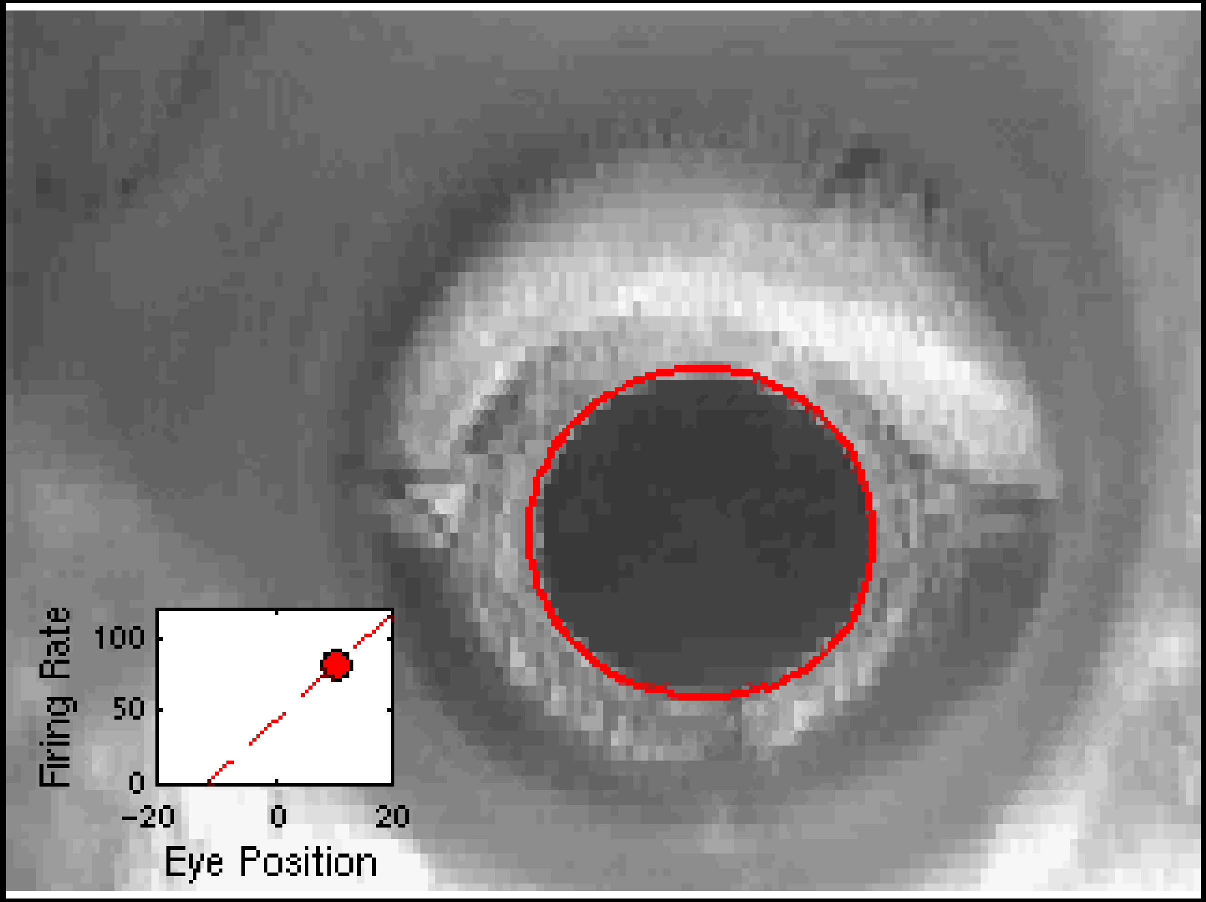
Eye movement neuron firing rate (spikes/sec)





Burst neurons code for eye velocity

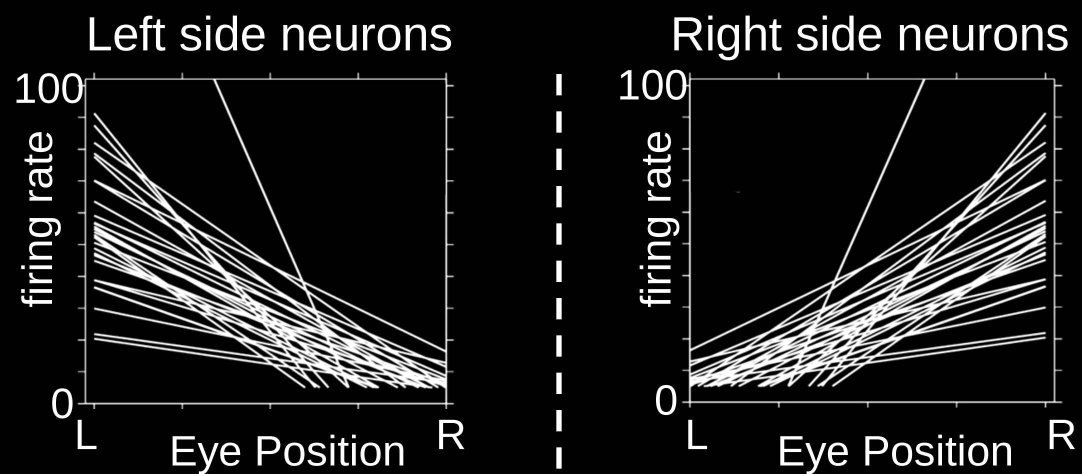
Integrator Neurons:
Firing Rate is Proportional to Eye Position



Network Architecture

(Aksay et al., 2000)

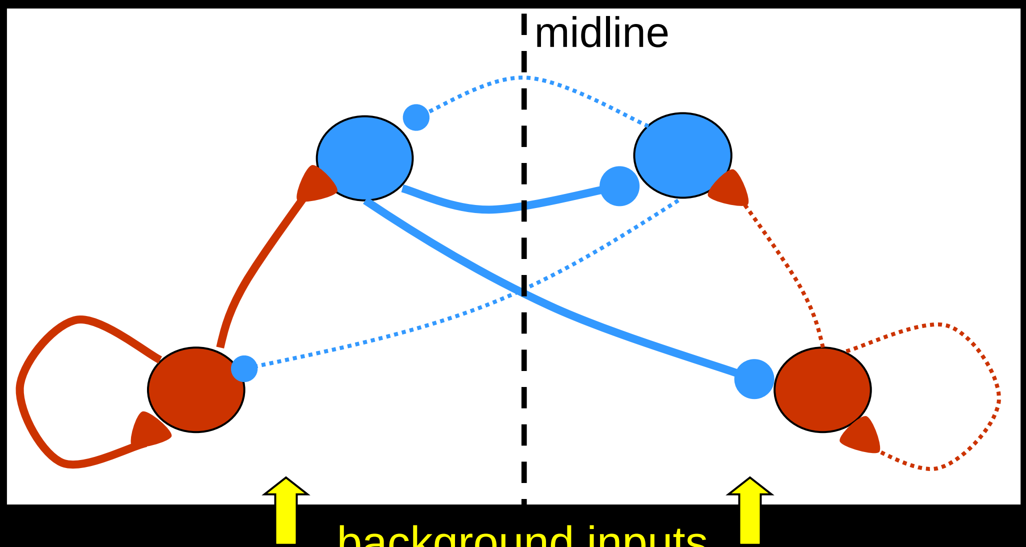
Firing rates:



4 neuron populations:

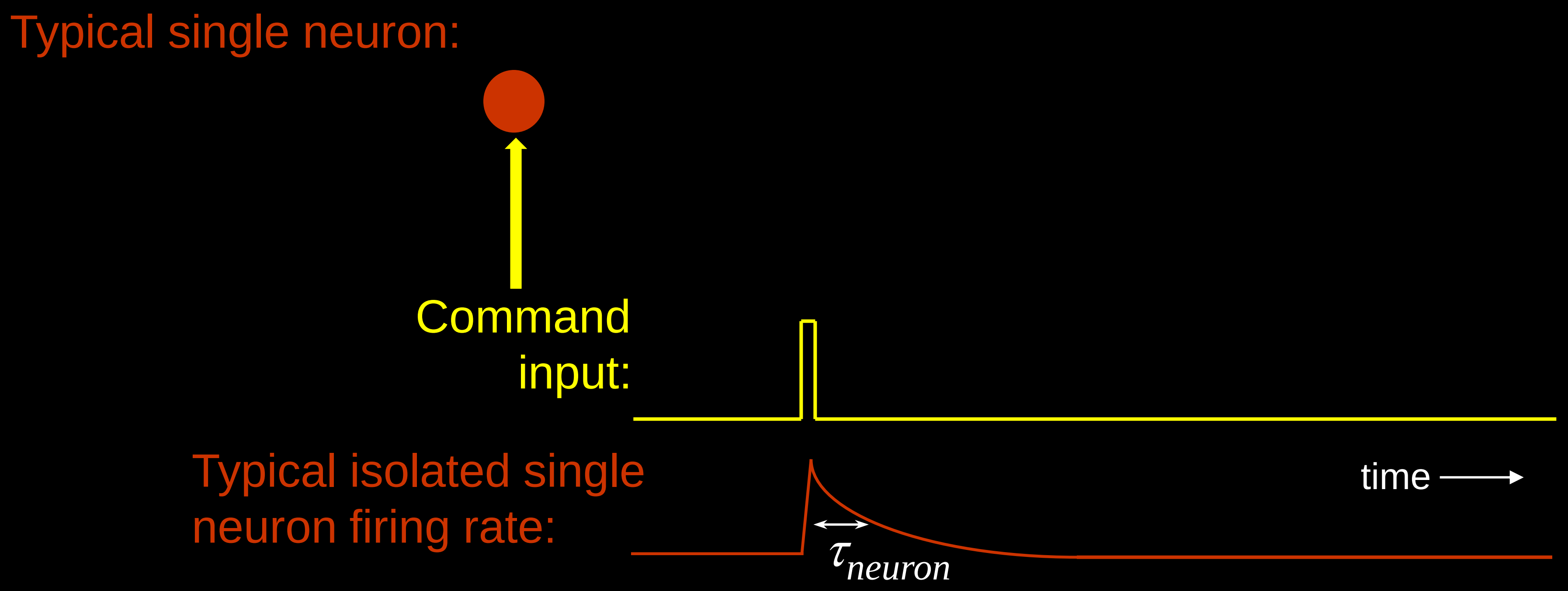
Inhibitory

Excitatory

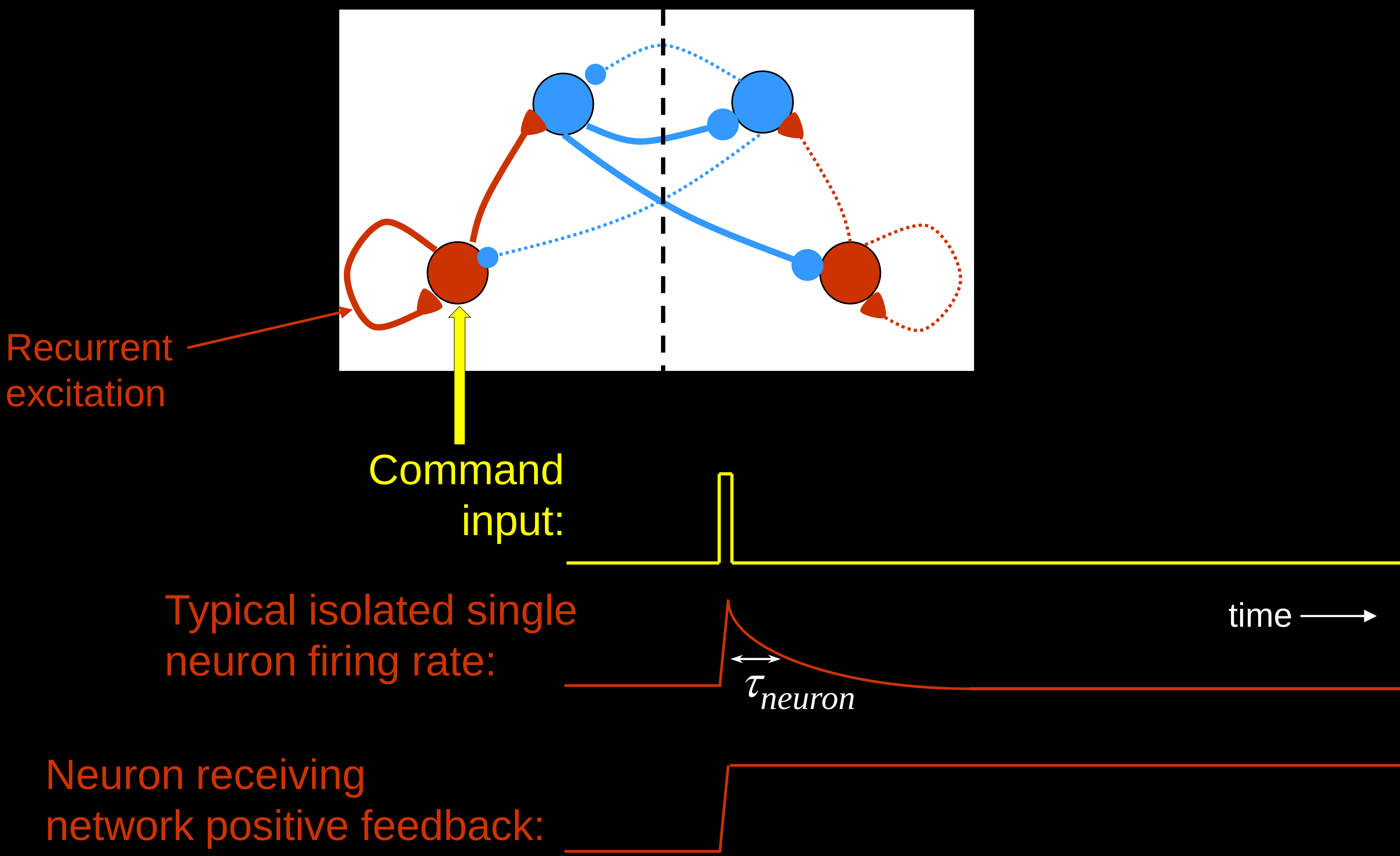


background inputs
& eye movement commands

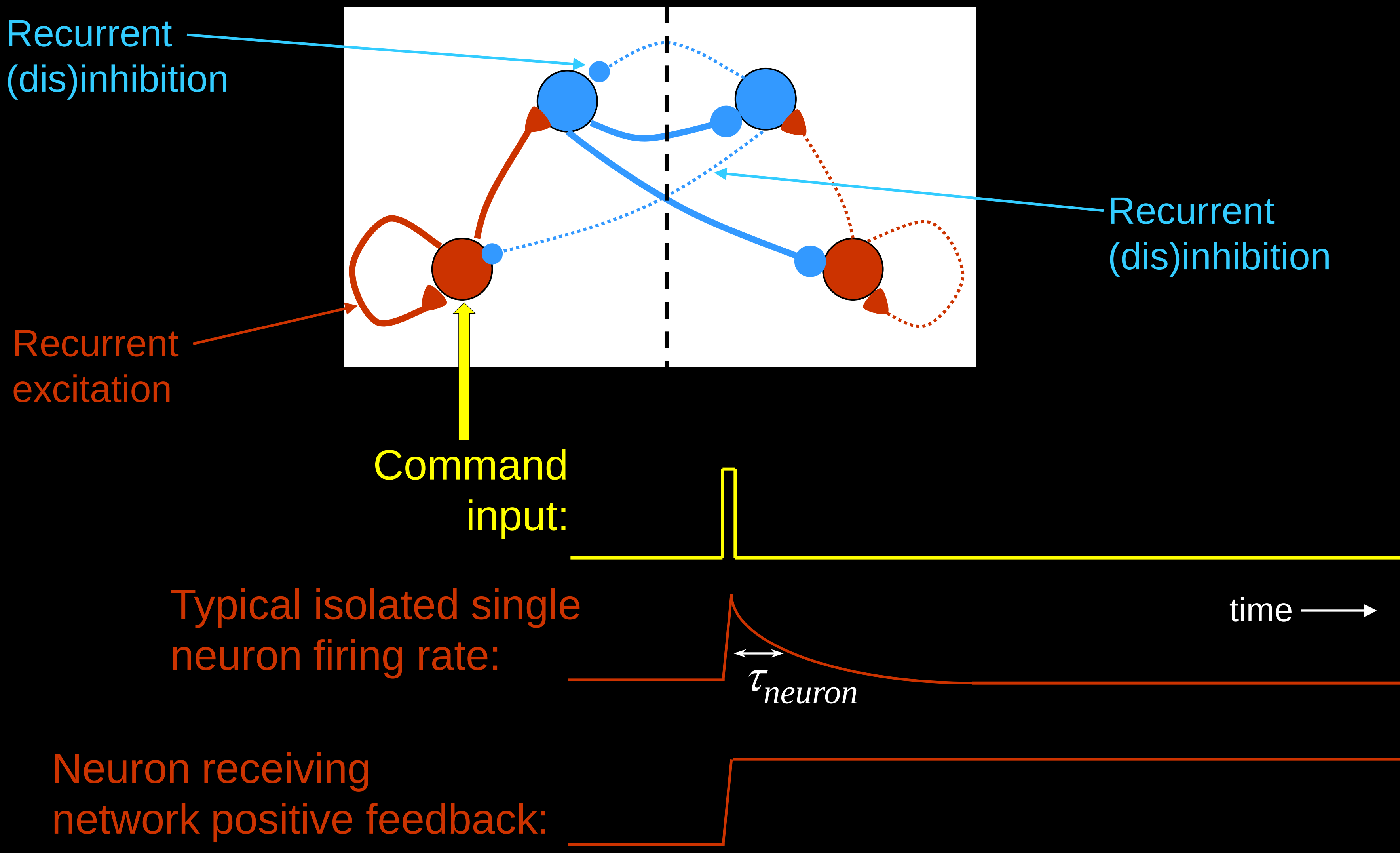
Traditional view of how persistent activity is generated: Network positive feedback



Traditional view of how persistent activity is generated: Network positive feedback



Traditional view of how persistent activity is generated: Network positive feedback



Fitting a conductance-based network model

Big Picture: Fit model by making a cost function that is constrained by and/or minimized when neurons match:

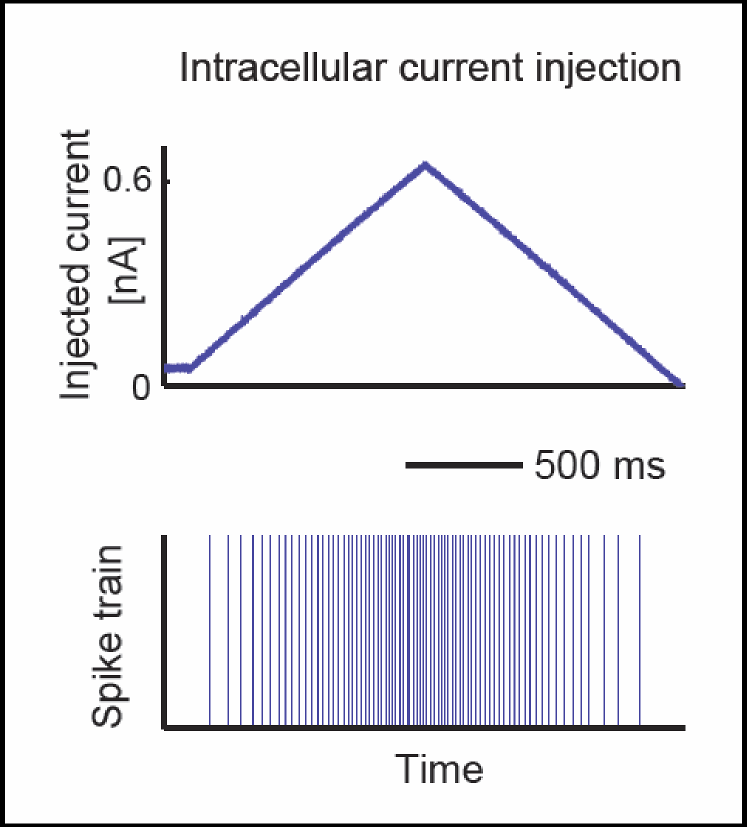
- Gross anatomical organization of excitation and inhibition
- Intracellular current injection experiments
- Single neuron firing rates during eye fixations (tuning curves)
- Patterns of drift following inactivation of part of network

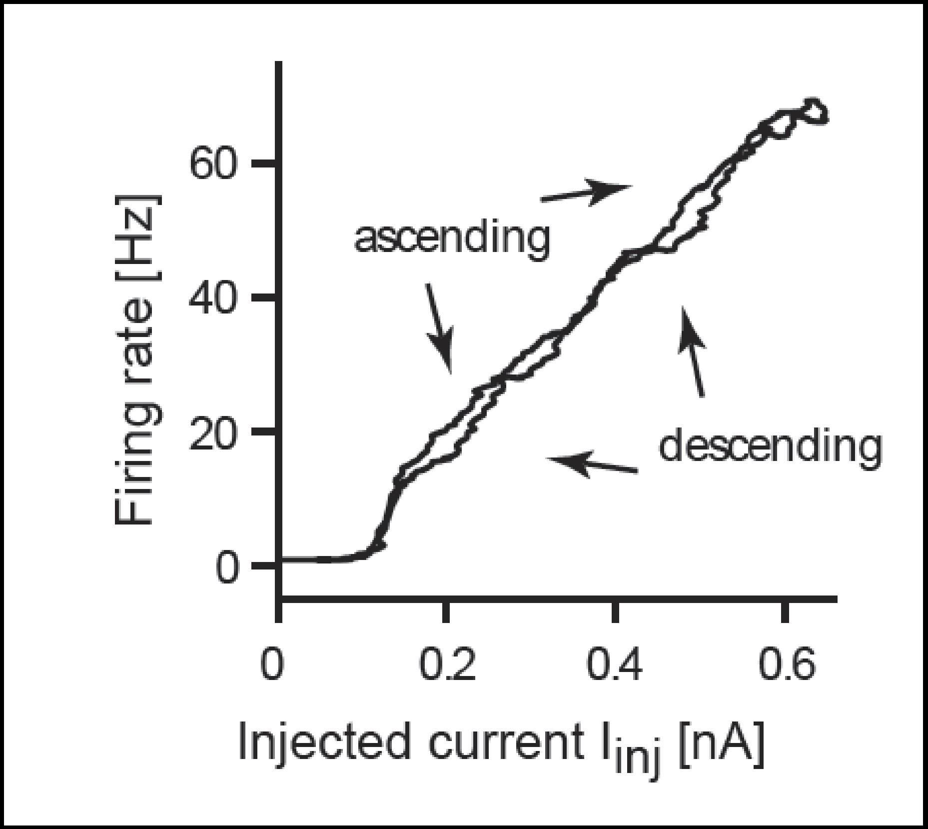
Program:

1) Fit a spiking model of single-neuron responses

2) Fit network connection strengths & nonlinearities to tuning curve data & inactivation experiments

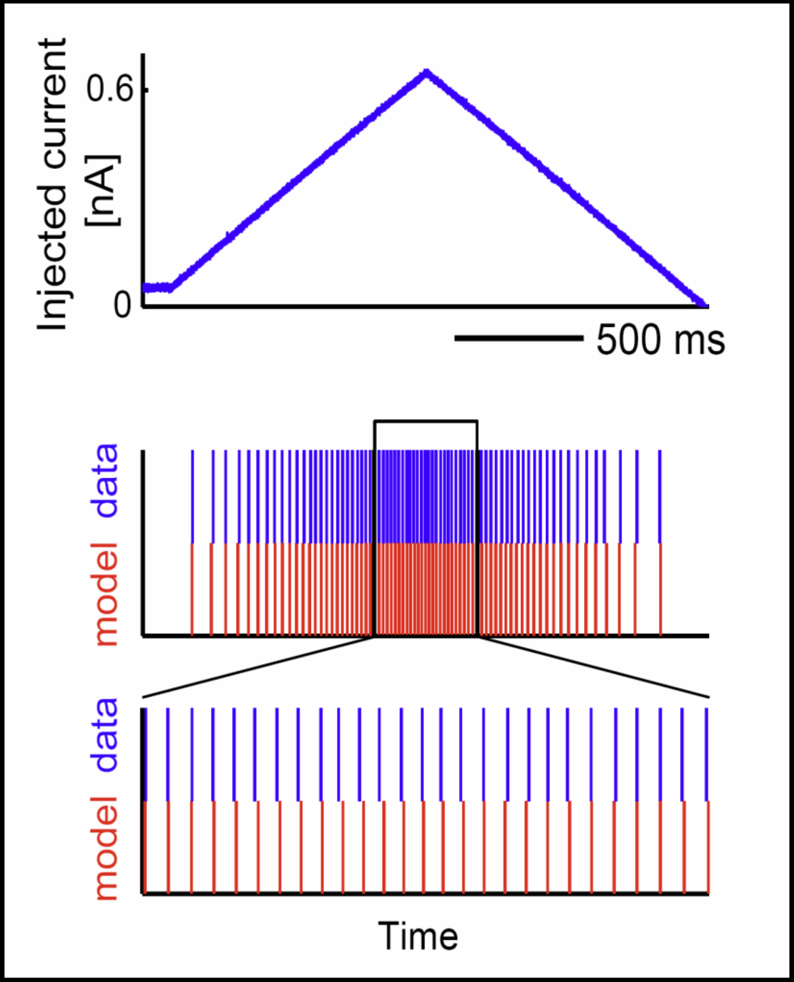
Experimental Data: Single Neuron



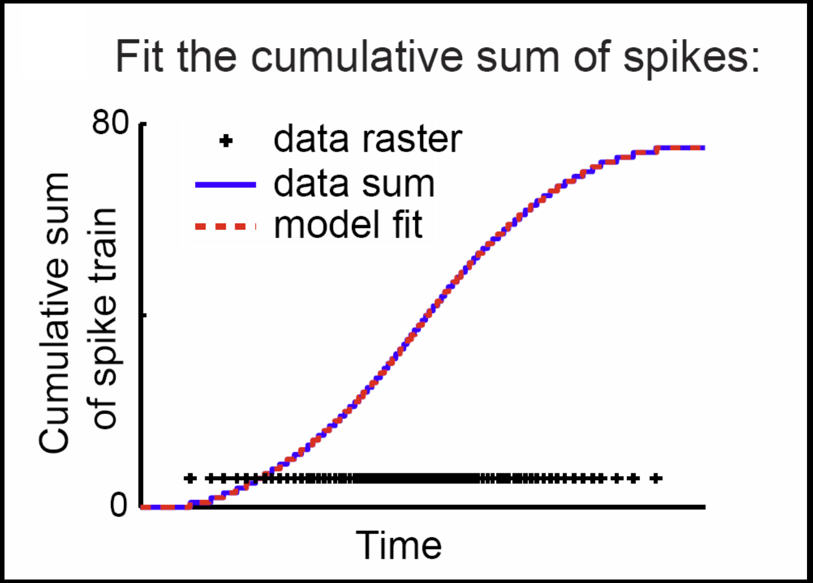


→ Single neuron has no memory!

Calibrating the spiking neuron model



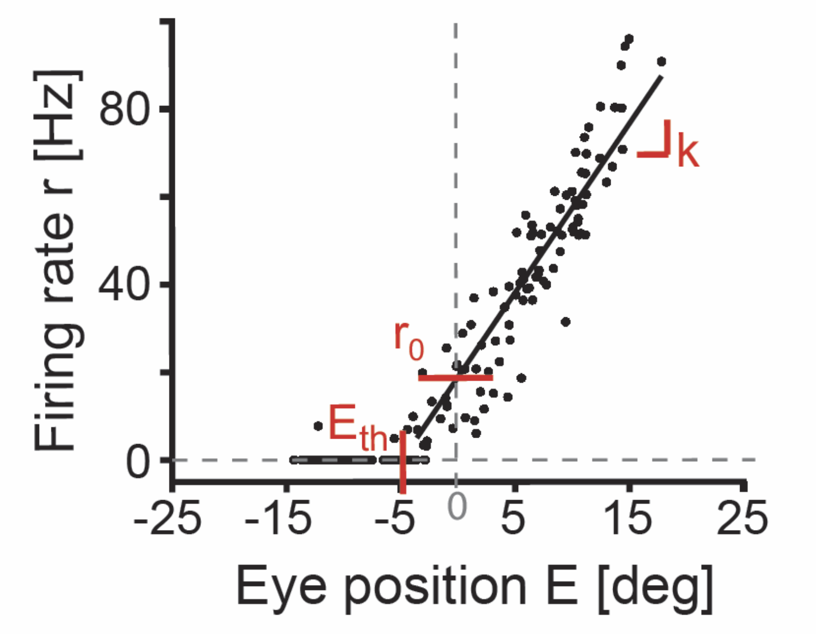
Single-compartment model with Leak, Na^+, K^+ (two types) channels

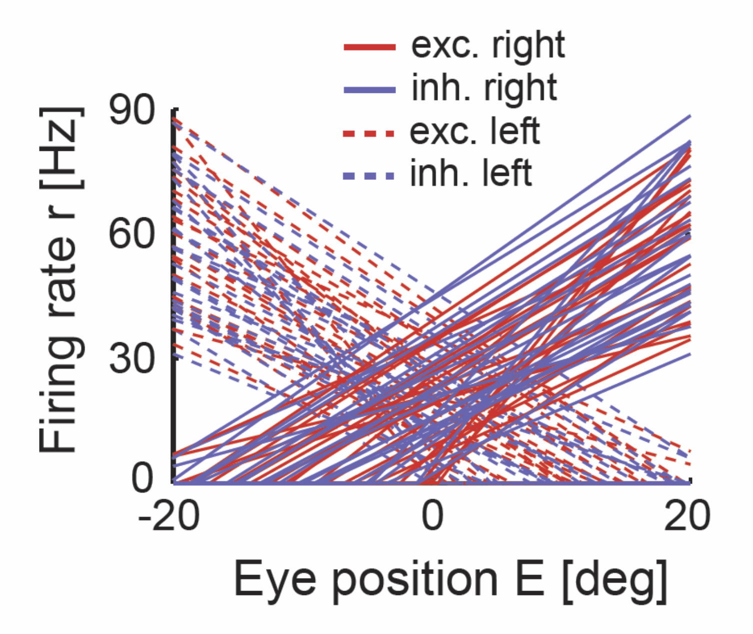


(D. Fisher et al., *in preparation*)

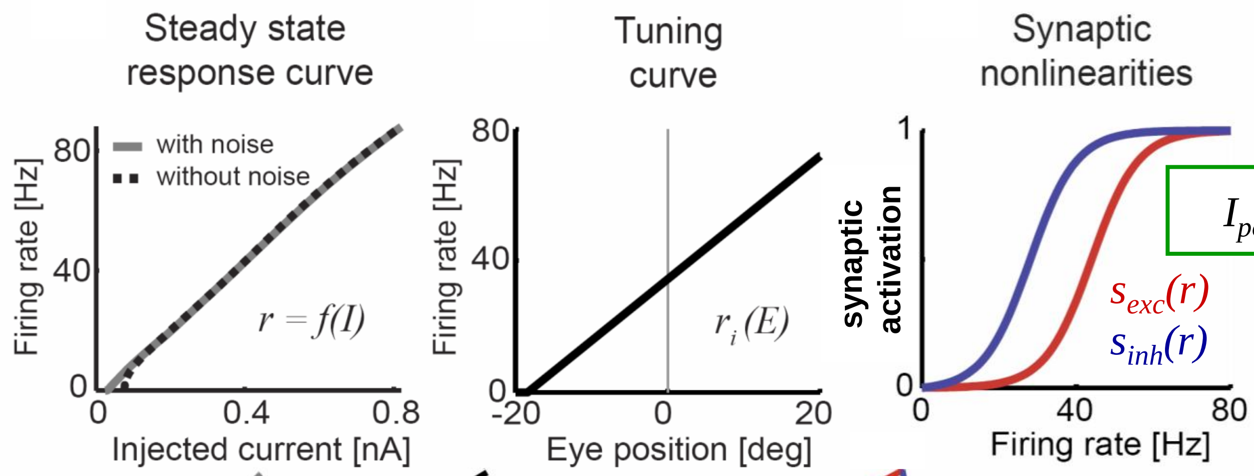
Experimental Tuning Curve Data: Persistent firing rate vs. eye position

- 100 neurons total, taken from database of experimental recordings





Fitting the Network Connections



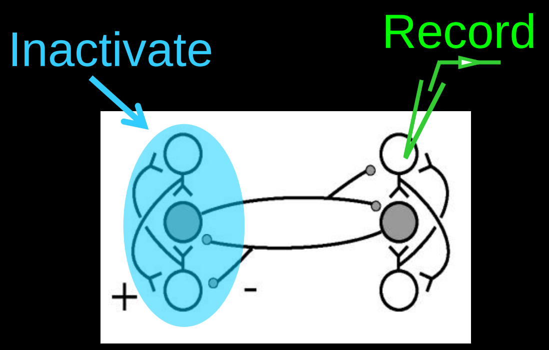
$$I_{post} = W \cdot s(r_{pre})$$

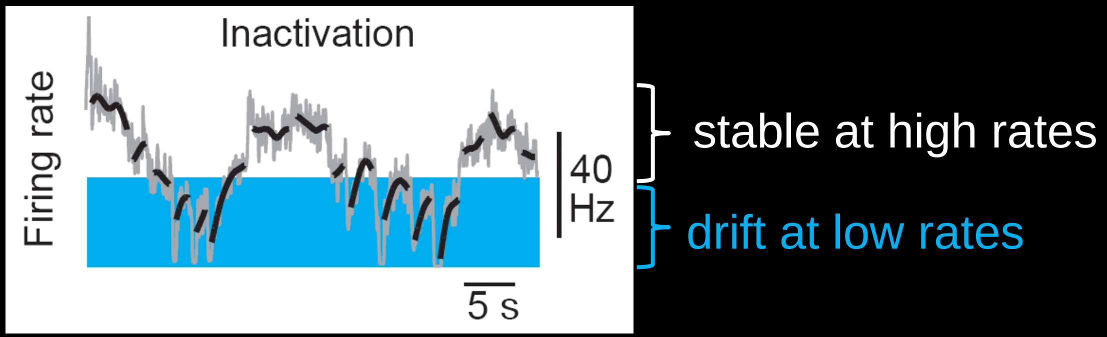
$$f^{-1}\left(r_i(E)\right) \overset{fit}{=} \sum_{j=exc} W_{ij}\, s_{exc}\left(r_j(E)\right) + \sum_{j=inh} W_{ij}\, s_{inh}\left(r_j(E)\right) + T_i$$

- current required to produce observed firing rate
- total excitatory current
- total inhibitory current
- constant background current

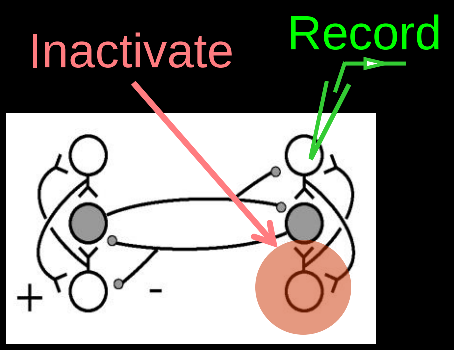
Inactivation Experiments Probing Inhibitory & Excitatory Interactions

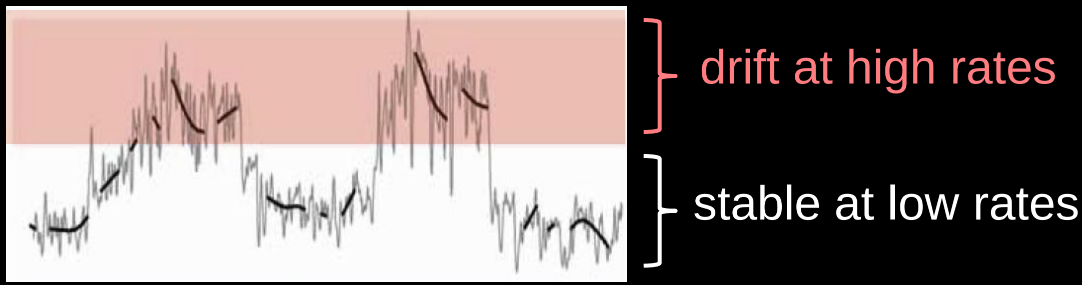
Experiment 1: Remove inhibition





Experiment 2: Remove excitation

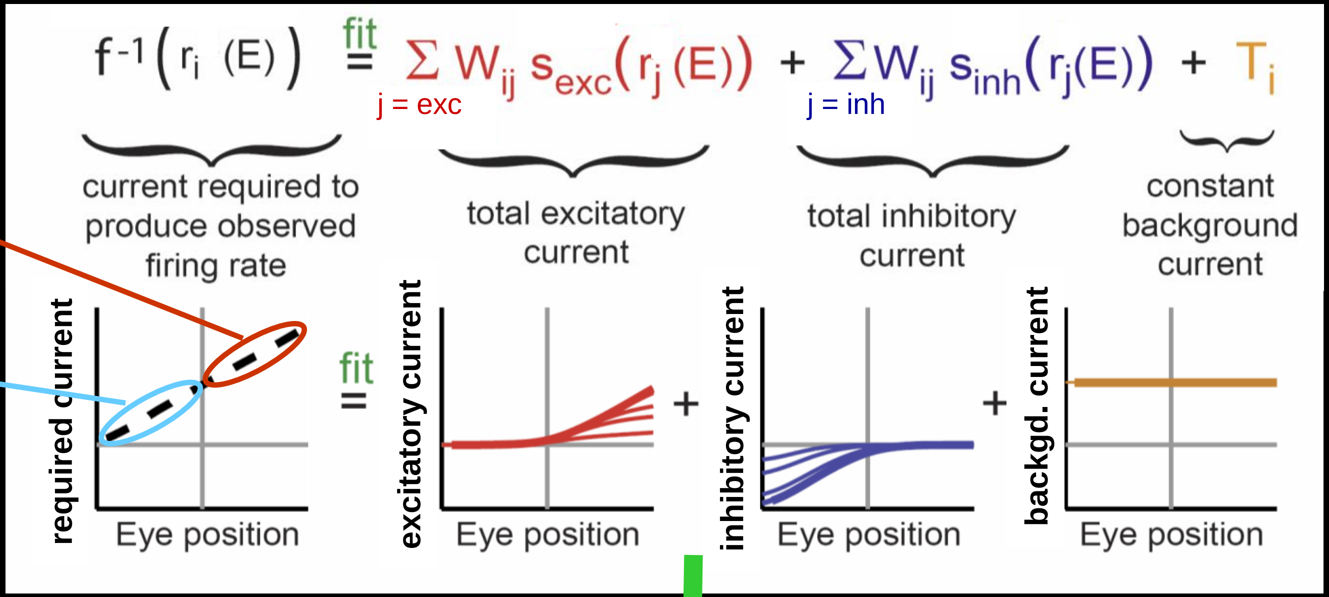


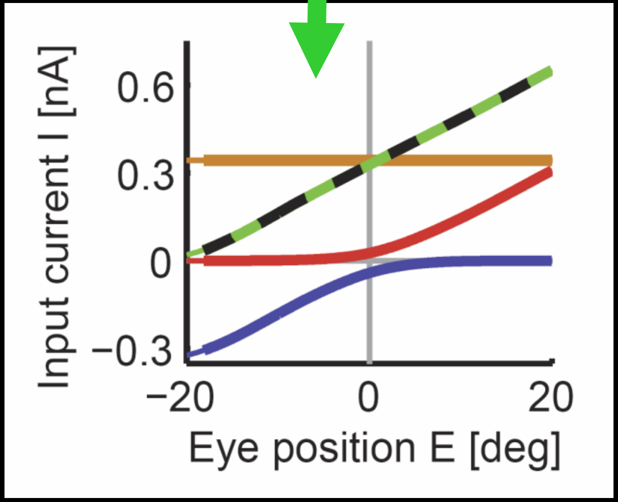


Fitting the Network Connections

maintained by same-side excitation

maintained by inhibition (and/or possibly by very local excitation)

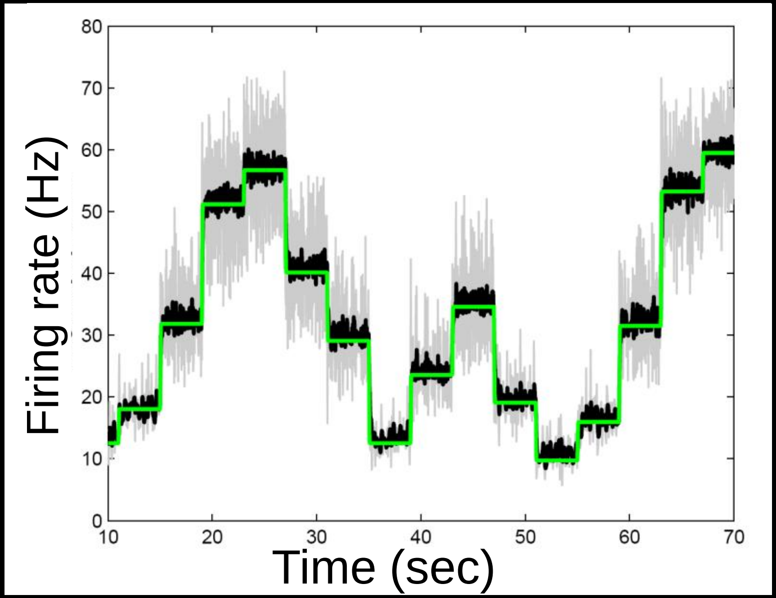




Summed currents

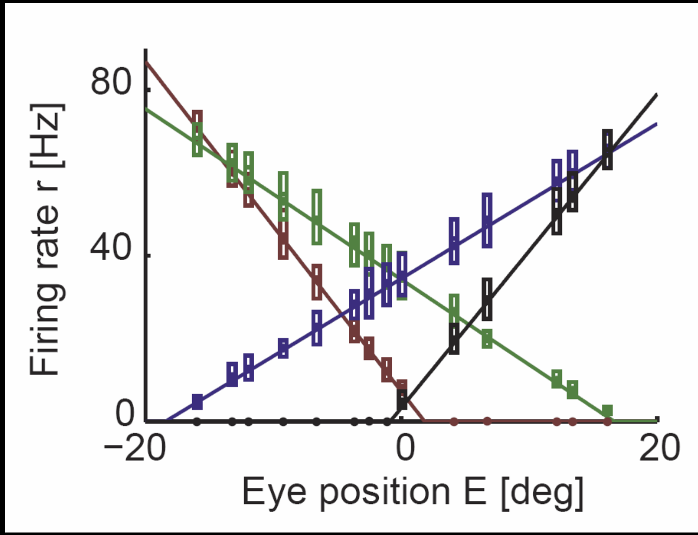
Simulation Results

Network integrates its inputs



gray = raw firing rate
(black = smoothed rate)
green = perfect integral

…and all neurons precisely match tuning curve data

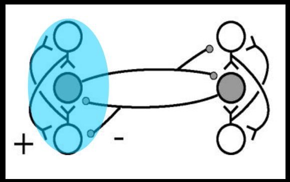


solid lines: experimental tuning curves

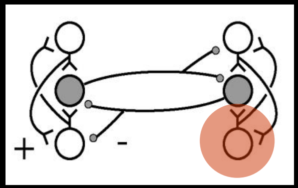
boxes: model rates (& variability)

Data & Model Following Inactivation

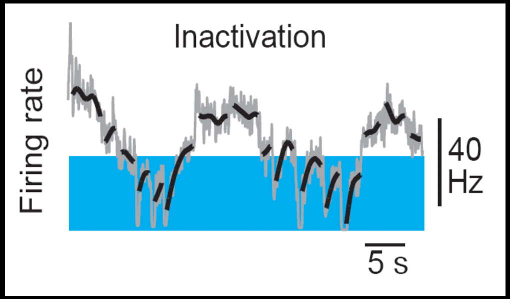
Remove inhibition

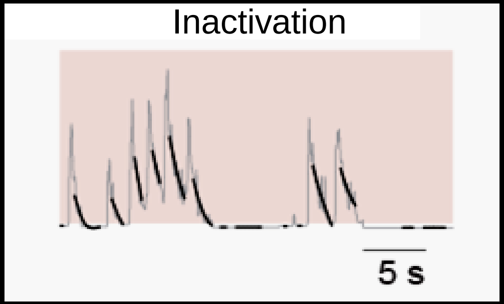


Remove excitation

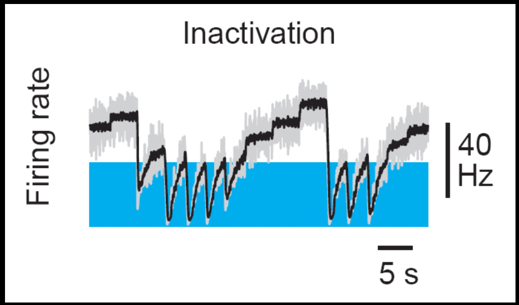


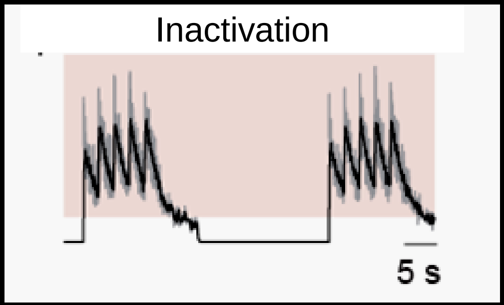
Experiments:





Model:



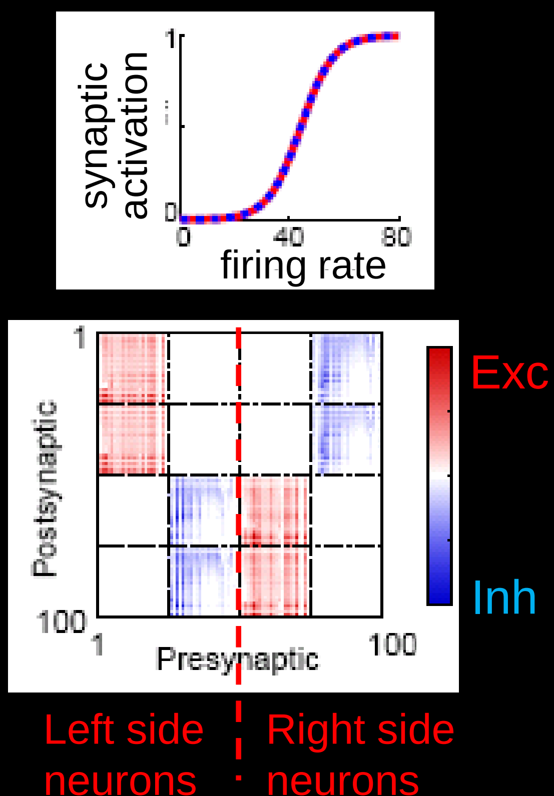


Several different networks can explain the data…

Synaptic nonlinearity s(r) & anatomical connectivity W_{ij} for 3 model networks:

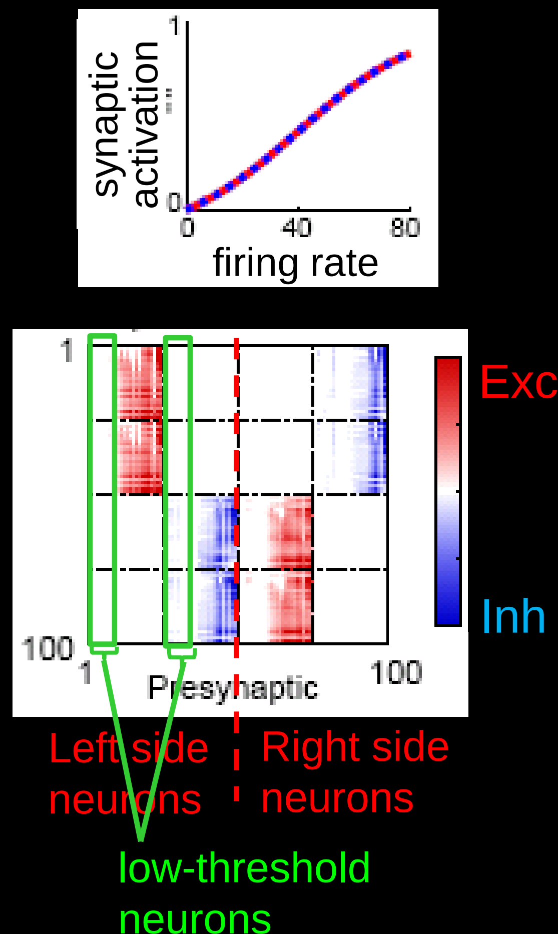
Class 1

- Synaptic thresholds
- Most neurons contribute



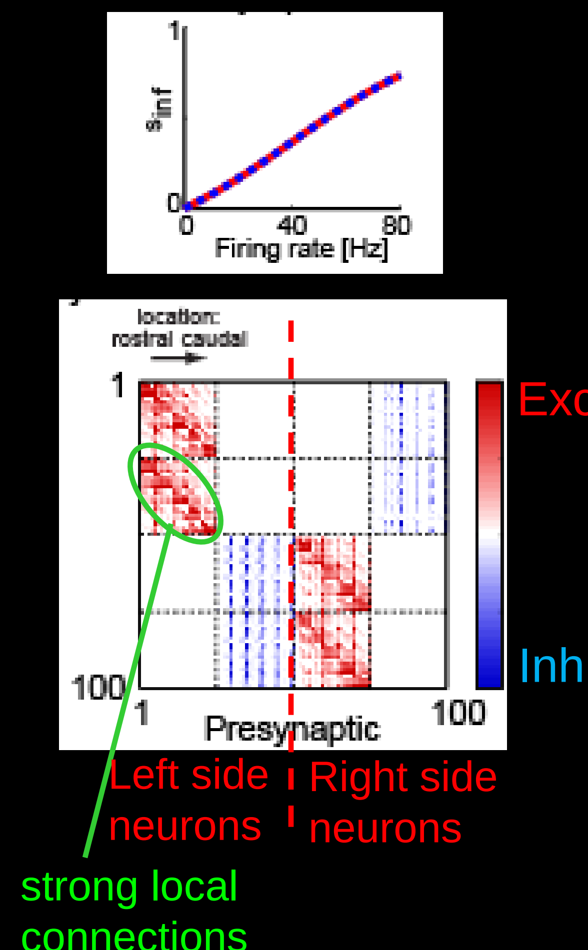
Class 2

- No synaptic thresholds
- Use high-threshold cells



Class 3

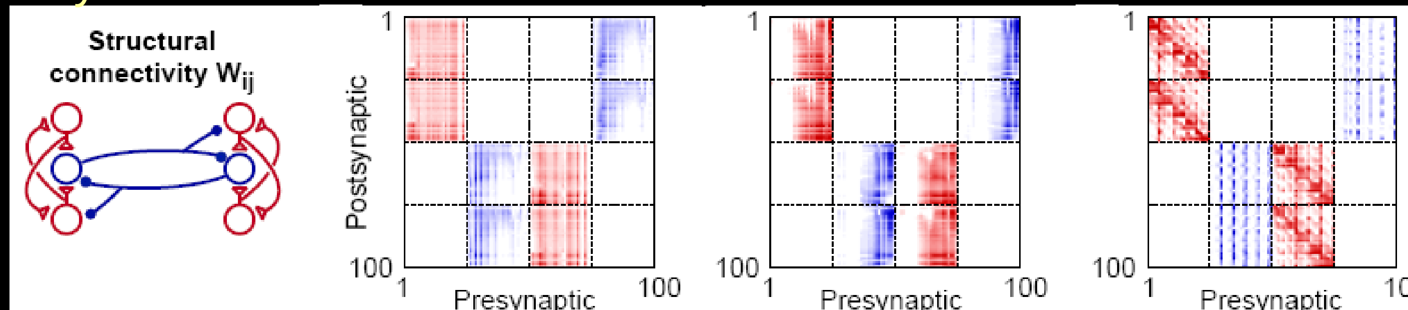
- Many synapse types
- Topographic excitation



…But accounting for nonlinearities shows that anatomical connectivity belies functional connectivity

Class 1 | Class 2 | Class 3

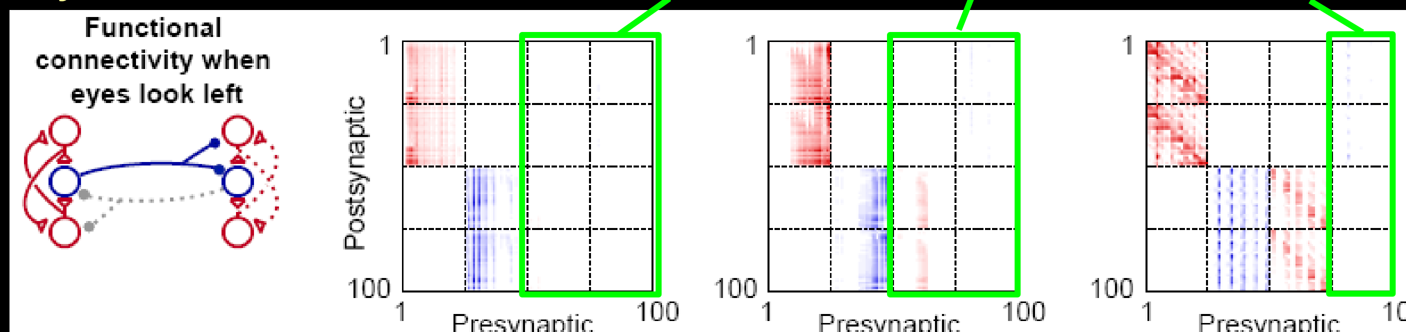
Anatomical connectivity:



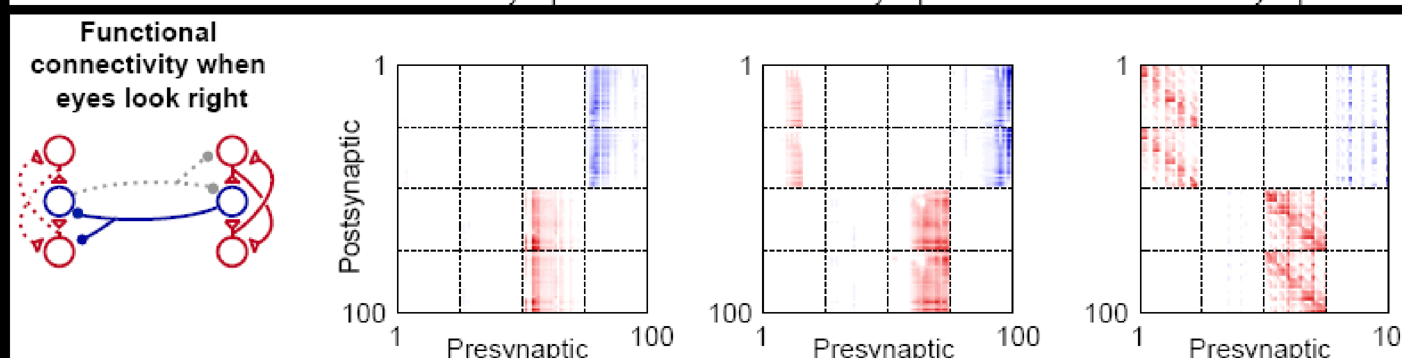
Functional connectivity:

right side (at least inhibition) disconnected

eyes to the left:

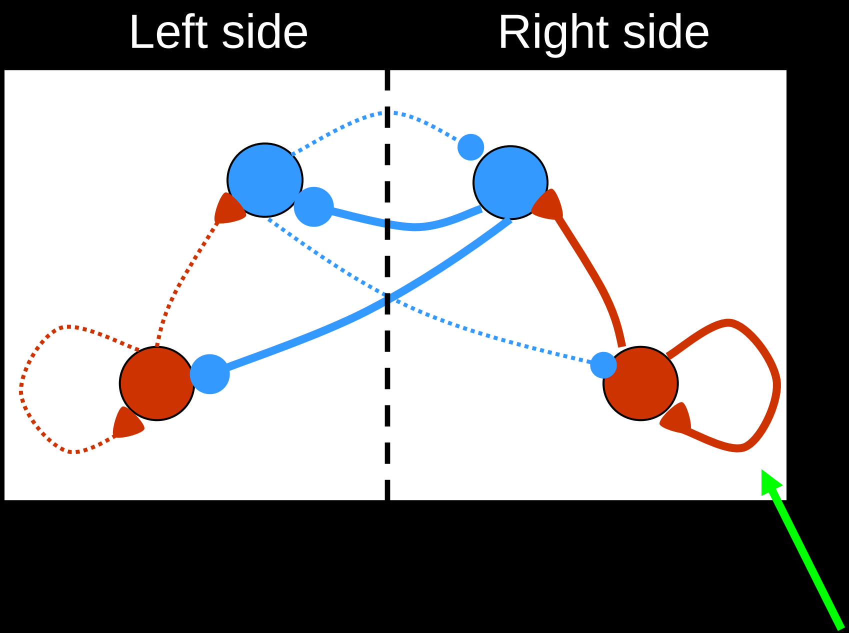


eyes to the right:



Mechanism for generating persistent activity

Network activity when eyes directed rightward:



Implications:

-The only positive feedback LOOP is due to **recurrent excitation**

-Due to thresholds, there is **no mutual inhibitory feedback loop**

→ **Excitation, not inhibition, maintains persistent activity!**

→ **Inhibition is *anatomically* recurrent, but *functionally* feedforward**

Conclusions

- Model fitting:
  - Fit persistent activity in a nonlinear network
  - Use cost function to *simultaneously* enforce several cellular & network experiments
- Results
  - Generates predicted synaptic nonlinearities & connectivities
  - Excitation, not inhibition maintains persistent activity
  - Suggests presence of a threshold process:

    Hypothesis: Excitatory process might be a bistable synapse/dendrite that adds a long cellular time constant & lessens the need to fine-tune network feedback

Acknowledgments

Theory (Goldman lab, UCD)

- Itsaso Olasagasti (USZ)
- Dimitri Fisher
- Sukbin Lim

Experiments

- David Tank (Princeton Univ.)
- Emre Aksay (Cornell Med.)
- Guy Major (Cardiff Univ.)
- Robert Baker (NYU Medical)