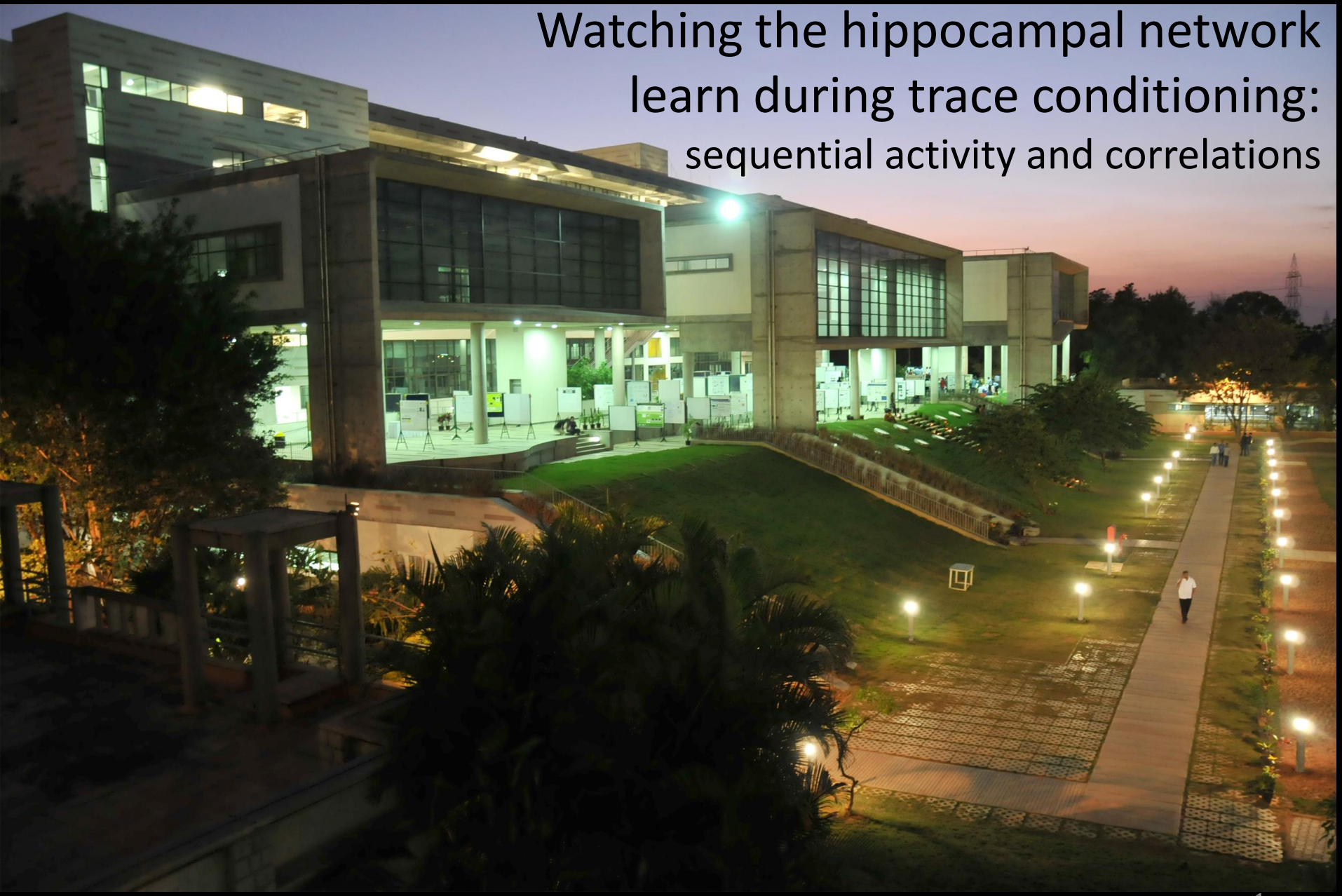


Watching the hippocampal network learn during trace conditioning:

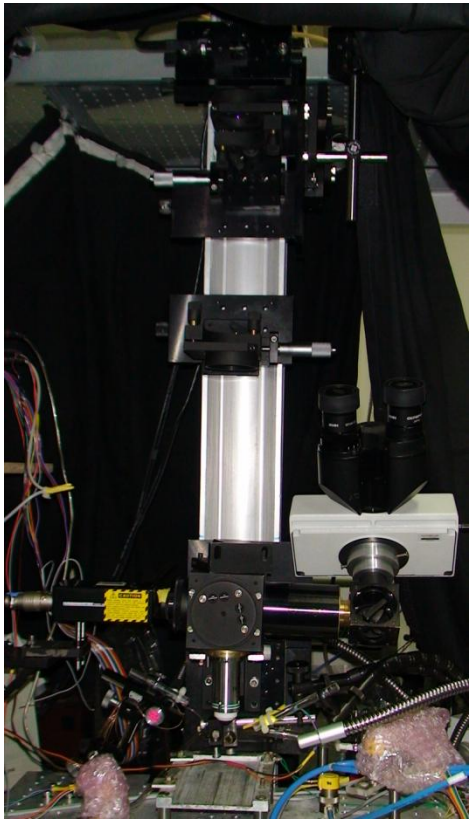
sequential activity and correlations

Upi Bhalla NCBS Bangalore

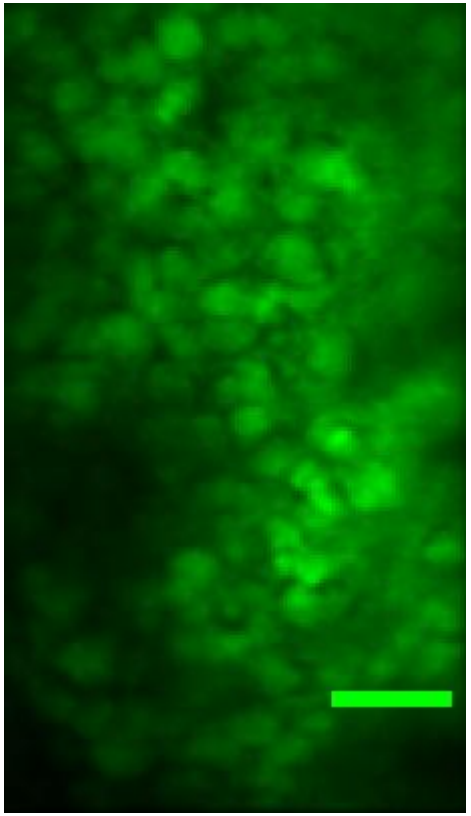
People and systems

Mehrab N. Modi

Ashesh Dhawale



Bheja Fry



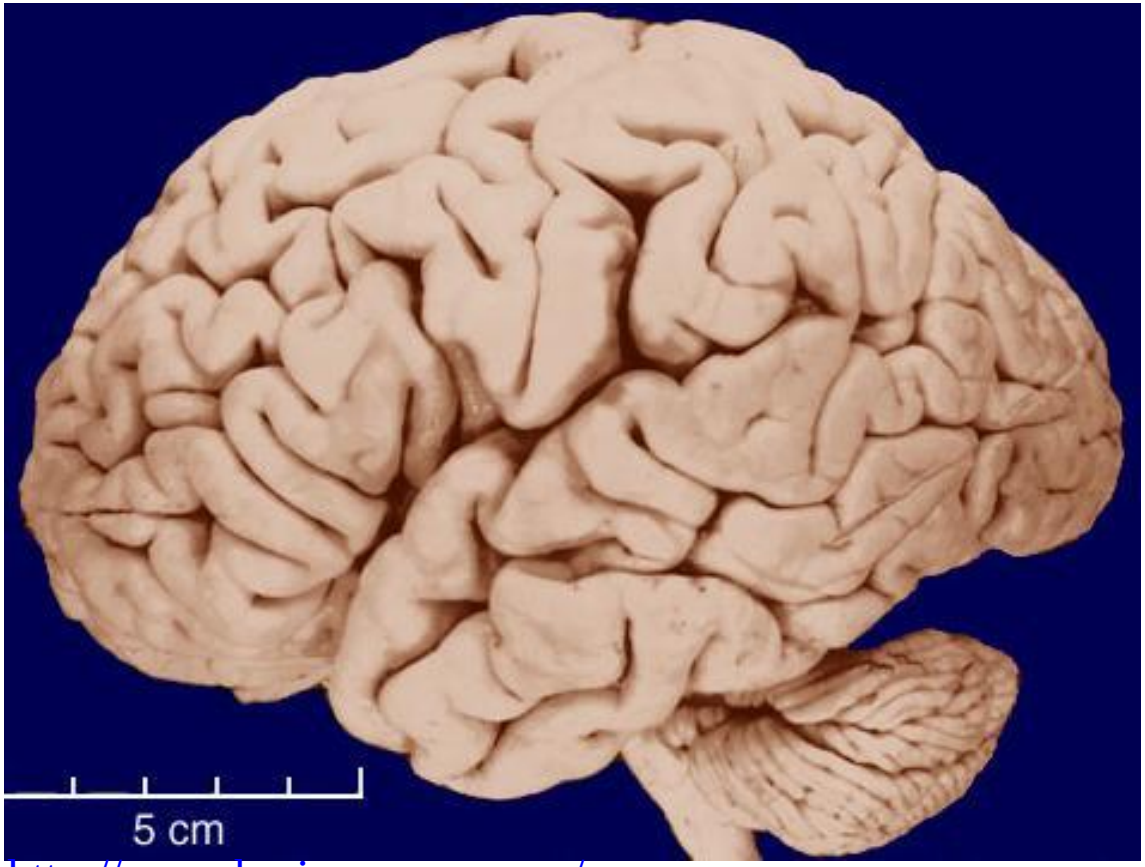
Mouse brain

K. Ananthamurthy

Aanchal Bhatia

The system

- Behaviour
- Systems
- Areas
- Circuits
- Neurons
- Dendrites
- Synapses
- Molecules



http://www.brainmuseum.org/
University of Wisconsin and Michigan State Comparative Mammalian Brain Collections; National Museum of Health and Medicine.

Questions on network learning

- What changes occur in activity?
- What changes occur in connectivity?
- What are the rules?
- How does multiscale signaling implement these rules?

Questions on network learning

- What changes occur in activity?
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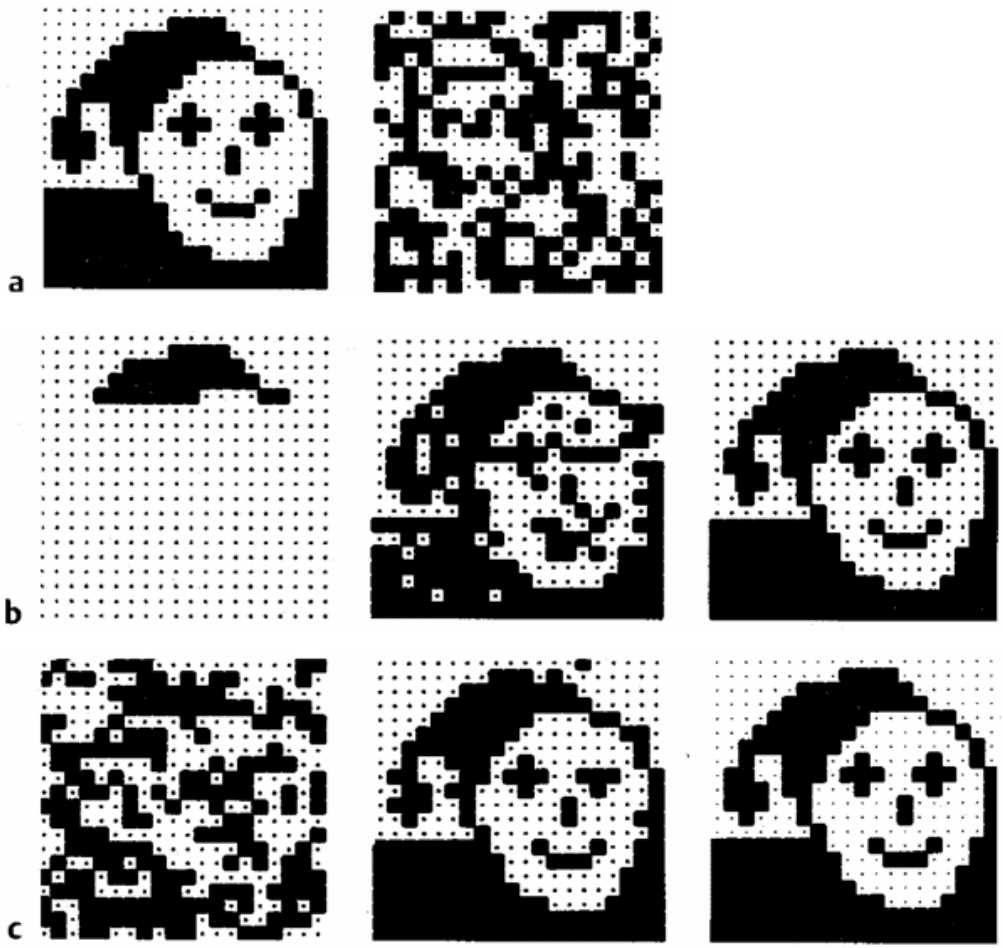
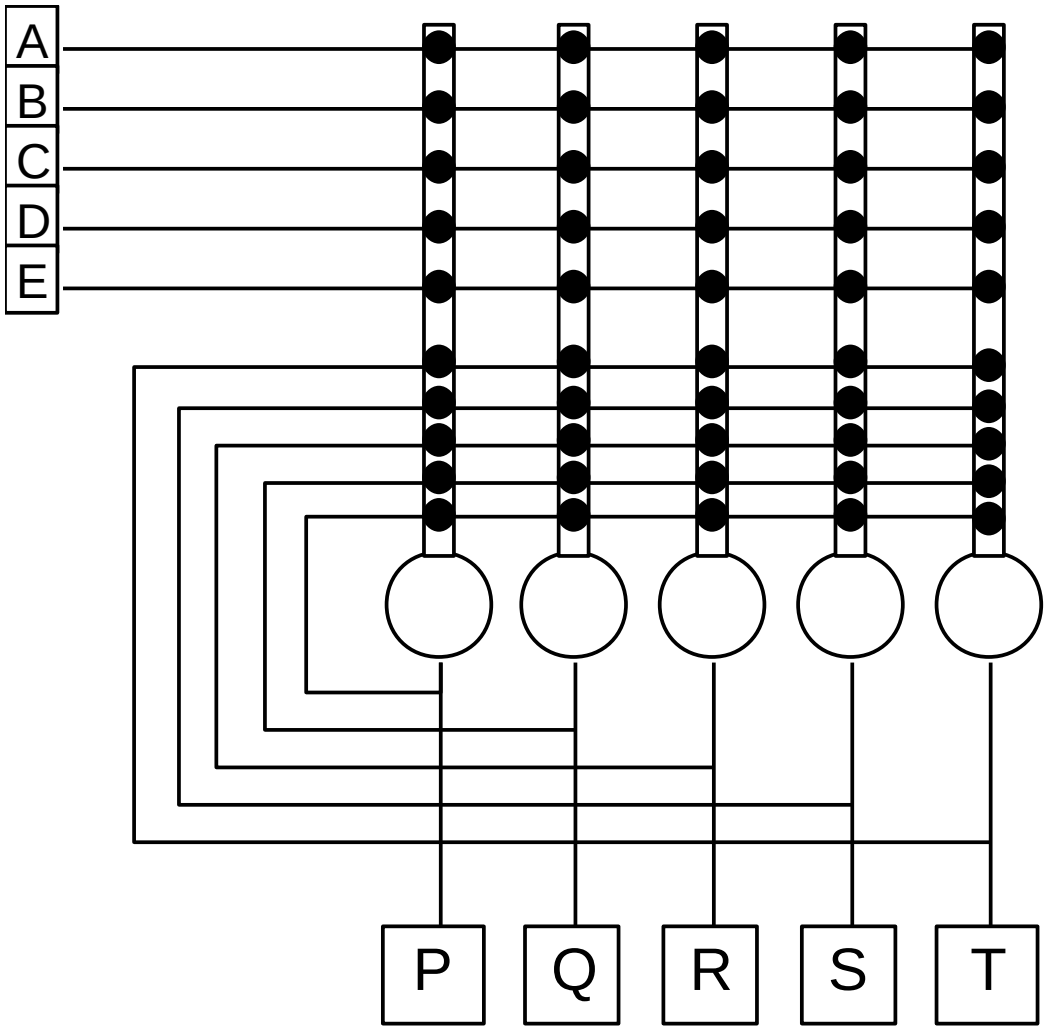
Pattern recognition and completion

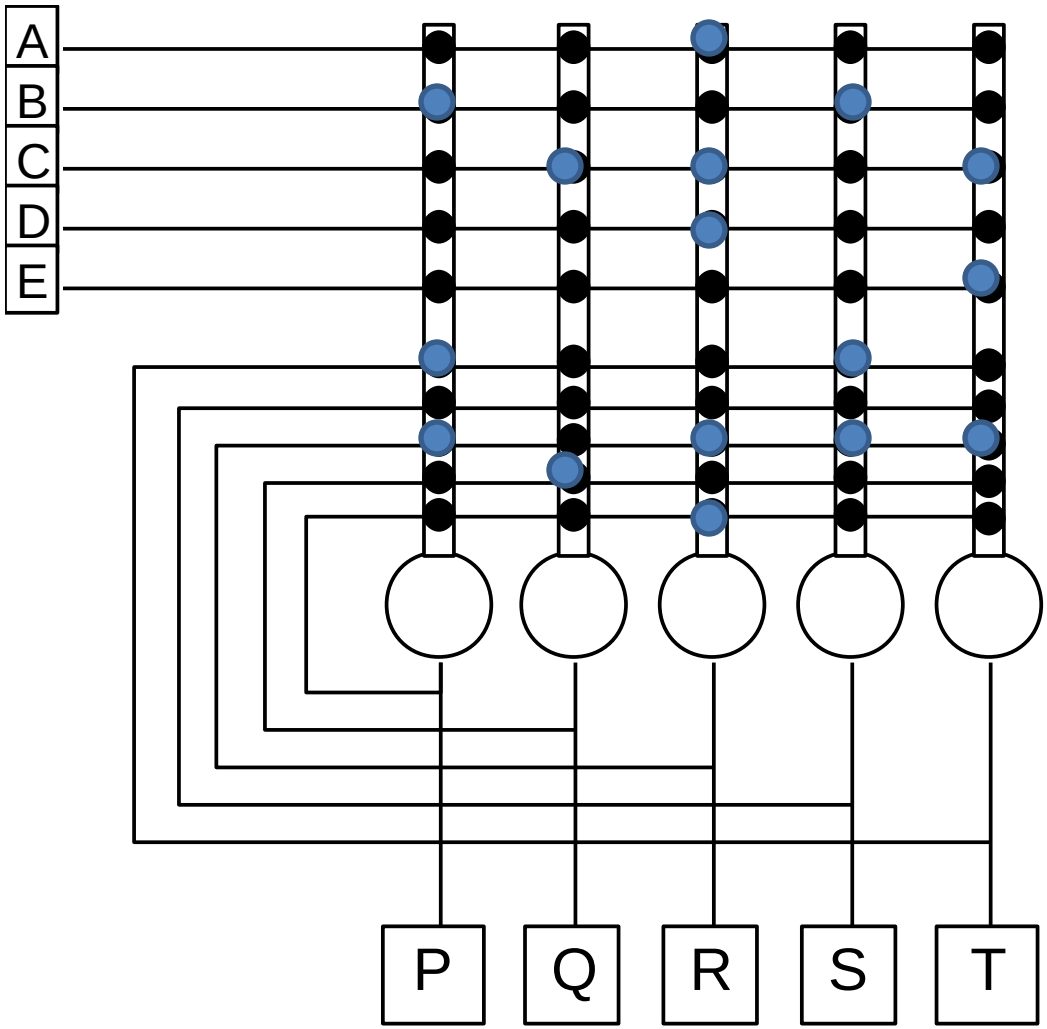


Neural Networks as Cybernetic Systems
Holk Cruse

Network models: Associative memory



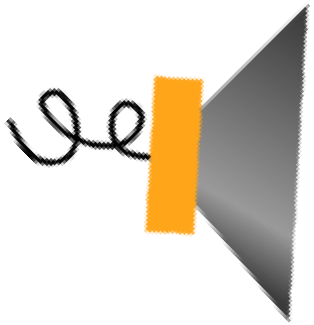
Synaptic weights define contents of this memory



Questions on network learning

- What changes occur in activity?
  - Readout of what has been stored
- What changes occur in connectivity?
  - Synaptic weights as a network basis for storage
  - Note that excitability and other changes may occur too.
- What are the rules?
- How does multiscale signaling implement these rules?

Classical Conditioning: an experimental model of memory



Tone - CS

Puff - US

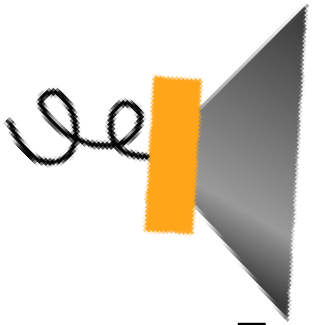
Stimulus presentation period

Neutral

Unconditioned Response

time

Hebbian Associations and Hetero-Associative Networks



Tone - Conditioned Stimulus (neutral)

Tone – representing neurons

Weak synapses

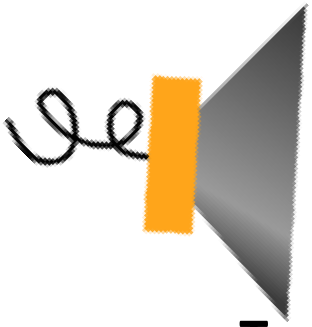
Strong synapses

Puff - Unconditioned Stimulus (aversive)

Puff – representing neurons

UR Trigger Neurons

Hebbian Associations and Hetero-Associative Networks



Tone - Conditioned Stimulus (neutral)

Tone – representing neurons

Strengthened synapses

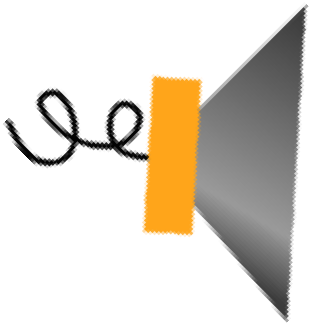
Strong synapses

Puff - Unconditioned Stimulus (aversive)

Puff – representing neurons

UR Trigger Neurons

Hebbian Associations



Tone - CS

Puff - US

Stimuli **co-presented**

time

Hebbian Associations

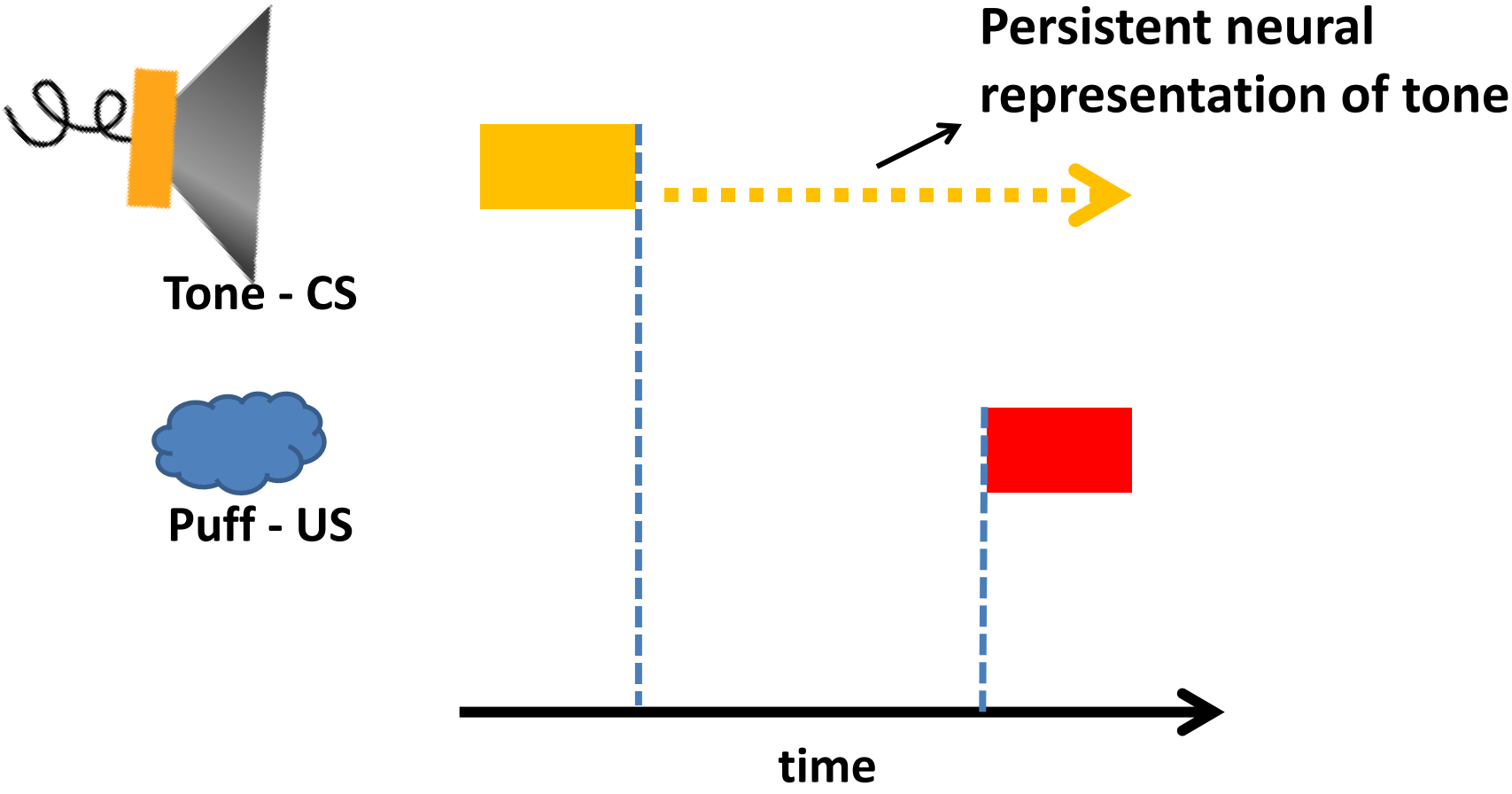
Tone - CS

Puff - US

Separated stimuli - ?

time

Hebbian Associations



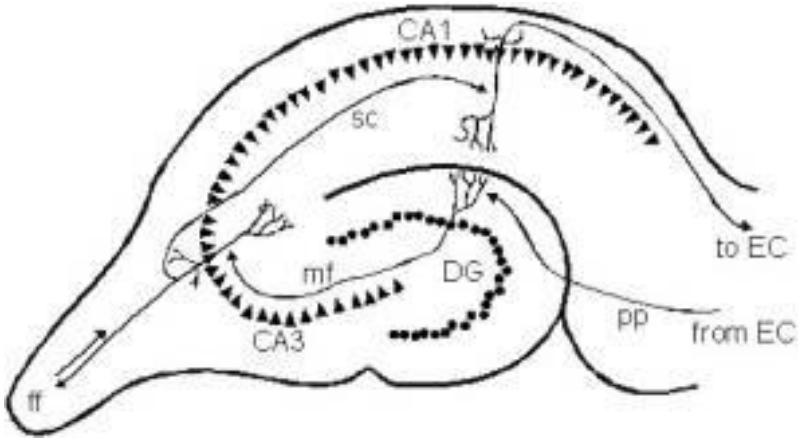
Functions, Circuit of the Mammalian Hippocampus

Mouse hippocampus: involved in memory formation, navigation

Multi-modal inputs to CA3 through DG

CA3 forms auto-associative network

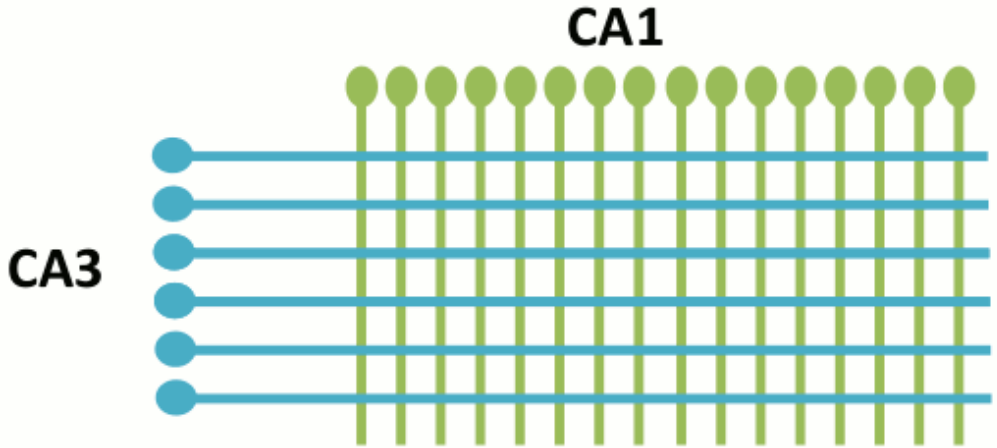
CA3-CA1 network hetero-associative, feed-forward



Hippocampal Circuit - Implications

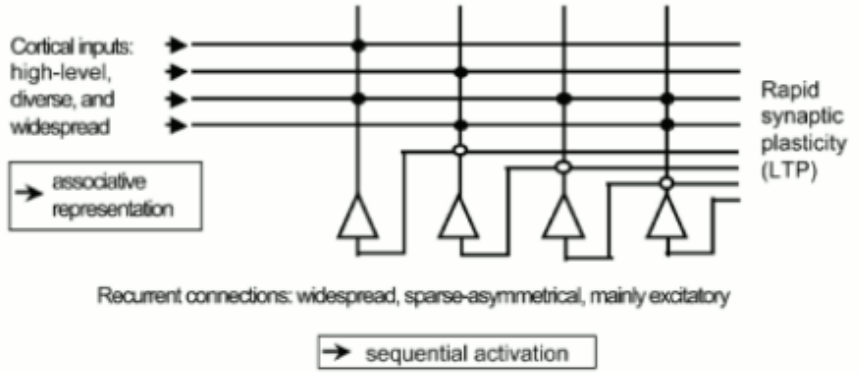
Feed-forward CA3-CA1 connections

Multi-modality coincidence detection



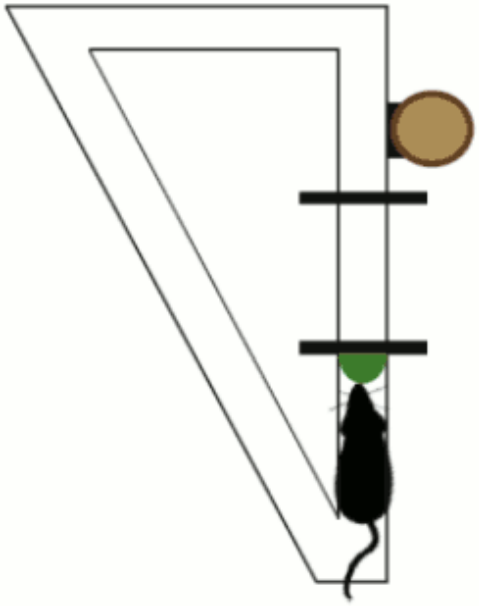
Recurrent CA3 connections

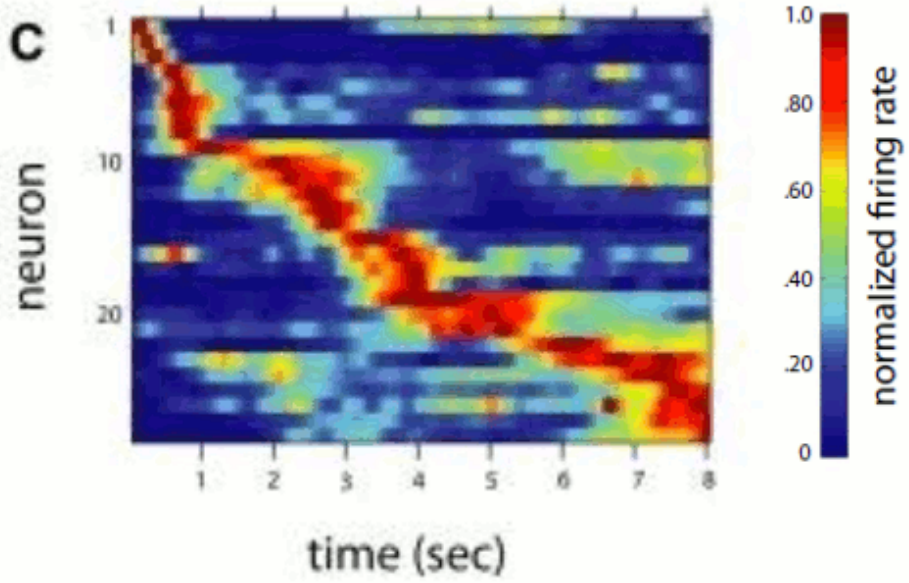
Possibility to form sequences



Eichenbaum, H., **Neuron**, 44, 109

Time Cells – Sequence of Cell Activity Encoding Time





McDonald, Eichenbaum *et al.* Neuron, 71, 737

Object – Trace – Odour Paired Associate task ; go/no-go

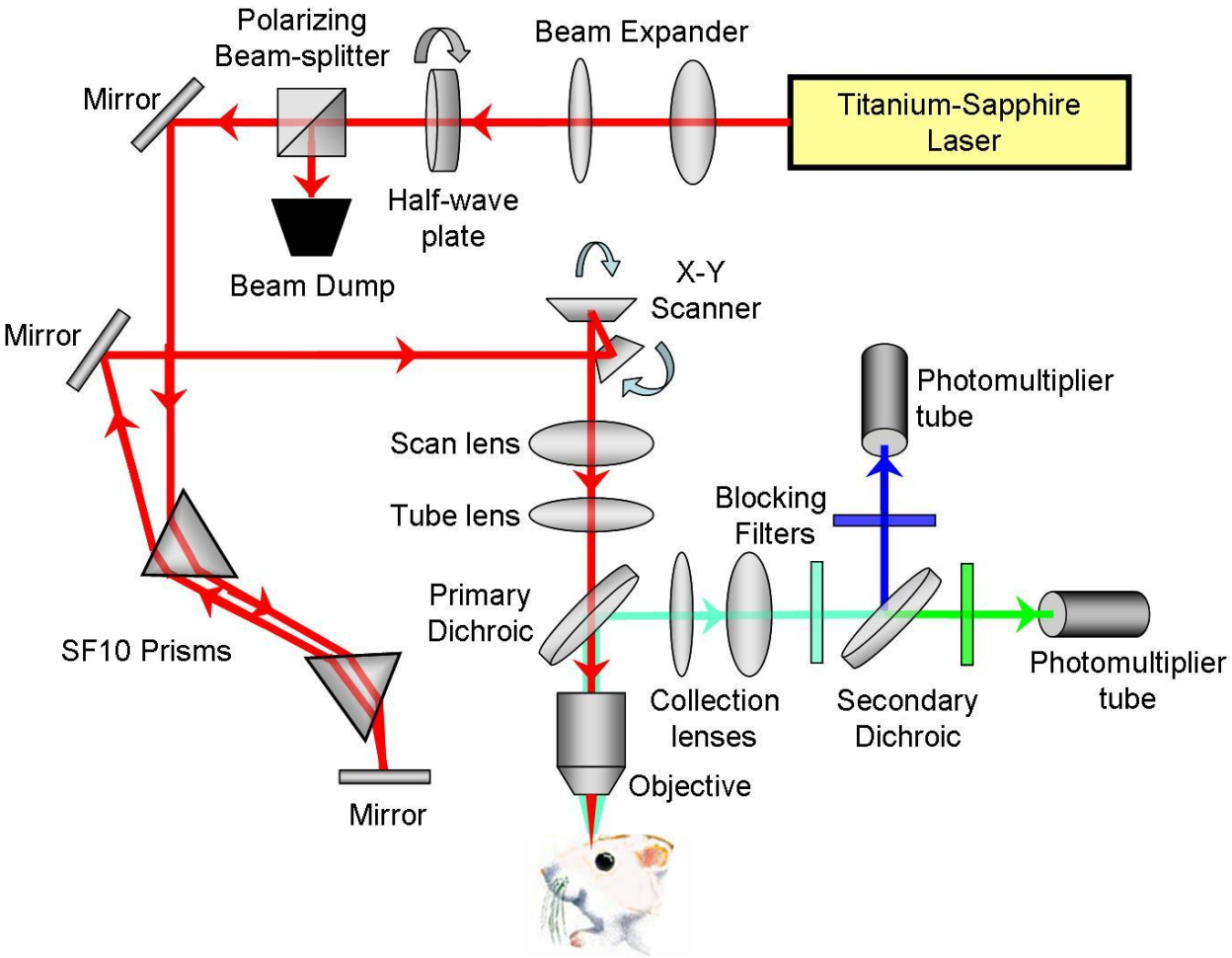
Space as a confound

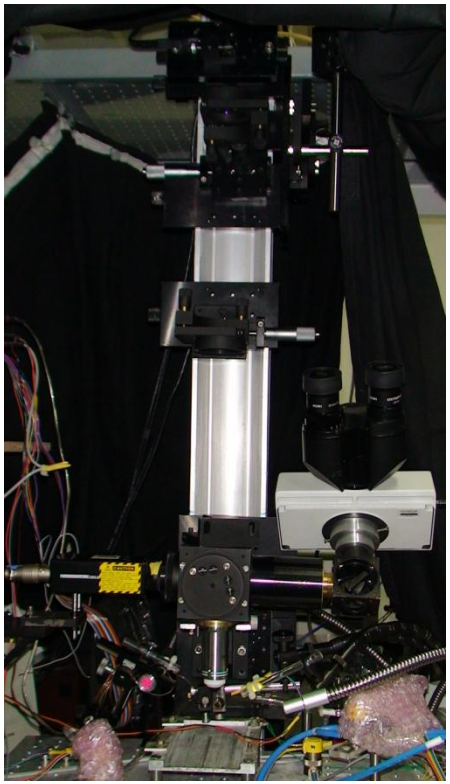
Experimental Paradigm

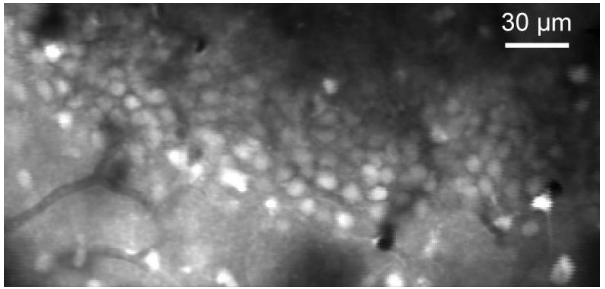
Many neurons (Network phenomenon)
2-Photon Microscopy in hippocampal CA1,
***in vivo*, awake**

Behavioural task - **Head-fixed**, trace maintenance through time
Trace eyeblink conditioning

Imaging of neural activity (in mouse hippocampus)

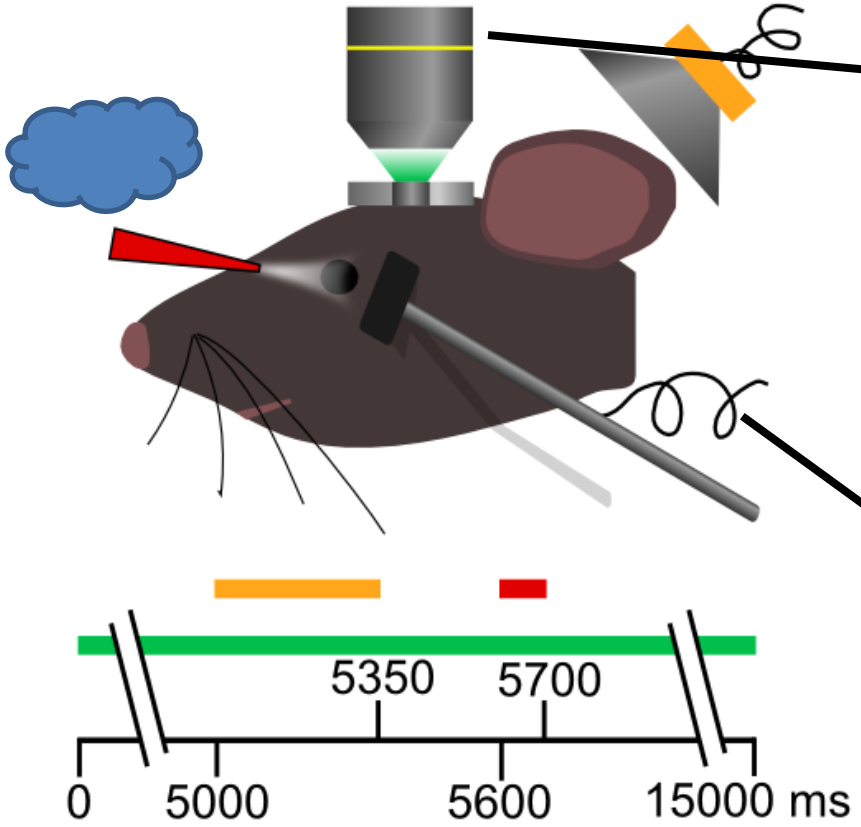




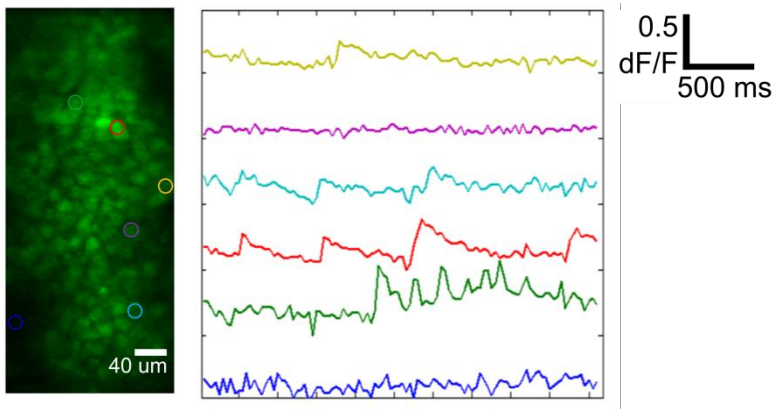


Experimental Paradigm

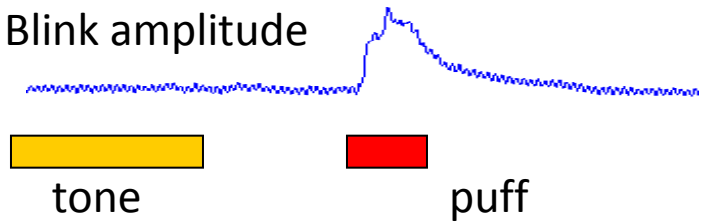
Trace Eyeblink Conditioning



Neuronal Activity Read-out



Behavioural Read-out



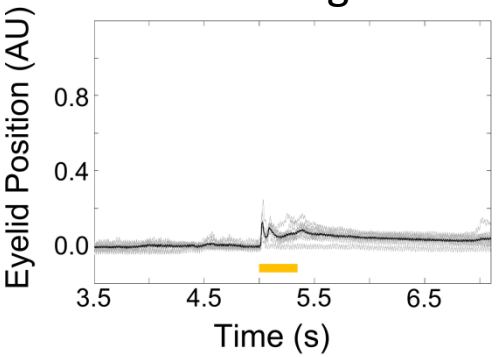
time

Behaviour Results – Learning in One Session

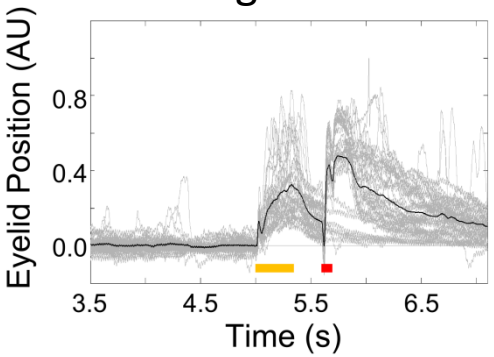
Surgery	2 hrs →	Control Session 30 Trials – Tone Alone Recorded Pre-Trial Tone Response	Training Session 50 Trials – Tone and Puff Recorded Tone, Puff Responses

- Mice show detectable Conditioned Responses (CRs) within a *single* training session

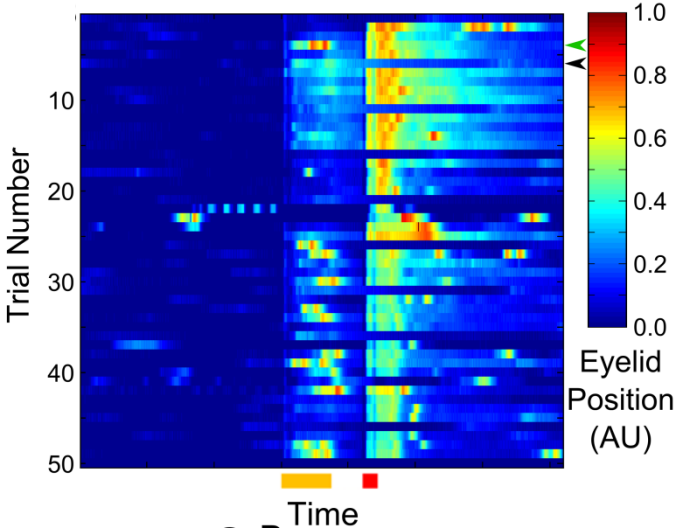
Pre-Training



Training Session



Training Session Trials

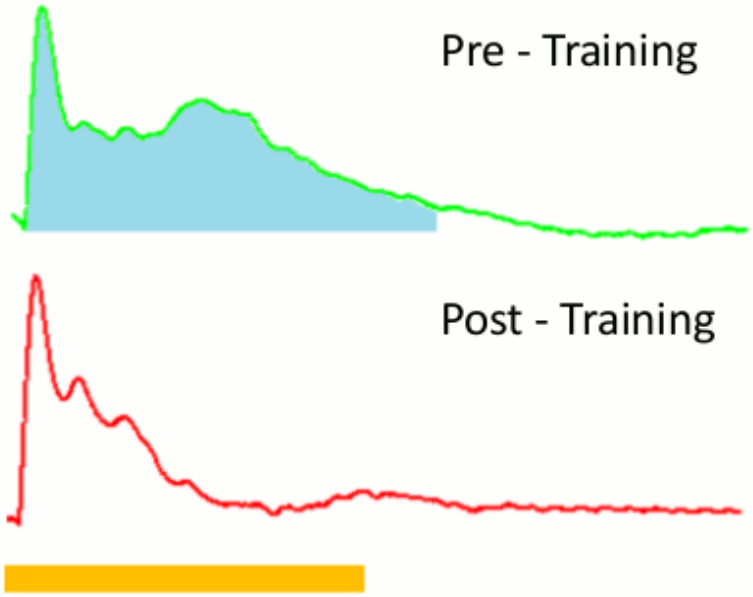


Behaviour Results (Trial Classification)

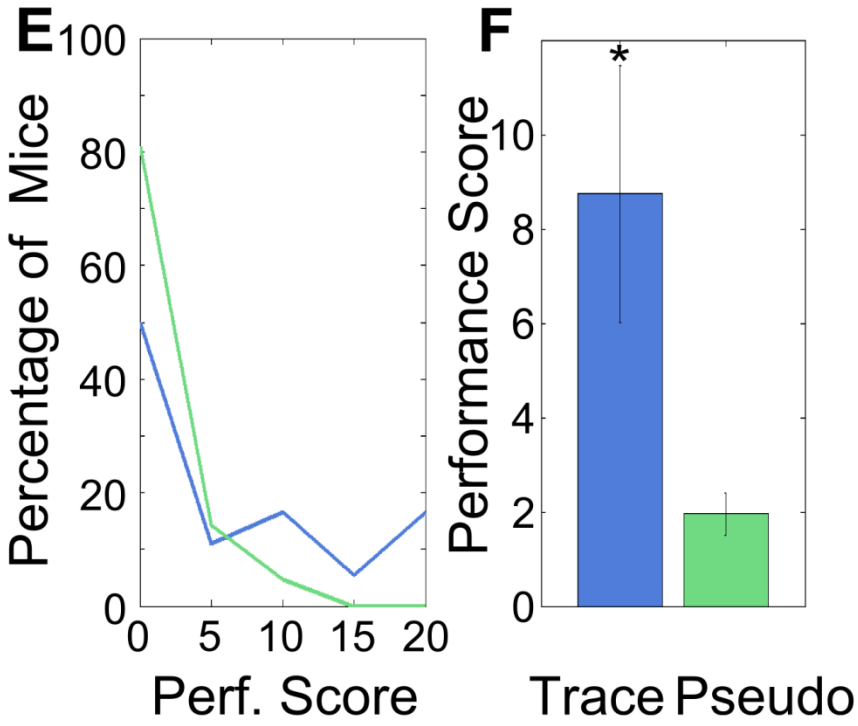
Pseudo-Conditioned Mouse

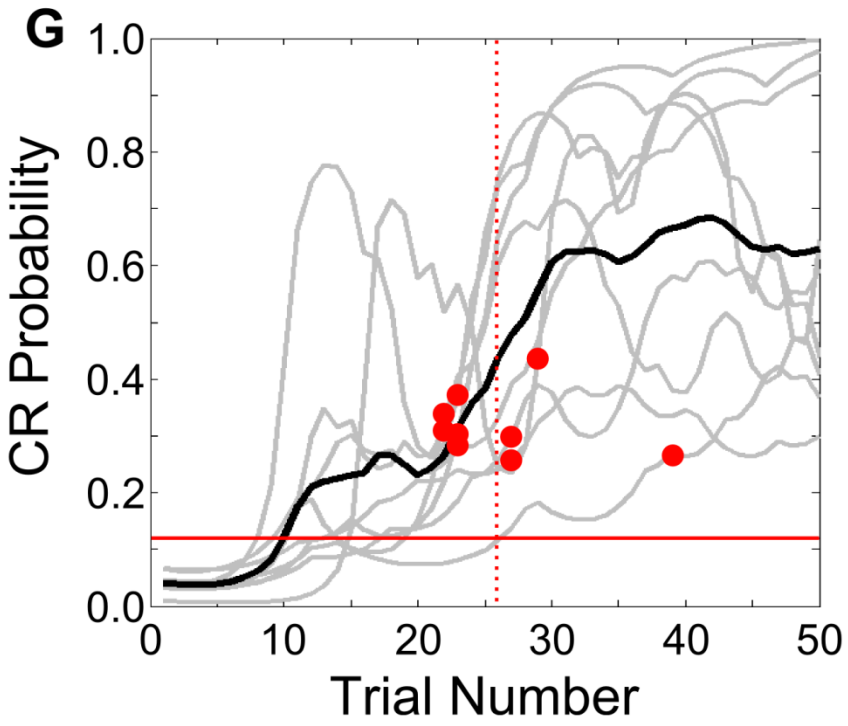
Threshold =
Mean(AOC) + 2 SD(AOC)

Classify Each Training
Trial based on Threshold



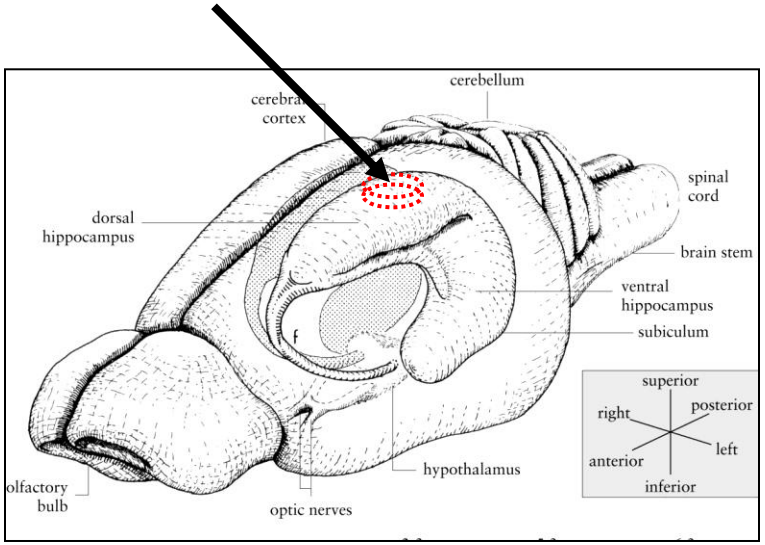
Behavior results

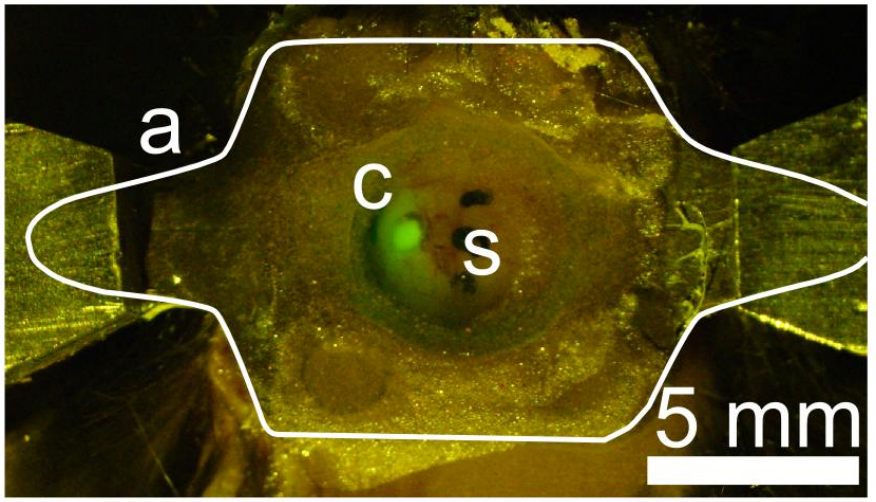


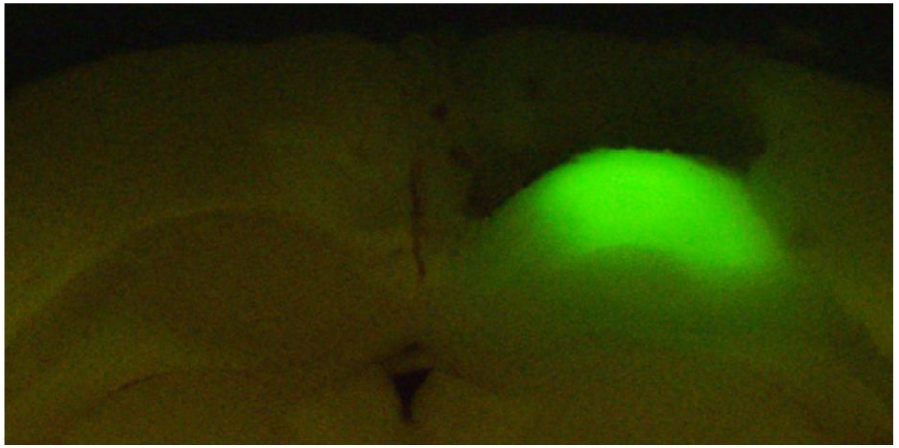


Awake, 2-Photon Imaging of CA1

Craniotomy, Aspirated Hole in Cortex







Awake, 2-Photon Imaging of CA1

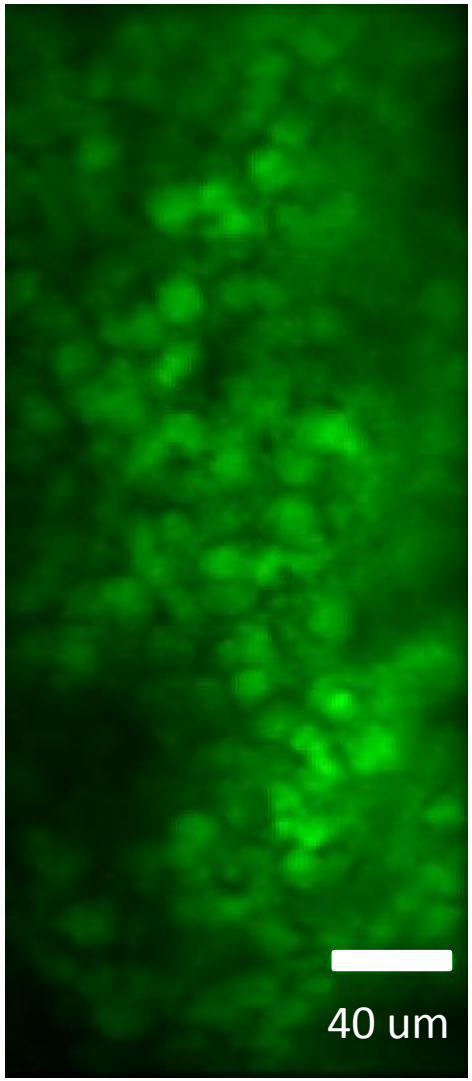
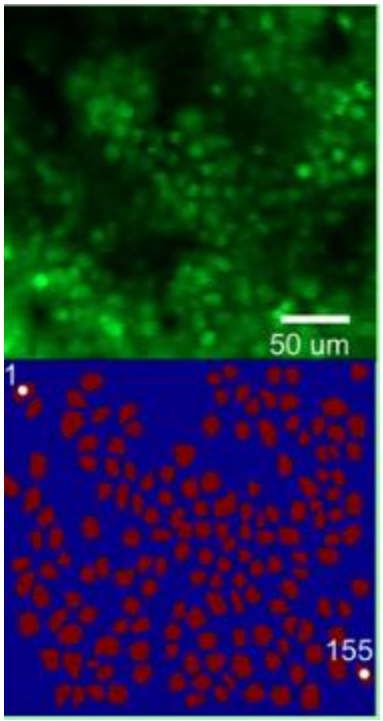
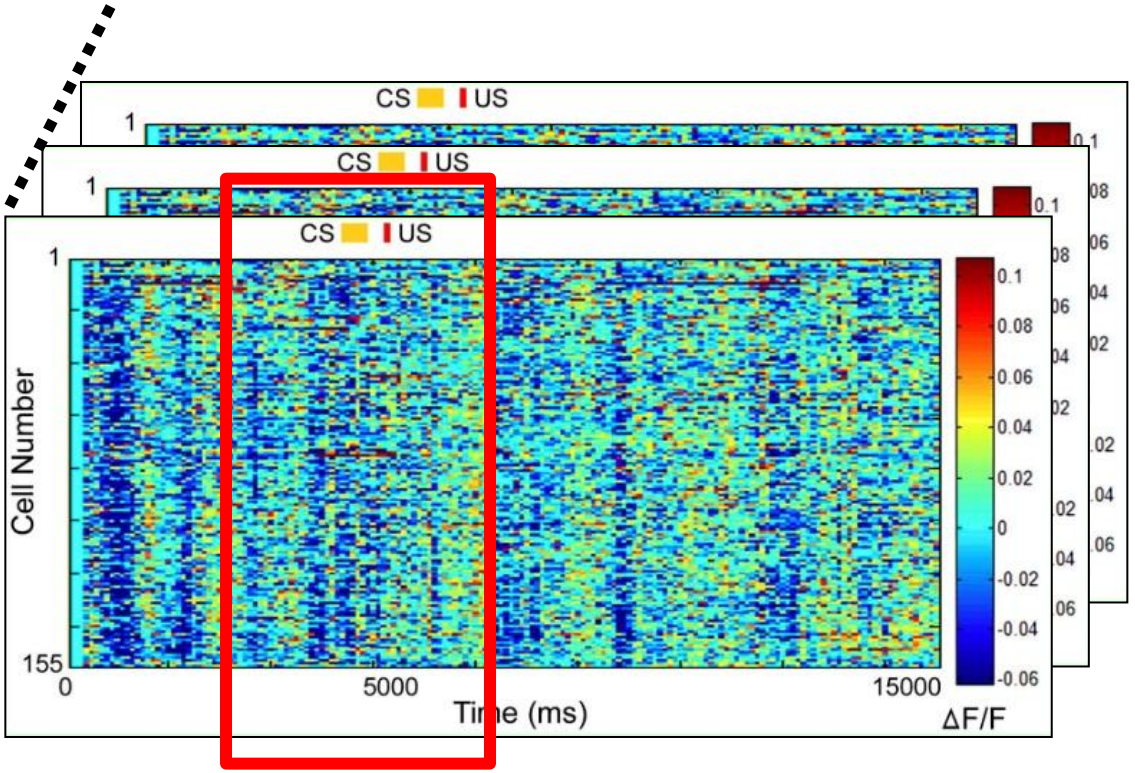


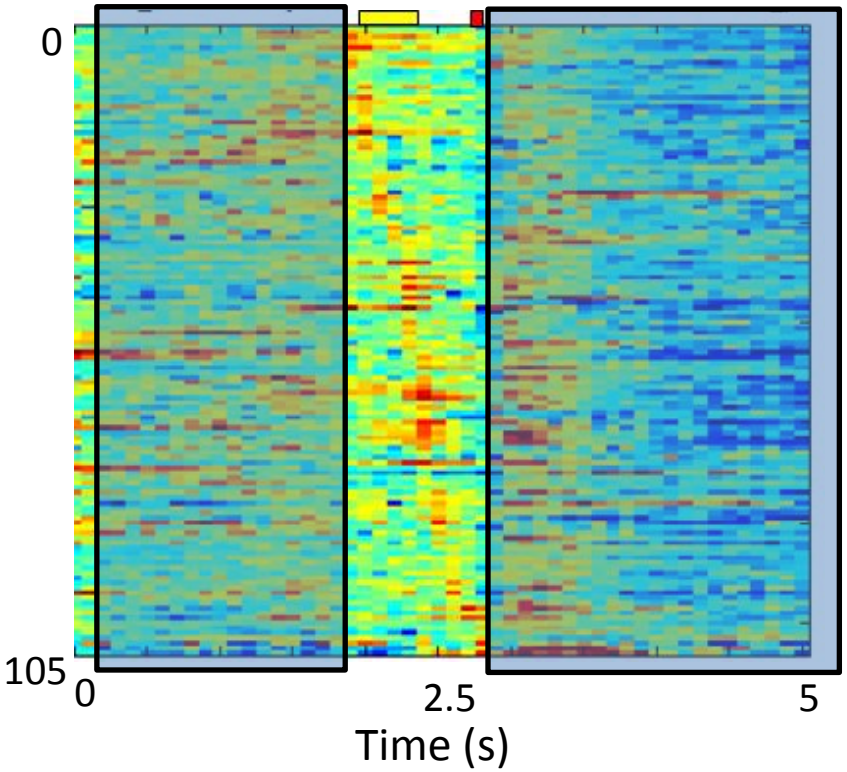
Image Processing



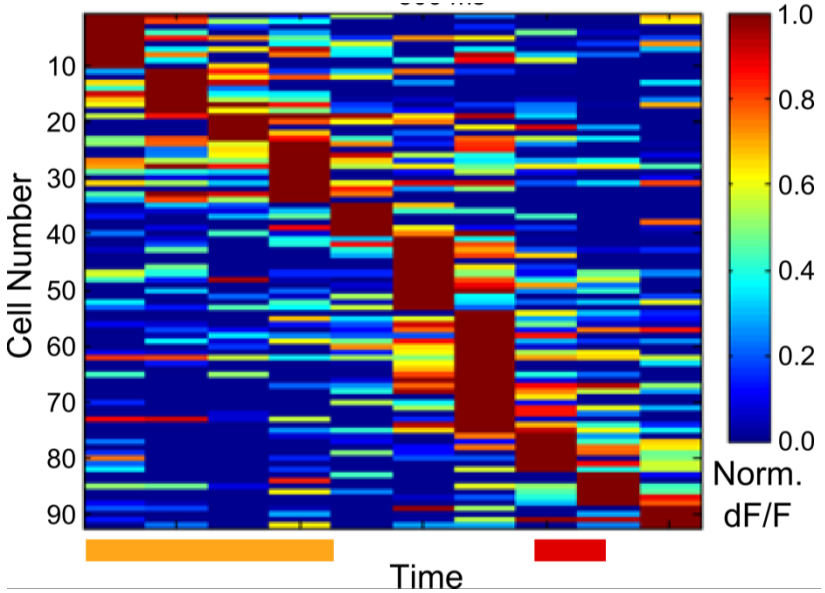


$$\Delta F/F_{framei} = \frac{F_{framei} - F_{baseline}}{F_{basline}}$$

Neuron Number

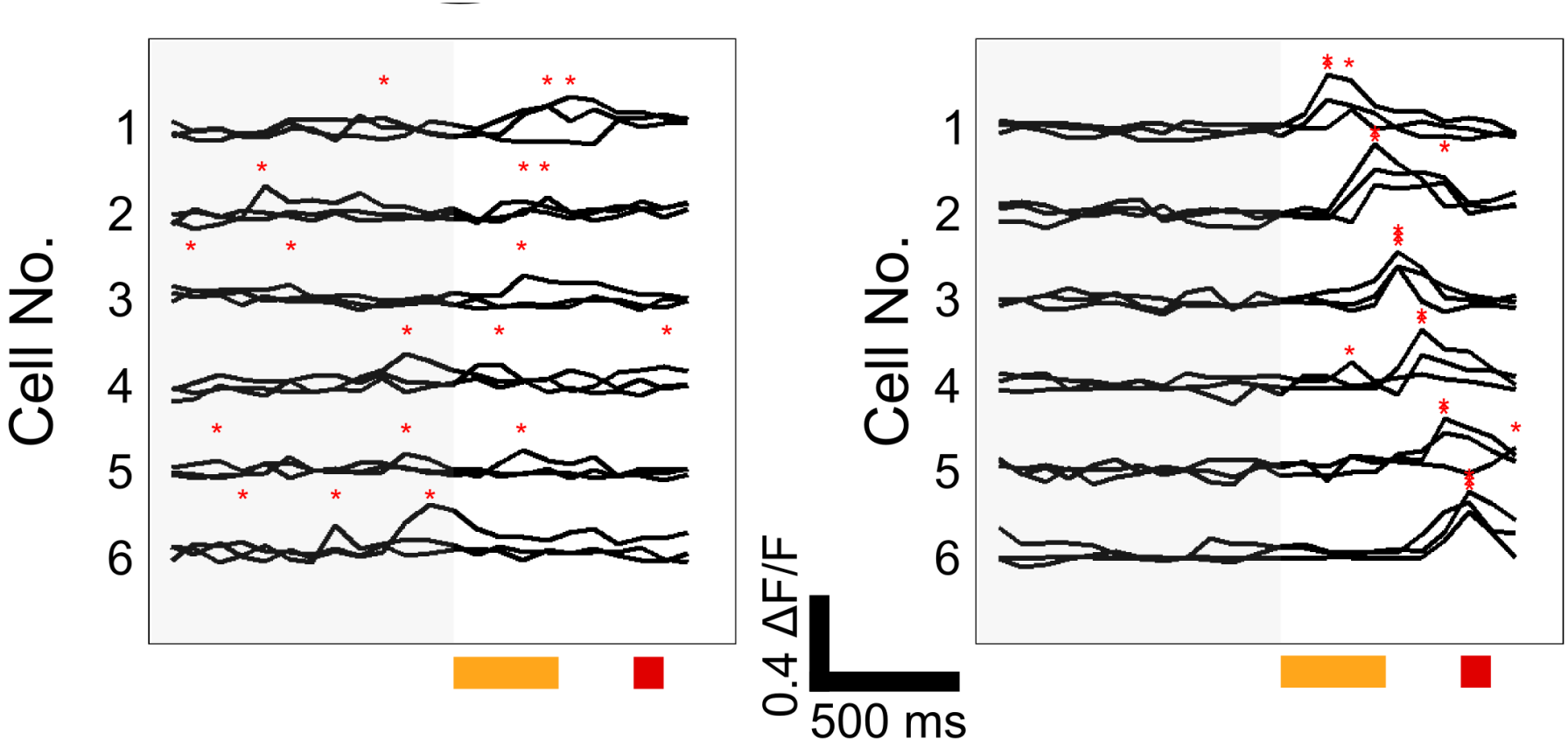


Each cell's dF/F response Normalised



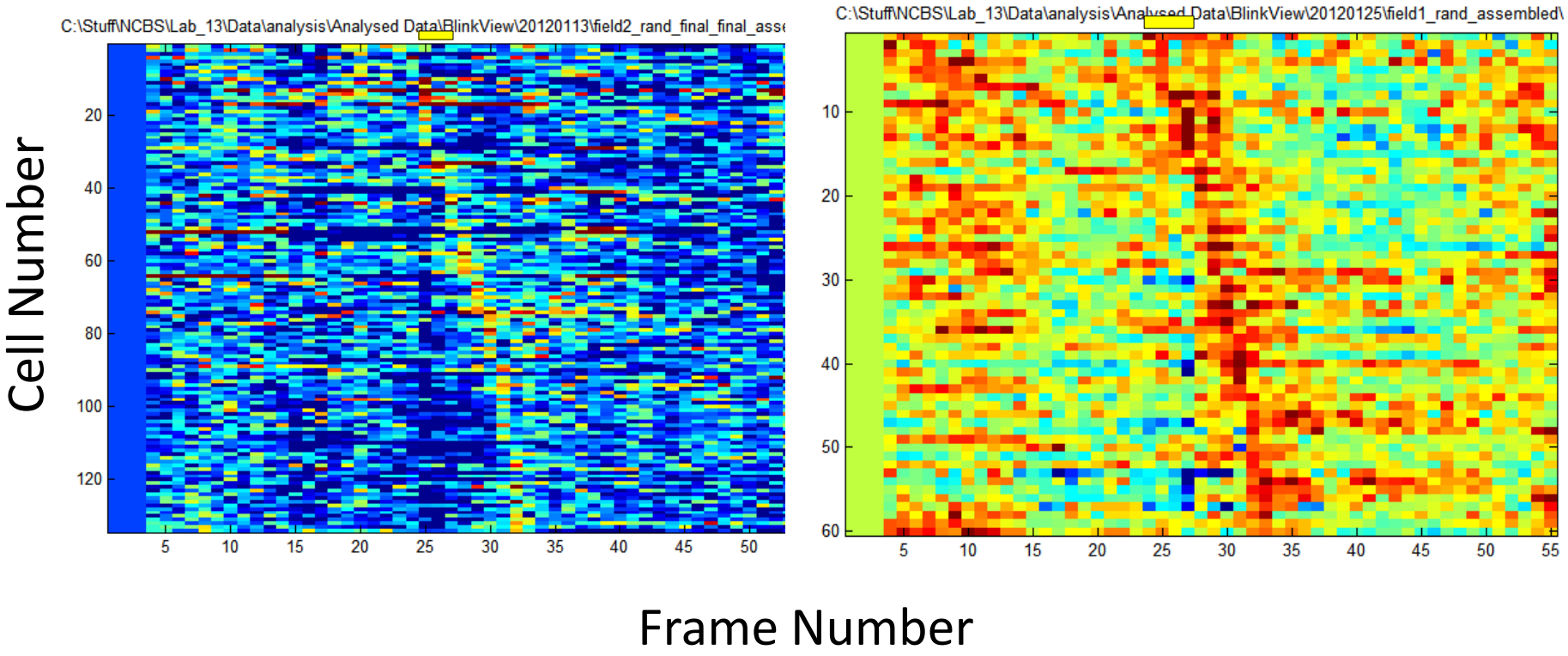
Fluorescence before and after learning

Same 6 cells



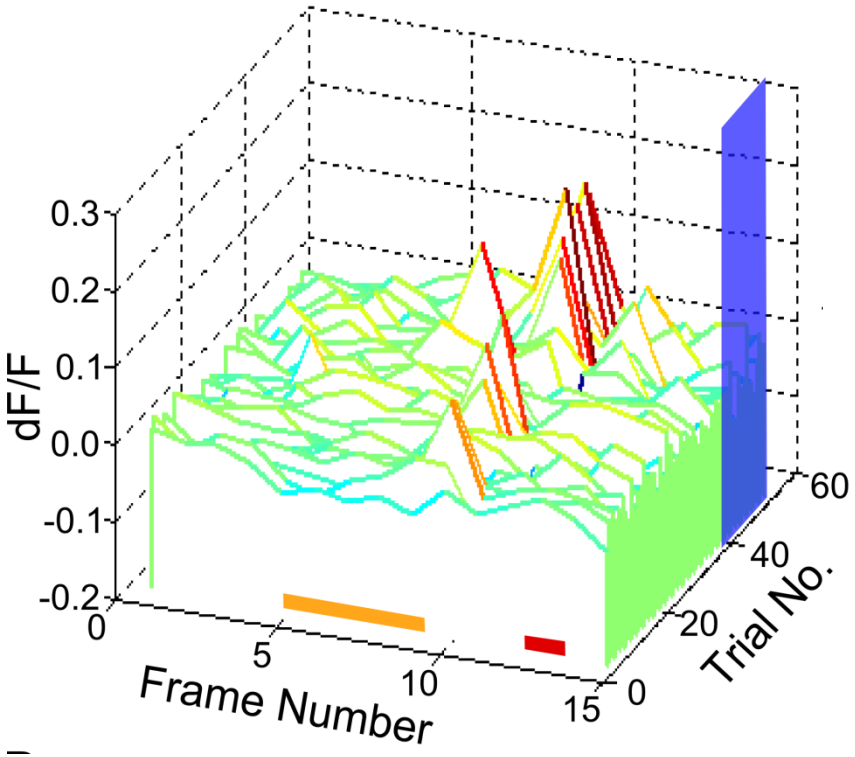
Time Cells in Pseudo-conditioned Mice

Do Time Cells have relevance to the Task?

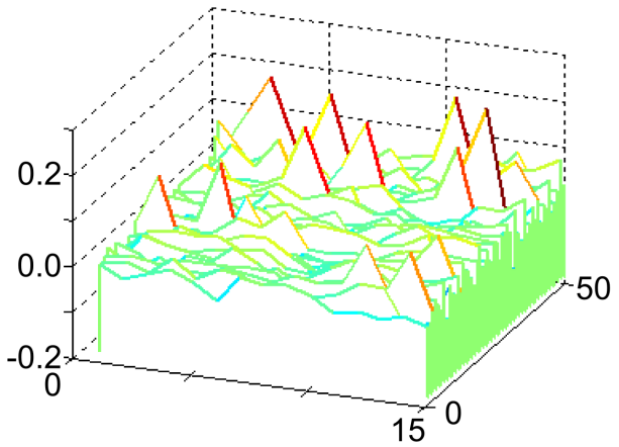


Ridge:Background Ratio – Measures time-specific firing of cells

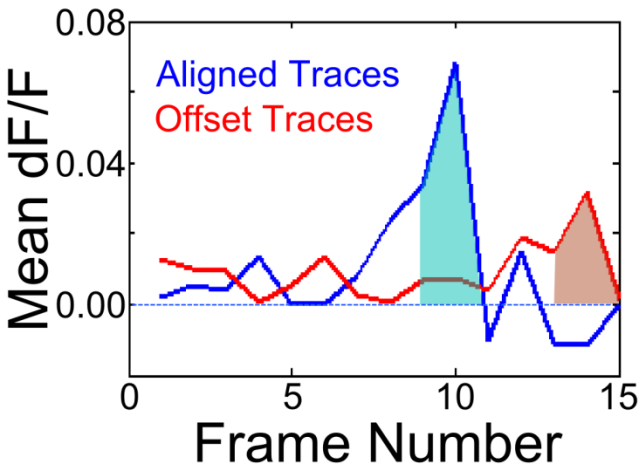
Time-Aligned dF/F Traces for a cell



Randomly Offset dF/F Traces



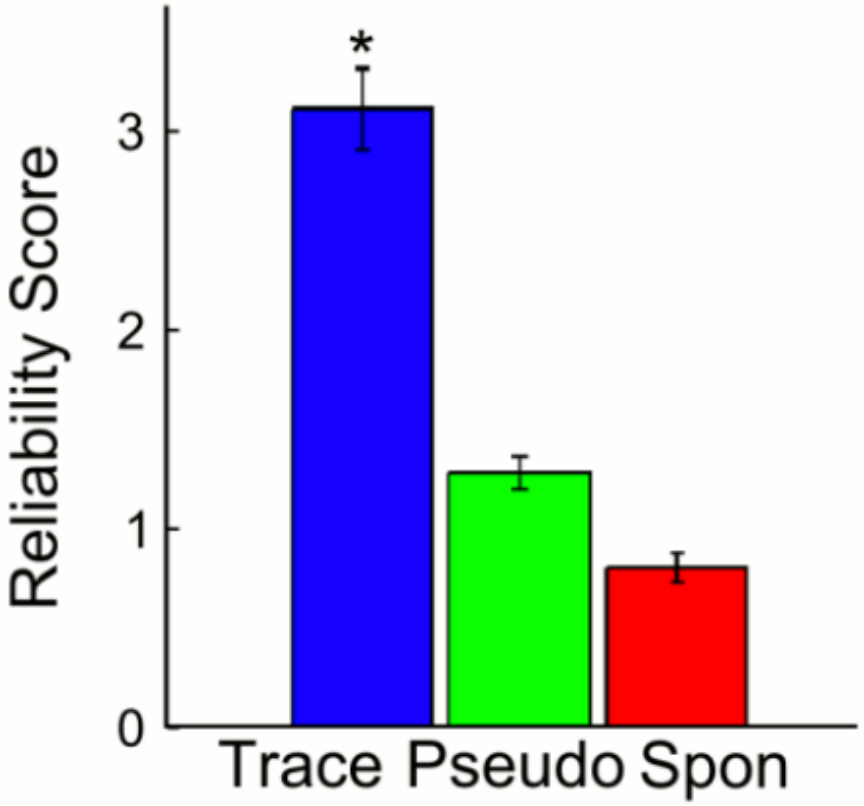
Averaged Traces



Ridge:Background Ratio = Shaded Area/Area under Rest of the Curve

Reliability Score – cells more reliable in Trace than in Pseudo, Spontaneous

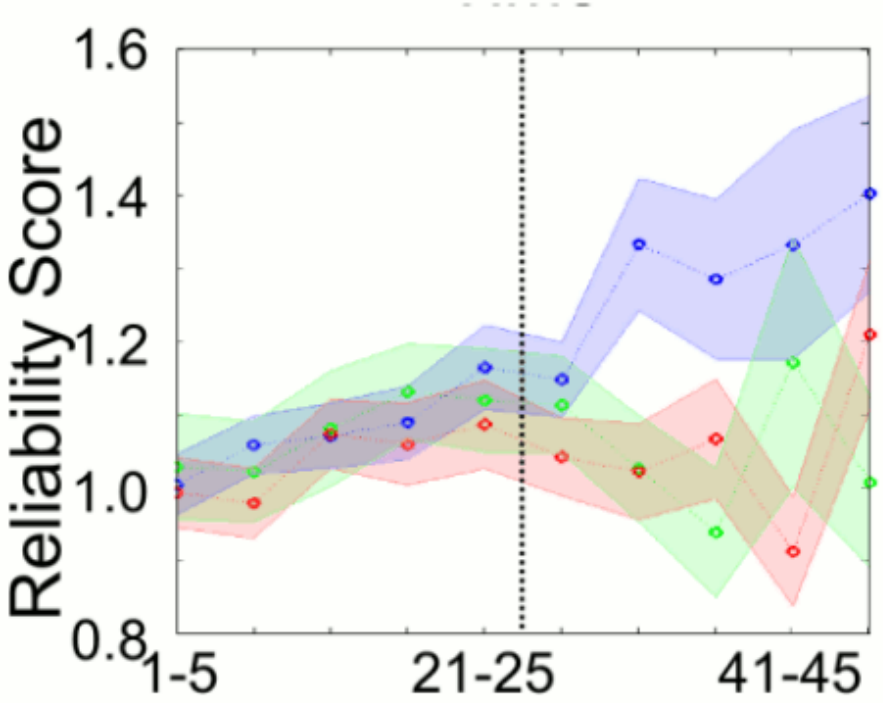
Trace Learners have high R:B Ratio, compared to randomly offset control

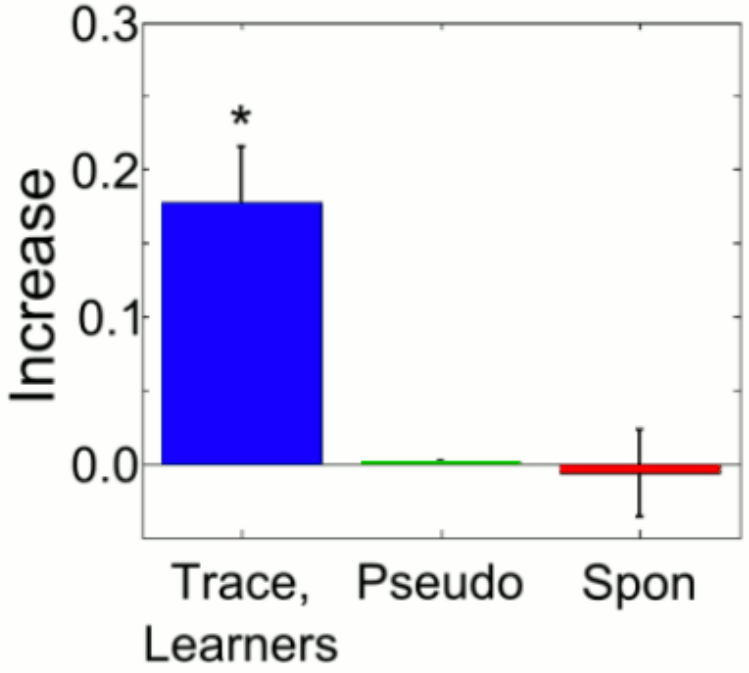


ANOVA p << 0.01, Tukey Kramer h.s.d.

Time Tuning Change Gradually, with Training

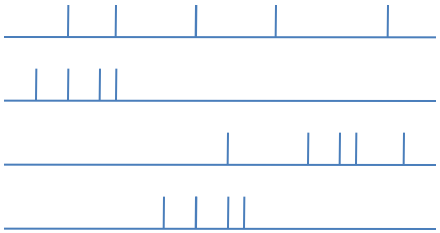
dF/F amplitude at time-Tuning centre increases with training

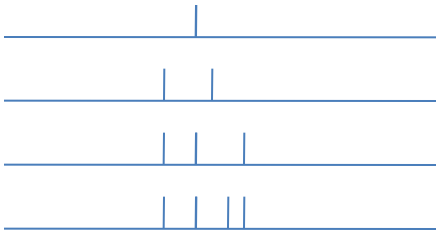




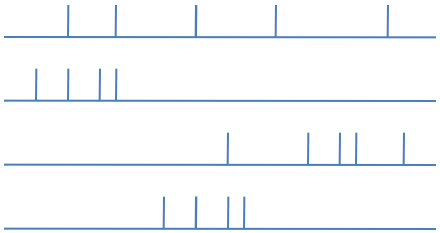
ANOVA $p < 0.01$, Tukey Kramer h.s.d.

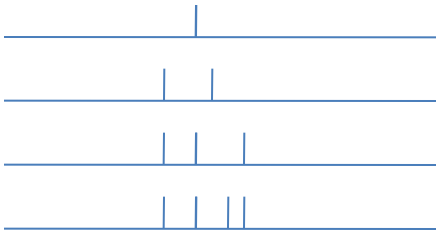
Does timing improve or firing probability improve?

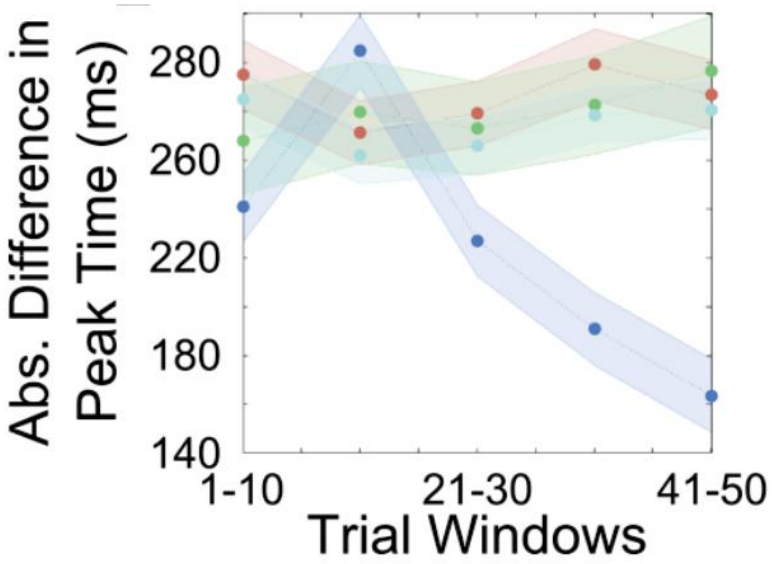




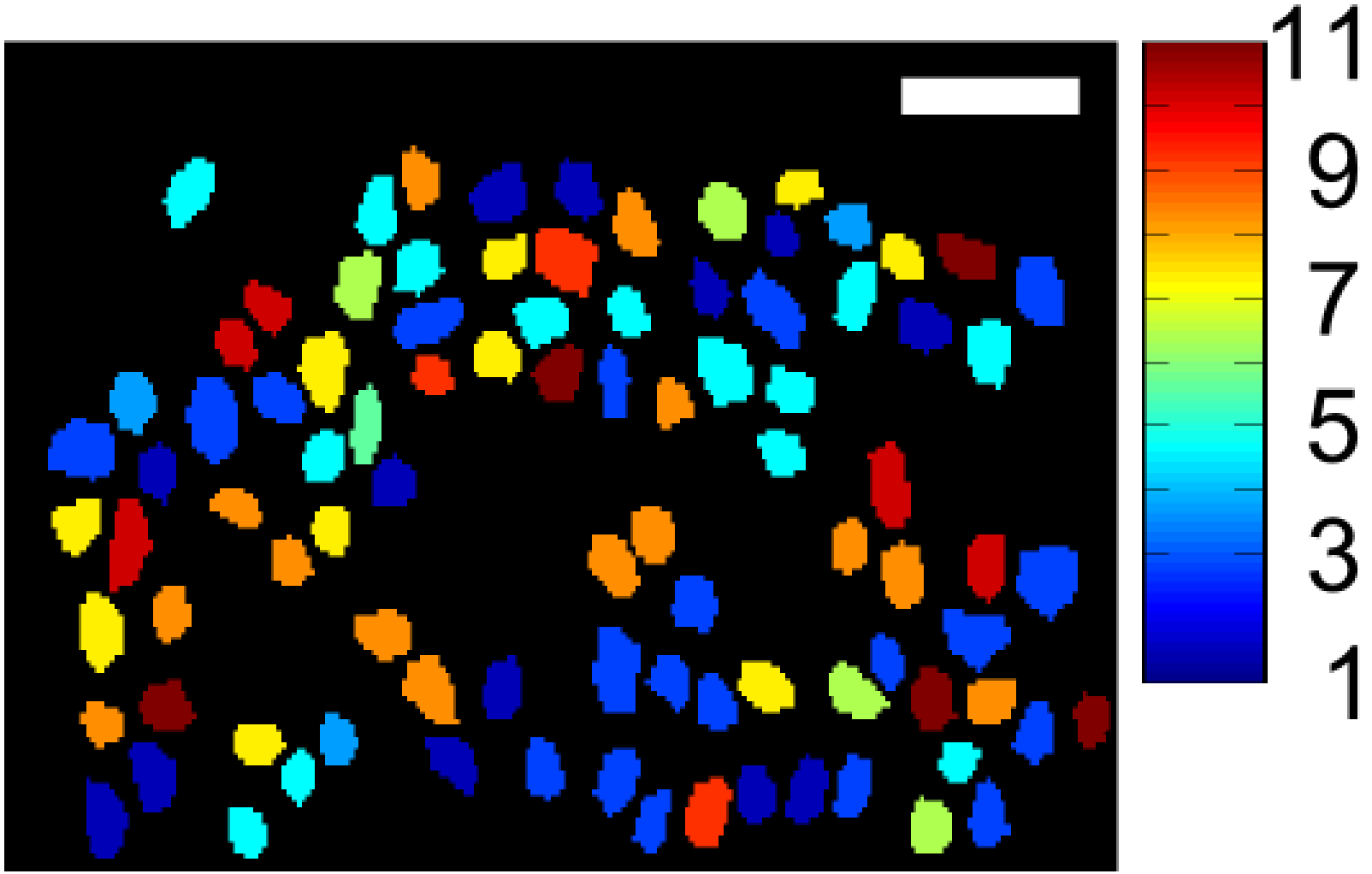
Does timing improve or firing probability improve?





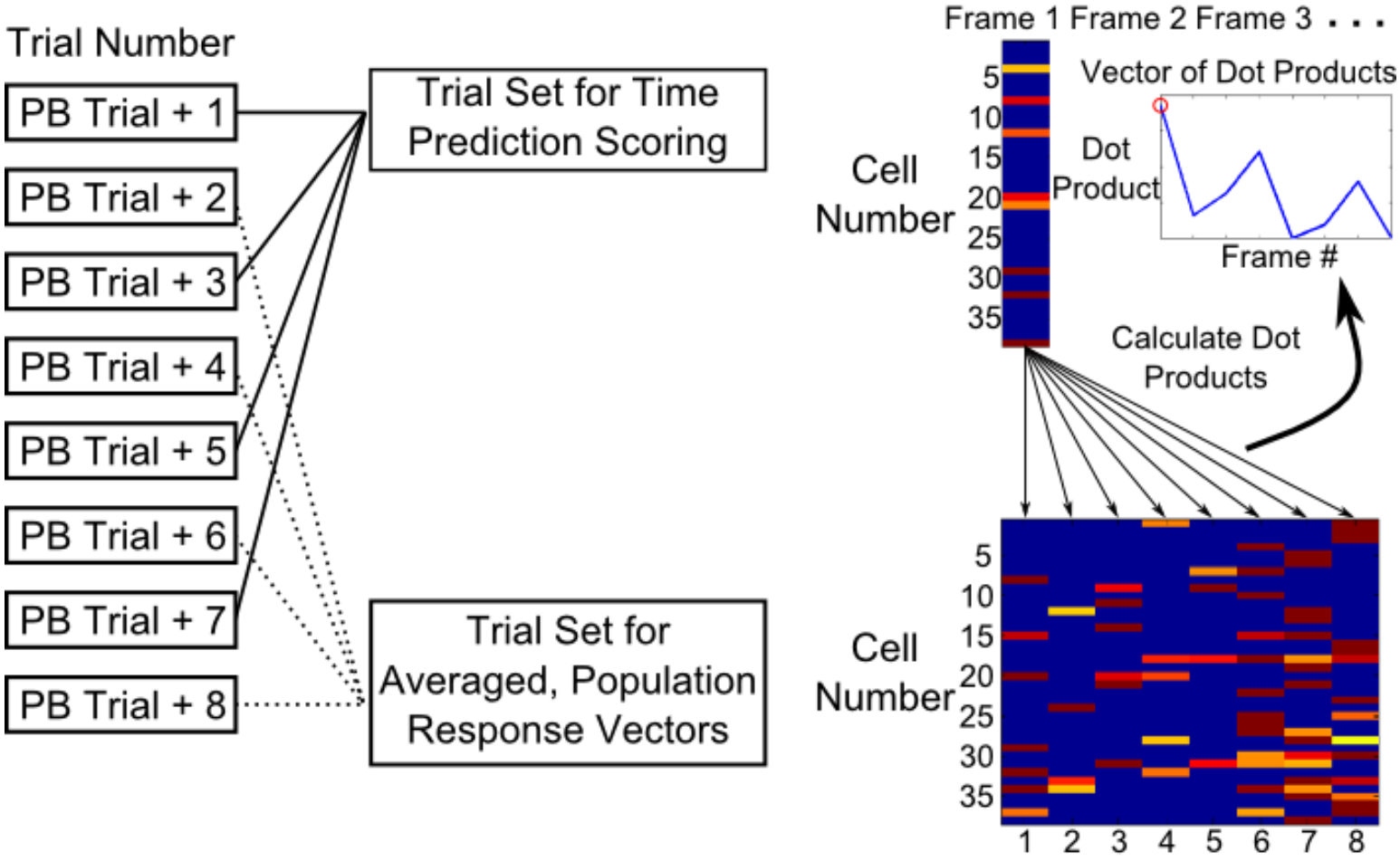


There is no spatial organization of time selective cells



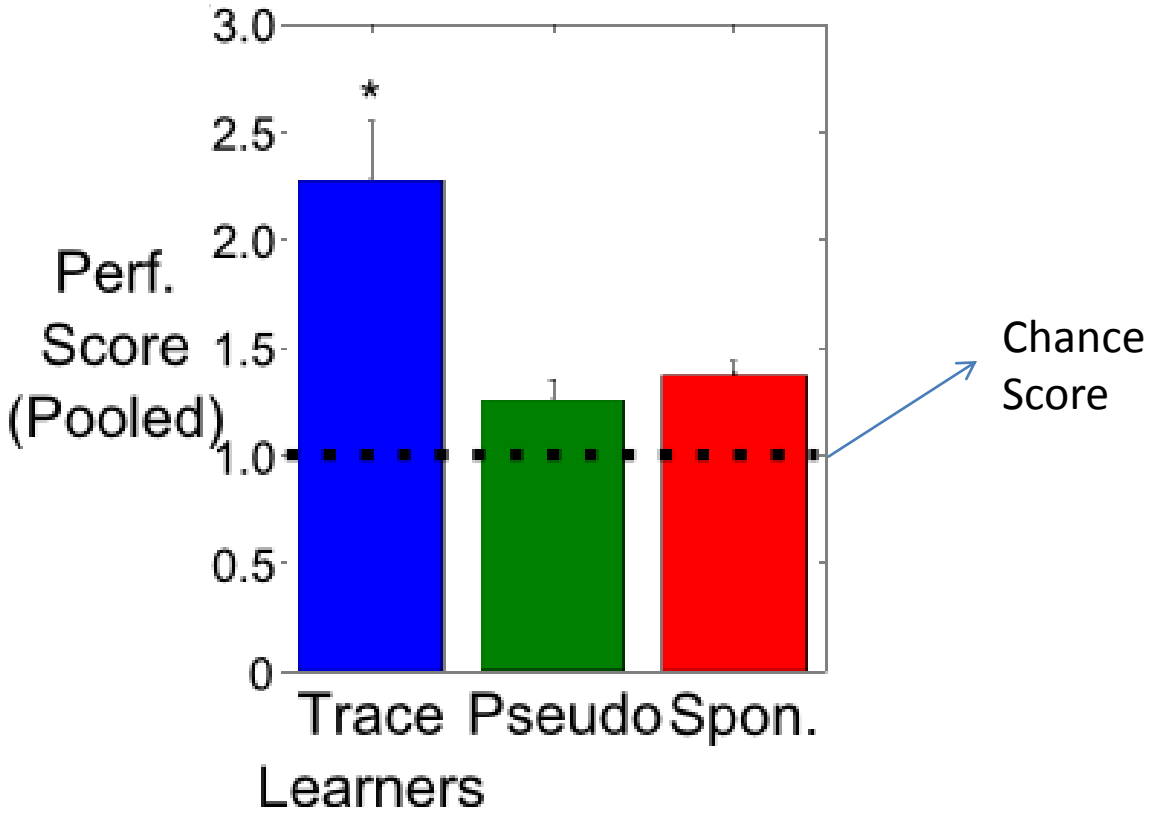
Can we decode time from activity in a single frame?

Schematic of Template-Matching Decoder



Single Trial decoding of time from dF/F population activity

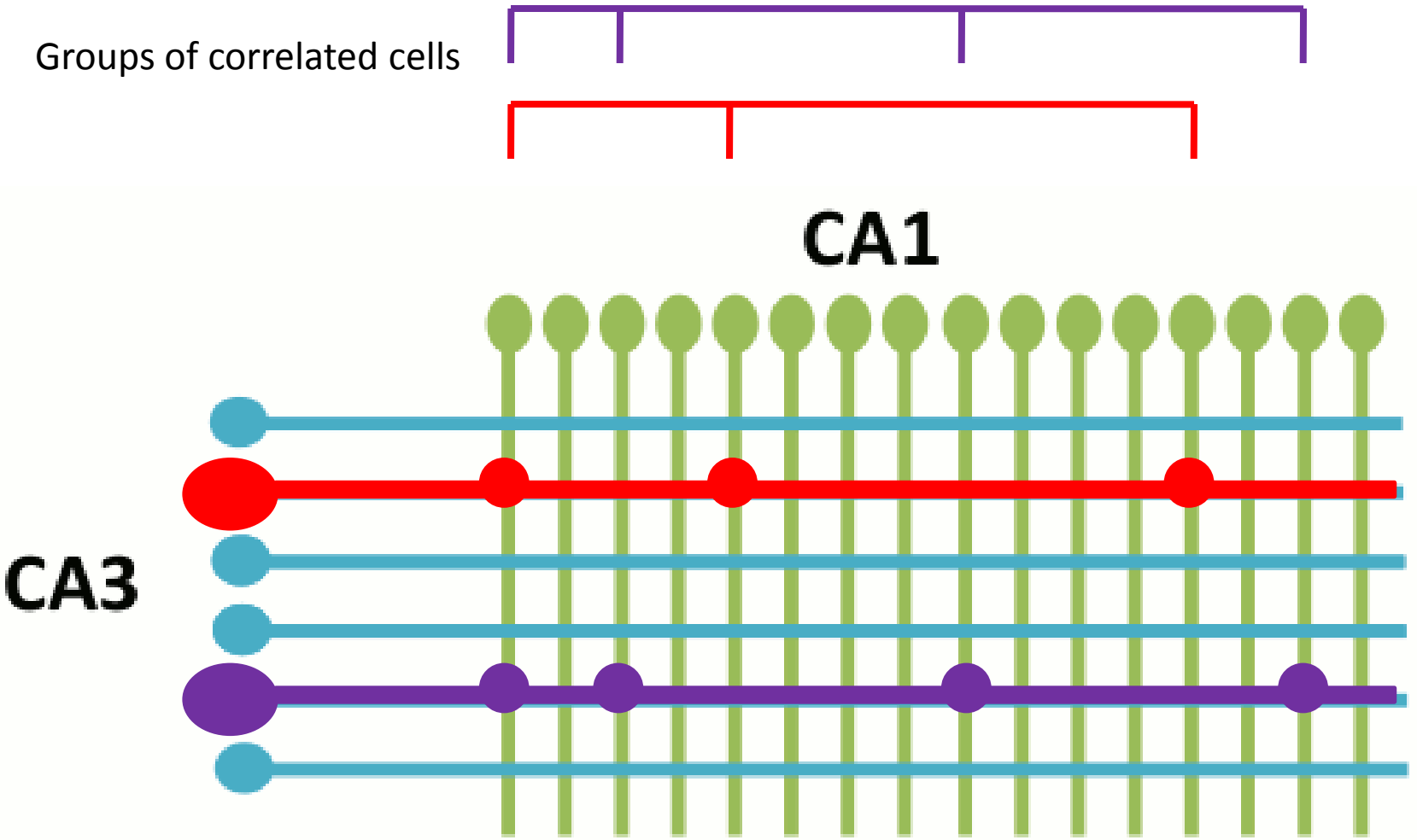
Trace Learners have Higher Decoder Performance Scores than Pseudo-conditioned and Spontaneous Data Scores



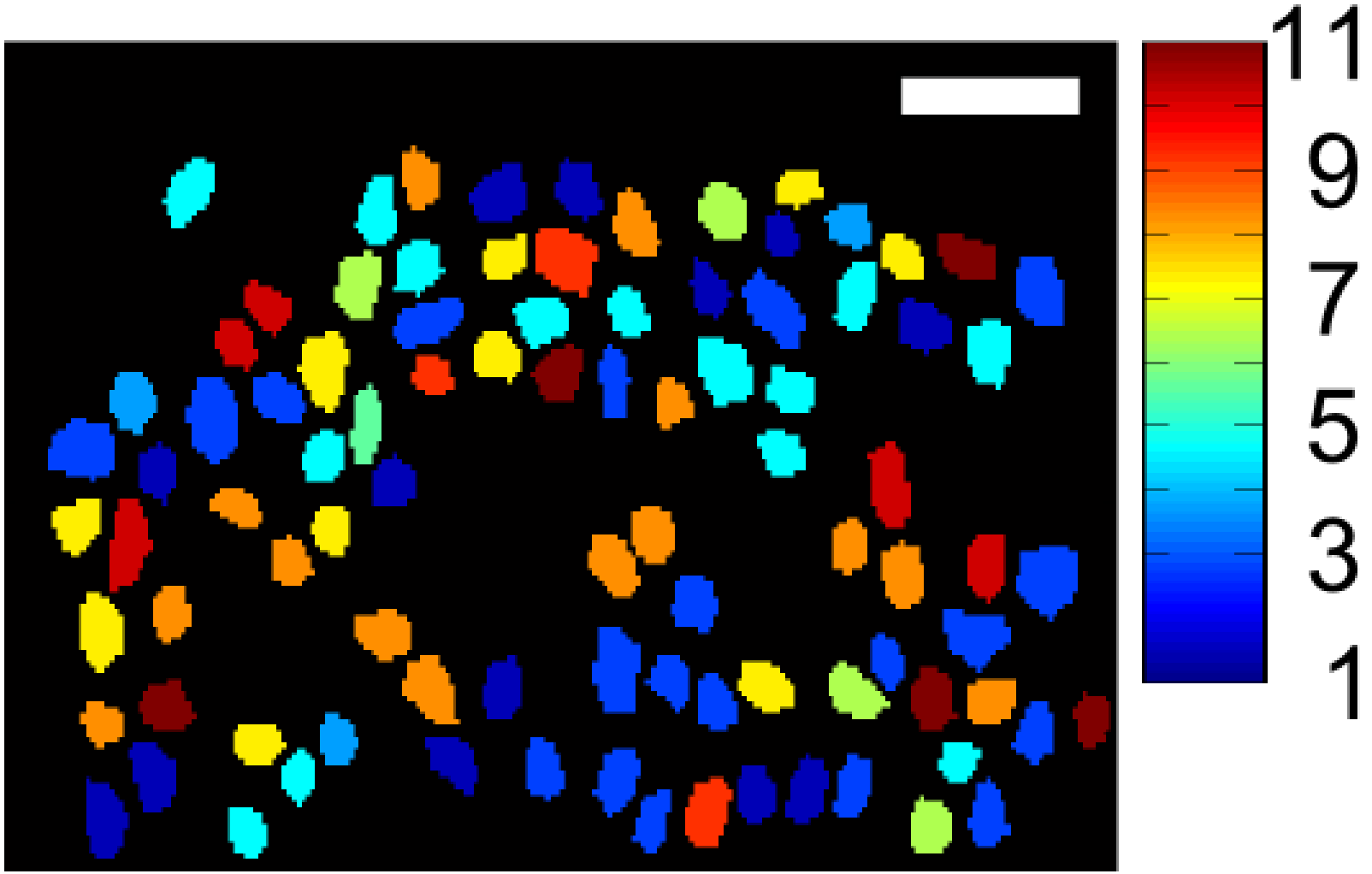
Questions on network learning

- What changes occur in activity?
- What changes occur in connectivity?
- What are the rules?
- How does multiscale signaling implement these rules?

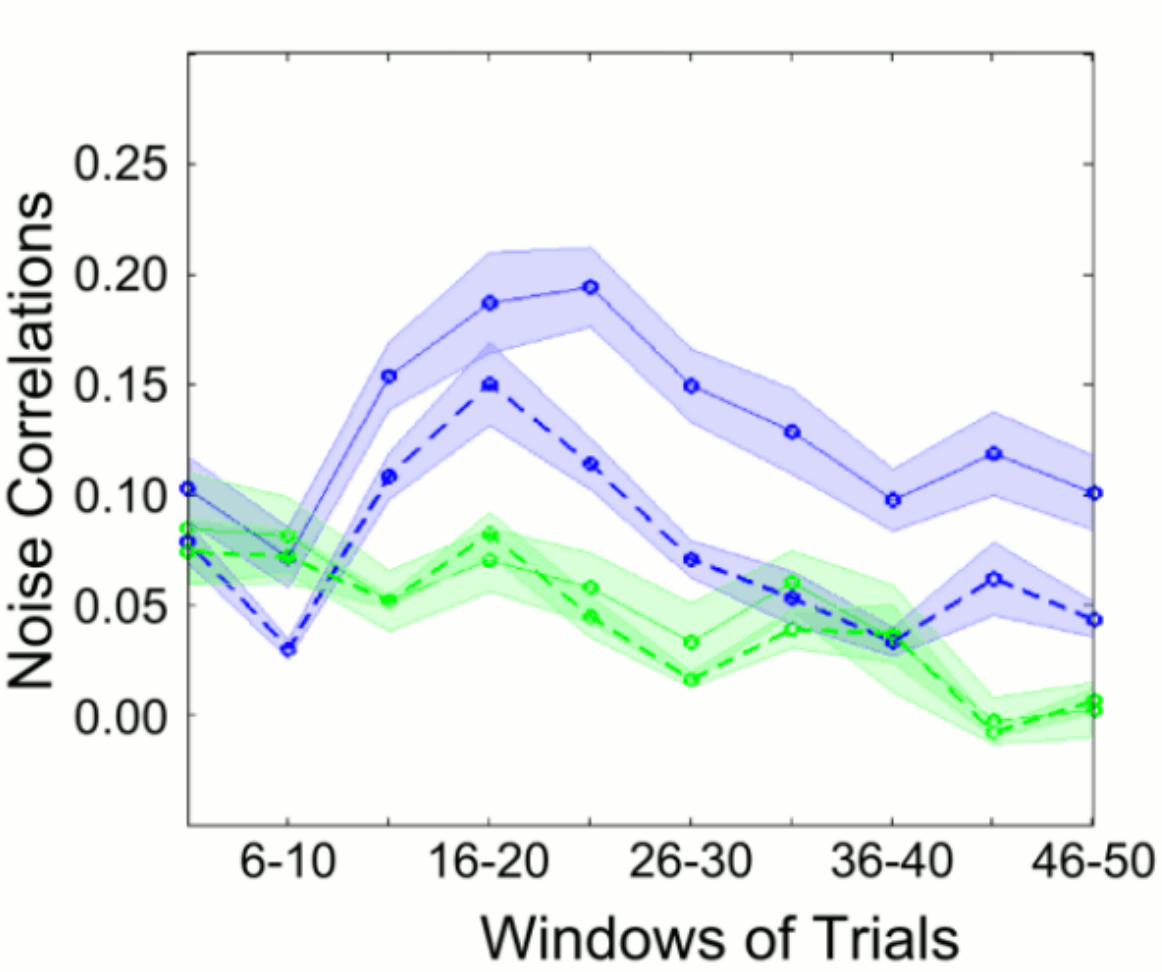
Connectivity and correlations



What happens to correlations between time selective cells?



Background Period Time-Cell Activity Correlations Increase During Training



Trace Learners, Cells Sharing Time Tuning

Trace Learners, Random Cell pairs

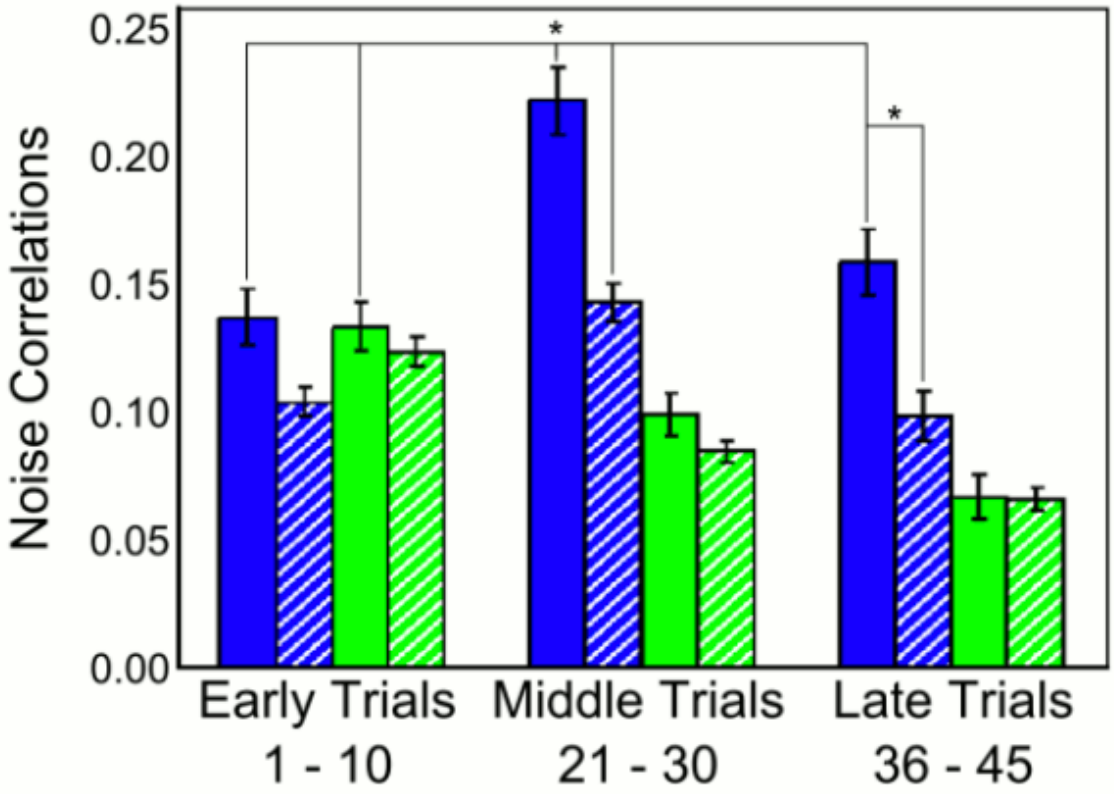
Trace Learners, Rand. trace Timing Offsets

Pseudo-cond, Cells Sharing Time Tuning

Pseudo-cond, Random Cell pairs

Pseudo-cond, Rand. trace Timing Offsets

Background Period Time-Cell Activity Correlations Increase During Training



Trace Learners, Cells Sharing Time Tuning

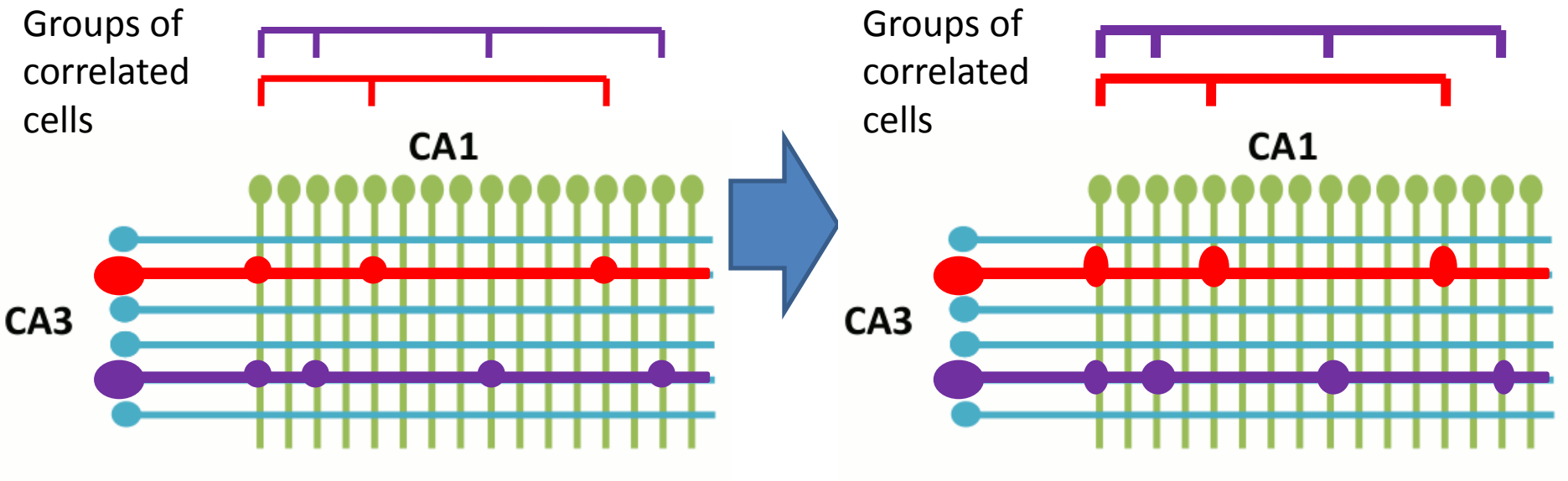
Trace Learners, Random Cell pairs

Pseudo-cond, Cells Sharing Time Tuning

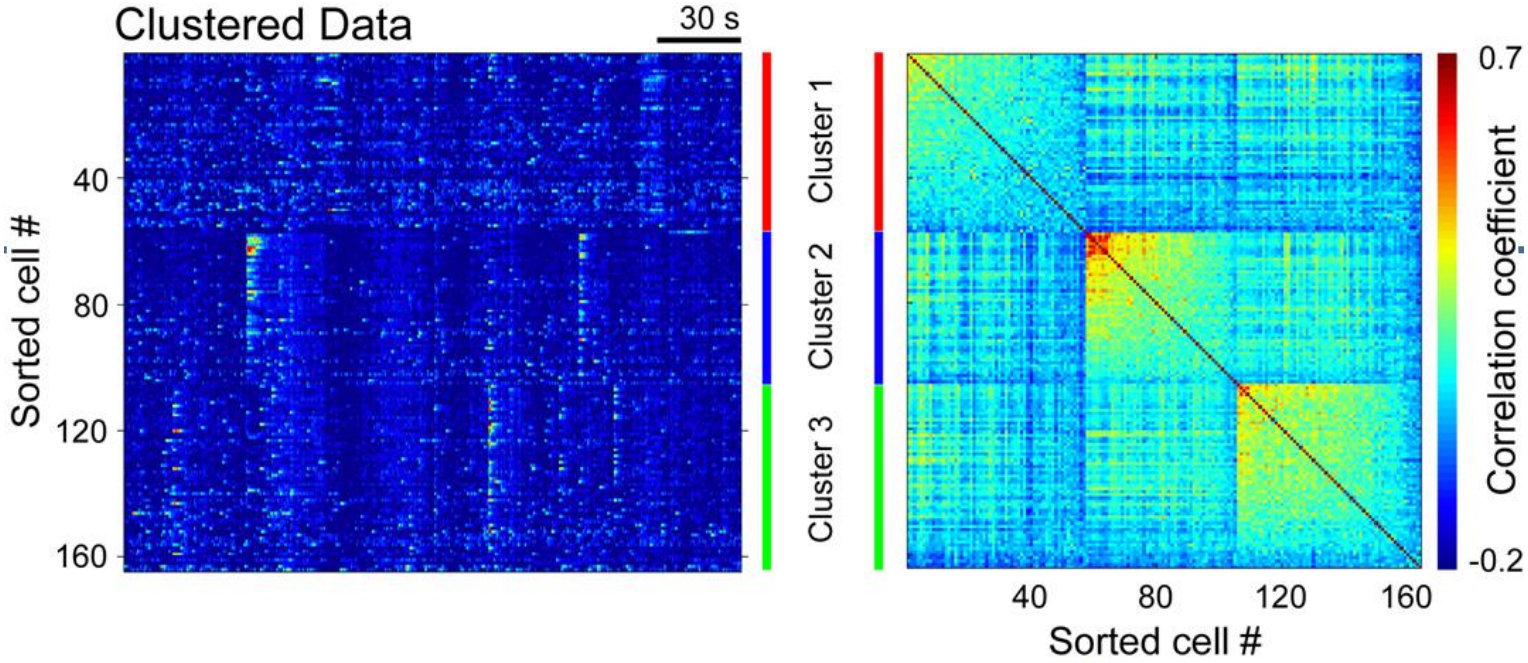
Pseudo-cond, Random Cell pairs

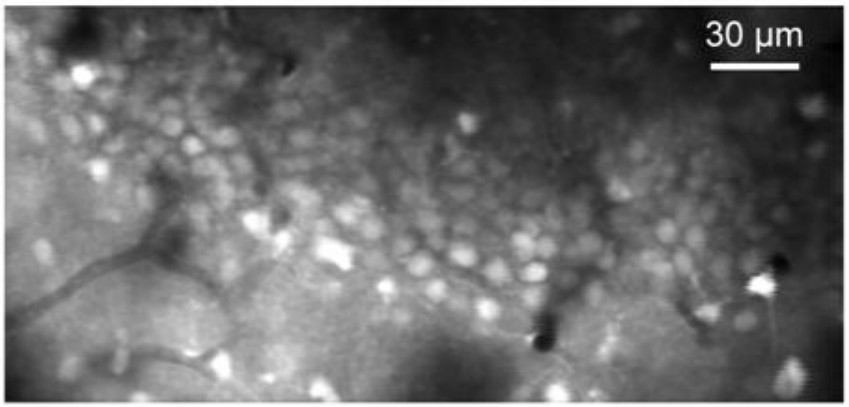
$p < 0.01$, ANOVA followed by Tukey-Kramer h.s.d.

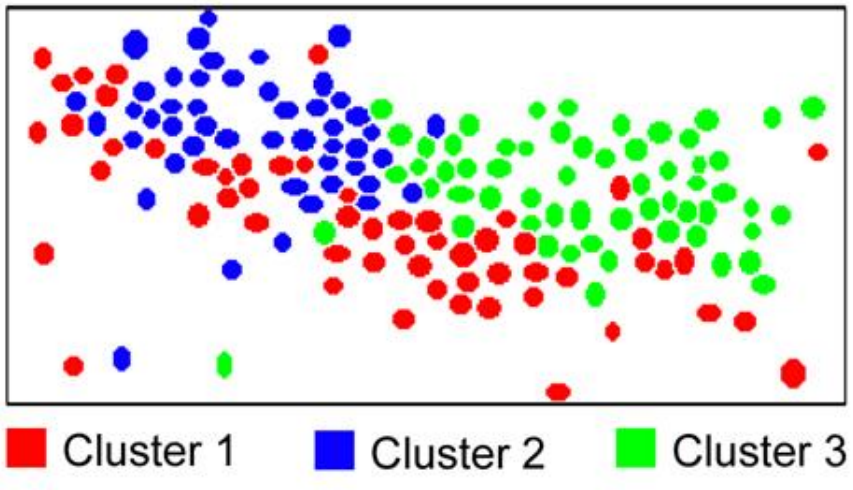
Cells with the same time-tuning become more correlated



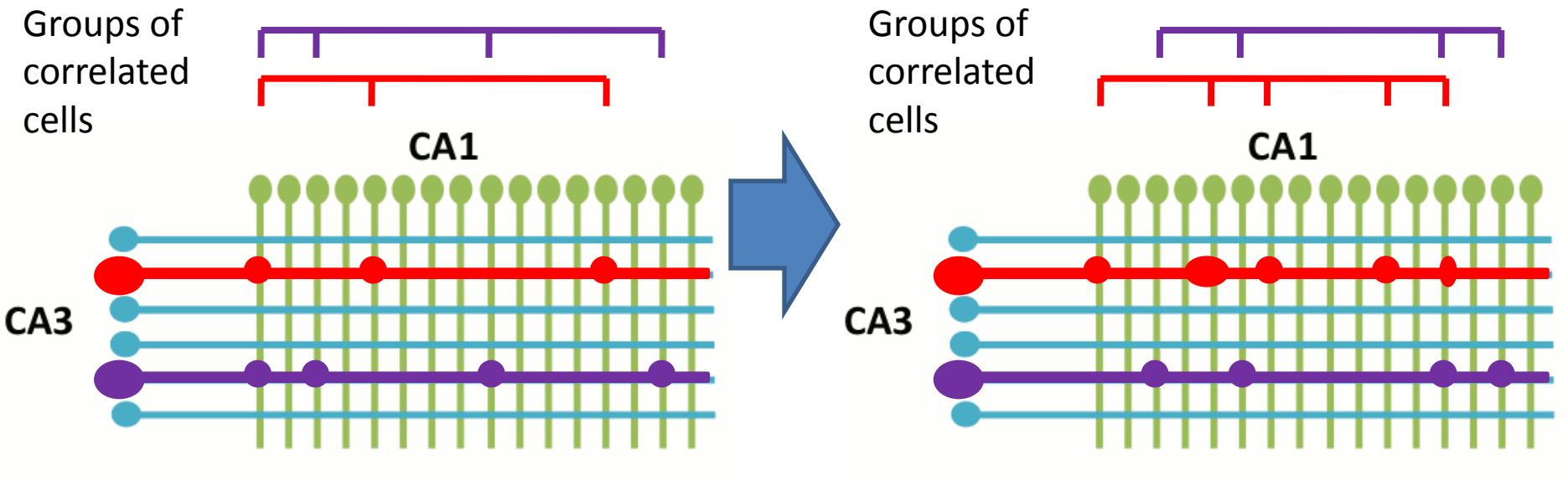
Cells cluster into correlated groups *before* training



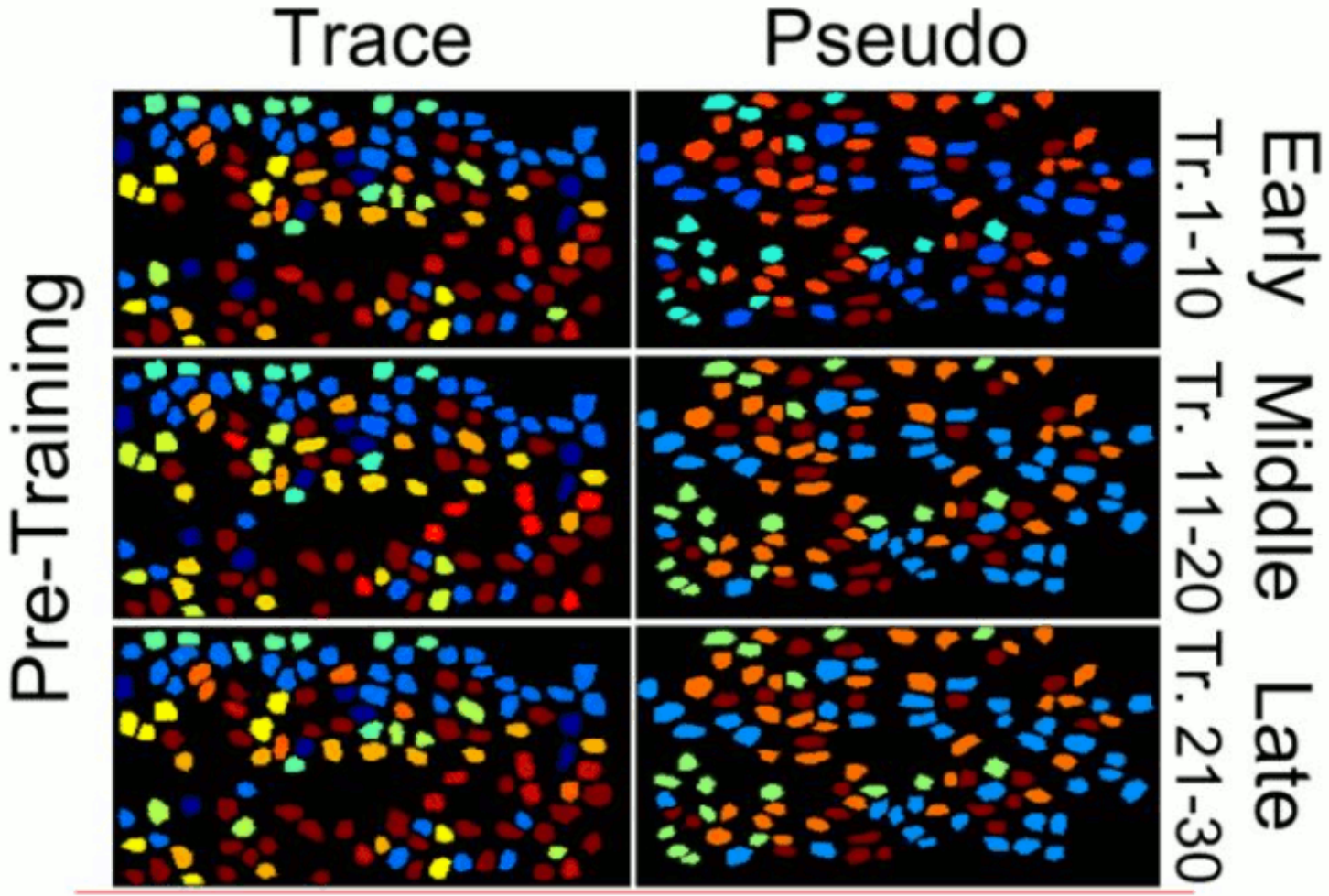




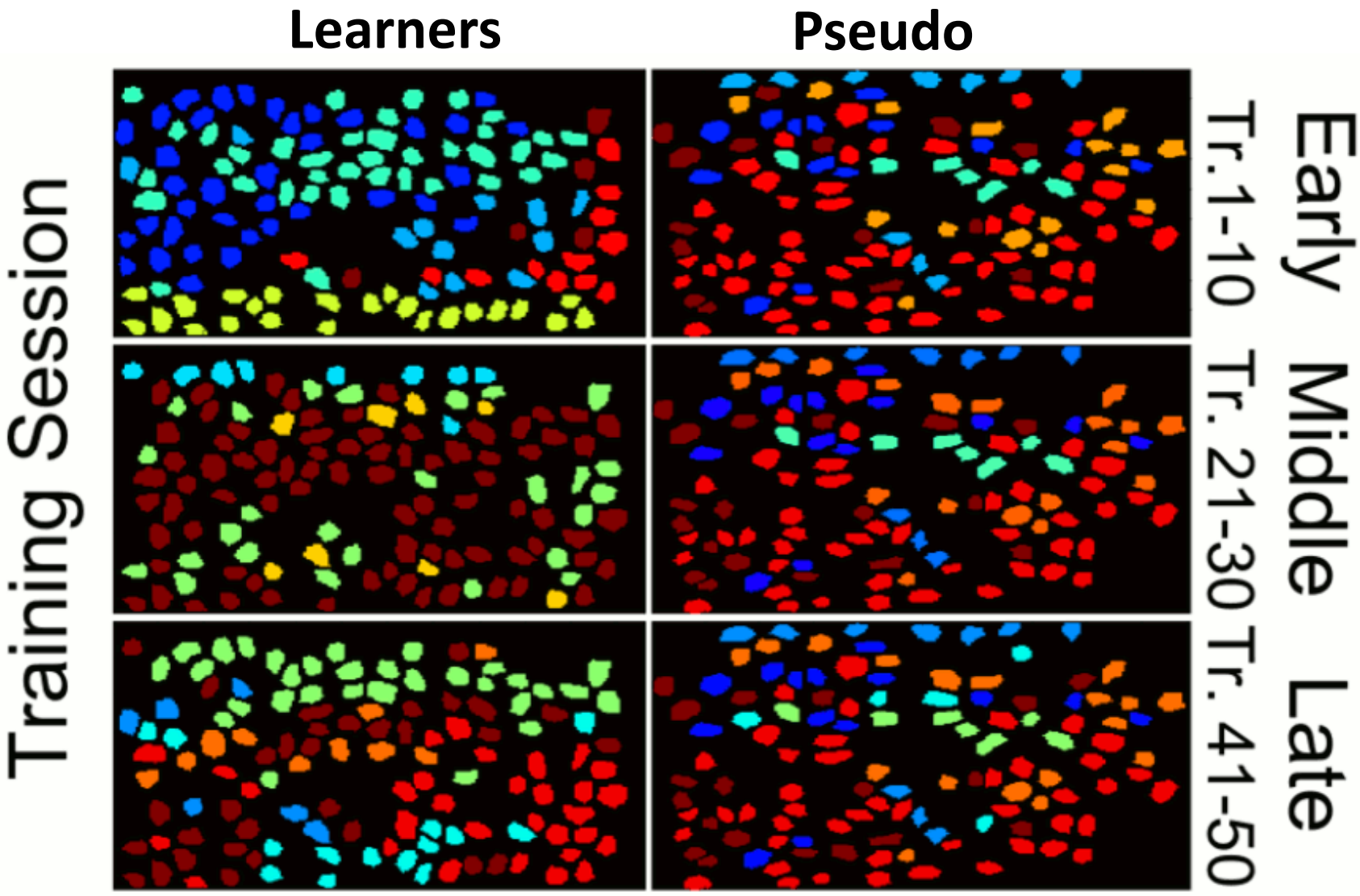
Correlations change if network learns



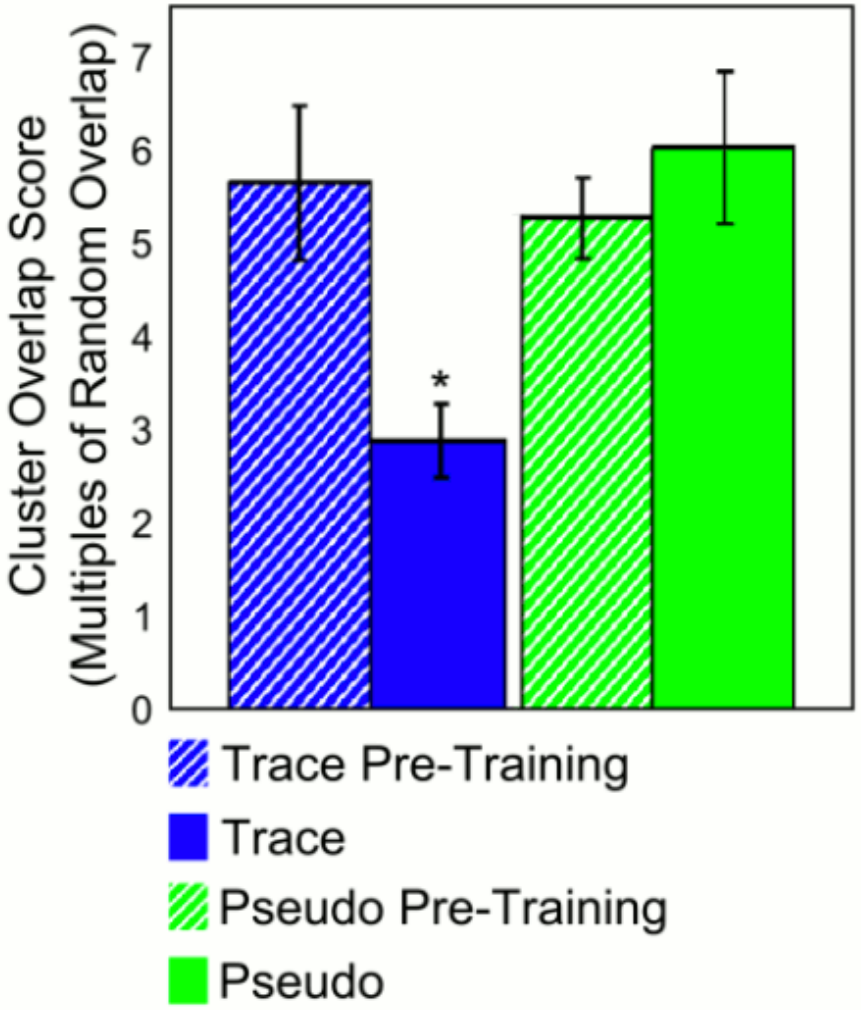
Cell-clusters are Stable Prior to Training



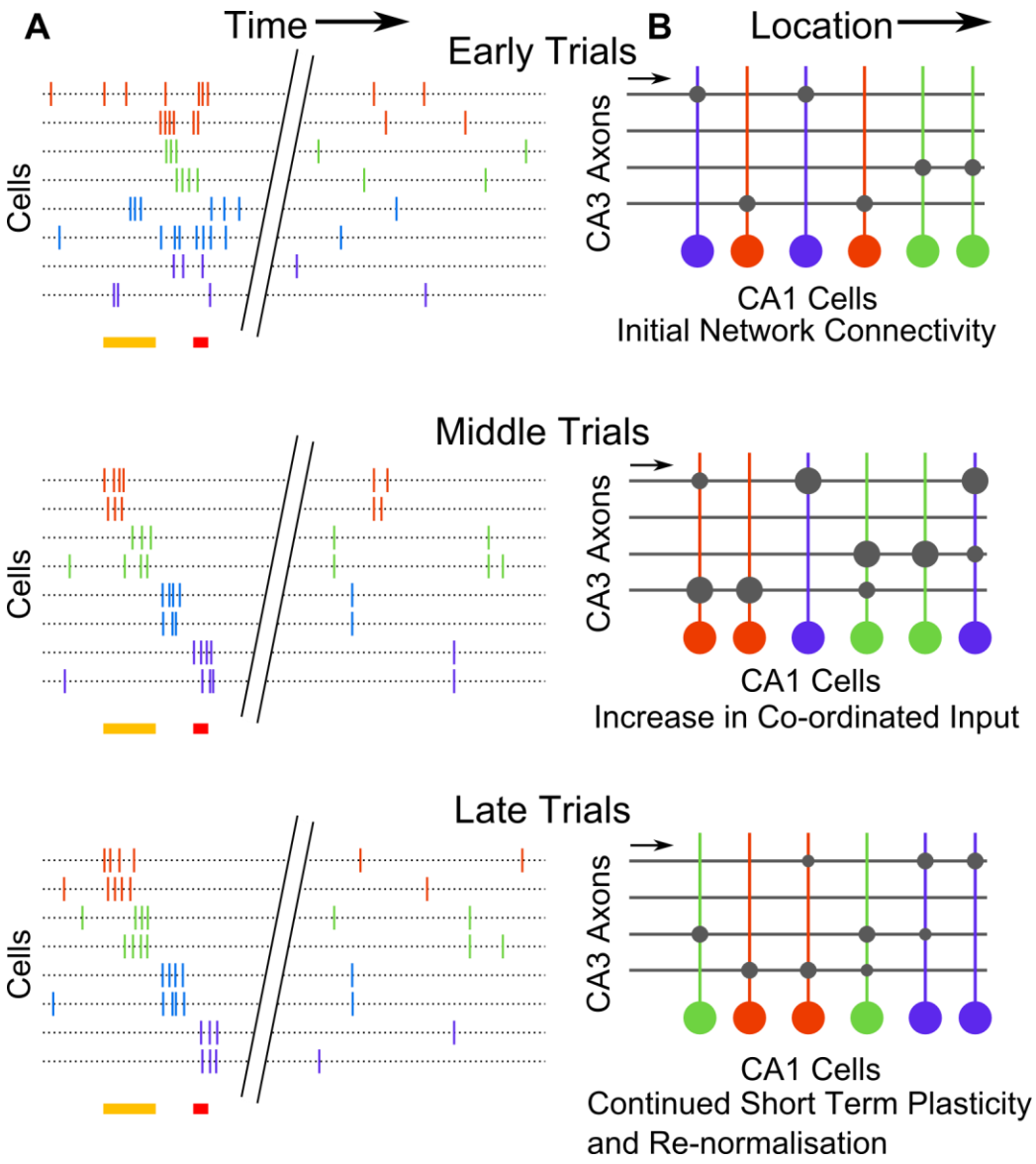
Cell clusters are destabilized only in learners



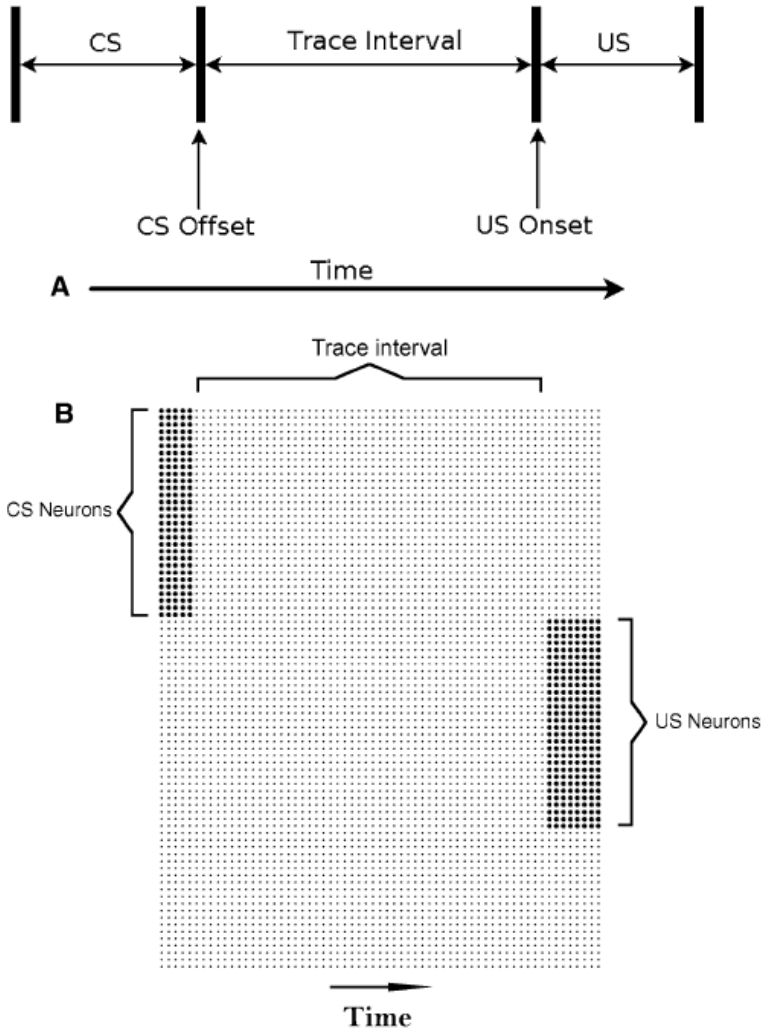
Cell-clusters are De-stabilised only in Trace Learners



Model of network learning



Existing models:
Levy et al. Biol. Cyb. 2005



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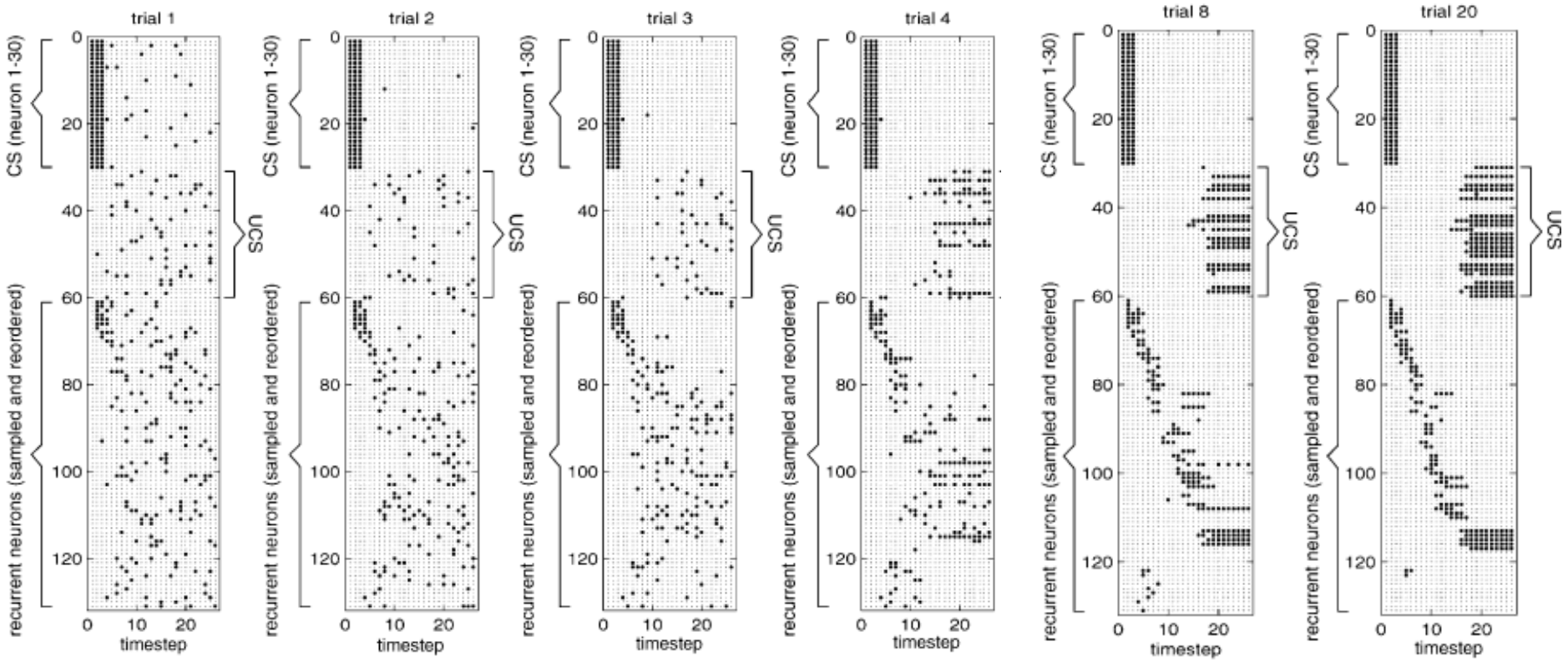

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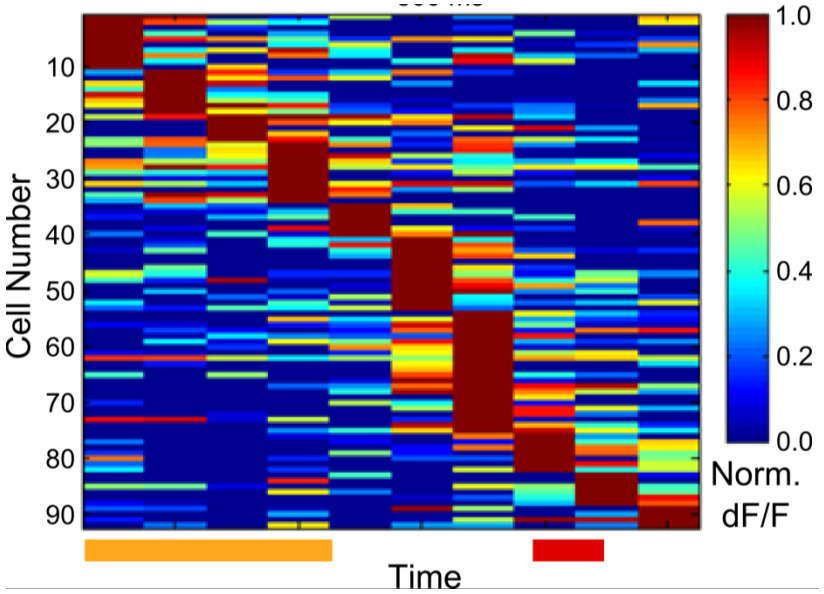

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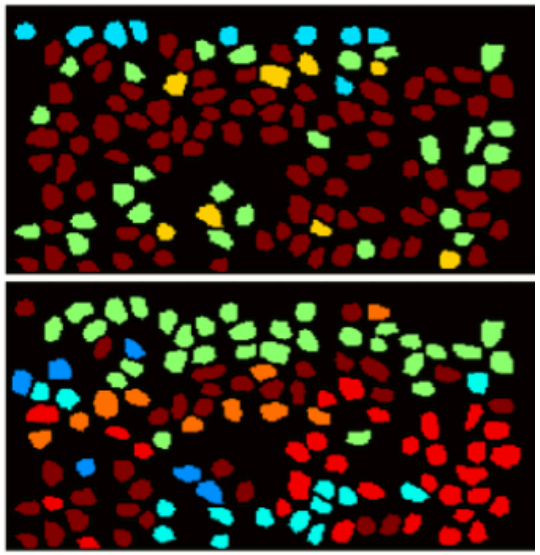
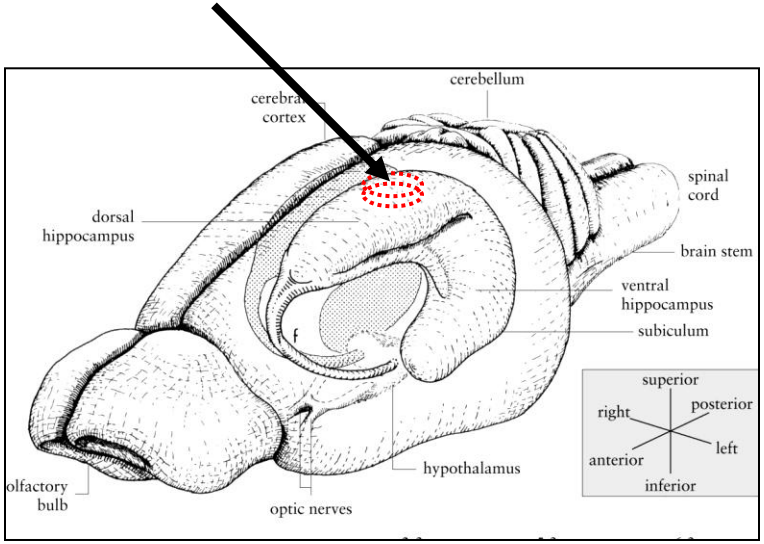
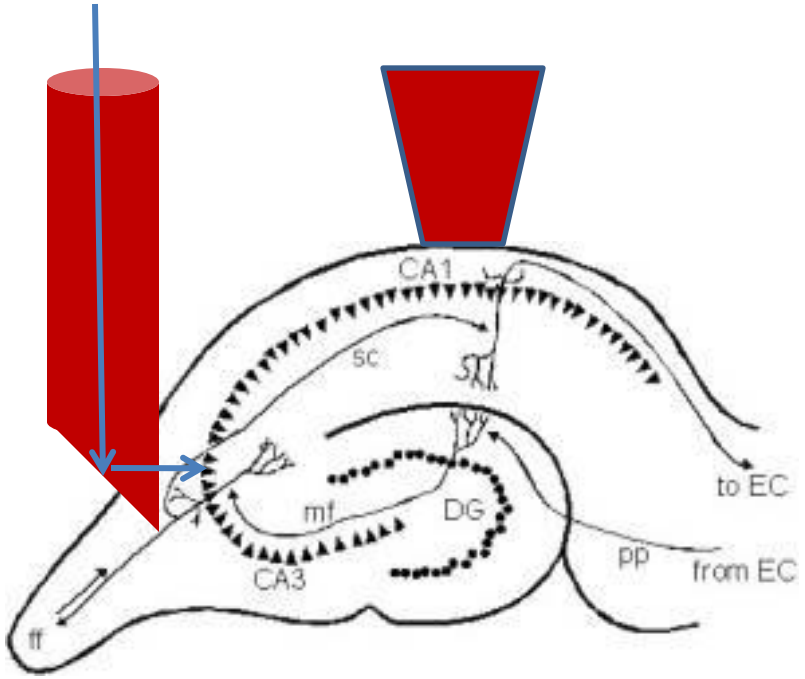


Where are the sequences generated?





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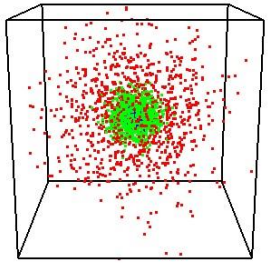
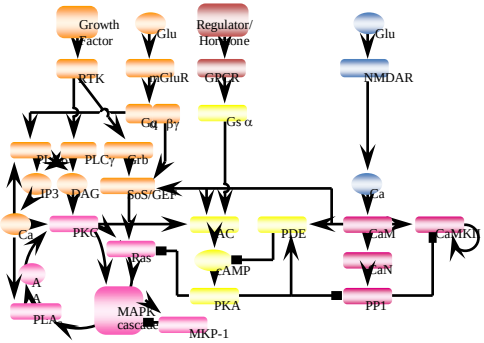
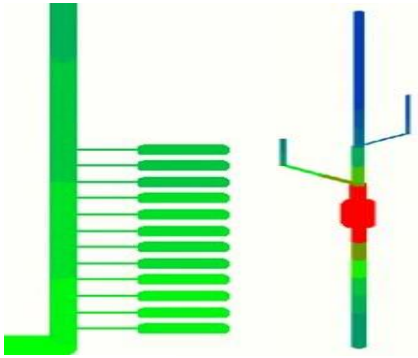


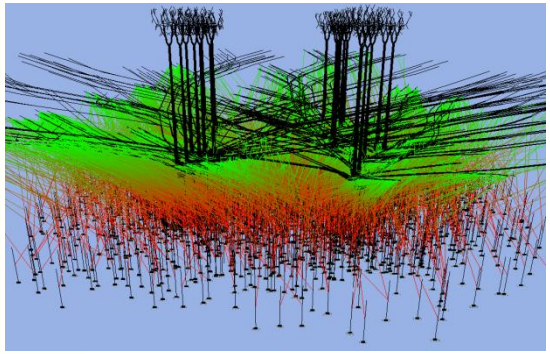
Molecules



Signaling networks

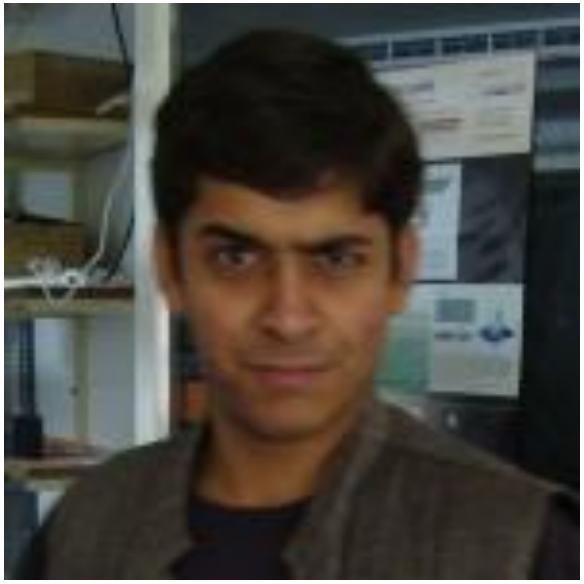


Cellular biophysics



Network

Thank you!



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Imaging Facility, Mechanical and Electronics Workshops

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