BIOPHYSICAL MODELS OF WORKING MEMORY

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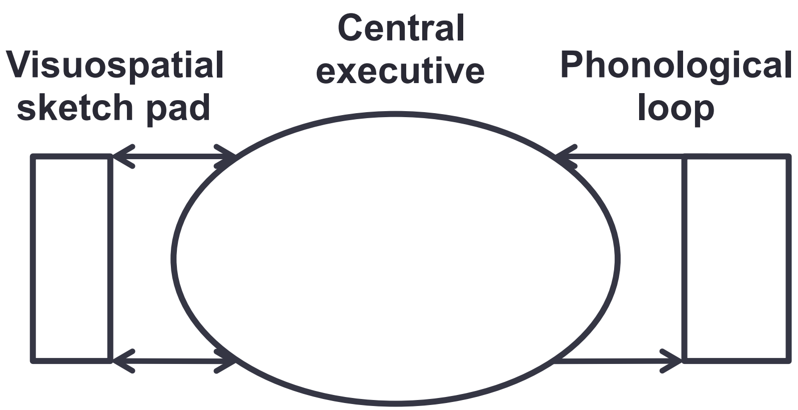
Theory

Working memory refers to the ability to temporarily retain information that was just experienced but no longer exists in the external environment.

Three subcomponents:

(i) the **central executive**, which is assumed to be an attention controlling system.
(ii) the **visuospatial sketch pad**, which manipulates visual images.
(iii) the **phonological loop**, which stores and rehearses speech-based information.



Baddeley, A. D. et. al. *The Psychology of Learning and Motivation.* 1974 **vol. 8**, 47-89.

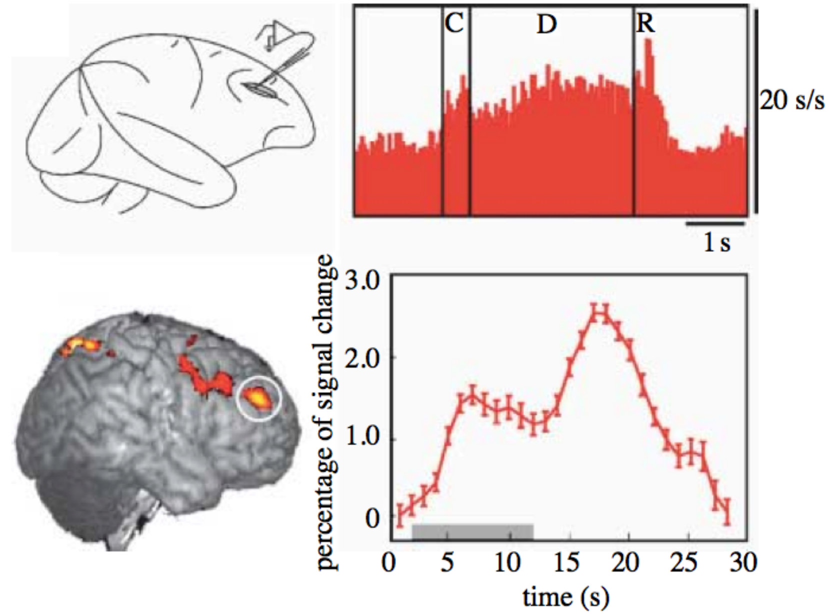
Evidence supporting this theory from *in vivo* studies (monkeys performing a visuospatial task).

Role of PFC in Working Memory

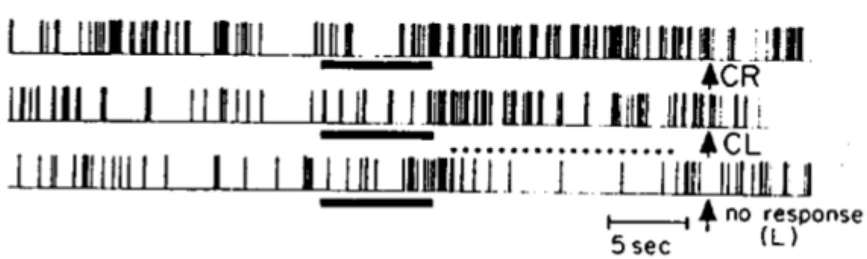
Neurons carry specific goal-related information across a temporal delay, in the absence of external cues, by enhancing their discharge rate.

Neurons switch from a low-activity baseline state into a stimulus-selective high-activity state which they maintain throughout the delay period, after which they return to the low-activity state.

Spontaneous breakdown of delay-type activity leads to associated errors in behavioral responses.



D'Esposito, M. *Phil. Trans. R. Soc. B* 2007 **362**, 761-772



Fuster, J.M. *J. Neurophysiol.* 1973 **36**, 61-78

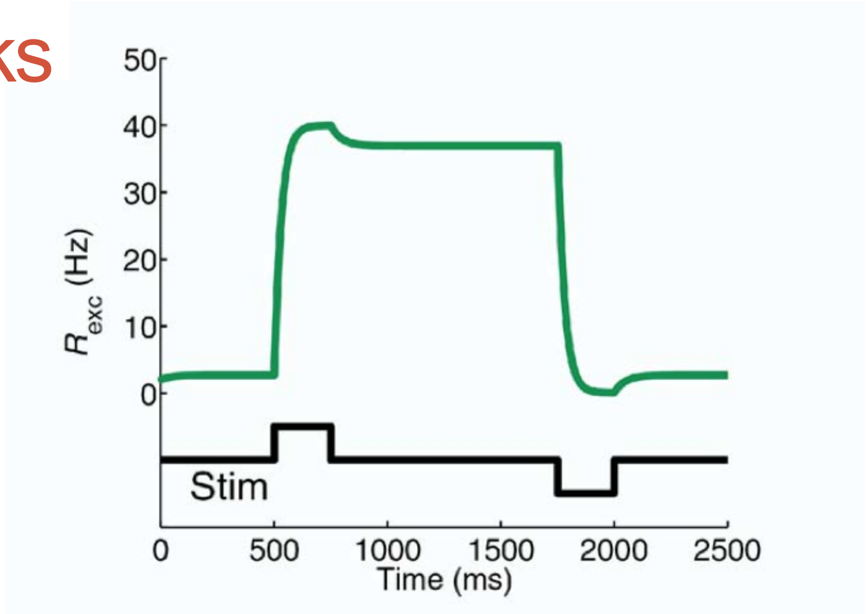
Bistability – neurons to networks

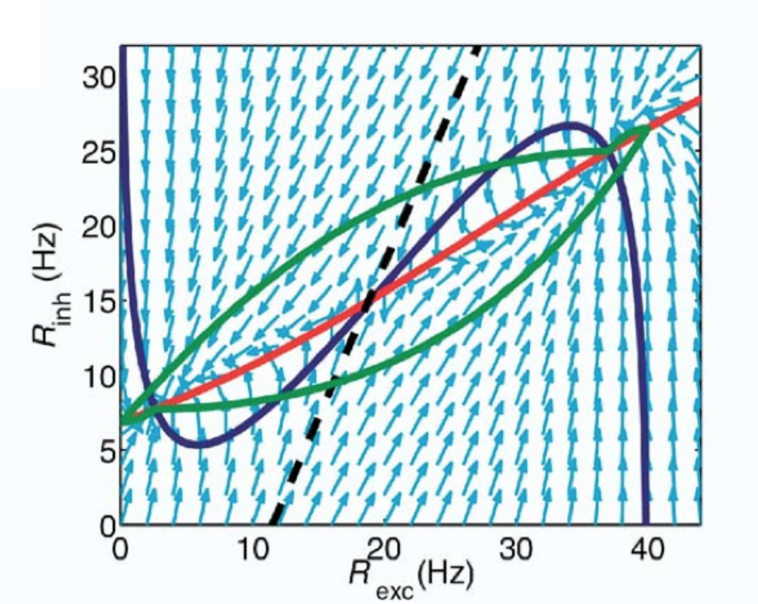
Internal events can switch networks back and forth between a low activity and high activity state.

Feedback inhibition keeps population on neurons in a low state as long as FR rate within population is low.

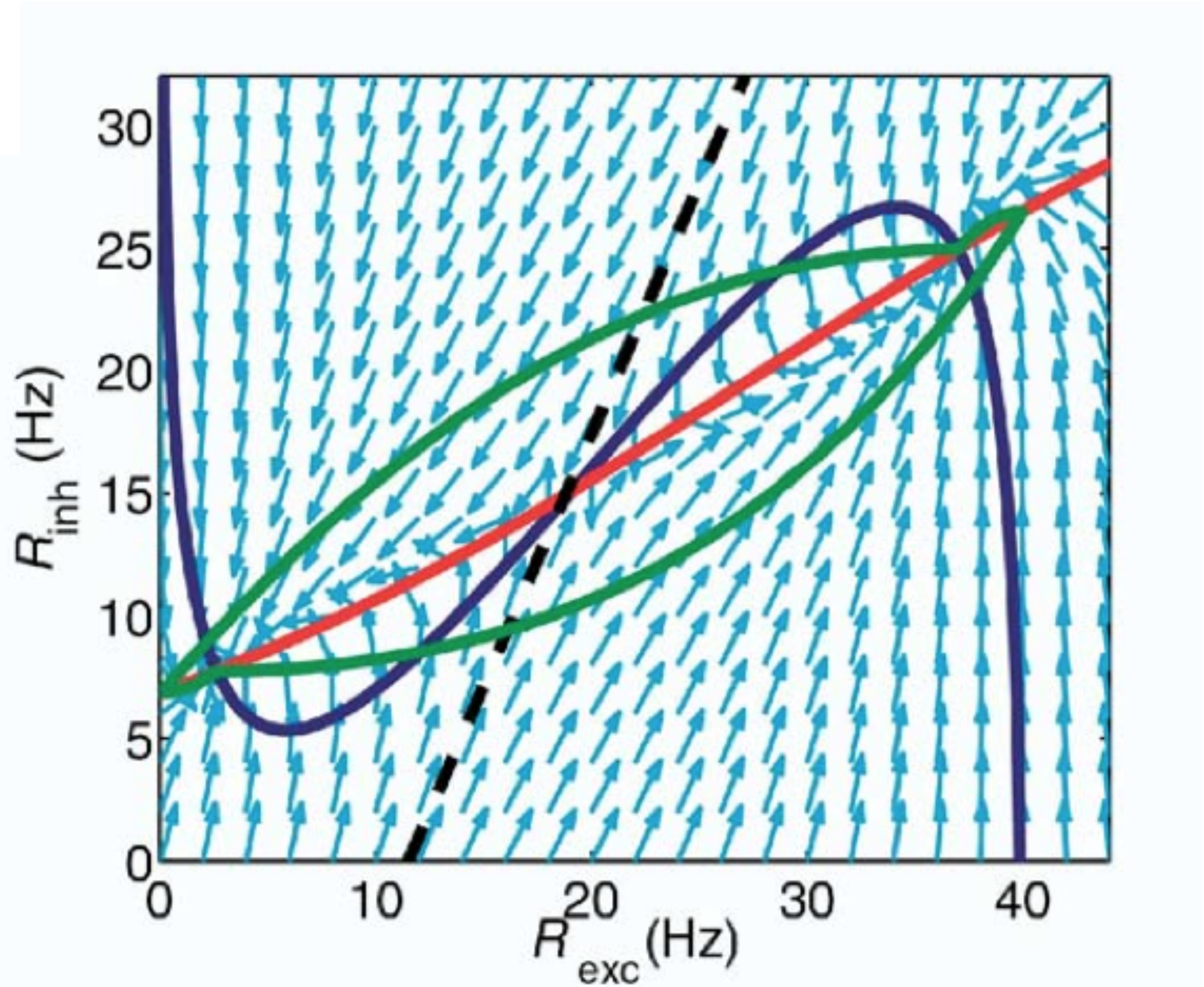
Once population crosses a threshold, recurrent excitation within the assembly overcomes the feedback inhibition. This drives the population into a high activity state.

The high activity state is maintained through a positive feedback loop between firing rate and recurrent excitatory input.





Durstewitz, D. et. al. *Neuroscience* 2006 **139**. 119-133



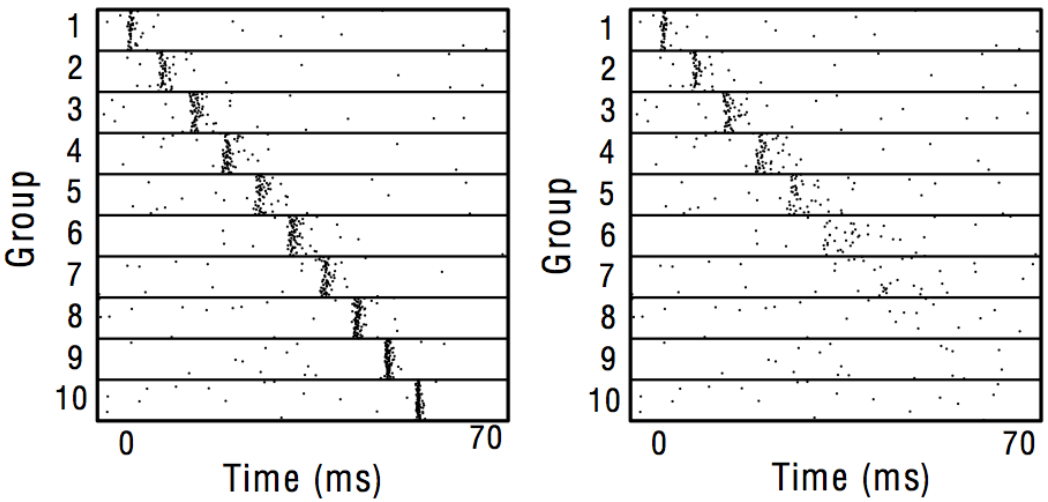
30
25
20
15
10
5
0
0
10
20
30
40
R_{inh} (Hz)
R_{exc} (Hz)

The Project

Our goal is to develop a model that can help explain the cellular mechanisms underlying persistent activity in neural networks.

Approach the problem by finding non-trivial (i.e. biophysically realistic) networks that function with high and low states.

Synfire Chain Model

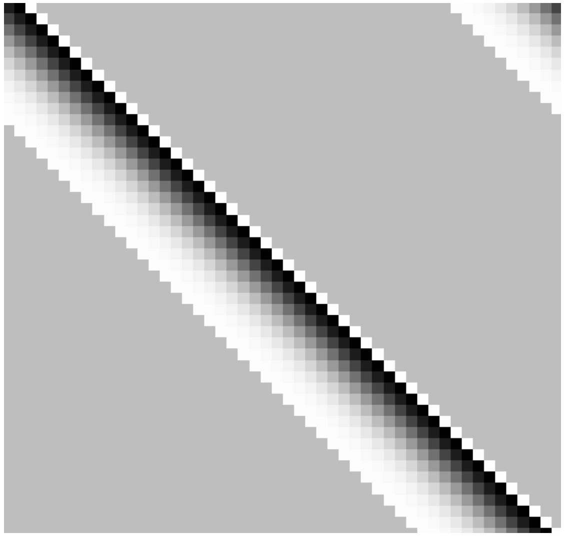


Diesmann, M. et. al. *Nature* 1999 **402**. 529-533

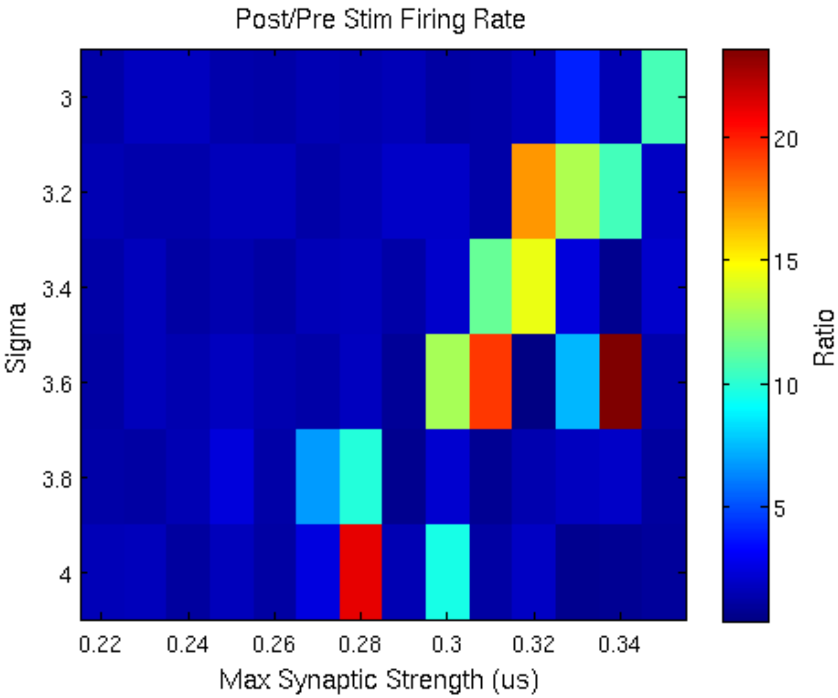
Connecting groups of neurons into circular feed-forward arrangements.

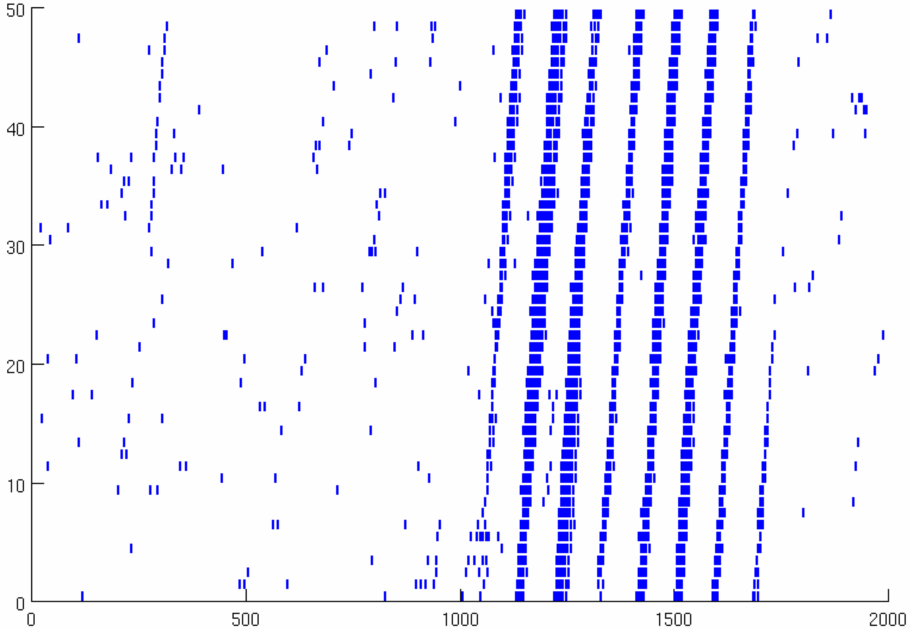
Can be used to hold persistent activity in a network.

Activation of chain caused by simultaneous stimulation of adjacent neurons.



Determining Model Parameters





Recurrent Excitation Networks

Activity maintained in the network through recurrent excitation.

Neurons that encode the same pattern form a cell assembly when excited by a specific stimulus.

The formation of these assemblies can be explained through various mechanisms:

Long term synaptic connection patterns acquired through Hebb-like learning.

- Working memory results from activation of previously stored pattern.

Increased ratio of NMDA:AMPA receptors.

- Experimental evidence: NMDA-receptor antagonists interfere with working memory tasks (Krystal J.H. et. al. *Arch. Gen. Psychiatry* 1994 **51**, 199-214).
- Dopamine (required for working memory function) modulation enhances NMDA-receptor-mediated-function.

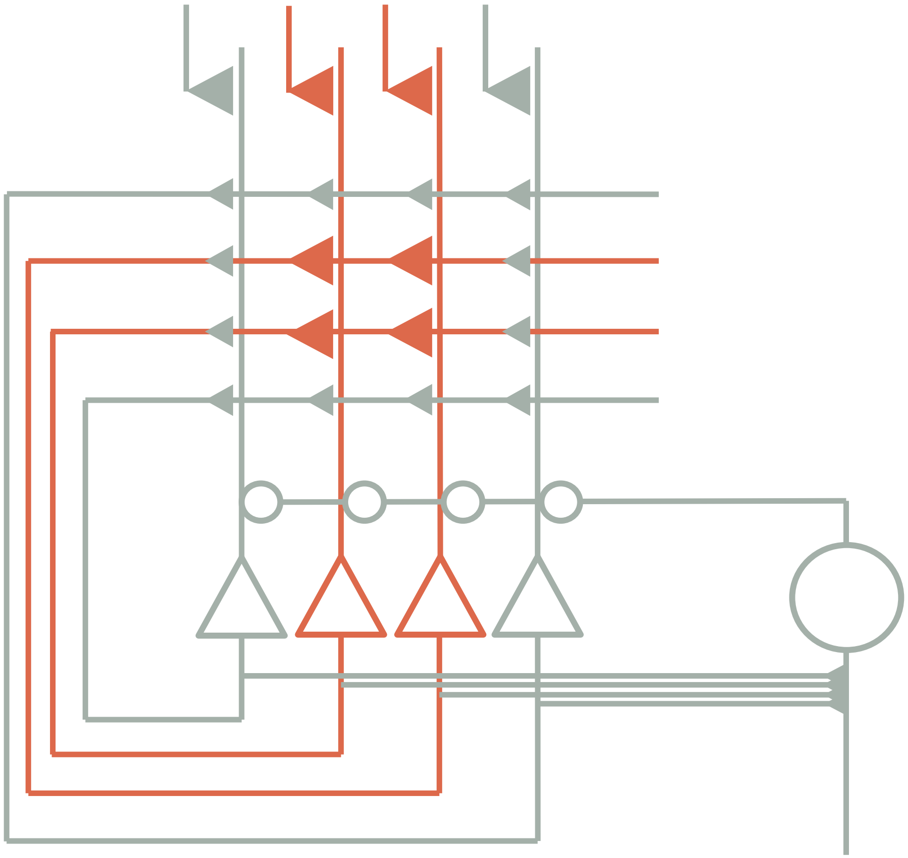
Persistent Activity through STDP

Neurons that collectively encode the same pattern are wired together reciprocally by strong excitatory synaptic weights.

Neurons that participate in different representations are connected by weak synaptic weights.

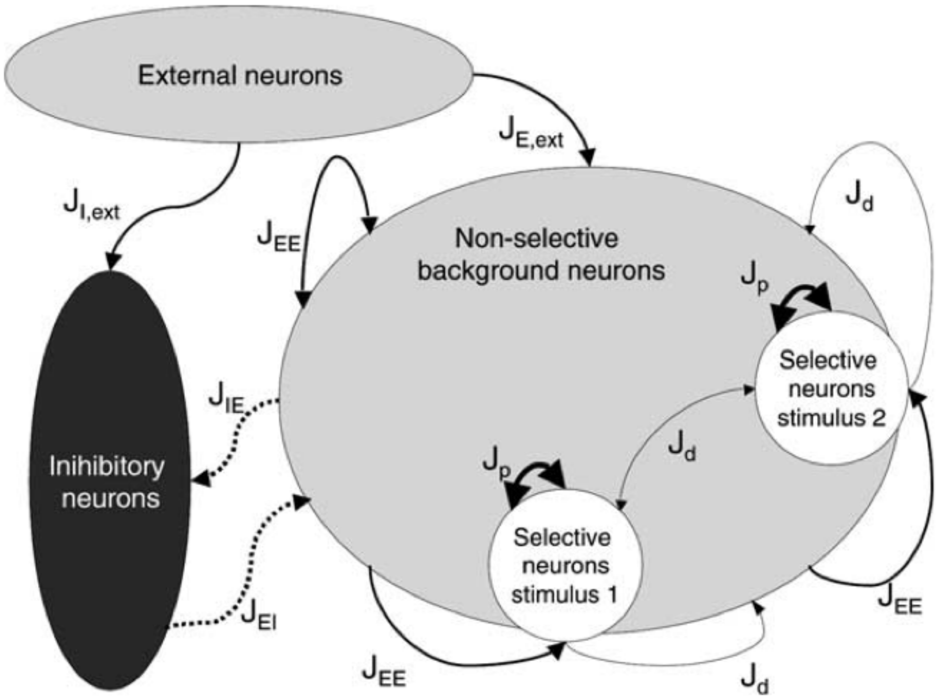
These connection patterns can be acquired through a Hebb-like learning rule that reinforces connections between coactive neurons.

Activation depends on synaptically stored patterns.



Durstewitz, D. et. al. *Nature Neuroscience* 2000 **3**, 1184-1191

Model Architecture



Del Giudice, P. et. al. *J. Physio.* 2003 **97** 659-681

Too complicated!

These networks rely on very fine tuned parameters in order to have bi-stable behavior

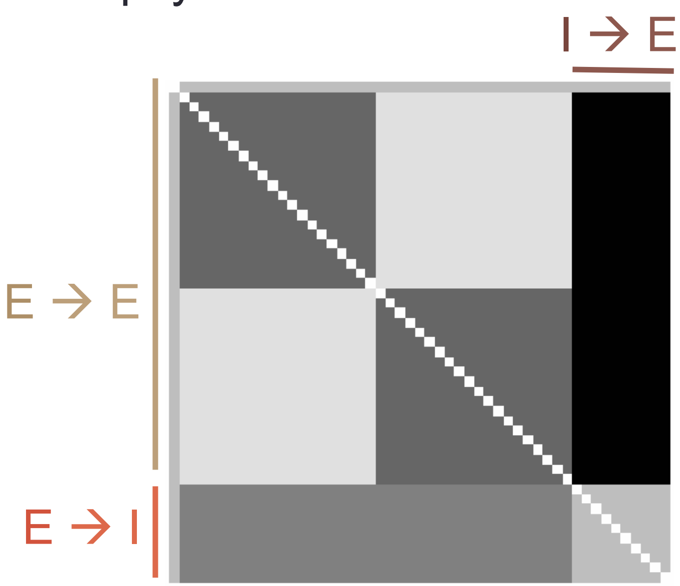
We had (a minimum of) 8!

Recurrent excitatory network employing NMDA-receptors

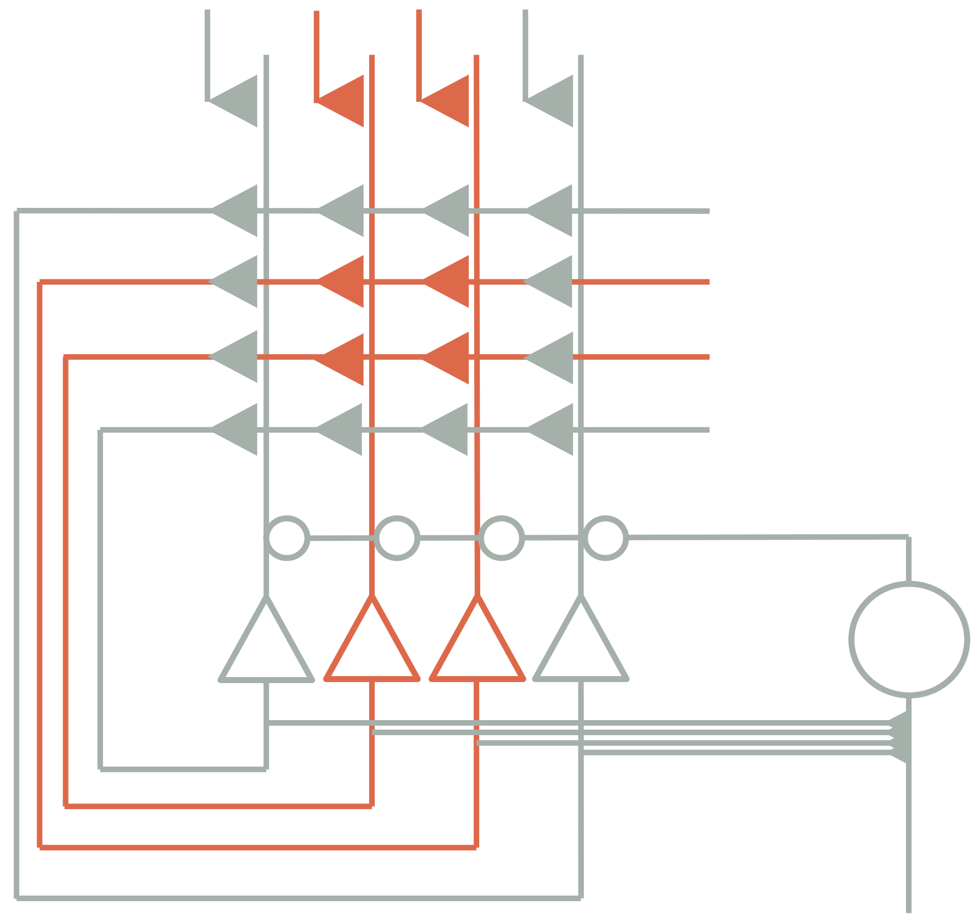
Addresses ability to retain completely novel stimuli, where there is no pre-existing synaptic template.

Architecture:

- Weakly connected overlapping subpopulations.
- NMDA receptors replace expsyn2EXCT.

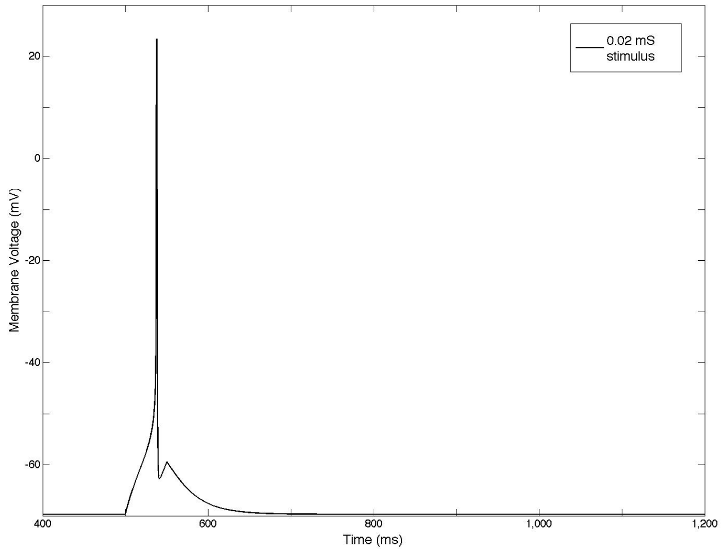


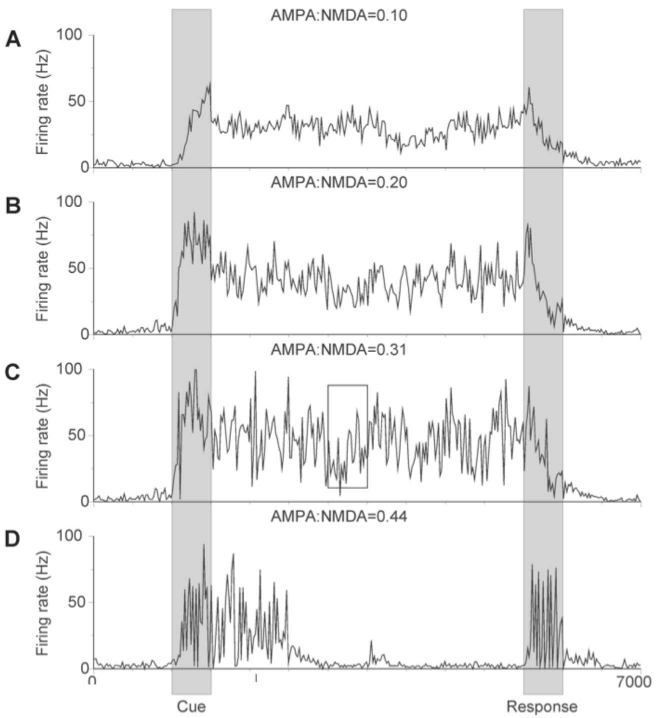
dark = higher synaptic weight

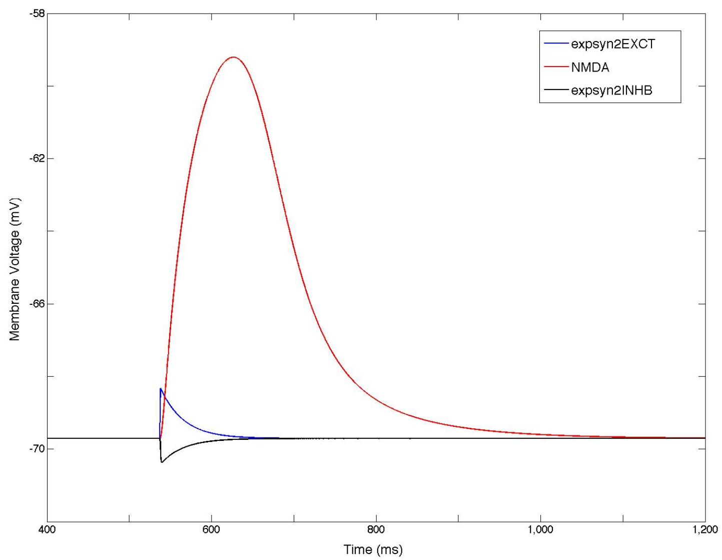


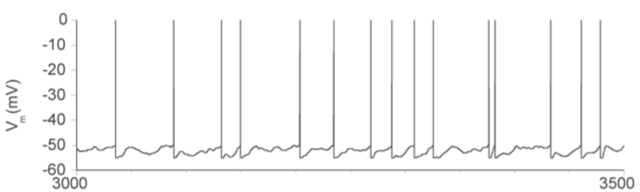
Lisman, J E, et. al. *Nature Neuroscience* 1998 **4(1) 273-275**

Comparing Post-Synaptic Response



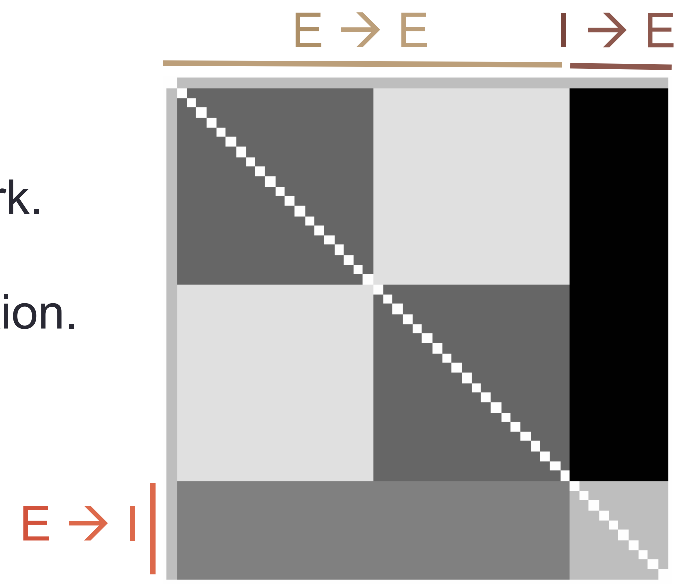






Constantinidis C. et. al. *Neuroscientist* 2004 **10**, 553-565

Model Parameters and Effects



Recurrent Excitatory Weights (E → E):

- determines overall excitability of the network.
- high enough to create persistent firing.
- low enough to prevent spontaneous activation.

Inhibition (I → E, E → I):

- tunes the excitability of the network (i.e. keeps network in check).
- E → I needs to be low enough so inhibitory neurons don't over-excite.
- preferable kept within a linear range.

Noise:

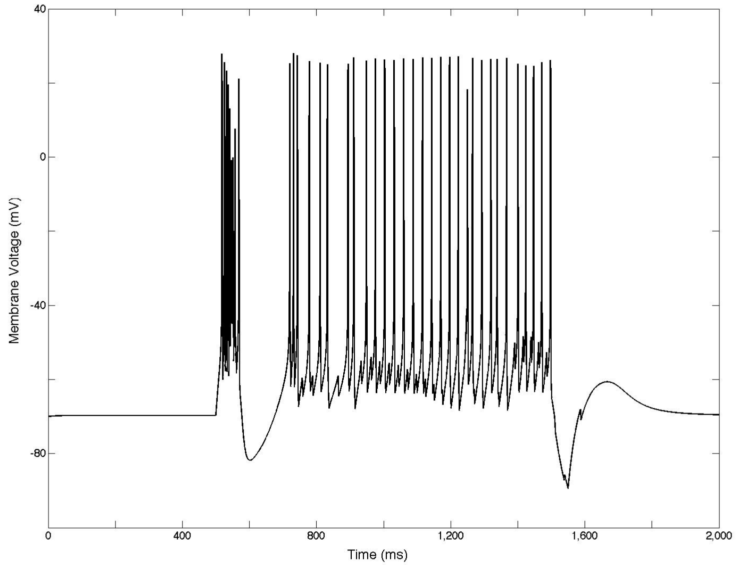
- controls baseline firing rate.
- controls robustness of bistability (more noise → less stable network)

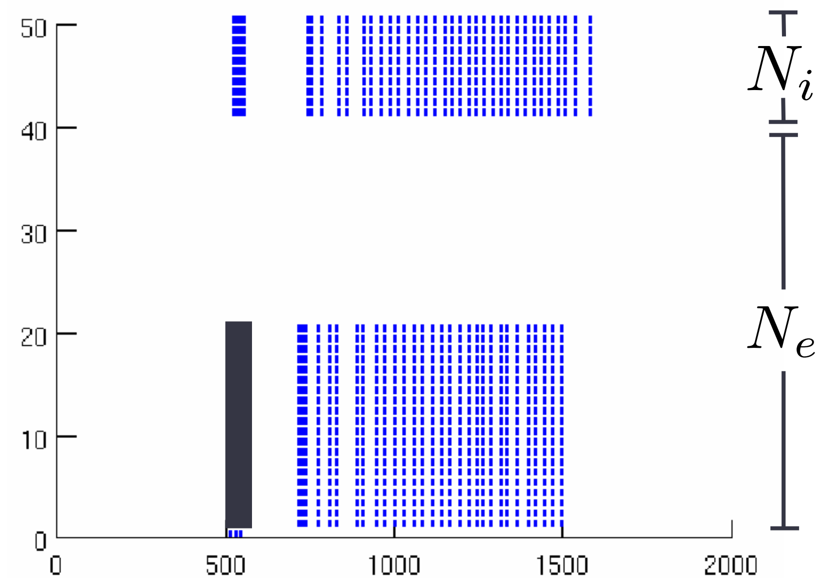
Number of Neurons:

- increasing the size of the network decreases the effect of noise.
- affects overall gain of other parameters.

Persistent Activity in Subpopulations: No Noise

= start of stimulus





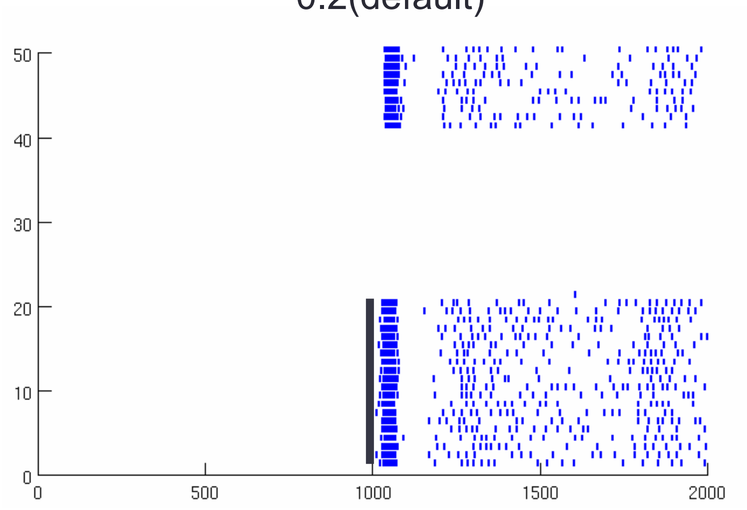
$$Excitatory = N_e = N_{[1:40]}$$

$$Inhibitory = N_i = N_{[40:50]}$$

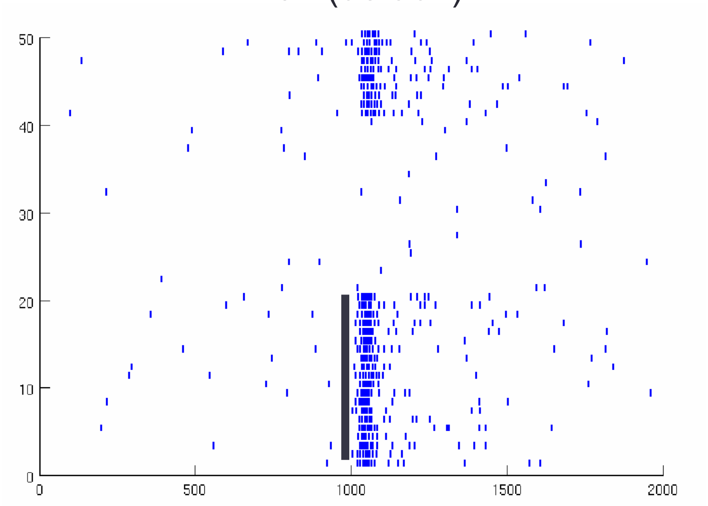
Persistent Activity in Subpopulations: Noise

▎= start of stimulus

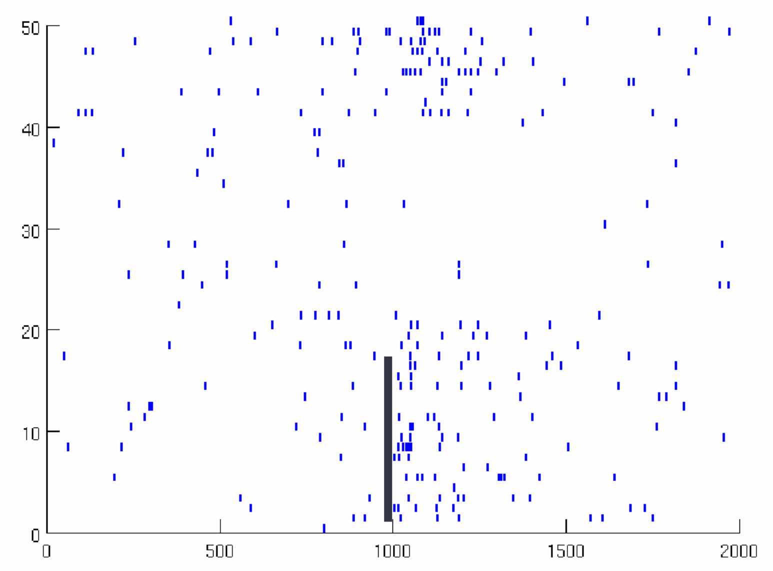
0.2(default)



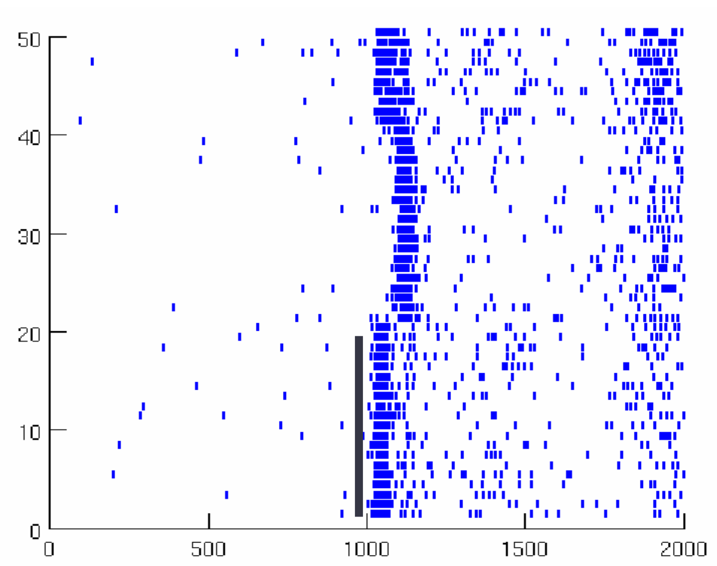
0.4(default)



0.6(default)



0.4(default) – increase synaptic weight



Conclusions

Models of working memory – at a cellular level, require bistability of firing rates.

There are many approaches to modeling this behavior with various degrees of biological relevance.

We were able to make an all excitatory, bi-stable network using a synfire chain architecture.

- This was found by investigating the behavior of the network as a function of the strength and width (sigma) of the connectivity.

We attempted to develop a more experimentally supported model using recurrent excitatory connections and either STDP or NMDA-receptors to form the cell assemblies.

We achieved a working bi-stable model using NMDA-receptors in low noise conditions (somewhat trivial condition).