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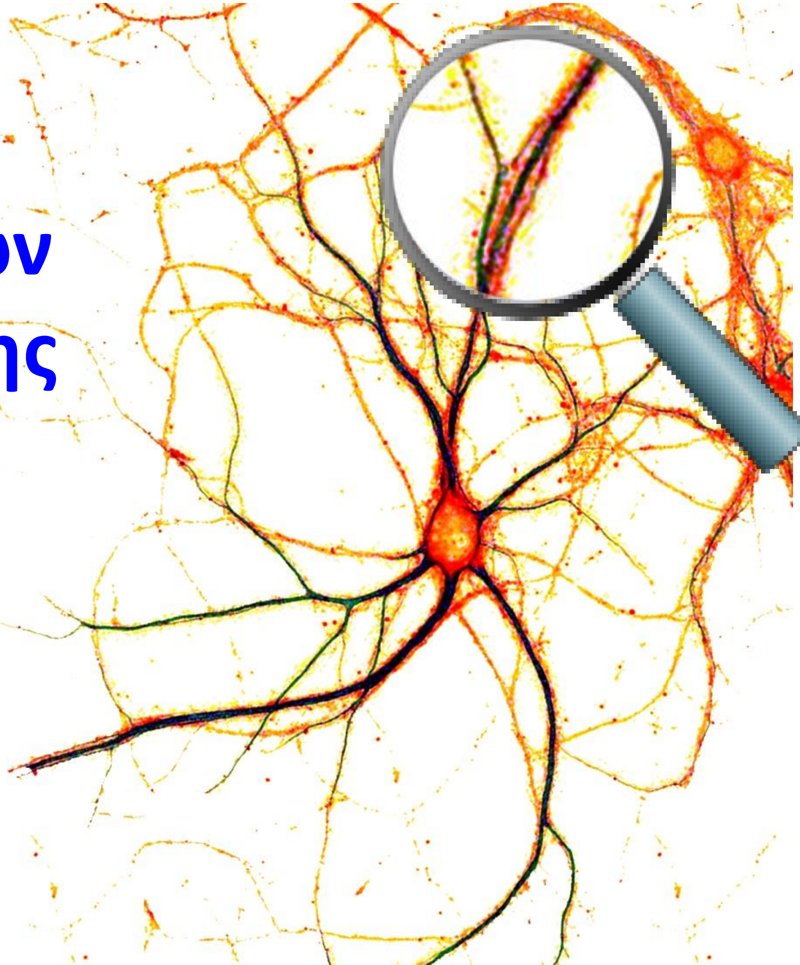
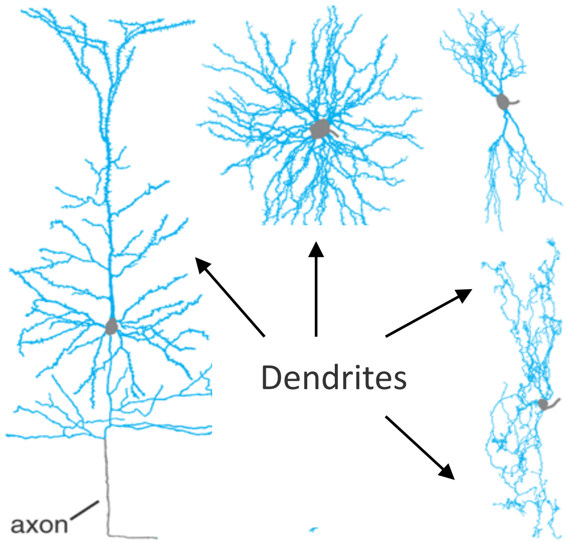
Ίδρυμα Τεχνολογίας και Έρευνας (ΙΤΕ)
www.dendrites.gr

Υπολογιστική διερεύνηση των νευρικών μηχανισμών μνήμης και μάθησης



WHAT?

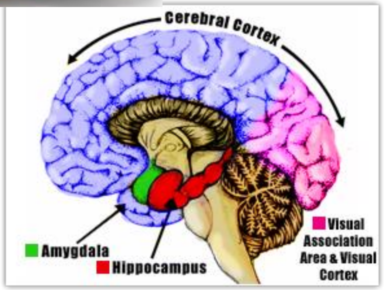


What is the role of dendrites in

- neuronal signal integration
- memory formation across levels (neuron, microcircuit network) & regions (hippocampus, PFC, amygdala, V1)

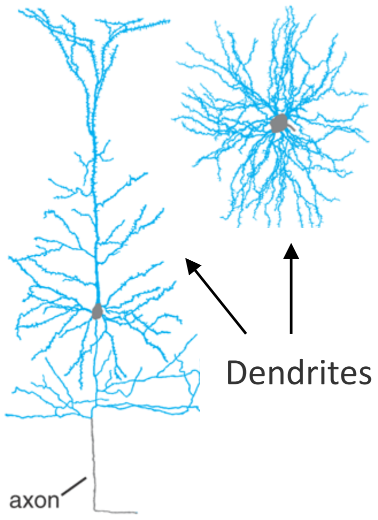
AIM: find a unifying function/model for dendrites across regions and abstraction levels

WHY?



Memory

- ability to learn, store and retrieve information
- remains a mystery, declines with age/diseases, affects many people → poor quality of life
- memory ⇔ brain's information processing units



Dendrites

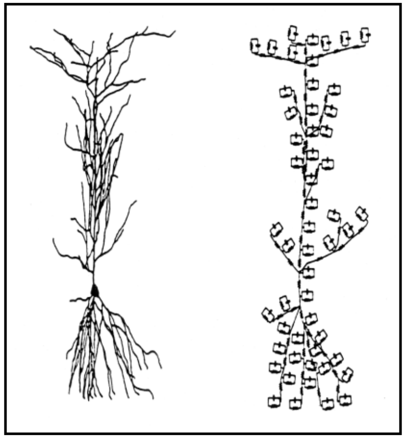
- thin processes that allow neuronal communication
- brain's main processing units: No 1 Candidates although not rigorously tested
- properties altered in memory loss
- no direct link between dendrites and memory

Understanding how dendrites contribute to memory formation is critical for understanding and treating memory deficits

HOW?

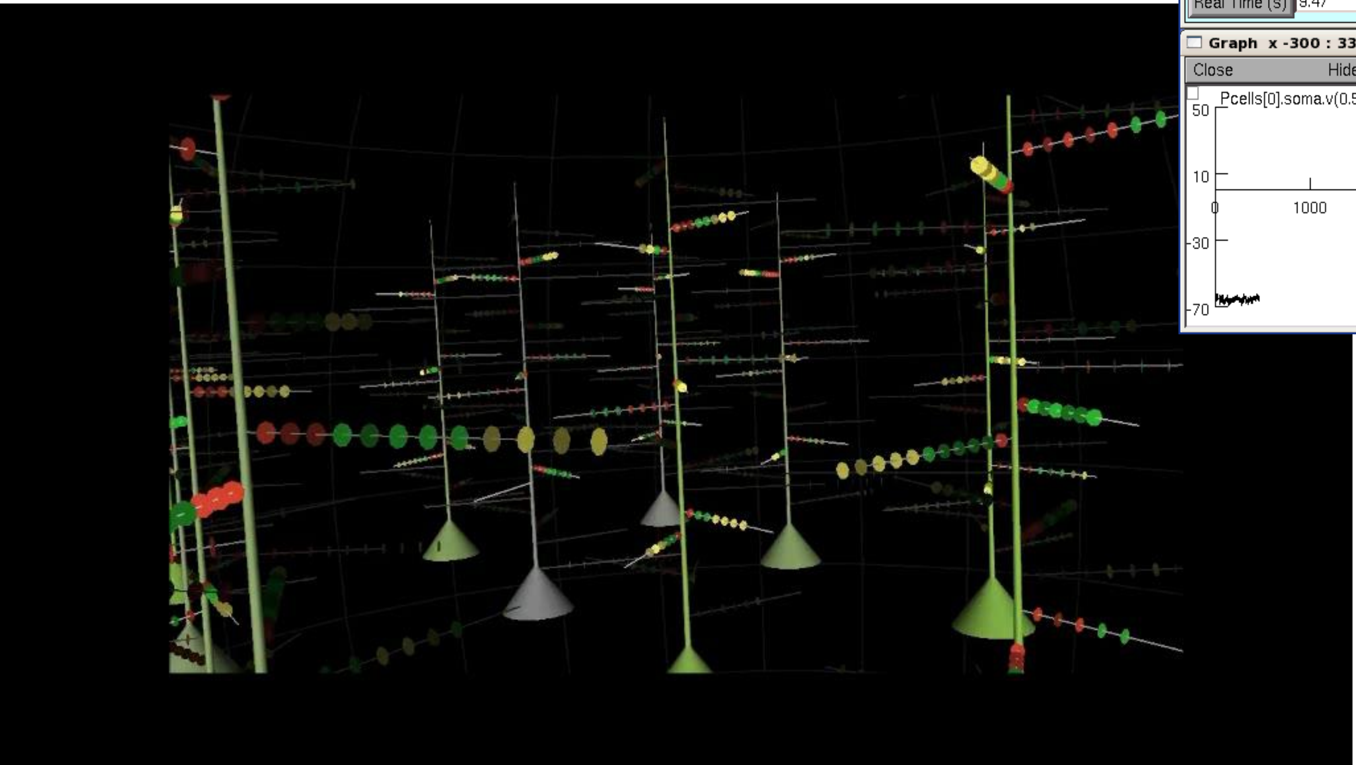
We use computational methods to investigate these questions

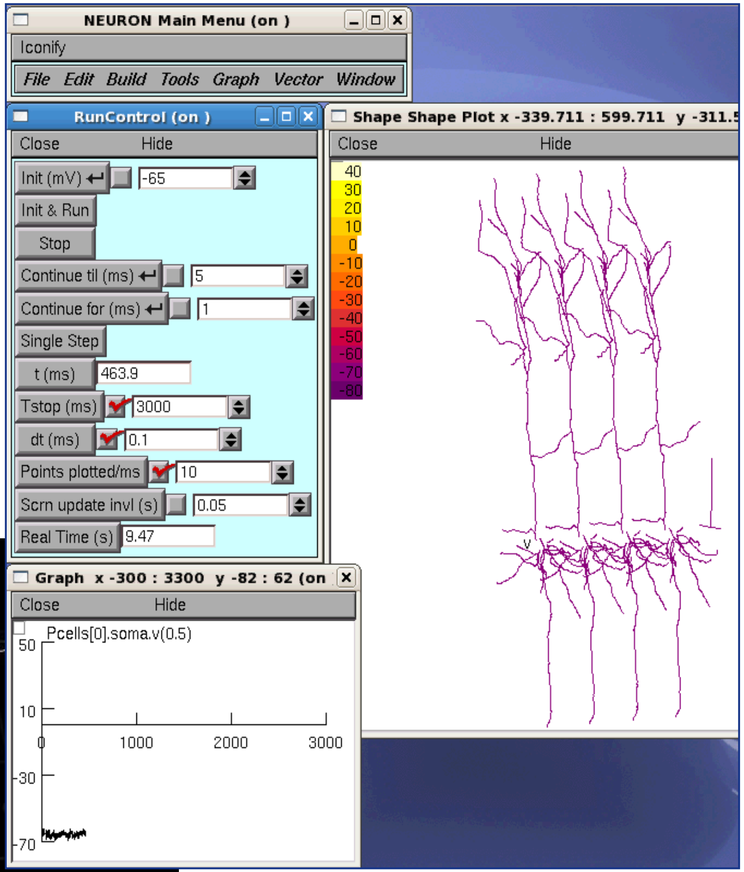
MODELS



Single neuron biophysical models

Simplified neuronal network models





Biophysical microcircuit models

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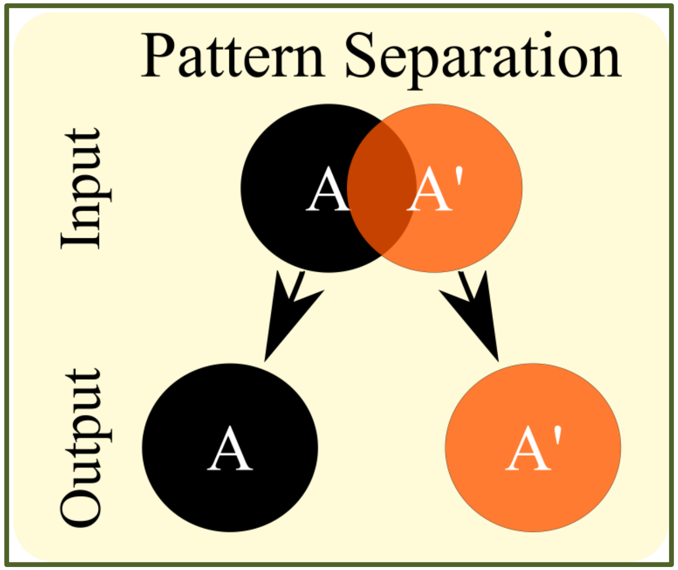
What have we learned from these models?

Two recent examples

Do dendrites help our ability to discriminate objects?

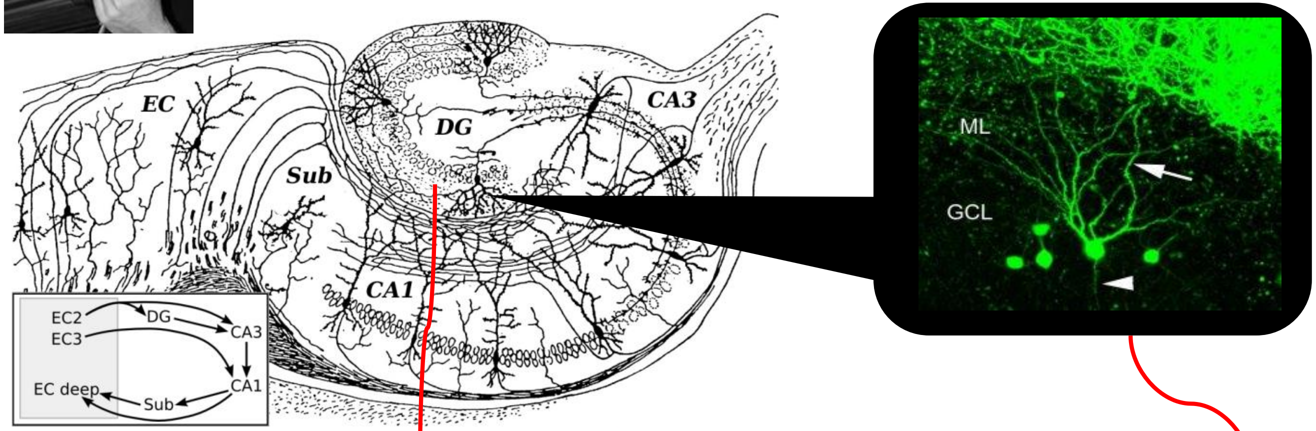
Pattern separation: Ability to discriminate between two similar objects; from Bakker et al., 2008.

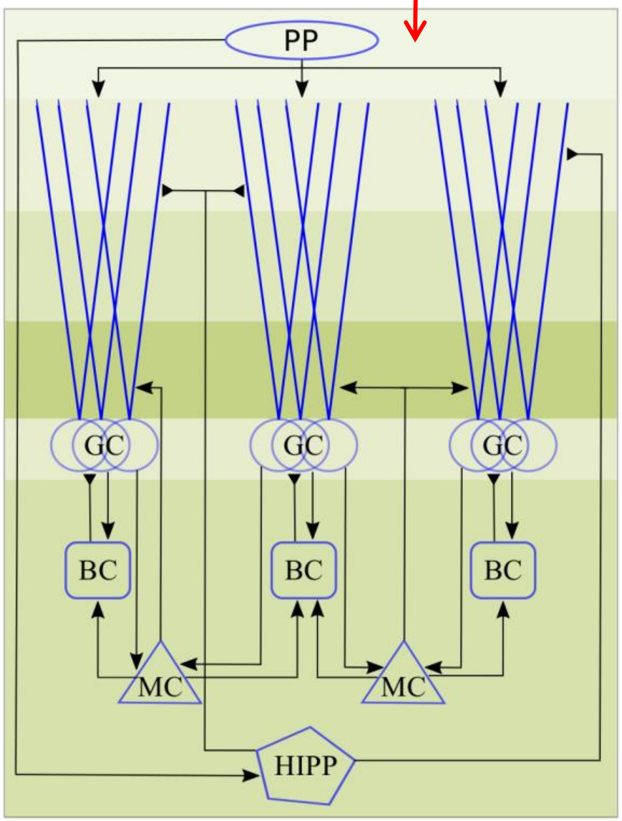


Computational task during which overlapping (similar) inputs are transformed to non-overlapping representations

Spiros Chavlis

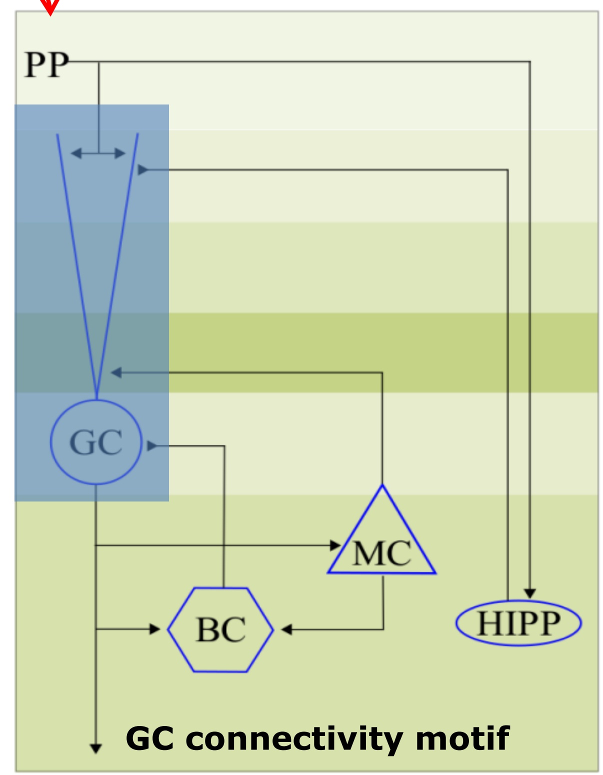
A DG network model considering GC dendrites





DG Network model

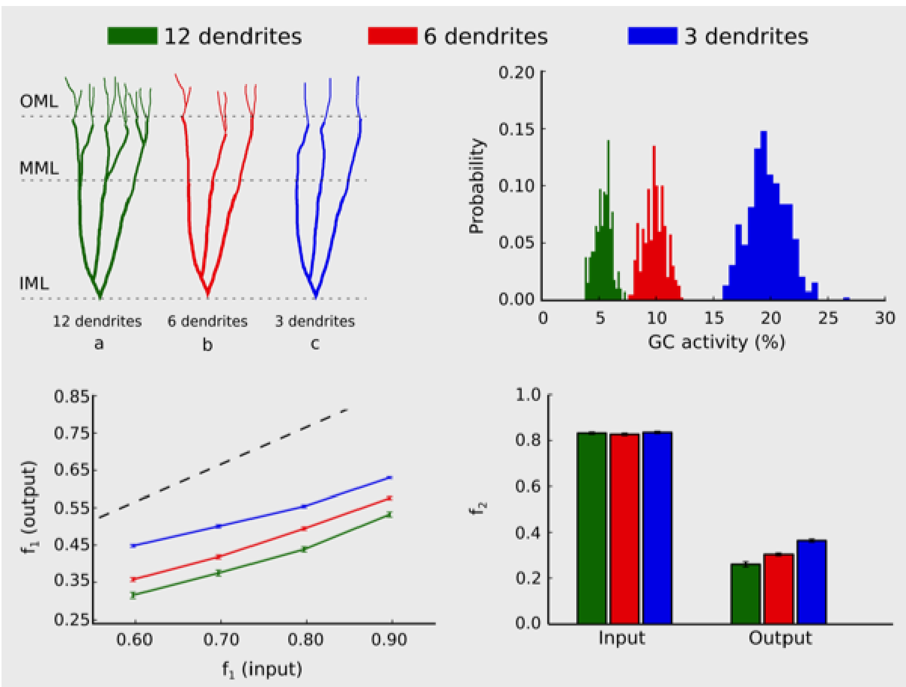
- 2000 GCs
  (in clusters of 20)
- 100 BCs
  (1 per cluster)
- 80 MCs
- 40 HIPP
- 400 ECs



DG dendrites aid pattern separation

Dendritic ablation

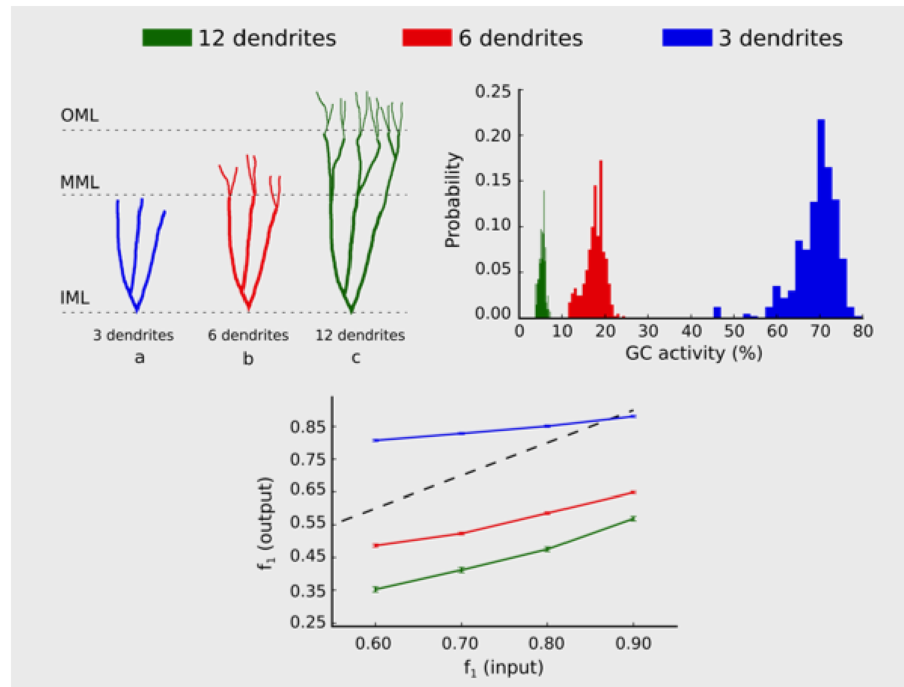
- GC models with 12, 6, 3 dendrites
- Same path length
- Same number of inputs



Pattern separation efficiency decreases with dendritic ablation; fewer dendrites → worse performance.

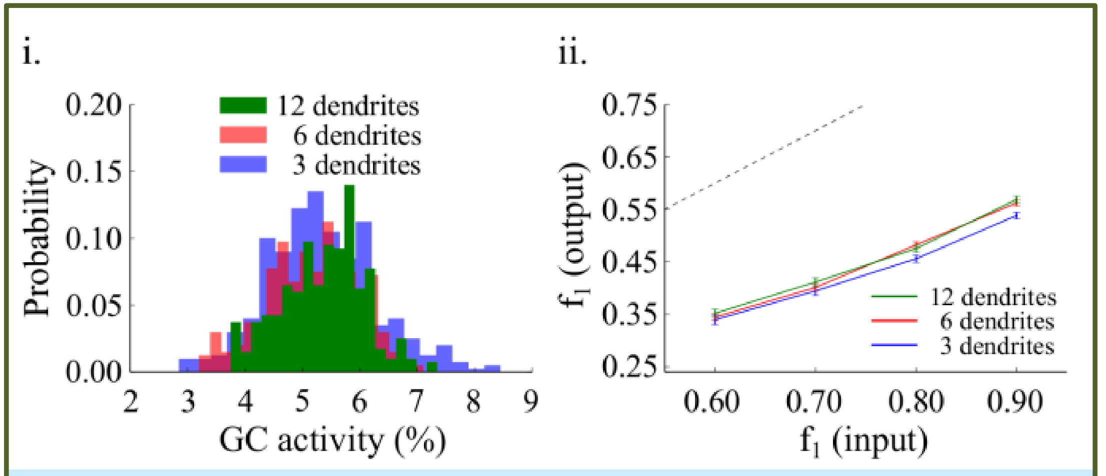
Dendritic growth

- GC models with 3, 6 and 12 dendrites
- Different path length
- Same number of inputs

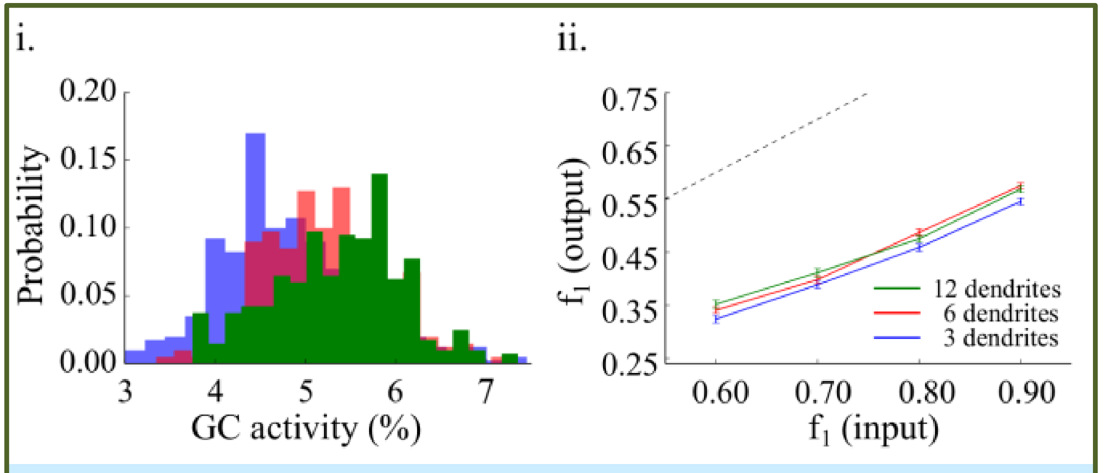


Pattern separation efficiency increases with dendritic growth; More, longer dendrites → better performance.

Matching sparsity also enhances pattern separation!



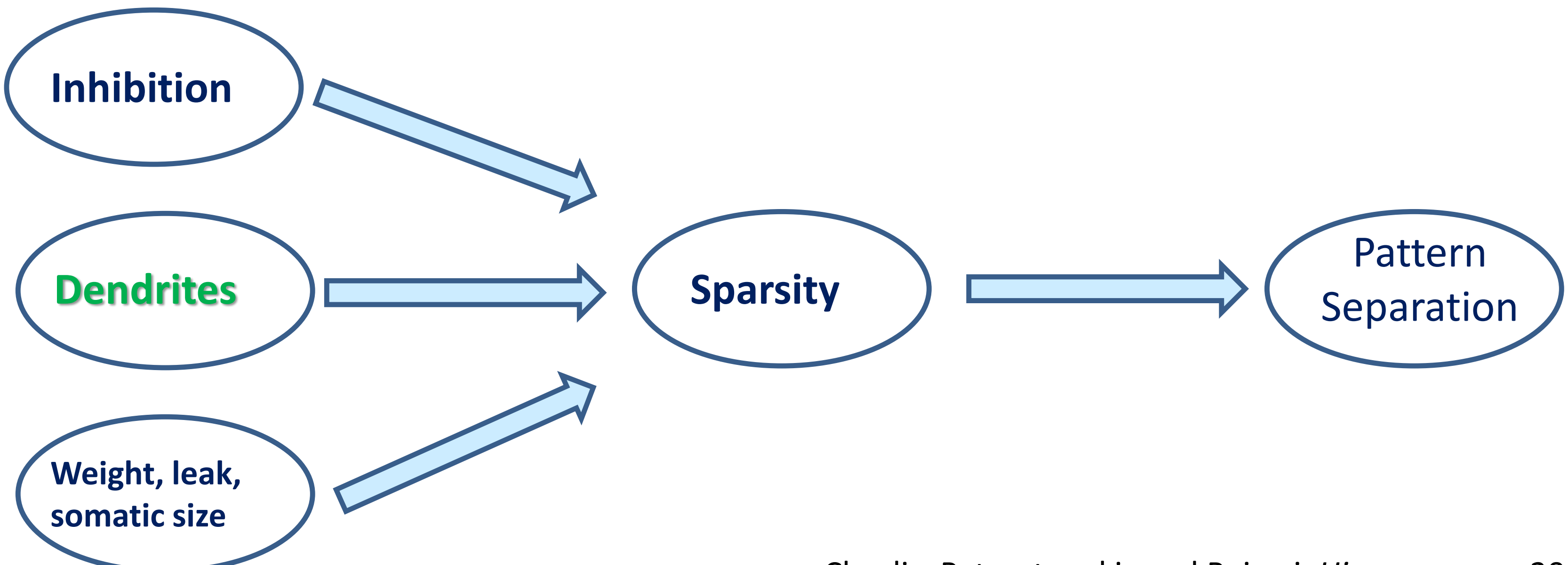
by modifying synaptic weights



by modifying the leak conductance

Key Predictions

- DG model that incorporated dendrites, realistic inhibition and has the ability to distinguish overlapping patterns
- **Dendrites facilitate pattern separation through mediating sparsity**
- Pattern separation can also be facilitated via synaptic weight, “leak” channel density and somatic dimensions modifications that enhance sparsity
- Sparsity seems to be the key determinant in pattern separation

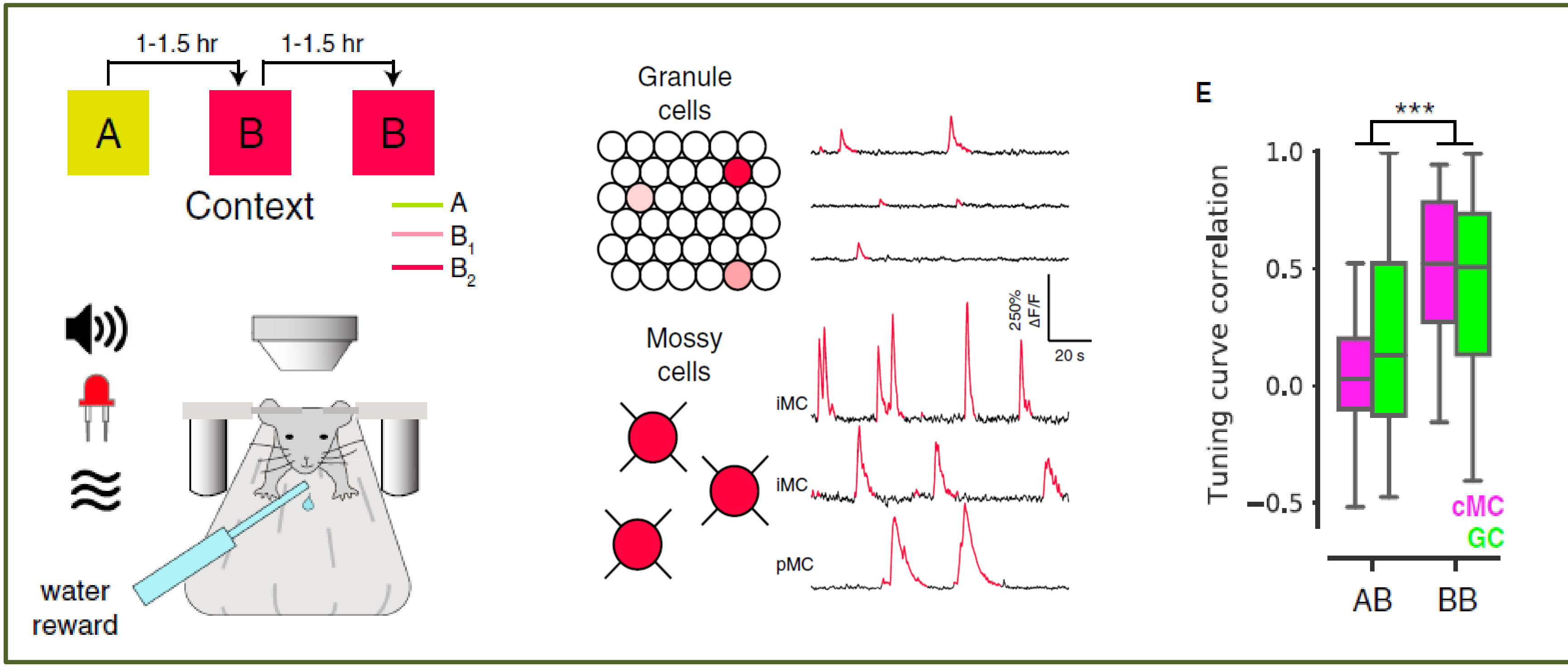


Chavlis, Petrantonakis and Poirazi, *Hippocampus,* 2016

Using our model to explain context discrimination in mice


Attila Losonczy
Columbia

Nathan Danielson

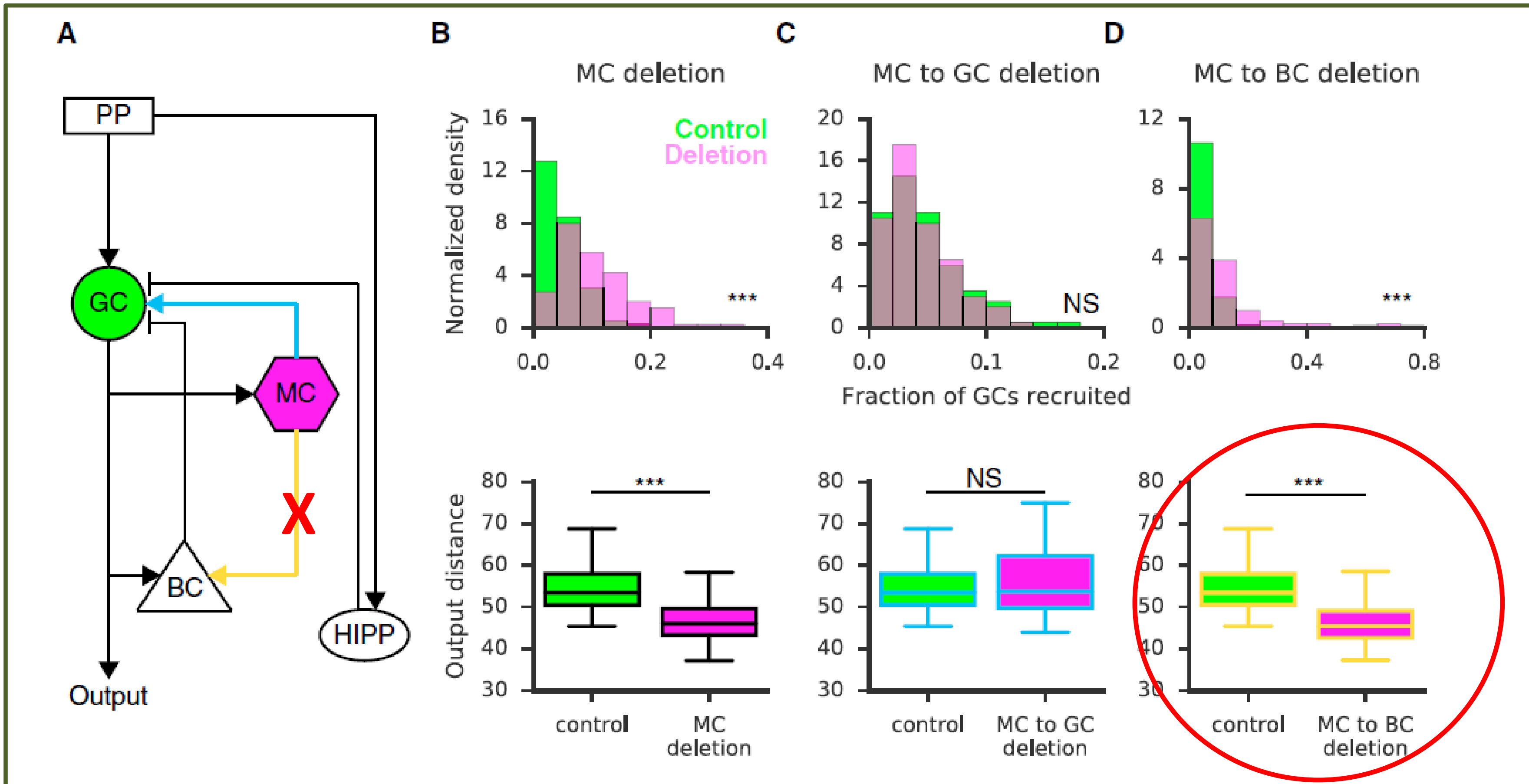


- MCs more excitable than GCs and less spatially tuned
- How do they contribute to context discrimination?

Danielson, et al., *Neuron*, 2017


Spiros Chavlis

Prediction/explanation: MCs contribute to pattern separation via increasing sparsity



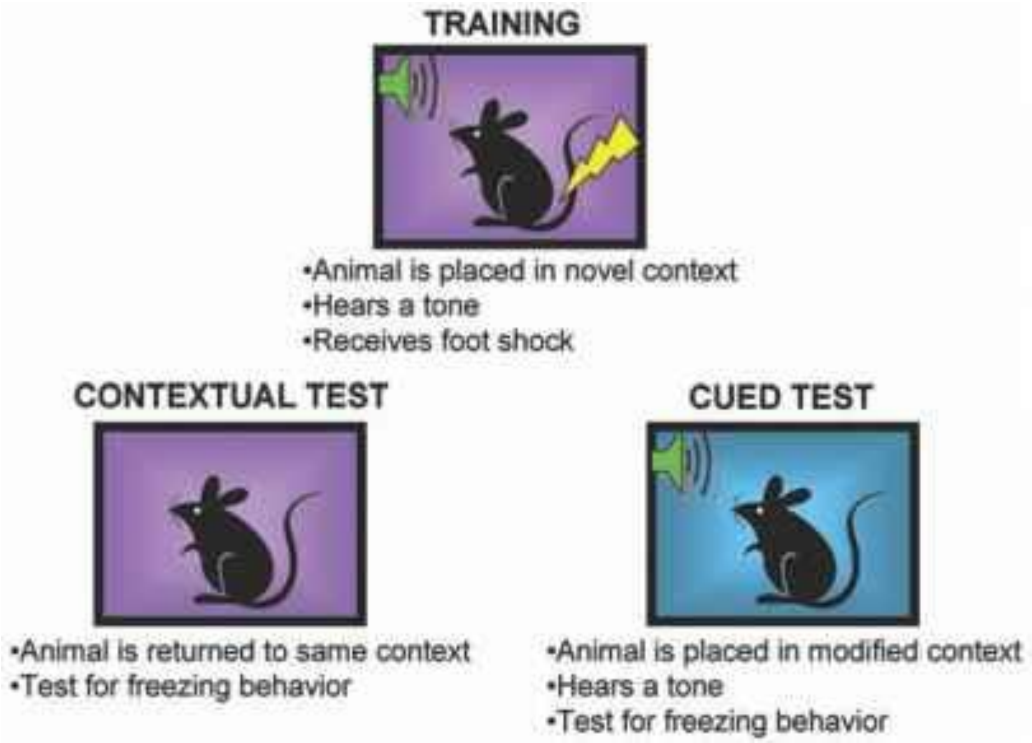
Danielson, et al., *Neuron*, 2017

How do we link information to form associative memories?

Associating memories

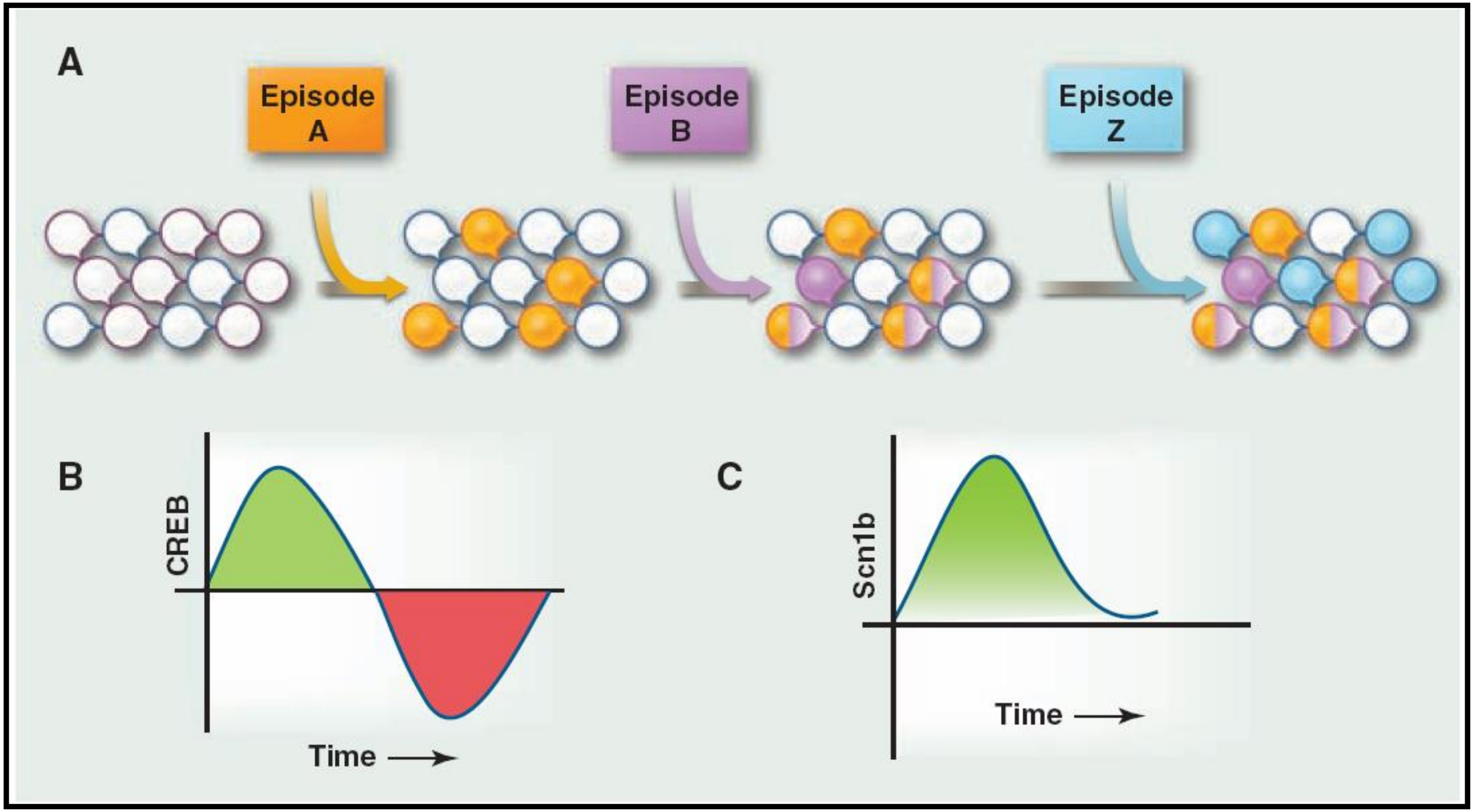
Memory associations for the word "fly"

Fear/context memory associations in mice



Alcino Silva
UCLA

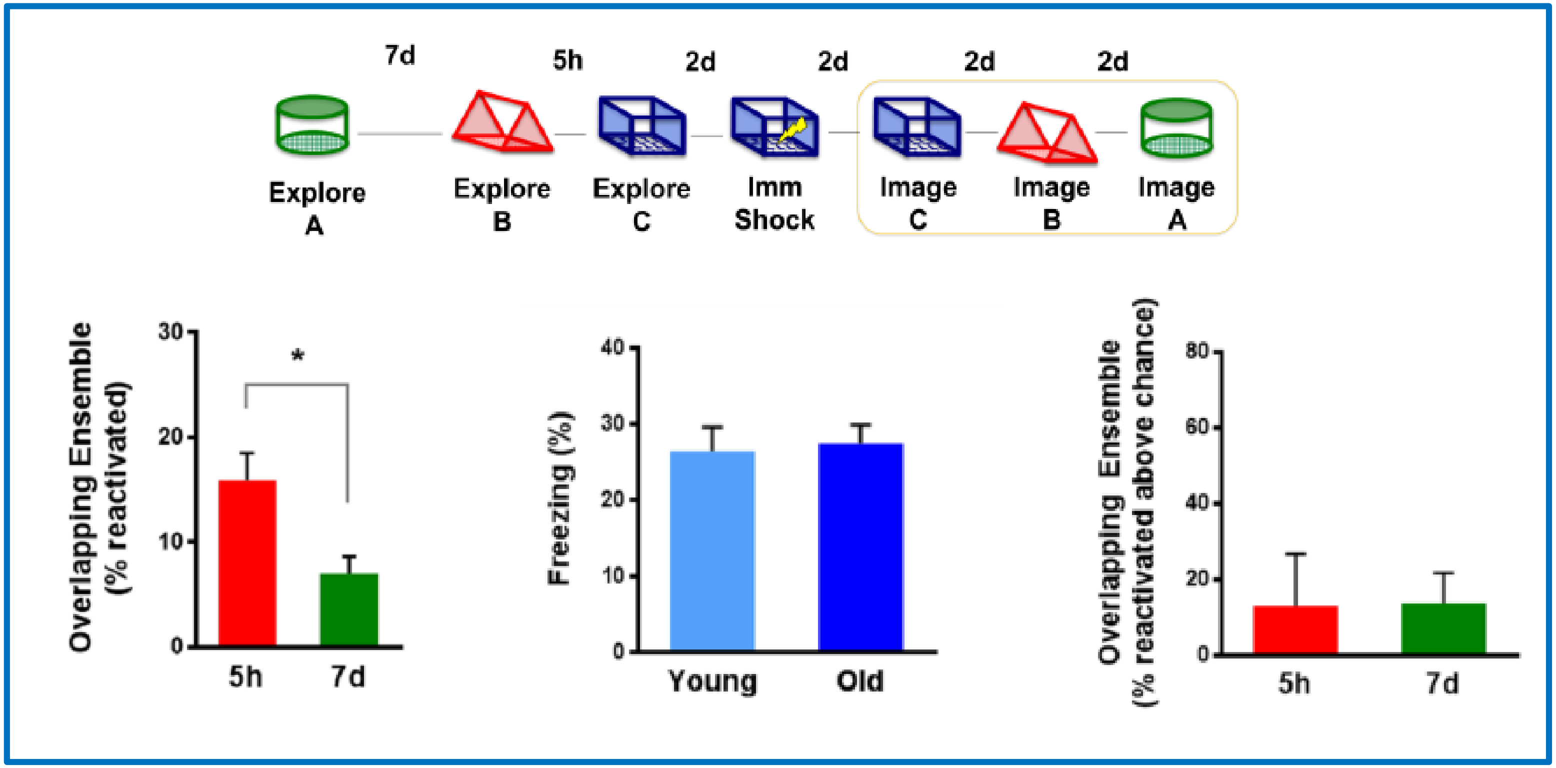
The neuronal overlap hypothesis:
Memories that are temporally close are stored in overlapping circuits



Silva et al, Science 2009

Associating memories via overlapping storage in neurons

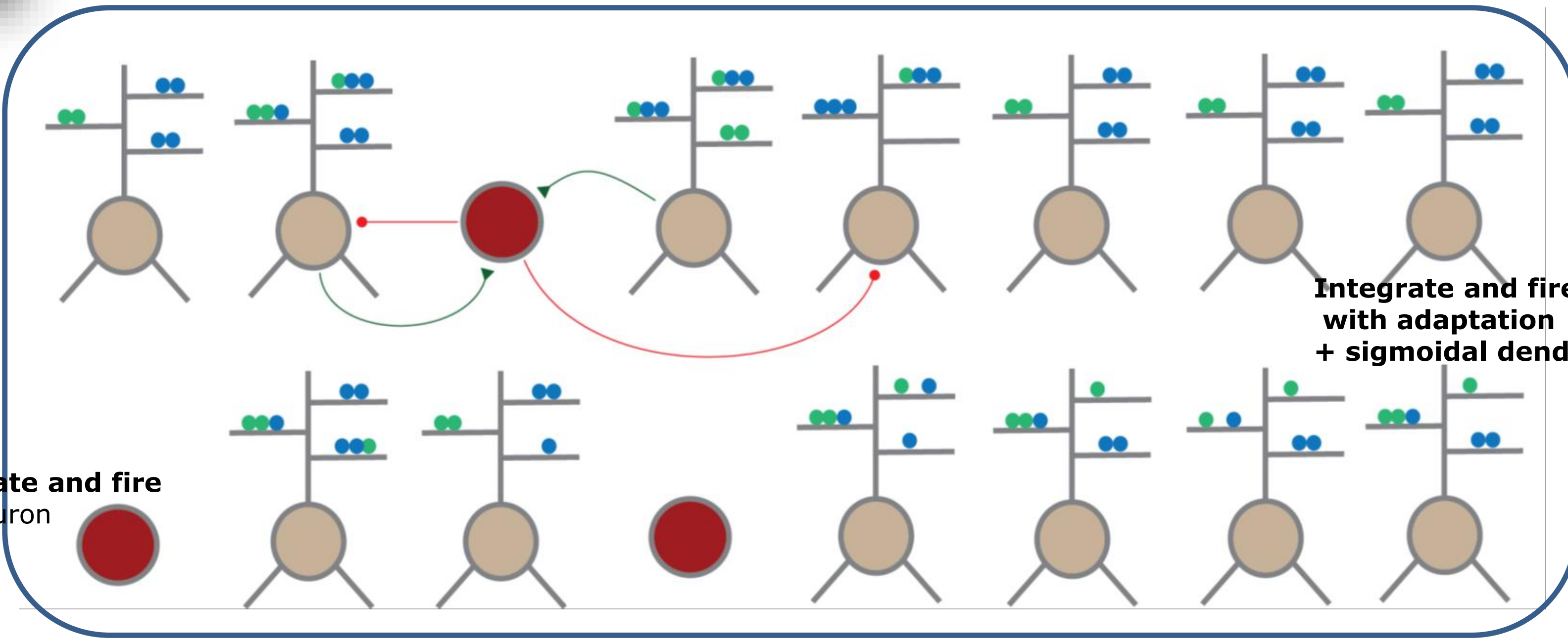
Indeed, the Silva lab showed that two memories are linked if learned within a few hours, due to **overlapping storage in common** neurons. This ability declines with age.



Cai et al, *Nature*, 2016

A large scale network model with active dendrites

George Kastellakis

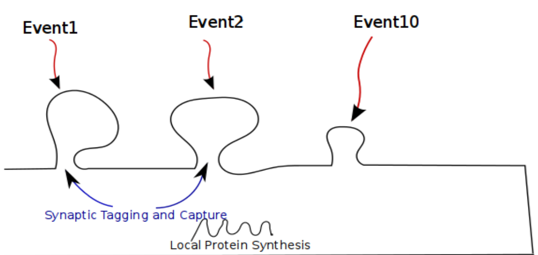


Plasticity rules

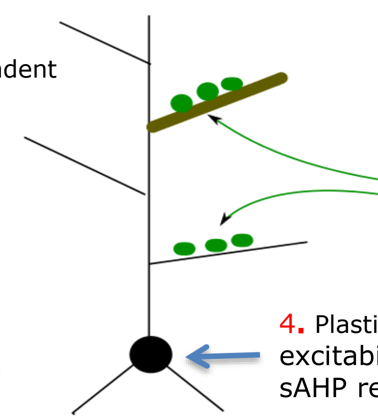
Nonlinear dendrites

1. Synaptic Tagging & Capture (STC)

1.1. Calcium dependent E-LTP/E-LTD

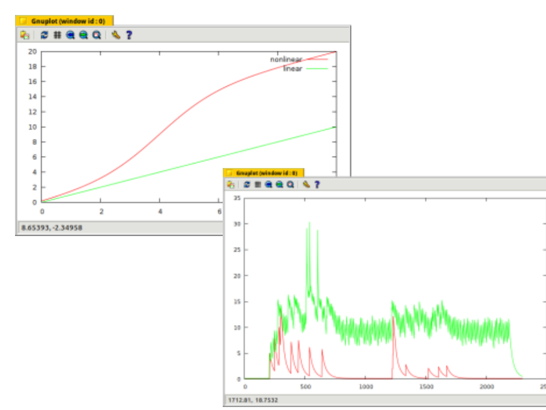


1.2 Local or Global Protein Synthesis (L-LTP/L-LTD)

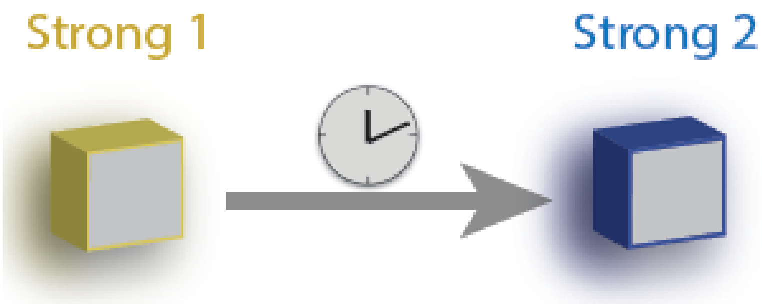


3. Homeostatic Plasticity (additive scaling)

4. Plasticity of neuronal excitability(learning-induced sAHP reduction)

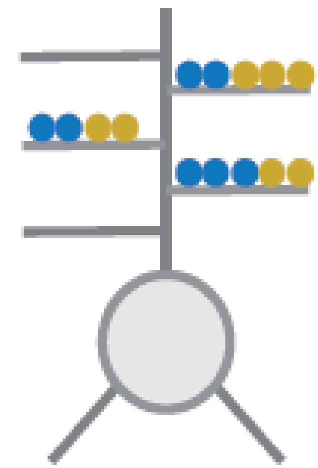


Encoding two memories



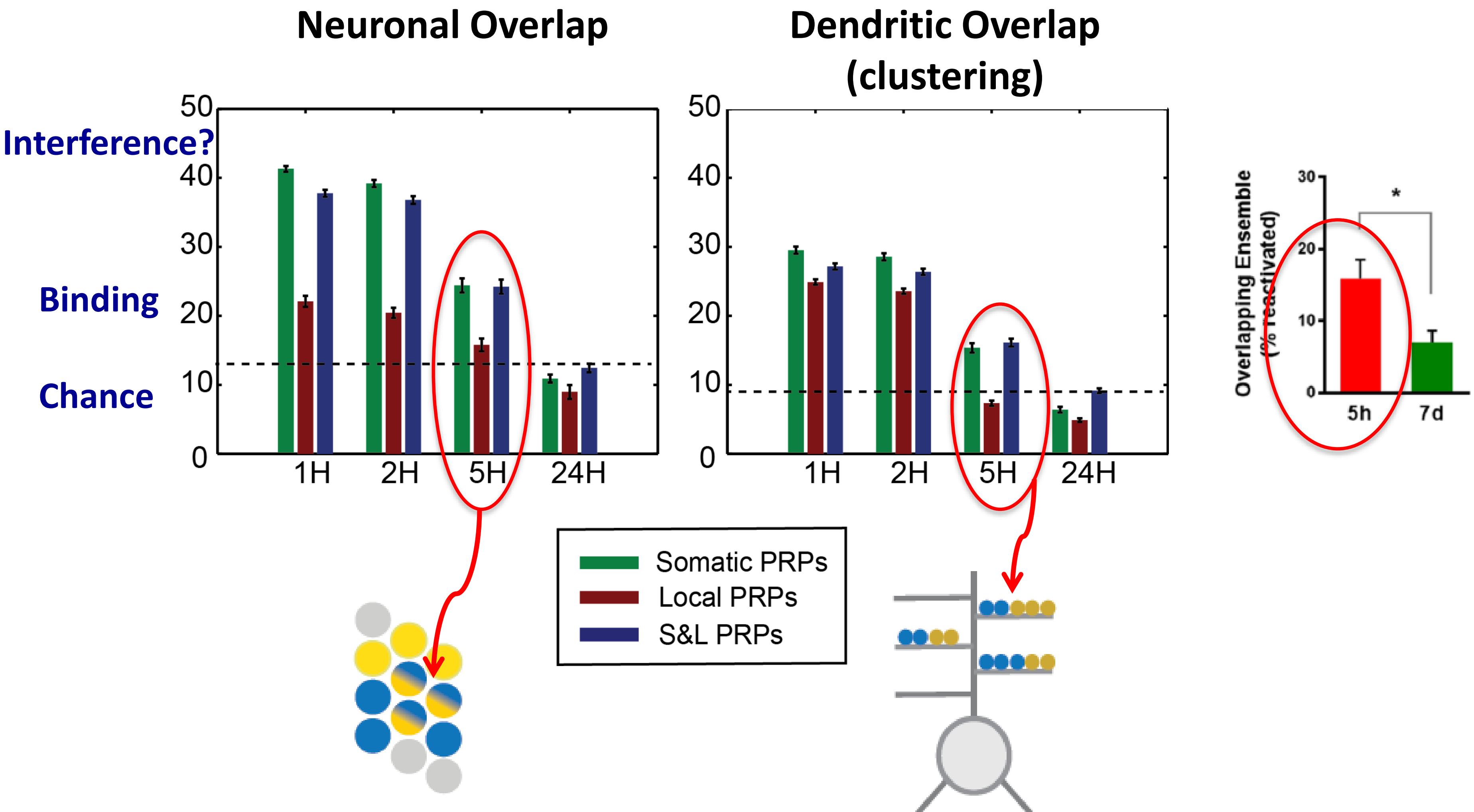
Two memories separated by several hours

Neuronal Overlap neurons coding for both memories



Dendritic Overlap branches with potentiated synapses from both memories

Encoding two memories



Kastellakis et al, *Cell Reports*, 2016

Summary

- Prediction: dendrites of CA1 pyramidal cells integrate inputs as semi-independent sigmoidal units. Verified
- Prediction: CA1 neurons act as 2-stage integrators. Evidence in favor
- Prediction: axons with correlated activity should wire together in the same dendrites (clustering). Verified to a large extent
- Prediction: dendritic synapse location may serve as a mechanism for stimulus specificity via the induction of dendritic spikes. Verified to a large extent in other neurons
- Prediction: dendrites enhance pattern separation via increasing sparsity. Pending
- Prediction: memories are linked through neuronal and dendritic overlaps, via synapse clustering. Some parts verified, others pending

George Kastellakis

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Stefanos Stamatiadis

Alexandra Tzilivaki
Theodore Tamiolakis
Kostas Petousakis
Michalis Pagkalos
Akis Linardos

Thank you for your attention!

SEVENTH FRAMEWORK PROGRAMME
MARIE CURIE ACTIONS
NSF
EMBO Young Investigator Programme
NeuroCure Exzellenzcluster
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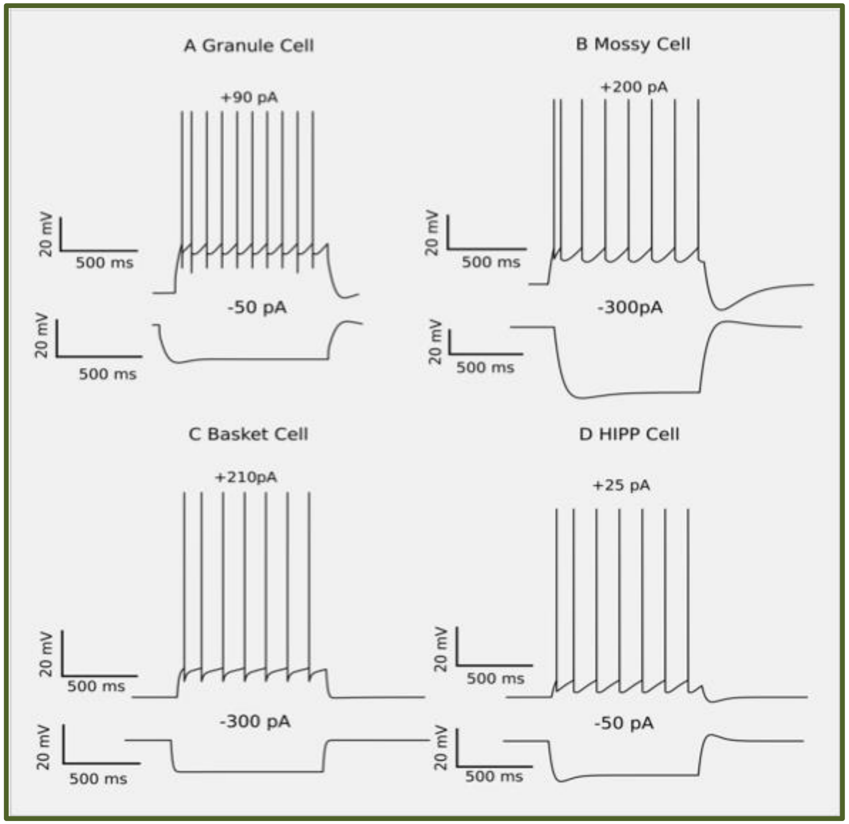
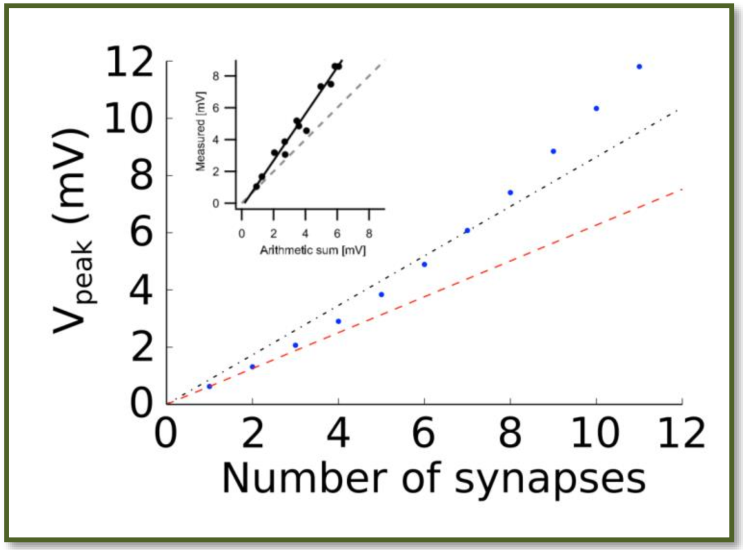
Simplified yet well validated



Realistic firing patterns for all modeled cell types.



I/O function of GCs with active dendrites. Synaptic stimulation in a single branch, Voltage @ soma

Inset adopted from Krueppel et al., 2011

Associative memory encoding in the network model

Presentation: Each stimulus is represented by a set of afferent axons which initially target 70% of the neurons of the (naïve) network at randomly selected dendrites.

Learning: Each stimulus (1s, 30 Hz Poisson train) is presented repeatedly to the network (for 4s) and plasticity (synaptic LTP/LTD, branch strength potentiation) takes place. Homeostatic mechanisms & plasticity of intrinsic excitability operate after learning.

Recall: By presenting S1 or S2 we recall the memory (S1+S2), we identify the neuronal population that is "recruited" by the memory and we characterize its properties.