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NEUROCURE
Exzellenzcluster

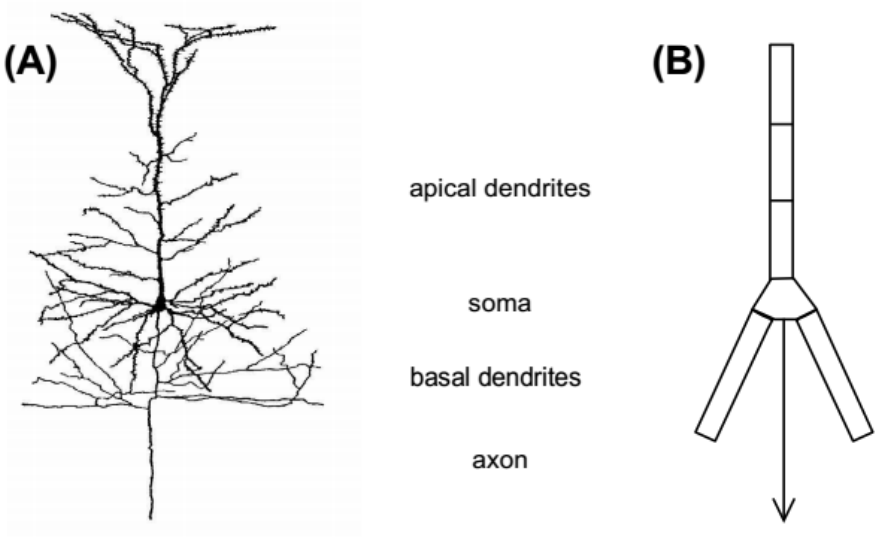
FENS KAVLI
NETWORK OF EXCELLENCE

Modelling dendrites

Overview

- Compartmental Models
- Cable theory
- Reduced models

Overview - compartmental models



- Conductance-based models of neurons are composed of multiple spatial compartments
- Can reproduce the electrical behavior of the cell to a high level of accuracy
- Allow experimentation that may not be physically possible
- Allow investigation of any biophysically relevant parameter spaces
- Useful for testing theories and hypotheses
- Inform and guide experimental investigation

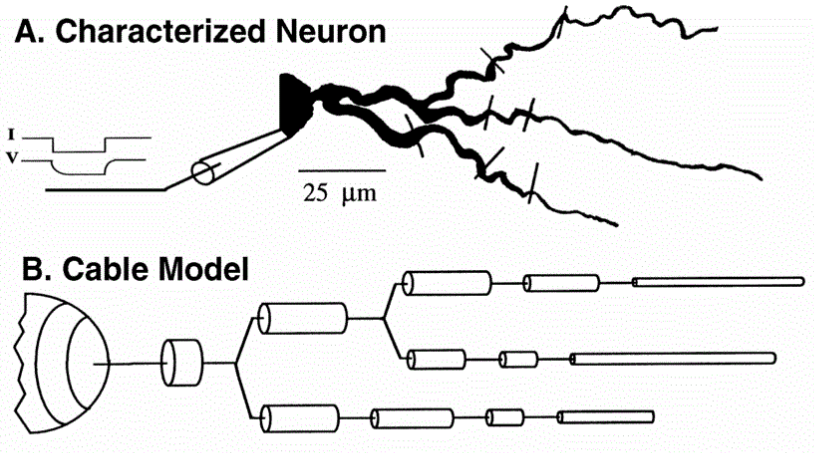
Dendritic facts

- Branching: Dendrites bifurcate repeatedly creating elaborate trees. Purkinje: ~400 terminal dendritic tips, motoneurons: ~10 tips. A type of neurons often has a unique branching pattern
- Diameters: Near the soma diameters can be a few µm. Diameter falls as they branch
- Dendrites are studded with dendritic spines (~0.1µm diameter, ~1µm length). In cortex, they receive the majority of excitatory input
- Dendritic tree length can vary greatly from 100-200 um to 1-2mm (motoneurons). Total dendritic tree length can exceed 1cm
- Majority of brain volume is occupied by dendrites

- Surface area of dendritic tree: 2000 – 750000 um^2
- Volume of a dendritic tree: up to 30000 um^3
- Synapses are not randomly distributed.
  - Inhibitory synapses are more proximal
  - Excitatory input sources may map to specific layers of a neuron
  - Excitatory inputs may be present in conjuction with inhibitory inputs away from the soma

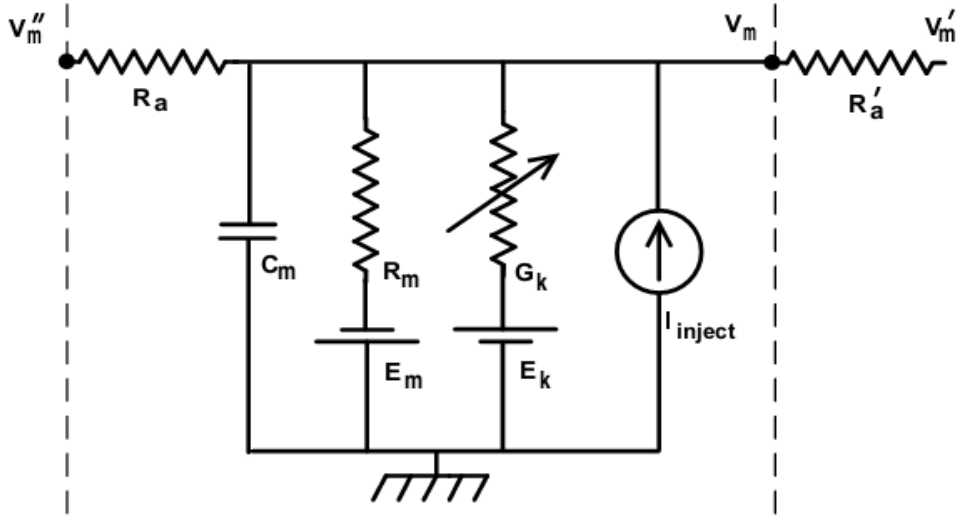
Equivalent Cylinder models

- The morphology of a neuron is broken down to a set of cylinders
- Cylinders are connected to each other through axial resistances
- Cylinders can have different lengths and diameters, and different, but uniform, membrane properties
- Every cylinder can be treated as an isopotential element



Bower , The Book of GENESIS, 2003

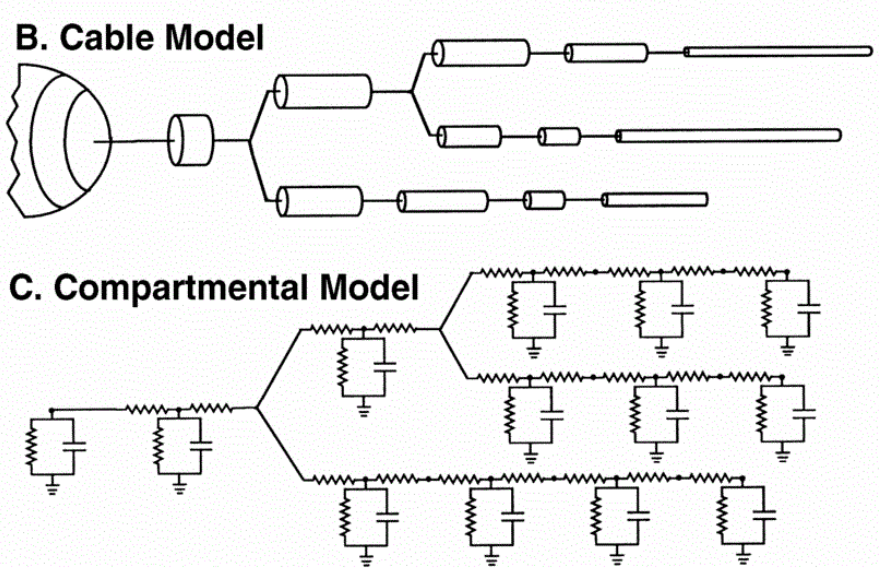
Equivalent Circuits



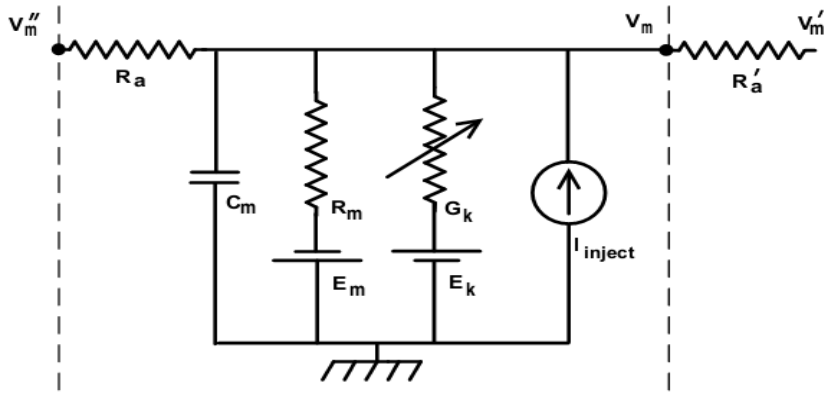
- In each cylinder voltage across the cell membrane v_m depends on:
  - passive properties of the membrane (membrane capacitance c_m and membrane resistance R_m)
  - voltage-dependent currents (e.g. G_k)
  - and external current input

Multi-compartmental models

- Compartments are connected with each other in series through the axial resistances (R_a)
- Axial resistance models the movement of electrical charge when there is a voltage differential across successive compartments.
- The equivalent circuit consists of a capacitor that simulates the non-conducting bilipid cell membrane and a resistor as an analog of the conducting ionic channels on the membrane.



Cable theory



$$\frac{l^2}{R_a}\frac{\partial^2 V_j}{\partial x^2} = C_m\frac{\partial V_j}{\partial t} + \frac{V_j}{R_m} + I_j.$$

$$\frac{V_m}{dt} = \frac{(E_m - V_m)}{R_m} + \sum_k[(E_k - V_m)G_k] + \frac{(V_m' - V_m)}{R_a'} + \frac{(V_m'' - V_m)}{R_a} + I_{inject}$$

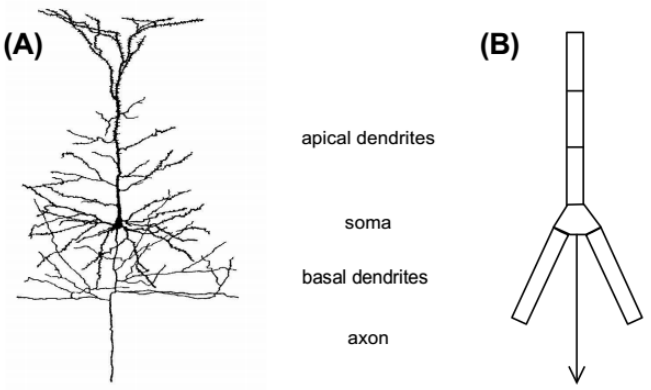
- Cable Theory solves the problem of the electric current flow in and out of a cylindrical core conductor
- The spatial spread of electrical signals over time is modeled with a nonlinear differential equation
- Neuronal simulator programs make use of a Taylor-series approximation of this equation

Input resistance

- At a given point in the dendritic tree, R_{in} is the ratio V_0/I_0 when a steady current I_0 is applied to that point
- R_{in} depends on the diameter of the cylinder
- A dendrite dp that bifurcates in two dendrites d1 and d2 behaves as a continuous cable for current that flows from parent to daughters if :
- Thus a branch point that obeys this rule is equivalent to a uniform cylinder
- Many types of dendritic trees obey this rule such as a-motoneurons, but others don't (cortical, hippocampal)
- This concept has been extended to dendritic trees (Rall 1959,1989)

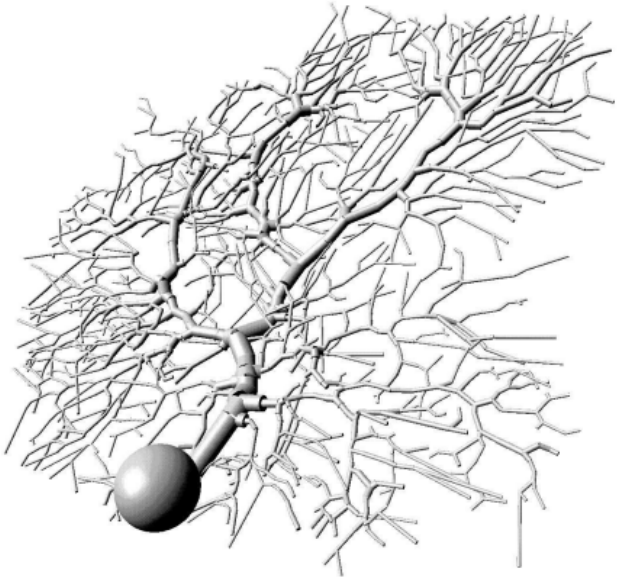
$$R_{in} = (1/\pi) d^{-3/2} \sqrt{R_M R_A}.$$

$$d_p^{3/2} = d_1^{3/2} + d_2^{3/2}.$$



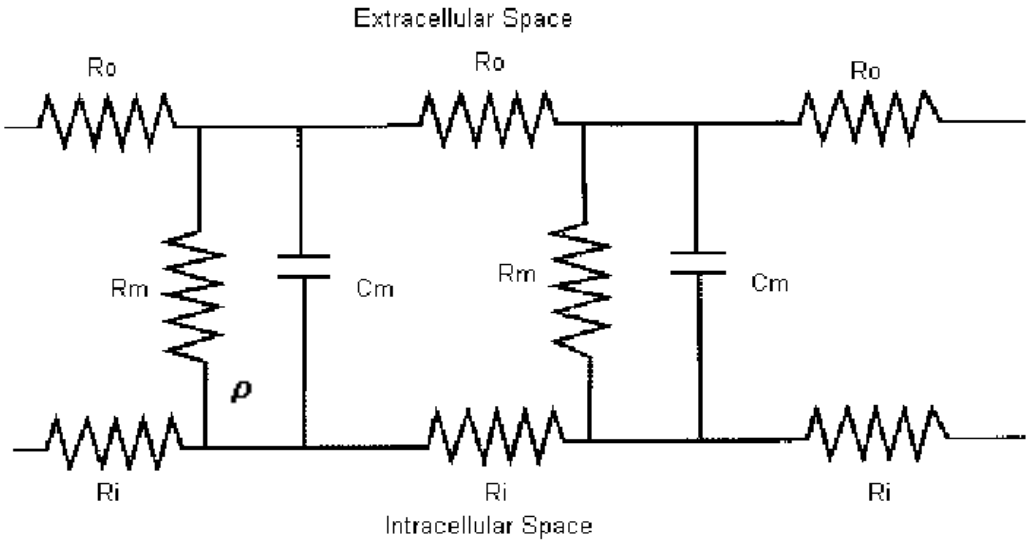
Modeling compartmental neurons

- Thousands of compartments may be used to simulate extended and complex dendritic trees such as the Purkinje cell
- Most models use 3D-reconstructions based on light microscopy images of biocytin-filled cells using specialized software (Neurolucida)
- Most models employ simplifications to reduce the number of simulated cylinders
- Reducing a number of passive dendritic trees to an equivalent passive cable is straightforward
- For active dendrites this is not possible due to the different local impedance of the reduced dendrite.
- Synaptic spines are often reduced to single points



DeSchutter 1994

Passive membrane properties



$$I_m = C_m\, dV/dt + g_m(V-E_m)$$

λ = distance at which $V=V_o*1/e = 0.37\ V_o$

$\lambda = R_m/(R_i+R_o)$ and since R_o is small

$$\lambda = R_m/R_i$$

(LENGTH or SPACE CONSTANT)

$$t = R_mC_m$$

(TIME CONSTANT)

- R_o = vanishingly small
- R_i = Dependent on cytoplasm resistivity and crossectional area:

  $R_i = (L/A)*r$ where

  r = cytoplasmic resisivity
- R_m = Dependent on specific membrane resistivity/cm^2

<u>Voltage attenuation with conduction</u>:

a) Along distance

$$V = V_o*e^{-x/\lambda}$$

b) With time

$$V = V_o * e^{-t/\tau}$$

From passive to active neurons

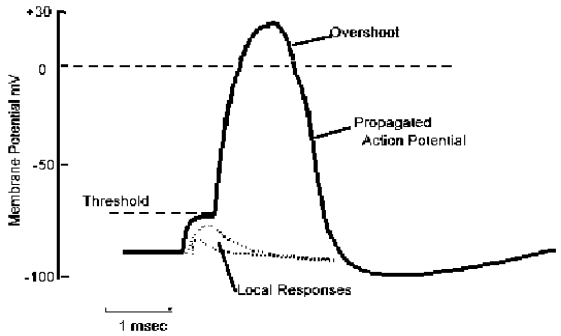
- For "short" cells passive propagation suffices to signal a potential change from one end to the other.

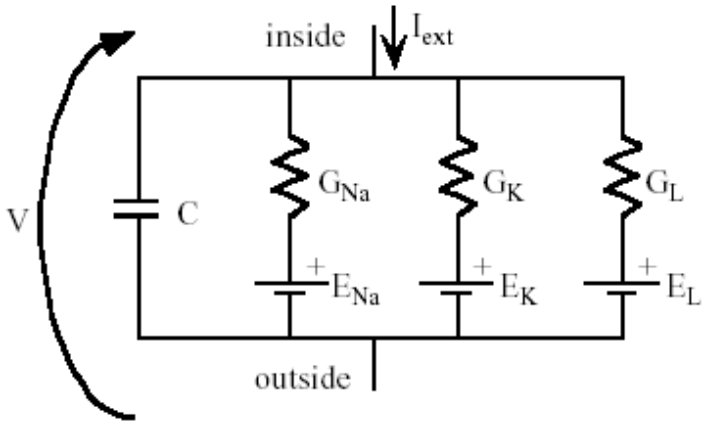
- If the axon is long, this is inadequate since changes at one end would decay away almost completely before reaching the other end.

- If the change in potential difference is large enough, then in a cylindrical configuration such as the axon, a pulse can actively propagate at full amplitude. The Hodgkin-Huxley Equations (1952)

Active membrane properties

Action Potential Generation





C_m	Membrane capacity
G_K	Voltage-dependent Potassium conductance
G_{Na}	Voltage-dependent Sodium conductance
G_L	Leak conductance

Hodgkin and Huxley (1952): they did a series of experiments using the giant axon of the squid to characterize the mechanisms of action potential generation

$$I_{ext} = C_m\, dV/dt + G_L(V-E_L) + G_K n^4(V-E_K) + G_{Na} m^3 h(V-E_{Na})$$

In reality, many more mechanisms are responsible for membrane potential changes, like Ca^{++} channels (I_{caT}, I_{caR}, I_{caL}), other types of K^+ channels (I_A, I_m, I_{sAHP}, I_{mAHP}) and Na^+ channels (I_{Nap}), pumping and buffering mechanisms e.t.c

Modeling active ion channels

Voltage-gated ion channels are sometimes open, sometimes closed, depending on the membrane potential and/or other factors.

Passive Ion Channels: $I_i = (V - E_i)/R_i$

Active Ion Channels: $I_i = P_i(V - E_i)/R_i$

Probability that ion channel is open

Persistent Channels (K+)

Potassium channels are only open when all 4 subunits are open.

n is the probability of the subunit being open.

$$P_K = n^4$$

$$\frac{\partial n}{\partial t} = \alpha_n(V)(1-n) - \beta_n(V)n$$

Modeling active ion channels

Voltage ending on
the mer

Passive
Active I

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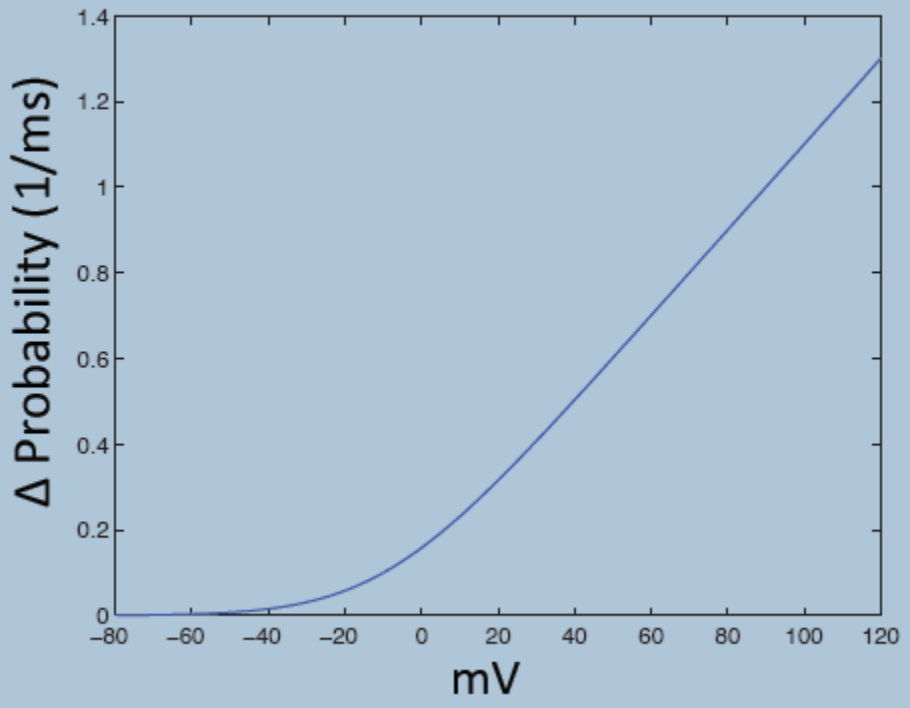
α_n is the change in probability that a closed subunit opens



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Modeling active ion channels

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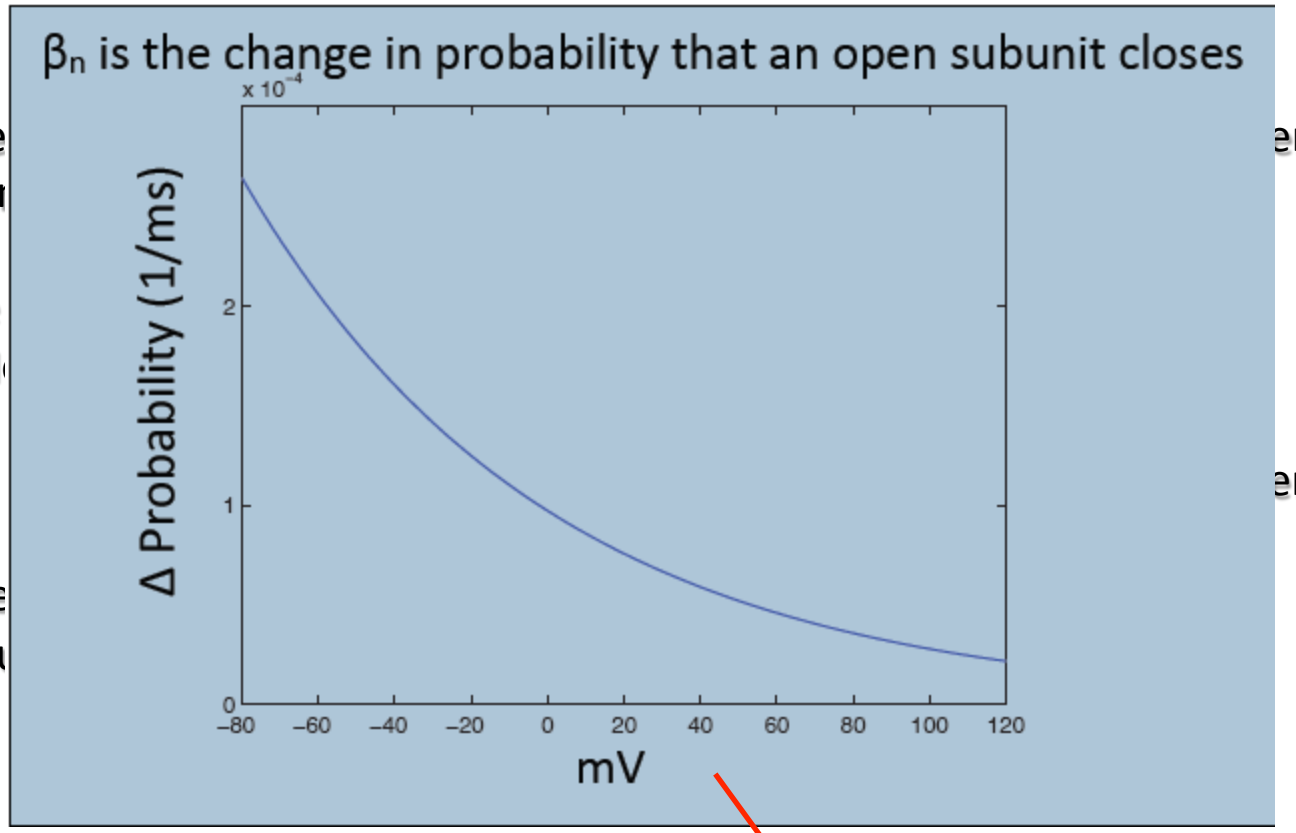

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Potassium channels are only open when all 4 subunits are open.

$$P_K = n^4$$

$$\frac{\partial n}{\partial t} = \alpha_n(V)(1-n) - \beta_n(V)n$$

$$\tau_n(V)\frac{\partial n}{\partial t} = -(n - n_\infty(V))$$

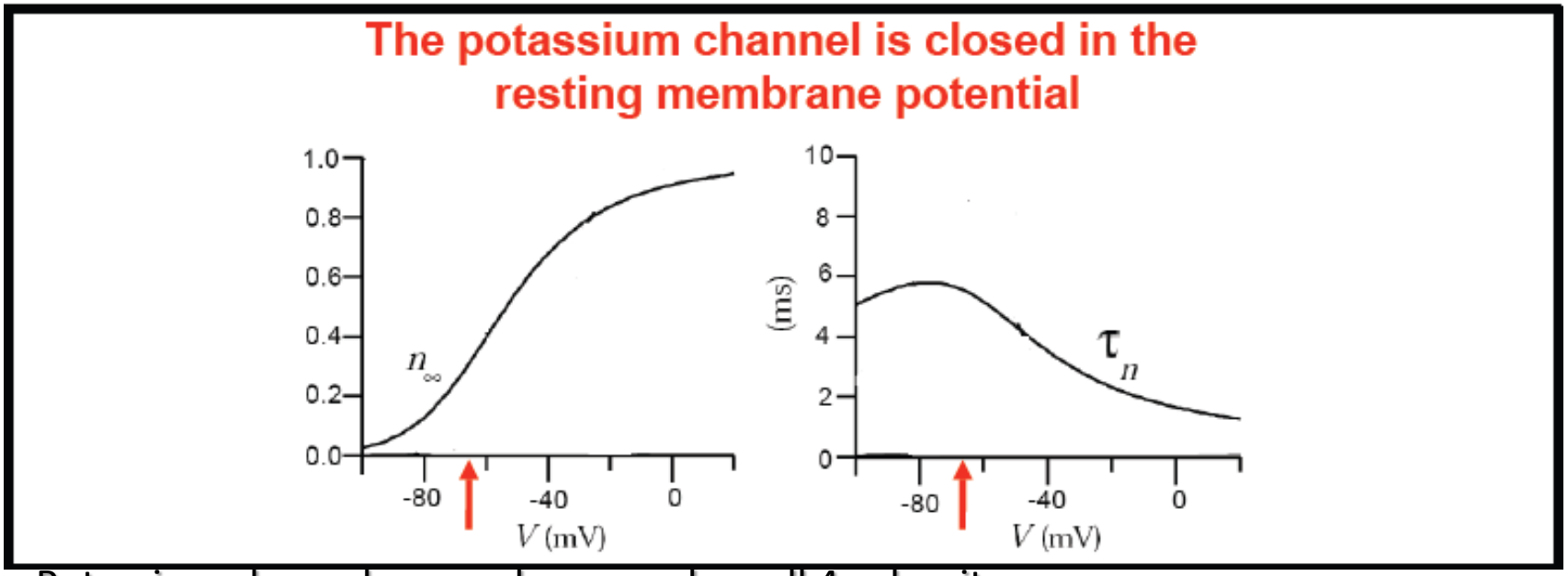
$$n(t) = n_\infty(V) + (n_0 - n_\infty(V))e^{\frac{t}{\tau_n(V)}}$$

initial value of n

steady state value of n (depends on V)

decay rate of n (depends on V)

Modeling active ion channels



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$$P_K = n^4$$

$$\frac{\partial n}{\partial t} = \alpha_n(V)(1-n) - \beta_n(V)n$$

$$\tau_n(V)\frac{\partial n}{\partial t} = -(n - n_\infty(V))$$

$$n(t) = n_\infty(V) + (n_0 - n_\infty(V))e^{\frac{t}{\tau_n(V)}}$$

$$\alpha_n(V) = \frac{0.01(V+55)}{1-\exp(-0.1(V+55))}$$

$$\beta_n(V) = 0.125\exp(-0.0125(V+65))$$

Active ion channels

Transient Sodium channels (Na+)

Transient sodium channels are only open when all 3 activation units (m) and the inactivation unit (h) are open.

$$P_{Na} = m^3 h$$

$$\frac{\partial m}{\partial t} = \alpha_m(V)(1-m) - \beta_m(V)m$$

$$\frac{\partial h}{\partial t} = \alpha_h(V)(1-h) - \beta_h(V)h$$

$$\alpha_m(V) = \frac{0.1(V+40)}{1-\exp(-0.1(V+40))}$$

$$\beta_m(V) = 4\exp(-0.0556(V+65))$$

$$\alpha_h(V) = 0.07\exp(-0.05(V+65))$$

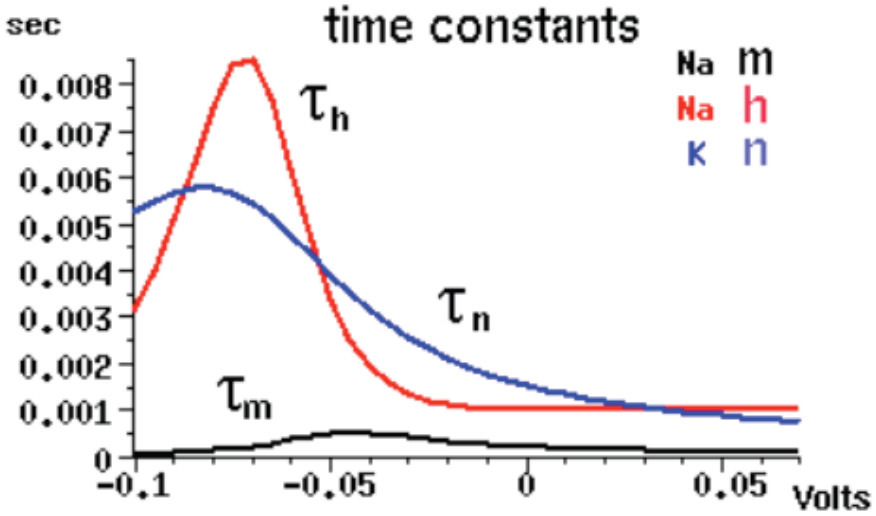
$$\beta_h(V) = \frac{1}{1+\exp(-0.1(V+35))}$$

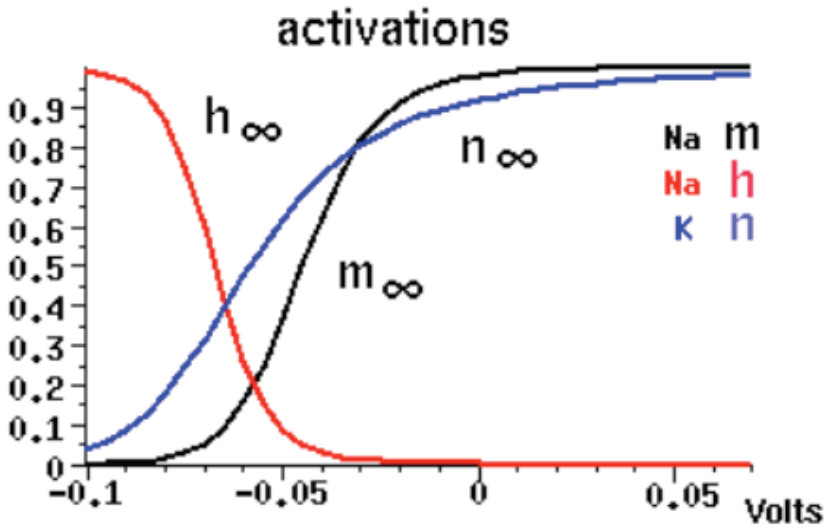
Action potentials

Na^+ activation units $\tau_m(V)\frac{\partial m}{\partial t} = -(m - m_\infty(V))$

Na^+ inactivation units $\tau_h(V)\frac{\partial h}{\partial t} = -(h - h_\infty(V))$

K^+ activation units $\tau_n(V)\frac{\partial n}{\partial t} = -(n - n_\infty(V))$

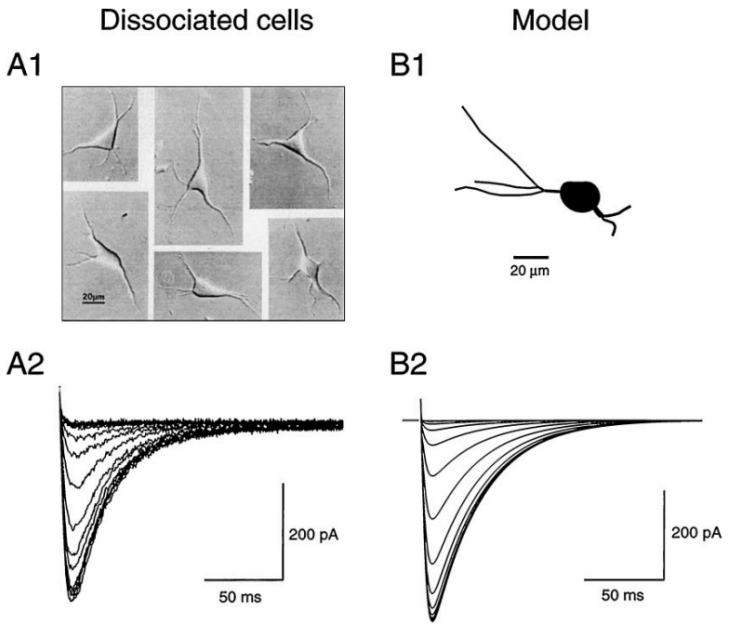




Larger τ means slower channel response to voltage

Model Calibration

- In order for a model neuron to perform as closely as possible to a real neuron, it needs to be constrained against all the available experimental data for the specific neuron type
- Calibration requires careful examination of the relevant literature, experimental evidence, as well as the intuition of the experimenter
- Voltage responses of the cell to *in vitro* current stimulation with varying simple currents can be used as benchmark for the model
- In order to constrain kinetic models, whole cell recordings are often used, attempting to match the model response to the recorded waveforms



Destexhe 1998

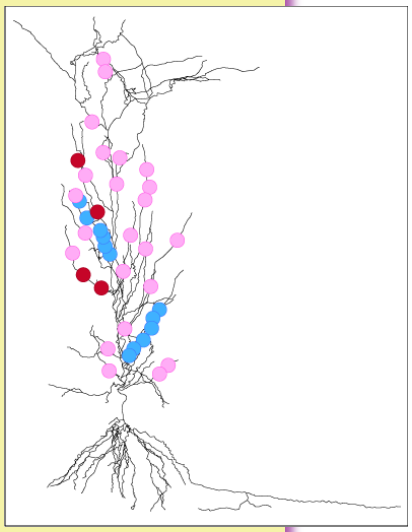
Examples of compartmental modeling studies from our lab

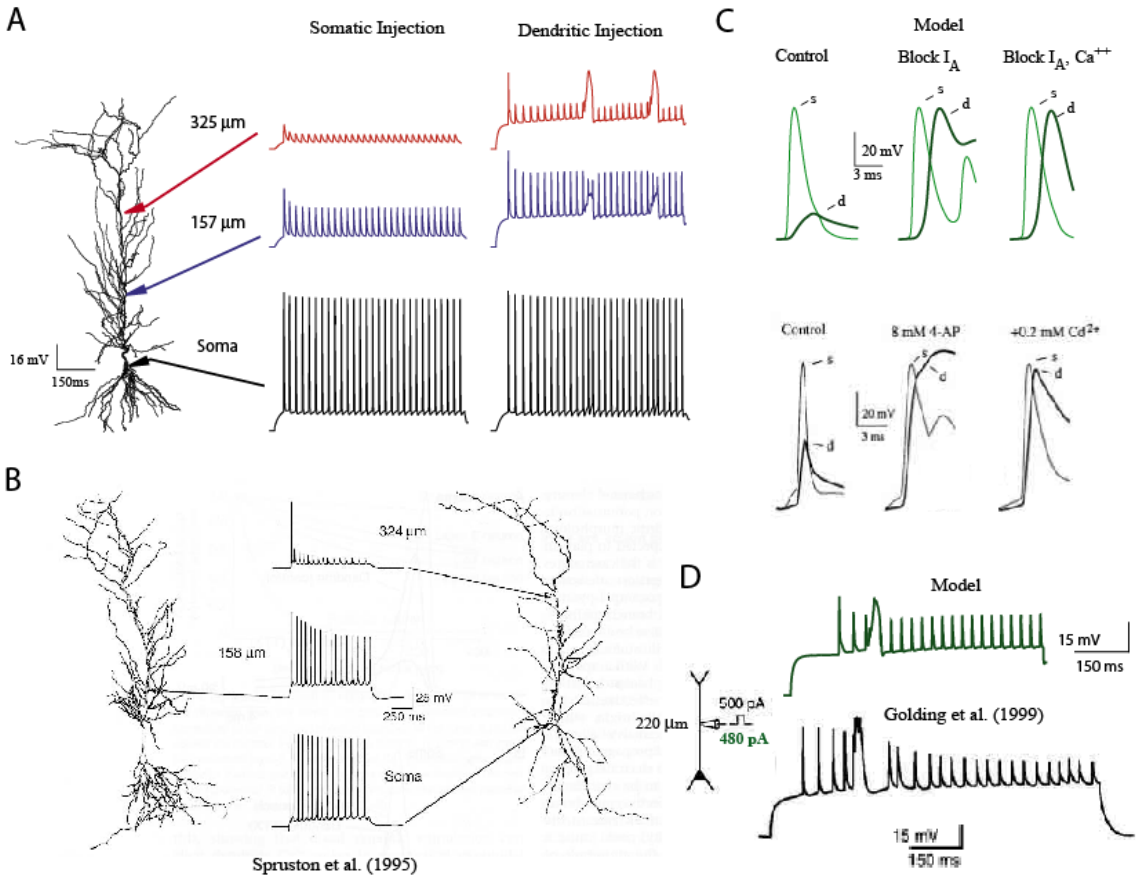
Single neuron: dendritic integration in a CA1 pyramidal cell model

Morphology
CA1 pyramidal cell
183 compartments
1830 sections

Channels
I_{Na}
I_{Kdr}
I_A
I_{Nap}
I_m
I_h
I_D
I_{CaT}
I_{CaR}
I_{CaL}
I_{CaN}
I_{fAHP}
I_{sAHP}
I_{mAHP}

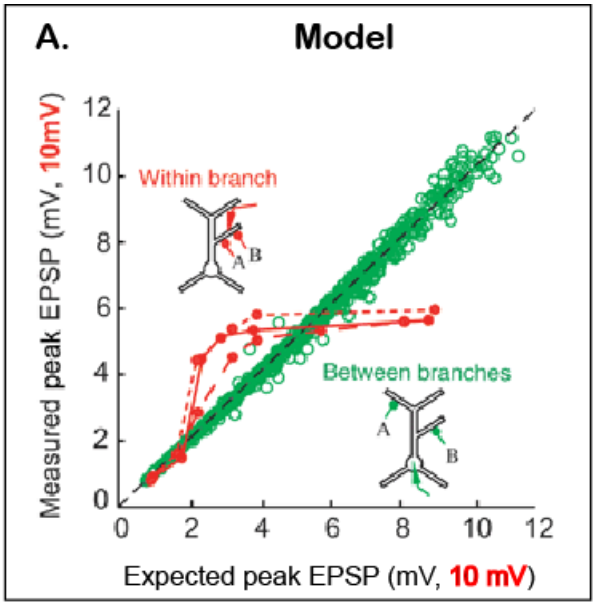
Synapses
NMDA, AMPA, $GABA_A$, $GABA_B$





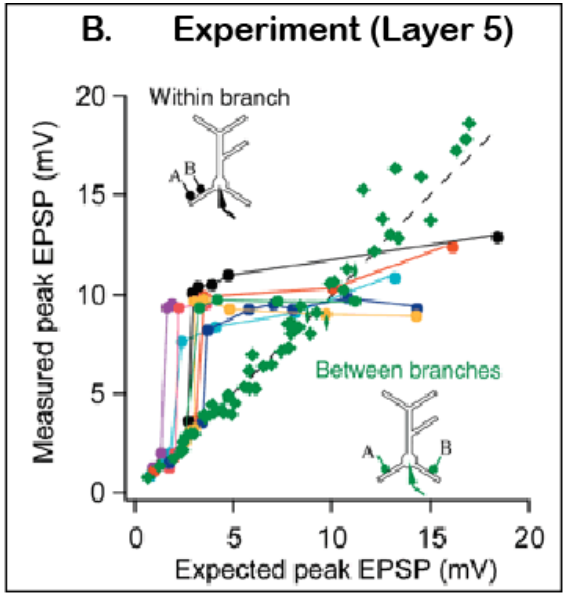
The model was heavily validated using multiple experimental data from in vitro studies

Prediction: dendrites integrate inputs like semi-independent sigmoidal units

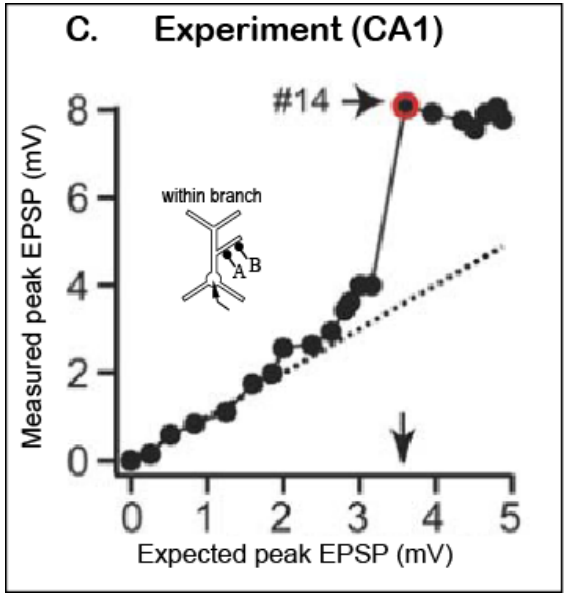


Poirazi et al, *Neuron*, 2003a

Experimental verification



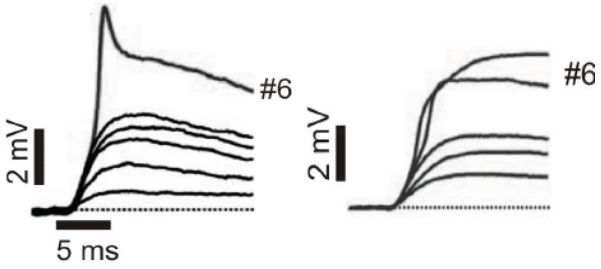
B. Polsky et al, *Nat. Neuro.*, 2004

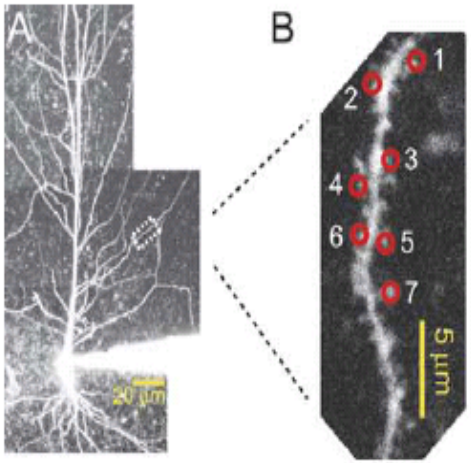


C. Losonczy & Magee, *Neuron*, 2006

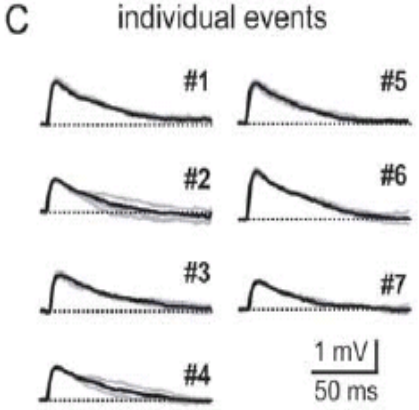
Coincidence detection in CA1 obliques

Synchronous stimulation → dendritic spikes

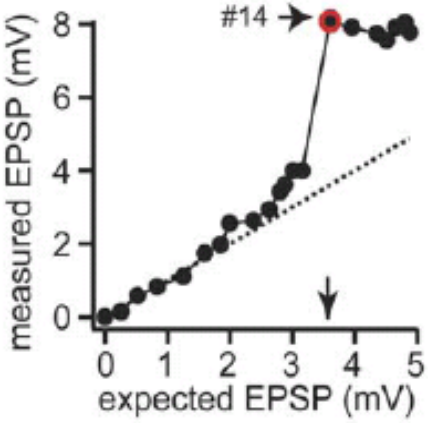




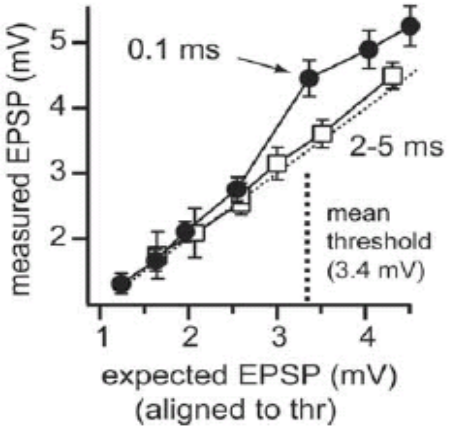
Multisite two-photon glutamate uncaging.
Single pulse stimulation.



Single Dendrite



Average



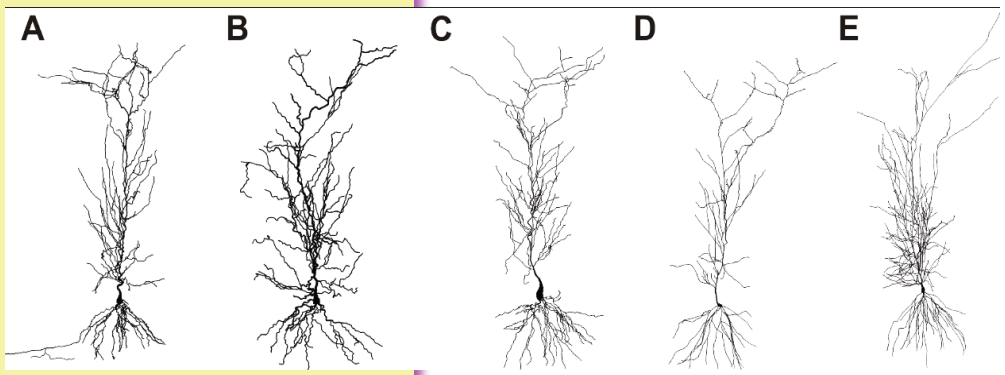
CA1 obliques detect (amplify) only synchronous inputs

Losonczy & Magee, Neuron, 2006
also see Ariav et al, J. Neurosc., 2003

Prediction: non-synchronous and bursty can also be detected

Channels

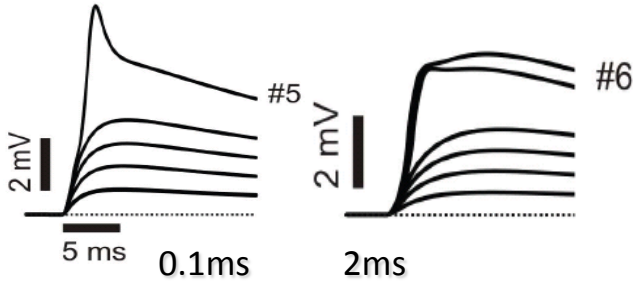
I_{Na}
I_{Kdr}
I_A
I_{Nap}
I_m
I_h
I_D
I_{CaT}
I_{CaR}
I_{CaL}
I_{CaN}
I_{fAHP}
I_{sAHP}
I_{mAHP}

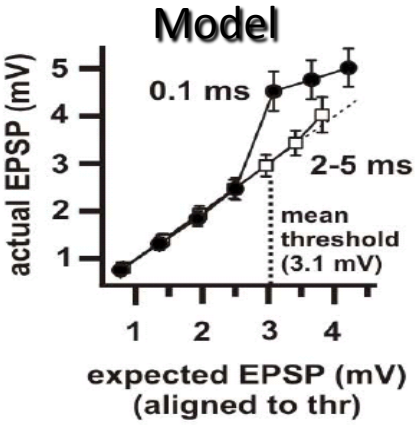


Synapses

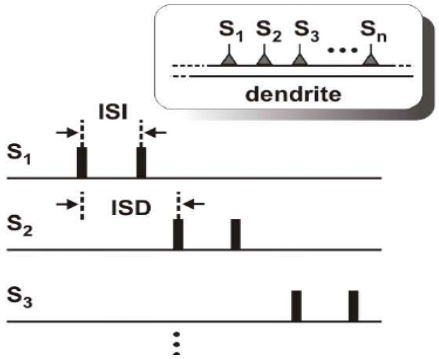
NMDA, AMPA, $GABA_A$, $GABA_B$

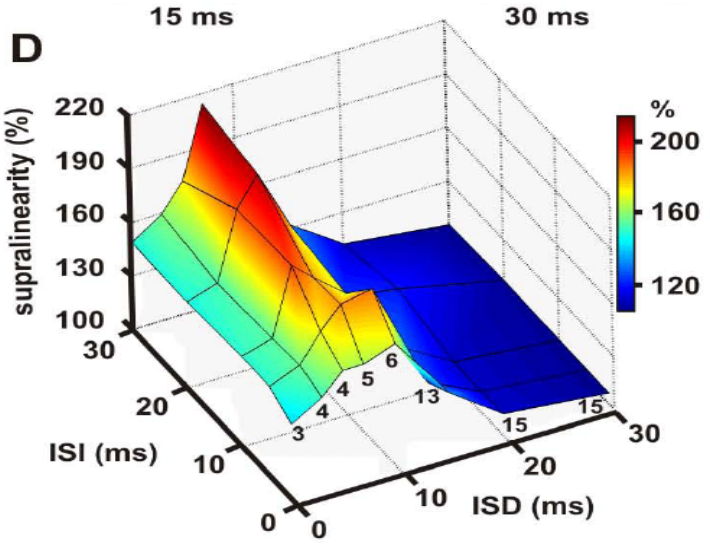
Synchronous stimulation
→ dendritic spikes





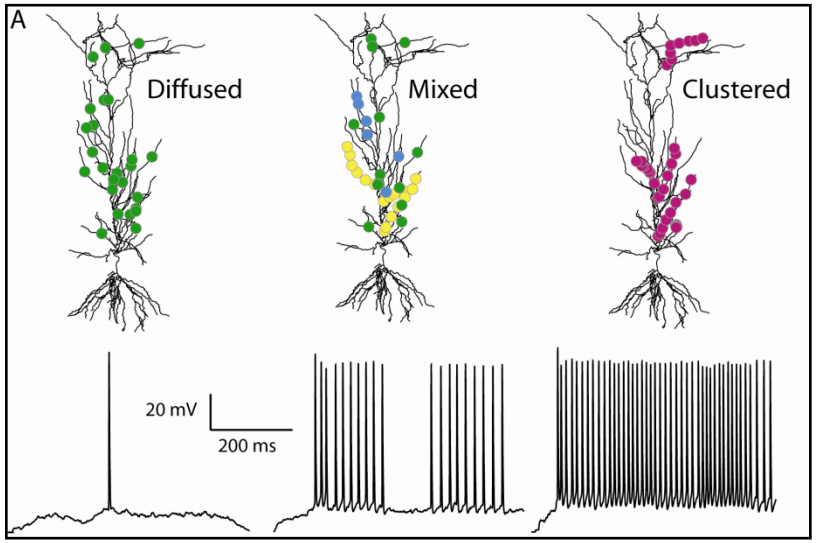
2-pulse stimulation



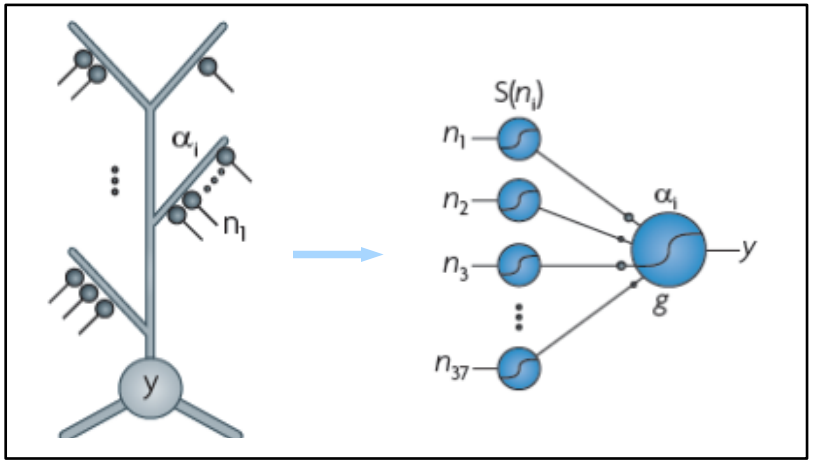


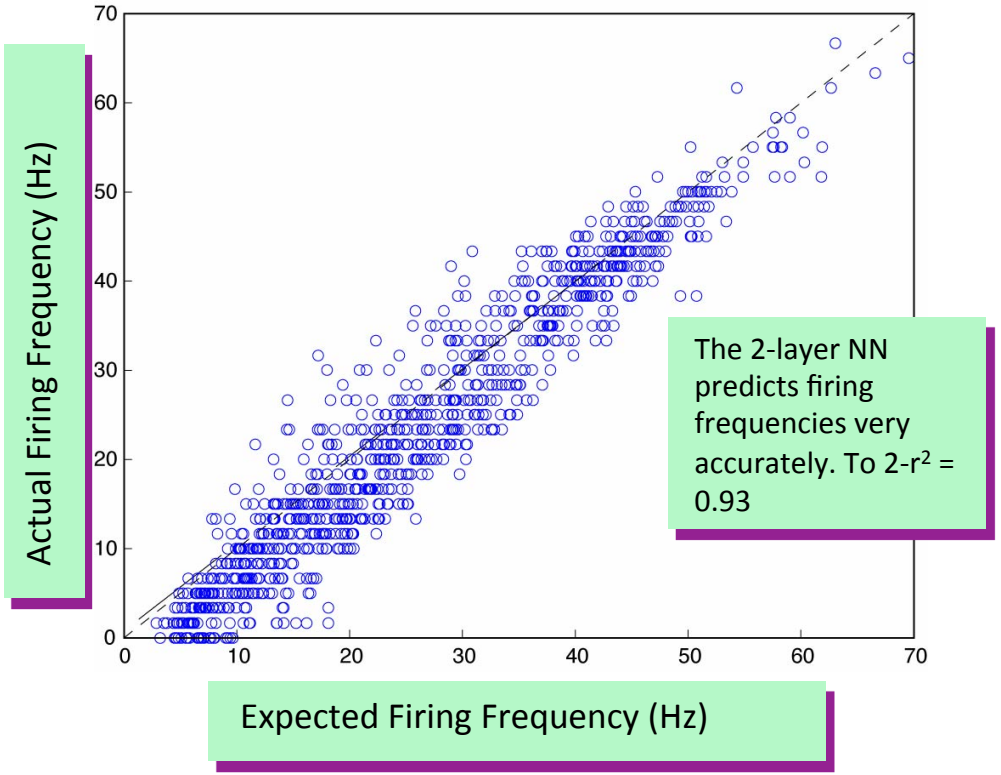
Gomez et al, Front. Comp. Neurosc., 2011

Prediction: CA1 pyramidal neuron as a 2-layer ANN



Measure firing rate in response to > 1000 different synaptic arrangements





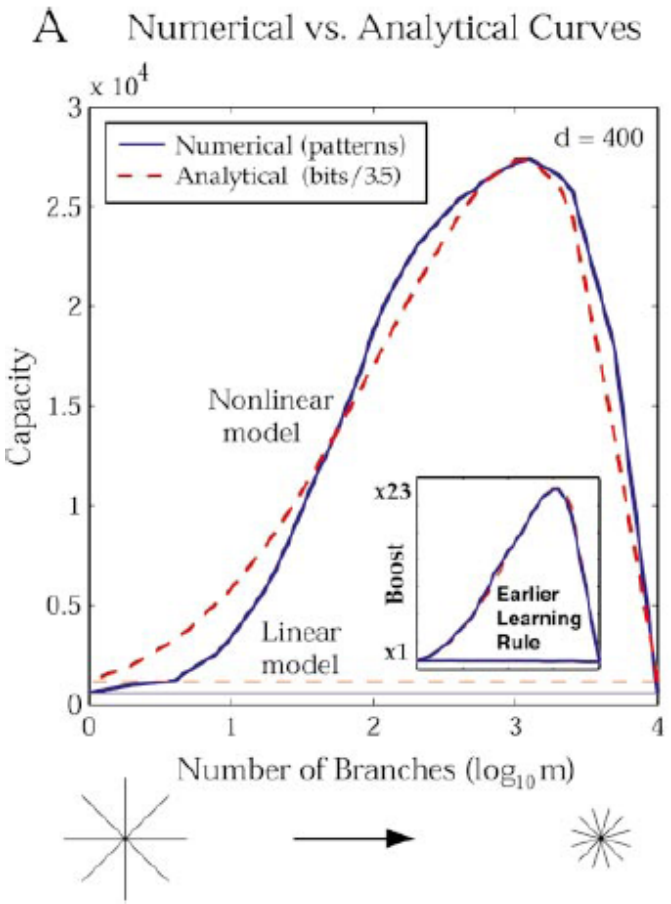
A simple 2-layer ANN abstraction predicts The average firing frequency of the model to > 1000 inputs patterns with high accuracy.

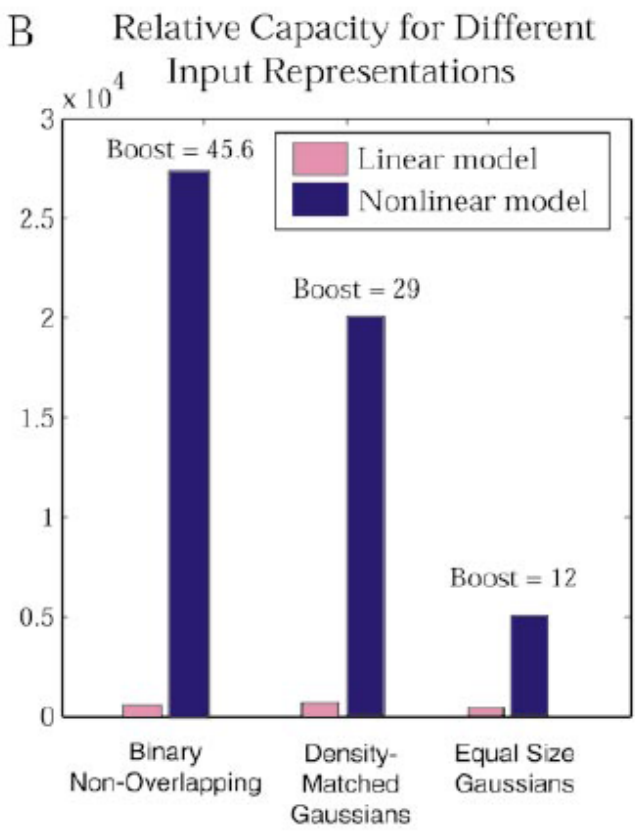
Poirazi et al, *Neuron*, 2003b

What is the benefit of having such neurons?

$$B_L = 2\log_2 \binom{s+d-1}{s}$$

$$B_N = 2\log_2 \binom{\binom{k+d-1}{k}+m-1}{m}$$

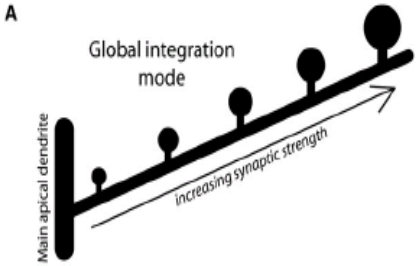




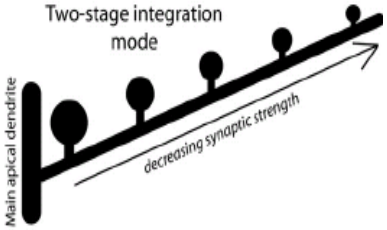
Poirazi & Mel, Neuron, 2001.

Nonlinear neurons can learn one order of magnitude (45 times) more memories than linear neurons.

Experimental support for 2-stage integration

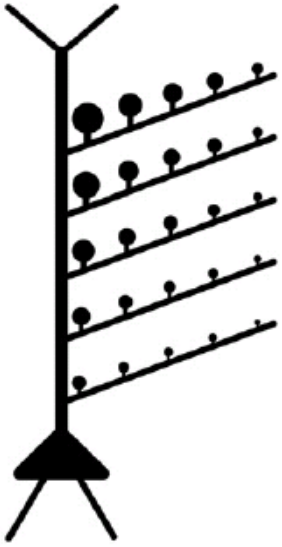


All inputs sum at the axon

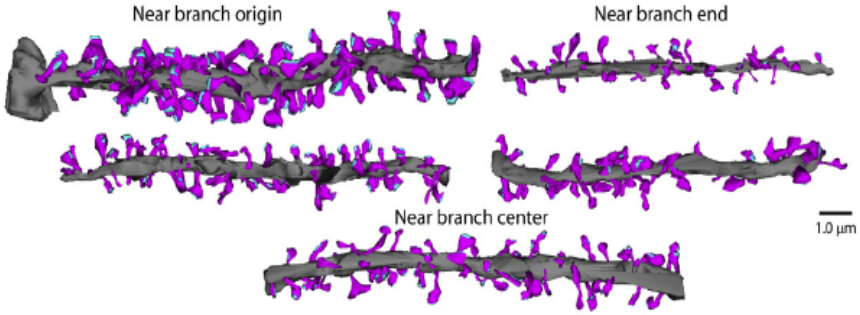


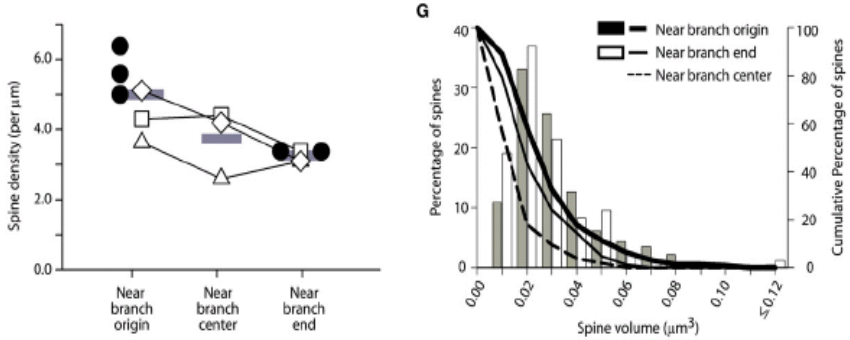
Inputs sum in the dendrite and outputs at the axon

Serial-section electron microscopy (ssEM) to reconstruct excitatory synapses along individually labeled (in vivo) apical oblique dendrites.



Proposed 2-stage model

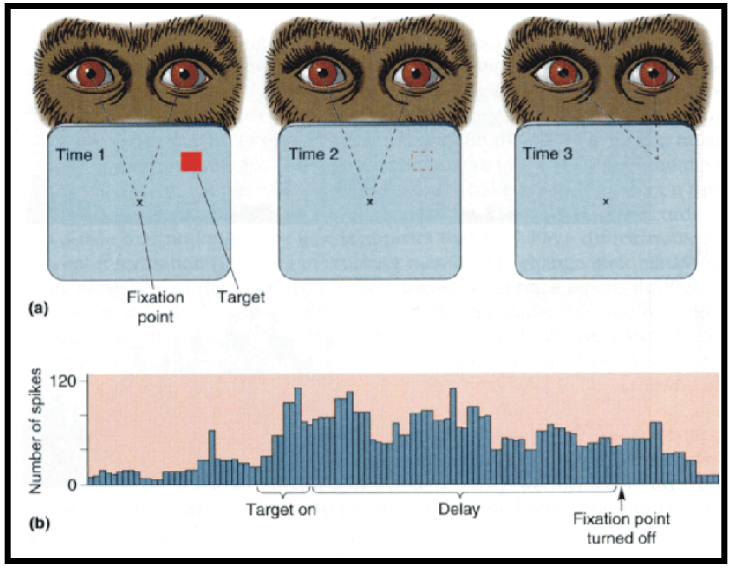




More and larger synapses are found close to the branch point

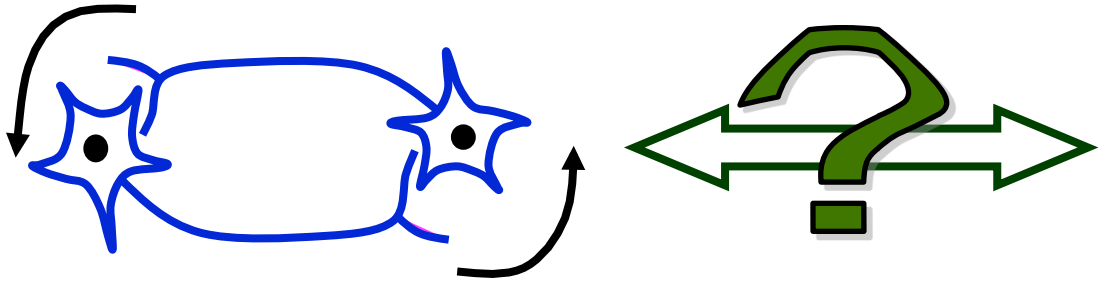
Katz et al, *Neuron*, 2009

Simulating working memory in the PFC



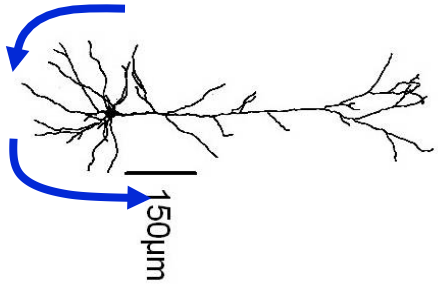
Goldman-Rakic, 1992

Synaptic mechanisms



Wang, 1999

Intrinsic mechanisms



Egorov et al, 2002

Single neuron: L5 PFC pyramidal neuron model expressing Persistent Activity

Kiki Sidiropoulou

Ionic membrane mechanisms

I_{Naf} - fast Na^+ current, includes slow inactivation

I_{Nap} – persistent Na^+ current

I_{Kdr} - delayed rectifier K^+current

I_A – A-type K^+ current

I_D – slow inactivating K^+ current

I_h – hyperpolarization activating current

I_{CaLc} – L-type Ca^{++} current

I_{CaN} – N-type Ca^{++} current

I_{CaR} – R-type Ca^{++} current

I_{CaT} – T-type Ca^{++} current

I_{fAHP} – fast Ca^{++} activated K^+ current

I_{sAHP} – slow Ca++ activated K+ current

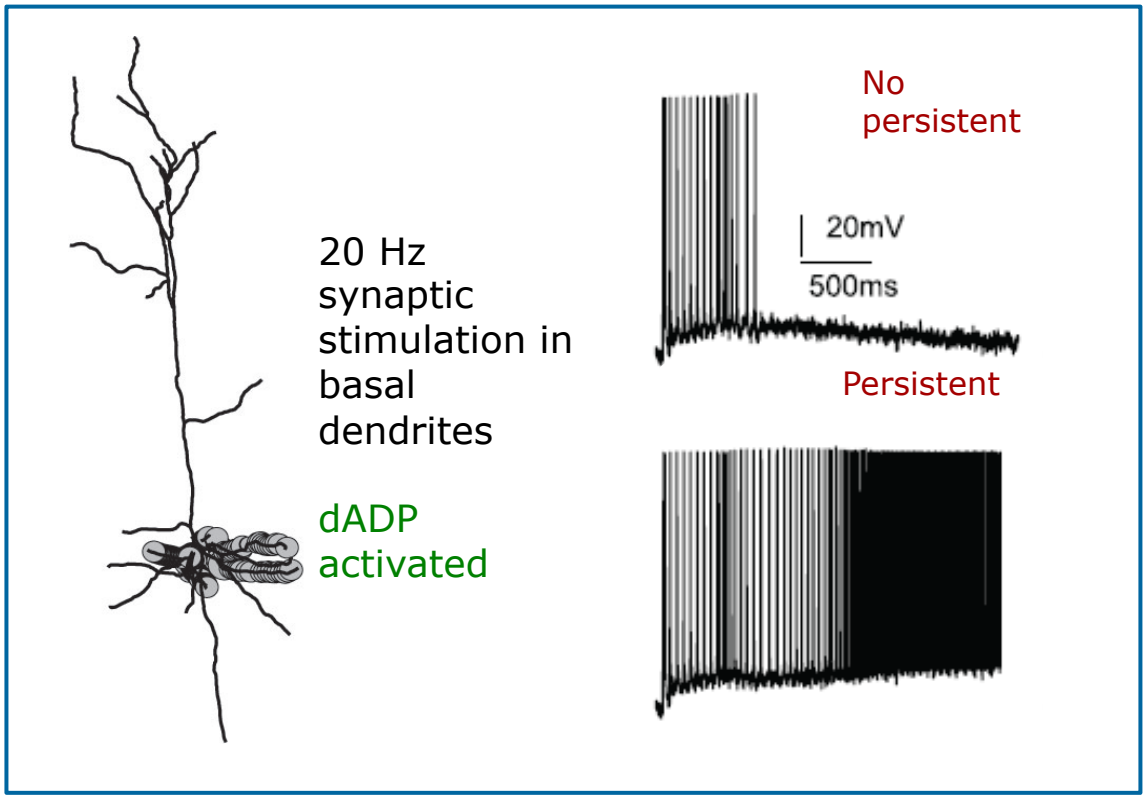
dADP -'ip3'-induced Ca++ release and CAN current

Mechanism for calcium buffering and extrusion

Mechanism for K+ extrusion

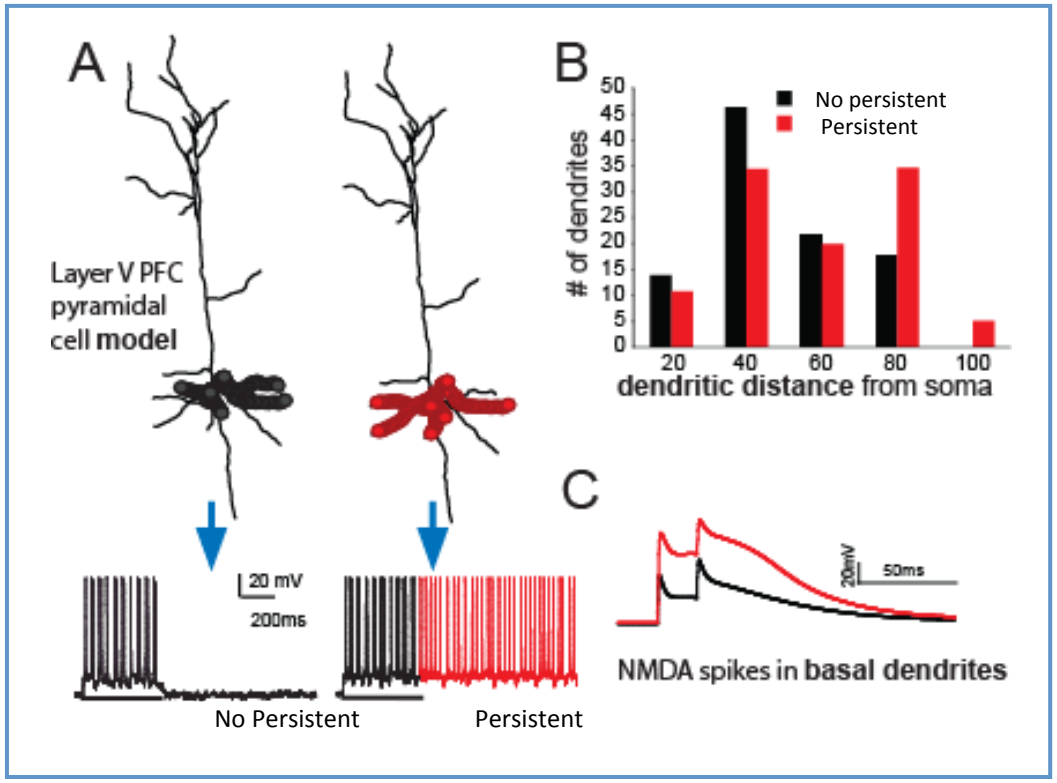
Synaptic Mechanisms

NMDA, AMPA, $GABA_A$, $GABA_B$



Persistent activity is induced with a probability, depending on the spatial arrangement of synaptic inputs onto basal dendrites.

Prediction: Persistent activity emerges when inputs are located in thin, terminal tips

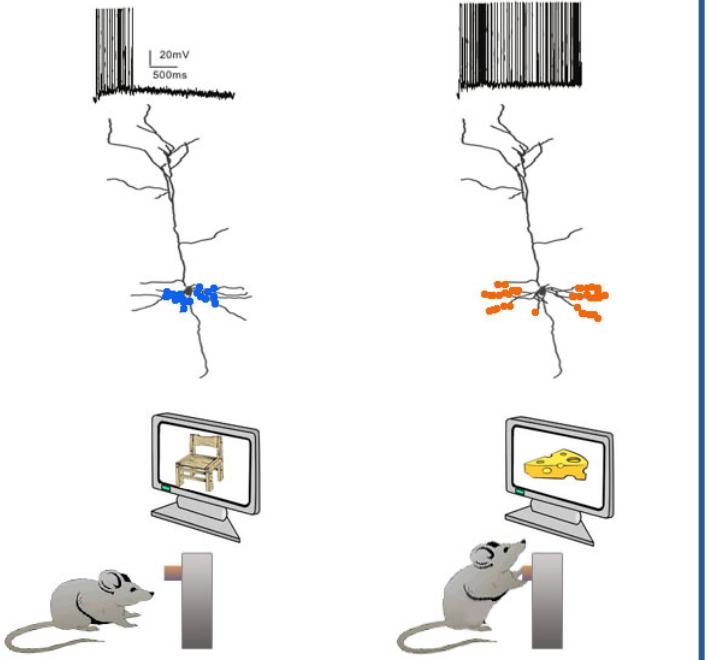


Persistent activity trials are associated with inputs located in more distal dendrites and larger NMDA spikes.

Since NMDA conductance is the same, dendritic morphology underlies differences in NMDA spikes.

Sidiropoulou and Poirazi, *PloS Comp. Biol.*, 2012

Prediction & support: a dendritic mechanism for input specificity



A dendritic mechanism for input specific persistent firing, based on NMDA spikes

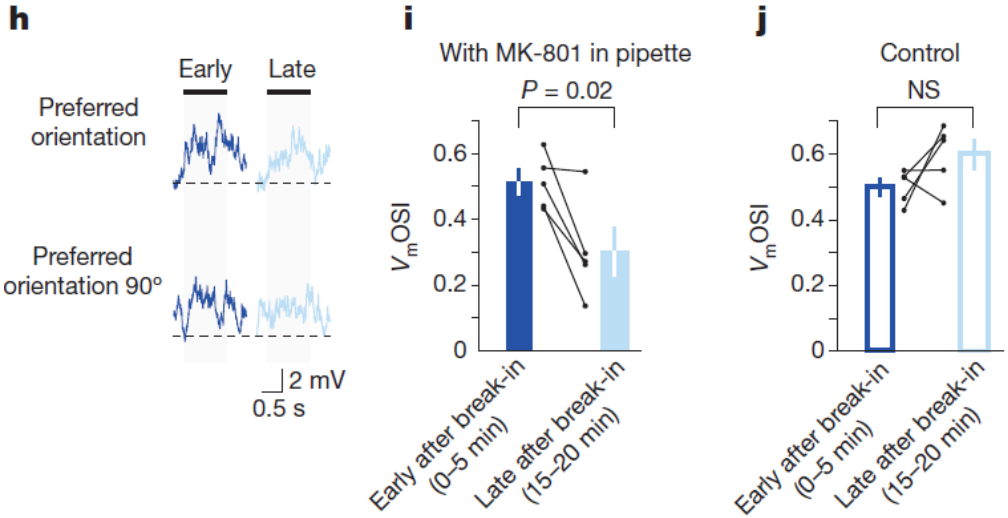


Figure 5. Dendritic mechanisms contribute to the selectivity of subthreshold orientation tuning in vivo.

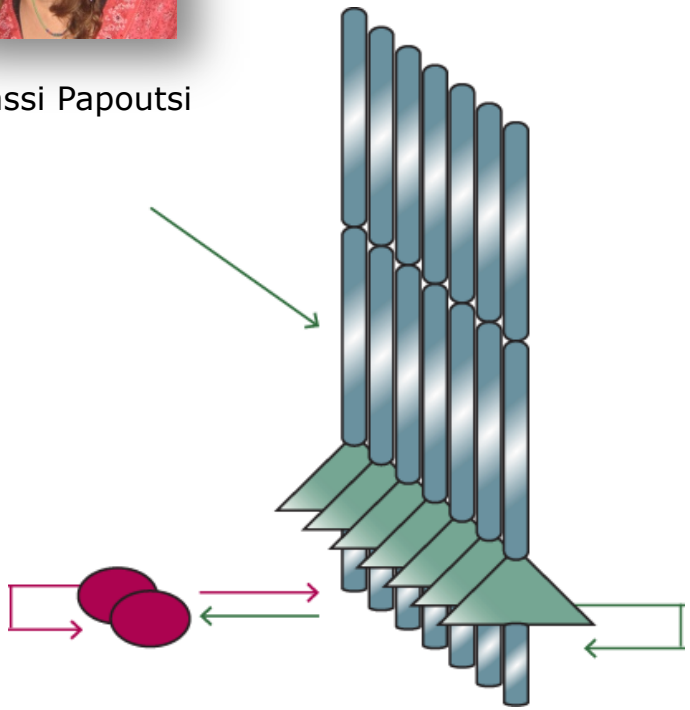
NMDA-dependent dendritic spikes increase the selectivity of neuronal responses to the orientation of a visual stimulus (orientation tuning)

Sidiropoulou and Poirazi, *PLoS Comp. Biol.,* 2012

Smith et al, *Nature*, 2013

Nassi Papoutsi

Microcircuit level: L5 PFC module expressing Persistent Activity



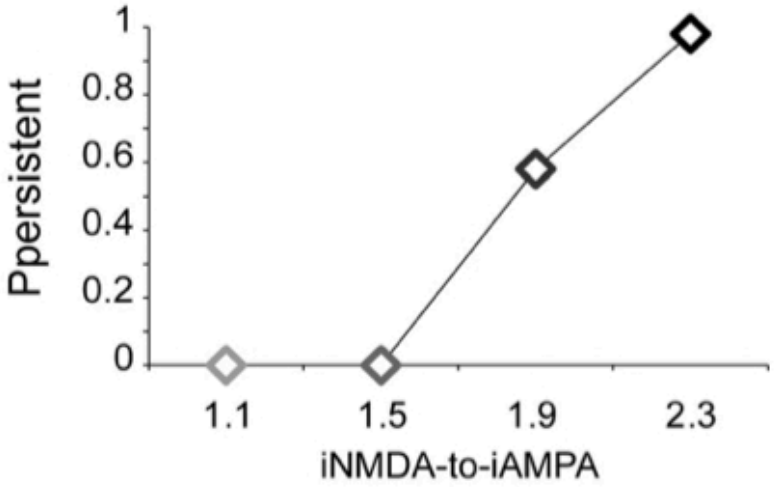
L5 PFC microcircuit

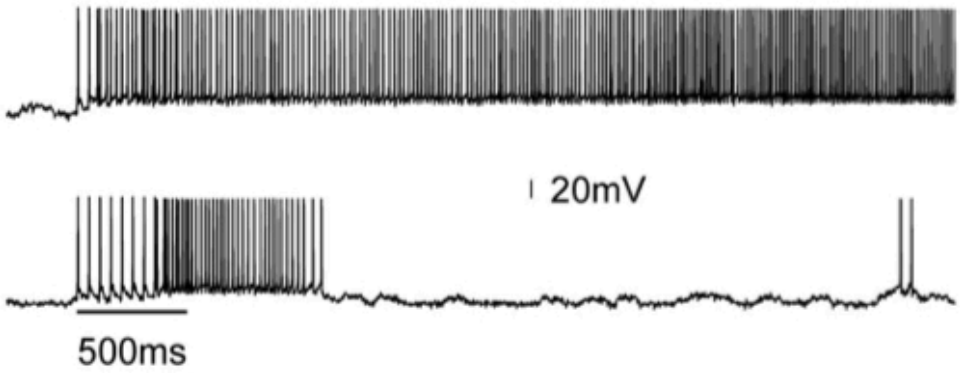
- Pyramidal neurons contain all mechanisms in the detailed single cell model
- Connectivity based on experimental anatomical and electrophysiological data
- Latencies of connections drawn from Gaussian distributions, in accordance with experimental data
- Membrane noise due to stochasticity in ionic currents (Poisson distribution)
- Background synaptic activity

Connectivity properties

Type of connection	Location	# of synapses	Reference
Thalamocortical (incoming)	Proximal dendrite	90	(Kuroda M et al., 1998)
Pyramidal recurrent	Basal dendrite	5	(Markram et al., 1997)
Pyramidal-to-interneuron	Soma	2	(Buhl et al., 1997)
Autapses in pyramidal neurons	Basal dendrite	1	(Lübke et al., 1996)
Interneuron-to-pyramidal	Soma	4	(Gabor Tamás et al., 1997)
Autapses in the interneuron	Soma	12 synaptic contacts producing ~350pA	(Bacci et al., 2003; G Tamás et al., 1997)

Persistent activity is induced in the microcircuit given sufficient NMDA current

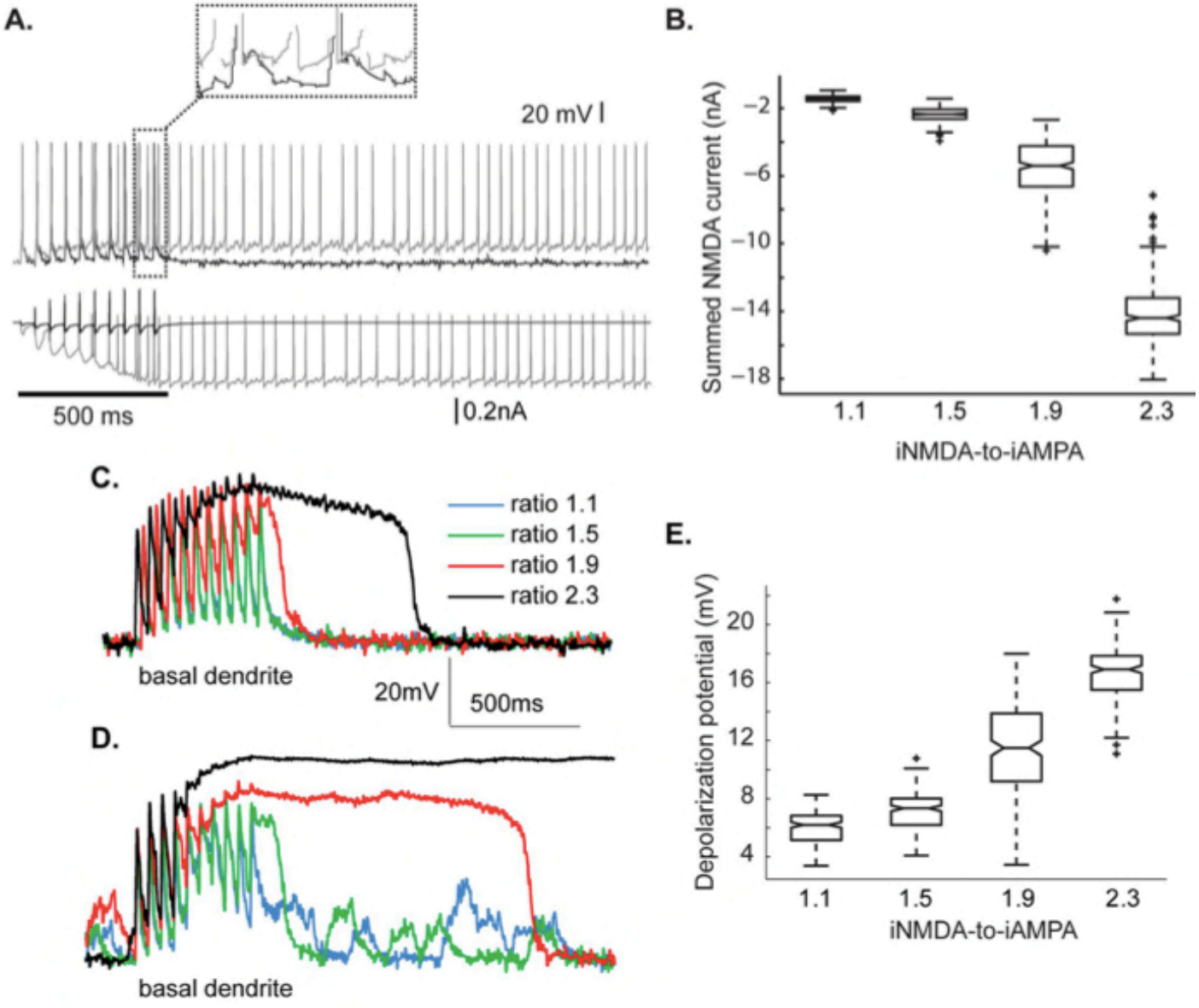




NMDA conductance is necessary for persistent activity induction.
Blockade of NMDA receptors eliminates persistent activity.

Papoutsi et al, *PloS Comp. Biol.,* 2014

Prediction: dendritic NMDA spikes are critical for persistent activity induction



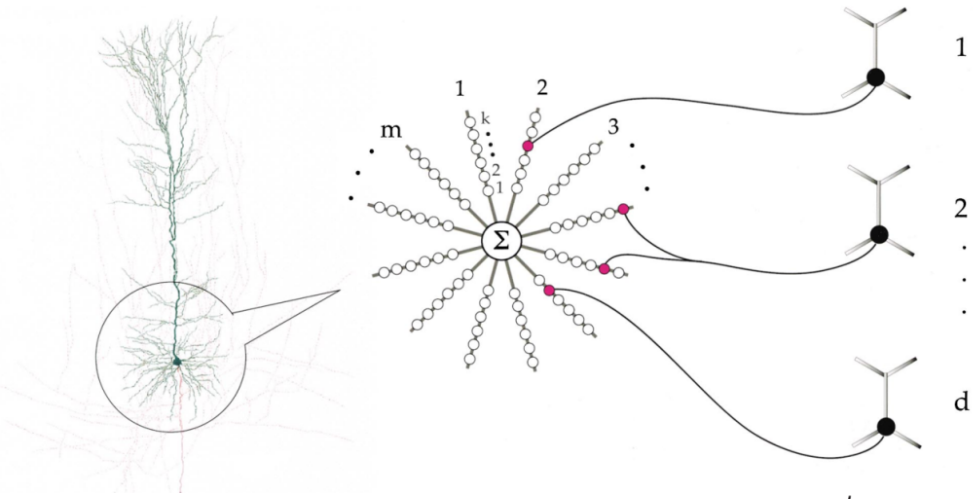
Summary

- 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: dendritic synapse location may serve as a mechanism for stimulus specificity via the induction of dendritic spikes. Supported experimentally in other neurons
- Prediction: dendritic NMDA spikes play a permissive role for the induction of persistent activity. Pending

Simplified dendritic models

- Why simplify dendrites?
  - More compact mathematical formulation
  - Easier to analyze theoretically and analytically
  - Make it easier to simulate neurons in large numbers
  - Comparison with the learning models of Artificial Neural Networks

Simplified model of a neuron with linear or sigmoidal dendrites

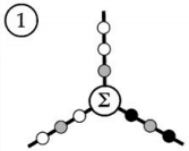
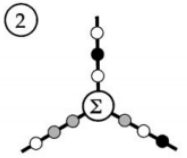


Dendritic response

Linear $a_L(\mathbf{x}) = \sum_{j=1}^{m} \sum_{i=1}^{k} w_{ij} x_{ij}$

Nonlinear $a_N(\mathbf{x}) = \sum_{j=1}^{m} b\left(\sum_{i=1}^{k} w_{ij} x_{ij} \right).$

A nonlinear cell can distinguish between wiring configurations

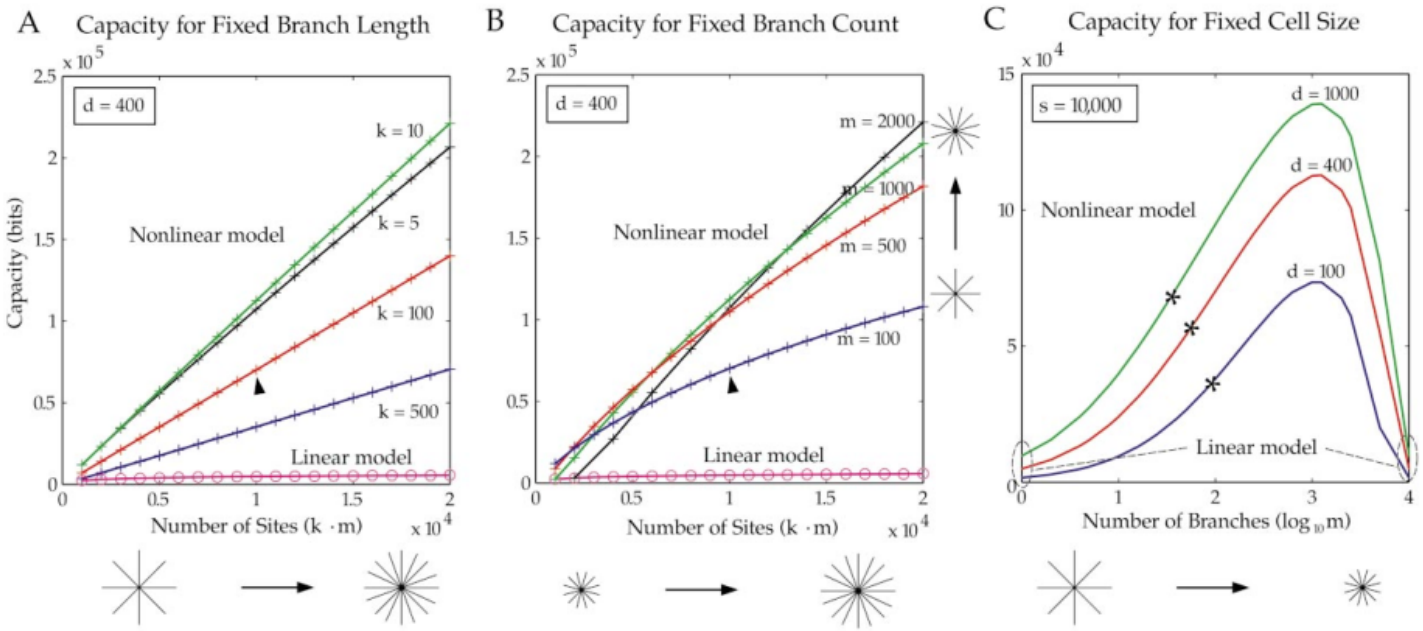
Wiring Configurations	d_1 d_2 d_3 $d,m,k = 3$	Linear Cell $a_L(\mathbf{x})$	Nonlinear Cell $a_N(\mathbf{x})$
1		$4x_1 + 3x_2 + 2x_3$	$b(2x_1 + x_2) +$ $b(2x_1 + x_2) +$ $b(x_2 + 2x_3)$
2		$4x_1 + 3x_2 + 2x_3$	$b(2x_1 + x_3) +$ $b(x_1 + 2x_2) +$ $b(x_1 + x_2 + x_3)$
	Total number of distinct i/o functions	110	220

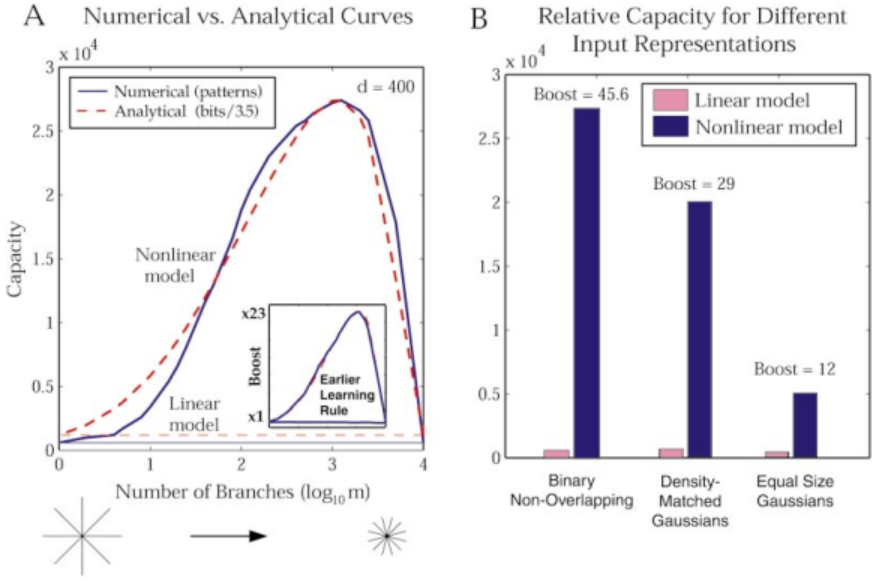
Cell output = excitatory - inhibitory $y(\mathbf{x}) = sgn\,[a^+(\mathbf{x}) - a^-(\mathbf{x})]$

- Cell is modeled as a set of m identical branches connected to a soma, where each branch contains k excitatory synaptic contacts.
- Each synapse is driven by one of d input lines and is given a small integer-valued weight.

Poirazi, Neuron 2001

Sigmoidal dendrites increase storage capacity





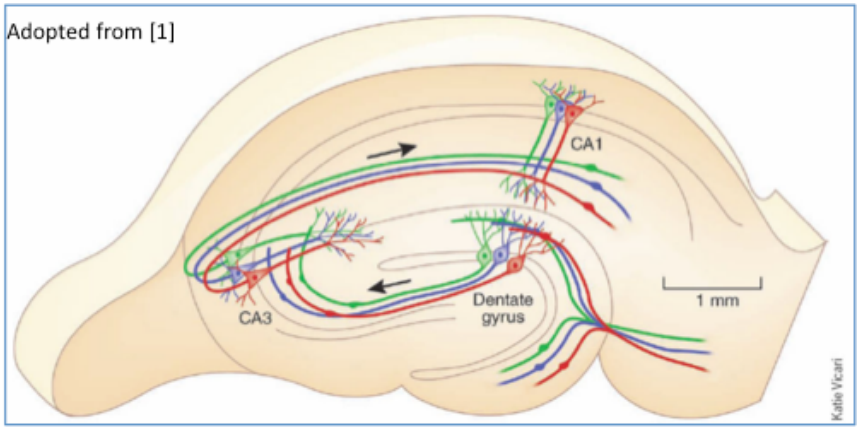
Storage capacity is increased 50-fold for the nonlinear compared to the linear model cell.

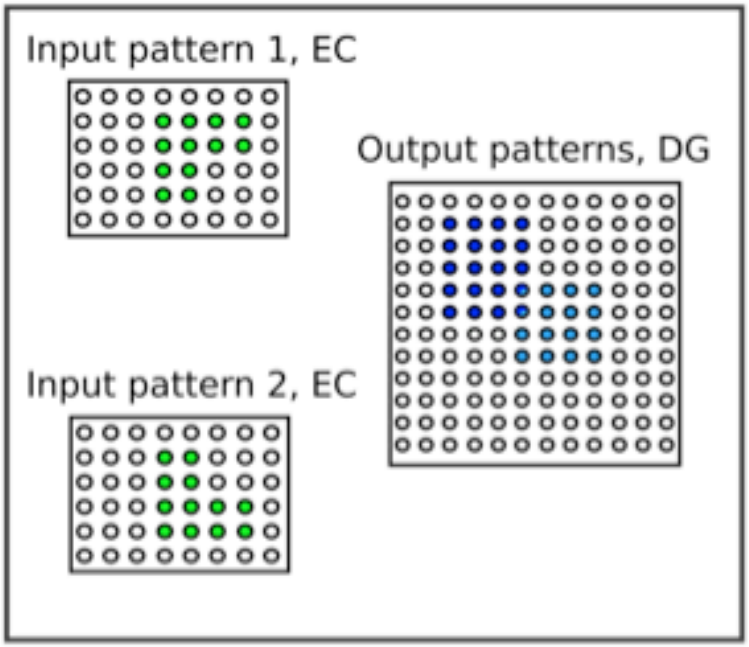
Poirazi, Neuron 2001

Spiros Chavlis

Network level: role of DG dendrites in Pattern Separation

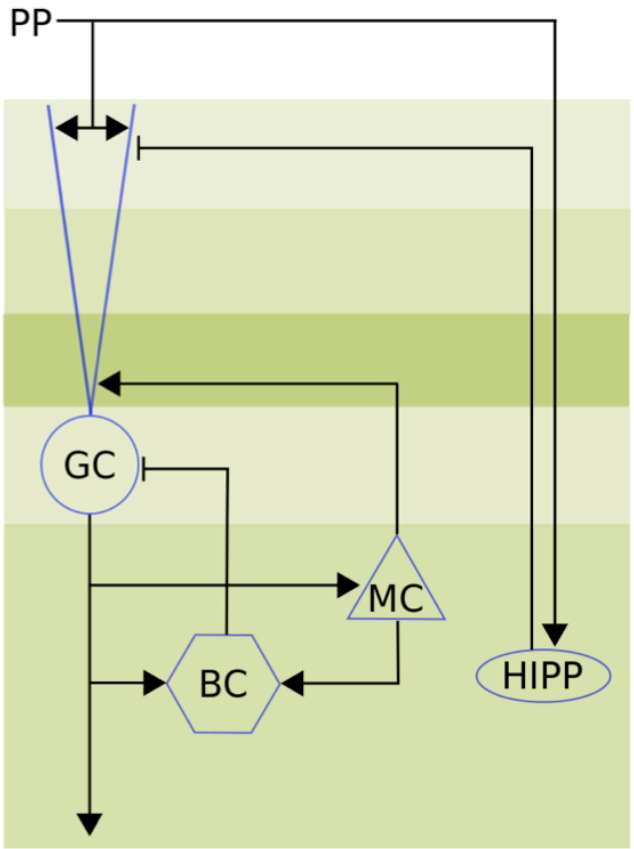
- **Pattern separation**: computational task which transforms overlapping (similar) input to non-overlapping representations

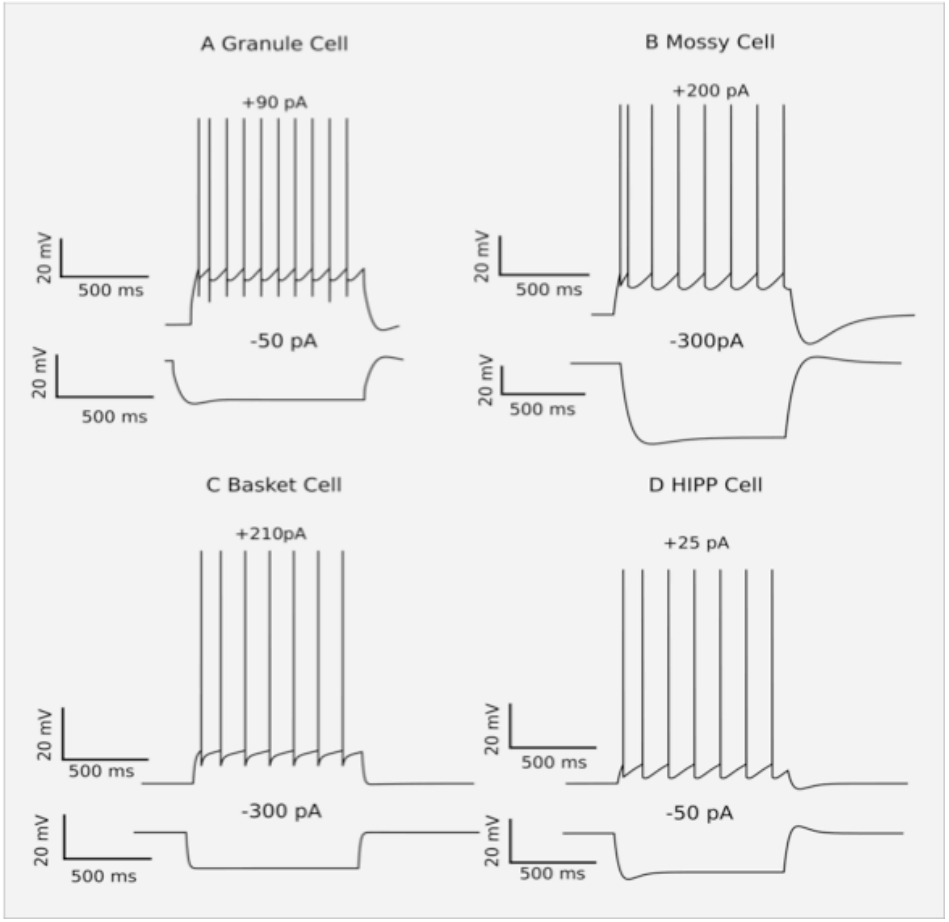




- **Dentate Gyrus**: hippocampal subregion that accomplishes this task

A simplified Dentate Gyrus network model





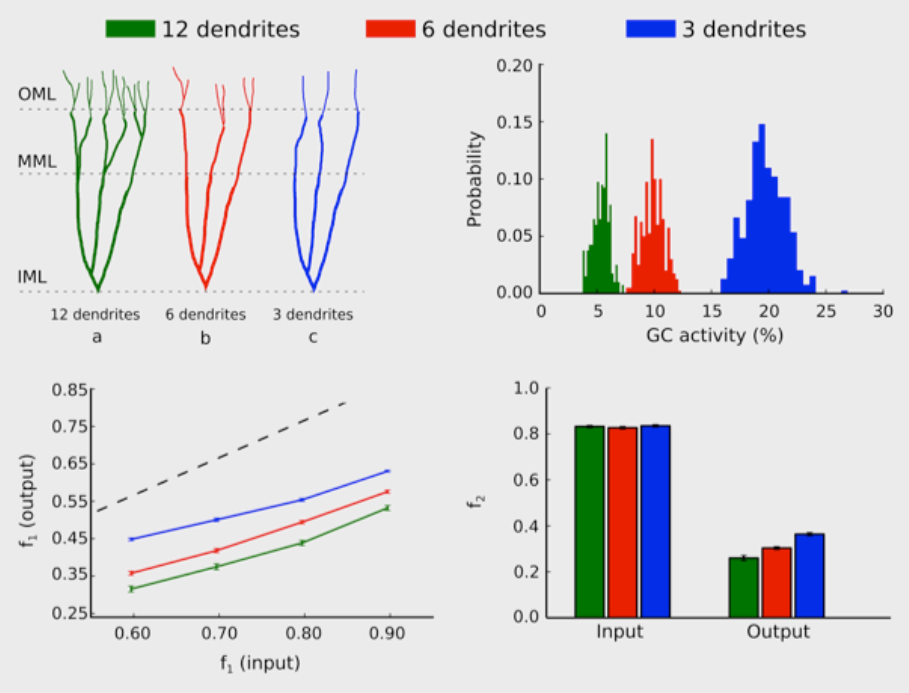
A simplified network model of the DG where Granule Cells are equipped with dendrites

Cell types are validated against experimental data

DG dendrites aid pattern separation

Dendritic ablation

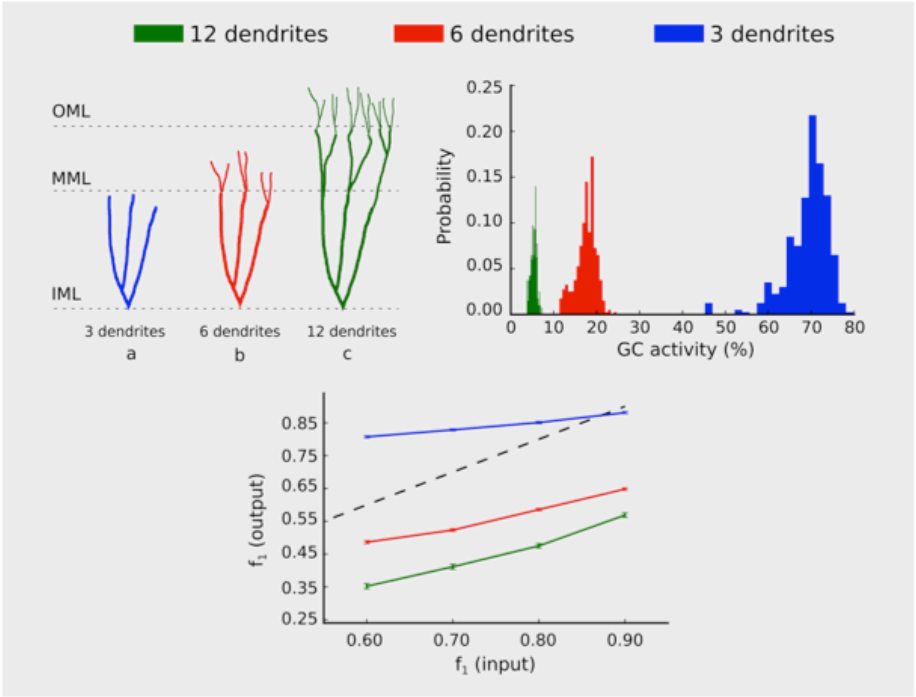
- GC models with 12, 6, 3 dendrites
- Same path length
- Same number of inputs



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



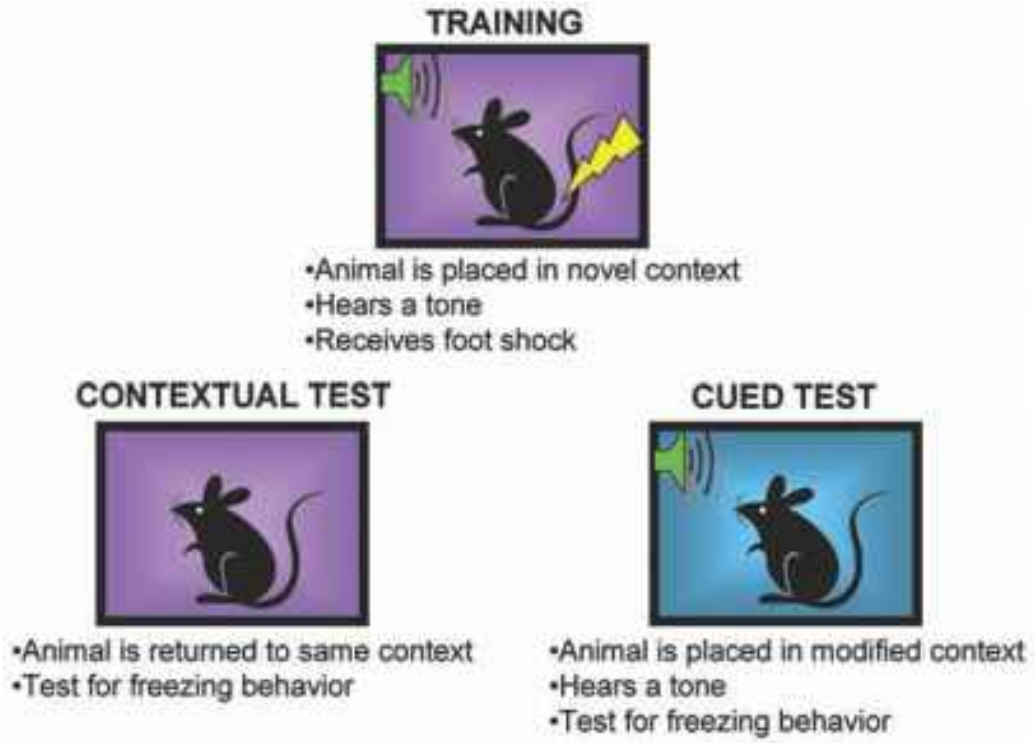
Pattern separation efficiency increases with dendritic growth; More, longer dendrites → better performance.

Chavlis et al, *Hippocampus*, 2016

Learning associative memories

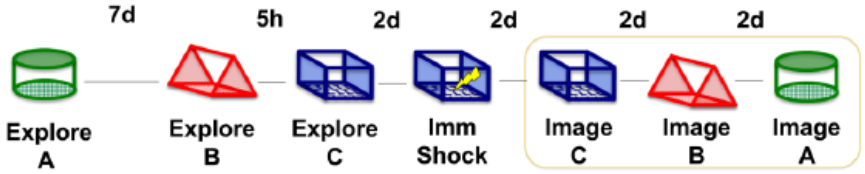
Memory associations for the word “fly”

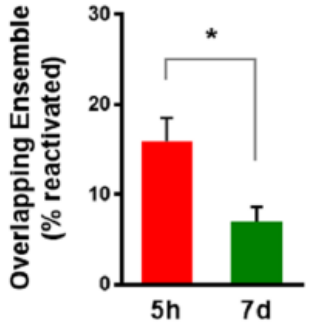
Fear/context memory associations in mice

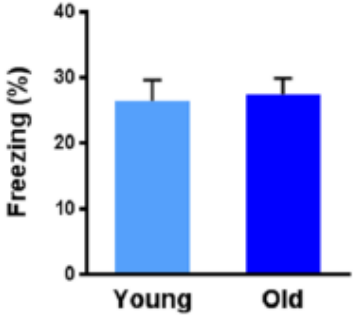


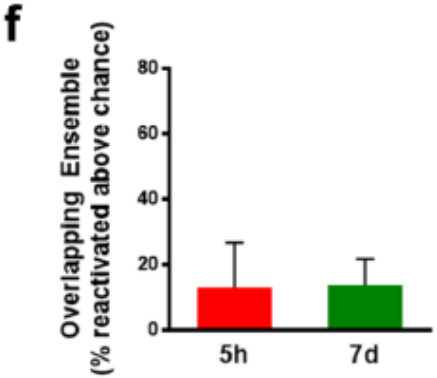
Network level: associating memories via neuronal overlaps

New findings (Cai, et al, Nature, 2016) show that two memories are linked if learned within a few hours, due to **overlapping storage in common** neurons. This ability declines with age.



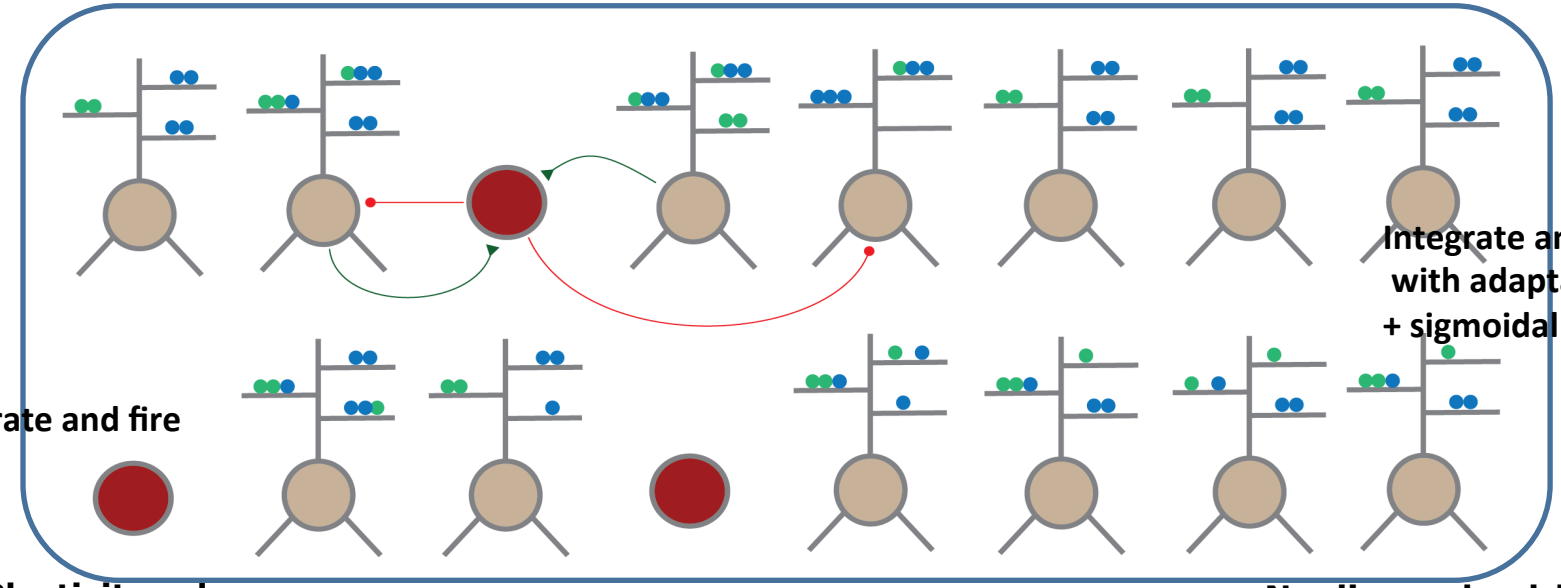






George Kastellakis

Associative memory network model

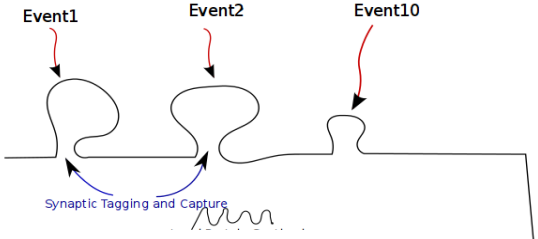


Plasticity rules

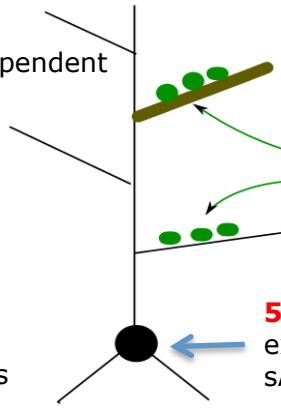
Nonlinear dendrites

1. Synaptic Tagging & Capture (STC)

1.1. Calcium dependent E-LTP/E-LTD



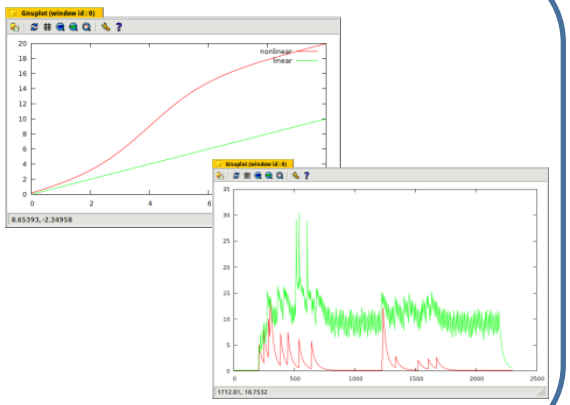
1.2 Local or Global Protein Synthesis (L-LTP/L-LTD)



3. Branch Strength Potentiation/homeostasis

4. Homeostatic Plasticity (additive scaling)

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

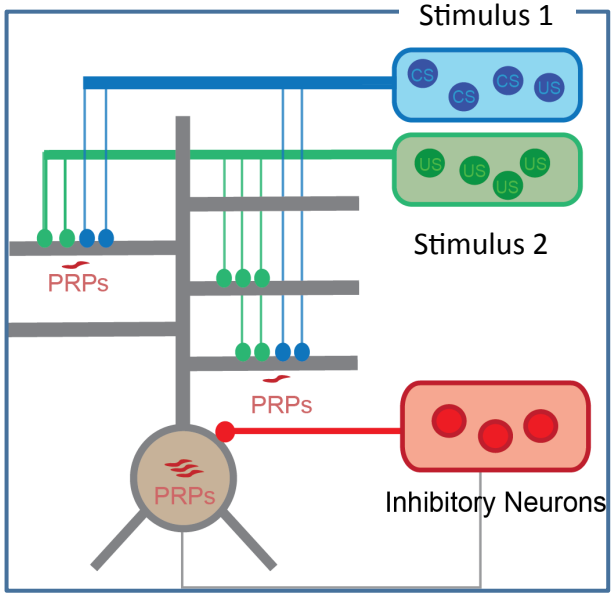


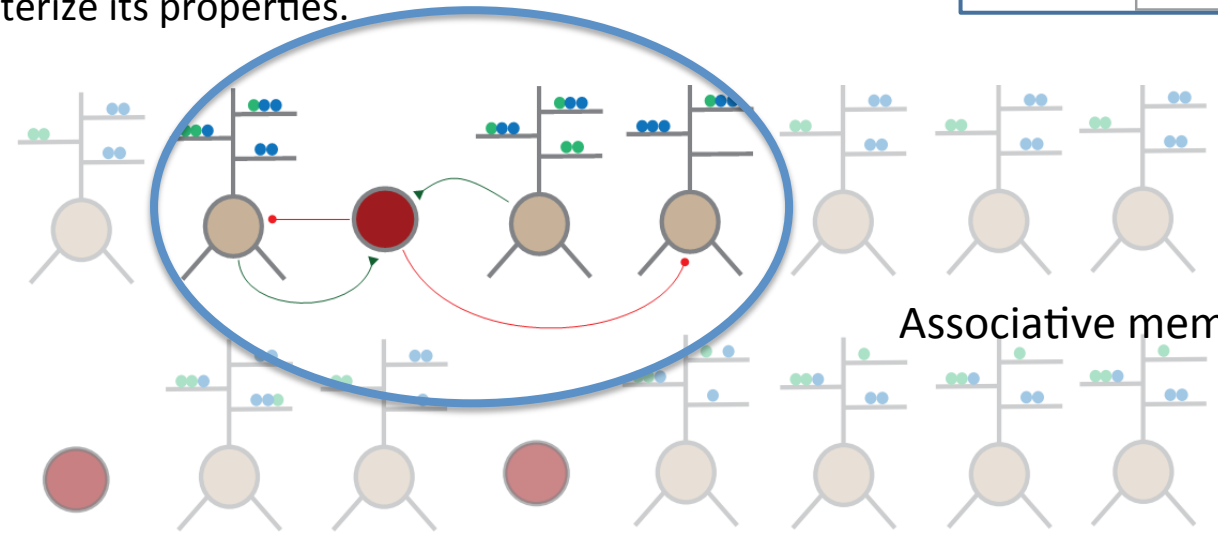
Associative memory encoding in the model

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.

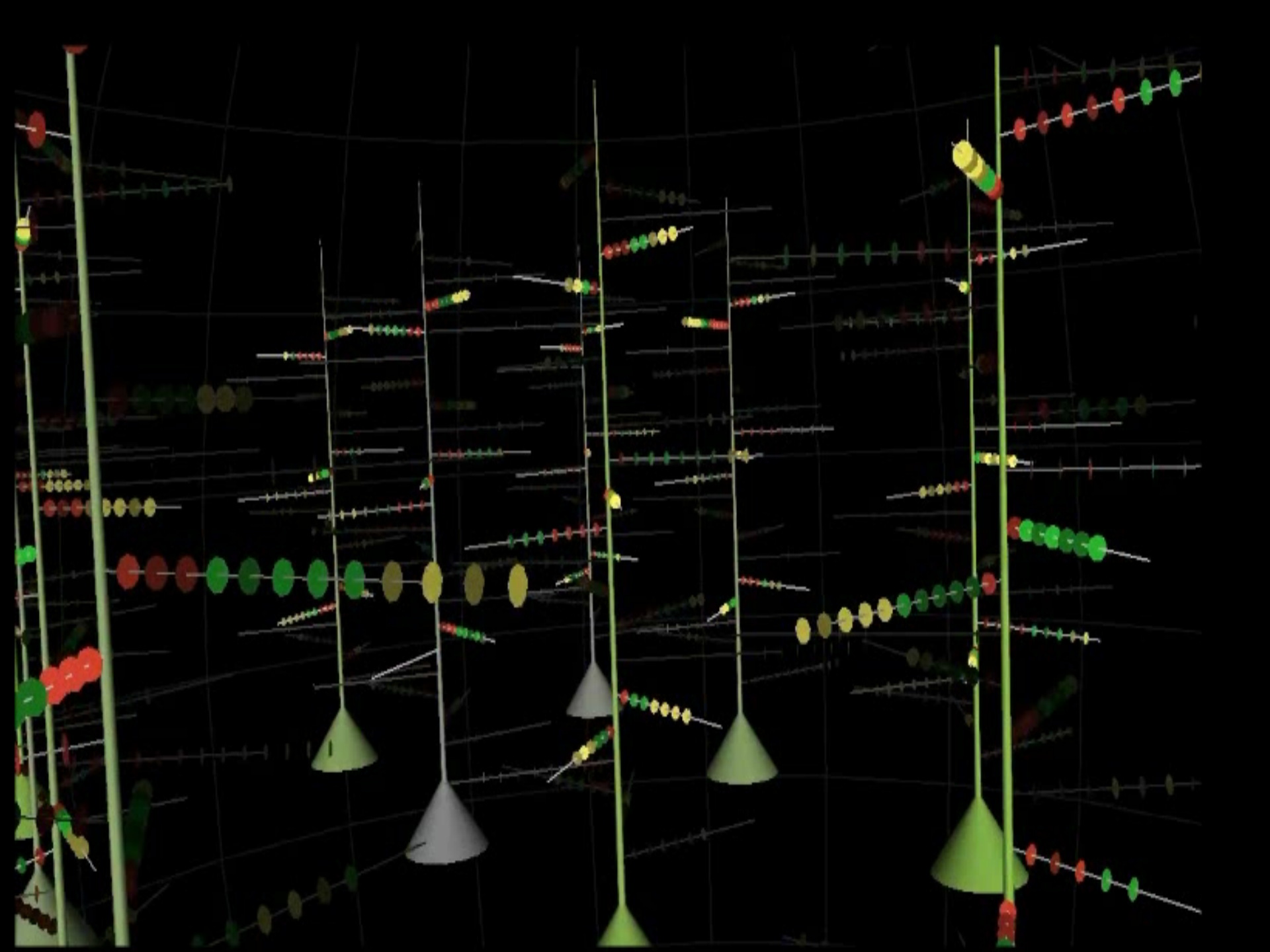
Learning: Each stimulus (1s, 30 Hz Poisson train) is presented repeatedly to the network (for 4s) and plasticity (synaptic LTP/LTD, branch strength potentiation) takes place. Homeostatic mechanisms & plasticity of intrinsic excitability operate after learning.

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.

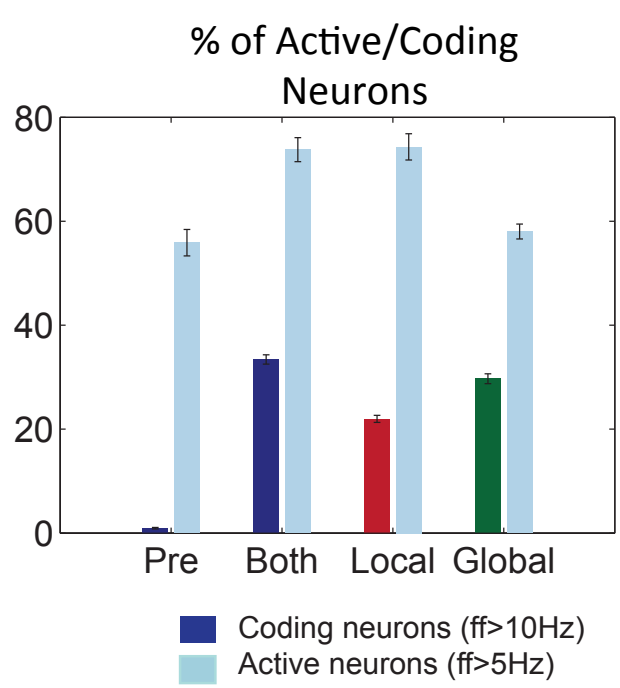


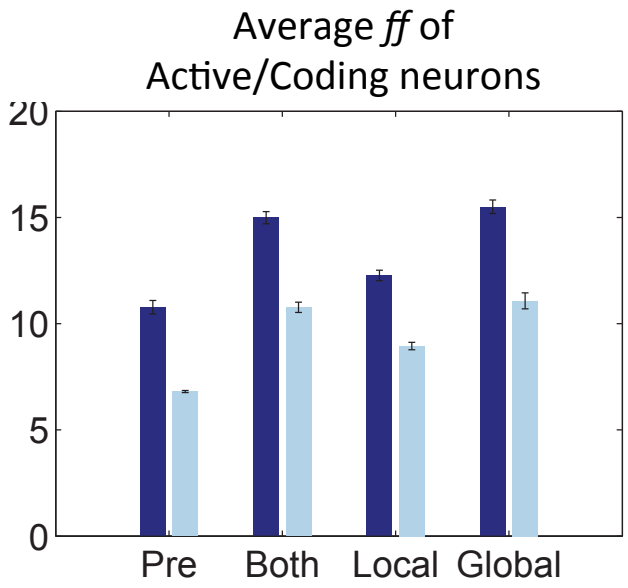


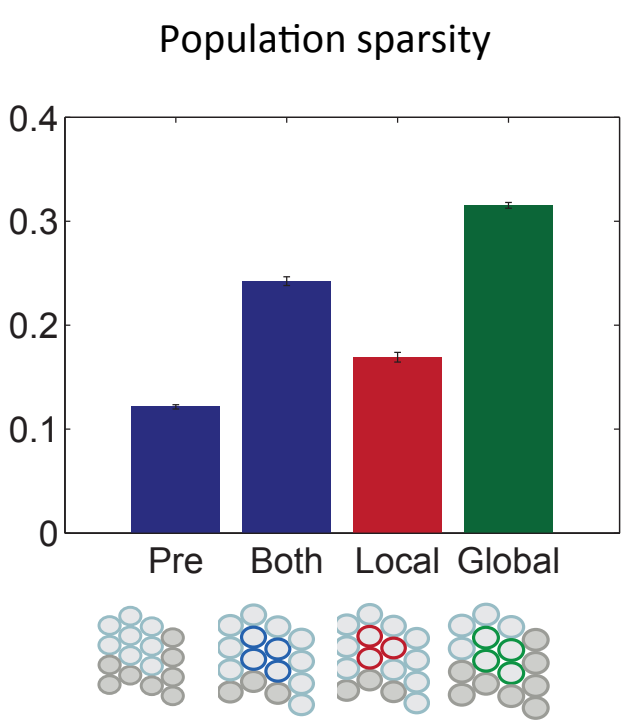
Associative memory M = S1 + S2



Encoding a single associative memory





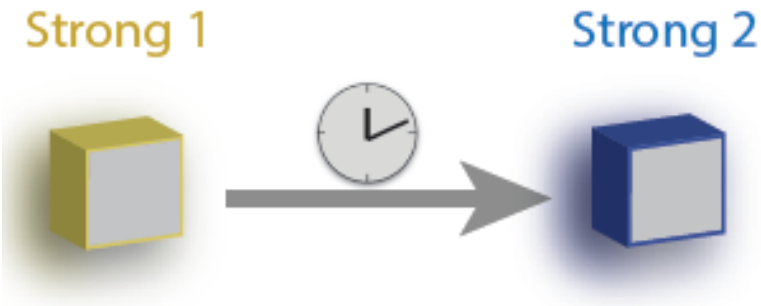


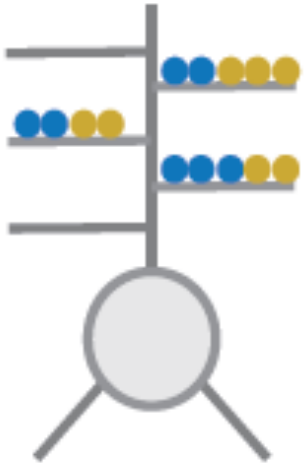
➢Successful encoding of a (S1+S2) pair leads to **20-30% of coding neurons** (*ff* >10Hz upon presentation of either S1 or S2)

➢The average *ff* of these neurons is **10-15 Hz**

➢The network response after learning is **much sparser** than before, especially under Global PRP conditions

Encoding two strong memories





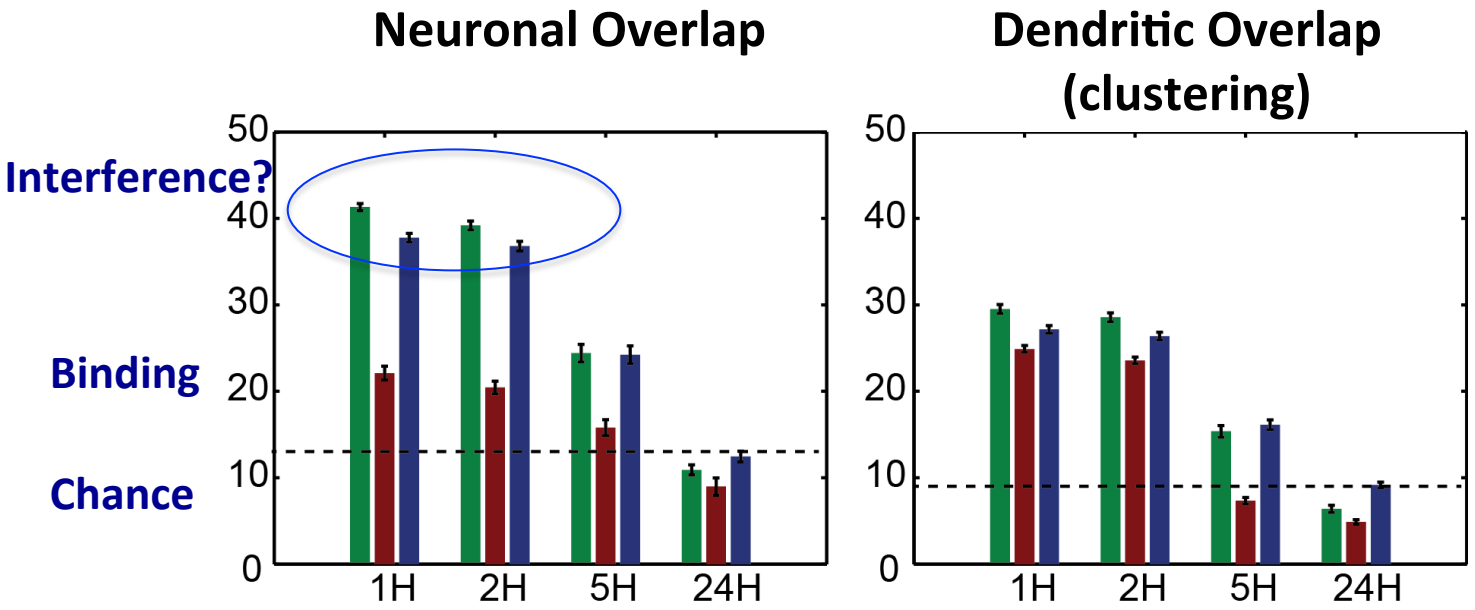
Two memories separated by several hours

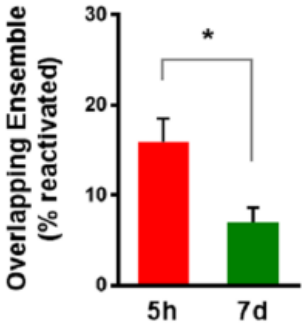
Neuronal Overlap
neurons coding for both memories

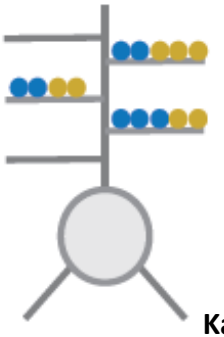
Dendritic Overlap
branches with potentiated synapses from both memories

Strong memory encoding leads to increased neuronal excitability of the encoding neurons. The increase lasts for 12 hours

Encoding two memories

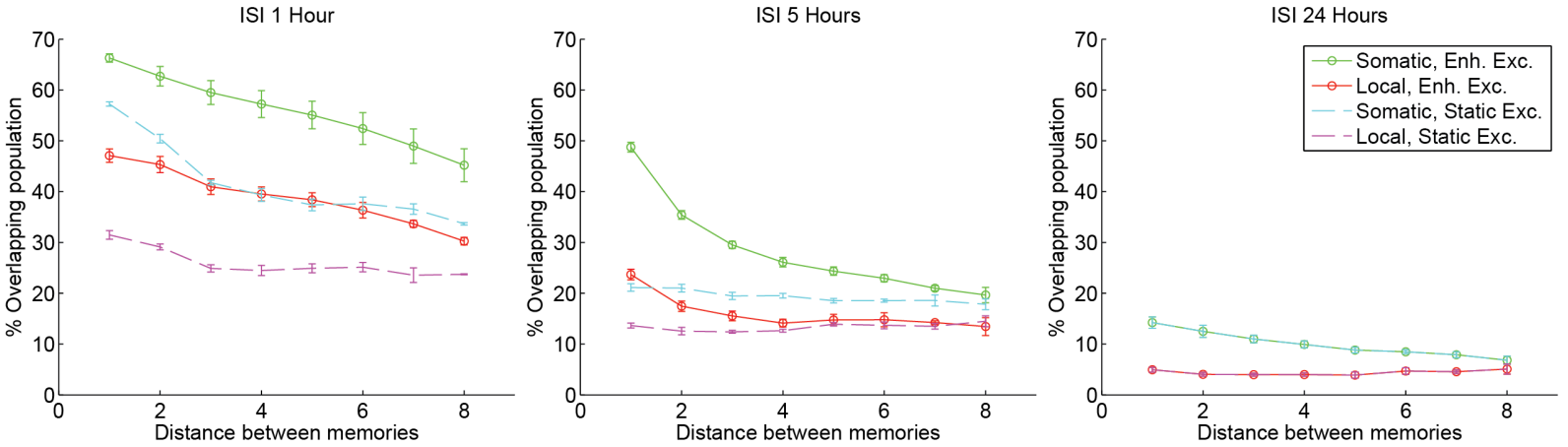




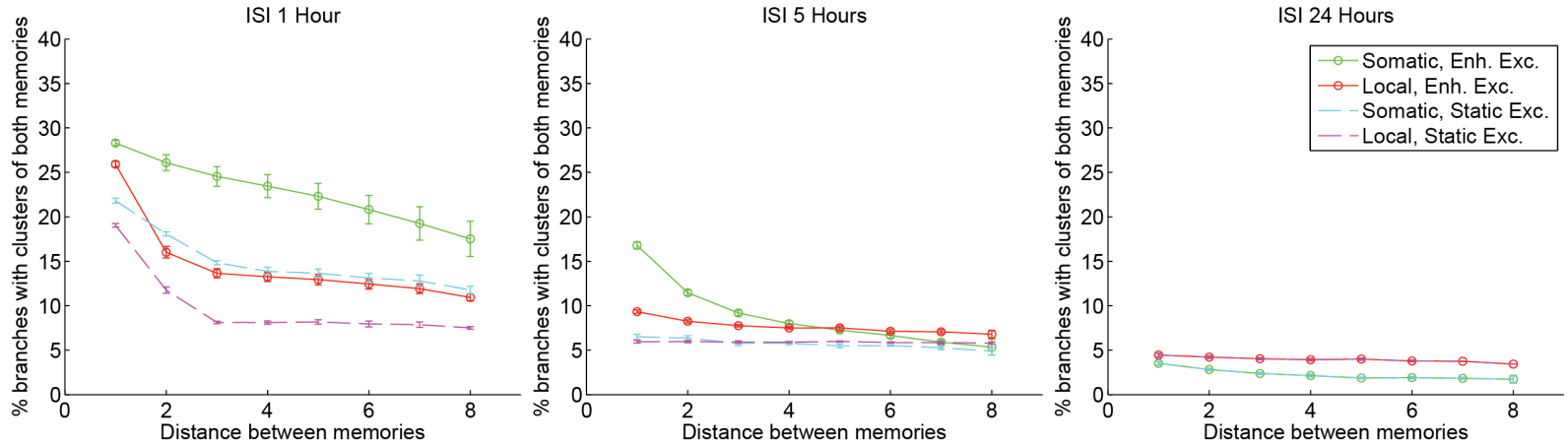


Kastellakis et al, *Cell Reports* 2016

Linking multiple memories across time

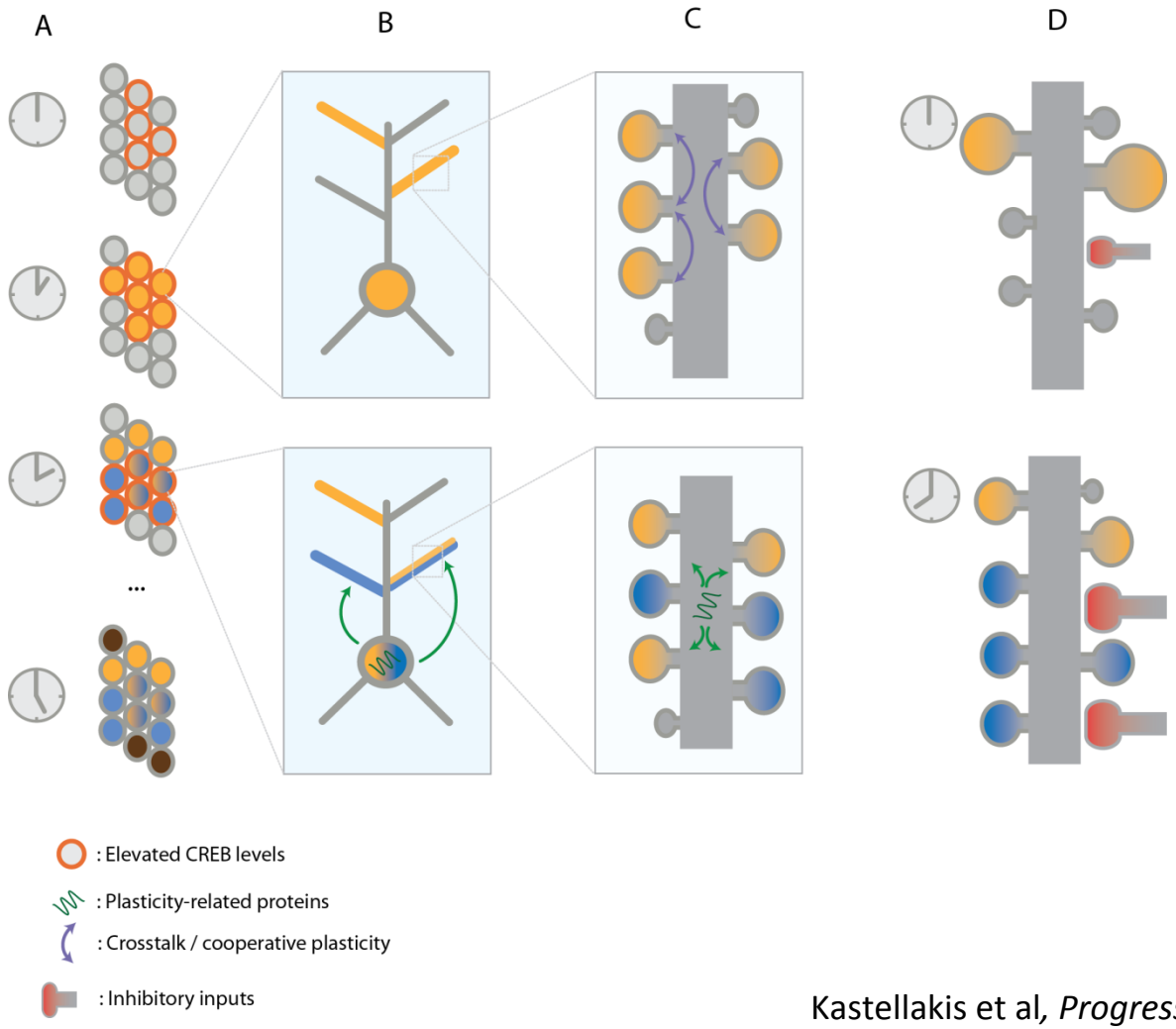


C



Prediction: memories are linked through neuronal and dendritic overlaps. Extend of linking depends on the mode of PRP synthesis/availability.

Linking memories via synapse clustering



Kastellakis et al, *Progress in Neurobiology*, 2015

Branch-Specific Plasticity Enables Self-Organization of Nonlinear Computation in Single Neurons

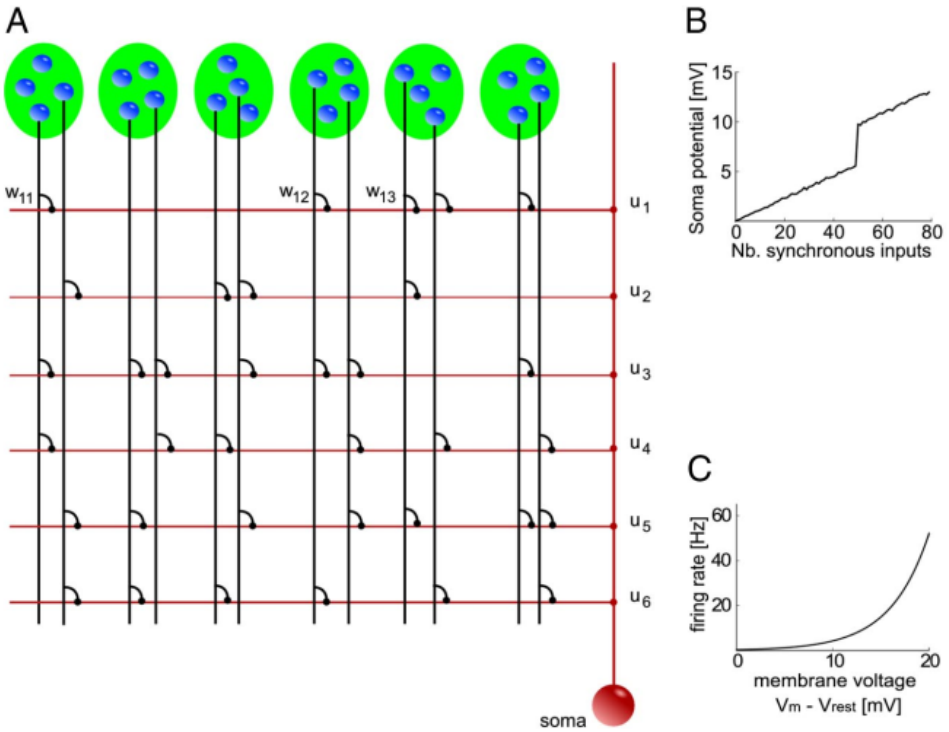
Soma response

$$v(t) = V_{\text{rest}} + \sum_{k=1}^{K} u^{\text{passive}} p_k(t) + u_k a_k(t),$$

$u^{passive}$: Passive component

u_k : coupling strength

a_k: active component (dend. spike)



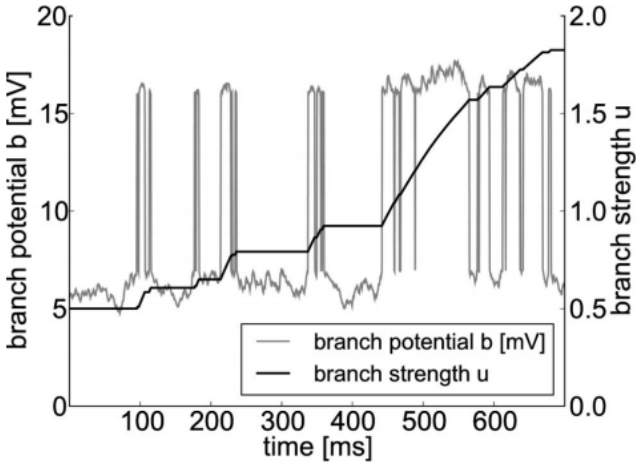
Inputs in nonlinear dendrites with plastic coupling strengths

Legenstein, J.Neurosci 2011

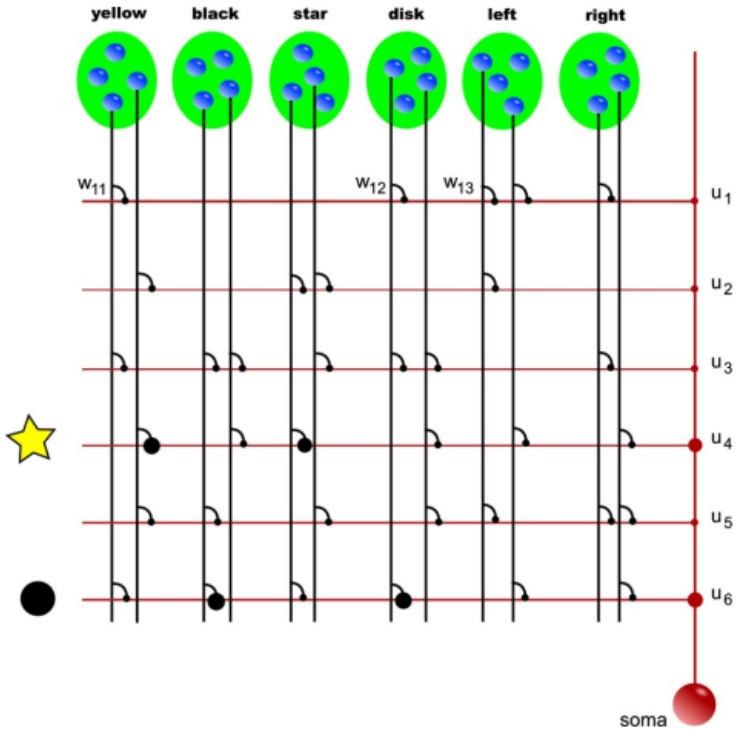
Feature binding in active dendrites

Dendritic spikes increase dendritic-somatic coupling strength

This is coupled with an STDP rule that is dependent on the depolarization of the dendritic branch



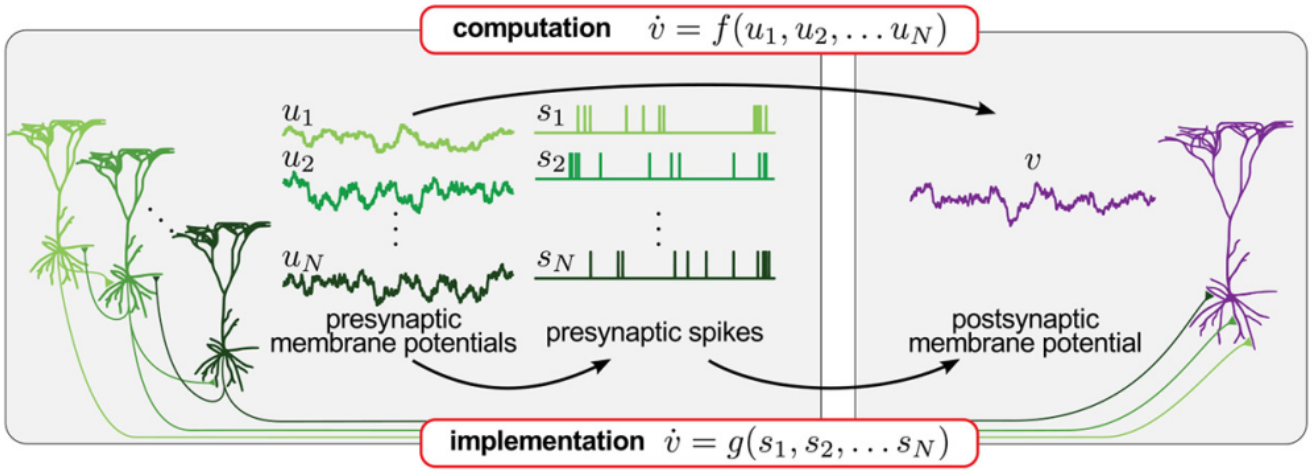
Together these allow each dendrite to discriminate a specific combination of input characteristics (binding), for example ‘yellow star’ and ‘black circle’



Legenstein, J.Neurosci 2011

Dendritic nonlinearities are tuned for efficient spike-based computations

Neurons optimize the transformation of presynaptic potentials to postsynaptic *u* via *f*



However this function is implemented in neuronal harware through presynaptic spikes via *g*

The authors sought to identify the properties that dendrites must have so that the computation is optimal i.e. f(u1,u2…) ≈ g(s1,s2…)

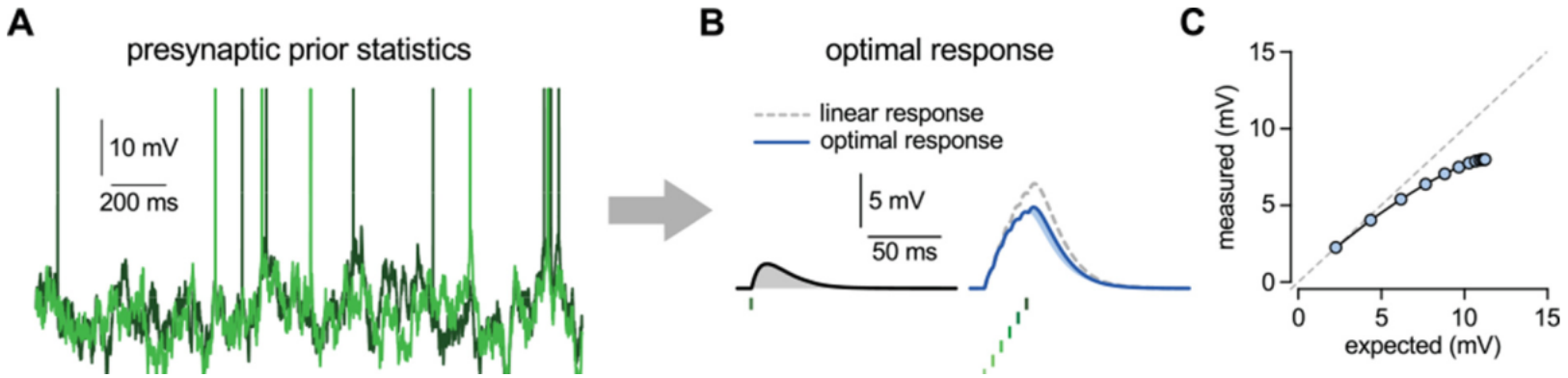
Assuming a simple nonlinear dendritic response model

$$v_{\text{den}}(t) = v_{\min} + (v_{\max} - v_{\min}) \frac{1}{1 + e^{-v_{\text{lin}}(t)}}$$

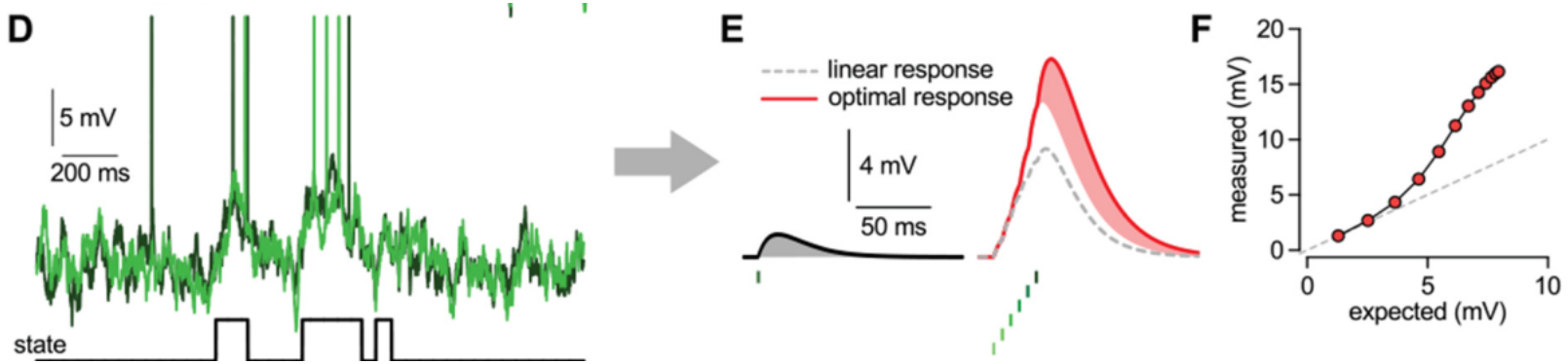
$$\dot{v}_{\text{lin}} = -\mathscr{A} v_{\text{lin}} + \mathscr{B} \mathrm{s}(t) - \mathscr{C}$$

Ujfalussy, eLife 2015

- The authors use their model to predict the optimal response of dendrites to realistic inputs from other neurons.
  - When inputs are uncorrelated, the optimal response is linear (averaging)



  - When inputs are correlated, the optimal response is nonlinear.



Ujfalussy, eLife 2015

Summary

- Prediction: dendrites of various cells integrate inputs as semi-independent sigmoidal units. Verified
- Prediction: sigmoidal dendritic integration increases storage capacity
- Prediction: The dendrites of DG cells contribute to pattern separation by enhancing sparsity. Pending
- Prediction: memories are linked through neuronal and dendritic overlaps. Verified Extend of linking depends on the mode of PRP synthesis/availability. Pending
- Prediction: sigmoidal dendrites become tuned to recognize associated information. Pending
- Prediction: active dendrites are tuned to implement spike-based computations. Explains data

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Thank you

for your attention!