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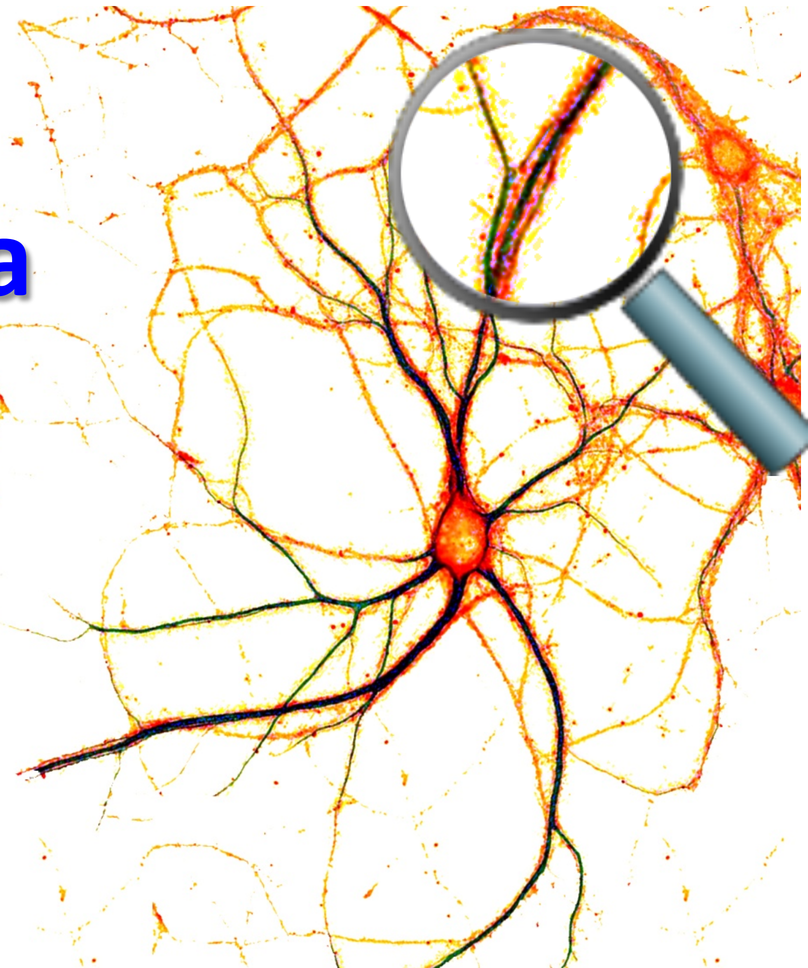
www.dendrites.gr

Dendrites: a bug or a feature?

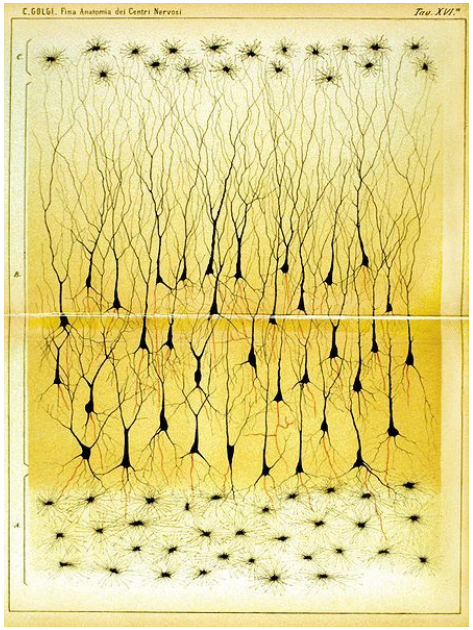


Overview

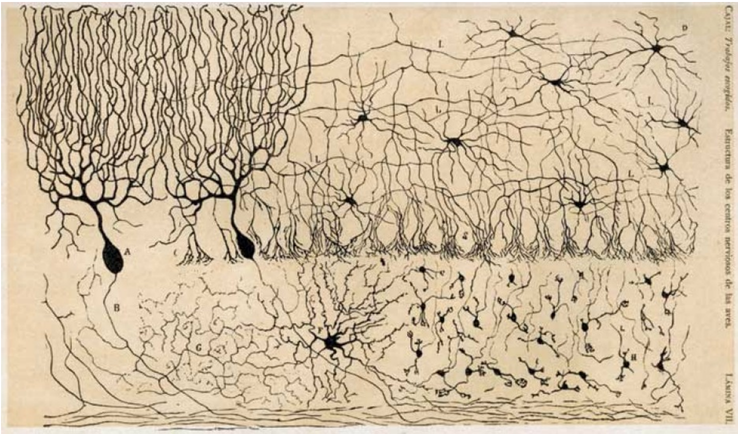
- Dendritic morphology
- Passive dendritic properties
- Signal integration in passive dendrites
- Active dendritic properties
- Functional implications of active dendrites
- Dendritic plasticity
- Dendrites as fundamental functional units

Dendrites

- From the Greek ‘Dendron’ =Tree
- First detailed description by Golgi (1873) with silver staining. He called them ‘protoplasmic prolongations’ and believed they served a nutrient role
- Cajal (1888) introduced the neuron doctrine:
  - *Neurons are units in which dendrites serve as the input site, and the axon as the output to other neurons*



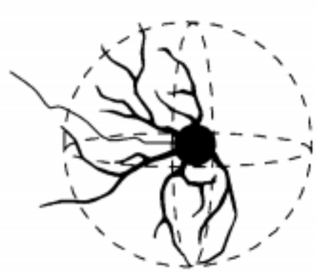
Golgi 1873



Cajal 1905

Dendritic Morphology

- Cells can be characterized by the number of dendrites, their extent, their radiation pattern etc
- Enormous variation in dendritic shapes makes them difficult to classify
- Can be unipolar or bipolar based on the orientation of processes
- (partial) Spherical radiation is a common pattern in non-laminated nuclei (e.g. thalamus)

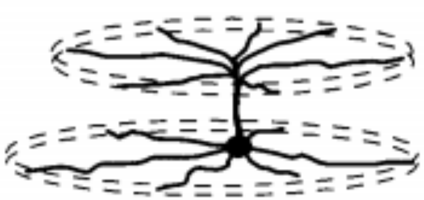
Pattern	Characteristics	Examples
Adendritic 	Cell body lacks dendrites	Dorsal root ganglion cells Sympathetic ganglion cells
Spindle radiation 	Two dendrites emerge from opposite poles of the cell body and have few branches	Lugaro cells Bipolar cells of cortex
Spherical radiation Stellate 	Dendrites radiate in all directions from cell body	Spinal neurons Neurons of subcortical nuclei (e.g. inferior olive, pons, thalamus, striatum) Cerebellar granule cells
Partial 	Dendrites radiate from cell body in directions restricted to a part of a sphere	Neurons at edges of 'closed' nuclei (e.g. Clarke's column, inferior olive, vestibular nuclei)

Dendrites, Stuart 2007

Lamination

- In laminated areas, laminar radiation allows specific input sources to target specific dendritic domains

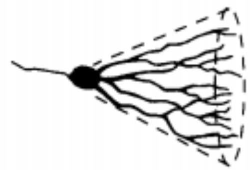
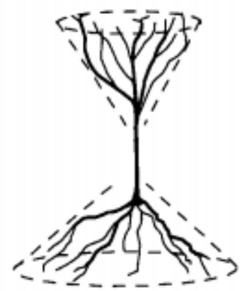
Laminar radiation

Planar		Dendrites radiate from cell body in all directions within a thin domain	Retinal horizontal cells
Offset		Plane of radial dendrites offset from cell body by one or more stems	Retinal ganglion cells
Multi		Cell has multiple layers of radial dendrites	Retinal amacrine cells

Dendrites, Stuart 2007

- Cylindrical radiation allow passing perpendicular axons to provide a broad distribution of inputs to the cell in globus pallidus.

- In biconical cells, the apical and basal domains are frequently targeted by different afferents e.g. CA1.

Pattern	Characteristics	Examples
Cylindrical radiation 	Dendrites ramify from a central soma or dendrite in a thick cylindrical (disk-shaped) domain	Pallidal neurons Reticular neurons
Conical radiation 	Dendrites radiate from cell body or apical stem within a cone or paraboloid	Granule cells of dentate gyrus and olfactory bulb Primary dendrites of mitral cells of olfactory bulb Semilunar cells of piriform cortex
Biconical radiation 	Dendrites radiate in opposite directions from the cell body	Bitufted, double bouquet, and pyramidal cells of cerebral cortex Vertical cells of superior colliculus
Fan radiation 	One or a few dendrites radiate from cell body in a flat fan shape	Cerebellar Purkinje cells

Dendrites, Stuart 2007

Signal Integration – classical view

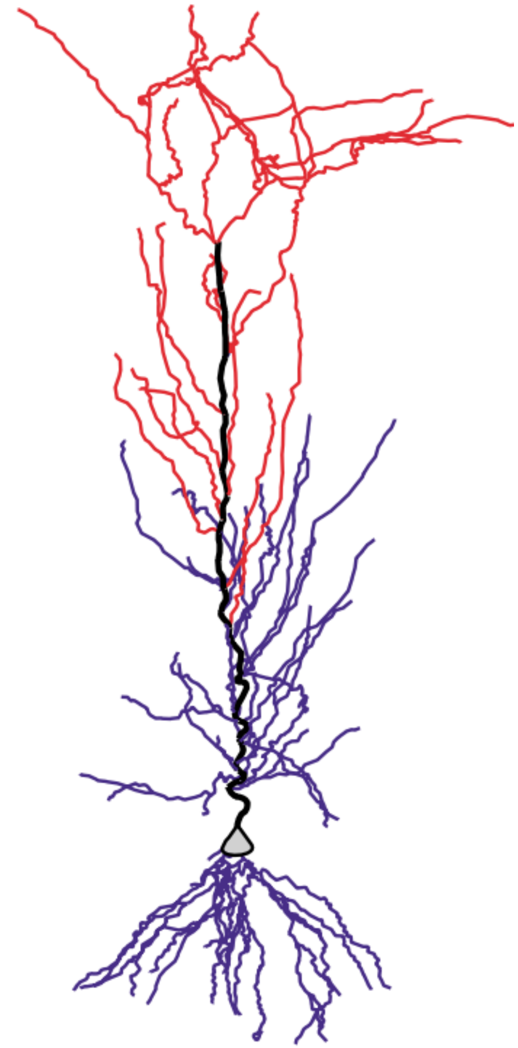
- Synaptic inputs generate PSPs in postsynaptic dendrites

- Dendritic signals are integrated in the axon to generate Action Potentials (APs)

- The Action Potential is the final output of neurons

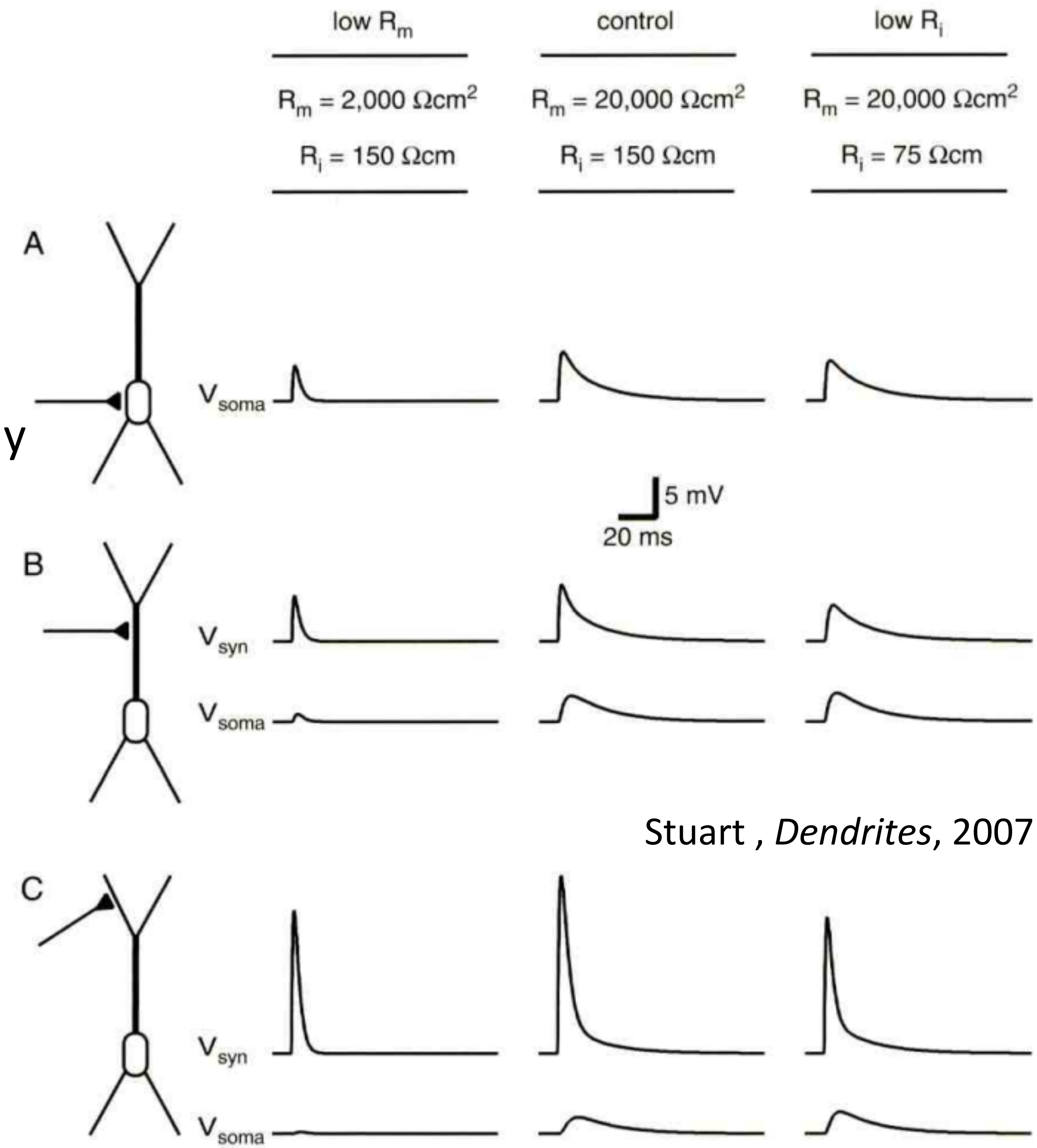
Passive properties of dendrites

- Single PSPs are usually not sufficient to initiate an AP
- Ability to influence the soma depends on PSP amplitude and degree of attenuation
- Passive properties:
  - Rm: membrane resistance
  - Cm: membrane capacitance
  - Ri: axial resistance



Passive properties and signal attenuation

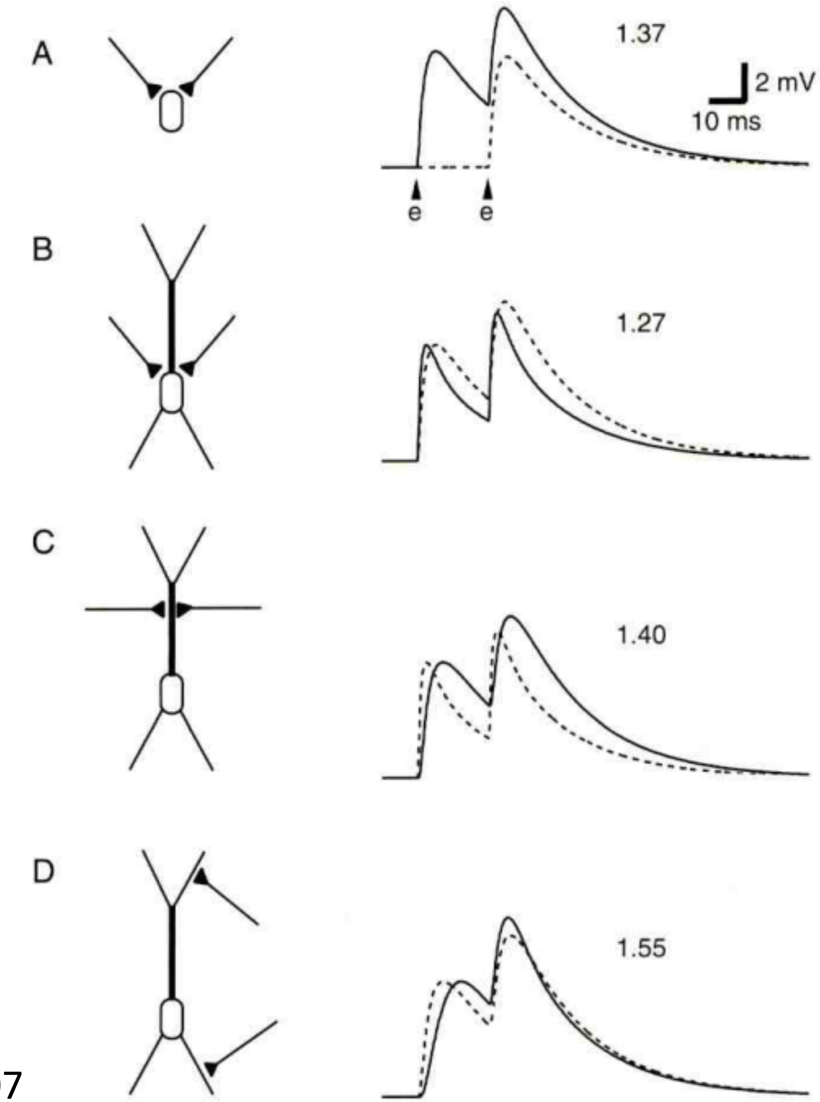
- Low Rm -> increased attenuation.
- Low Ri -> decreased attenuation.
- Attenuation is more pronounced for synapses away from the soma.
- Integration is affected by the position of synapses in dendrites.
- Depolarization by a synapse activation causes a slight reduction in the driving force for the synaptic current of nearby synapses.



Stuart , *Dendrites*, 2007

Passive dendrites influence EPSP summation

- Integration of two synaptic inputs to a somatic compartment only (A)
- Dendrites accelerate the decay of somatic EPSP (B)
- Moving synapses from soma to dendrites slows down EPSPs (C)
- Separating synapses to different dendrites maximizes summation



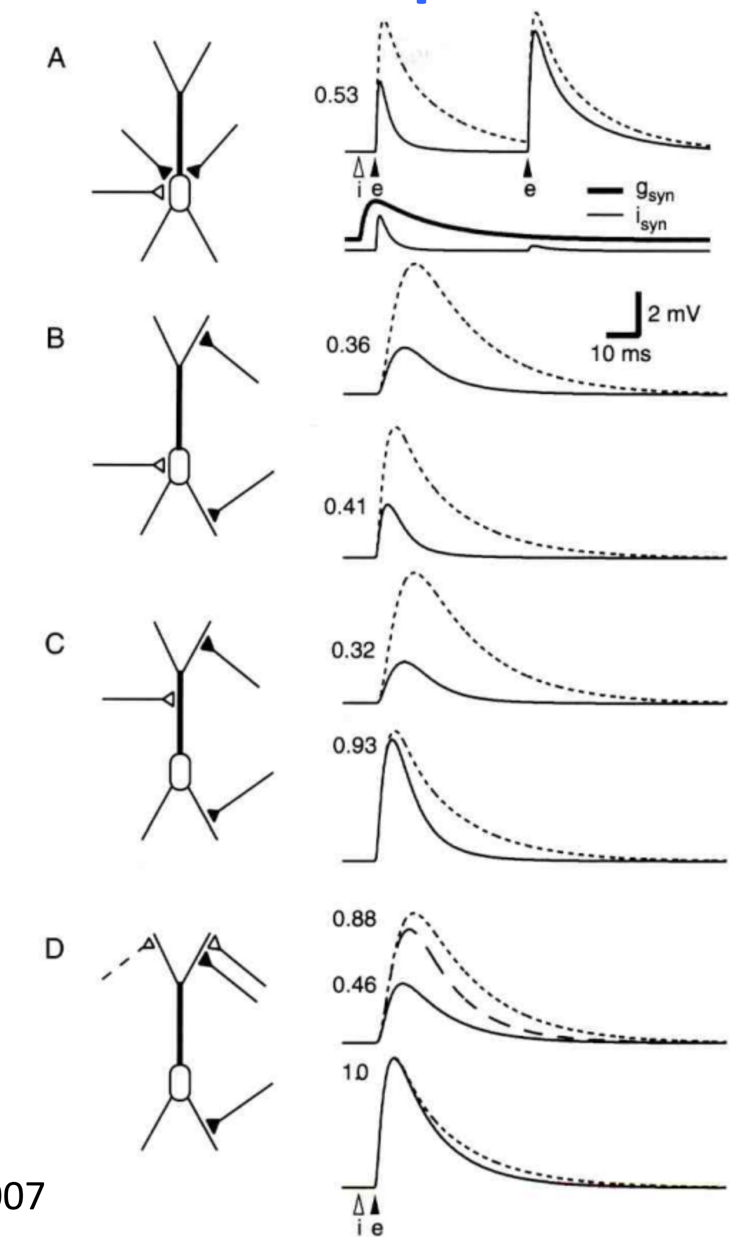
Stuart , *Dendrites*, 2007

Excitation-inhibition interaction

- Inhibition limits the way excitatory synaptic inputs summate
  – Counters the depolarizing effects of excitation
  – Critically determines spike timing
  – Can synchronize spiking in population of neurons
  – Limits the time window for temporal summation
  – Feed-forward inhibition can limit the duration of excitatory inputs
  – Feedback inhibition can limit the duration of spiking

Excitation-inhibition example

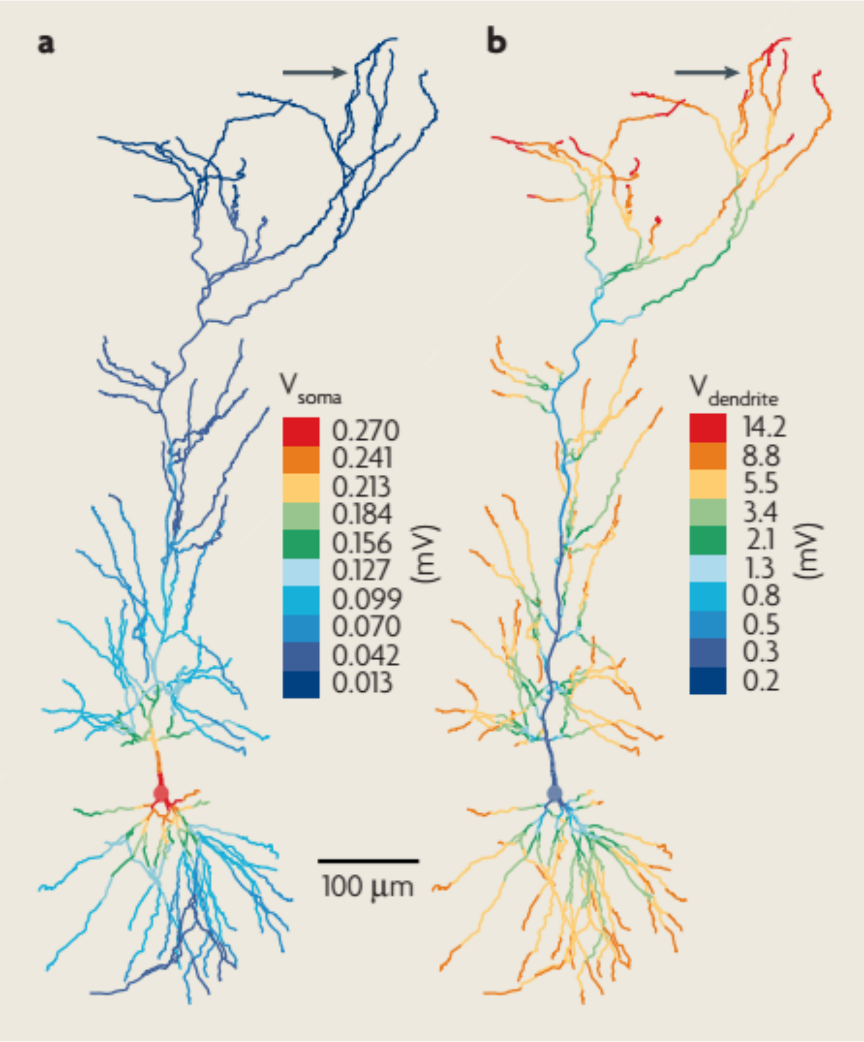
- Inhibition counters somatic excitation (A)
- Reduces dendritic signals differently for each dendrite (B)
- Gating of individual dendritic inputs (C, D)



Stuart , *Dendrites*, 2007

Dendritic signal attenuation

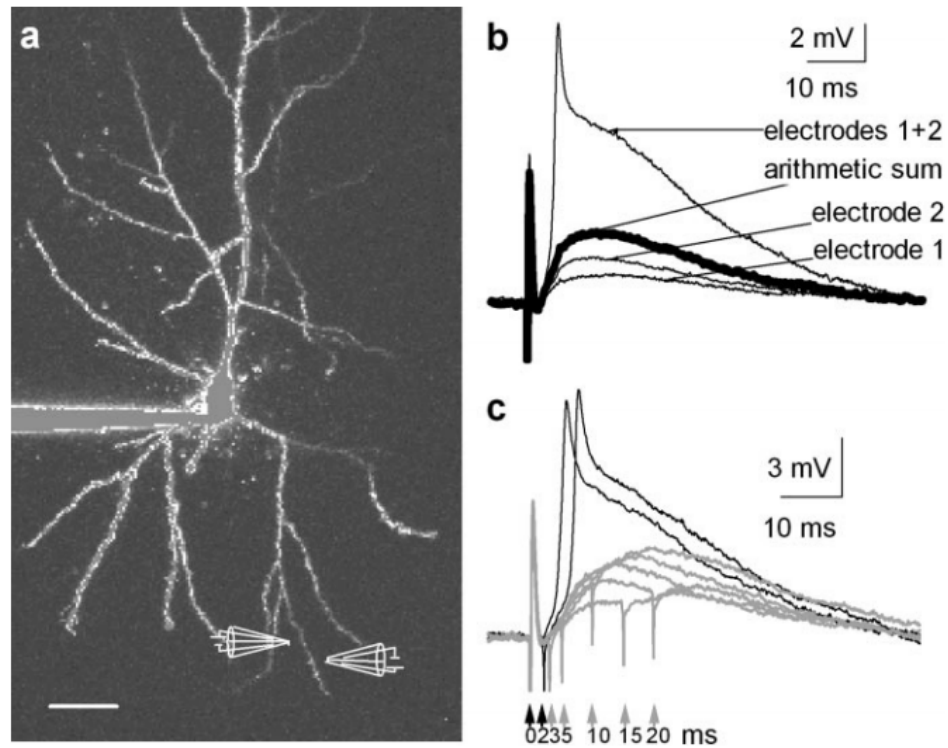
- Synapses located further from soma may attenuate 100-fold before they are able to affect the somatic output of the cell
- Faster EPSPs are attenuated more than slower EPSPs
- However:
  - Small-diameter dendrites increase input impendance and thus increase EPSP amplitude locally
  - Synapses compensate for dendritic distance by scaling up their synaptic conductance.



Spruston, *Nat.Rev.Neuro.*, 2008

Active properties of dendrites

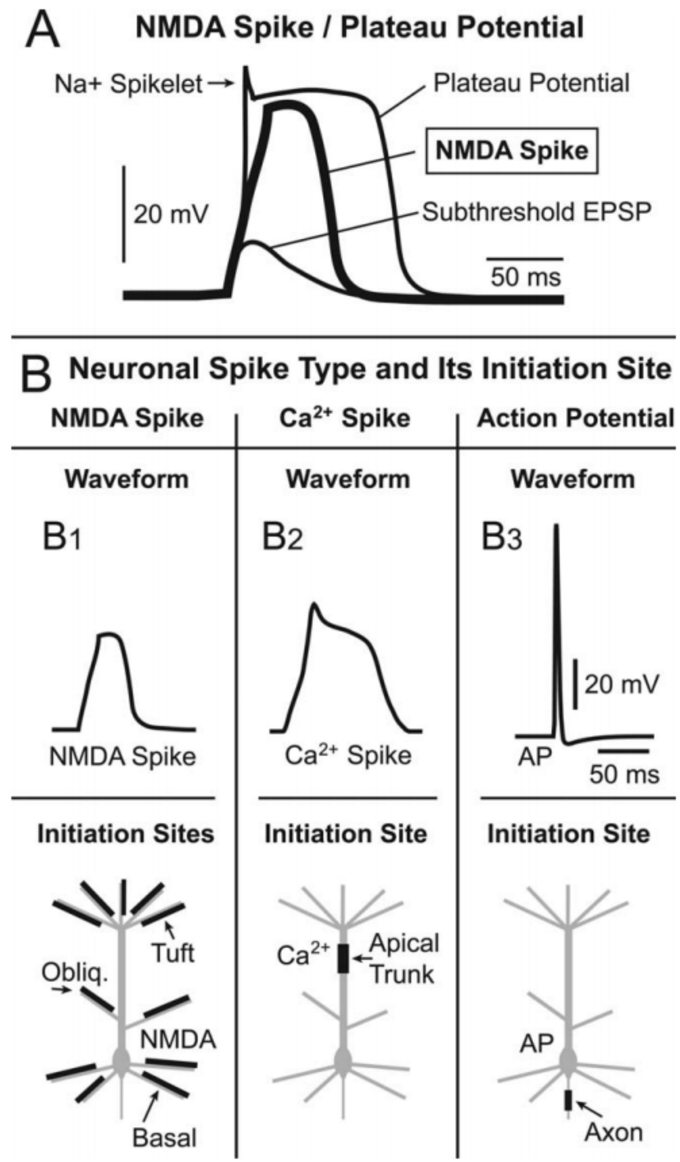
- Dendrites contain a variety of voltage-gated ion channels and support localized regenerative events (dendritic spikes)
- Evidence for dendritic spike generation is provided from dendritic patch-recordings
- In L5 cortical & hippocampal pyramidal neurons dendritic spikes are promoted by strong synaptic excitation
- Contributions from Na^{+} and Ca^{2+} channels
- Dendritic spikes uncoupled from somatic APs have been observed in Purkinje cells & hippocampal interneurons



Ariav 2003

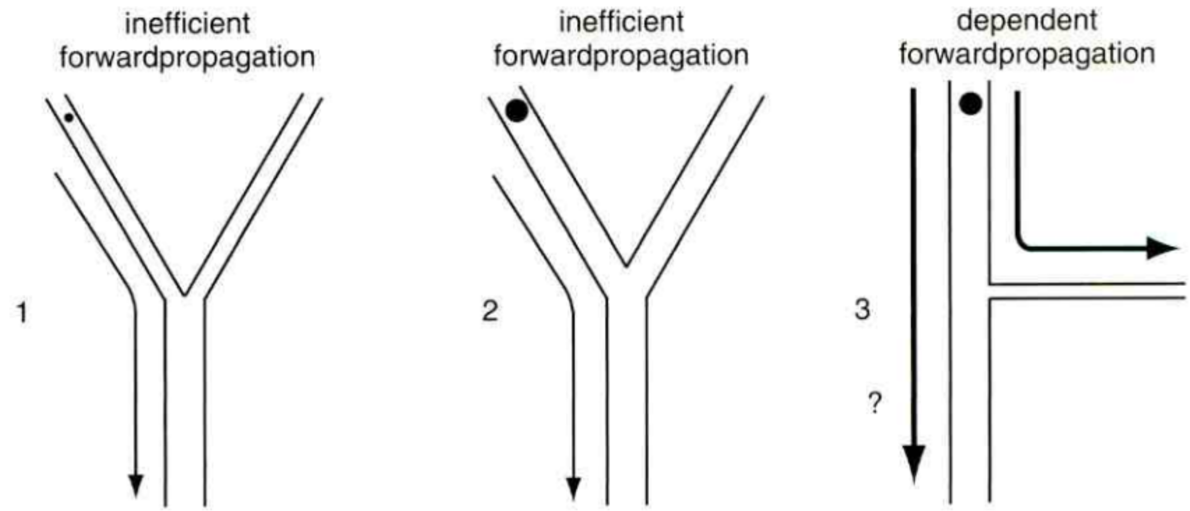
Dendritic NMDA spikes

- Local regenerative membrane potential spikes
- Contributed from NMDA receptors
- When relieved from Mg block, and bound to glutamate, the I-V relationship of NMDAr current has similar form to the sodium channel, thus able to fire a regenerative spike
- Each neurite (basal, oblique, tuft etc) supports a characteristic spike
- NMDA spikes characterized by plateau potential of 50-100msec



Ariav 2003

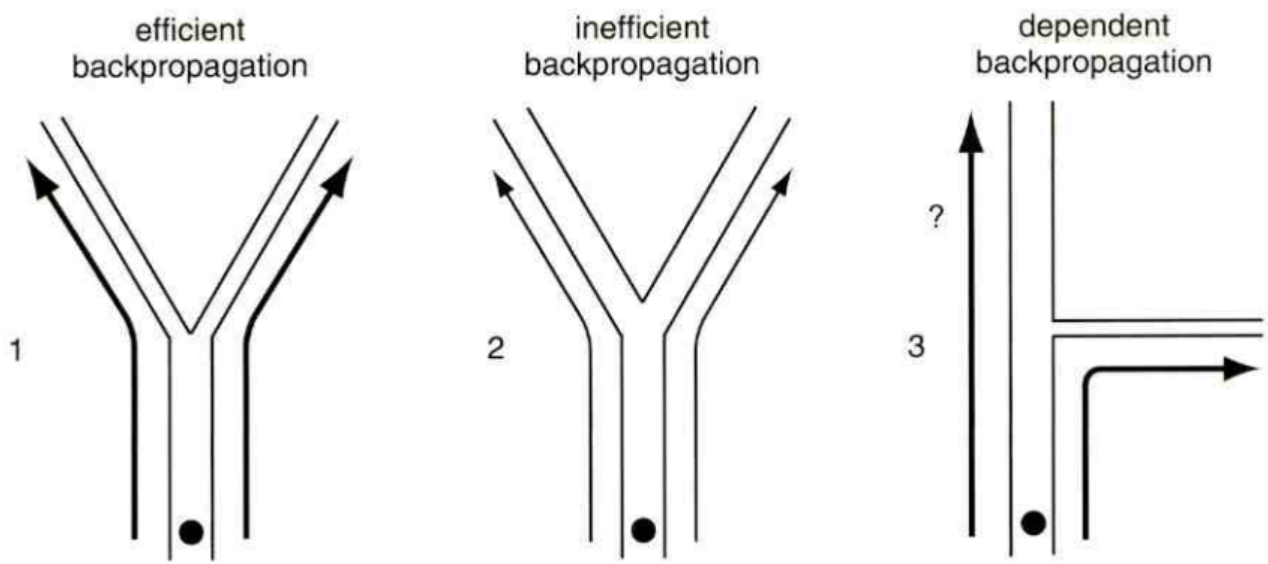
Dendritic spike propagation



- In pyramidal neurons, dendritic spikes propagate unreliably to the soma
- Propagation depends on dendritic geometry, channel density, inhibition, previous activity and neuromodulation
- Spike propagation in branch points depends on the diameter ratio of parent/ daughter dendrite (1,2): Spikes attenuate as they pass to larger branches
- Propagation is influenced by the excitability of obliques: short obliques provide return current to promote propagation (3)
- Backpropagating action potential may limit the propagation of dspikes
- Non-uniform K-channel distribution and inhibition also affect the propagation of dspikes to the soma

Stuart , *Dendrites*, 2007

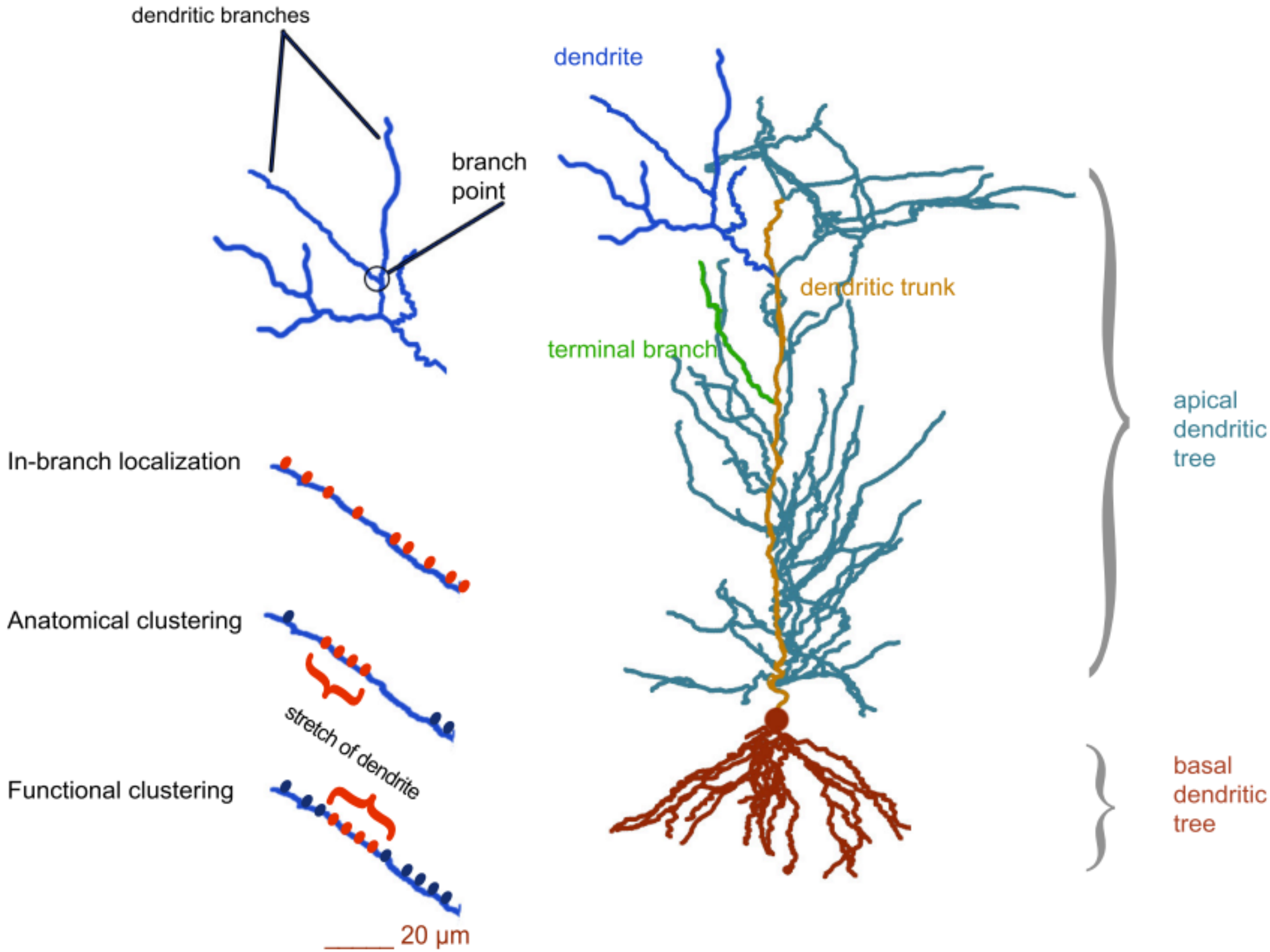
Back-propagating(BPAP) action potentials



- Dendritic geometry also affects back-propagation of APs into the dendrites
- Back-propagation is more efficient when the daughter dendrites are smaller-diameter
- Propagation past oblique branches depends on the geometry of the oblique branch (3)

Stuart , *Dendrites*, 2007

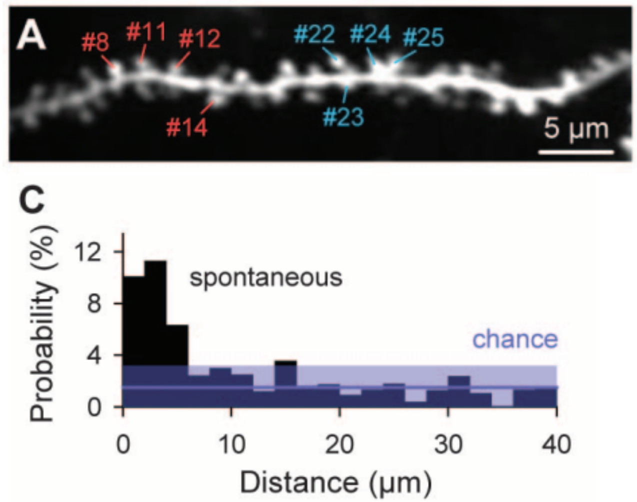
Clustering of synaptic inputs



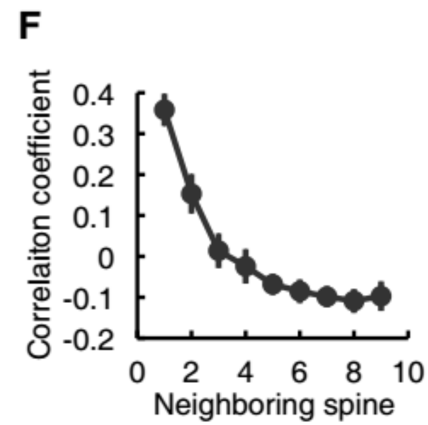
Kastellakis et al, Progress in Neurobiology, 2015

Evidence for synapse clustering

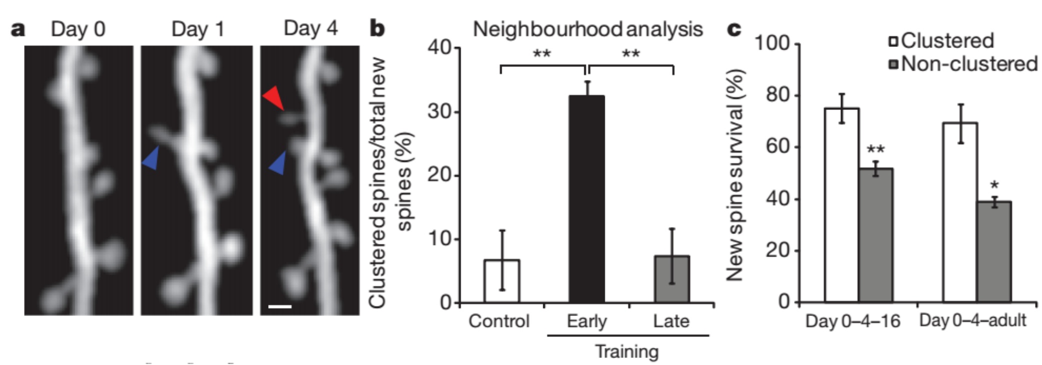
- Synapses are co-activated in vivo in barrel cortex (Takahashi 2012)
- AMPA enrichment is correlated in nearby spines (Makino 2011)
- Repeated motor learning induces increase in clustered synapses (Fu, 2012)



Takahashi, 2012



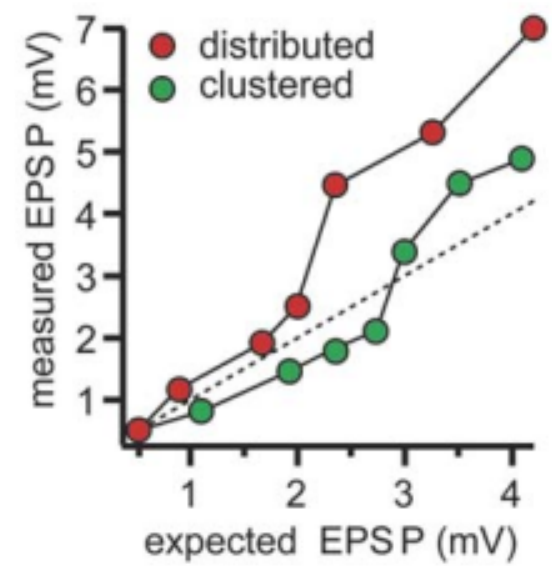
Makino, 2011

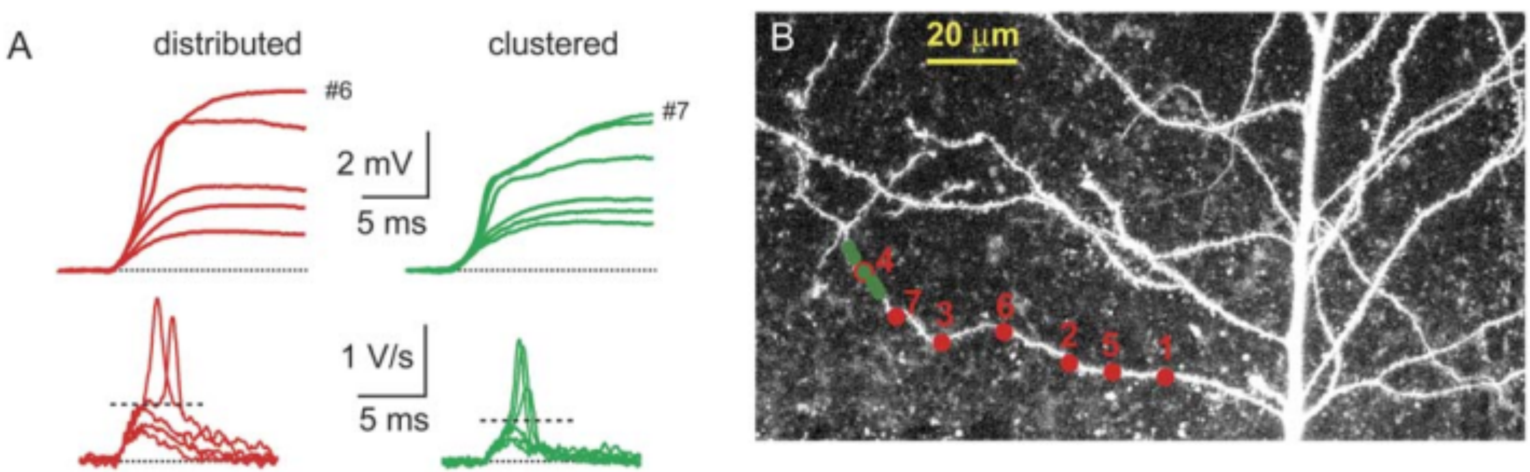


Fu, 2012

Clustering of synapses promotes dendritic nonlinear responses

- Clustering of synapses within a branch, as well as temporal synchrony of synaptic inputs lead to dendritic spike generation which elicits a nonlinear response in the EPSP at the soma.
- This suggests that dendrites can act as nonlinear computational units

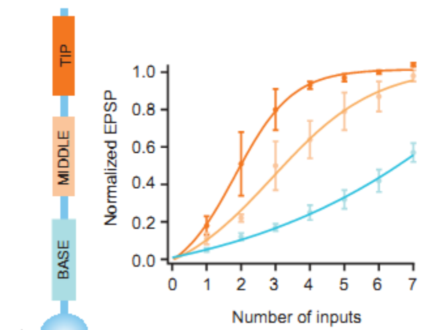




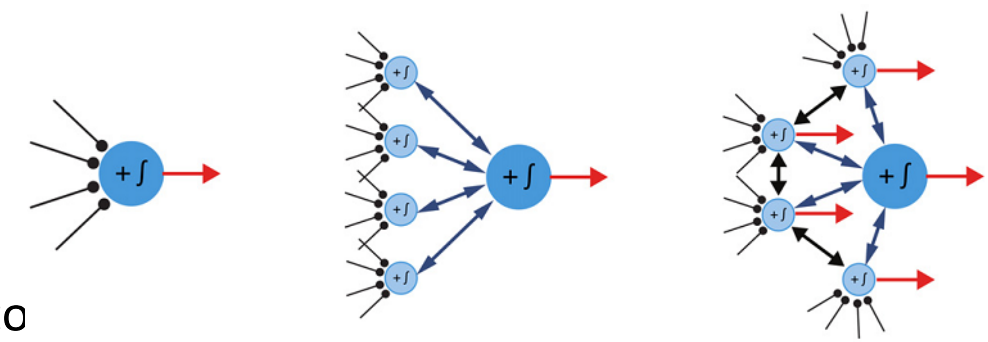
Losonczy Neuron 2006

Active dendrites and functional implications

- Active dendrites can summate incoming signals nonlinearly, thus enabling the implementation of complex functions such as sequence detection (Branco and Hausser, 2011), information binding (Legenstein et al, 2011), associative learning (Kastellakis et al, 2016), sharpening or orientation tuning (Wilson et al, 2016) etc

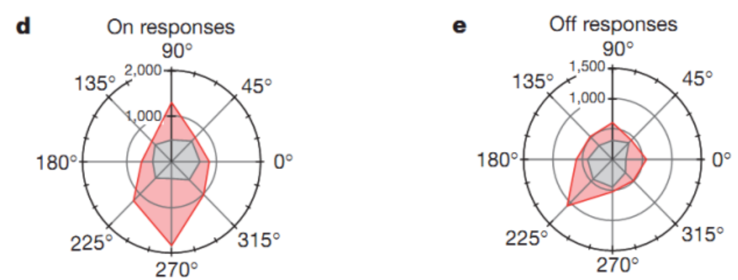


Branco, Neuron 2010



Current Opinion in Neurobiology

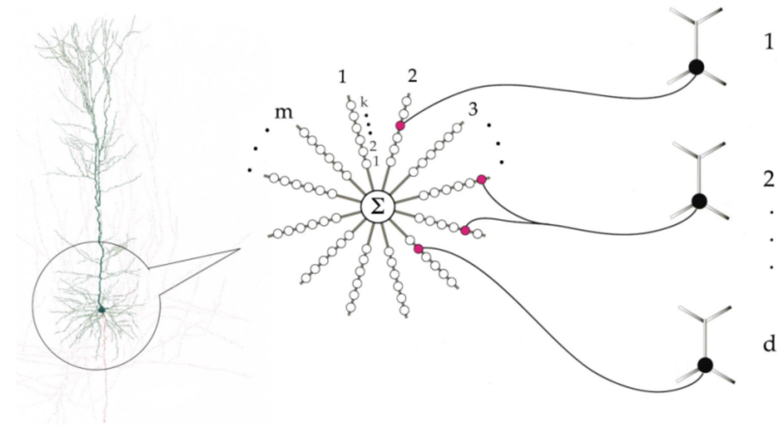
- Synapse clustering allows neurons to compartmentalize function and plasticity
  - Functional tuning of barrel cortex neurons
  - Enriched environments increase compartmentalization

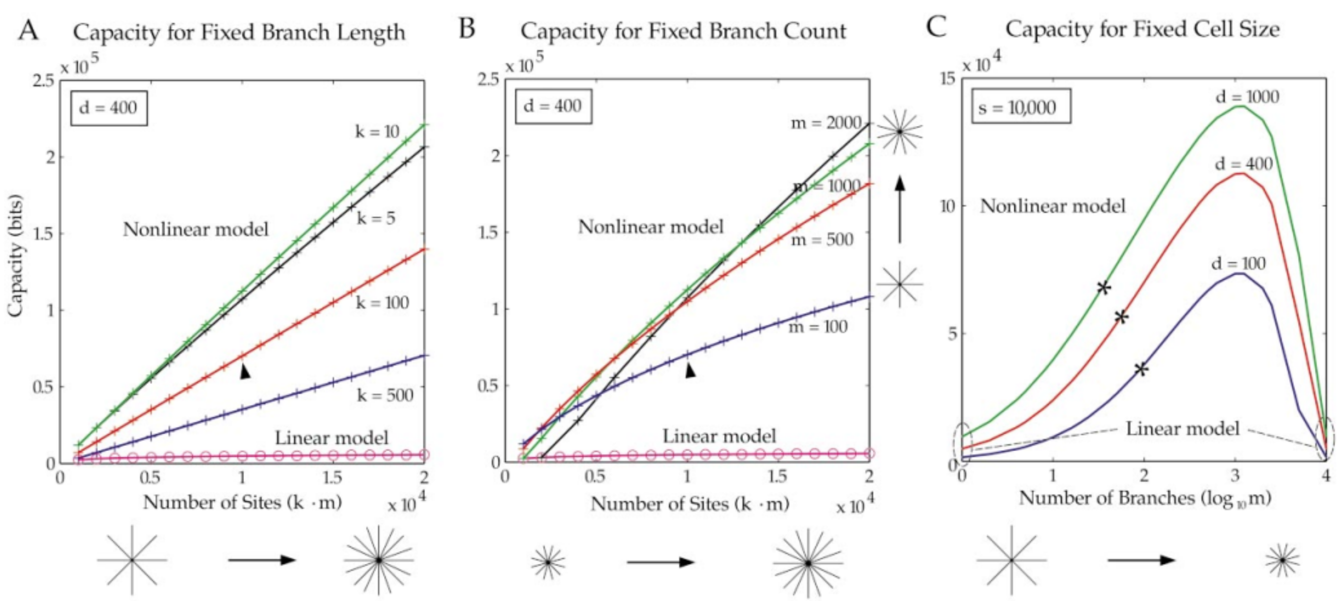


Lavzin, Nature 2012

Dendritic nonlinearities increase storage capacity

- Computational studies show that the capacity of neurons is greatly increased by nonlinear dendritic units
- The increase in capacity is linked to the grouping of afferent inputs to specific dendritic branches, i.e. synapse clustering of functionally related synapses increases memory capacity

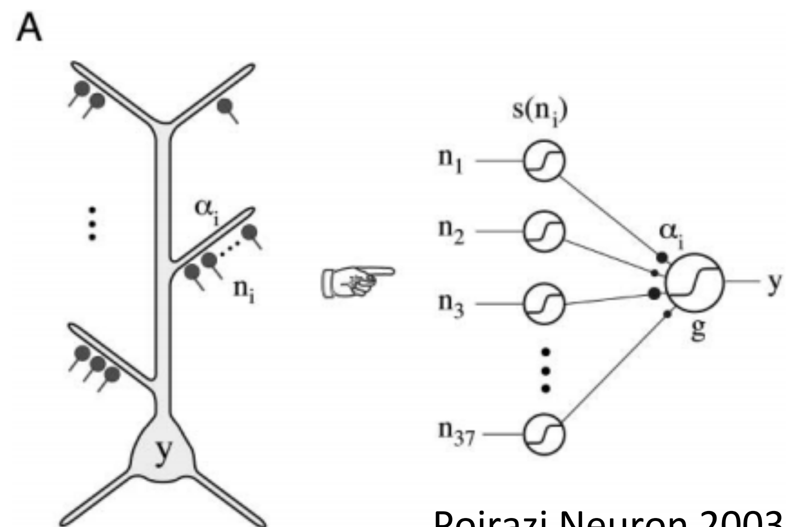




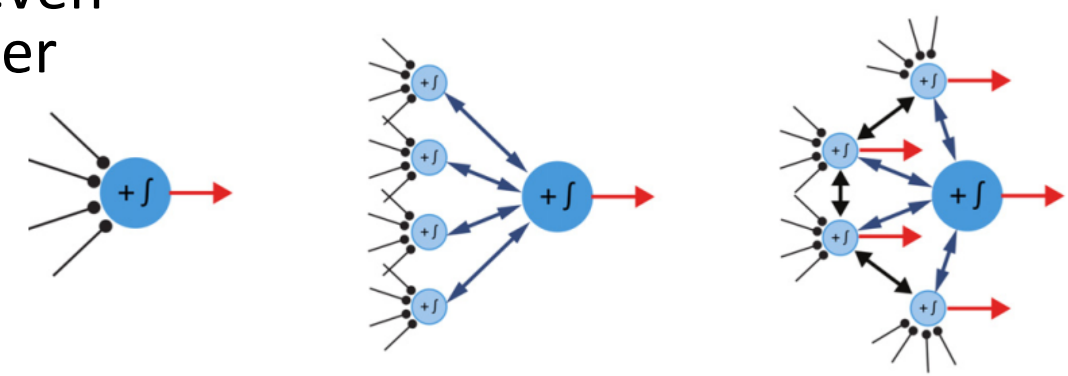
Poirazi Neuron 2001

Dendrites provide additional layers of computation

- Modeling shows that the firing rate of CA1 neuron can be well approximated by a 2-layer neural network
- Bidirectional communication between dendrites, as well as local release of neurotransmitters by dendrites has been suggested to lead to an even more elaborate multi-layer abstraction



Poirazi Neuron 2003



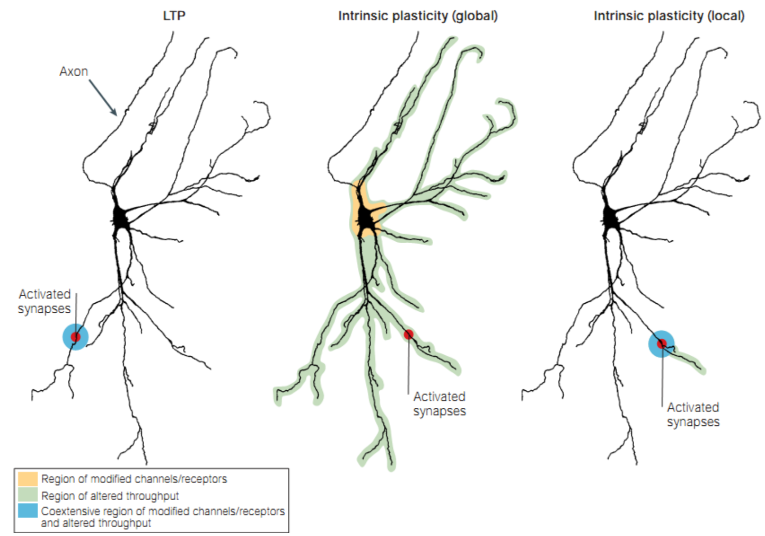
Branco Cur Opin. Neurobiol. 2003

Dendritic Plasticity

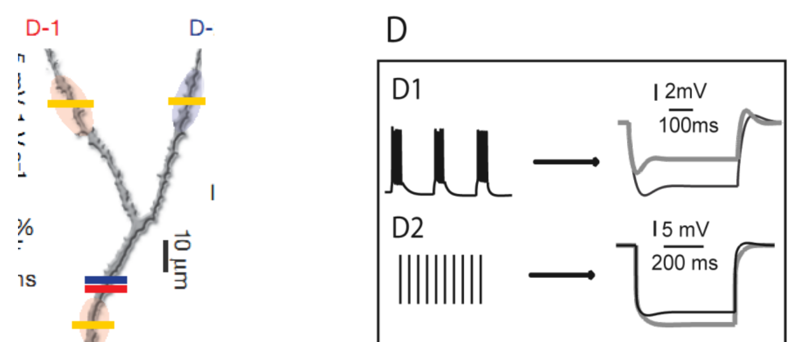
- Dendrites are the primary sites of Hebbian plasticity
- Dendrites contain machinery for the production and confinement of PRPs
- Dendritic spines are able to display rapid activity-related plasticity
- Cooperativity allows the formation of synaptic clusters
- Plasticity is NMDA dependent
- Dendritic spikes alone can trigger plasticity even without somatic depolarization

Intrinsic Plasticity

- Regulation of dendritic excitability affects neuronal output
- Dendritic spike generation
  - Prior activity can temporarily inhibit dspikes
- Ion channel plasticity may be local
  - Enriched environment
  - Stimulation
- A-type regulation after LTP
- Regulation can be local – Branch Strength Potentiation



Zhang, NN 2003



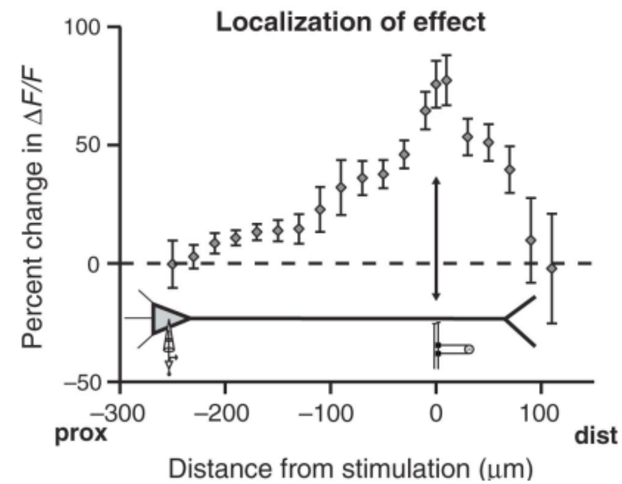
Papoutsi et.al., 2012

Examples - Intrinsic Plasticity

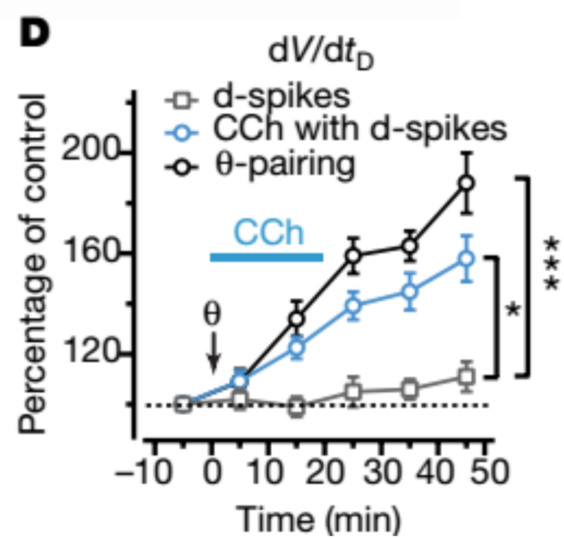
- Stimulation and LTP in a dendritic region can alter the excitability of the branch -> dendritic excitability can be plastic (Frick 2004)

- The coupling between dendritic spikes and the soma is plastic (Branch strength potentiation, Losonczy 2008)

- Changes are mediated via regulation of A-type K channels



Harvey, Science 2008

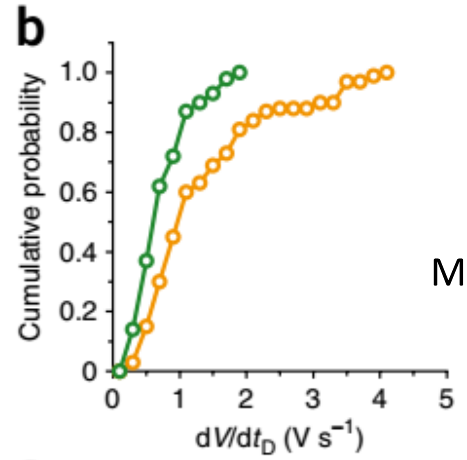


Losonczy, Nature 2008

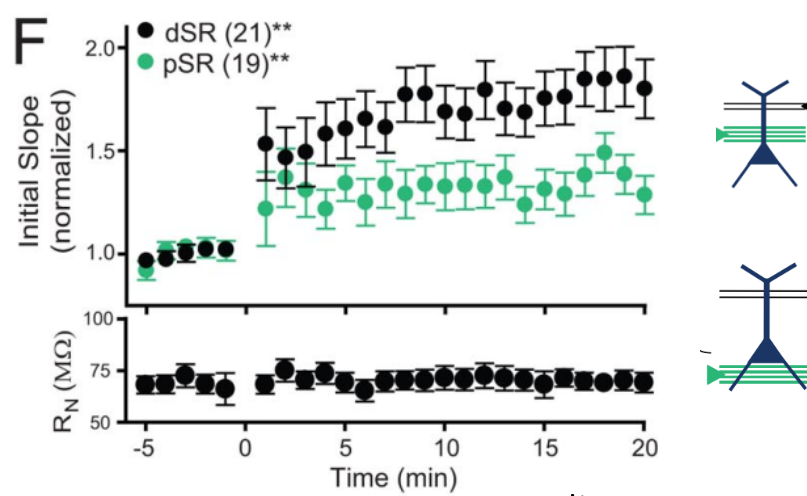
Examples - Intrinsic and Local Hebbian Plasticity

- Experience in an enriched environment increased propagation of dendritic Na+ spikes in a subset of individual dendritic branches in CA1 pyramidal neurons and this effect is mediated by localized down-regulation of A-type K+ channel function (Makara 2009)

- Local dendritic stimulation is more effective in eliciting LTP in hippocampal neurons than back-propagating action potentials. (Hardie 2009)

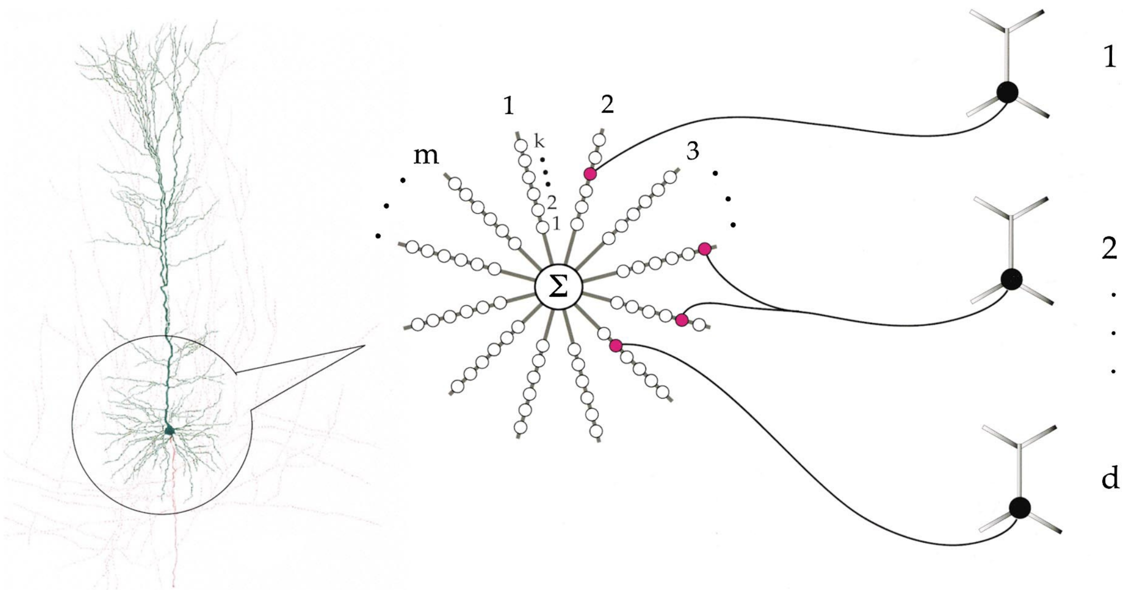


Makara, Nat. Neuro 2009



Hardie, J. Neuro 2009

Wiring Plasticity



Dendrites can perform local, nonlinear computations

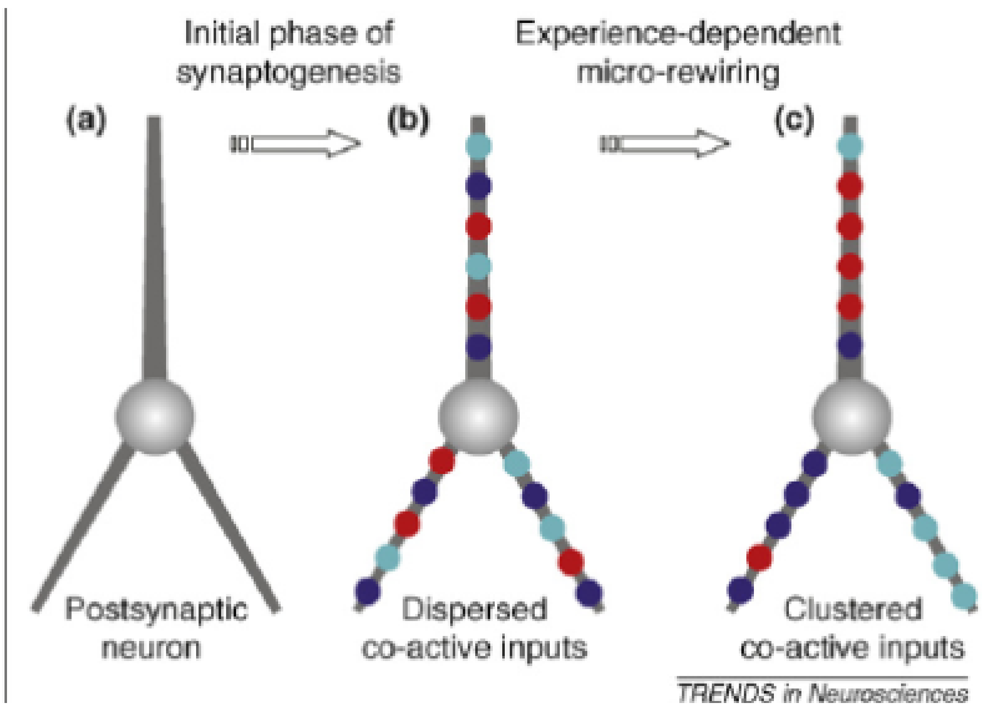
Rewiring (structural plasticity) can occur in the adult brain

Rewiring is activity dependent

Can activity-dependent synaptic clustering serve as an alternative memory storage mechanism?

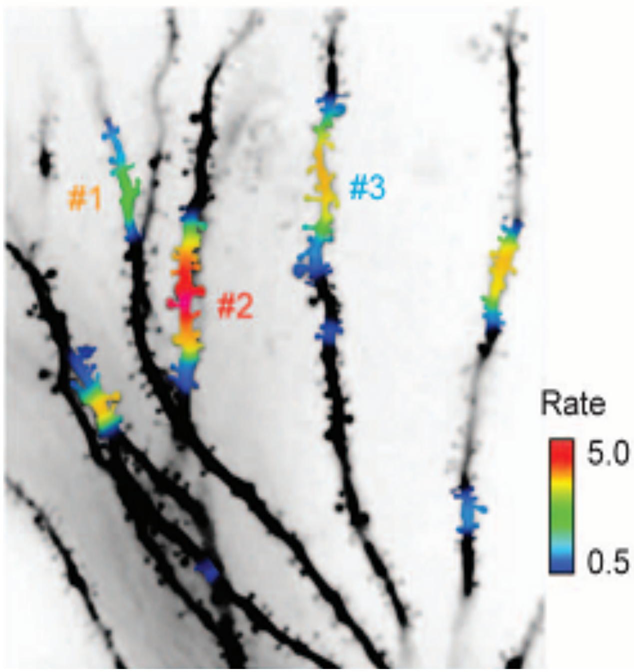
The clustering hypothesis

Neurons that are co-activated and project to the same target neuron tend to form synapses on the same dendritic branch.



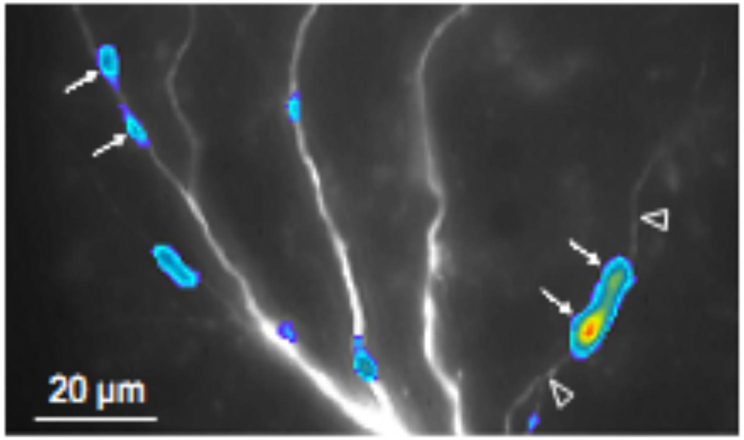
W.M. DeBello, TINS, 2008

Clustered Synaptic Activation



Takahashi et al, Science, 2012

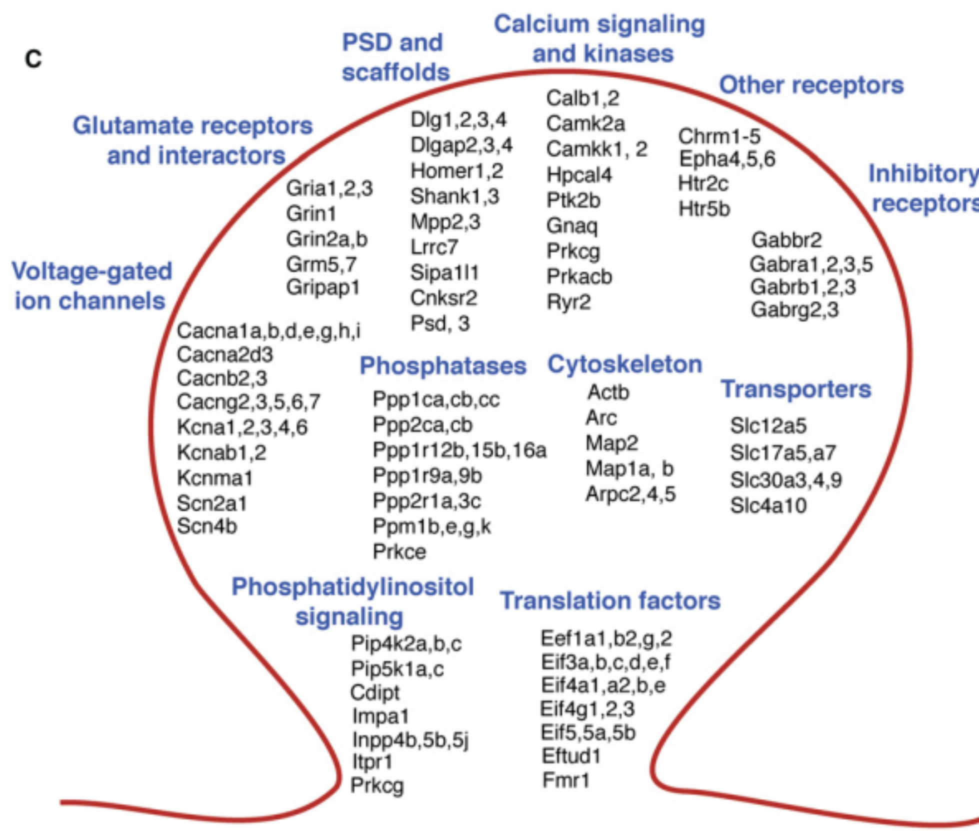
Kleindienst et al, Neuron, 2011



Correlated activation of neighboring spines
in vitro
in vivo
ex vivo

Local translation in dendrites

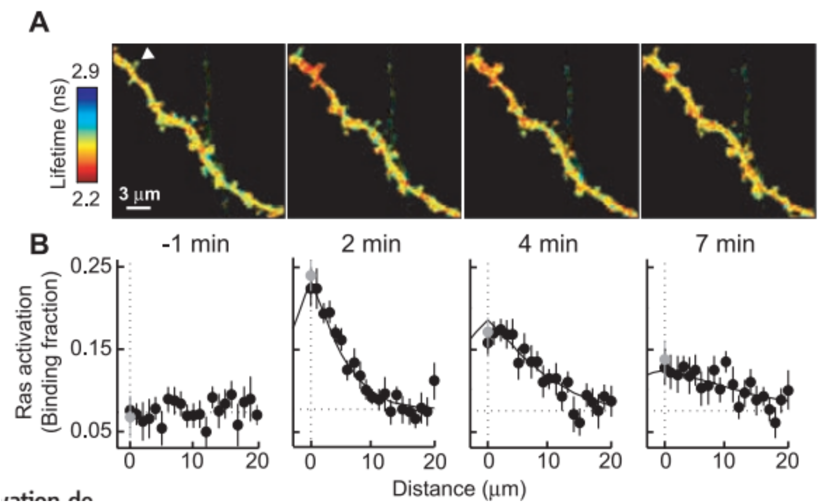
- Dendrites contain the entire translational machinery necessary for protein synthesis (polyribosomes, enzymes, membranous cisterns)
- mRNAs required for plasticity can be trafficked to dendrites
- A wide range of mRNAs, including mRNAs required for plasticity and ionic channels have been found to be localized in synaptic regions



Cajigas, Neuron 2012

Local Chemical Integration

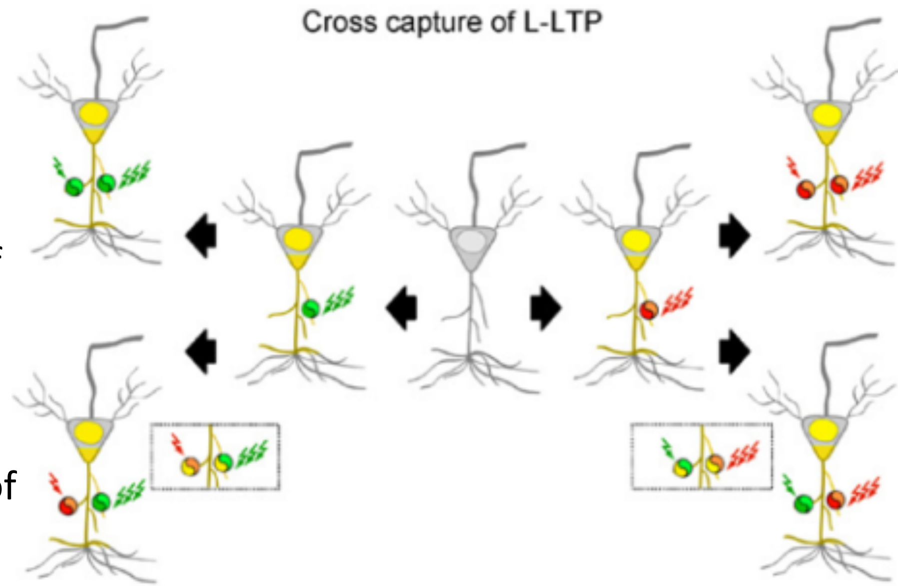
- Local biochemical pathways can be activated with Calcium influx
- Calcium provided by stimulated synapses or second-messenger pathways
- Spread of calcium signaling depends on geometry, activated pathways and buffering
- Example:
  - CaMKII translocation is spreading over dendritic tree
  - Calcium-dependent Ras activity diffuses locally in the branch (Harvey,2008)

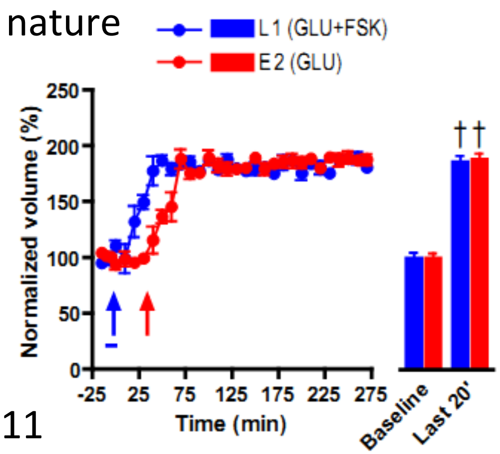


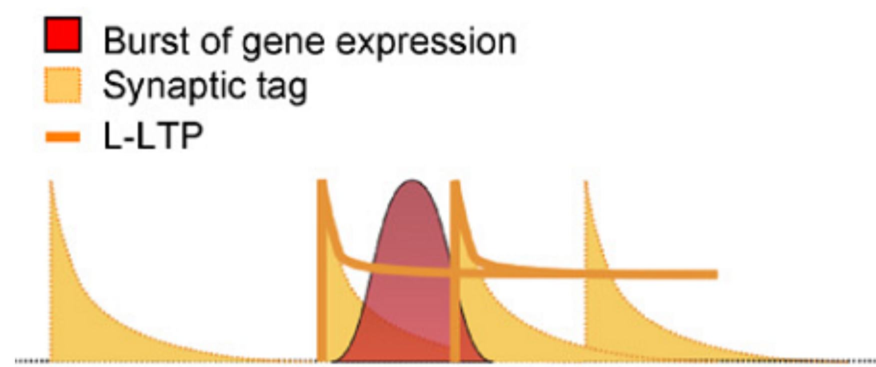
Harvey, Science 2008

Synaptic Tagging and Capture

- A model for the specificity and associativity of late-LTP in synapses
- LTP Consolidation requires PRPs
- Synaptic activity creates synaptic tag
- Strong postsynaptic activation leads to synthesis of PRPs
- Synapses tagged within ~hours can capture PRPs from any plasticity-generating event
- Demonstrated in distinct CA1 pathways and pairs of spines
- Confined to distances < 70nm → dendritic branches
- Suggested competitive nature

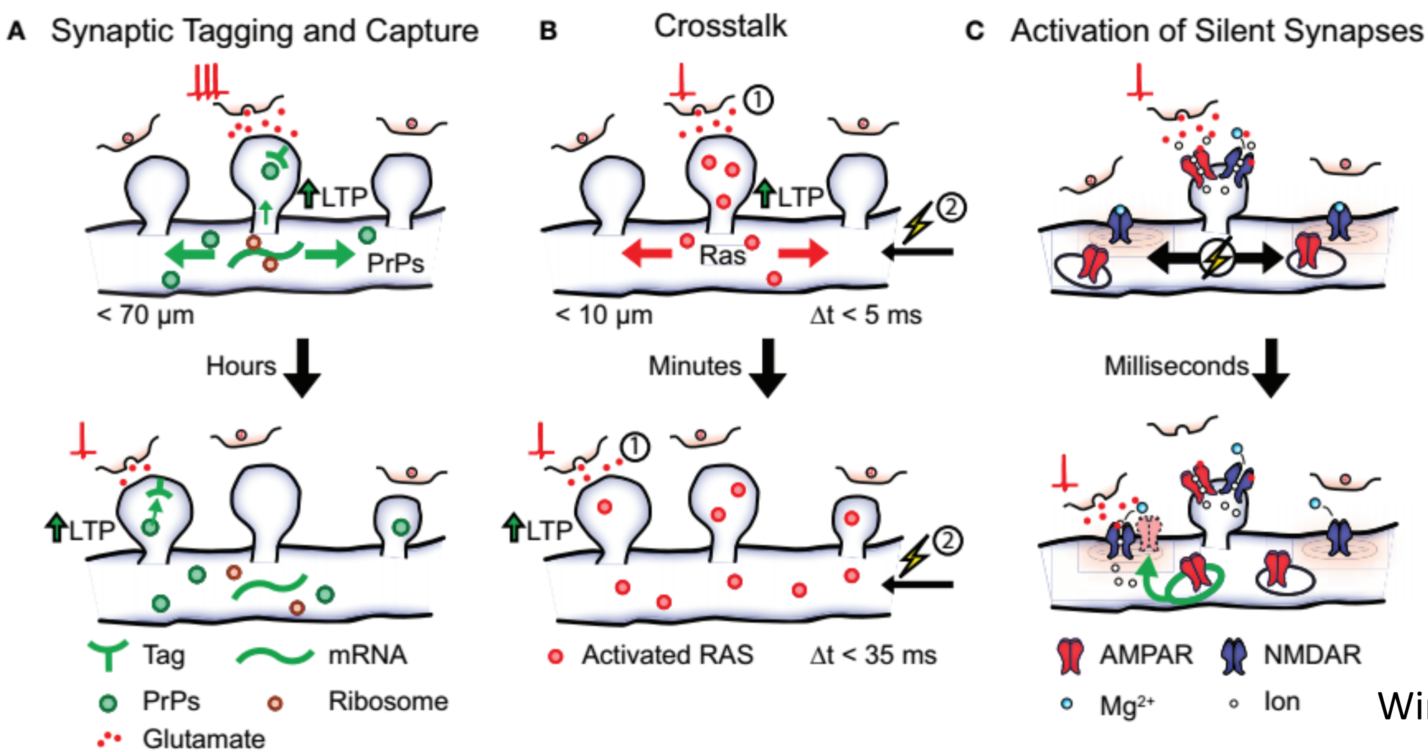






Govindarajan , Neuron 2011

Local LTP cooperativity enables clustering



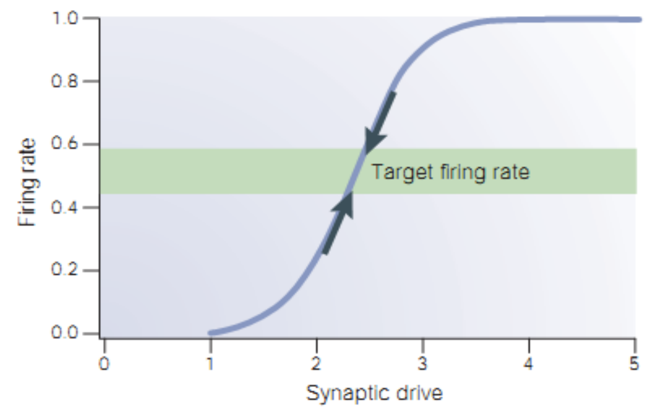
Winnubst, 2012

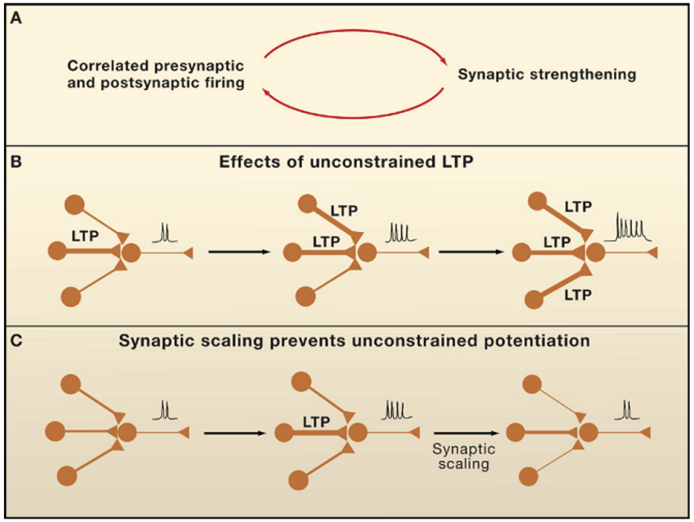
Several local plasticity mechanisms can establish synapse clustering:

- Synaptic Tagging and Capture
- Spread of signaling, e.g. Ras
- Activation of nearby silent synapses

Homeostasis

- Hebbian plasticity is a positive feedback mechanism → unstable
- Stability-promoting mechanism→ homeostasis
- Both slow-time course and fast-time course mechanisms have been found
- Synaptic scaling has been found in cultures
- Local homeostatic regulation has been found in single synapses as well
- Plasticity of inhibition runs in parallel
- Intrinsic plasticity mechanisms also subserve homeostasis

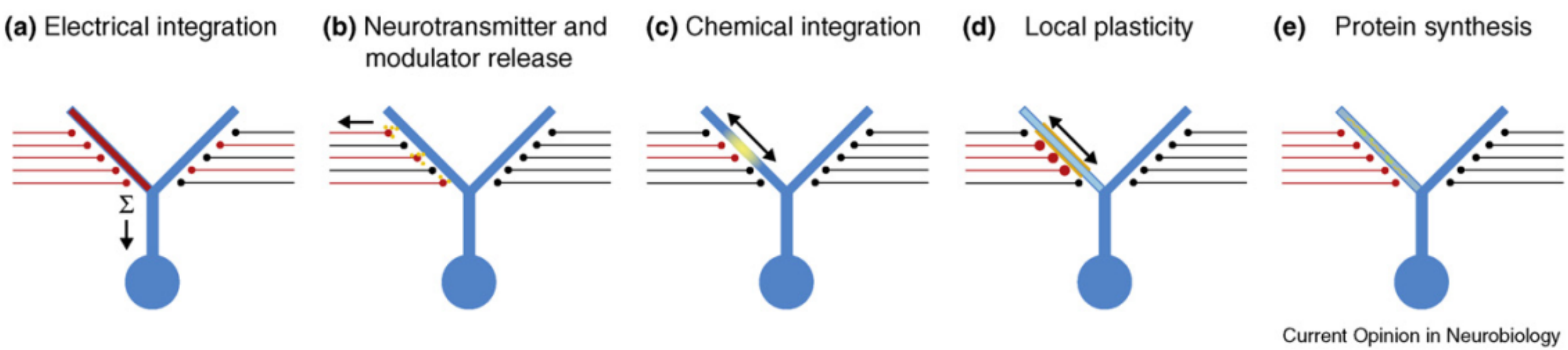




Turrigiano , Cell 2008

Dendrites as fundamental functional units

- Dendritic branches can compartmentalize function on many levels
- Dendrites can compute locally and also perform storage
- Compartmentalization of neuronal function enables higher computational capacity as well as higher storage capacity
- **Single dendrites can act as the fundamental functional unit in the nervous system**



Branco, Cur. Opin. Neurobiology 2010

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Thank you

for your attention!

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