Investigating structural plasticity in brain networks using computational modelling

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The plastic—but stable—brain: Hebbian/Homeostatic plasticity

- “Neurons that fire together, wire together.”[1]
- “The more things change, the more they stay the same.”[2]

[1] Hebb, D. O. *The organization of behavior: A neuropsychological theory.* 1949

[2] Turrigiano, G. G. Homeostatic plasticity in neuronal networks: the more things change, the more they stay the same. *Trends in neurosciences* **22,** 221–227 (1999)

The plastic—but stable—brain: Hebbian/Homeostatic plasticity
- “Neurons that fire together, wire together.”[1]
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What underlies large scale reorganisation?

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- Merzenich, M. M. *et al.* Somatosensory cortical map changes following digit amputation in adult monkeys. *Journal of Comparative Neurology* **224,** 591–605 (1984)
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- A computational model allows us to:
  - investigate every entity in the network: variables from neurons, their neurites, all synapses,
  - modify any parameters to analyse changes in network behaviour: neuronal parameters, synaptic parameters, other network parameters,
  - run multiple analyses in parallel,
  - do it in less time than biological experiments[1].

[1] Simulations take a week each, but that's still faster than a multi-month laboratory experiment.

Methods: How?

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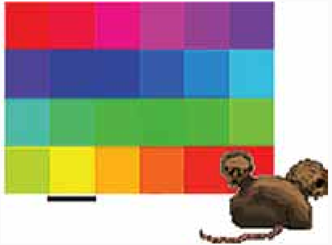
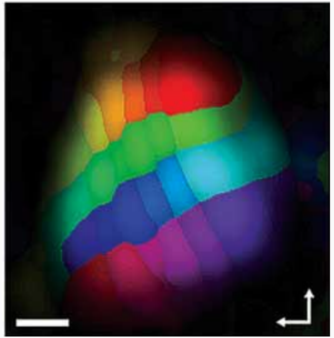
Peripheral lesion protocol I: topographic mapping





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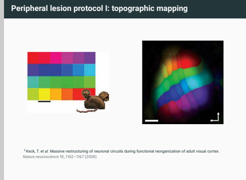
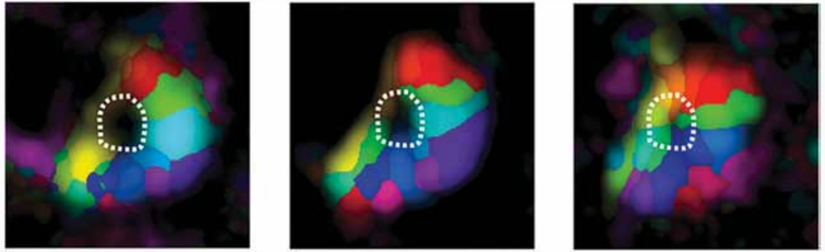


1. The protocol is pretty standard. Here, for a study in the visual cortex, the retinal field of a rat or a mouse is mapped.

Peripheral lesion protocol II: after peripheral lesion



- Dotted region encloses the Lesion Projection Zone (LPZ)
- Inward “repair”.

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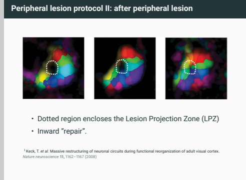
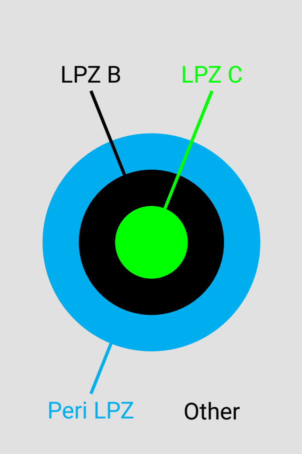
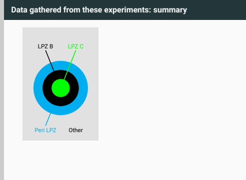


1. Then, a part of the retina is lesioned. This cuts off inputs to a part of the visual cortex, as shown in the first figure. This forms the Lesion Projection Zone (LPZ). By repeated imaging of the region over months, the reorganisation of the network is tracked.
2. Other lesion studies use similar methods: digit removal, whisker trimming, and so on—anything that cuts off projecting activity on to a set of neurons.

Data gathered from these experiments: summary





1. So, if this a simple schematic, of the regions around the LPZ, this is what we know from these studies.

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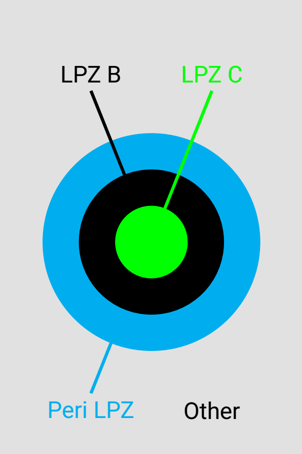
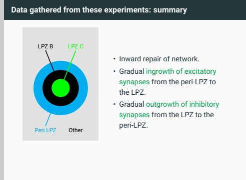


- Inward repair of network.
- Gradual ingrowth of excitatory synapses from the peri-LPZ to the LPZ.
- Gradual outgrowth of inhibitory synapses from the LPZ to the peri-LPZ.



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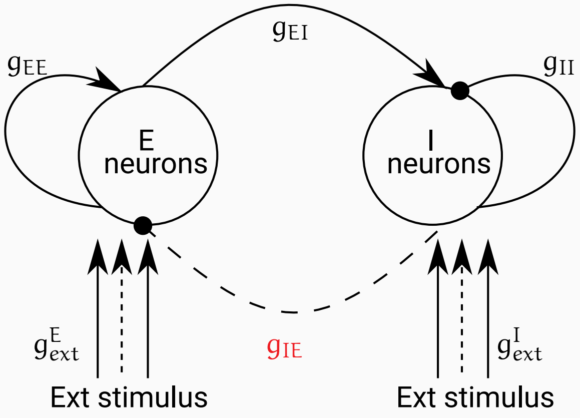
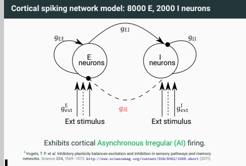
Cortical spiking network model: 8000 E, 2000 I neurons



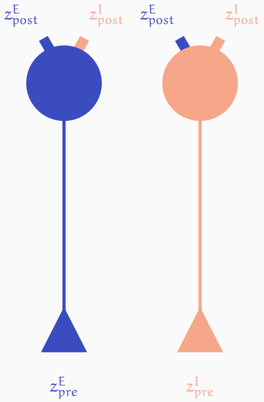
Exhibits cortical Asynchronous Irregular (AI) firing.

[1] Vogels, T. P. *et al.* Inhibitory plasticity balances excitation and inhibition in sensory pathways and memory networks. *Science* **334,** 1569–1573. http://www.sciencemag.org/content/334/6062/1569.short (2011)

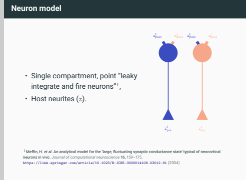


Neuron model

- Single compartment, point “leaky integrate and fire neurons”[1],
- Host neurites (z).

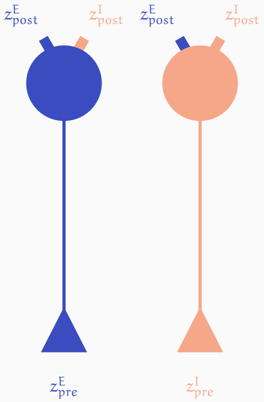


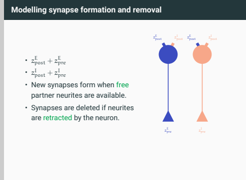
[1] Meffin, H. *et al.* An analytical model for the ‘large, fluctuating synaptic conductance state’ typical of neocortical neurons in vivo. *Journal of computational neuroscience* **16,** 159–175. `https://link.springer.com/article/10.1023/B:JCNS.0000014108.03012.81` (2004)



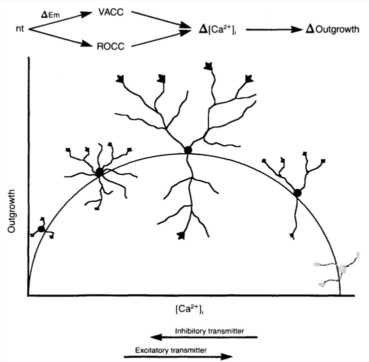
Modelling synapse formation and removal

- $z^{\mathrm{E}}_{\mathrm{post}} + z^{\mathrm{E}}_{\mathrm{pre}}$
- $z^{\mathrm{I}}_{\mathrm{post}} + z^{\mathrm{I}}_{\mathrm{pre}}$
- New synapses form when free partner neurites are available.
- Synapses are deleted if neurites are retracted by the neuron.

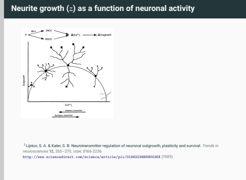




Neurite growth (z) as a function of neuronal activity



[1] Lipton, S. A. & Kater, S. B. Neurotransmitter regulation of neuronal outgrowth, plasticity and survival. *Trends in neurosciences* **12,** 265–270. ISSN: 0166-2236. http://www.sciencedirect.com/science/article/pii/016622368990026X (1989)



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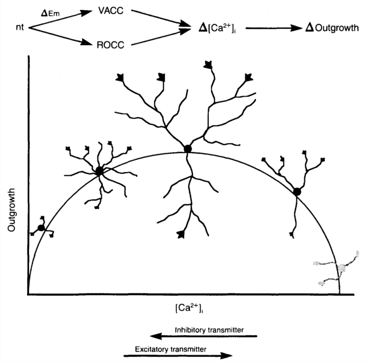

- $[Ca^{2+}]$ correlates with neuronal activity,
- serves a homeostatic function.

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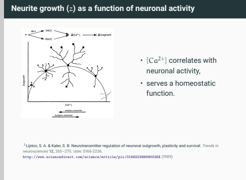
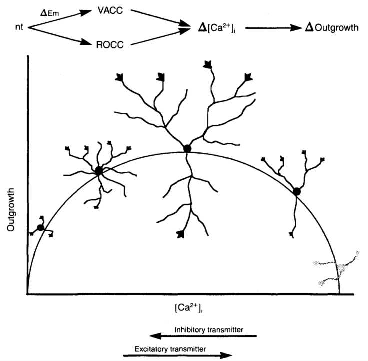
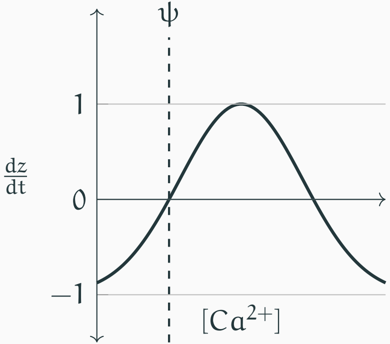


Neurite growth (z) modelled as a Guassian function of activity





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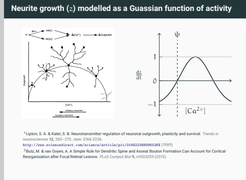
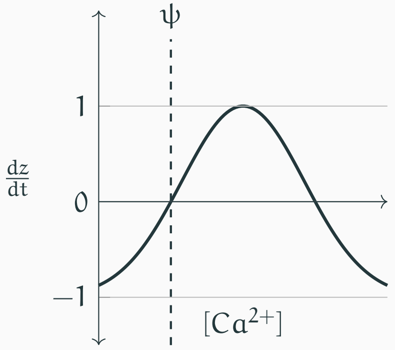
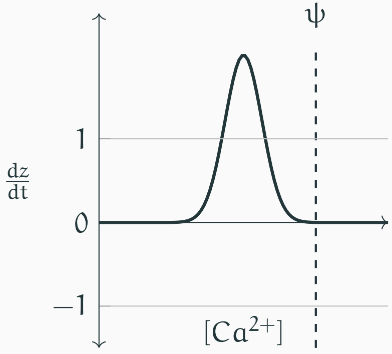
[2] Butz, M. & van Ooyen, A. A Simple Rule for Dendritic Spine and Axonal Bouton Formation Can Account for Cortical Reorganization after Focal Retinal Lesions. *PLoS Comput Biol* **9,** e1003259 (2013)

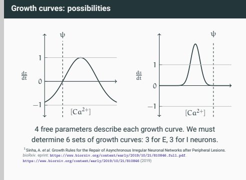




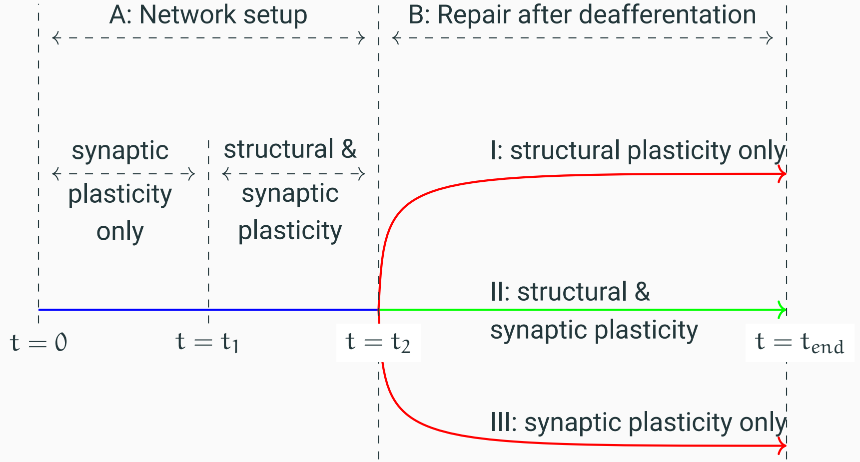


4 free parameters describe each growth curve. We must determine 6 sets of growth curves: 3 for E, 3 for I neurons.

[1] Sinha, A. *et al.* Growth Rules for the Repair of Asynchronous Irregular Neuronal Networks after Peripheral Lesions. *bioRxiv.* eprint: `https://www.biorxiv.org/content/early/2019/10/21/810846.full.pdf`. `https://www.biorxiv.org/content/early/2019/10/21/810846` (2019)



Replicate peripheral lesion protocol



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└─Methods: How?

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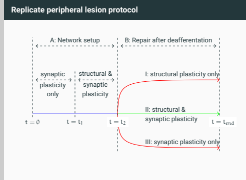

Results: a few years later

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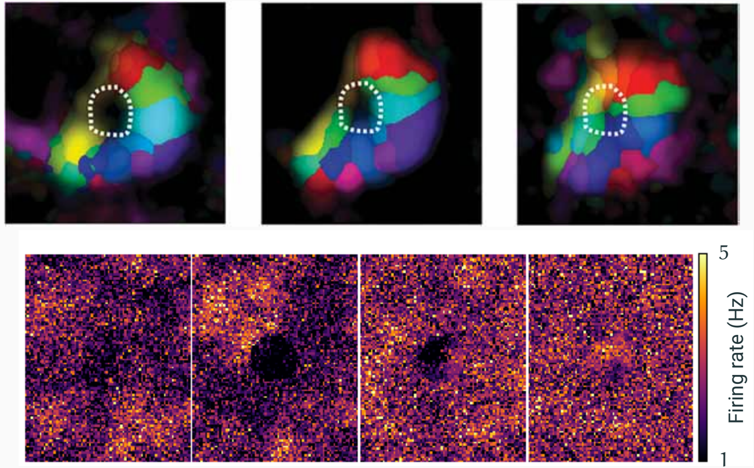
Reproduction of deafferentation and repair



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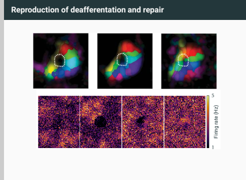
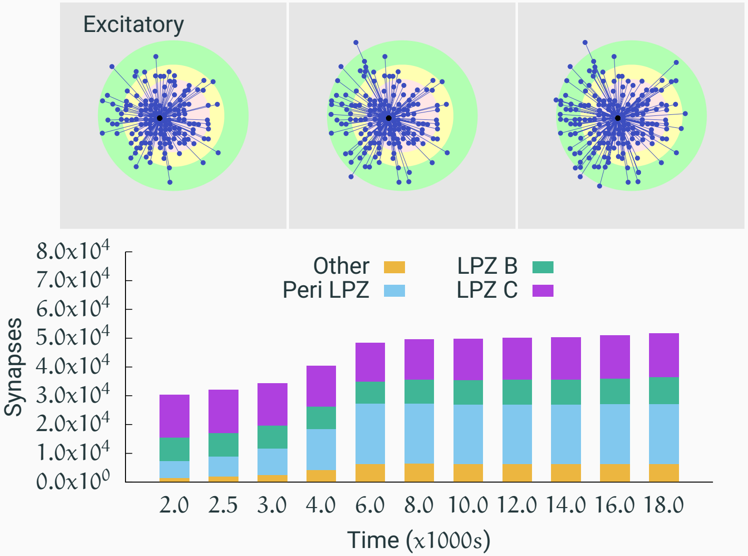
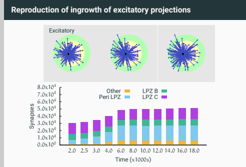
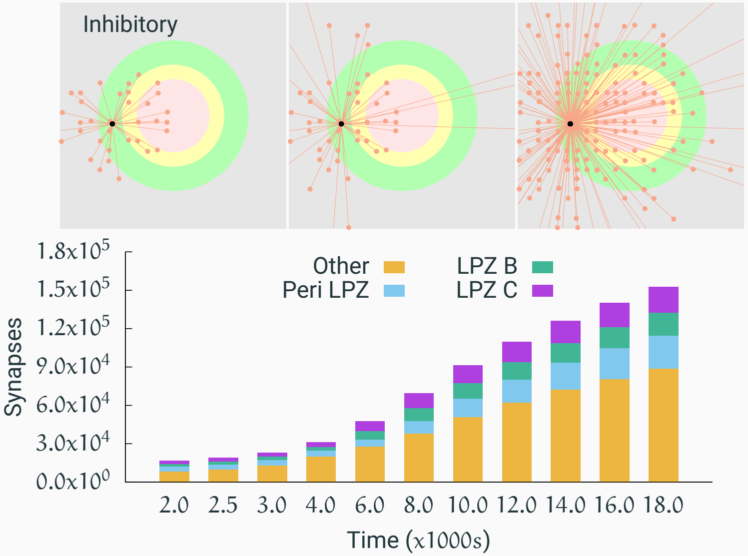


Reproduction of ingrowth of excitatory projections





Reproduction of outgrowth of inhibitory projections



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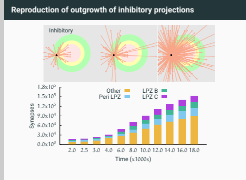
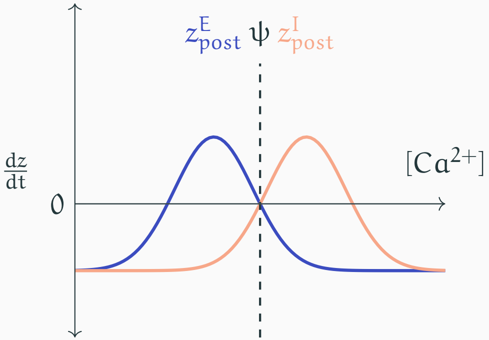
└─Results: a few years later

└─Reproduction of outgrowth of inhibitory



Resultant activity dependent growth rules: post-synaptic



2020-01-18

Investigating structural plasticity in brain networks using computational modelling
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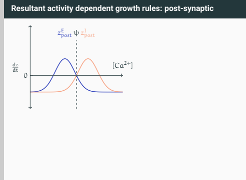

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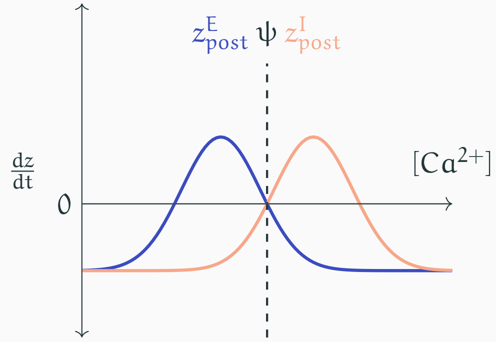

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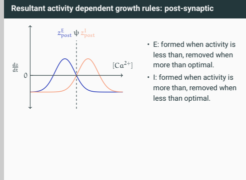

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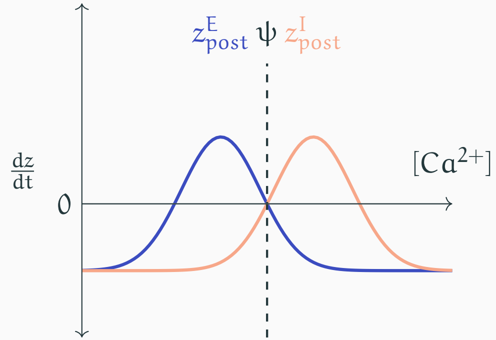

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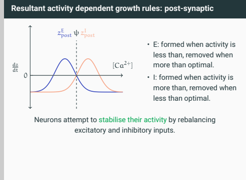

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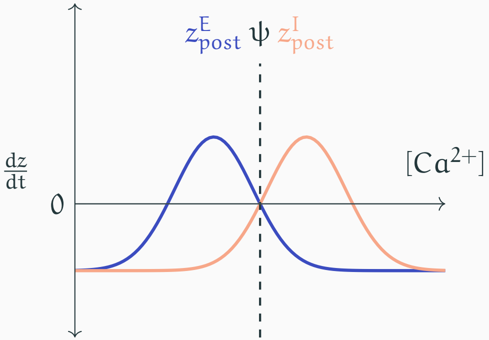

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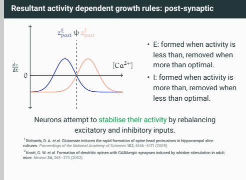
[2] Knott, G. W. *et al.* Formation of dendritic spines with GABAergic synapses induced by whisker stimulation in adult mice. *Neuron* **34,** 265–273 (2002)



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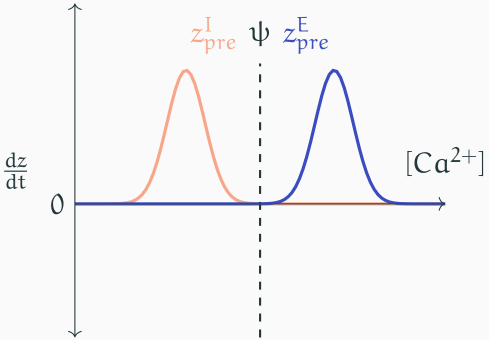

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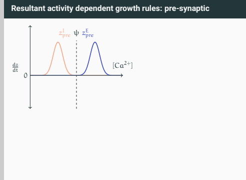
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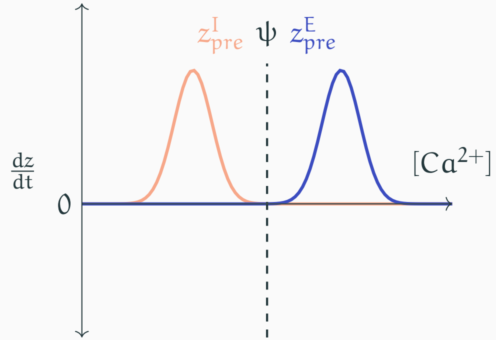

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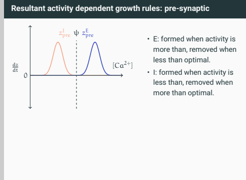

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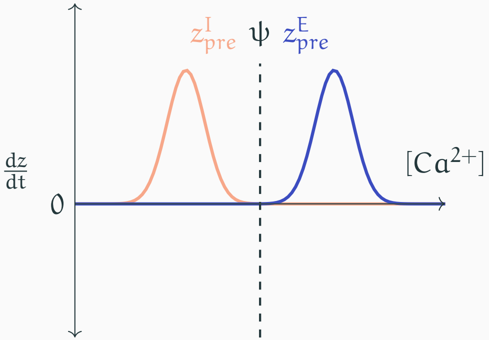

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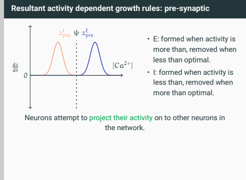

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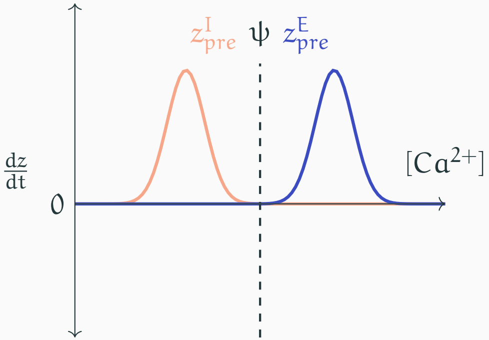

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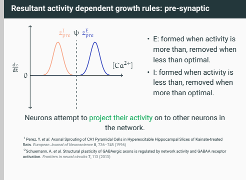
[2] Schuemann, A. *et al.* Structural plasticity of GABAergic axons is regulated by network activity and GABAA receptor activation. *Frontiers in neural circuits* **7,** 113 (2013)



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Free/Open Source Software vs Open Science

Users should have the freedom to share, study, and modify software[1].

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NeuroFedora: volunteer driven initiative

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