

Investigating structural plasticity in brain networks using computational modelling

Ankur Sinha
PhD candidate
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└ Context: what and why?

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

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

- “Neurons that fire together, wire together.”¹

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- “The more things change, the more they stay the same.”²

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└ Synaptic plasticity: the popular plasticity

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What underlies large scale reorganisation?

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- Calford, M. B. & Tweedale, R. Immediate and chronic changes in responses of somatosensory cortex in adult flying-fox after digit amputation. *Nature* **332**, 446–448 (1988)
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- Rajan, R. et al. Effect of unilateral partial cochlear lesions in adult cats on the representation of lesioned and unlesioned cochleas in primary auditory cortex. *Journal of Comparative Neurology* **338**, 17–49 (1993)

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Imaging confirms structural plasticity in lesion studies

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Also confirms structural plasticity in the unlesioned adult brain

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- not only do the strengths of existing synapses change,
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- How? Why?

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Simulate a computational model of peripheral lesioning to study the reorganisation process.

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└ Context: what and why?

└ Aim

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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 experiments¹.

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

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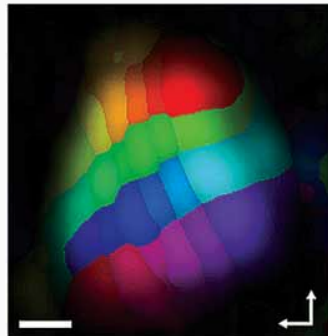
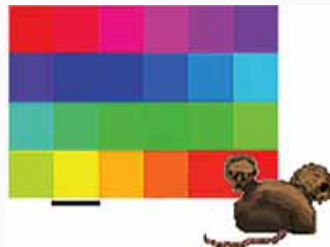
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└─ Methods: How?

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Peripheral lesion protocol I: topographic mapping



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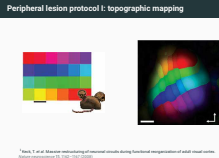
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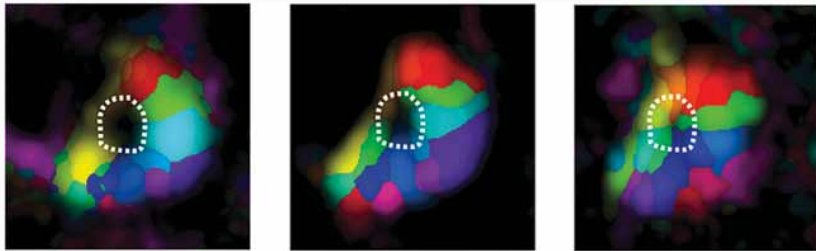
└ Methods: How?

└ Peripheral lesion protocol I: topographic

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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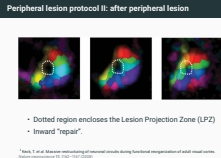
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Methods: How?

Peripheral lesion protocol II: after peripheral

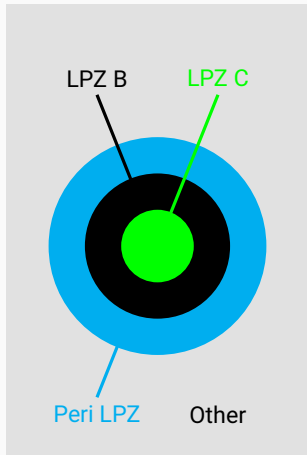
1. Then, a part of the retina is lesioned. This cuts off inputs to a part of the visual cortex, as shown in the first figure. This forms the Lesion Projection Zone (LPZ). By repeated imaging of the region over months, the reorganisation of the network is tracked.
2. Other lesion studies use similar methods: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



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Data gathered from these experiments: summary



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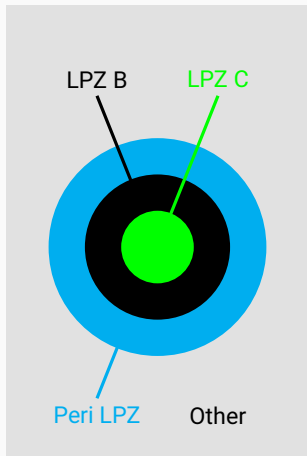
└ Methods: How?

└ Data gathered from these experiments:

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



Data gathered from these experiments: summary



- 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.

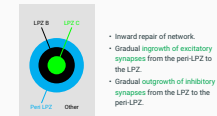
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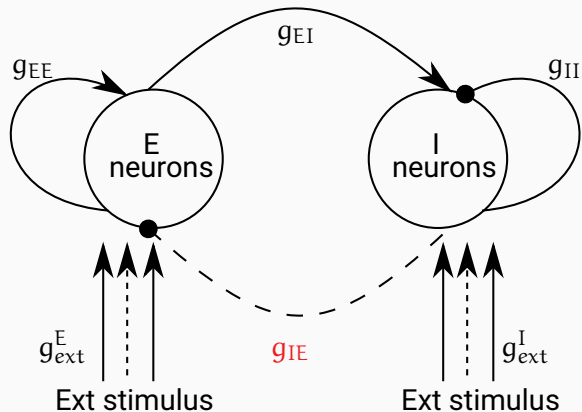
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Cortical spiking network model: 8000 E, 2000 I neurons



Exhibits cortical **Asynchronous Irregular (AI)** firing.

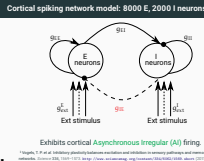
¹ Vogels, T. P. et al. Inhibitory plasticity balances excitation and inhibition in sensory pathways and memory networks. *Science* **334**, 1569–1573. <http://www.sciencemag.org/content/334/6062/1569.short> (2011)

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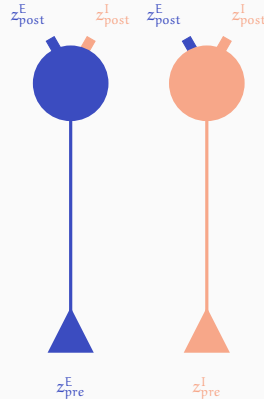
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└ Methods: How?

└ Cortical spiking network model: 8000 E, 2000 I



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



¹Meffin, 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.

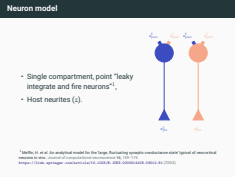
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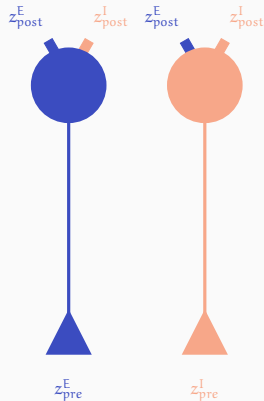
└ Methods: How?

└ Neuron model



Modelling synapse formation and removal

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



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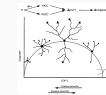
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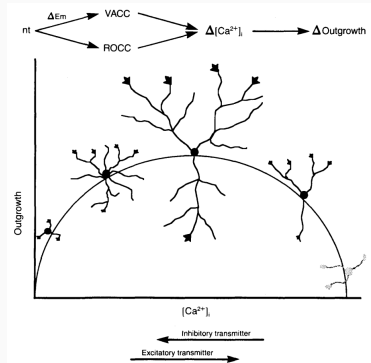
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¹ Lipton, S. A. & Kater, S. B. Neurotransmitter regulation of neuronal outgrowth, plasticity and survival. *Trends in neurosciences* 12, 265–270. ISSN: 0166-2236.
<http://www.sciencedirect.com/science/article/pii/016622368990026X> (1989)

Neurite growth (z) as a function of neuronal activity



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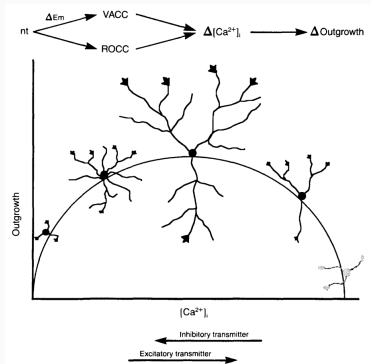
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└ Neurite growth (z) as a function of neuronal

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

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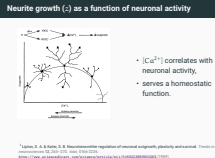
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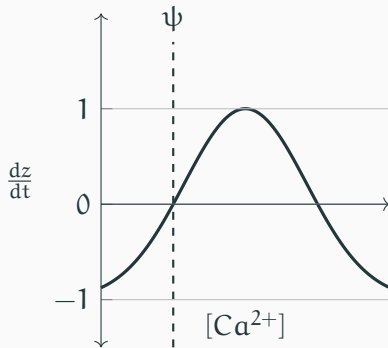
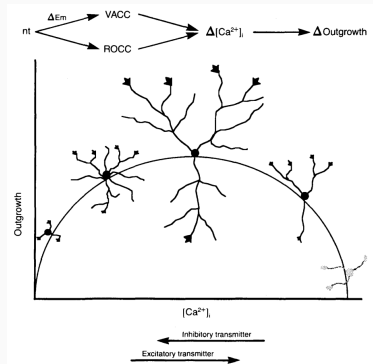
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└ Methods: How?

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



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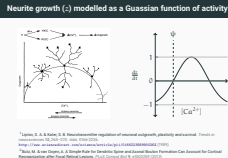
²Butz, M. & van Ooyen, A. A Simple Rule for Dendritic Spine and Axonal Bouton Formation Can Account for Cortical Reorganization after Focal Retinal Lesions. *PLoS Comput Biol* **9**, e1003259 (2013)

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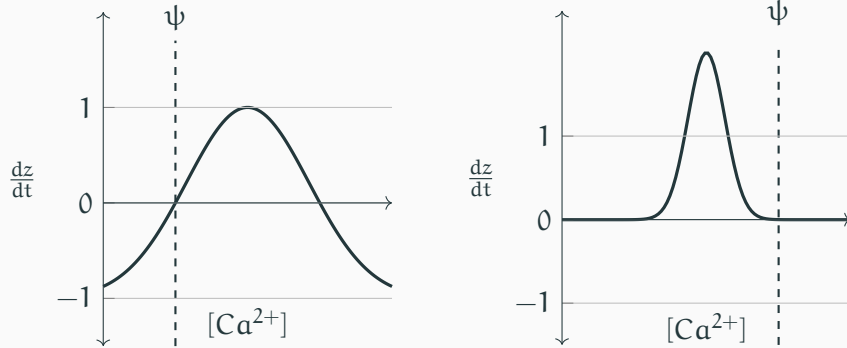
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└ Neurite growth (z) modelled as a Gaussian



Growth curves: possibilities



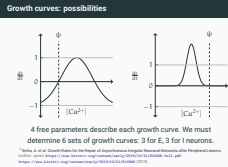
4 free parameters describe each growth curve. We must determine 6 sets of growth curves: 3 for E, 3 for I neurons.

¹Sinha, 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>.
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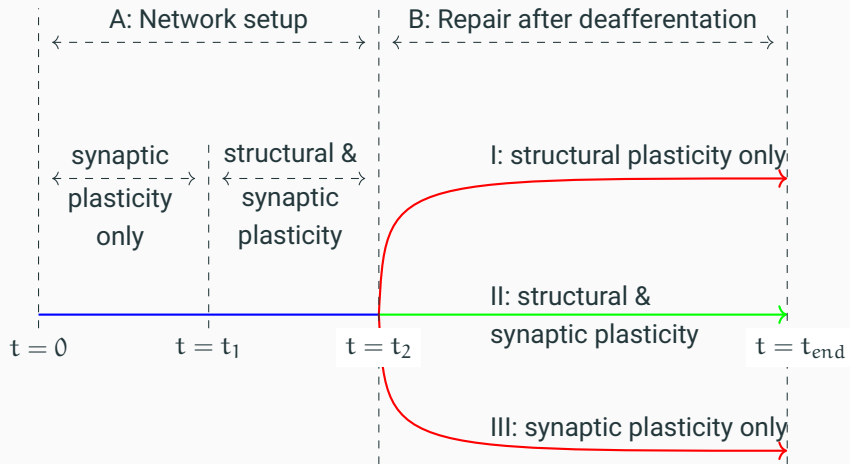
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└ Growth curves: possibilities



Replicate peripheral lesion protocol



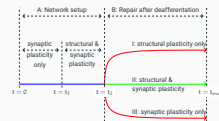
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└ Methods: How?

└ Replicate peripheral lesion protocol

Replicate peripheral lesion protocol



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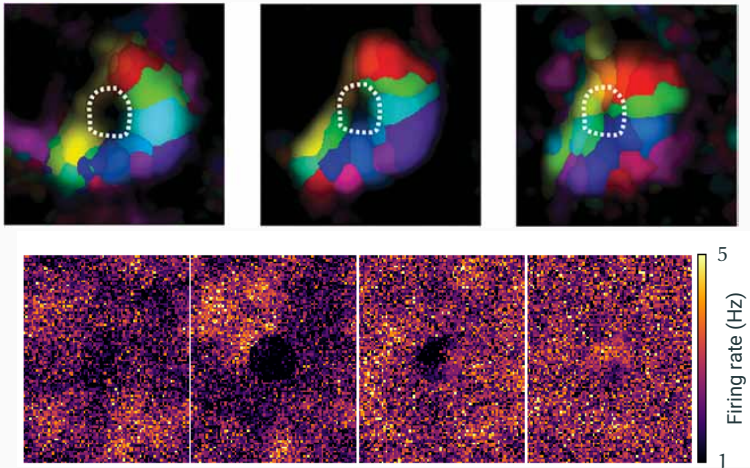
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└ Results: a few years later

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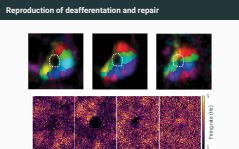
Reproduction of deafferentation and repair



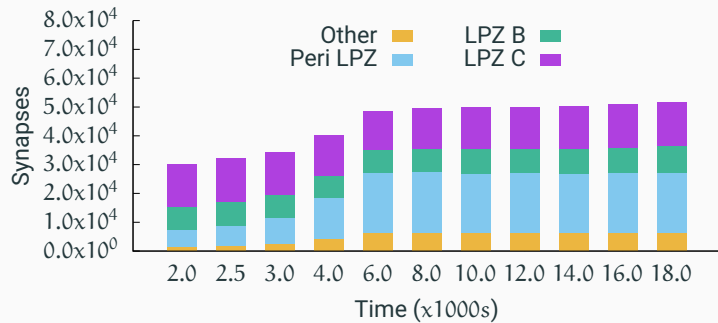
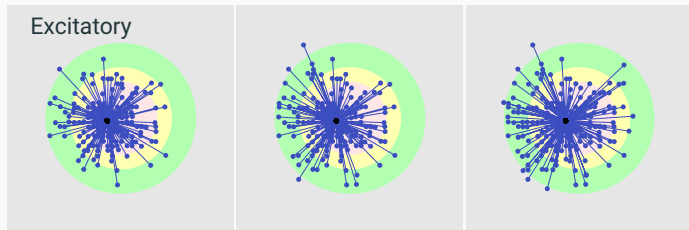
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Reproduction of ingrowth of excitatory projections



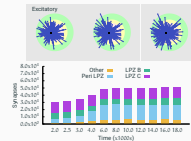
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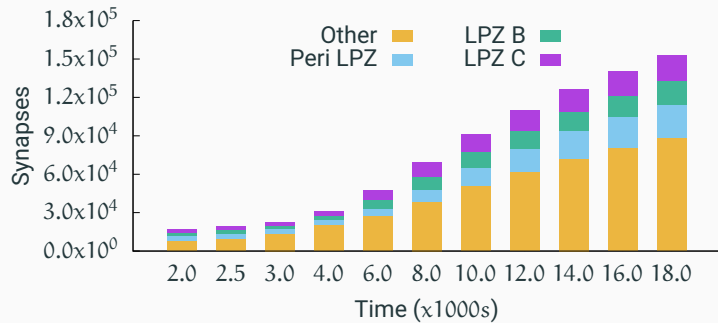
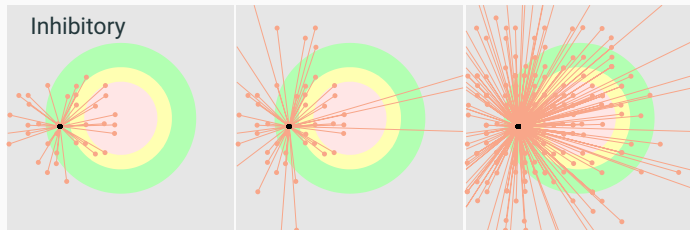
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Reproduction of ingrowth of excitatory

Reproduction of ingrowth of excitatory projections



Reproduction of outgrowth of inhibitory projections



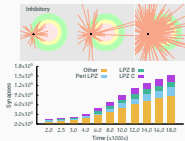
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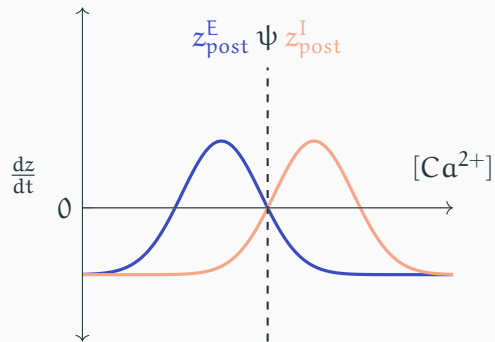
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Resultant activity dependent growth rules: post-synaptic

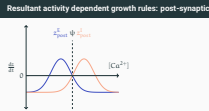


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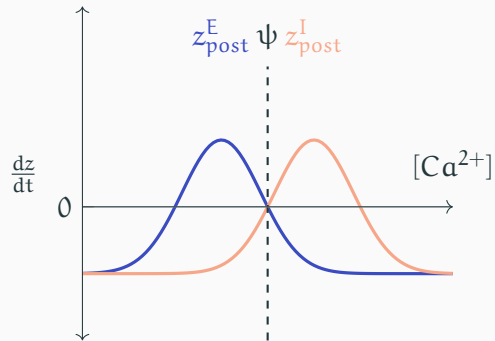
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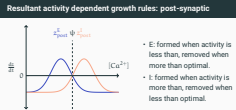
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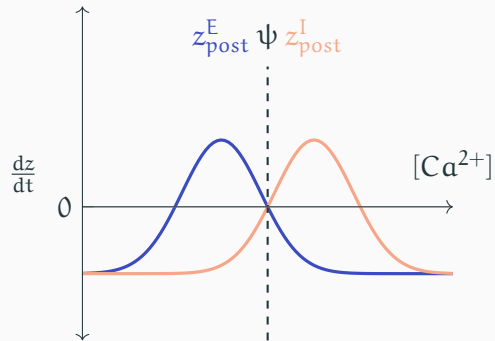
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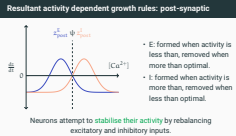
Neurons attempt to **stabilise their activity** by rebalancing excitatory and inhibitory inputs.

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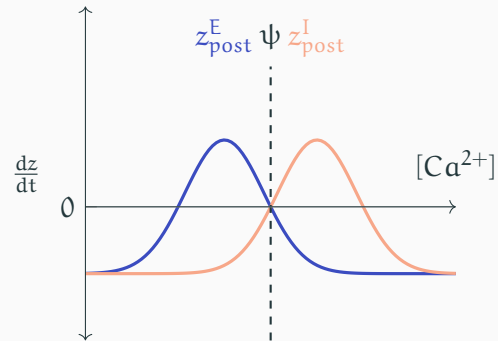
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¹Richards, D. A. *et al.* Glutamate induces the rapid formation of spine head protrusions in hippocampal slice cultures. *Proceedings of the National Academy of Sciences* **102**, 6166–6171 (2005)

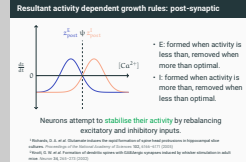
²Knott, G. W. *et al.* Formation of dendritic spines with GABAergic synapses induced by whisker stimulation in adult mice. *Neuron* **34**, 265–273 (2002)

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Investigating structural plasticity in brain networks using computational modelling

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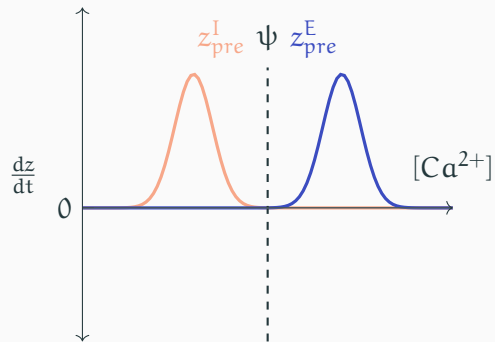
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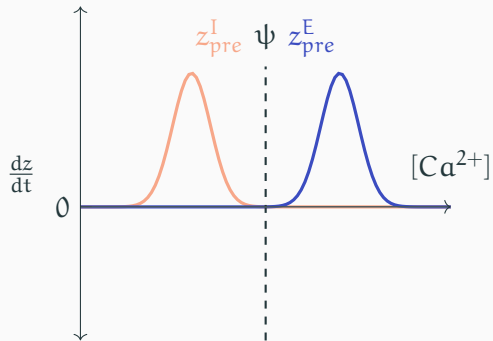
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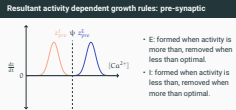
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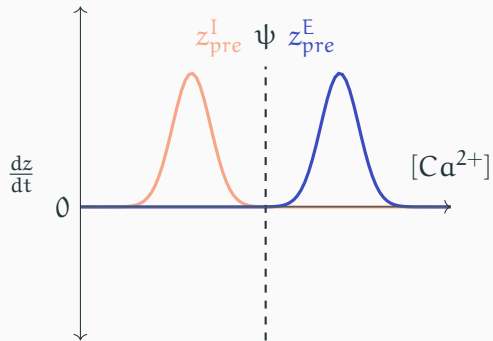
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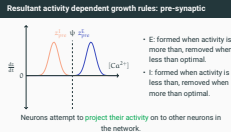
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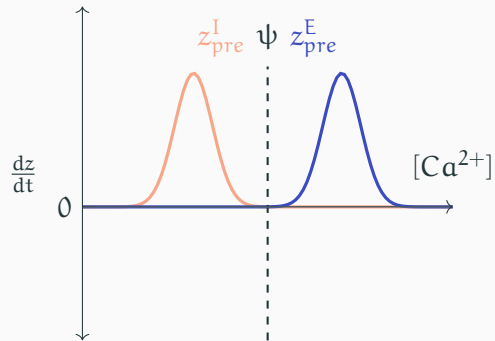
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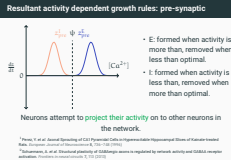
²Schumann, A. et al. Structural plasticity of GABAergic axons is regulated by network activity and GABAA receptor activation. *Frontiers in neural circuits* **7**, 113 (2013)

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Investigating structural plasticity in brain networks using computational modelling

Results: a few years later

Resultant activity dependent growth rules:



Structural and synaptic plasticity are both necessary

- Only synaptic plasticity: no repair.

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Results: summary

- Reproduced peripheral lesion experiments in a computational model.
- Suggested testable hypotheses on the activity dependent growth of all neurites.
- Proposed that individual neurons may stabilise their activities by modifying their input connectivity.
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Limitations: summary

- Point, single compartment neurons: ignore Calcium compartmentalisation,
- No growth factors were taken into consideration,
- Other plasticity mechanisms...

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using computational modelling

└ NeuroFedora: Free Software for Free Neuroscience

NeuroFedora: Free Software for Free
Neuroscience

- is heavily software dependent.
- software is frequently complex to install, deploy, maintain, update.
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Users should have the freedom to **share, study, and modify** software¹.

Everyone should have the freedom to **share, study, and modify** scientific material².

¹Free software foundation: [fsf.org](https://www.fsf.org)

²Open source for neuroscience: opensourceforneuroscience.org

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└─ NeuroFedora: Free Software for Free Neuro-
science

└─ Free/Open Source Software vs Open Science



- Enable Free/Open science:

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└ NeuroFedora: Free Software for Free Neuro-
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└ NeuroFedora: volunteer driven initiative

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Current status: software

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- Documentation: <https://neuro.fedoraproject.org>
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