

## Investigating structural plasticity in brain networks using computational modelling

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## Context: what and why?

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

- “Neurons that fire together, wire together.”<sup>1</sup>
- “The more things change, the more they stay the same.”<sup>2</sup>

<sup>1</sup>Hebb, D. O. *The organization of behavior: A neuropsychological theory*. 1949

<sup>2</sup>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)

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### Synaptic plasticity: the popular plasticity

- changes in efficacy of **existing** synapses,
- changes in structure are ignored<sup>1</sup>.

<sup>1</sup>Even though structural changes in spines and boutons underlie modulation of synaptic efficacy.

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### What underlies large scale reorganisation?

- Rasmusson, D. D. Reorganization of raccoon somatosensory cortex following removal of the fifth digit. *Journal of Comparative Neurology* 205, 313–326 (1982)
- Wall, J. T. & Cusick, C. G. Cutaneous responsiveness in primary somatosensory (SI) hindpaw cortex before and after partial hindpaw deafferentation in adult rats. *The Journal of neuroscience* 4, 1499–1515 (1984)
- Merzenich, M. M. *et al.* Somatosensory cortical map changes following digit amputation in adult monkeys. *Journal of Comparative Neurology* 224, 591–605 (1984)
- 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)
- Heinen, S. J. & Skavenski, A. A. Recovery of visual responses in foveal V1 neurons following bilateral foveal lesions in adult monkey. *Experimental Brain Research* 83, 670–674 (1991)
- 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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### Two theories:

- “unmasking” of pre-existing synaptic connections,
- formation of new synapses (**structural plasticity**).

<sup>1</sup>Rasmusson, D. D. Reorganization of raccoon somatosensory cortex following removal of the fifth digit. *Journal of Comparative Neurology* 205, 313–326 (1982)

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### Imaging confirms structural plasticity in lesion studies

- Darian-Smith 1994
- Florence, S. L. *et al.* Large-scale sprouting of cortical connections after peripheral injury in adult macaque monkeys. *Science* 282, 1117–1121 (1998)
- Keck, T. *et al.* Massive restructuring of neuronal circuits during functional reorganization of adult visual cortex. *Nature neuroscience* 11, 1162–1167 (2008)
- Keck, T. *et al.* Loss of sensory input causes rapid structural changes of inhibitory neurons in adult mouse visual cortex. *Neuron* 71, 869–882. ISSN: 0896-6273. <http://www.sciencedirect.com/science/article/pii/S0896627311005642> (2011)
- Marik, S. A. *et al.* Large-scale axonal reorganization of inhibitory neurons following retinal lesions. *Journal of Neuroscience* 34, 1625–1632 (2014)

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### Also confirms structural plasticity in the unlesioned adult brain

- Holtmaat, A. J. G. D. *et al.* Transient and Persistent Dendritic Spines in the Neocortex In Vivo. *Neuron* 45, 279–291. ISSN: 0896-6273. <http://www.sciencedirect.com/science/article/pii/S0896627305000048> (2005)
- Stettler, D. D. *et al.* Axons and Synaptic Boutons Are Highly Dynamic in Adult Visual Cortex. *Neuron* 49, 877–887. ISSN: 0896-6273. <http://www.sciencedirect.com/science/article/pii/S0896627306001358> (2006)
- Marik, S. A. *et al.* Axonal dynamics of excitatory and inhibitory neurons in somatosensory cortex. *PLoS Biology* 8, e1000395 (2010)
- Chen, J. L. *et al.* Clustered dynamics of inhibitory synapses and dendritic spines in the adult neocortex. *Neuron* 74, 361–373 (2012)
- Villa, K. L. *et al.* Inhibitory Synapses Are Repeatedly Assembled and Removed at Persistent Sites In Vivo. *Neuron* 89, 756–769. ISSN: 1097-4199 (4 2016)

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## So:

- not only do the strengths of existing synapses change,
- **whole synapses are formed and removed.**
- How? Why?

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## Aim

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

- 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<sup>1</sup>.

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

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## Methods: How?

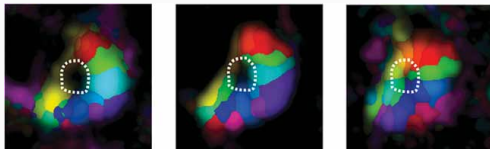
## Peripheral lesion protocol I: topographic mapping



<sup>1</sup> Keck, T. et al. Massive restructuring of neuronal circuits during functional reorganization of adult visual cortex. *Nature neuroscience* 11, 1162–1167 (2008)

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## Peripheral lesion protocol II: after peripheral lesion

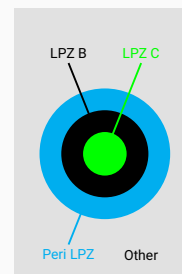


- Dotted region encloses the Lesion Projection Zone (LPZ)
- Inward "repair".

<sup>1</sup> Keck, T. et al. Massive restructuring of neuronal circuits during functional reorganization of adult visual cortex. *Nature neuroscience* 11, 1162–1167 (2008)

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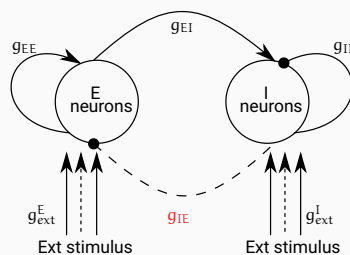
## Data gathered from these experiments: summary



- 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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## Cortical spiking network model: 8000 E, 2000 I neurons



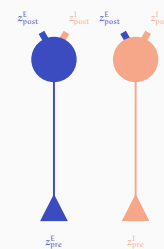
Exhibits cortical **Asynchronous Irregular (AI)** firing.

<sup>1</sup> 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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## Neuron model

- Single compartment, point "leaky integrate and fire neurons"<sup>1</sup>,
- Host neurites (z).

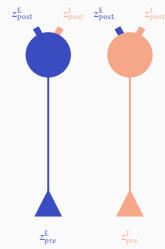


<sup>1</sup> Meffin, H. et al. An analytical model for the 'large, fluctuating synaptic conductance state' typical of neocortical neurons in vivo. *Journal of computational neuroscience* 16, 159–175. <https://link.springer.com/article/10.1023/B:JONS.0000014108.03012.81> (2004)

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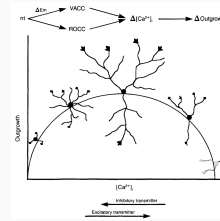
## Modelling synapse formation and removal

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



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## Neurite growth ( $z$ ) as a function of neuronal activity

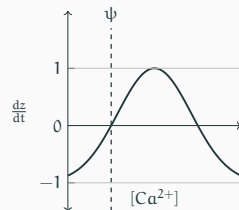
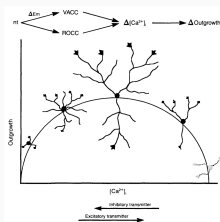


- $[Ca^{2+}]$  correlates with neuronal activity,
- serves a homeostatic function.

<sup>1</sup>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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## Neurite growth ( $z$ ) modelled as a Gaussian function of activity

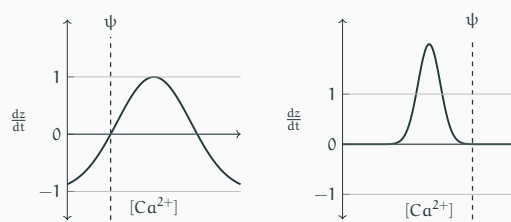


<sup>1</sup>Lipton, S. A. & Kater, S. B. Neurotransmitter regulation of neuronal outgrowth, plasticity and survival. *Trends in neurosciences* 12, 265–270. ISSN: 0166-2236. <http://www.sciencedirect.com/science/article/pii/016622368990026X> (1989)

<sup>2</sup>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)

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## Growth curves: possibilities

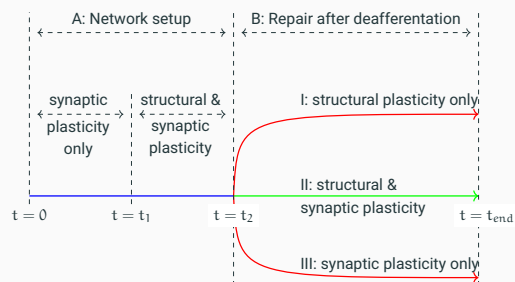


4 free parameters describe each growth curve. We must determine 6 sets of growth curves: 3 for E, 3 for I neurons.

<sup>1</sup>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>. Full1. pdf. <https://www.biorxiv.org/content/early/2019/10/21/810846> (2019)

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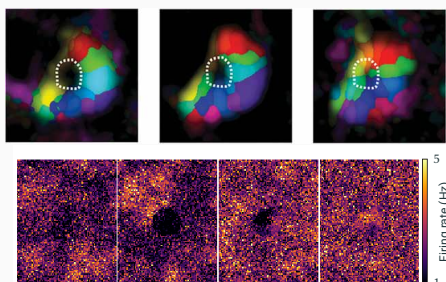
## Replicate peripheral lesion protocol



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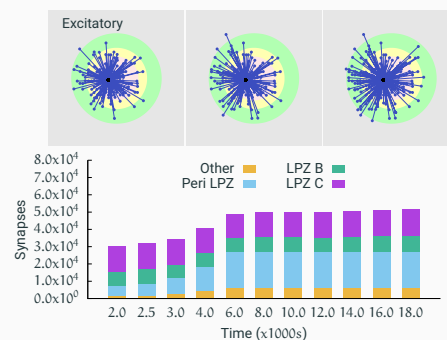
## Results: a few years later

## Reproduction of deafferentation and repair



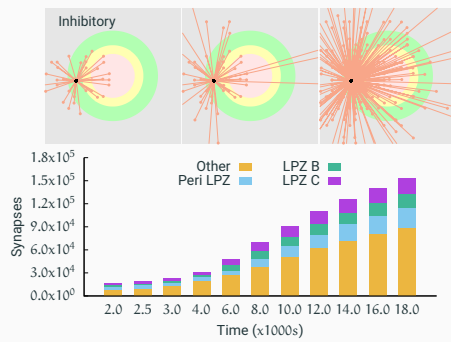
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## Reproduction of ingrowth of excitatory projections



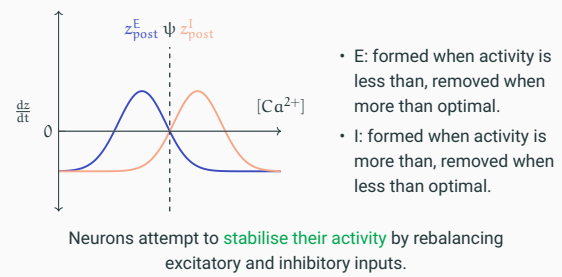
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## Reproduction of outgrowth of inhibitory projections



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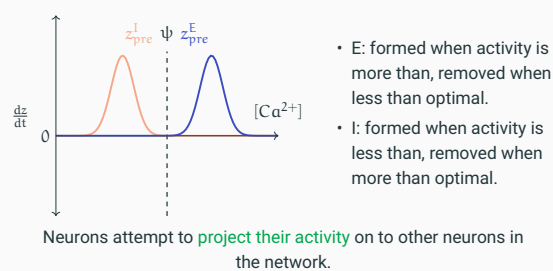
## Resultant activity dependent growth rules: post-synaptic



<sup>1</sup>Richards, 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)  
<sup>2</sup>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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## Resultant activity dependent growth rules: pre-synaptic



<sup>1</sup>Perez, Y. et al. Axonal Sprouting of CA1 Pyramidal Cells in Hyperexcitable Hippocampal Slices of Kainate-treated Rats. *European Journal of Neuroscience* 8, 736–748 (1996)  
<sup>2</sup>Schuemann, A. et al. Structural plasticity of GABAergic axons is regulated by network activity and GABA<sub>A</sub> receptor activation. *Frontiers in neural circuits* 7, 113 (2013)

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## Structural and synaptic plasticity are both necessary

- Only synaptic plasticity: no repair.
- Only structural plasticity: repair, but network does not stabilise; results in high, epileptic firing rates.

While **structural plasticity** is required for **large scale reorganisation** in synaptic connectivity, **synaptic plasticity** is required to **fine tune** the balance between excitation and inhibition to stabilise the network.

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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.
- Indicated that structural and synaptic plasticity both serve distinct roles and are both necessary.

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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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## NeuroFedora: Free Software for Free Neuroscience

## Modern neuroscience

- is **heavily software dependent**.
- software is frequently **complex** to install, deploy, maintain, update.
- software is **rarely checked for correctness (!)**.
- Neuroscientists hail from **diverse academic backgrounds**.
- Scientists are trying to move towards being more **Open**:
  - data, methods, analysis, simulations, publishing, collaboration...

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## Free/Open Source Software vs Open Science

Users should have the freedom to **share, study, and modify** software<sup>1</sup>.

**Everyone** should have the freedom to **share, study, and modify** scientific material<sup>2</sup>.

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

<sup>2</sup>Open source for neuroscience: [opensourceforneuroscience.org](https://opensourceforneuroscience.org/)

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## NeuroFedora: volunteer driven initiative

- Enable **Free/Open science**:
  - provide researchers (end-users):
    - ready to use **tested** tools.
  - help developers (upstream)
    - collect feedback from users.
    - make software improvements.
    - implement software development standards.

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## Current status: software

- Ready to download ISO for computational neuroscience,
- Plethora of tools ready to install and use:
  - **Computational modelling**: NEST, Neuron, Genesis, Brian, LEMS, COPASI...
  - **Neuroimaging**: dicomanonymiser, dipy, fsleyes, jnifti, mne-bids, nilearn, nistats, octave-dicom, pybids, petlink, pynetdicom...
  - **Utilities**:  $\text{\LaTeX}$ , the Python science stack, daily use productivity tools...
- **180** tools in queue<sup>1</sup>

<sup>1</sup><https://pagure.io/neuro-sig/NeuroFedora/issues>

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## Current status: team

- **15 volunteers**: mainly Free/Open Source Software enthusiasts.
- Limited domain knowledge.

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## NeuroFedora: links

- Documentation: <https://neuro.fedoraproject.org>
- Blog <https://neuroblog.fedoraproject.org>
- IRC channel: #fedora-neuro on Freenode.net<sup>1</sup>.
- Telegram channel: @NeuroFedora<sup>2</sup>.
- Mailing list on [lists.fedoraproject.org](https://lists.fedoraproject.org)<sup>3</sup>.

<sup>1</sup>#fedora-neuro on Freenode

<sup>2</sup>@NeuroFedora on Telegram

<sup>3</sup>neuro-sig@lists.fedoraproject.org

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## Search: NeuroFedora



[neuro.fedoraproject.org](https://neuro.fedoraproject.org)

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