

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.”¹
- “The more things change, the more they stay the same.”²

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

²Turrigiano, 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 ignored¹.

¹Even 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**).

¹Rasmusson, 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, C. & Gilbert, C. D. Axonal sprouting accompanies functional reorganization in adult cat striate cortex. *Nature* 368, 737–740 (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 Feb. 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 experiments¹.

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

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Methods: How?

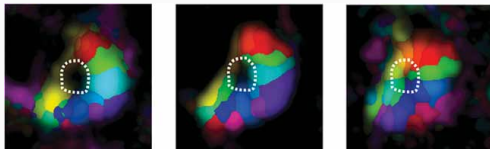
Peripheral lesion protocol I: topographic mapping



¹ 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

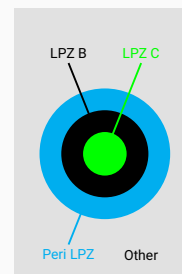


- Dotted region encloses the Lesion Projection Zone (LPZ)
- Inward "repair".

¹ 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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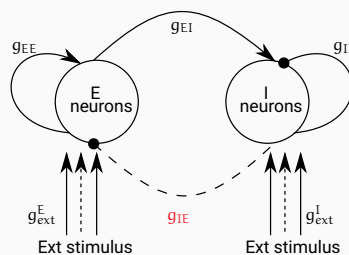
Data gathered from these experiments: summary



- 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



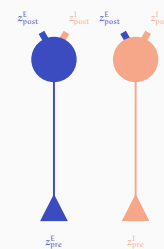
Exhibits cortical **Asynchronous Irregular (AI)** firing.

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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Neuron model

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

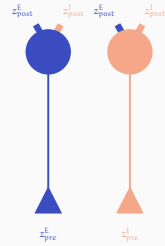


¹ Meffin, H. et al. An analytical model for the 'large, fluctuating synaptic conductance state' typical of neocortical neurons in vivo. *Journal of computational neuroscience* 16, 159–175. <https://link.springer.com/article/10.1023/B:JONS.0000014108.03012.81> (2004)

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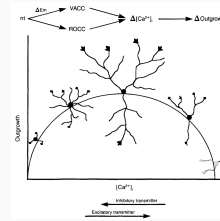
Modelling synapse formation and removal

- $z_{\text{post}}^E + z_{\text{pre}}^E$
- $z_{\text{post}}^I + z_{\text{pre}}^I$
- 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

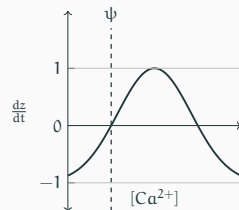
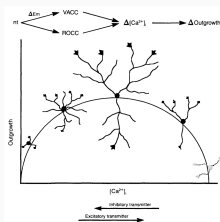


- $[Ca^{2+}]$ correlates with neuronal activity,
- serves a homeostatic function.

¹Lipton, 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

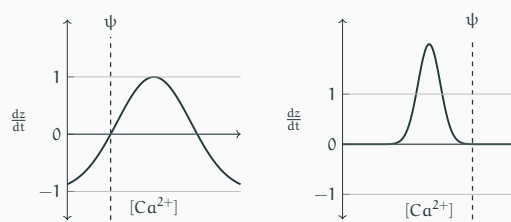


¹Lipton, S. A. & Kater, S. B. Neurotransmitter regulation of neuronal outgrowth, plasticity and survival. *Trends in neurosciences* 12, 265-270. ISSN: 0166-2236. <http://www.sciencedirect.com/science/article/pii/016622368990026X> (1989)

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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Growth curves: possibilities

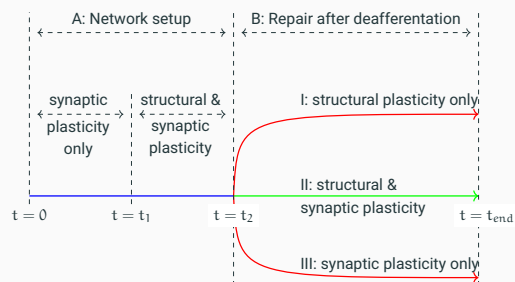


4 free parameters describe each growth curve. We must determine 6 sets of growth curves: 3 for E, 3 for I neurons.

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

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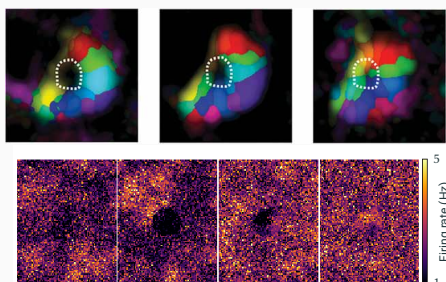
Replicate peripheral lesion protocol



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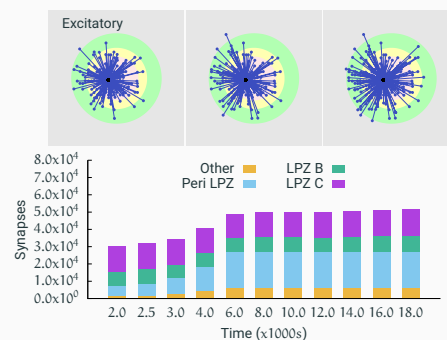
Results: a few years later

Reproduction of deafferentation and repair



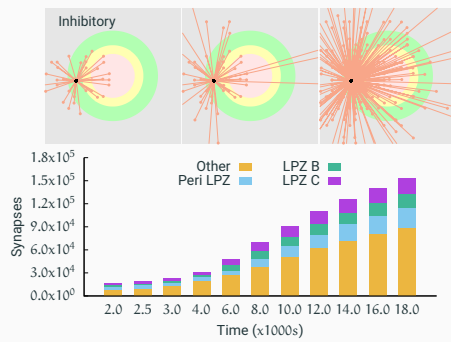
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Reproduction of ingrowth of excitatory projections



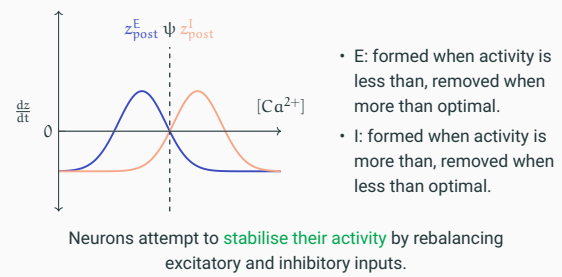
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Reproduction of outgrowth of inhibitory projections



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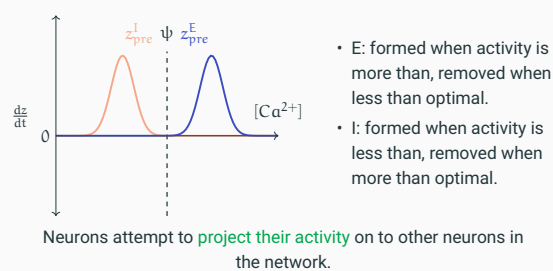
Resultant activity dependent growth rules: post-synaptic



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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Resultant activity dependent growth rules: pre-synaptic



¹Perez, 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)
²Schuemann, A. et al. Structural plasticity of GABAergic axons is regulated by network activity and GABA_A 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** 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: 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**: \LaTeX , the Python science stack, daily use productivity tools...
- **180** tools in queue¹

¹<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.net¹.
- Telegram channel: @NeuroFedora².
- Mailing list on lists.fedoraproject.org³.

¹#fedora-neuro on Freenode

²@NeuroFedora on Telegram

³neuro-sig@lists.fedoraproject.org

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Search: NeuroFedora



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Sources and license

github.com/sanjayankur31/20200117-KARMA-presentation

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