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

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- "Neurons that fire together, wire together."[1]

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

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)

Synaptic plasticity: the popular plasticity

- changes in efficacy of existing synapses,

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- changes in efficacy of existing synapses,
- changes in structure are ignored[1].

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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)

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- 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)

Two theories:

- “unmasking” of pre-existing synaptic connections,

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Two theories:

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

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

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)

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- 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)

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)

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- 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)

So:

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

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- whole synapses are formed and removed.
- How? Why?

Aim

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

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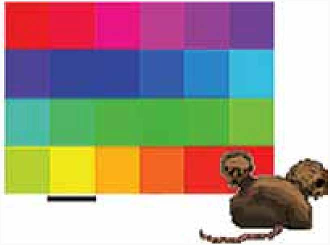
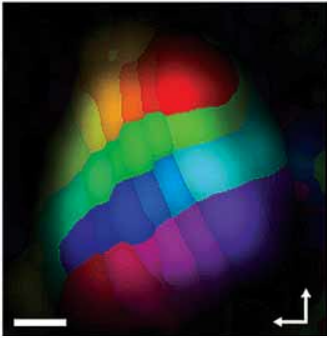
- A computational model allows us to:
  - investigate every entity in the network: variables from neurons, their neurites, all synapses,
  - modify any parameters to analyse changes in network behaviour: neuronal parameters, synaptic parameters, other network parameters,
  - run multiple analyses in 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?

Peripheral lesion protocol I: topographic mapping





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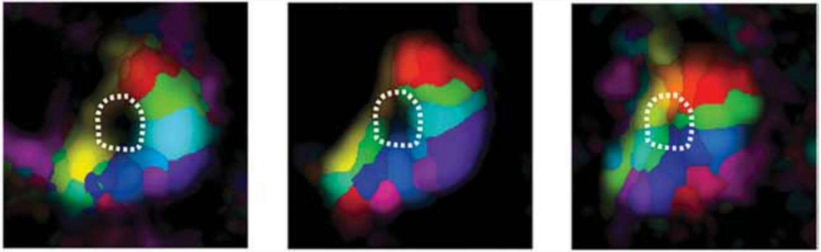
Peripheral lesion protocol II: after peripheral lesion



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

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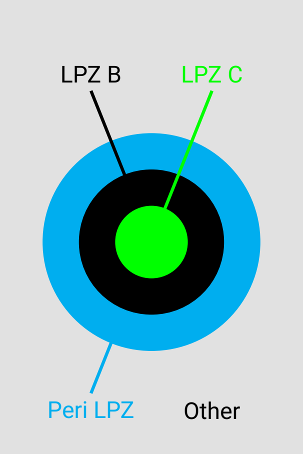
Data gathered from these experiments: summary



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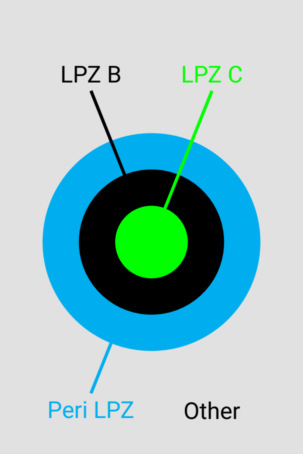
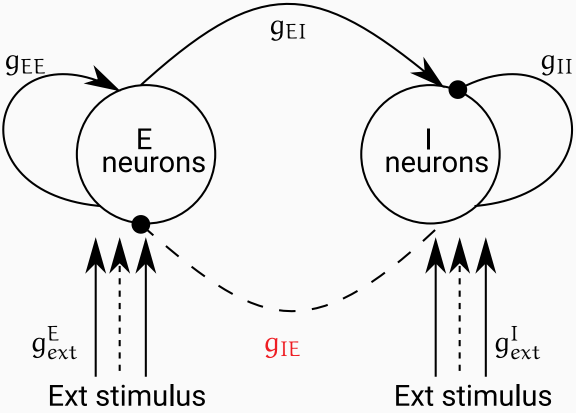


- Inward repair of network.
- Gradual ingrowth of excitatory synapses from the peri-LPZ to the LPZ.
- Gradual outgrowth of inhibitory synapses from the LPZ to the peri-LPZ.

Cortical spiking network model: 8000 E, 2000 I neurons

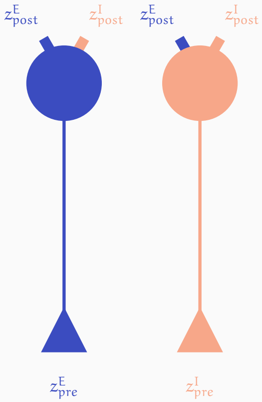


Exhibits cortical Asynchronous Irregular (AI) firing.

[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

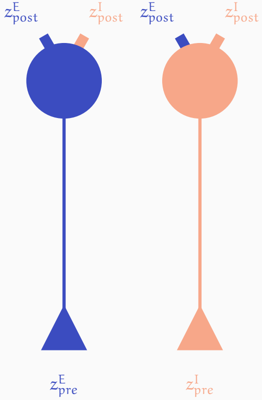
- Single compartment, point “leaky integrate and fire neurons”[1],
- Host neurites (z).



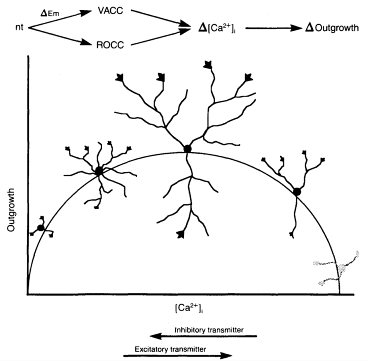
[1] Meffin, H. *et al.* An analytical model for the ‘large, fluctuating synaptic conductance state’ typical of neocortical neurons in vivo. *Journal of computational neuroscience* **16,** 159–175. https://link.springer.com/article/10.1023/B:JCNS.0000014108.03012.81 (2004)

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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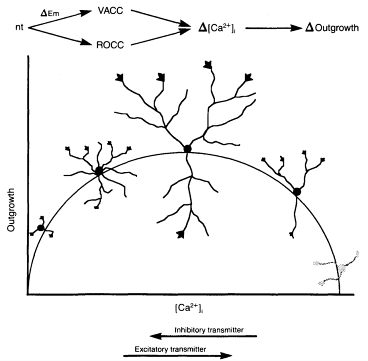
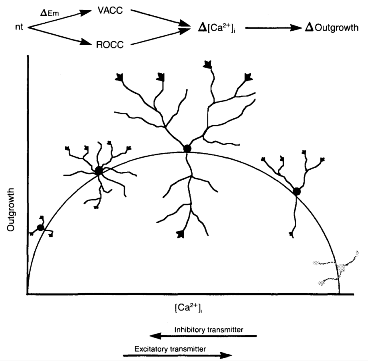
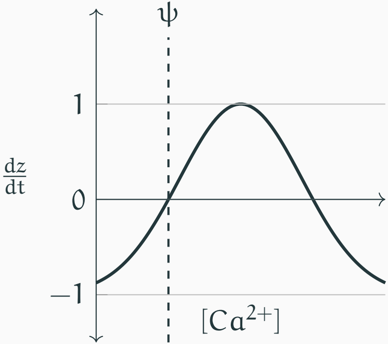


- $[Ca^{2+}]$ correlates with neuronal activity,
- serves a homeostatic function.

[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) modelled as a Guassian function of activity

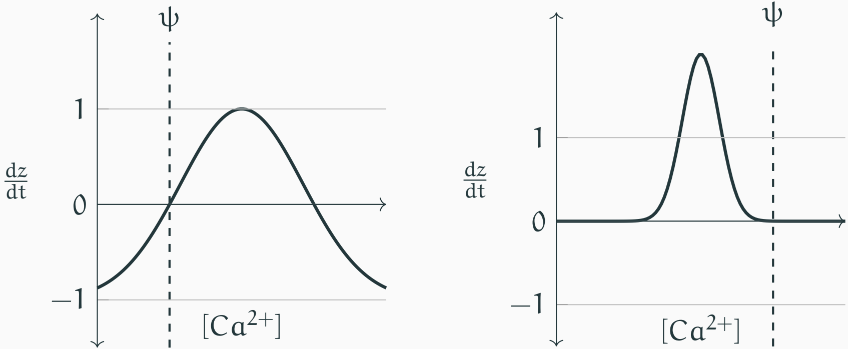




[1] Lipton, S. A. & Kater, S. B. Neurotransmitter regulation of neuronal outgrowth, plasticity and survival. *Trends in neurosciences* **12,** 265–270. ISSN: 0166-2236. http://www.sciencedirect.com/science/article/pii/016622368990026X (1989)

[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)

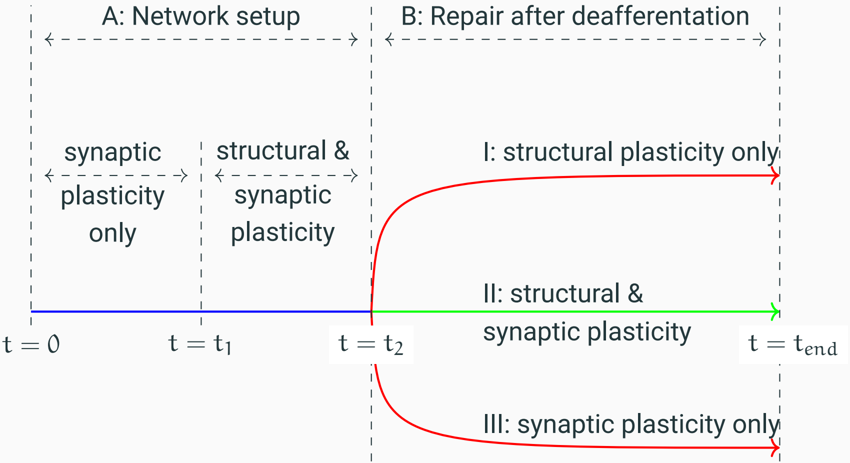
Growth curves: possibilities



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

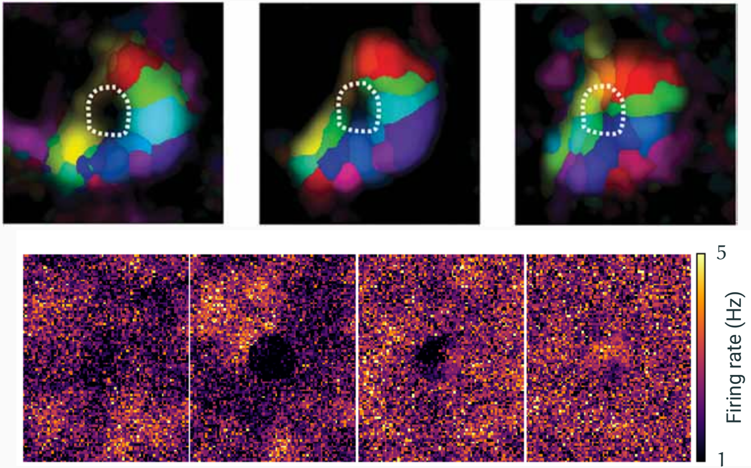
[1] Sinha, A. *et al.* Growth Rules for the Repair of Asynchronous Irregular Neuronal Networks after Peripheral Lesions. *bioRxiv.* eprint: https://www.biorxiv.org/content/early/2019/10/21/810846.full.pdf. https://www.biorxiv.org/content/early/2019/10/21/810846 (2019)

Replicate peripheral lesion protocol

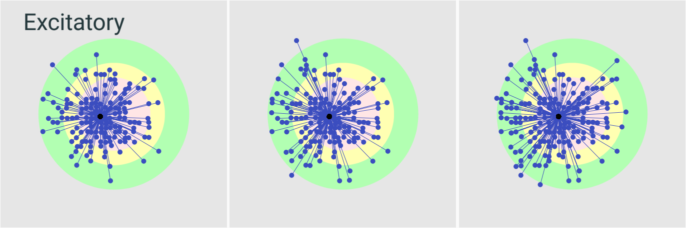


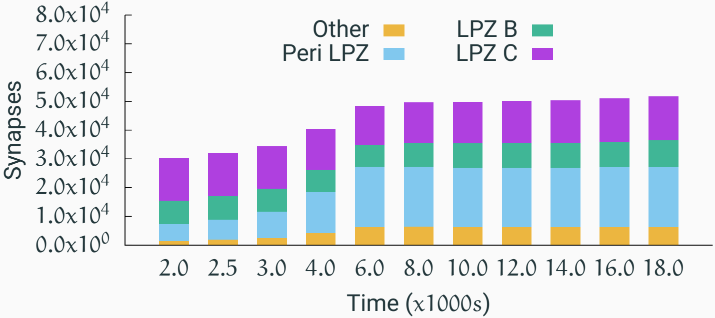
Results: a few years later

Reproduction of deafferentation and repair

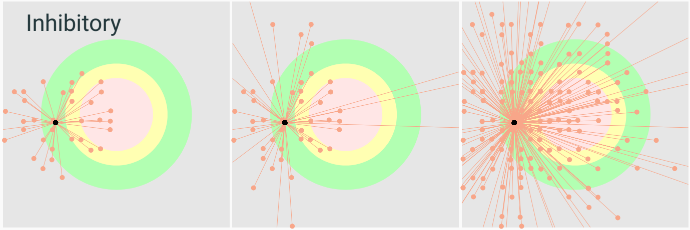


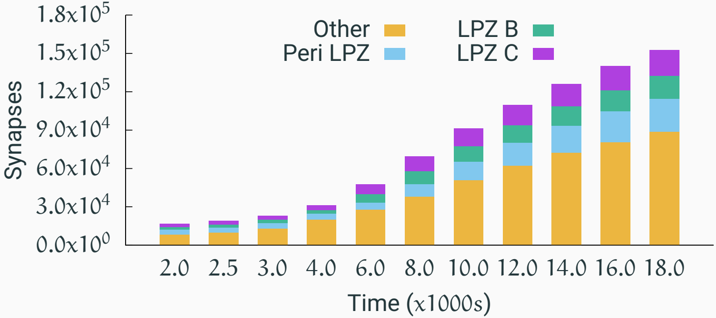
Reproduction of ingrowth of excitatory projections



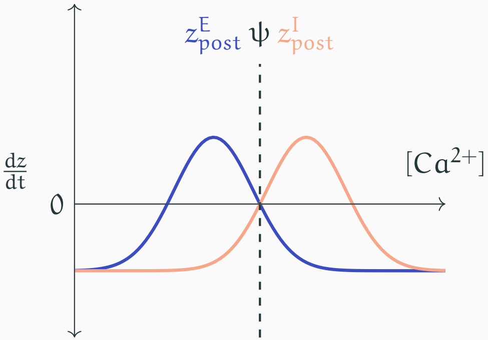


Reproduction of outgrowth of inhibitory projections





Resultant activity dependent growth rules: post-synaptic



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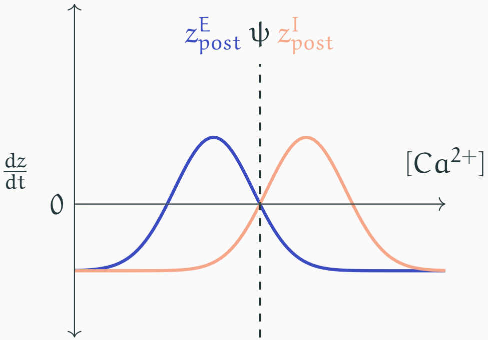

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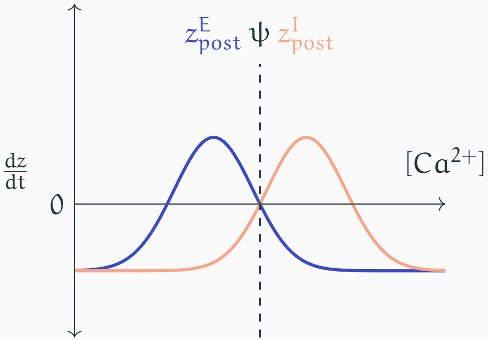

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Neurons attempt to stabilise their activity by rebalancing excitatory and inhibitory inputs.

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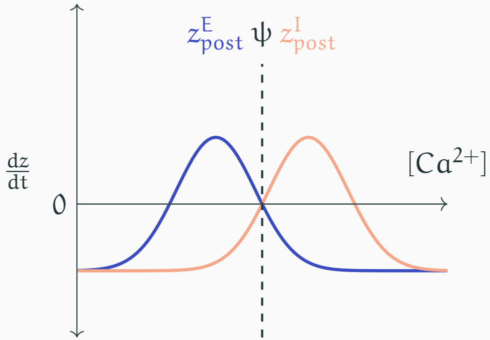

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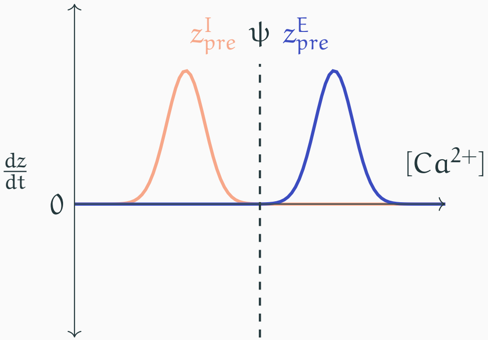
[1] Richards, D. A. *et al.* Glutamate induces the rapid formation of spine head protrusions in hippocampal slice cultures. *Proceedings of the National Academy of Sciences* **102,** 6166–6171 (2005)

[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)

Resultant activity dependent growth rules: pre-synaptic



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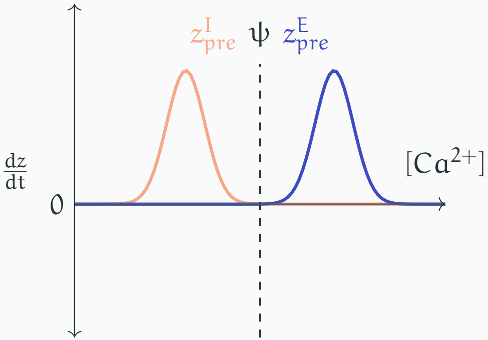

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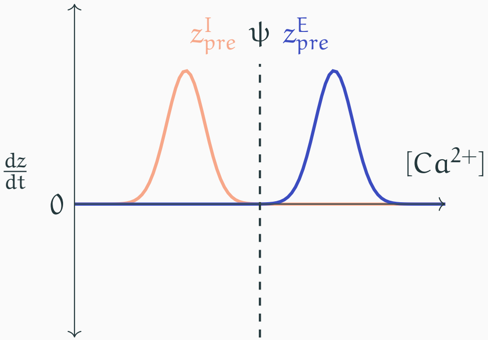

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Neurons attempt to project their activity on to other neurons in the network.

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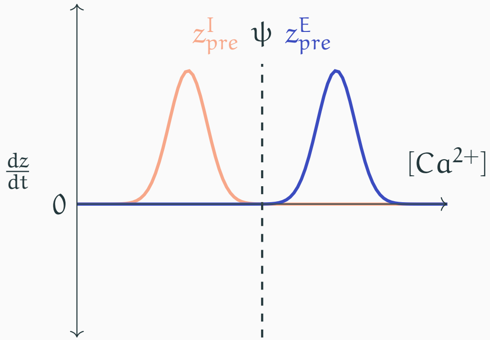

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[2] Schuemann, A. *et al.* Structural plasticity of GABAergic axons is regulated by network activity and GABAA receptor activation. *Frontiers in neural circuits* **7,** 113 (2013)

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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.

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.

Limitations: summary

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

NeuroFedora: Free Software for Free Neuroscience

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- Neuroscientists hail from diverse academic backgrounds.
- Scientists are trying to move towards being more Open:
  - data, methods, analysis, simulations, publishing, collaboration…

Free/Open Source Software vs Open Science

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

Everyone should have the freedom to share, study, and modify scientific material[2].

[1] Free software foundation: fsf.org

[2] Open source for neuroscience: opensourceforneuroscience.org

NeuroFedora: volunteer driven initiative

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  - help developers (upstream)
    - collect feedback from users.
    - make software improvements.
    - implement software development standards.

Current status: software

- Ready to download ISO for computational neuroscience,

[1] https://pagure.io/neuro-sig/NeuroFedora/issues

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- 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...
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  - Utilities: LaTeX, the Python science stack, daily use productivity tools…
- 180 tools in queue[1]

[1] https://pagure.io/neuro-sig/NeuroFedora/issues

Current status: team

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

NeuroFedora: links

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

[1] #fedora-neuro on Freenode
[2] @NeuroFedora on Telegram
[3] neuro-sig@lists.fedoraproject.org

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