Investigating the activity dependent dynamics of synaptic structures using biologically realistic modelling of peripheral lesion experiments

Discussion of my Ph.D. research

Ankur Sinha

29/03/2019

2019-03-29

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Context

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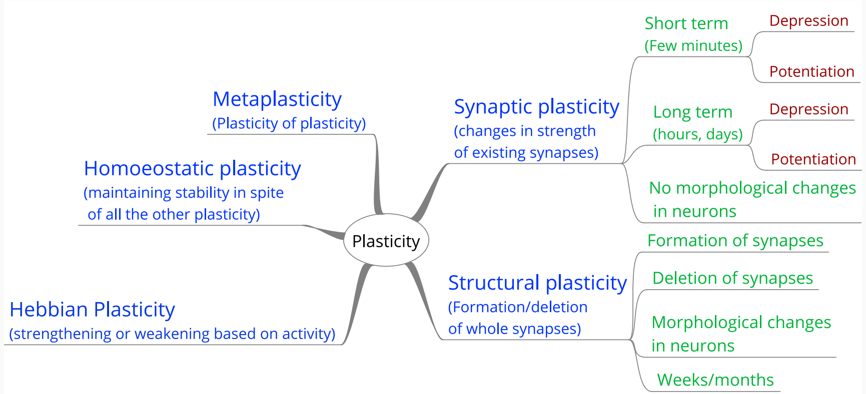
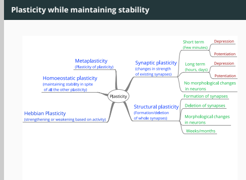
Plasticity while maintaining stability





1. We know there are multiple plasticity mechanisms active all at once. Hebbian plasticity underlies learning, but de-stabilises networks. Homeostatic plasticity ensures that even when learning occurs, the network remains in a stable state
2. Generally, though, when we speak of these, we refer to synaptic plasticity only. But, lots of evidence now confirms that, in fact, structural plasticity is active in the adult brain. So not only are synaptic weights changing, the connectivity of networks is changing too!
3. So, it isn't hard to imaging how if changes in synaptic strengths makes plasticity-stability an issue, how the removal and formation of whole synapses would have a much larger effect to plasticity-stability.
4. For the purpose of our analysis, we do not consider the

Synaptic structures are dynamic in the adult brain

1. Chen, J. L. *et al.* Structural basis for the role of inhibition in facilitating adult brain plasticity. *Nature neuroscience* **14,** 587–594 (2011)
2. Marik, S. A. *et al.* Axonal dynamics of excitatory and inhibitory neurons in somatosensory cortex. *PLoS Biology* **8,** e1000395 (2010)
3. Marik, S. A. *et al.* Large-scale axonal reorganization of inhibitory neurons following retinal lesions. *Journal of Neuroscience* **34,** 1625–1632 (2014)
4. Stettler, D. D. *et al.* Axons and Synaptic Boutons Are Highly Dynamic in Adult Visual Cortex. *Neuron* **49,** 877–887. ISSN: 0896-6273 (2006)
5. Gogolla, N. *et al.* Structural plasticity of axon terminals in the adult. *Current opinion in neurobiology* **17,** 516–524 (2007)
6. Holtmaat, A. J. G. D. *et al.* Transient and Persistent Dendritic Spines in the Neocortex In Vivo. *Neuron* **45,** 279–291. ISSN: 0896-6273 (2005)
7. Chen, J. L. *et al.* Clustered dynamics of inhibitory synapses and dendritic spines in the adult neocortex. *Neuron* **74,** 361–373 (2012)
8. Trachtenberg, J. T. *et al.* Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex. *Nature* **420,** 788–794 (2002)
9. 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)

1. In the adult brain, now that we have the tech to look in at the microscopic structures that form synapses, we see that these are highly dynamic. They sprout and retract, forming and removing synapses. However, this must happen in a way that the brain remains functional: so, are their Hebbian and Homeostatic components of structural plasticity too?

Evidence of homeostatic structural plasticity: lesion studies

1. 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)
2. Rasmusson, D. D. Reorganization of raccoon somatosensory cortex following removal of the fifth digit. *Journal of Comparative Neurology* **205,** 313–326 (1982)
3. 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)
4. Pons, T. P. *et al.* Massive cortical reorganization after sensory deafferentation in adult macaques. *Science* **252,** 1857–1860 (1991)
5. Allard, T. *et al.* Reorganization of somatosensory area 3b representations in adult owl monkeys after digital syndactyly. *Journal of neurophysiology* **66,** 1048–1058 (1991)
6. Darian-Smith, C. & Gilbert, C. D. Axonal sprouting accompanies functional reorganization in adult cat striate cortex. *Nature* **368,** 737–740 (1994)
7. Darian-Smith, C. & Gilbert, C. D. Topographic reorganization in the striate cortex of the adult cat and monkey is cortically mediated. *The journal of neuroscience* **15,** 1631–1647 (1995)
8. Florence, S. L. *et al.* Large-scale sprouting of cortical connections after peripheral injury in adult macaque monkeys. *Science* **282,** 1117–1121 (1998)
9. 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)

Evidence of homeostatic structural plasticity: lesion studies

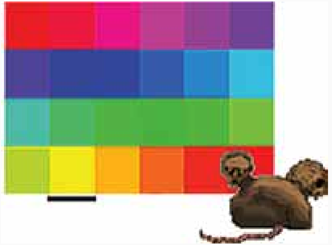
1. The simplest way of studying homeostatic mechanism is to nudge the network out of its stable state. Lesion studies have, for a long time, observed structural changes after peripheral lesioning. A peripheral lesion is where you dont destroy the network itself, but you disrupt the input to it—we'll come to this in detail later.

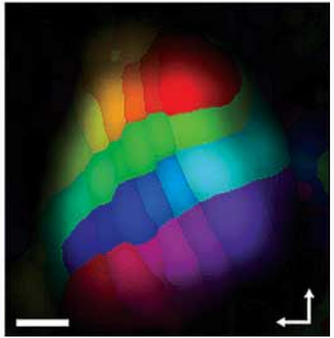
Detailed lesion experiments to study synaptic structures

1. Chen, J. L. *et al.* Structural basis for the role of inhibition in facilitating adult brain plasticity. *Nature neuroscience* **14,** 587–594 (2011)
2. Marik, S. A. *et al.* Axonal dynamics of excitatory and inhibitory neurons in somatosensory cortex. *PLoS Biology* **8,** e1000395 (2010)
3. Yamahachi, H. *et al.* Rapid axonal sprouting and pruning accompany functional reorganization in primary visual cortex. *Neuron* **64,** 719–729 (2009)
4. Hickmott, P. W. & Steen, P. A. Large-scale changes in dendritic structure during reorganization of adult somatosensory cortex. *Nature neuroscience* **8,** 140–142 (2005)
5. Keck, T. *et al.* Massive restructuring of neuronal circuits during functional reorganization of adult visual cortex. *Nature neuroscience* **11,** 1162–1167 (2008)
6. 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 (2011)
7. Trachtenberg, J. T. *et al.* Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex. *Nature* **420,** 788–794 (2002)

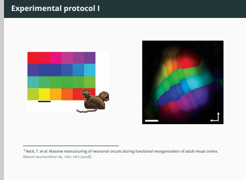
1. With more tech, neuroscientists have been able to mark, track, and analyse micro-structures that are involved in synapses: boutons, spines, dendritic trees. So, there's recently quite a bit of data from these.

Experimental protocol I



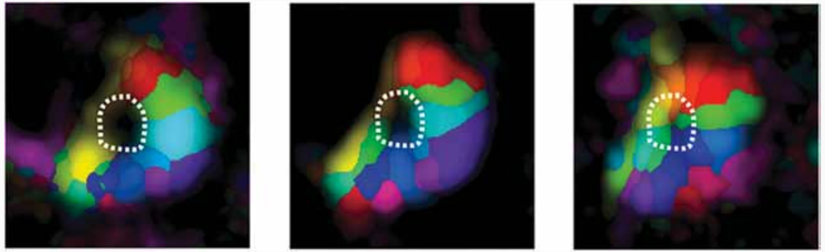


[1] Keck, T. *et al.* Massive restructuring of neuronal circuits during functional reorganization of adult visual cortex. *Nature neuroscience* **11,** 1162–1167 (2008)

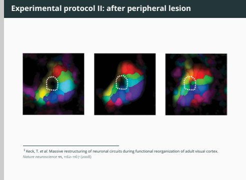


1. The protocol is pretty standard. Here, for a study in the visual cortex, the retinal field of a rat or a mouse is mapped.

Experimental protocol II: after peripheral lesion

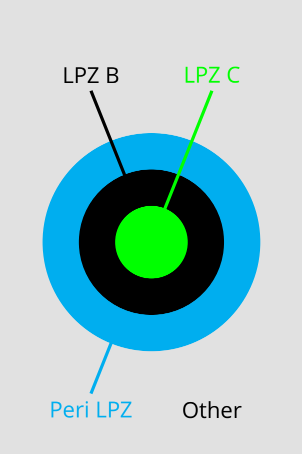


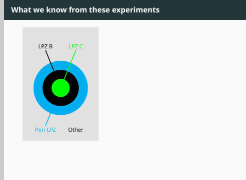
[1] Keck, T. *et al.* Massive restructuring of neuronal circuits during functional reorganization of adult visual cortex. *Nature neuroscience* **11,** 1162–1167 (2008)



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.

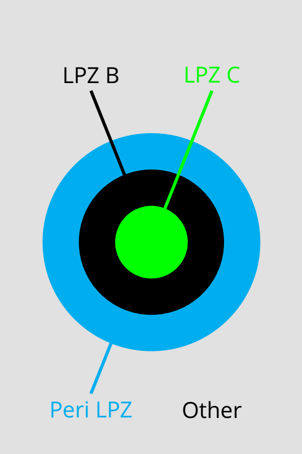
What we know from these experiments



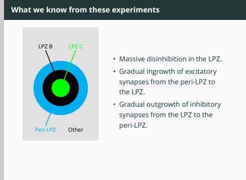


1. So, if this a simple schematic, of the regions around the LPZ, this is what we know from these studies.
2. To permit a window for structural re-organisation.
3. To make up for lost excitation.
4. To make up for lost inhibition.

What we know from these experiments



- Massive disinhibition in the LPZ.
- 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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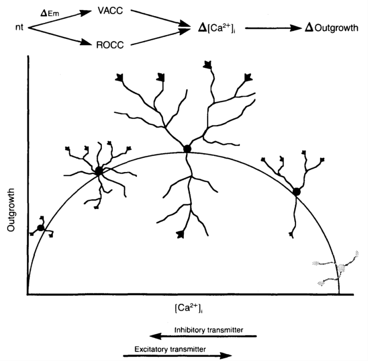
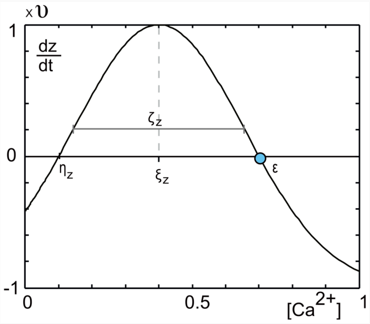
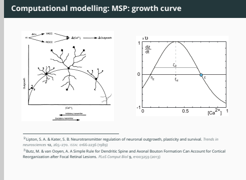
Computational modelling: MSP: growth curve





[2] Lipton, S. A. & Kater, S. B. Neurotransmitter regulation of neuronal outgrowth, plasticity and survival. *Trends in neurosciences* **12,** 265–270. ISSN: 0166-2236 (1989)

[3] 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)



1. In the paper, we simply cite this bit and discuss it briefly, but here I'll explain it in more detail here.
2. Computational modelling stems from evidence from decades years ago. It was established that outgrowth depends on the change in the Calcium concentration in neurons.
3. So, in this figure, we see that a neurotransmitter causes a change in the Calcium of the neuron, and that causes some change in its outgrowth.
4. What this suggests, is that there's an optimal level of Calcium for neurons to have "normal" growth.
5. Based on this, Butz and van Ooyen came up with a framework for modelling structural plasticity. In this, they modelled the rate of change of synaptic elements as a Gaussian function of the neuron's Calcium concentration.

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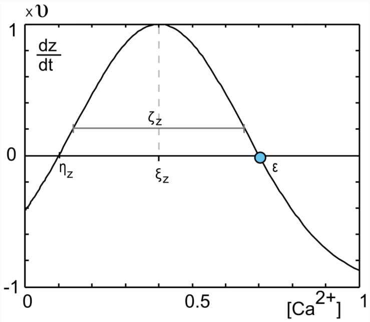
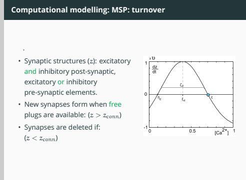
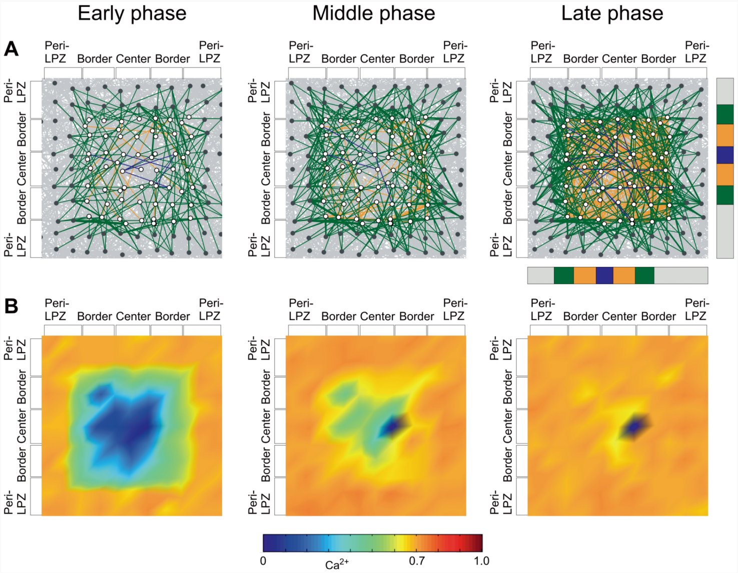
- Synaptic structures (z): excitatory and inhibitory post-synaptic, excitatory or inhibitory pre-synaptic elements.
- New synapses form when free plugs are available: ($z > z_{\text{conn}}$)
- Synapses are deleted if: ($z < z_{\text{conn}}$)

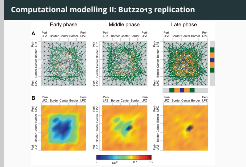




1. A stable fixed point where nothing occurs. If activity is less, sprouting, if more, retraction, but if very less, retraction
2. Note that they applied the same for excitatory and inhibitory post-synaptic elements
3. And, the same for all neurons: excitatory and inhibitory.

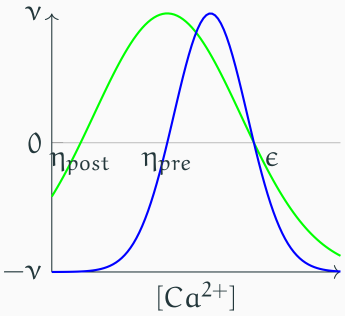
Computational modelling II: Butz2013 replication

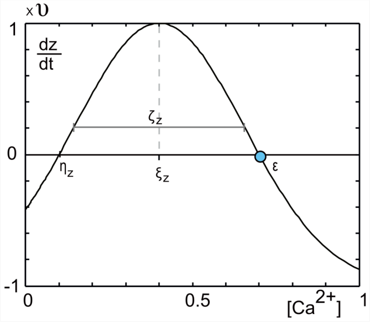


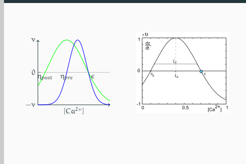


1. They replicated the peripheral lesion study, as you see.
2. You have repair from the outside in, and you have ingrowth of excitatory axons.

Computational modelling II: Butz2013 results







1. They suggested that post-synaptic elements should form at a lower activity level than pre-synaptic elements
2. They used an arbitrary homeostatic point, for all neurons
3. No discussion of inhibitory circuit here.
4. No discussion of biological realism of the model either.

Methods: our approach

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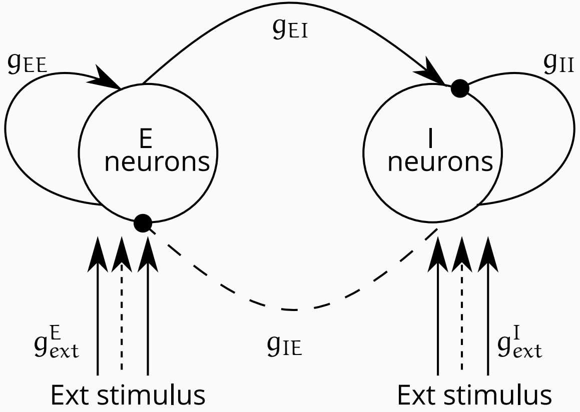
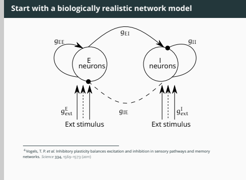
Start with a biologically realistic network model



[4] Vogels, T. P. *et al.* Inhibitory plasticity balances excitation and inhibition in sensory pathways and memory networks. *Science* **334**, 1569–1573 (2011)



1. We decided to start with a biologically realistic model: a cortical model proposed by Vogels et al.
2. This includes realistic conductances, for example.
3. This model is balanced by homeostatic inhibitory synaptic plasticity, and exhibits AI characteristics similar to cortical networks
4. This model does not have any spatial information incorporated it, but to model the LPZ and spatial analysis we do need it.

Extensions

- Probabilistic formation of synapses, also: “longer” inhibitory than excitatory connections[1].
- Probabilistic deletion of synapses (incorporating evidence that stronger synapses have less likelihood of removal[2]).
- Further generalisation of growth curves.

[5] Citation buried in my lab logs somewhere!

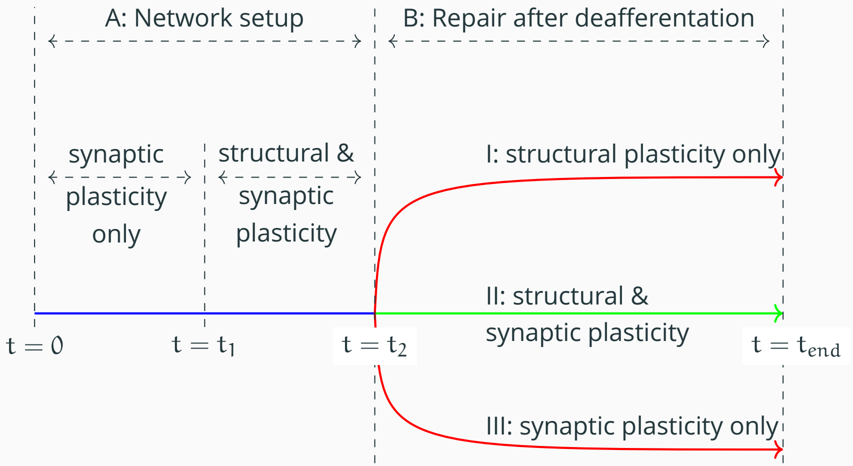
[6] Knott, G. W. *et al.* Spine growth precedes synapse formation in the adult neocortex in vivo. *Nature neuroscience* **9,** 1117–1124 (2006)

Extensions

- Probabilistic formation of synapses, also: “longer” inhibitory than excitatory connections[1].
- Probabilistic deletion of synapses (incorporating evidence that stronger synapses have less likelihood of removal[2]).
- Further generalisation of growth curves.

1. A few of these were made while incorporating spatial information in the model, keeping in mind that we want’ to keep the model as realistica as we can manage.

Simulation protocol



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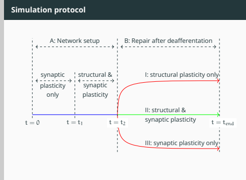


1. Explain the simulation protocol.

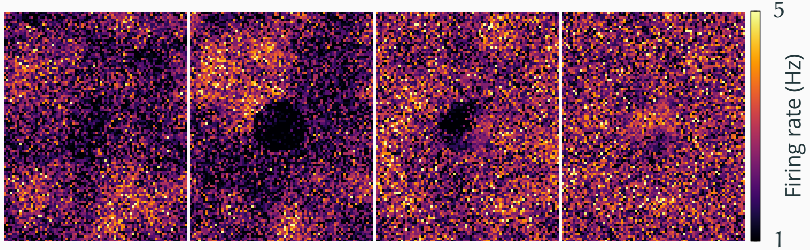
Results and discussion

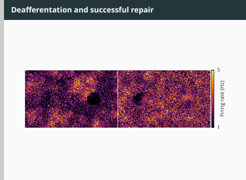
2019-03-29

Investigating the activity dependent dynamics of synaptic structures using biologically realistic modelling of peripheral lesion experiments

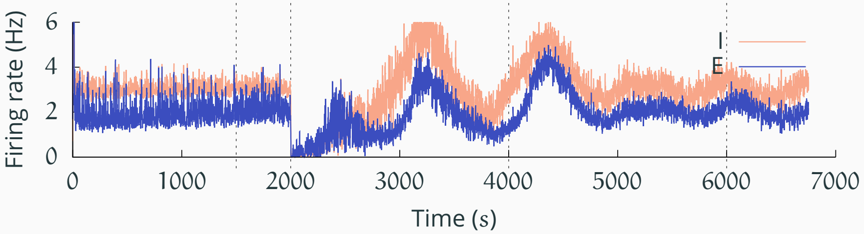
└─Results and discussion

Deafferentation and successful repair





Deafferentation and repair: LPZ



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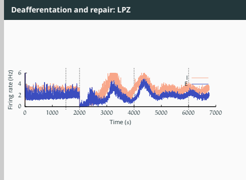
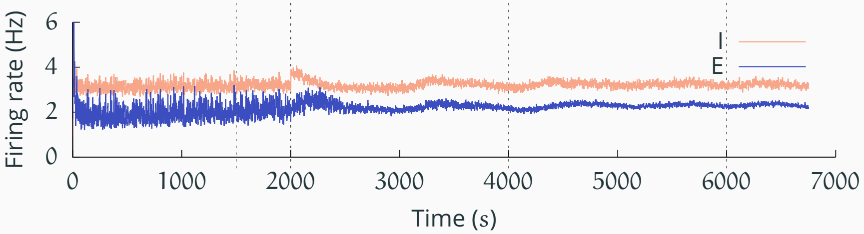
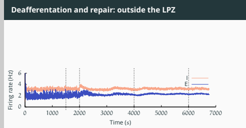


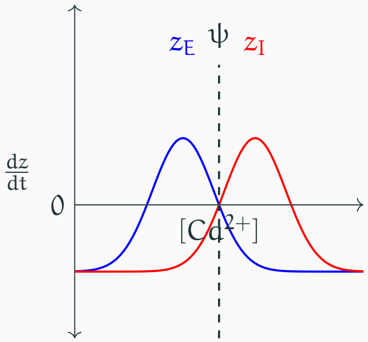
Deafferentation and repair: outside the LPZ



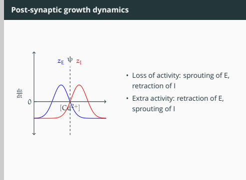


1. This is something different now: the activity outside the LPZ goes up after deafferentation
2. First indication that previous models werent thorough enough.

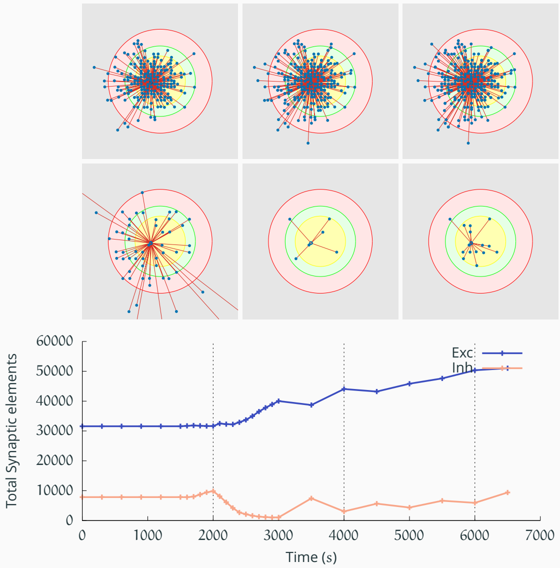
Post-synaptic growth dynamics



- Loss of activity: sprouting of E, retraction of I
- Extra activity: retraction of E, sprouting of I



Resultant turnover: LPZ



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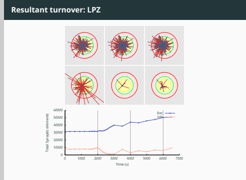
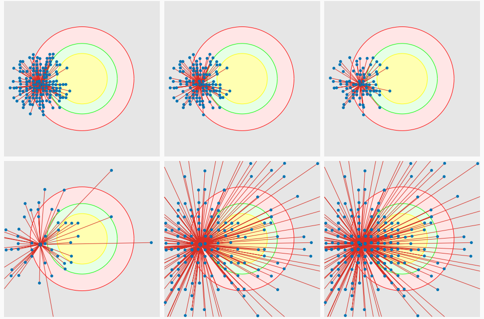
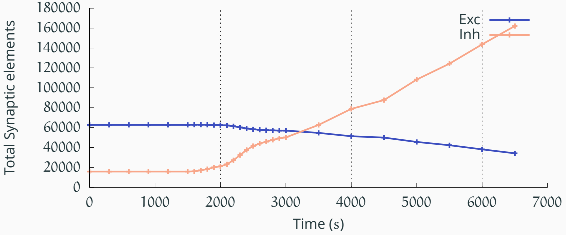
└─Results and discussion



Resultant turnover: outside LPZ





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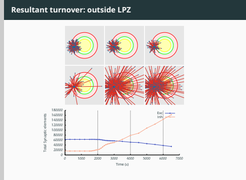
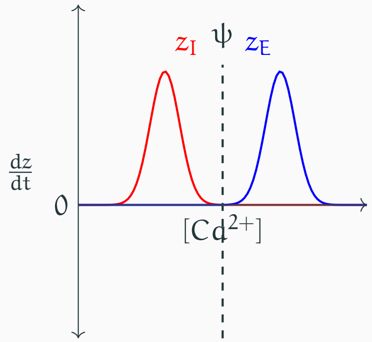
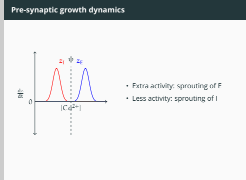


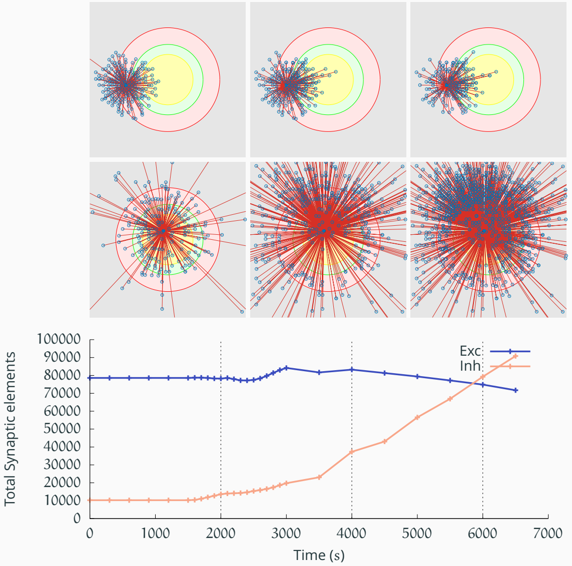
Pre-synaptic growth dynamics

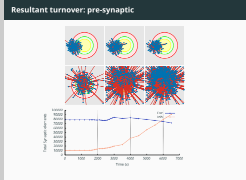


- Extra activity: sprouting of E
- Less activity: sprouting of I

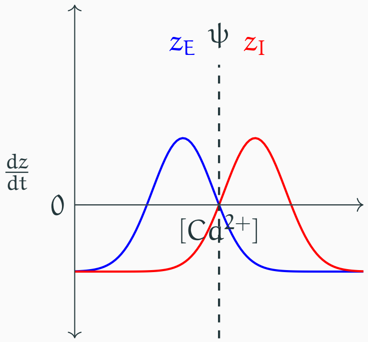


Resultant turnover: pre-synaptic

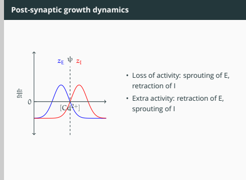




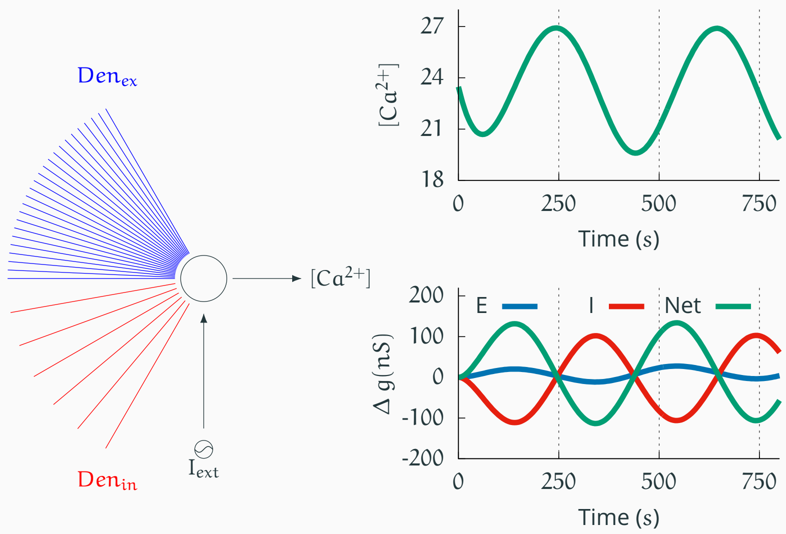
Post-synaptic growth dynamics



- Loss of activity: sprouting of E, retraction of I
- Extra activity: retraction of E, sprouting of I



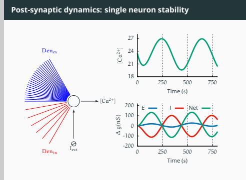
Post-synaptic dynamics: single neuron stability



2019-03-29

Investigating the activity dependent dynamics of synaptic structures using biologically realistic modelling of peripheral lesion experiments

└─Results and discussion



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