

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

Discussion of my Ph.D. research

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Ankur Sinha

29/03/2019

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

2020-01-16

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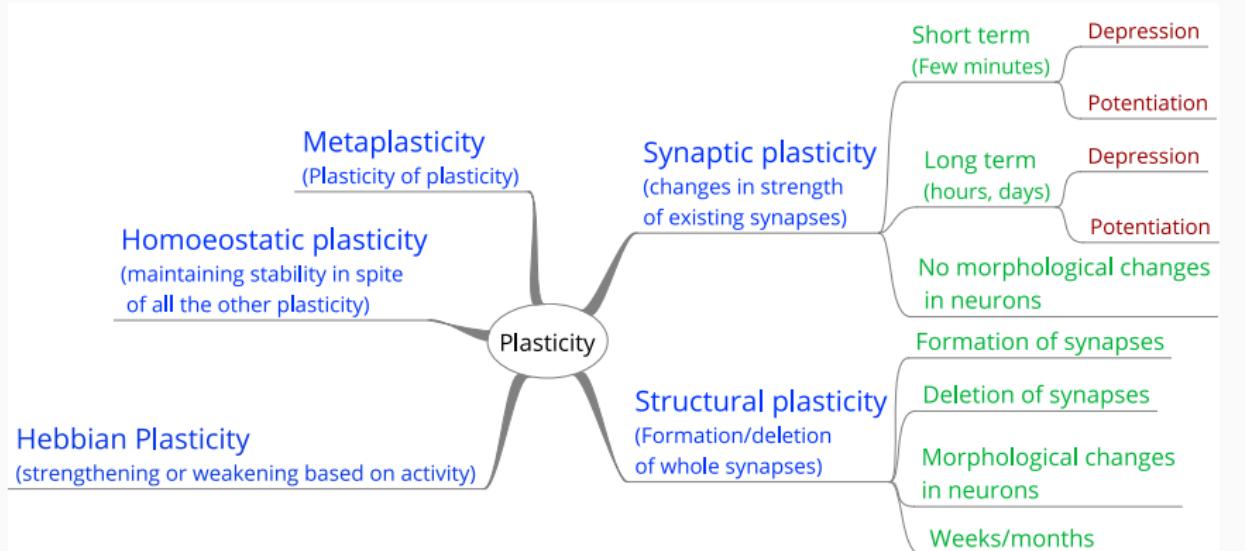
Investigating the activity dependent dynamics of  
synaptic structures using biologically realistic modelling  
of peripheral lesion experiments  
└ Context

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## Context

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# Plasticity while maintaining stability

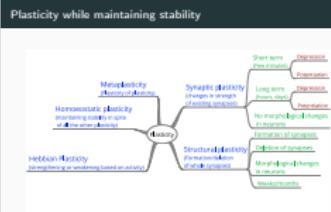


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Investigating the activity dependent dynamics of synaptic structures using biologically realistic modelling of peripheral lesion experiments

Context

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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 imagine 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 modulation

# 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.  
<http://www.sciencedirect.com/science/article/pii/S0896627306001358> (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.  
<http://www.sciencedirect.com/science/article/pii/S0896627305000048> (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)

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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?

- Synaptic structures are dynamic in the adult brain
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# 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)

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

## Context

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 don't destroy the network itself, but you disrupt the input to it—we'll come to this in detail later.

1. Wall, J. T. & Cusick, C. G. Cutaneous responsiveness in primary somatosensory (SI) hindpaw cortex 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)
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# Detailed lesion experiments to study synaptic structures

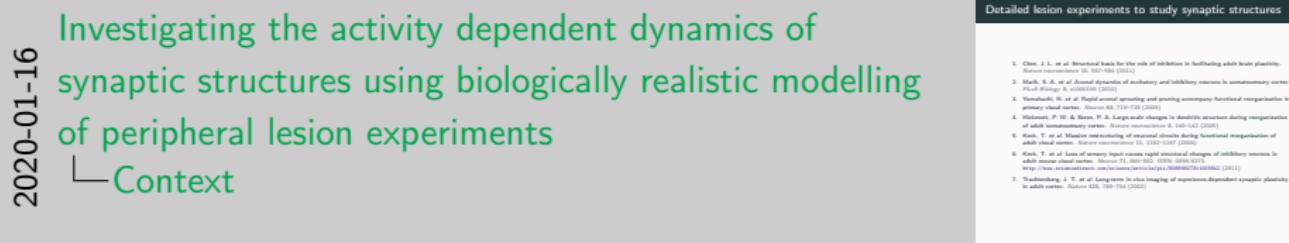
1. Chen, J. L. et al. Structural basis for the role of inhibition in facilitating adult brain plasticity. *Nature neuroscience* 14, 587–594 (2011)
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3. Yamahachi, H. et al. Rapid axonal sprouting and pruning accompany functional reorganization in primary 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.  
<http://www.sciencedirect.com/science/article/pii/S0896627311005642> (2011)
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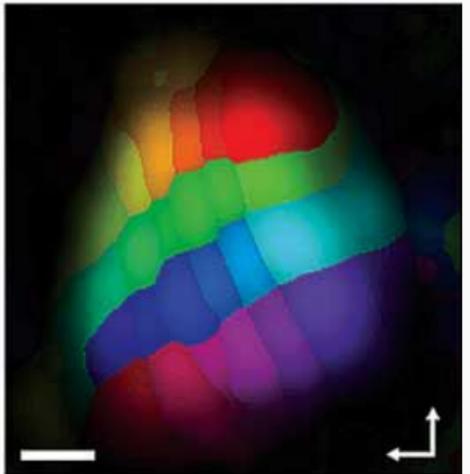
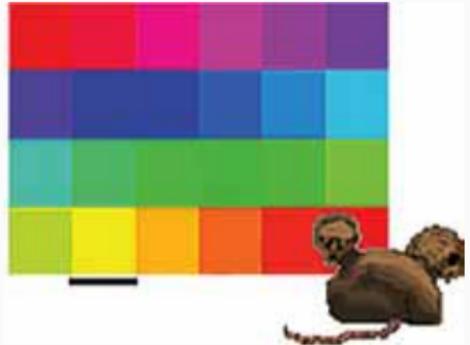
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1. With more tech, neuroscientists have been able to mark, track, and analyse micro-structures that are involved in synapses: boutons, spines, dendritic trees. So, there's recently quite a bit of data from these.

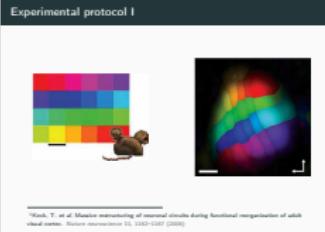
# Experimental protocol I



<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)

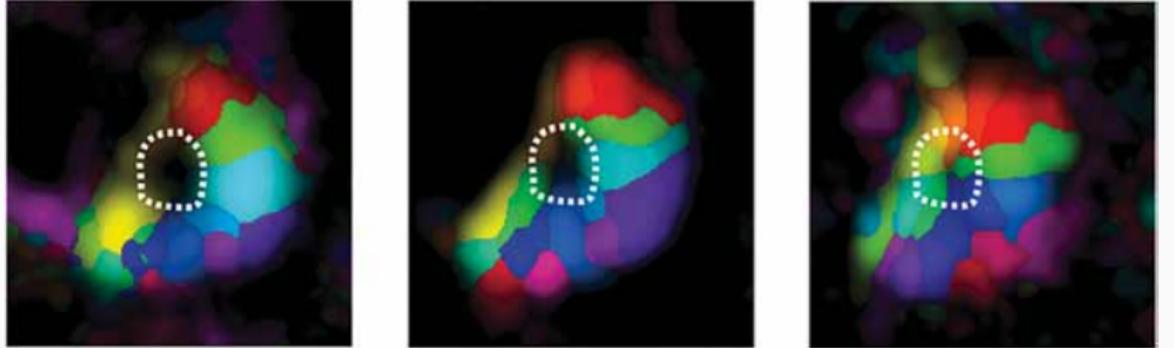
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## Experimental protocol II: after peripheral lesion



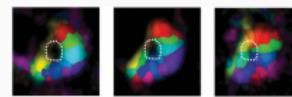
<sup>1</sup> Keck, T. et al. Massive restructuring of neuronal circuits during functional reorganization of adult visual cortex. *Nature neuroscience* 11, 1162–1167 (2008)

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

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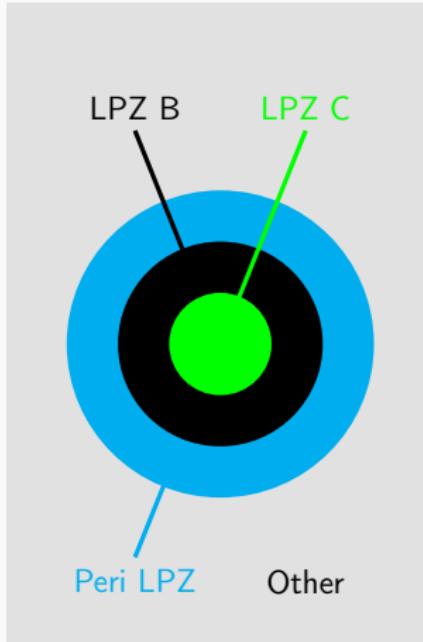
Experimental protocol II: after peripheral lesion



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



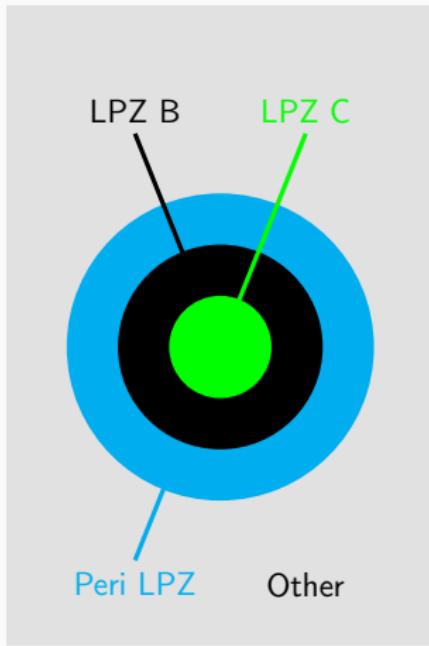
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What we know from these experiments



# 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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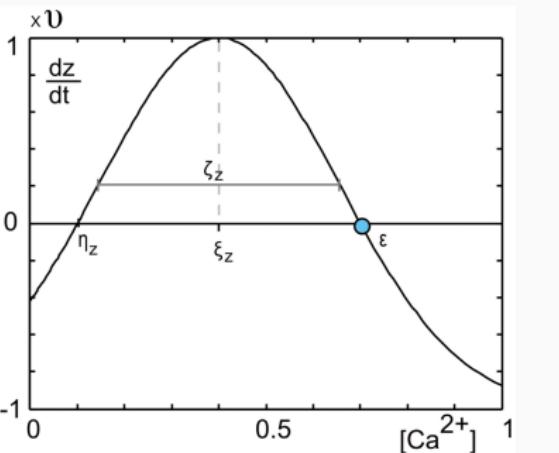
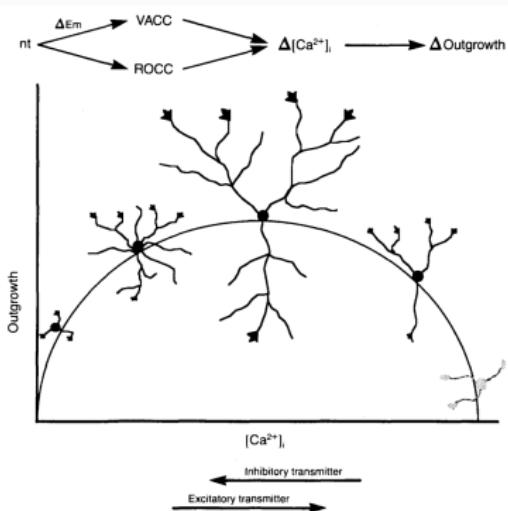
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What we know from these experiments



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- Gradual outgrowth of inhibitory synapses from the LPZ to the peri-LPZ.

# Computational modelling: MSP: growth curve



<sup>2</sup>Lipton, S. A. & Kater, S. B. Neurotransmitter regulation of neuronal outgrowth, plasticity and survival. *Trends in neurosciences* 12, 265–270. ISSN: 0166-2236.

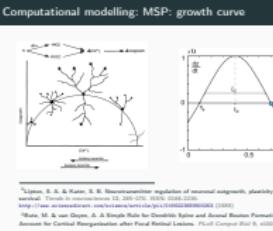
<http://www.sciencedirect.com/science/article/pii/016622368990026X> (1989)

<sup>3</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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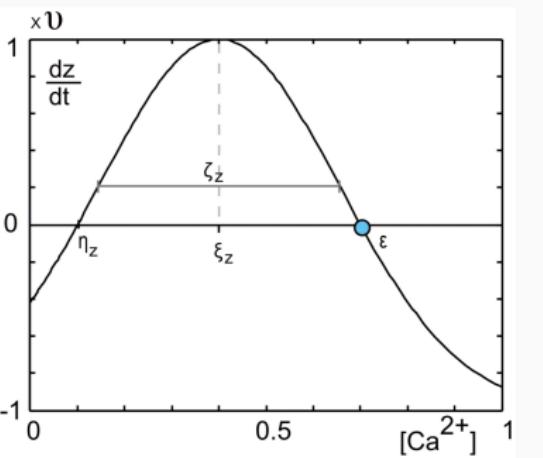
## Context

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.



# Computational modelling: MSP: turnover

- 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: ( $z < z_{\text{conn}}$ )



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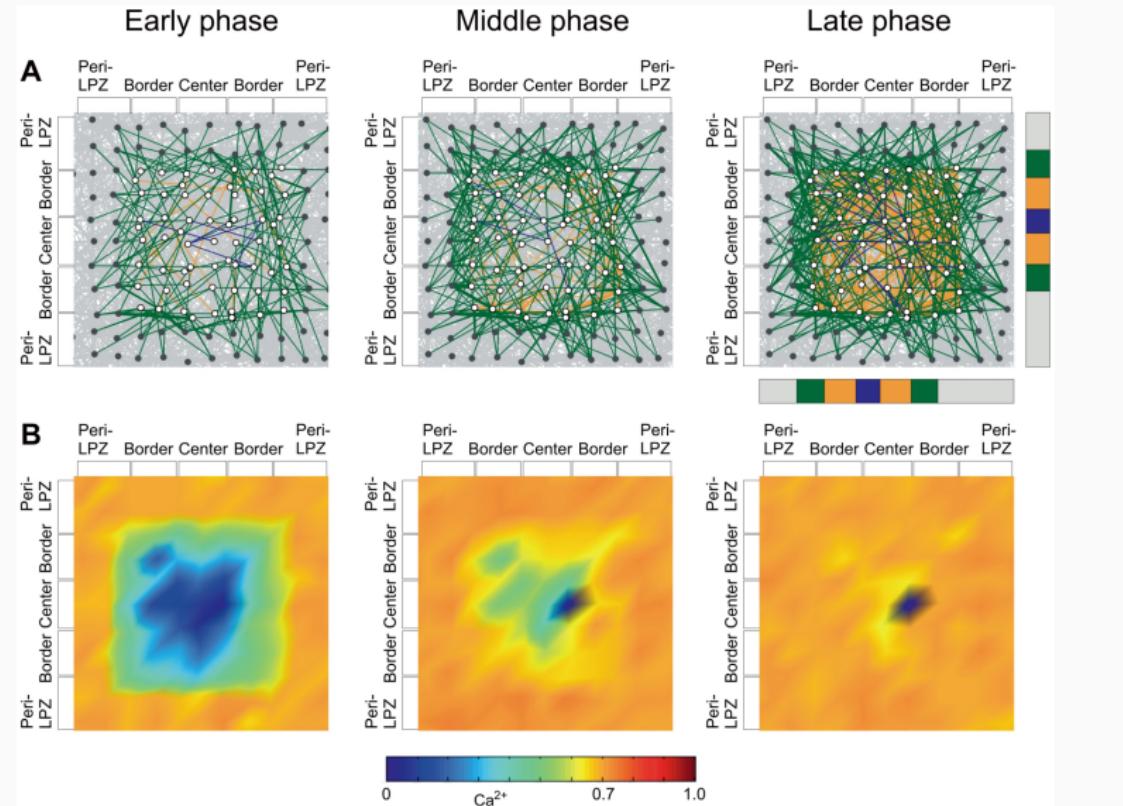
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Computational modelling: MSP: turnover

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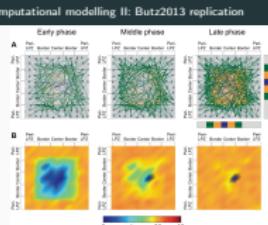
# Computational modelling II: Butz2013 replication



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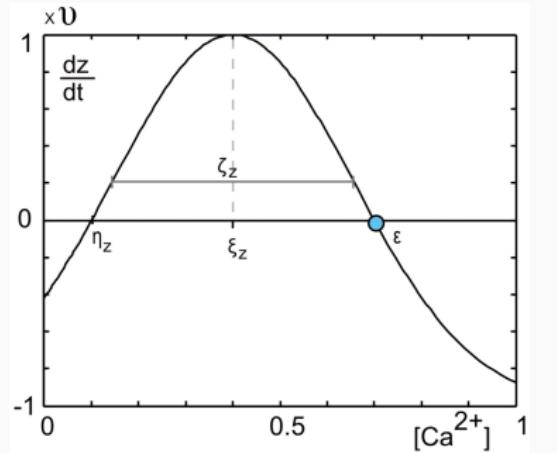
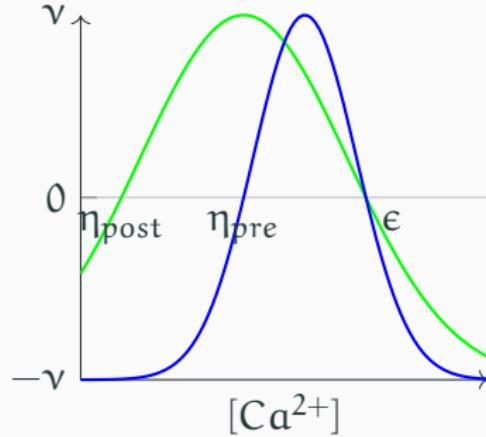
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1. They replicated the peripheral lesion study, as you see.
2. You have repair from the outside in, and you have ingrowth of excitatory axons.

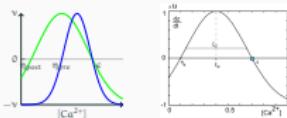
## Computational modelling II: Butz2013 results



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Computational modelling II: Butz2013 results



## Methods: our approach

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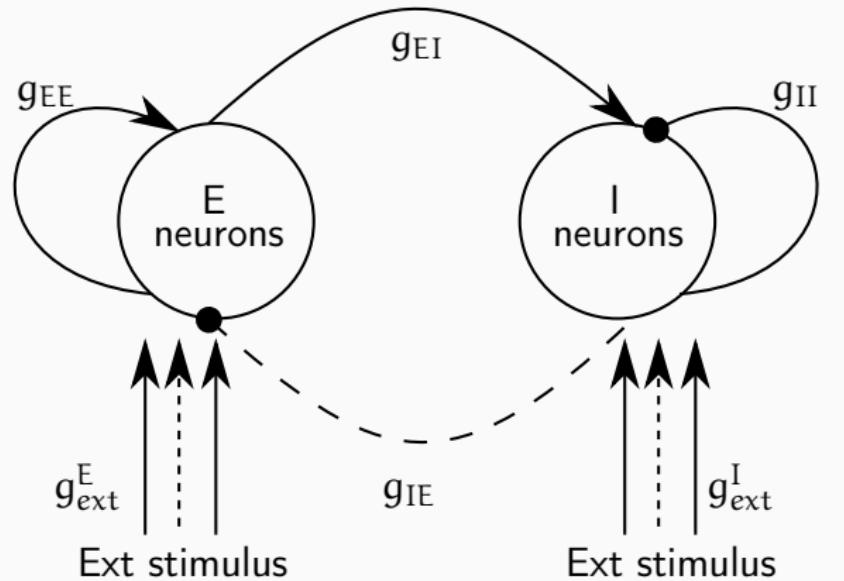
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Methods: our approach

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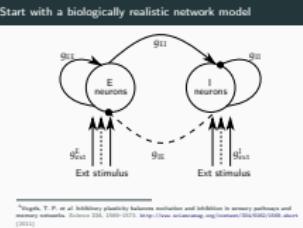
## Start with a biologically realistic network model



<sup>4</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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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.

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

<sup>5</sup>Citation buried in my lab logs somewhere!

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

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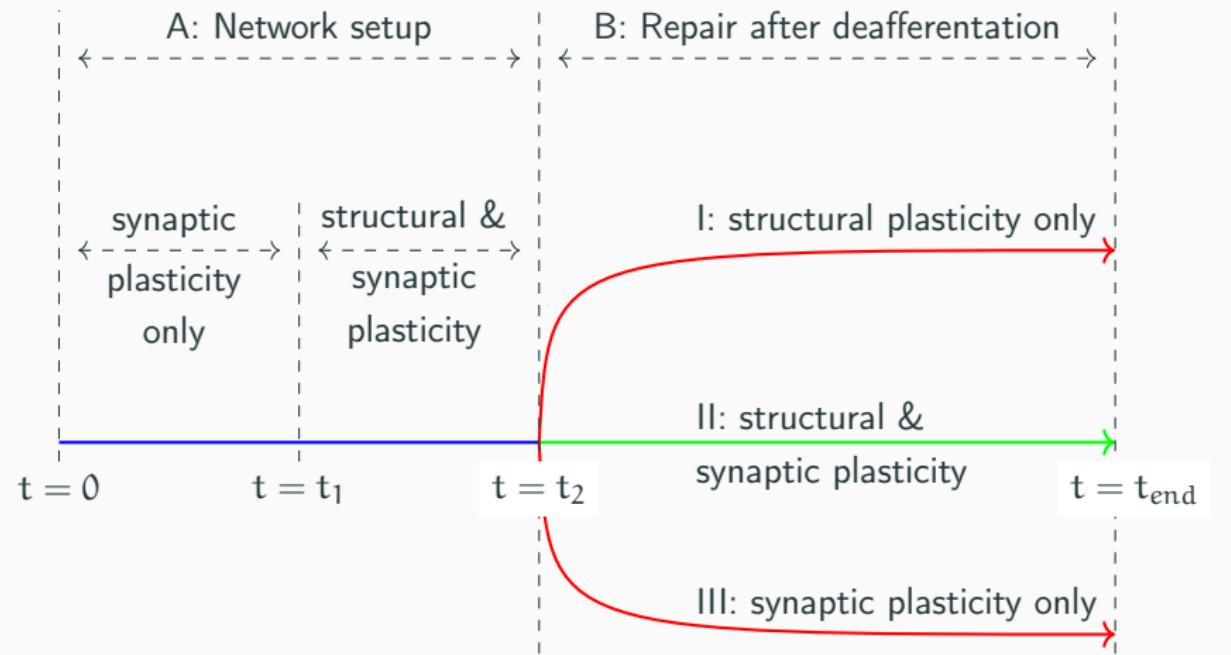
### └ Methods: our approach

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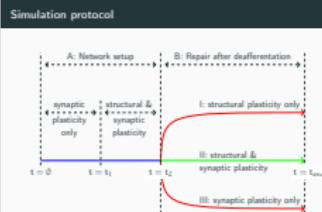
# Simulation protocol



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1. Explain the simulation protocol.

## Results and discussion

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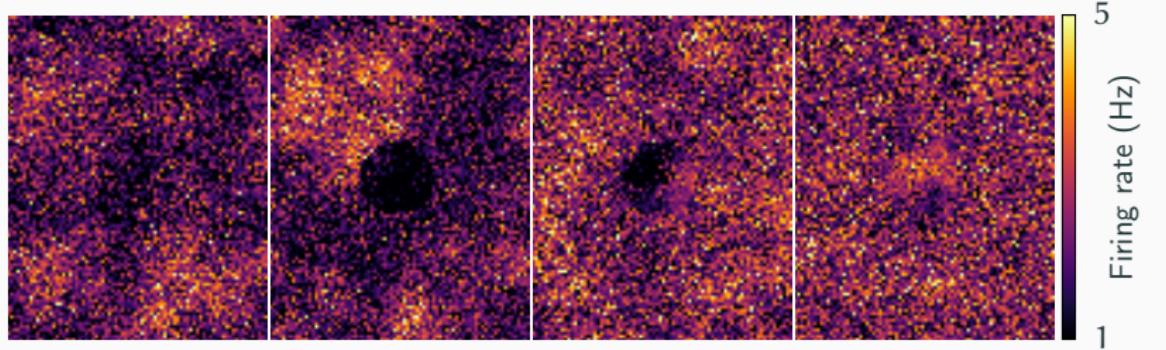
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# Deafferentation and successful repair

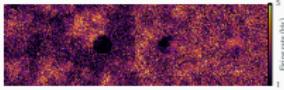


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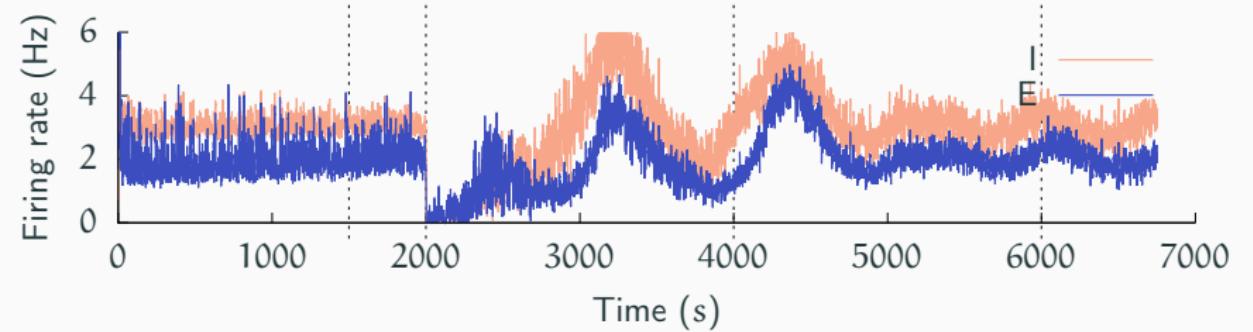
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Deafferentation and successful repair

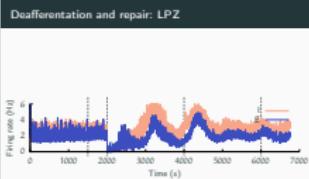


## Deafferentation and repair: LPZ

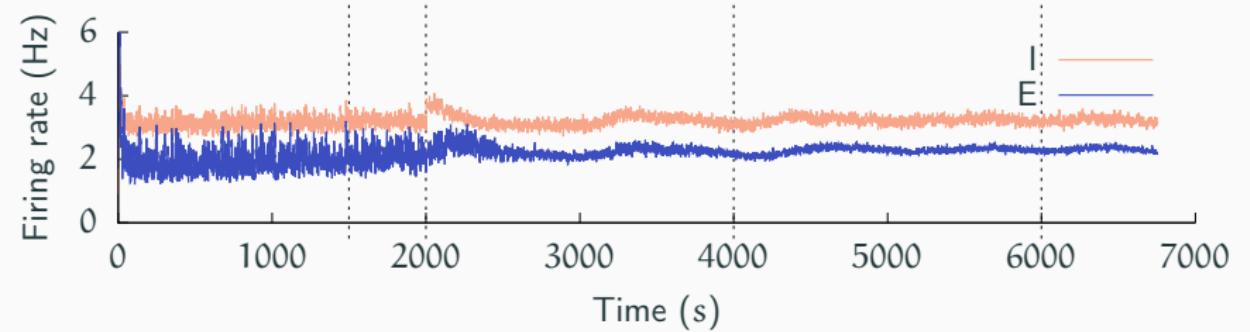


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# Deafferentation and repair: outside the LPZ



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