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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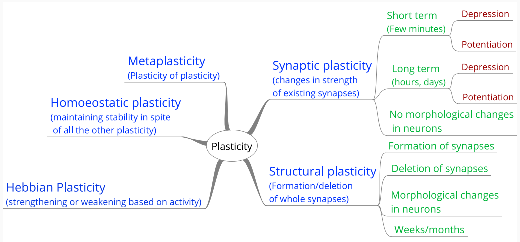
29/03/2019

Context

Plasticity while maintaining stability



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)

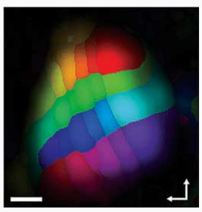
Evidence of homeostatic structural plasticity: lesion studies

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)

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)

Experimental protocol I

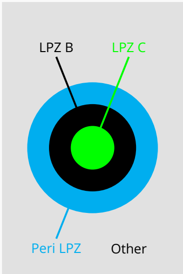


[1] Keck, T. *et al.* Massive restructuring of neuronal circuits during functional reorganization of adult visual cortex. *Nature neuroscience* **11,** 1162–1167 (2008)

Experimental protocol II: after peripheral lesion

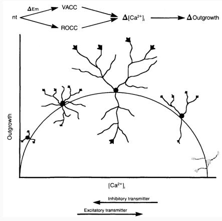
[1] Keck, T. *et al.* Massive restructuring of neuronal circuits during functional reorganization of adult visual cortex. *Nature neuroscience* **11,** 1162–1167 (2008)

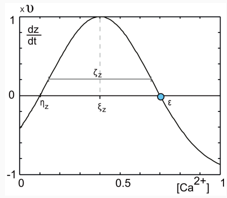
What we know from these experiments



- 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.

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)

Computational modelling: MSP: turnover

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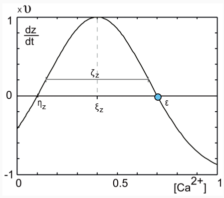
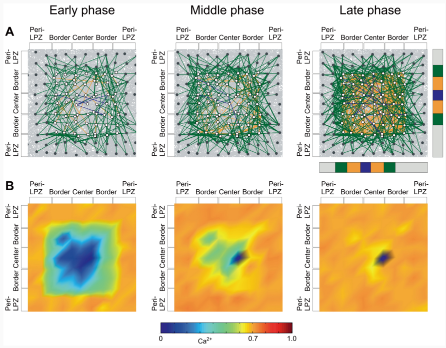
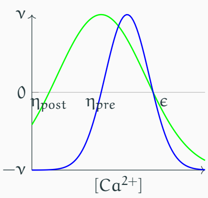
- Synaptic structures (z): excitatory and inhibitory post-synaptic, excitatory or inhibitory pre-synaptic elements.
- New synapses form when free plugs are available: $(z > z_{conn})$
- Synapses are deleted if: $(z < z_{conn})$

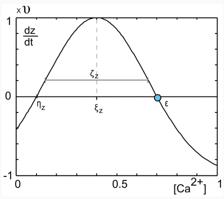


Computational modelling II: Butz2013 replication



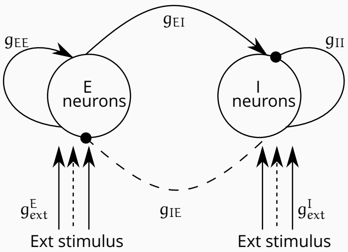
Computational modelling II: Butz2013 results





Methods: our approach

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)

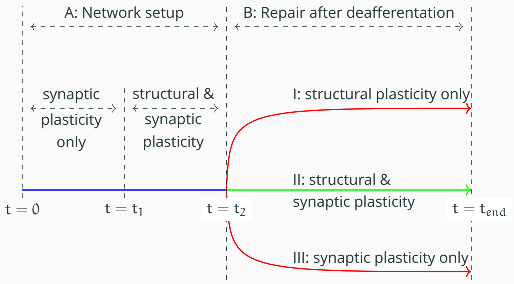
Extensions

- 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!

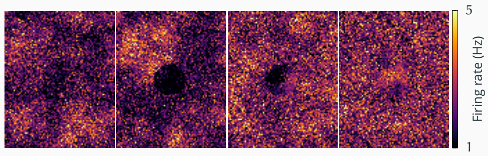
[6] Knott, G. W. *et al.* Spine growth precedes synapse formation in the adult neocortex in vivo. *Nature neuroscience* **9,** 1117–1124 (2006)

Simulation protocol

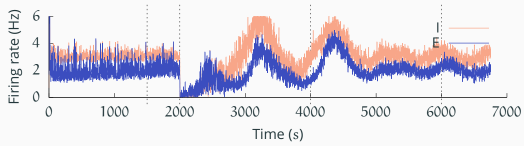


Results and discussion

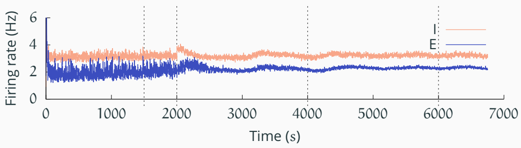
Deafferentation and successful repair



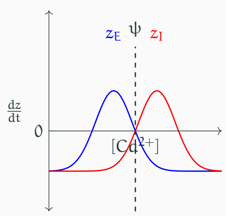
Deafferentation and repair: LPZ



Deafferentation and repair: outside the LPZ

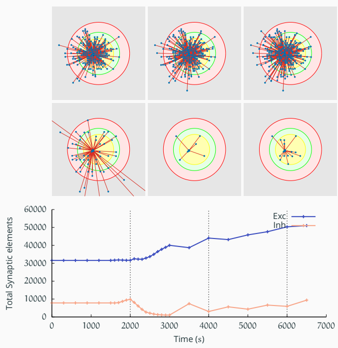


Post-synaptic growth dynamics

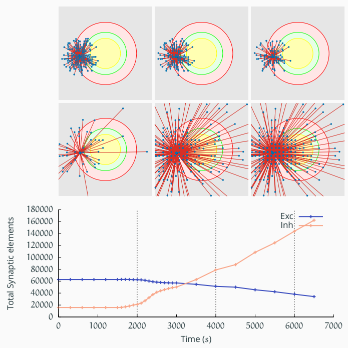


- Loss of activity: sprouting of E, retraction of I
- Extra activity: retraction of E, sprouting of I

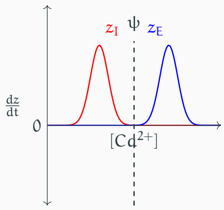
Resultant turnover: LPZ



Resultant turnover: outside LPZ



Pre-synaptic growth dynamics



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