Investigating structural plasticity in brain networks using computational modelling

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17/01/2020

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]

[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,
- changes in structure are ignored[1].

[1] Even though structural changes in spines and boutons underlie modulation of synaptic efficacy.

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)

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)
- 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)
- 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.
- How? Why?

Aim

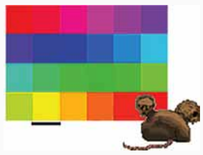
Simulate a computational model of peripheral lesioning to study the reorganisation process.

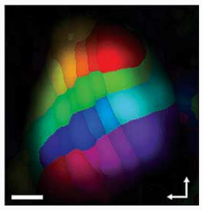
- A computational model allows us to:
  - investigate every entity in the network: variables from neurons, their neurites, all synapses,
  - modify any parameters to analyse changes in network behaviour: neuronal parameters, synaptic parameters, other network parameters,
  - run multiple analyses in parallel,
  - do it in less time than biological experiments[1].

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

Methods: How?

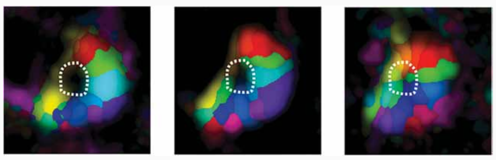
Peripheral lesion protocol I: topographic mapping





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

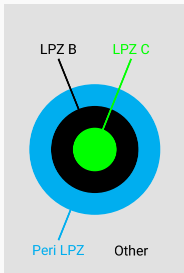
Peripheral lesion protocol II: after peripheral lesion



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

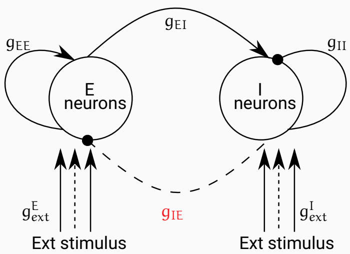
[1] Keck, T. *et al.* Massive restructuring of neuronal circuits during functional reorganization of adult visual cortex. *Nature neuroscience* **11**, 1162–1167 (2008)

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.

Cortical spiking network model: 8000 E, 2000 I neurons

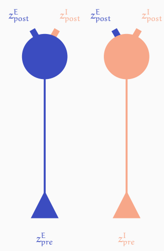


Exhibits cortical Asynchronous Irregular (AI) firing.

[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

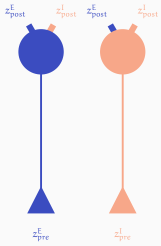
- Single compartment, point "leaky integrate and fire neurons"[1],
- Host neurites (z).



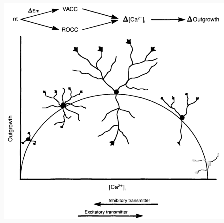
[1] Meffin, H. *et al.* An analytical model for the 'large, fluctuating synaptic conductance state' typical of neocortical neurons in vivo. *Journal of computational neuroscience* **16**, 159–175. https://link.springer.com/article/10.1023/B:JCNS.0000014108.03012.81 (2004)

Modelling synapse formation and removal

- $z^{E}_{post} + z^{E}_{pre}$
- $z^{I}_{post} + z^{I}_{pre}$
- New synapses form when free partner neurites are available.
- Synapses are deleted if neurites are retracted by the neuron.



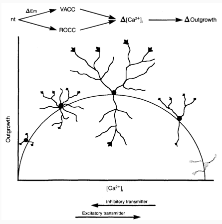
Neurite growth (z) as a function of neuronal activity

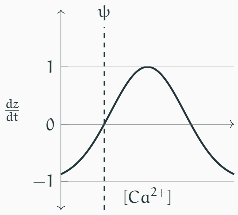


- $[Ca^{2+}]$ correlates with neuronal activity,
- serves a homeostatic function.

[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

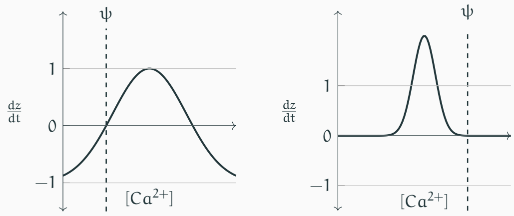




[1] Lipton, S. A. & Kater, S. B. Neurotransmitter regulation of neuronal outgrowth, plasticity and survival. *Trends in neurosciences* **12,** 265–270. ISSN: 0166-2236. http://www.sciencedirect.com/science/article/pii/016622368990026X (1989)

[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)

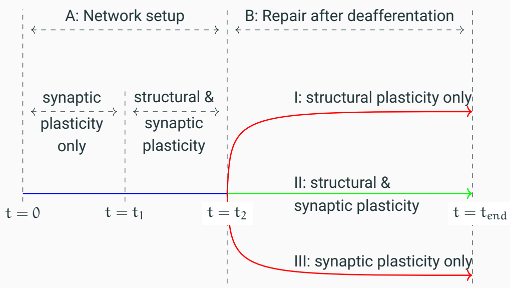
Growth curves: possibilities



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

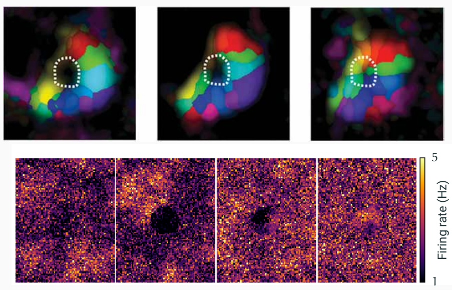
[1] Sinha, A. *et al.* Growth Rules for the Repair of Asynchronous Irregular Neuronal Networks after Peripheral Lesions. *bioRxiv.* eprint: https://www.biorxiv.org/content/early/2019/10/21/810846.full.pdf. https://www.biorxiv.org/content/early/2019/10/21/810846 (2019)

Replicate peripheral lesion protocol

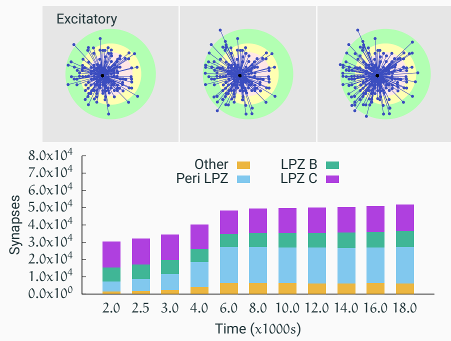


Results: a few years later

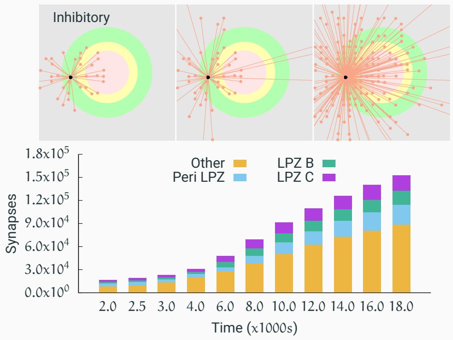
Reproduction of deafferentation and repair



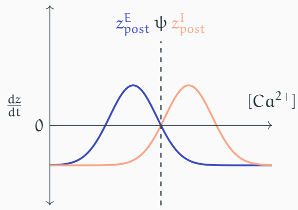
Reproduction of ingrowth of excitatory projections



Reproduction of outgrowth of inhibitory projections



Resultant activity dependent growth rules: post-synaptic



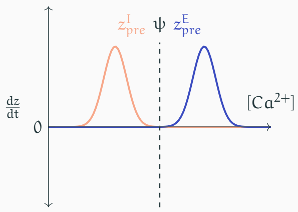
- E: formed when activity is less than, removed when more than optimal.
- I: formed when activity is more than, removed when less than optimal.

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

[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



- E: formed when activity is more than, removed when less than optimal.
- I: formed when activity is less than, removed when more than optimal.

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

[1] Perez, 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)

[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)

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.

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

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. . .

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

- 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.

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 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].

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