

# Investigating structural plasticity in brain networks using computational modelling

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**Context: what and why?**

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# The plastic—but stable—brain: Hebbian/Homeostatic plasticity

- “Neurons that fire together, wire together.”<sup>1</sup>
- “The more things change, the more they stay the same.”<sup>2</sup>

<sup>1</sup>Hebb, D. O. *The organization of behavior: A neuropsychological theory*. 1949

<sup>2</sup>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<sup>1</sup>.

<sup>1</sup>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**).

<sup>1</sup>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?

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

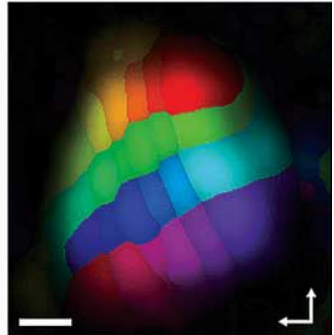
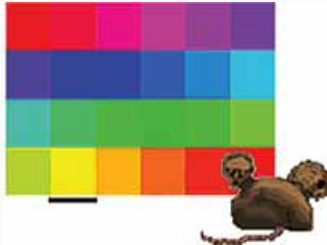
- A **computational model** allows us to:
  - investigate every entity in the network: variables from neurons, their neurites, all synapses,
  - modify any parameters to analyse changes in network behaviour: neuronal parameters, synaptic parameters, other network parameters,
  - run multiple analyses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

<sup>1</sup> Simulations take a week each, but that's still faster than a multi-month laboratory experiment.

## Methods: How?

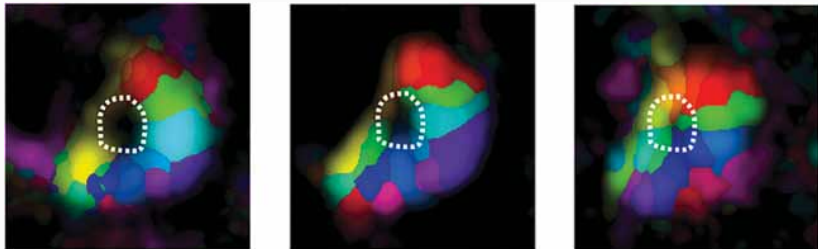
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# Peripheral lesion protocol I: topographic mapping



<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)

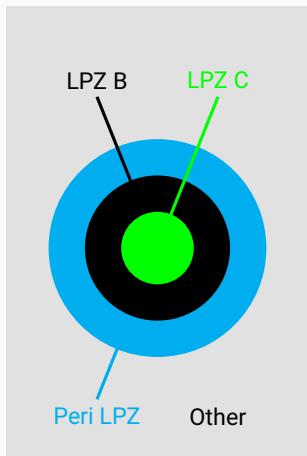
## Peripheral lesion protocol II: after peripheral lesion



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

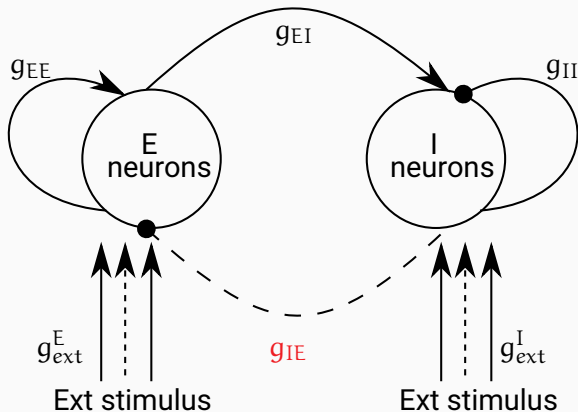
<sup>1</sup>Keck, T. *et al.* Massive restructuring of neuronal circuits during functional reorganization of adult visual cortex. *Nature neuroscience* **11**, 1162–1167 (2008)

## 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

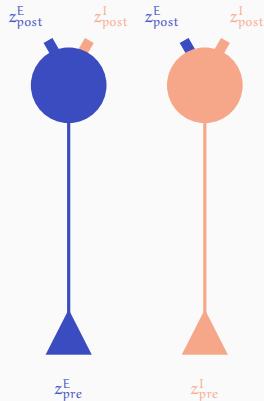


Exhibits cortical **Asynchronous Irregular (AI)** firing.

<sup>1</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)

# Neuron model

- Single compartment, point “leaky integrate and fire neurons”<sup>1</sup>,
- Host neurites ( $z$ ).



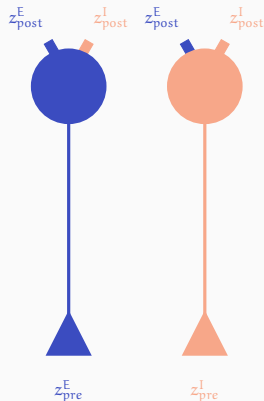
<sup>1</sup> Meffin, H. et al. An analytical model for the ‘large, fluctuating synaptic conductance state’ typical of neocortical neurons in vivo. *Journal of computational neuroscience* **16**, 159–175.

<https://link.springer.com/article/10.1023/B:JCNS.0000014108.03012.81> (2004)

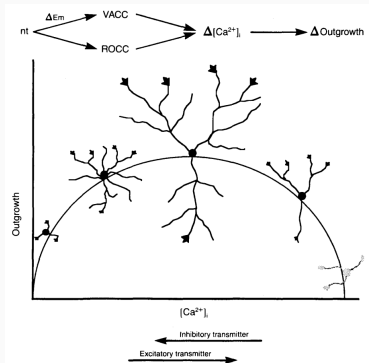


# Modelling synapse formation and removal

- $z_{\text{post}}^E + z_{\text{pre}}^E$
- $z_{\text{post}}^I + z_{\text{pre}}^I$
- 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

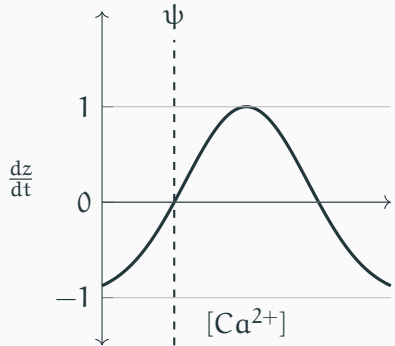
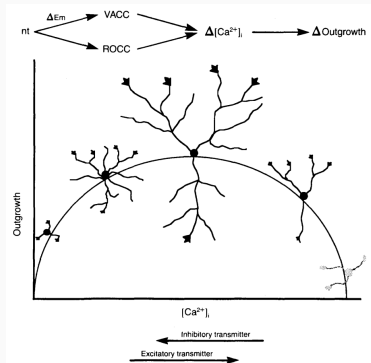


- $[Ca^{2+}]$  correlates with neuronal activity,
- serves a homeostatic function.

<sup>1</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)

# Neurite growth ( $z$ ) modelled as a Gaussian function of activity

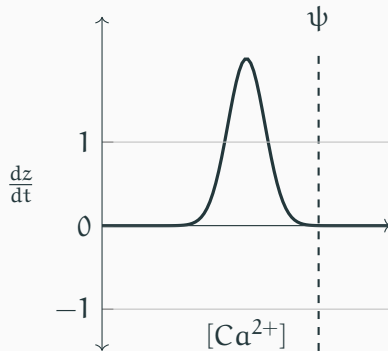
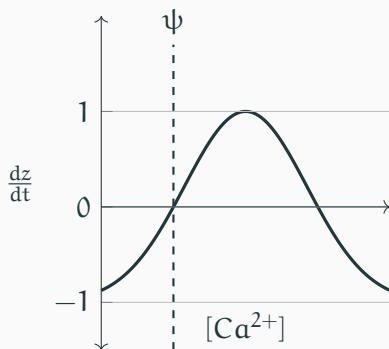


<sup>1</sup>Lipton, S. A. & Kater, S. B. Neurotransmitter regulation of neuronal outgrowth, plasticity and survival. *Trends in neurosciences* **12**, 265–270. ISSN: 0166-2236.

<http://www.sciencedirect.com/science/article/pii/01662236890026X> (1989)

<sup>2</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)

# Growth curves: possibilities



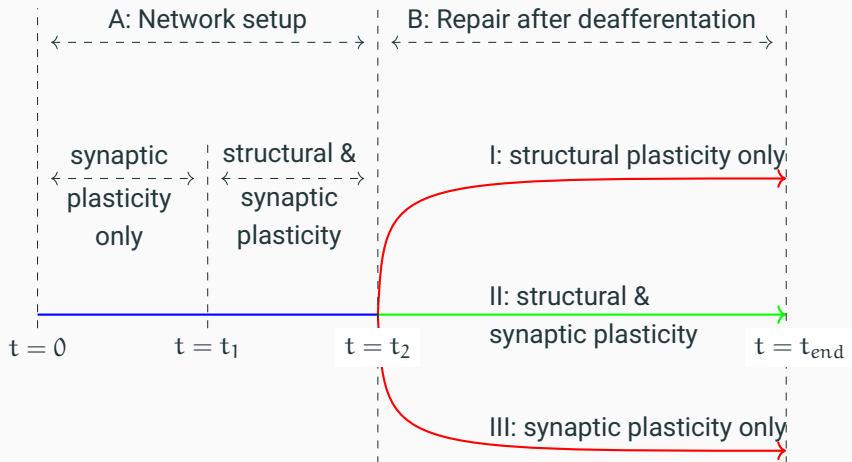
4 free parameters describe each growth curve. We must determine 6 sets of growth curves: 3 for E, 3 for I neurons.

<sup>1</sup>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)

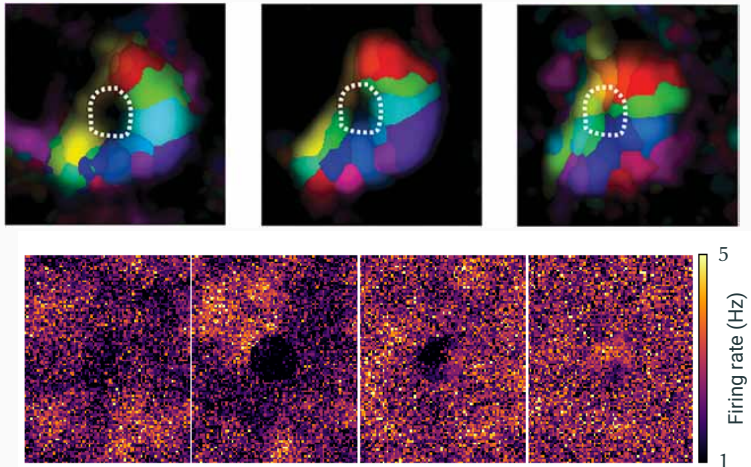
# Replicate peripheral lesion protocol



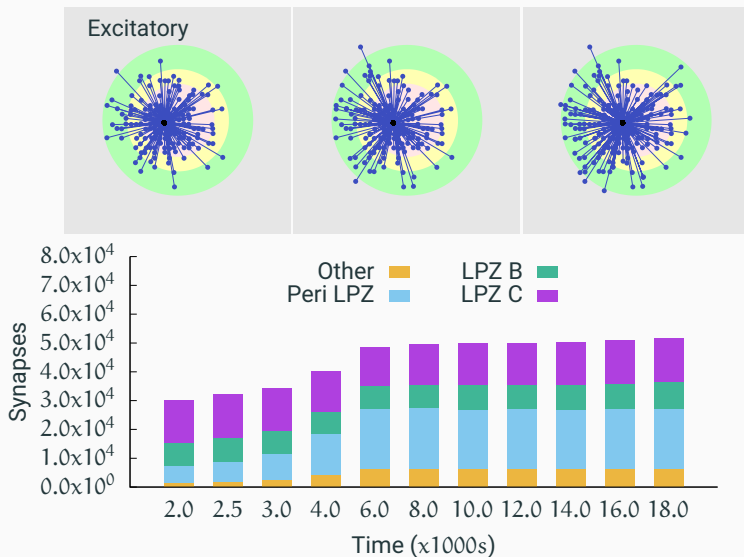
**Results: a few years later**

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# Reproduction of deafferentation and repair

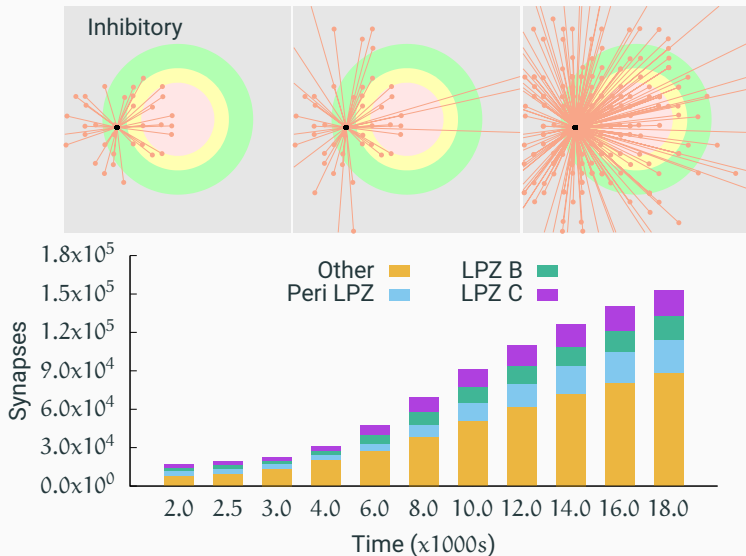


# Reproduction of ingrowth of excitatory projections

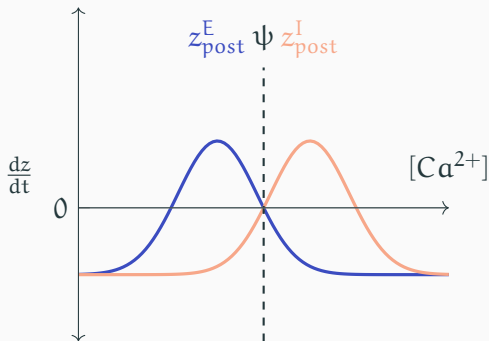




# Reproduction of outgrowth of inhibitory projections



# Resultant activity dependent growth rules: post-synaptic



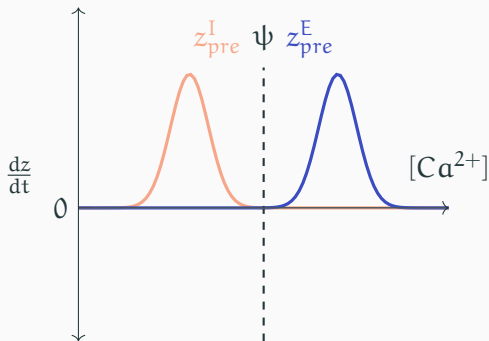
- E: formed when activity is less than, removed when more than optimal.
- I: formed when activity is more than, removed when less than optimal.

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

<sup>1</sup>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)

<sup>2</sup>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.

<sup>1</sup>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)

<sup>2</sup>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

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- 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<sup>1</sup>.

**Everyone** should have the freedom to **share, study, and modify** scientific material<sup>2</sup>.

<sup>1</sup>Free software foundation: [fsf.org](https://www.fsf.org)

<sup>2</sup>Open source for neuroscience: [opensourceforneuroscience.org](https://opensourceforneuroscience.org)

- 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:**  $\text{\LaTeX}$ , the Python science stack, daily use productivity tools...
- **180** tools in queue<sup>1</sup>

<sup>1</sup><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<sup>1</sup>.
- Telegram channel: @NeuroFedora<sup>2</sup>.
- Mailing list on [lists.fedoraproject.org](https://lists.fedoraproject.org)<sup>3</sup>.

<sup>1</sup> #fedora-neuro on Freenode

<sup>2</sup> @NeuroFedora on Telegram

<sup>3</sup> [neuro-sig@lists.fedoraproject.org](mailto:neuro-sig@lists.fedoraproject.org)



[neuro.fedoraproject.org](https://neuro.fedoraproject.org)