Growth rules for repair of asynchronous irregular network models following peripheral lesions

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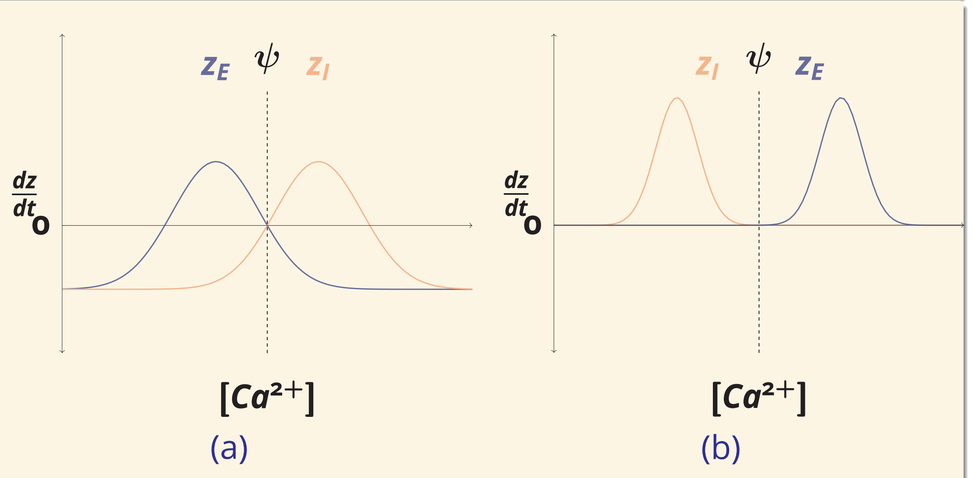
Homeostatic changes in neurite morphology and network connectivity based on neuronal activity.

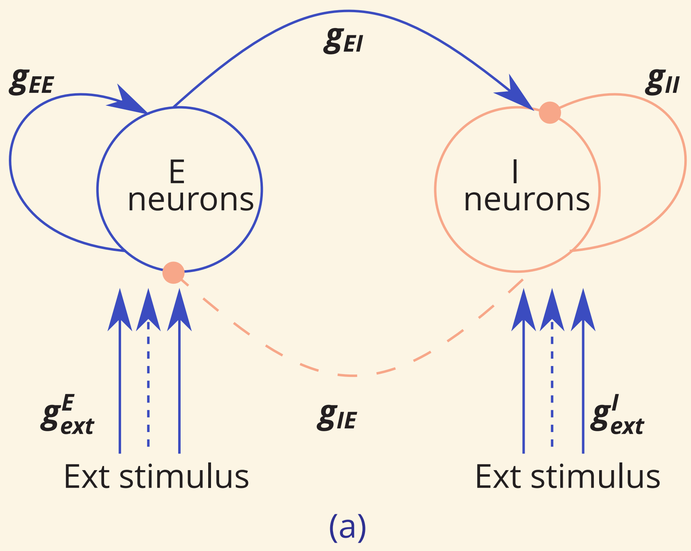
Peripheral lesion experiments report the restoration of activity to deprived neurons by massive reorganisations in network connectivity, indicating the presence of homeostatic structural plasticity [2]. Dendritic and axonal structures sprout or retract depending on the neuronal calcium concentration, but the exact mechanisms underlying these activity dependent structural changes of neurites remain unclear [1]. By reproducing experimentally observed changes in synaptic connectivity during the repair process in a biologically realistic spiking neural network model, we propose testable hypotheses on how synaptic structures react to changes in neuronal activity. Our results suggest that excitatory (z_E) and inhibitory (z_I) neurons react to changes in activity in opposite ways. Our simulations also predict that homeostatic structural plasticity and homeostatic synaptic plasticity are both necessary for network repair.

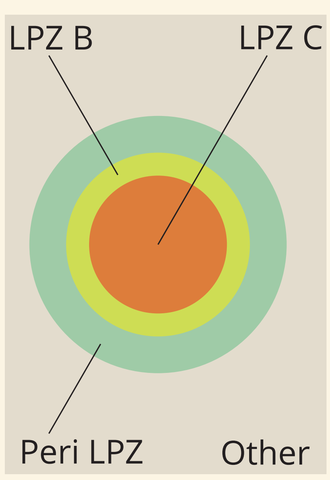
Excitatory and inhibitory synaptic elements respond to changes in neuronal activity in opposite ways.

The figures show our model of activity-dependent dynamics of synaptic elements (dz/dt) as functions of a neuron's time averaged activity (represented by $[Ca^{2+}]$). **Figure 1a:** post-synaptic elements of a neuron react to deviations in activity from the optimal level (ψ) by countering the changes in excitatory or inhibitory inputs to restore the balance of excitation and inhibition (E-I balance). For both excitatory and inhibitory neurons, excitatory dendritic elements sprout when the neuron experiences a reduction in its activity, and retract when the neuron receives extra activity. For all neurons, inhibitory dendritic elements sprout when the neuron has extra activity and retract when the neuron is deprived of activity. **Figure 1b:** In excitatory neurons, axonal sprouting is stimulated by extra activity. In inhibitory neurons, on the other hand, deprivation in activity stimulates axonal sprouting.



Our new model of network rewiring after peripheral lesioning reproduces experimental observations.





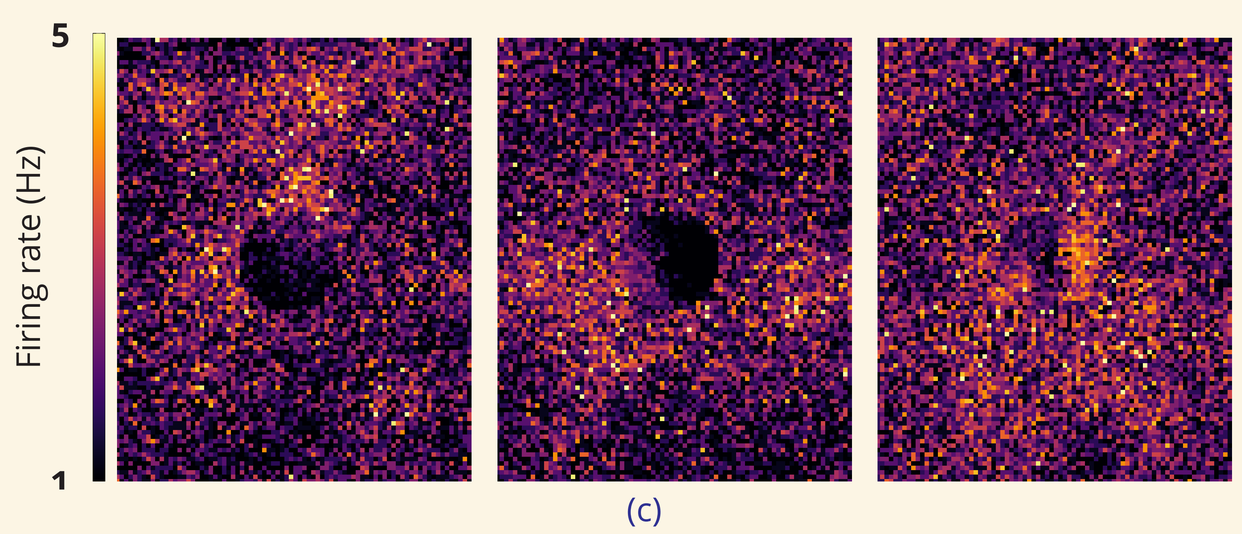


Figure 2a: Excitatory (E) and inhibitory (I) neurons are distributed on a two dimensional toroid, and connected such that all synapses other than IE are static. IE synapses are modulated by homeostatic inhibitory Spike-timing Dependent Plasticity (STDP). Structural plasticity applies to all synapses. **Figure 2b:** (not to scale) The network is divided into four regions for analysis: Lesion Projection Zone (LPZ) C: centre of LPZ, LPZ B: inner border of LPZ, peri-LPZ: outer border of LPZ, and other neurons. **Figure 2c:** Recovery of activity over time: The network is permitted to achieve its balanced Asynchronous Irregular (AI) low frequency firing regime under the action of inhibitory synaptic plasticity. Our structural plasticity mechanism is then activated. Neurons in the LPZ are then deafferented and the network is allowed to repair itself under the action of our structural plasticity mechanism.

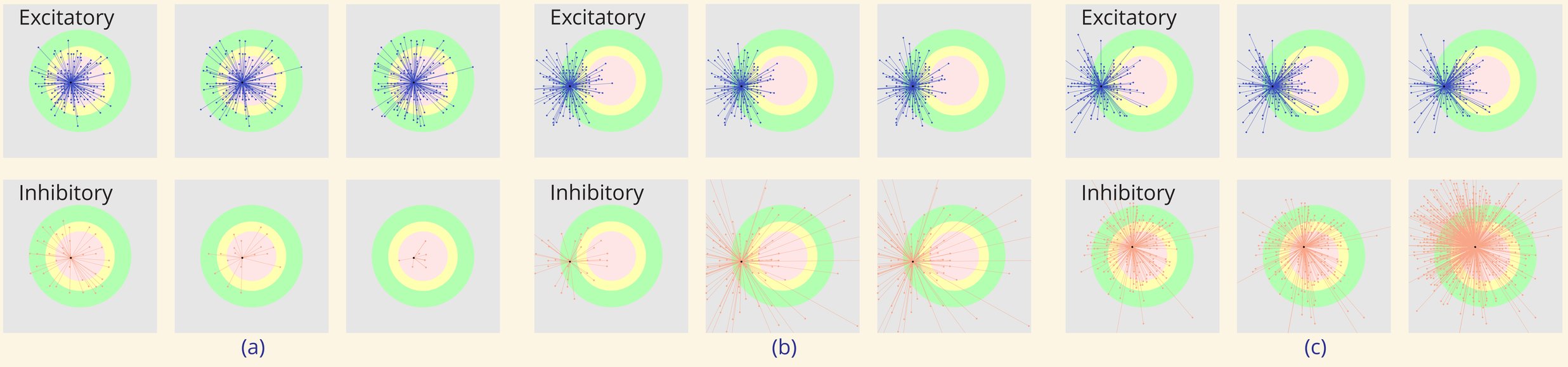


Figure 3a: in our simulations, neurons in the LPZ gain excitatory and lose inhibitory inputs to restore excitatory activity, in line with experimental evidence. **Figure 3b:** neurons outside the LPZ gain inhibitory but lose excitatory inputs to reduce their activity, also in line with experimental reports. Our model predicts that unlike neurons in the LPZ, neurons outside it experience a gain in activity due to a net loss in inhibition. **Figure 3c:** outgoing axonal elements from an excitatory neuron in the peri-LPZ (top) and in inhibitory neuron in the LPZ (bottom). Our simulation replicates experiments showing that neurons outside the LPZ project excitatory axons into the LPZ to transfer activity via these lateral projections to deprived neurons. On the other hand, our model also correctly reproduces the outgrowth of inhibitory axons from the LPZ to adjoining regions.

References

1. 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).
2. Sammons, R. P. & Keck, T. Adult plasticity and cortical reorganization after peripheral lesions. *Current Opinion in Neurobiology* **35.** Circuit plasticity and memory, 136–141. ISSN: 0959-4388 (2015).