Compensatory effects of dendritic retraction on excitability and induction of synaptic plasticity

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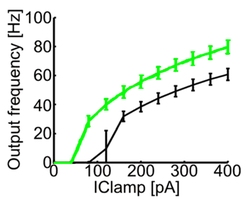
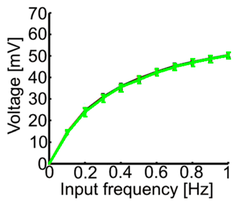
1 Introduction

- Denervation of connections from the entorhinal cortex induce **loss of synapses** and subsequently **dendritic retraction** in the postsynaptic target area containing granule cells of the dentate gyrus [1].
- Previous models showed dendritic retraction is capable of increasing the excitability of neurons thus compensating for the denervation-evoked loss of synapses. However, this was shown only for stochastically stimulated AMPA synapses [2, *see figures below*].

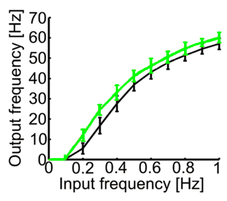
Therefore, here we investigate the consequences of dendritic retraction for **1. firing rate homeostasis** and **2. NMDAR-dependent synaptic plasticity** in compartmental dentate granule cell models driven by AMPA/NMDA synapses.



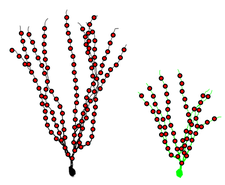
Due to higher input resistance, denervated granule cell models (green) show **higher excitability** (firing rates) than healthy control (black) cells after current injection into the soma



Homeostasis of somatic voltage response is present in **passive** denervated dendrites after stochastic (Poisson) stimulation of AMPA synapses with increasing input frequency



The **greater excitability** (*left*) compensates for the **smaller number of synapses** in denervated dendrites leading to **firing rate homeostasis** (shown for stochastic stimulation of AMPA synapses)

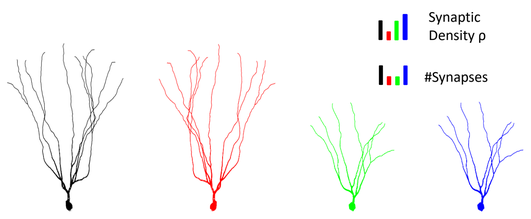


Equal synaptic density → reduced number of synapses in smaller cells

Simulations from Platschek et al. 2016

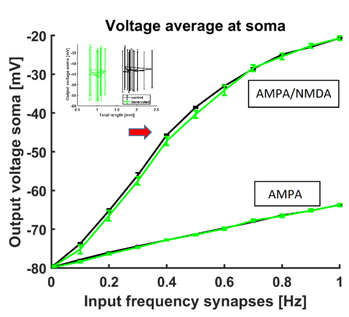
2 Methods

- C**ompartmental modeling** in the NEURON environment and newly established **T2N software** [3,4].
- Reconstructed mouse **granule cells** (GCs, 15 cells) were used as well as compared to **artificial cells** [5,6].
- We used an established biophysical model of a detailed granule cell [4] and Mainen-Sejnowski spiking model (ModelDB online database #2488) [7]. Excitatory AMPA and NMDA synapses were homogeneously distributed in the dendritic tree and simulated as biexponential conductance changes (AMPA: rise time = 0.2ms , decay time = 2.5ms; NMDA: rise time = 0.33ms , decay time = 50ms) with lognormal weights ~ (μ,σ^2). Simulations were performed in ''active'' as well as ''passive'' cells.
- Stimulation protocol: a) a Poisson generated spike train between 0.1 and 1 Hz for stochastically activated synapses and b) a 100Hz high-frequency input to the synapses.
- Inhibitory synapses with positive E_{GABA} shift due to change in KCC2 pump in denervated cells [8].
- As output we computed the somatic voltage and the firing rate. Backpropagating action potential was analyzed. Synaptic NMDA current was a measure of capability for synaptic plasticity induction.



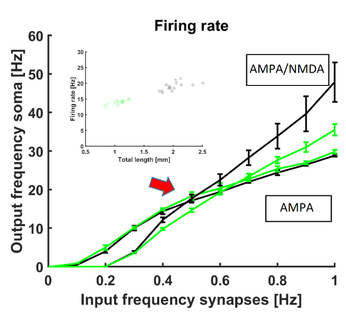
Granule cell morphologies. *black*: control cell, *green*: denervated cell with same synaptic density ρ as control, *red*: control cell with low synaptic density ρ but same number of synapses as denervated cell, *blue*: denervated cell with high synaptic density ρ but same number of synapses as control cell

3 Distributed synaptic stimulation leads to similar somatic voltage responses in passive & similar firing rates in active GC models

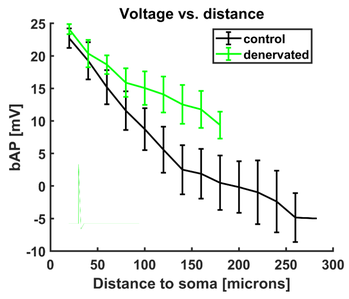


Left: Somatic voltage for passive granule cells, synaptic poisson stimulation, AMPA and AMPA/NMDA synapses, control and denervated granule cell compared

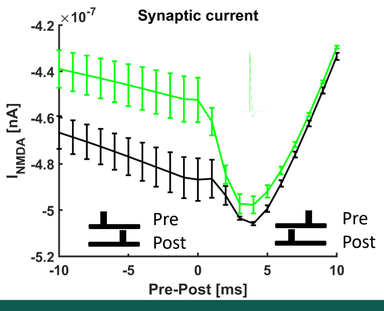
Right: Somatic firing frequency for active granule cells



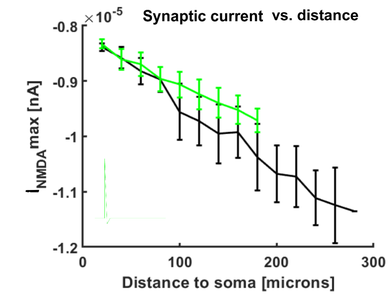
4 The enhanced backpropagating action potential (bAP) reduces the inward NMDA current in granule cell models slightly

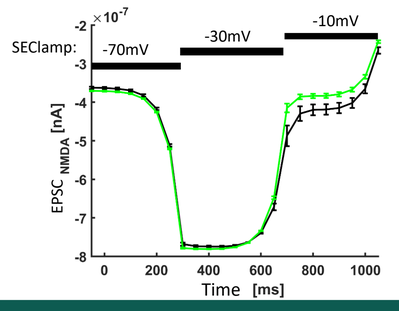


Left: Attenuation of somatically induced bAP in granule cell, *Right*: Corresponding readout of maximum synaptic inward current (negative) over distance to soma. While bAP is enhanced in denervated cells the NMDA current is reduced.

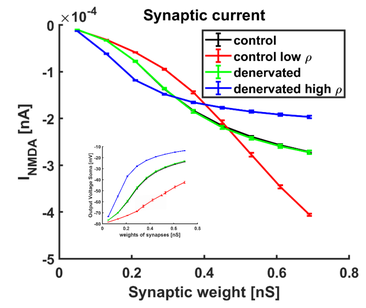


Left: Different timing of postsynaptic induction of bAP and presynaptic readout of synaptic current, *Right*: EPSC for different somatic holding voltage steps. **NMDAR activation is impaired when voltage depolarization is high, e.g. close to E_{NMDA}=0mV.**

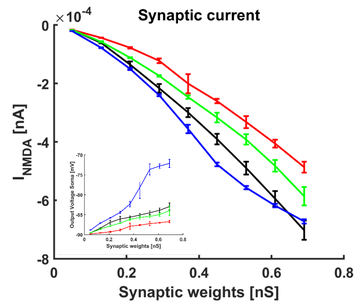




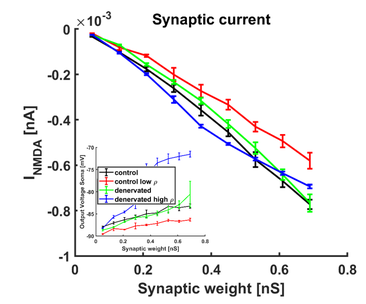
5 Similar synaptic NMDA currents are present in denervated GC models with retracted dendrites despite their loss of synapses



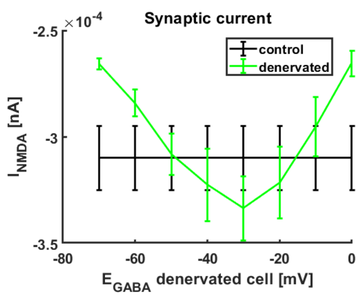
Left: Synaptic inward NMDA current (negative) for passive granule cell models, AMPA/NMDA synapses stochastically activated
Right: Synaptic current for active granule cells, AMPA/NMDA synapses 100Hz activation. Enhanced bAP and excitability are coming together: similar NMDA currents present



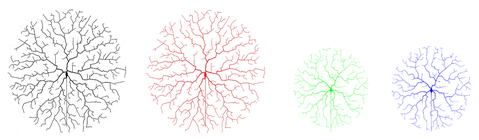
6 Denervation-induced positive shift in E_{GABA} enhances the boost of NMDAR activation & can lead to full NMDA current compensation



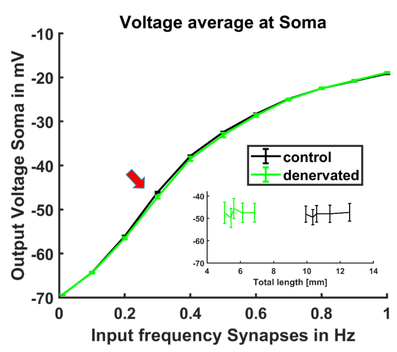
Left: Synaptic NMDA current for active granule cells, inhibitory synapses added (density: 50% of AMPA) with 100Hz activation, E_{GABA} control = -70mV and E_{GABA} denervated = -40mV
Right: Synaptic NMDA current for different inhibitory equilibrium potentials (E_{GABA}) of denervated granule cells which is enhanced between -60mV and -20mV



7 Generalisation to other dendritic morphologies: Firing rate homeostasis and compensation of NMDAR activation is present in artificial dendritic morphologies

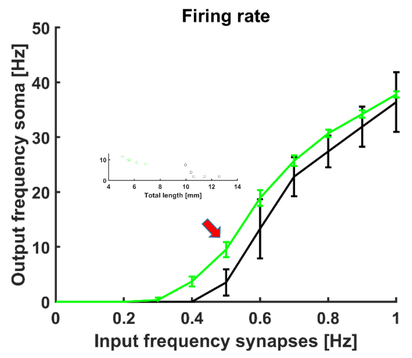


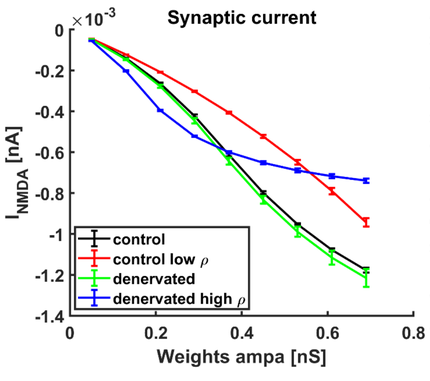
Artificial cells constructed with TREES toolbox (5 cells, minimum spanning tree, balancing factor 0.3-0.7 [6]) and Mainen-Sejnowski spiking model (ModelDB #2488 [7])



Left: Homeostasis of somatic voltage in passive artificial cells with stochastically stimulated AMPA/NMDA synapses

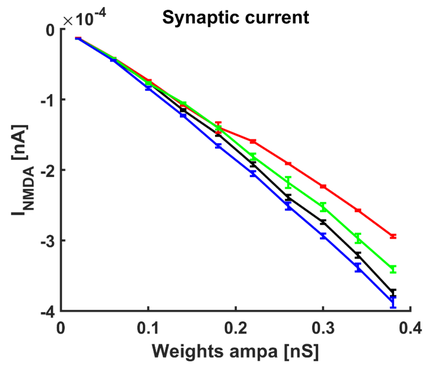
Right: Somatic firing rate homeostasis in active artificial cells with stochastically activated AMPA/NMDA synapses





Left: Homeostasis of synaptic NMDA current in passive, artificial cells with AMPA/NMDA synapses (Poisson activation)

Right: Partial compensation of synaptic NMDA current in active, artificial cells with stimulated AMPA/NMDA synapses (100Hz)



Conclusion

- For **passive** models, driven by distributed AMPA/NMDA synapse stimulation, somatic output **voltage homeostasis** was **present** both in granule cells and artificial cell morphologies.
  → a general principle **independent of particular dendritic morphology**.
- Due to different ion channel composition/distribution, models with **active** dendrites, driven by AMPA/NMDA synapse stimulation**, firing rate homeostasis** was **partially present** in granule cells and fully present in artificial cells.
- **Backpropagation of action potentials** was **enhanced** in the denervated regions of the granule cells as well as artificial cells. This enhancement **impaired** the NMDAR activation boost slightly when close to E_{NMDA}.
- Dendritic retraction leads to a **compensatory boost of NMDAR activation** which might support homeostasis for the induction of **NMDAR-dependent synaptic plasticity.**
- **Positive shift in E_{GABA}** (inhibitory ionic plasticity) can contribute to **homeostasis of NMDAR-dependent synaptic plasticity.**

References

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