Multi-scale model of hyperpolarisation-mediated plasticity in the Medial Vestiubular Nucleus

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ICSB 2018

Vestibulo-ocular reflex (VOR)

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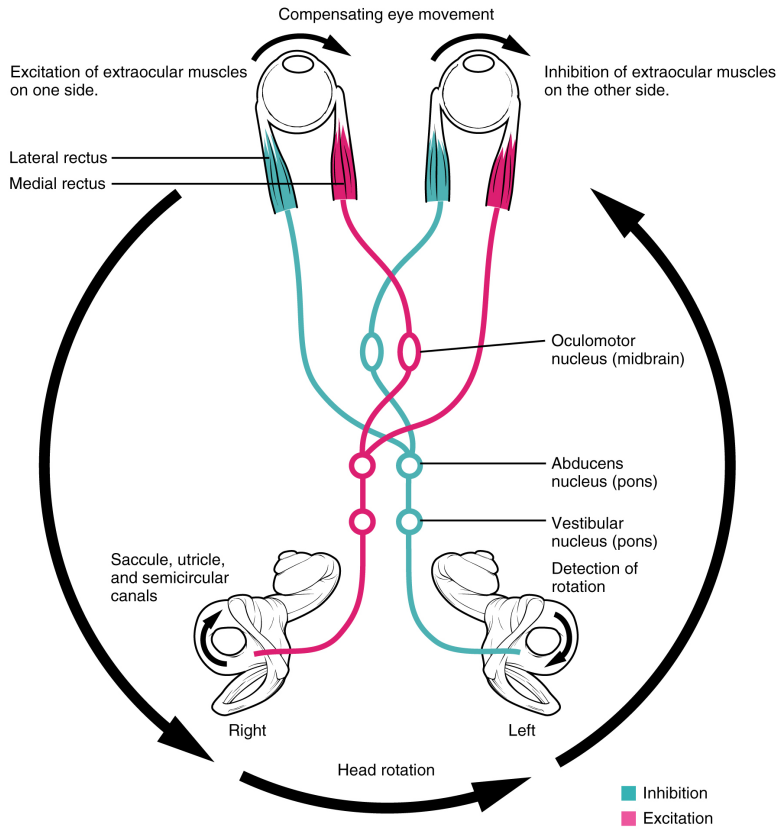

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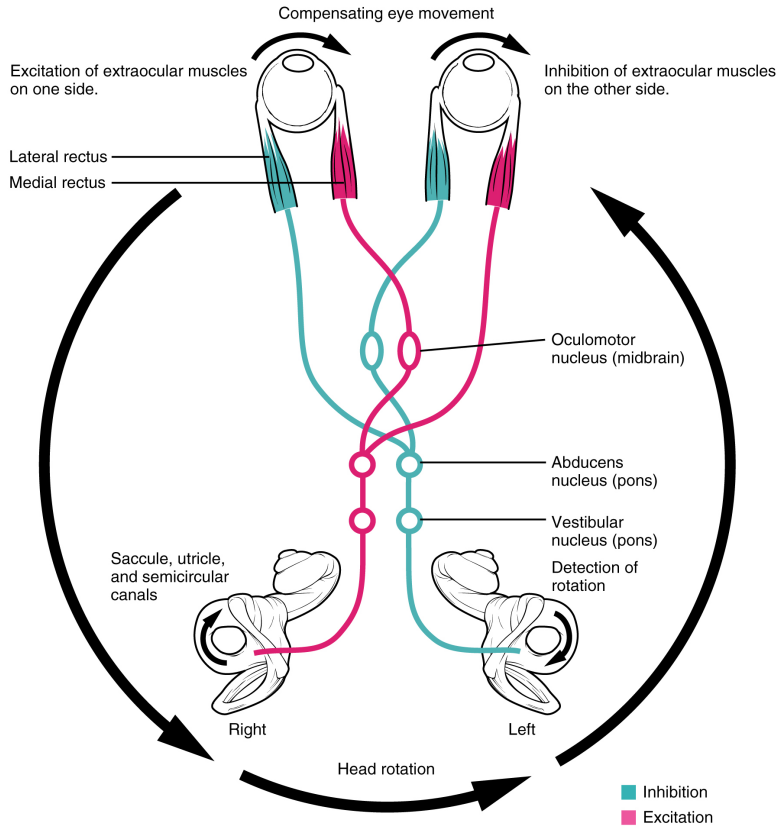

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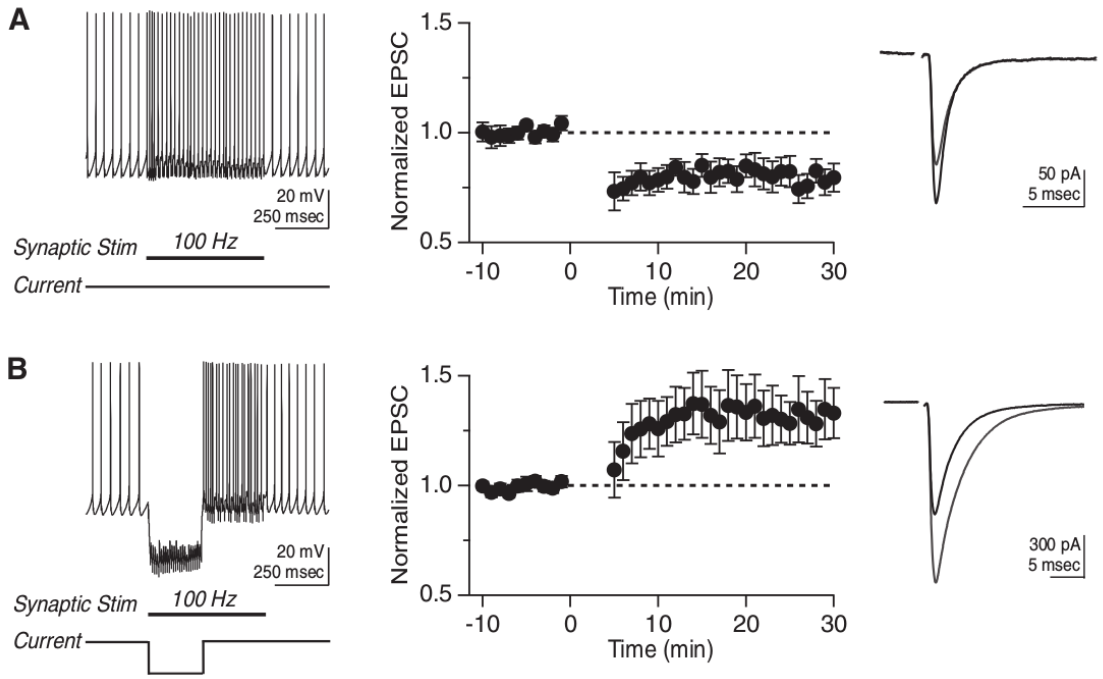
- The VOR involves neurons in the medial vestibular nucleus (MVN)
- MVN neurons show plasticity (to correct for retinal slip)
- Excitatory input from vestibular organs, inhibitory input from the cerebellum
- No dendritic spines!

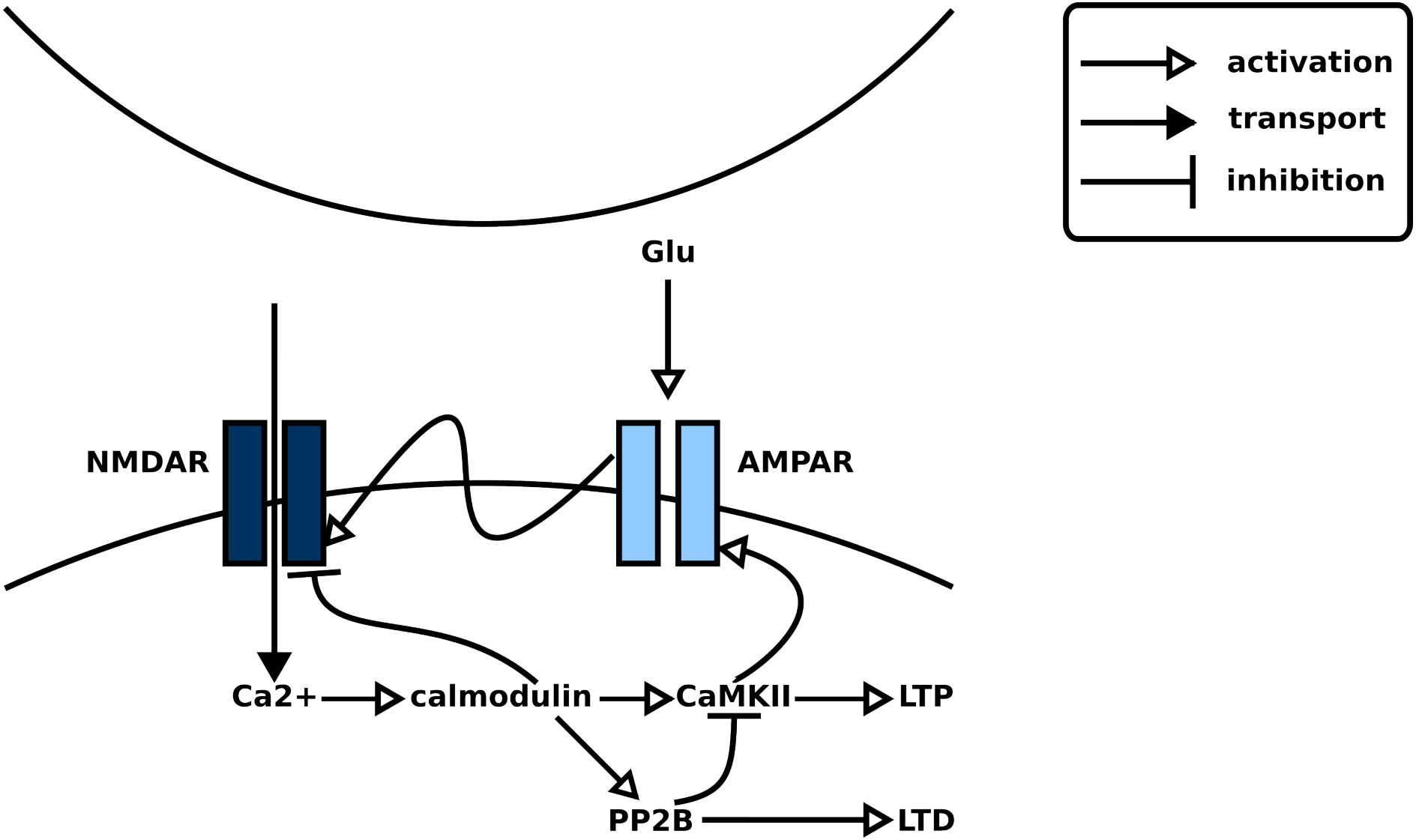
Regulation of MVN neurons

Synaptic plasticity arises from proximity of inhibitory (hyperpolarising) and excitatory inputs.

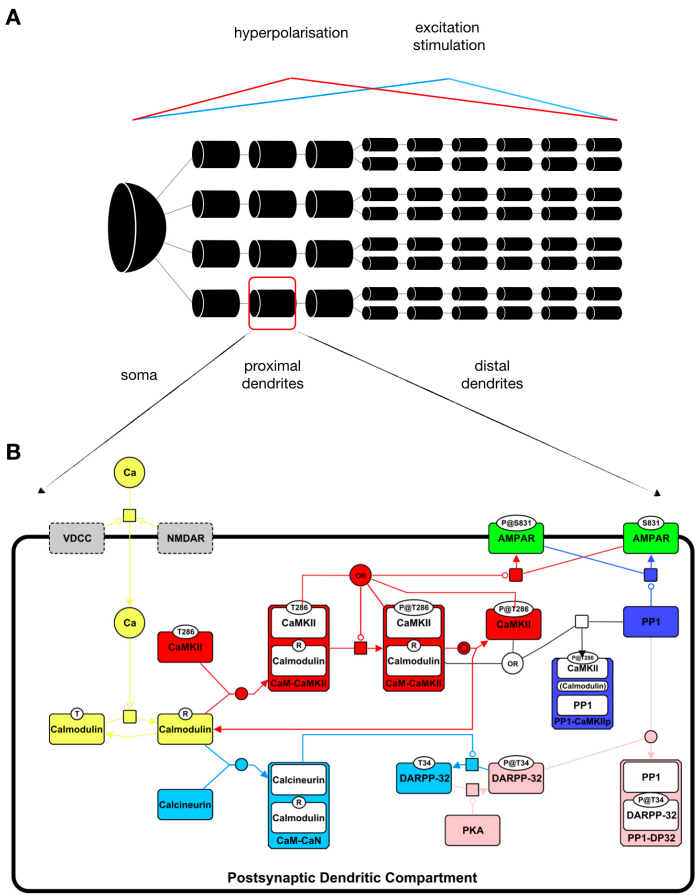


McElvain et al. *Neuron*, 2010.

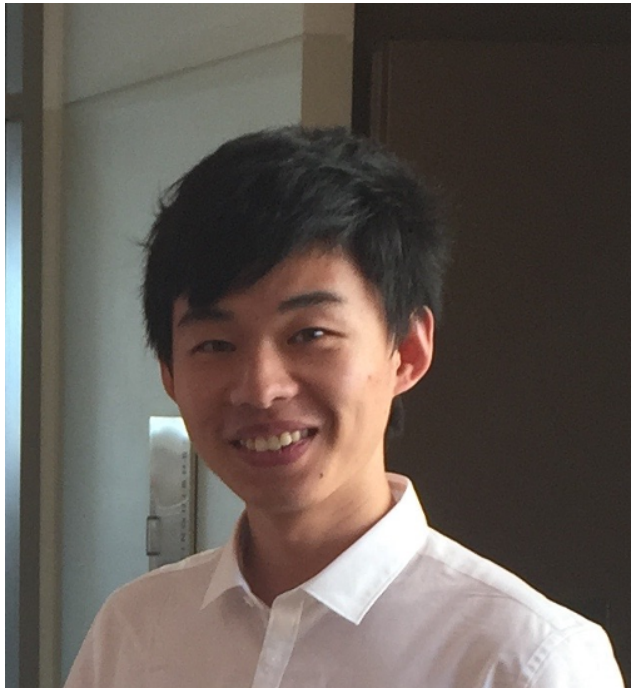
NMDAR-dependent LTP - a simplistic view



Multi-scale model of hyperpolarisation-gated plasticity



Xie et al. *bioRxiv 418228, 2018*



- **Yubin Xie**, Edinburgh
- Marcel Kazmierczyk, Edinburgh
- Bruce Graham, Stirling
- Mayank Dutia, Edinburgh

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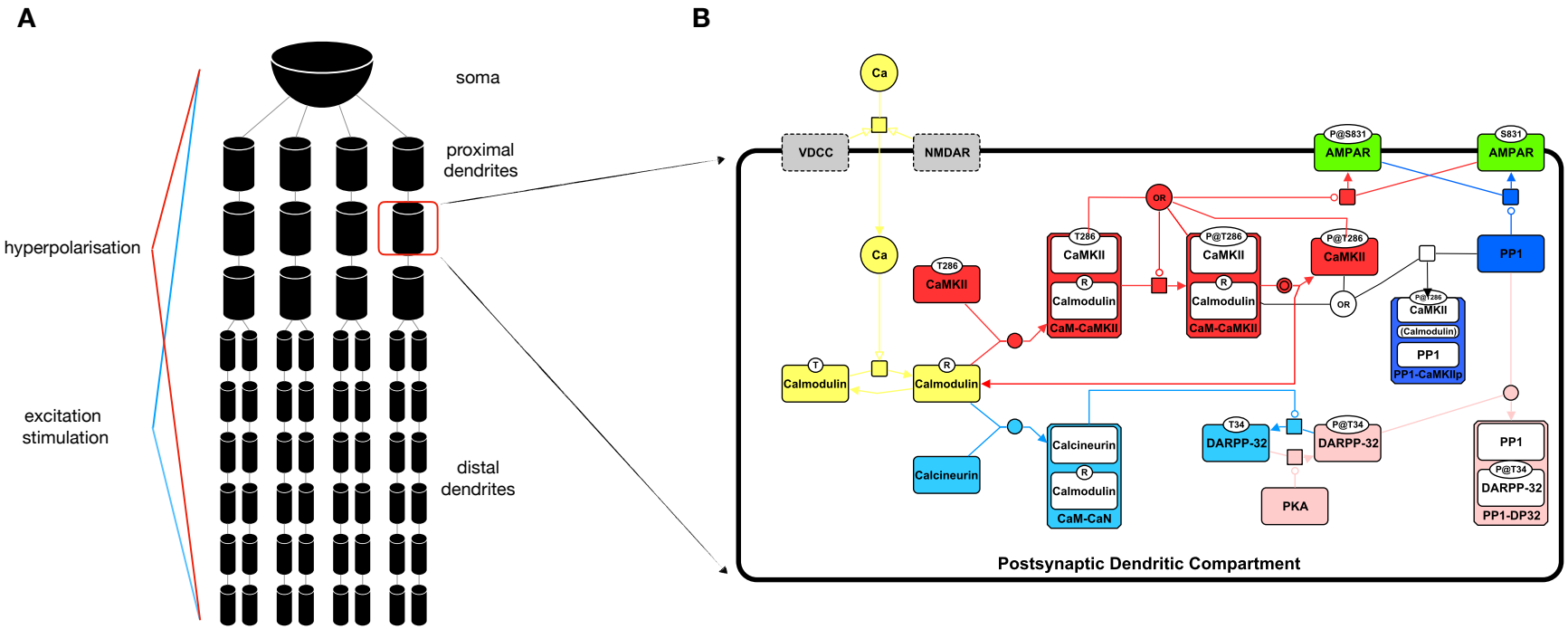
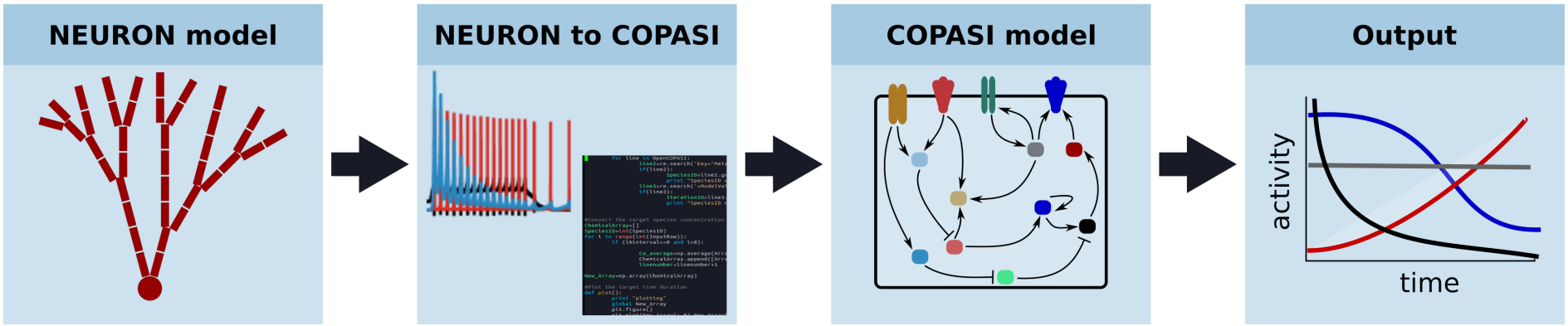


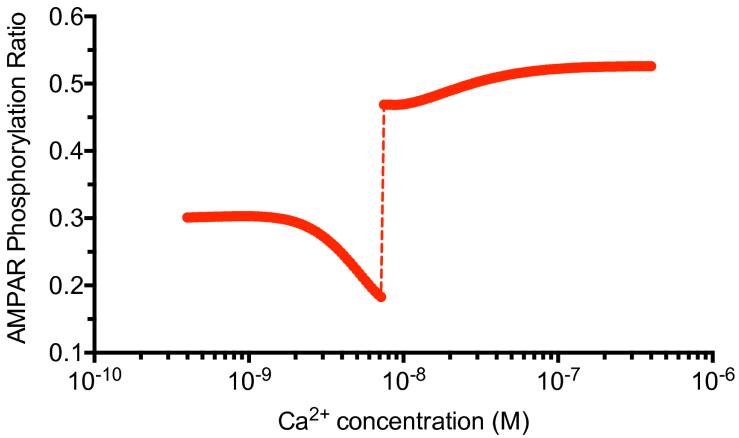
Multi-scale modelling framework



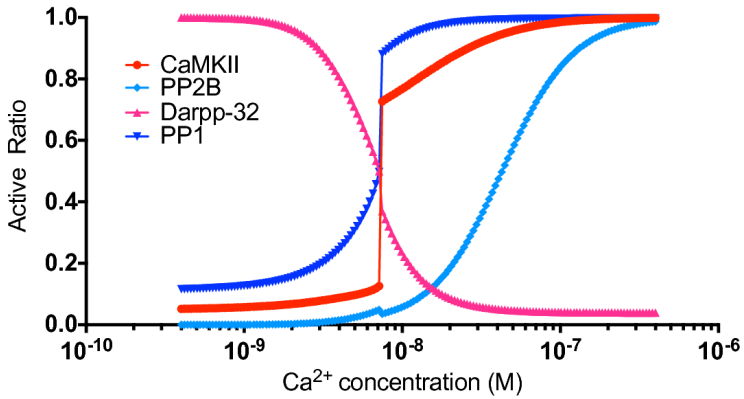
- NEURON model based on Quadroni and Knopfel, *J Neurophysiol*, 1994
- COPASI model based on Li *et al.*, *PLoS ONE*, 2012

Model reproduces bistability in response to Calcium

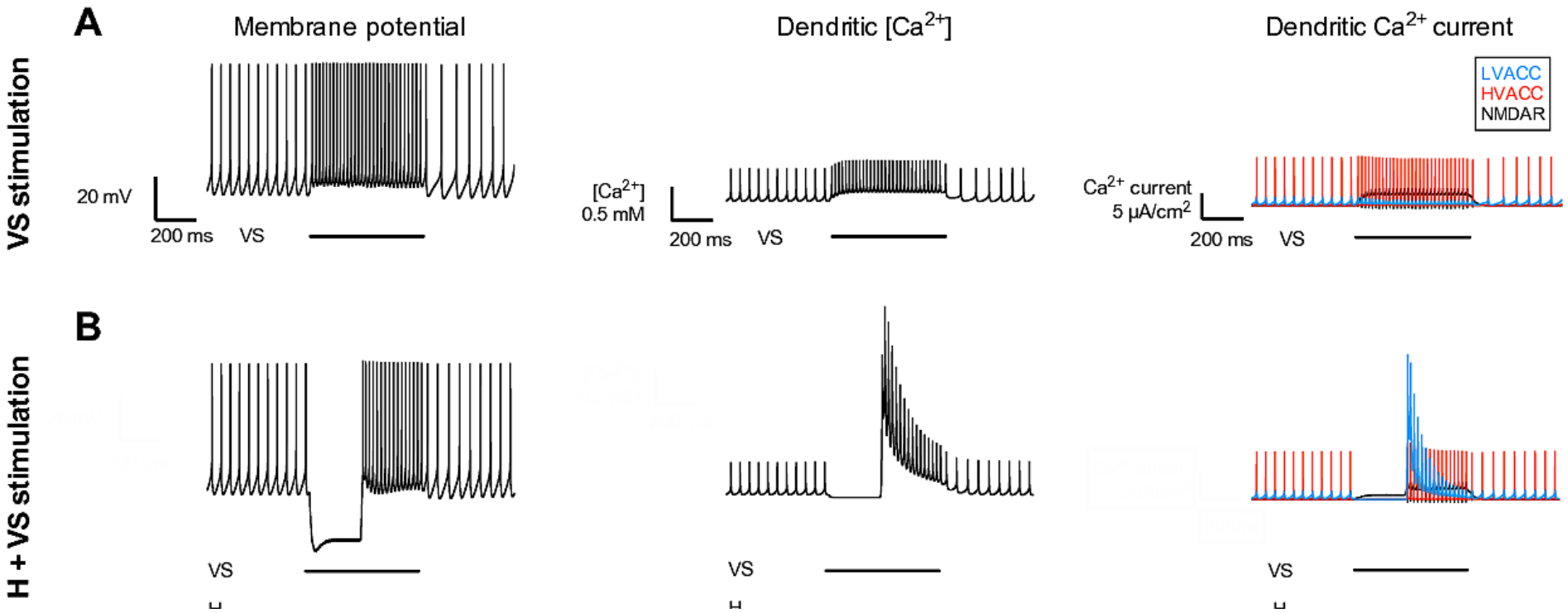
AMPA receptor activation



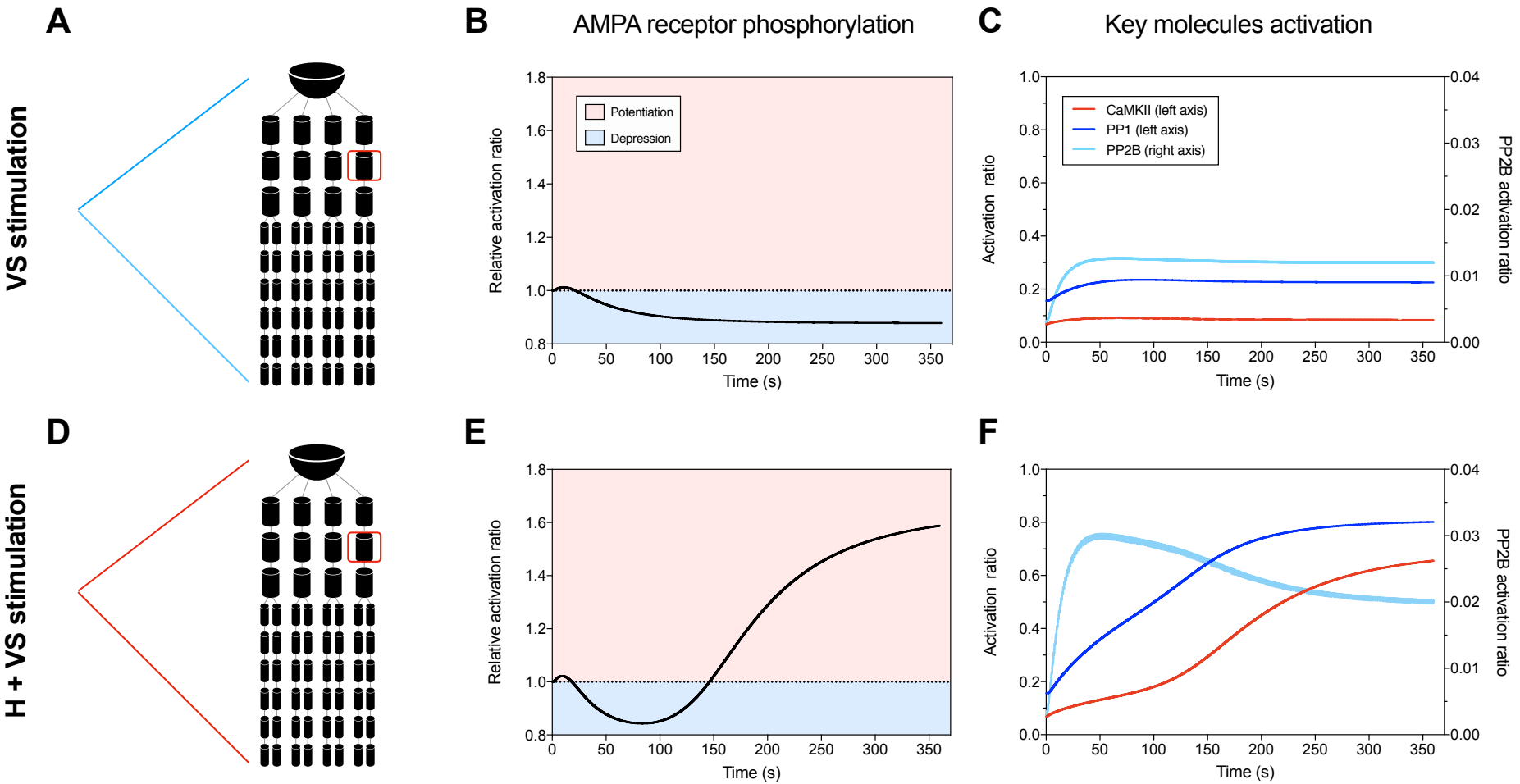
Bistability of kinases and phosphatases



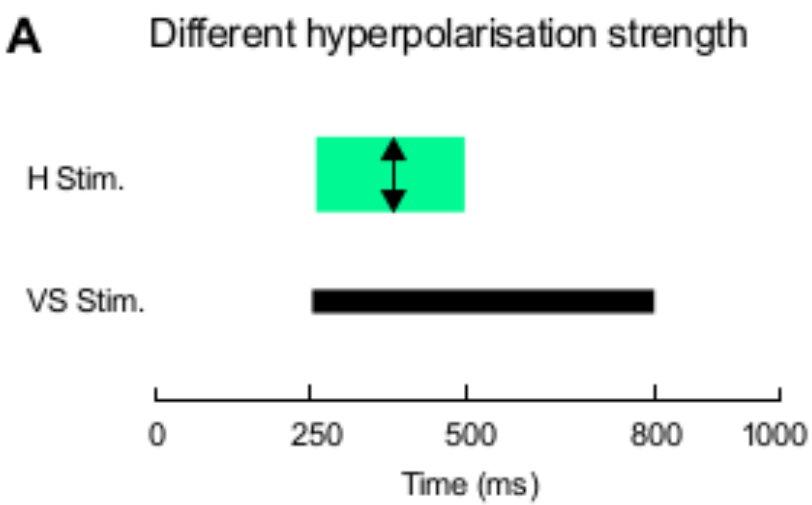
Hyperpolarisation followed by stimulation leads to larger Ca^{2+} influx than stimulation alone. LVACC are key to this.

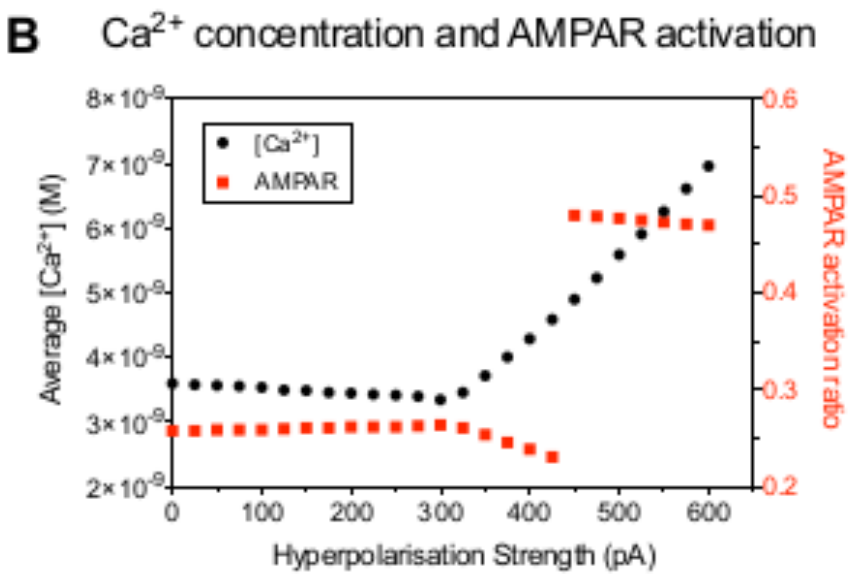


Hyperpolarisation + stimulation activates AMPARs; stimulation alone reduces AMPAR activation.



Plasticity depends on hyperpolarisation strength.





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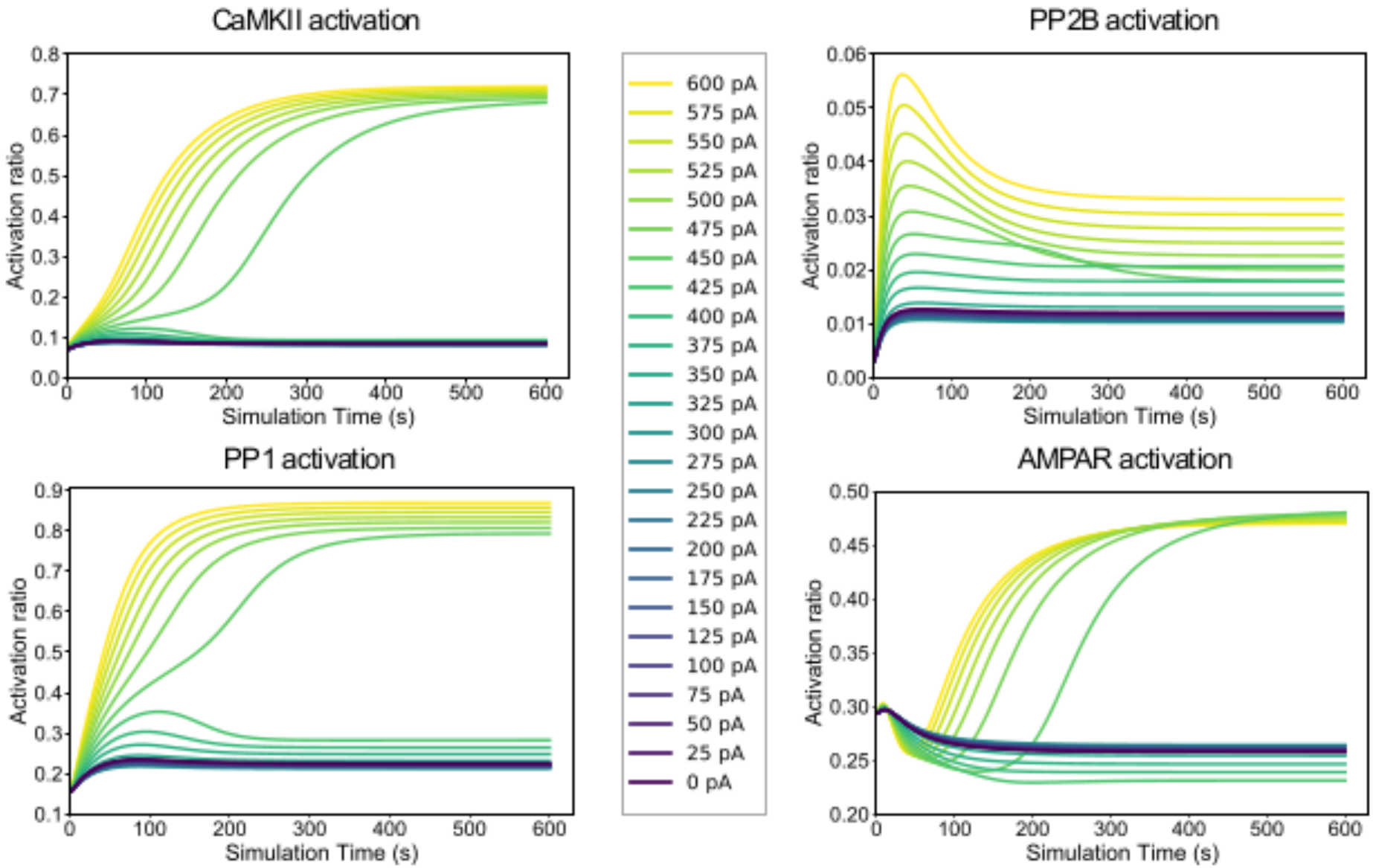
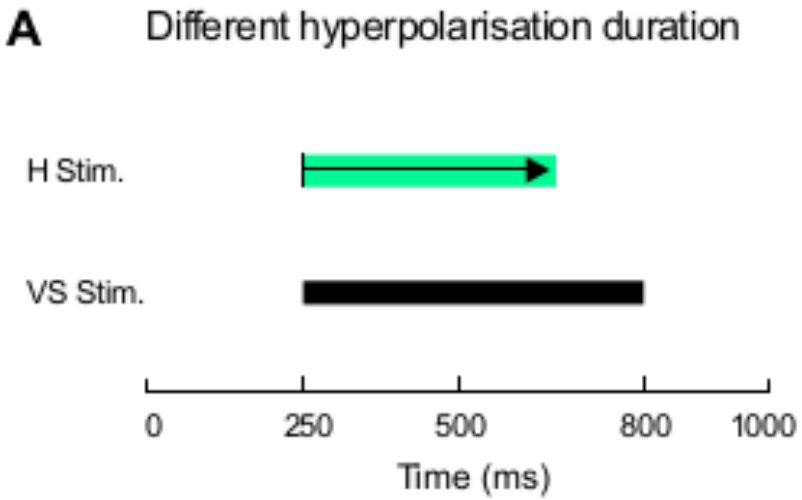
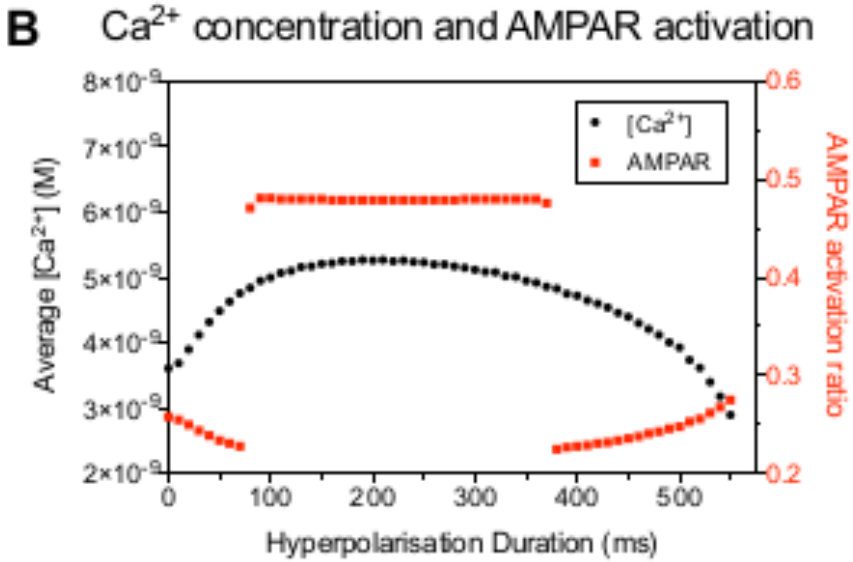
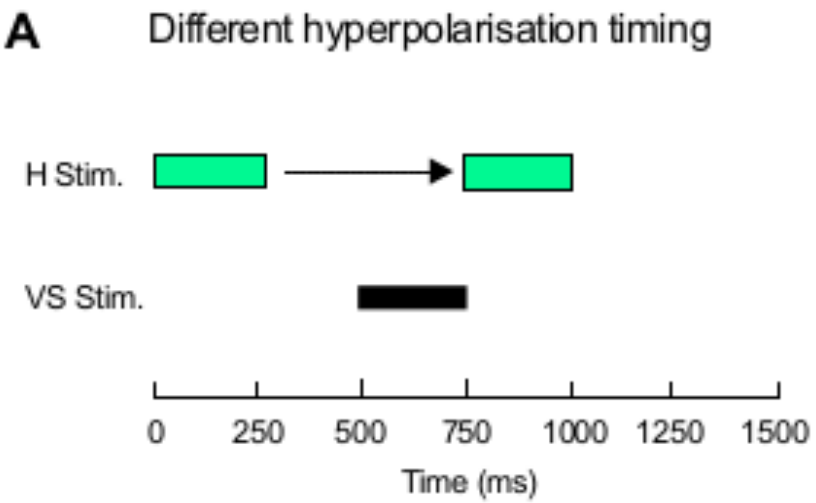


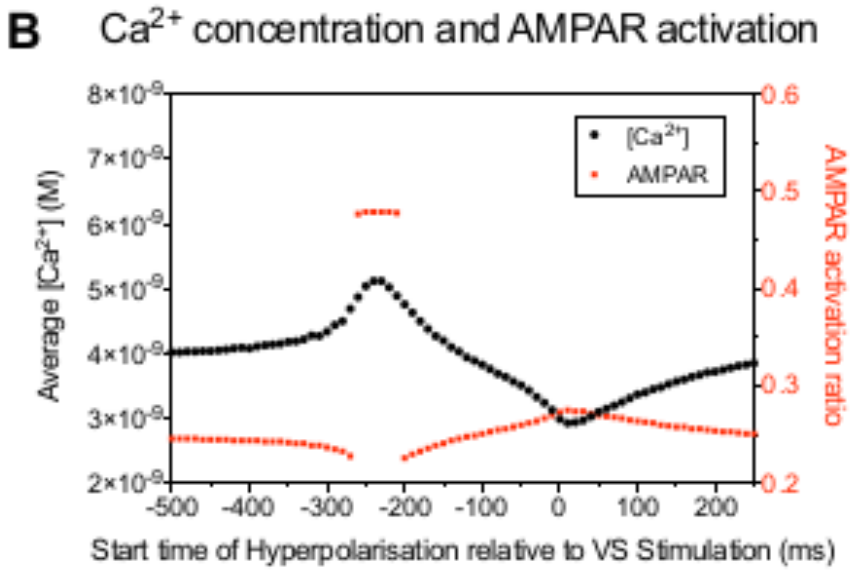
Plasticity depends on the duration of hyperpolarisation.





Plasticity depends on the relative timing of hyperpolarisation and stimulation.





Take-home messages

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- We can build models that bridge scales (electrical and chemical) to get a deeper insight into synaptic plasticity.

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- We can build models that bridge scales (electrical and chemical) to get a deeper insight into synaptic plasticity.
- Hyperpolarisation-gated synaptic plasticity depends on LVACC activity and the balance between kinases and phosphatases.
- Hyperpolarisation-gated synaptic plasticity depends non-linearly on the strength, duration, and timing of the hyperpolarising stimulus.

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New Results

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A multi-scale model reveals cellular and physiological mechanisms underlying hyperpolarisation-gated synaptic plasticity

Yubin Xie, Marcel Kazmierczyk, Bruce P Graham, Mayank B. Dutia, Melanie I Stefan

doi: https://doi.org/10.1101/418228

Posted September 21, 2018.

This article is a preprint and has not been peer-reviewed [what does this mean?].

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Abstract

Neurons in the medial vestibular nucleus (MVN) display hyperpolarisation-gated synaptic plasticity, where inhibition believed to come from cerebellar cortical Purkinje cells can induce long-term potentiation (LTP) or long-term depression (LTD) of vestibular nerve afferent synapses. This phenomenon is thought to underlie the plasticity of the vestibulo-ocular reflex (VOR). The molecular and cellular mechanisms involved are largely unknown. Here we present a novel multi-