NeuroDisco! Fine-tuning brain cells with light-evoked electrical activity

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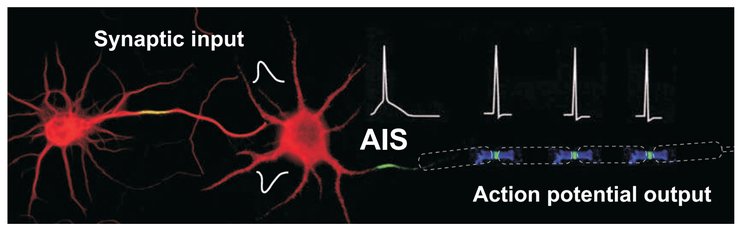
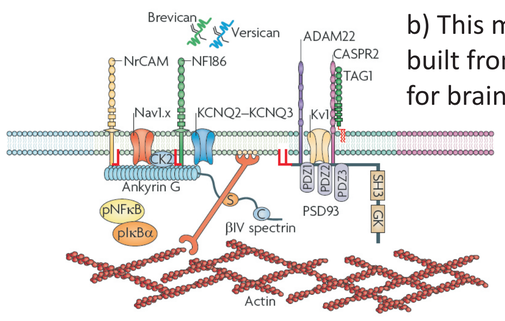
SET for BRITAIN

Background

a) The brain consists of billions of inter-connected cells, or neurons, which work by sending electrical signals to one another. These signals, called action potentials, initiate in a structure within the neuron known as the axon initial segment, or AIS.



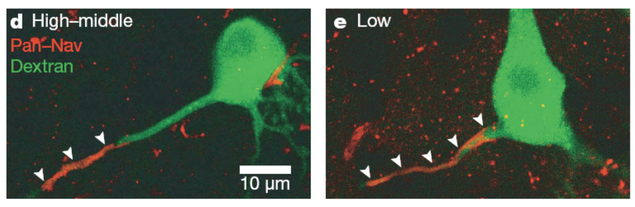
Rasband 2010 Nat Rev Neurosci 11:552



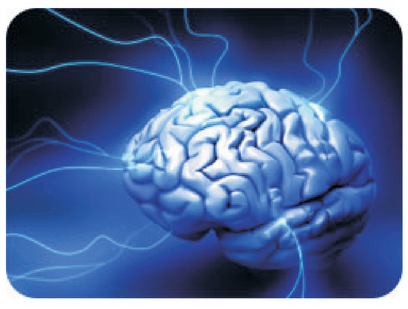
Rasband 2010 Nat Rev Neurosci 11:552

b) This makes the AIS, which is a highly-specialised structure built from multiple molecular components, absolutely crucial for brain function in health and in disease.

c) The position of the AIS varies considerably from neuron to neuron, and this variation has been linked to cells' information-processing capabilities.



Kuba et al. Nature 444:1069

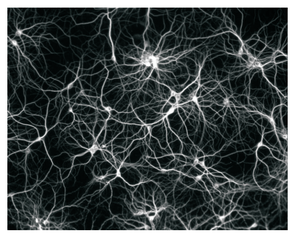


d) And we know that the brain depends on electrical activity not only to operate as a mature organ, but also to develop appropriately: almost every stage of brain maturation is influenced by the electrical activity of its constituent neurons.

How is AIS position determined?

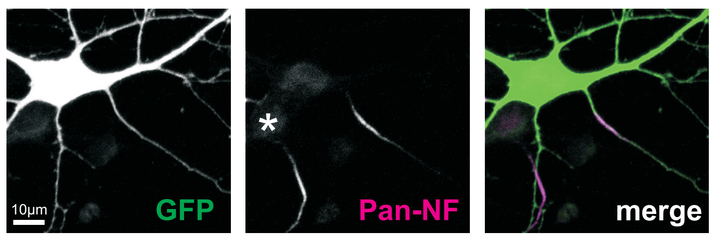
Might electrical activity be involved?

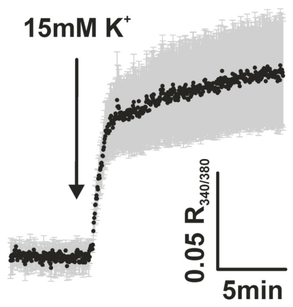
① The approach



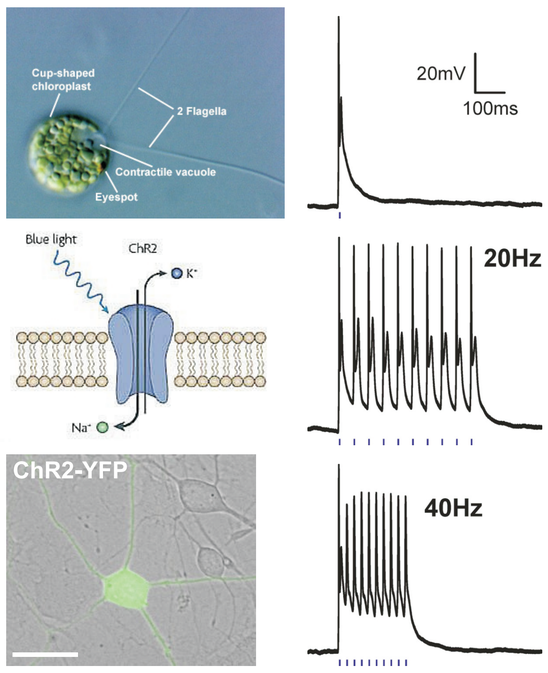
a) We use dissociated cultures of hippocampal neurons...

b) ...where we can fluorescently label AIS-specific proteins.

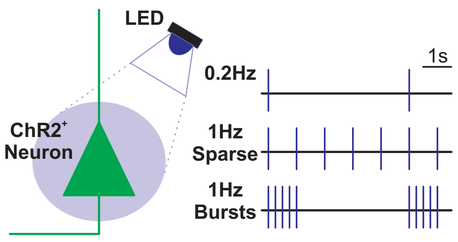




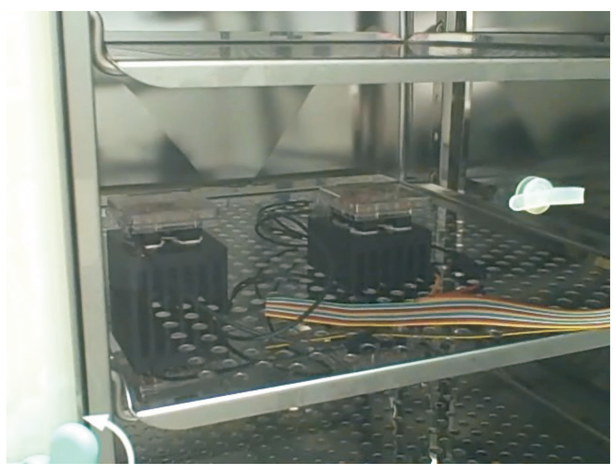
c) We can increase neuronal activity across all cells in the culture (here reflected in increased calcium entry) by simply increasing the concentration of K^+ ions in the media.

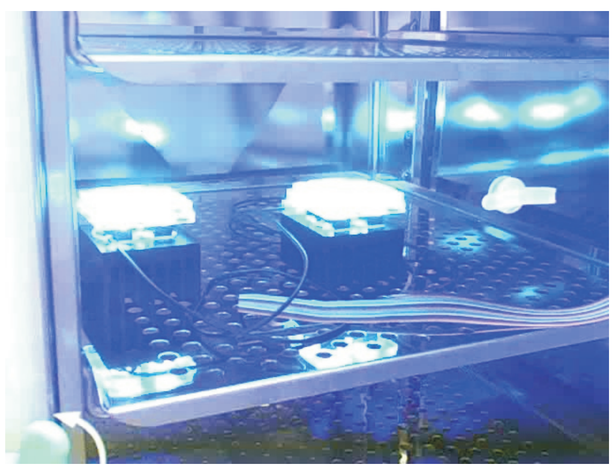


d) But for precise control of neuronal activity in space and time, we use a light-gated ion channel called channelrhodopsin-2 (ChR2) to make our neurons light-sensitive.



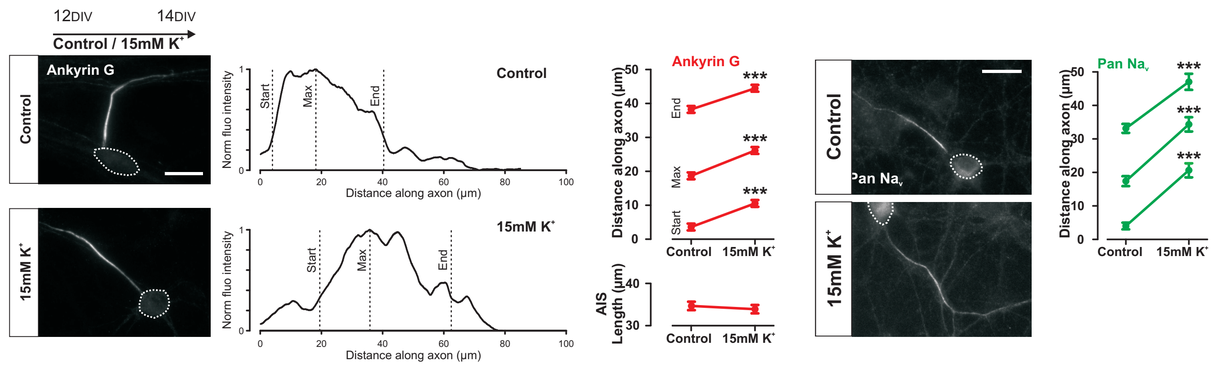
e) So by growing neuronal cultures on top of blue LEDs (our NeuroDisco!) we can 'dial-in' whatever pattern of activity we like.



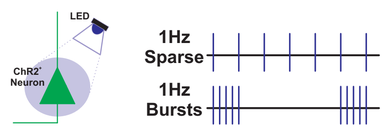


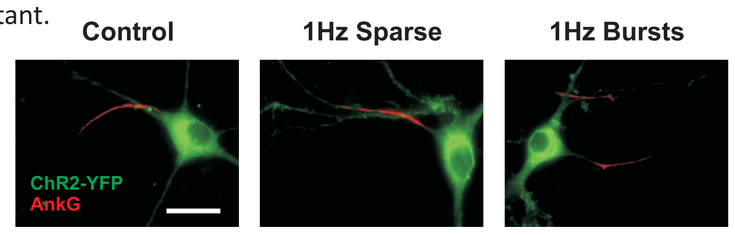
② Major findings (Grubb & Burrone 2010 Nature 465:1070)

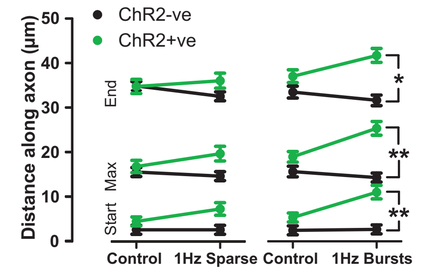
a) Chronic activation with elevated K^+ produces a distal shift in AIS location. This is an entire cellular subregion moving along the axon in response to changes in electrical activity!



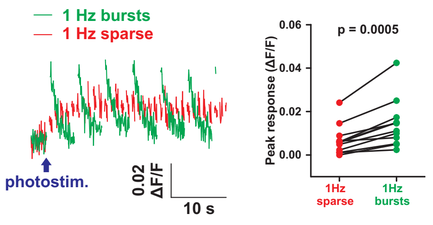
b) NeuroDisco stimulation shows i) the 'decision' to move the AIS is taken by each neuron independently and ii) certain patterns of activity are more effective at producing AIS movement, even when the overall rate of activity remains constant.





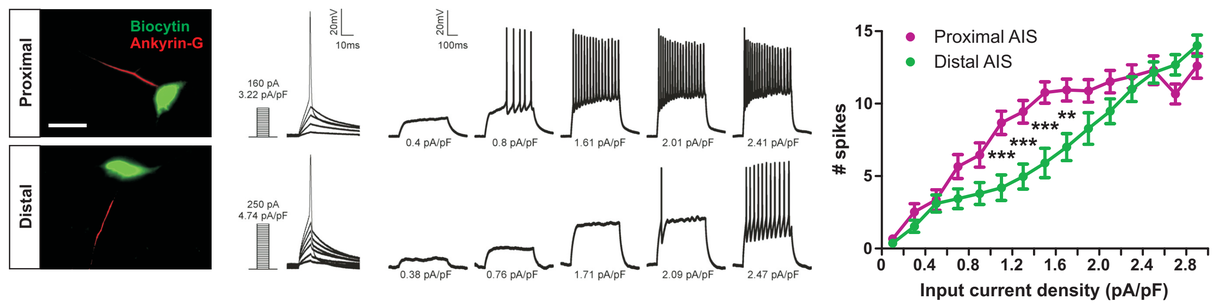


c) What's more, these patterns are associated with particular features of intracellular Ca^{2+} dynamics.



③ What does it mean?

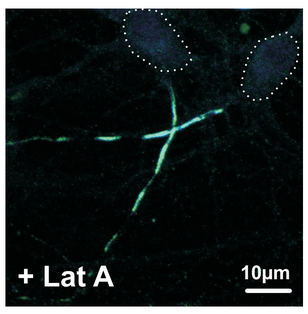
a) We used electrophysiological recordings to show that cells with more distal AISs are less excitable.



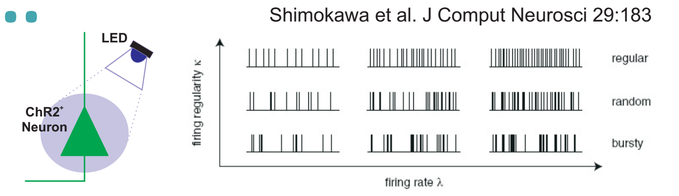
b) So activity-dependent AIS relocation might be a 'homeostatic' response: increased activity leads to AIS movement, which then brings activity levels back to their normal range This could have crucial implications during normal brain development, and in disorders of neuronal excitability such as epilepsy.

④ Coming soon...

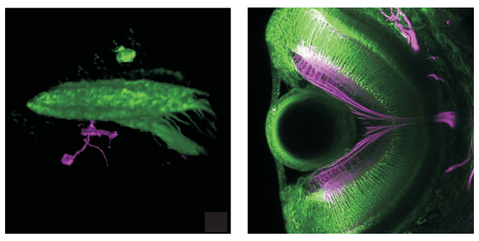
How exactly does the AIS move?



Shimokawa et al. J Comput Neurosci 29:183



A systematic exploration of 'activity codes' for AIS position (with Nick Lesica, UCL).



Watching AIS movement live and in vivo in the zebrafish visual system (with Martin Meyer, KCL).

Thanks to Juan Burrone, Annisa Chand, Mark Evans, and Tom Watkins

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