

Calcium-induced calcium release in neurons

Yulia Timofeeva (Centre for Complexity Science, office D2.12)

E-mail: y.timofeeva@warwick.ac.uk

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Neurons are a specialised part of the extremely complex structure of the nervous system. They generate electrical signals in response to chemical and other inputs and transmit them to other cells. Although both experimental and theoretical work has been going on for more than a century to try and understand signal processing in neurons, the role of an individual cell in neural computation is still the subject of debate.

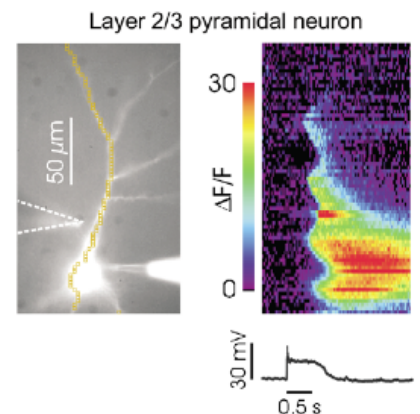
It is well known that Ca^{2+} ions are an important second messenger in all living cells and critical for a large number of cellular functions. Neurons have an elaborate endoplasmic reticulum (ER) (a calcium source) that extends throughout the cell and can be considered as a neuron-within-a-neuron, in that together with the plasma membrane it creates a binary membrane system and plays integrative roles between different parts of neurons. Two classes of Ca^{2+} oscillations or waves are readily distinguished: those that depend primarily on the influx of Ca^{2+} through voltage-gated calcium channels (VGCCs) from the extracellular space, and those that depend primarily on Ca^{2+} release from the ER. Experimental studies demonstrate that calcium channels open in response to membrane depolarisation and in turn cause further depolarisation by generating calcium-dependent action potentials (AP). At the same time the propagation of an AP produces an increase in calcium concentration with the generation of rich spatiotemporal patterns, from widespread Ca^{2+} influx to heterogeneous Ca^{2+} transients. Moreover, the sensitivity of ryanodine receptors (RyRs) and the inositol (1,4,5)-trisphosphate IP_3 receptors IP_3Rs to Ca^{2+} results in the amplification of calcium signalling through the regenerative process known as Ca^{2+} -induced Ca^{2+} release (CICR).

Some theoretical work on combining Ca^{2+} and membrane voltage dynamics in nerve cells has been proposed earlier. However, the spatially extended nature of neurons combined with the heterogeneous distribution of voltage-dependent and Ca^{2+} -sensitive channels has received far less attention. The main aim of this project is to investigate the role of the CICR process in generating spatiotemporal Ca^{2+} signals. We start by considering a semi-infinite dendritic cable with the lumped soma attached to it. The cell membrane will be equipped with discretely distributed VGCCs. Influx of Ca^{2+} through these channels is expected to initiate the CICR mechanism which triggers Ca^{2+} release from the ER through calcium-sensitive channels (RyRs) placed at discrete locations along the ER. Mimicking the nonlinear properties of both VGCC and RyRs by threshold processes the model may be solved in terms of the well-known time translation invariant Green's function (that has to satisfy appropriate boundary conditions at the soma). The project will incorporate both theoretical and numerical components and focus on studying the effect of variations in system parameters and the presence of the lumped soma on intracellular Ca^{2+} waves.

This work can potentially be extended to a PhD project which will incorporate more biological aspects into modelling of intracellular calcium dynamics in neurons and include components of analysis and computation.

Some relevant publications:

1. M E Larkum, S Watanabe, T Nakamura, N Lasser-Ross, W N Ross (2003) Synaptically activated Ca^{2+} waves in layer 2/3 and layer 5 rat neocortical pyramidal neurons *Journal of Physiology* Vol 549(2).
2. A Verkhratsky (2005) Physiology and pathophysiology of the calcium store in the endoplasmic reticulum of neurons *Physiological Reviews*, Vol 85.
3. Y Timofeeva, S Coombes (2003) Wave bifurcation and propagation failure in a model of calcium release, *Journal of Mathematical Biology*, Vol 47.



Synaptic stimulation evokes Ca^{2+} waves in neurons [1]