Propagation of intercellular calcium waves

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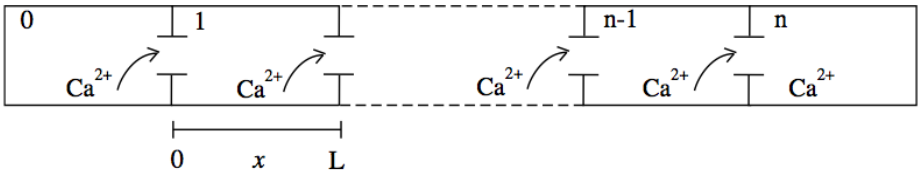
Calcium is a highly versatile intra- and inter-cellular medium that is known to regulate many different cellular processes, from cell division and differentiation to cell death. Ca^{2+} oscillations occur either spontaneously or as a result of stimulation by an external signal such as a hormone or a neurotransmitter. Besides the rhythms encountered in electrically excitable cells, these oscillations represent the most widespread oscillatory phenomenon at the cellular level and are often associated with the propagation of Ca^{2+} waves within the cytosol and also between adjacent cells. The observed Ca^{2+} waves in many types of cells are believed to be the result of Ca^{2+} diffusion between Ca^{2+} release sites. An initiated wave of increased intracellular Ca^{2+} can spread from cell to cell to form an intercellular wave. This intercellular propagation appears to be mediated by the passage of Ca^{2+} or IP_3 (a second messenger known to raise the level of cytosolic Ca^{2+}) through gap junctions.

The main goal of this project is to investigate the issue of wave propagation failure through a cell culture as a function of cell-cell coupling parameters. Intracellular calcium dynamics in each cell will be described by the so-called Fire-Diffuse-Fire (FDF) model, which uses a threshold process to mimic the nonlinear properties of Ca^{2+} channels. Although the FDF model can support both continuous and discrete distributions of Ca^{2+} release sites this study will focus on the discrete case. Multiple cells will be connected by gap junctions which carry the intercellular Ca^{2+} fluxes that are proportional to the concentration differences across the gap junctions. As a starting point a linear cell array will be considered. The discreteness of Ca^{2+} release channels breaks translation symmetry and many of the standard techniques for travelling wave analysis no longer apply. However, the linearity between Ca^{2+} release events in the FDF model means that it may be solved in terms of the well-known time translation invariant Green's function (that has to satisfy appropriate boundary conditions at the gap junctions). The project will incorporate both theoretical (construction of the Green's function for multiple cells with gap junctions, analysis of wave propagation failure) and numerical (model's implementation) components. A notion of IP_3 sensitivity can also be incorporated in the model by considering an IP_3 dependent threshold for Ca^{2+} release. The obtained results will be compared with the case of continuous distribution of Ca^{2+} channels studied earlier [1]. The outcome of the project will be of interest to computational and experimental cell biologists alike.



This work can potentially be extended to a PhD project which will incorporate more biological aspects into modelling of intercellular calcium dynamics and include components of analysis and computation. Modelling will involve interaction with experimentalists and will be guided by data from the lab of Dr John Love (School of Biosciences, University of Exeter).

Relevant publications:

1. Y Timofeeva (2003) PhD thesis "Oscillations and Waves in Single and Multi-cellular Systems with Free Calcium" http://www.dcs.warwick.ac.uk/~yulia/thesis.pdf
2. Y Timofeeva and S Coombes (2003) Wave bifurcation and propagation failure in a model of calcium release, *Journal of Mathematical Biology*, Vol 47, 249–269.