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A Parallel Modelling Algorithm for Simulating Calcium Release in Cells

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Abstract:
Using a spatially discretised model structure to represent the behaviour of calcium release sites in a cell, this paper presents a parallel solution algorithm which treats each release site as an independent sub-system, and manages inter-site data communication on a global timestep. When compared to the equivalent single-thread solution algorithm, the parallel method features a negligible reduction in accuracy, and improves computation time scaling from a quadratic, $O(n^2)$ to a linear, $O(n)$, with respect to the number of release sites, n, in the model.

Keywords: Parallel, Modelling, Biology, Simulation

1. INTRODUCTION

Normal heart function relies on coordinated, rhythmic contractions of billions of muscle cells within the heart. In turn, rhythmic contraction of each cell depends on release of calcium ions (Ca^{2+}) from approximately 20,000 release sites distributed throughout each cell. Parallel computing provides a tool for understanding how the physiological process within each release site and within each cell integrate to produce the observable heart rhythm.

A non-linear model of calcium release in heart cells, developed by Cannell et al. (2013a), considers mechanisms of buffering, diffusion and stochastic triggering for a small population of release sites inside a single cell. For large-scale simulations, the model has been discretised to decrease the structural complexity at each release site.

The intended purpose of the model is to understand how groups of Ca^{2+} release sites produce the experimentally observable phenomena of Ca^{2+} sparks and waves. Sparks, named for the bursts of light they produce in the presence of fluorescent indicators, are localised Ca^{2+} release events that occur at a single site (Kong et al., 2013). Ca^{2+} waves are release events which require the coordinated activation of adjacent release sites, and produce an increase in cytoplasmic calcium concentration which propagates like a wave throughout the cell. The physiological details of the wave phenomenon remain unclear, and a better understanding would enable further studies of the effect of various pharmaceutical drugs on wave properties and ultimately on heart rhythm.

With all major dynamics considered, the resulting model is stiff in nature, and requires a sophisticated solver algorithm to minimise computation time and ensure accuracy. This model had been solved as a single-thread, single-Jacobian process, causing simulations to become prohibitively long for models on the order of 100 sites, while a full-scale 20,000-site cell model results in a system order greater than 10^6. To enable such large scale simulations, finding a more time-efficient modelling approach is necessary such that the full-scale model can be explored, modified and interpreted in more convenient time frames.

Parallel model structures have been succesfully developed to simulate various diffusion-based processes which are similar in nature to the calcium release problem. The results from Shaikh et al. (2011), Stern et al. (2014) and Li et al. (2010) show the potential of parallel methods to provide accurate results with reasonable computation times if the model is partitioned in a manner which exploits the different time constants of the system.

In this paper, the biological model is split into independent subsystems based on the varying diffusion dynamics in different regions of the system. A parallel solution algorithm is formulated which solves the individual subsystems in a multi-thread environment, with a communication update interval maintained on a global timestep. Several extrapolation methods are tested within the parallel framework to identify the most accurate and robust technique. The computation time of the new algorithm scales linearly $O(n)$ with the number of release sites, n, in the model. Further improvements are also achieved through the treatment of the Jacobian and global step-size control.

The paper is organised as follows: Section II provides an overview of the discretised release model relevant to large-scale simulations, and highlights the dynamics present in a single release site. Section III presents the several competing methods of parallelisation and assesses their accuracy in the calcium release context. Section IV theoretically and experimentally validates the linearization of solution time scaling. Section V outlines some additional numerical techniques which can further optimise computation time, and Section VI concludes the paper.

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2. THE CALCIUM RELEASE MODEL

2.1 Geometry

In heart muscle cells, the release of calcium into the general cytoplasm is dictated by the behaviour of dyads located throughout the cell's structure. The dyad consists of several components (Cannell et al., 2013a):

(1) T-tubule which allows extracellular calcium to enter the cell at the dyad junction.
(2) Distributed calcium store (LSR) inside the cell, with a terminal (TSR) located in close proximity to the ion channel of the T-tubule, creating a 'dyadic cleft'.
(3) Cluster of calcium release channels (ryanodine receptors or 'RyRs') on the surface of the TSR, which open and close to control the diffusion of calcium from the store into the cleft and general cytoplasm of the cell.

In the simplified model, each dyad is contained within a cube shaped 'voxel' which contains discrete elements relevant to the release process. Each element will possess a lumped concentration for Ca^{2+}, as well as concentrations for a selection of buffers and indicators. The number of state variables in a single voxel is of the order of 10^2. Figure 1 provides a conceptual diagram of the geometry for a discretised voxel, and indicates the typical flow of calcium within and between release sites.

2.2 Transport of Materials

In modelling the concentrations of substances in the cell, mechanisms of diffusion, buffering and active pumping are considered. With the model split into discrete blocks of cytoplasm, the equations governing these transport mechanisms must also be discretised around the defined volume elements. For the case of calcium, the concentration in a particular volume of cytoplasm is given by (Cannell et al., 2013a)

$$\frac{\mathrm{d}[Ca^{2+}]}{\mathrm{d}t} = \sum_{i=1}^{p} D_i([Ca_i^{2+}] - [Ca^{2+}]) + \sum_{i=1}^{r} F_{RyR,i} - F_{SERCA} - \sum_{i=1}^{b} F_{buffer,i}, \quad (1)$$

where $[Ca^{2+}]$ is the calcium concentration in the volume. On the RHS of (1), the first term describes diffusion from p neighbouring volume elements, with their own calcium concentrations $[Ca_i^{2+}]$, and diffusion coefficients D_i to the volume of interest. The second term is an expression for the calcium fluxes, $F_{RyR,i}$, from r open receptors, which is applicable for volumes inside the dyad cleft. In some volume elements, a 'SERCA pump' is present which actively transfers calcium from the general cytoplasm to the longitudinal SR, giving rise to the F_{SERCA} flux. Lastly, there are several other substances which bind to calcium, removing the free ions from solution. These buffering reactions are summarised by $F_{buffer,i}$ fluxes to each of the b buffers present in the volume.

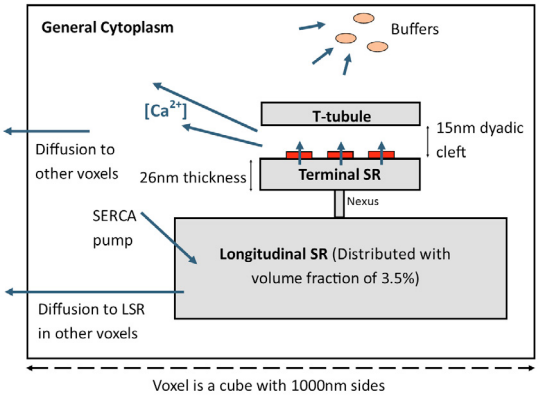

Fig. 1. Voxel geometry for a single dyad, Ca^{2+} release site

The buffering fluxes have a linear form, and for each buffer B_i in the volume, the flux is defined by

$$F_{buffer,i} = k_{on,i}[B_i][Ca^{2+}] - k_{off,i}[CaB_i],$$

where $k_{on,i}$ and $k_{off,i}$ are buffer-specific constants, $[B_i]$ is the concentration of the unbound buffer in the volume, and $[CaB_i]$ is the concentration of the calcium-bounded buffer. The SERCA flux out of the general cytoplasm is governed by the non-linear equation,

$$F_{SERCA} = k_1\left(\frac{k_2[Ca^{2+}]^2}{1 + k_2[Ca^{2+}]^2} - k_3\right),$$

for some fixed constants k_1, k_2 and k_3. The RyR fluxes further increase the model complexity, as they depend on the open probabilities of receptors in the area,

$$F_{RyR,i} = k_4 P_{RyR,i}([Ca_{TSR}^{2+}] - [Ca^{2+}]),$$

where the calcium concentration of the terminal store (TSR) is given by $[Ca_{TSR}^{2+}]$, k_4 is a constant, and $P_{RyR,i}$ is the open probabilty of the i'th receptor in the volume. The open probabilities are themselves dependent on a stochastic triggering process which is executed at 50ms intervals. A more comprehensive mathematical description of the model can be obtained from Cannell et al. (2013a), and its supplement (Cannell et al., 2013b).

2.3 Release Site Dynamics

Ideally, in order to parallelise the release model, the boundaries for the proposed sub-systems should have a slow rate of information exchange with respect to the dynamics internal to the sub-systems. An investigation of the 'spark' dynamics at a single release site was performed to provide evidence that the voxels themselves are viable candidates for conversion to parallel subsystems.

A spark begins when the dyad is triggered and receptors latch open, allowing Ca^{2+} to flood out from the TSR into the junction before diffusing to the general cytoplasm and neighbouring release sites. After a brief period, the Ca^{2+} concentration in the TSR reduces to a level that cannot continue supporting flux into the dyadic cleft, hence the receptors begin re-closing (Cannell et al., 2013a), (Kong et al., 2013). Figure 2 shows the calcium concentrations for several important volumes during a release site spark. It can been seen in plot A that a sharp concentration spike occurs at the centre of the cleft, where calcium floods out of the store through the receptors. The TSR concentration (plot B) has a corresponding sharp decrease as its calcium store depletes. The general cytoplasm (plot C) has a significantly slower calcium influx than the dyadic cleft, and the relative magnitude of the increase is far smaller. The dominant behaviour in the LSR (plot D) is a slow rise in concentration driven by the SERCA pump.