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Modelling cell cycle synchronisation in networks of coupled radial glial cells

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HIGHLIGHTS

- A model of radial glial cells coupled via extracellular ATP diffusion is considered.
- Analysis reveals dependence of cell cycle synchronisation on ATP release timing.
- ATP release at G1/S cell cycle transition promotes synchronous solutions.
- Results may help us to understand the origins of neurodevelopmental disorders.

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ABSTRACT

Radial glial cells play a crucial role in the embryonic mammalian brain. Their proliferation is thought to be controlled, in part, by ATP mediated calcium signals. It has been hypothesised that these signals act to locally synchronise cell cycles, so that clusters of cells proliferate together, shedding daughter cells in uniform sheets. In this paper we investigate this cell cycle synchronisation by taking an ordinary differential equation model that couples the dynamics of intracellular calcium and the cell cycle and extend it to populations of cells coupled via extracellular ATP signals. Through bifurcation analysis we show that although ATP mediated calcium release can lead to cell cycle synchronisation, a number of other asynchronous oscillatory solutions including torus solutions dominate the parameter space and cell cycle synchronisation is far from guaranteed. Despite this, numerical results indicate that the transient and not the asymptotic behaviour of the system is important in accounting for cell cycle synchronisation. In particular, quiescent cells can be entrained on to the cell cycle via ATP mediated calcium signals initiated by a driving cell and crucially will cycle in near synchrony with the driving cell for the duration of neurogenesis. This behaviour is highly sensitive to the timing of ATP release, with release at the G_1/S phase transition of the cell cycle far more likely to lead to near synchrony than release during mid G_1 phase. This result, which suggests that ATP release timing is critical to radial glia cell cycle synchronisation, may help us to understand normal and pathological brain development.

1. Introduction

Radial glial cells give rise to the vast majority of neurons in the neocortex (Noctor et al., 2001). Only present for a brief period during embryonic development when they proliferate, all radial glial cells eventually differentiate into neurons. It has been demonstrated that radial glia communicate via adenosine tri-phosphate (ATP) (Weissman et al., 2004)which is released via hemichannels (Li et al., 1996). The question of exactly when during the cell cycle hemichannels form has not been definitively answered in the literature. The experiments of Weissman et al. (2004) suggest that they may form in, or near, S-phase. Bittman and LoTurco (1999) investigated hemichannel opening in populations of ventricular zone cells which included radial glia. They found that the point of the cell cycle which corresponds to hemichannel opening is highly variable; opening was observed for part of G_1, as well as during the entirety of G_1 and also for part of S-phase and was not necessarily consistent for every cell in the population.

ATP is one of the primary means by which radial glia communicate and influences proliferation. By inhibiting the normal function of ATP receptors for one hour Weissman et al. (2004) observed that the proportion of cells labelled with BrdU (indicating S-phase entry) was 54.7% that of the case where ATP receptors were allowed to function as normal. Although the key downstream factor affecting proliferation was not identified in the study, in radial glia ATP leads, via a G-protein cascade, to inositol

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1,4,5-trisphosphate (IP_3) mediated calcium release from the endoplasmic reticulum (ER) (Weissman et al., 2004). Importantly there is evidence that calcium influences cell cycle progression in many cell types (Berridge, 1995; Berridge et al., 2000). Calcium, via calcium/calmodulin dependent kinases, causes an increase in Cyclin D activity (Kahl and Means, 2003, 2004; Morris et al., 1998; Tombes et al., 1995; Rasmussen and Rasmussen, 1995), a key cell cycle protein crucial for G_1 progression. In addition to the roll of ATP in cellular proliferation it has also been conjectured that the ATP mediated calcium signalling mechanism is responsible for synchronising the cell cycles of clusters of radial glia (Weissman et al., 2004). Release from a handful of cells may have the effect of synchronising the cell cycles within a cluster, or cohort, of cells as well as recruiting cells in G_0 on to the cell cycle (see Fig. 1). Synchronised radial glia lead to the birth of daughter cells from the cohort in an ordered, regular fashion. It has been speculated that the neurons which originate from the same synchronised cohort go on to reside in the same cortical layer (Weissman et al., 2004). Hence, radial glia synchronisation has implications for the architecture of the developing mammalian brain.

In Barrack et al. (2014), we introduced a model for coupled calcium-cell cycle dynamics in a single radial glial cell which is outlined in Appendix A. We showed that ATP mediated calcium release led to a modest increase in the frequency of the cell cycle. The modulation in frequency, in itself, could not explain the experimentally observed fluctuations in proliferation rates associated with ATP. However, our analysis revealed an area of multistability in which stable fixed points and limit cycle solutions coexist. This area allows for a proliferating radial glial cell to recruit an otherwise quiescent cell onto the cell cycle via an ATP mediated calcium signalling mechanism. This in turn could explain the changes in cellular proliferation which have been observed experimentally (Weissman et al., 2004).

In this paper we investigate whether, and under what conditions, an ATP mediated calcium signalling mechanism leads to cell cycle synchronisation of clusters of radial glia. Systems of cells coupled via extracellular ATP on one and two dimensional lattices are considered and the system dynamics are studied via bifurcation analysis and direct numerical simulations. We consider clusters in which all cells are initially cycling and, because our previous work suggests that quiescent cell recruitment is extremely important, we also investigate cell cycle synchrony under the scenario in which some cells within the cluster are initially dormant. Our results indicate that stable synchronous solutions are far from guaranteed. However, our model does permit trajectories where cells cycle in near synchrony for a period of time consistent with the period of neurogenesis in mammals. For our model, cells have a greater propensity to synchronise when ATP is released at the G_1/S phase transition rather than during mid G_1 phase of the cell cycle. As radial glial cell cycle synchronisation is crucial for the regular formation of the neocortex, these results may shed light on the causes of some neurodevelopment disorders which stem from irregular cortical formation.

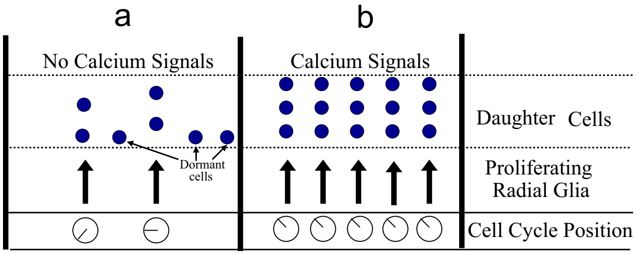

Fig. 1. Schematic illustrating how ATP mediated calcium signals initiated by a small number of cycling cells may not only recruit otherwise quiescent cells on to the cell cycle but also synchronise the cell cycles of radial glial cells, so that clusters of cells cycle in unison. (a) No calcium present. Here two cells proliferate in an asynchronous manner (represented by the position of the clock hands) whilst the remainder remain dormant and do not cycle. (b) Dormant cells are recruited on to the cell cycle via ATP mediated calcium release from cycling cells which also has the effect of synchronising cell cycles, leading to the shedding of daughter cells in uniform sheets.

This paper is structured as follows. In Section 2 we outline our model for ATP mediated calcium-cell cycle coupling in radial glia. In Section 3, we present our results before concluding with a discussion in Section 4.

2. The model

Our single cell model, introduced in Barrack et al. (2014), is comprised of a cell cycle component based on the model of Obeyesekere et al. (1999) and an ATP mediated calcium release component based on the model of Bennett et al. (2005). The cell cycle model includes five dynamical variables including Cyclin D/Cdk4, Cyclin E/Cdk2, unphosphorylated retinoblastoma tumour suppressor protein (RB) and phosphorylated RB bound to the E2F transcription factor. These proteins drive a cell through G_1 phase into S phase of the cell cycle. The model also includes a ‘cell progression indicator’ variable which indirectly represents the kinases, phosphatases and proteases responsible for driving the cell through the remainder of S, G_2 and M phases of the cell cycle. The ATP mediated calcium release model component accounts for calcium release from ER and includes variables for extra and intracellular ATP concentrations, proportion of external $P2Y_1$ receptors bound to ATP, G-protein activation and IP_3 production. In our model, the coupling between the calcium dynamics and cell cycle dynamics is mediated via the Cyclin D production rate which we make an increasing function of calcium in the cell. Each cell is coupled to its nearest neighbours via extracellular ATP. This ensures that when cells are cycling an ATP signal is passed on to its nearest neighbours which regenerate the signal by releasing their own ATP. As it is unclear when exactly hemichannels form and ATP is released two model variants with different ATP release patterns are considered. In the first variant, which we refer to as the ‘Cyclin D model variant’, hemichannel opening and ATP release is dependent on Cyclin D and ATP release occurs during mid G_1 phase of the cell cycle. In the second variant, which we refer to as the ‘R_s model variant’, ATP is released at the G_1/S phase transition. Here, R_s denotes phosphorylated RB bound to the E2F transcription factor. The model equations and parameters are given in Appendix A.

3. Results

In order to investigate the hypothesis of Weissman et al. (2004) that ATP mediated calcium signals act to synchronise the cell cycles of clusters of radial glia, first we study the dynamics of multicellular systems for both model variants via bifurcation analysis and direct numerical simulation. We begin by conducting bifurcation analysis on two cell systems using the Cyclin D synthesis rate a'_{d2} of the second cell as the control parameter (Fig. 2). a'_{d2} plays a crucial role in our model as it affects the frequency of oscillation of the cell cycle and can control whether the second cell oscillates at all. Furthermore, in reality there will be small physiological differences between radial glial cells and the parameter a'_{d2} can be regarded as a proxy for these differences. For the Cyclin D dependent model variant (Fig. 2a and c), the stability of a limit cycle solution branch is lost at a torus bifurcation point (Kuznetsov, 1998) (TB at $a'_{d2} \approx 0.380$), where it gives rise to quasi-periodic torus solutions. At $a'_{d2} \approx 0.377$ a different limit cycle solution branch with higher Cyclin D concentrations is created via a saddle node bifurcation ($FP1^D$). Additional pairs of