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Diffusion driven oscillations in gene regulatory networks

Cicely K Macnamara *, Mark AJ Chaplain

School of Mathematics and Statistics, Mathematical Institute, University of St Andrews, KY16 9SS, United Kingdom

HIGHLIGHTS

- Spatio-temporal modelling of synthetic gene regulatory networks.
- Prediction of critical distance between gene-site and protein production site.
- First spatio-temporal modelling of n-gene repressilators.
- First spatio-temporal modelling of activator–repressor systems.
- Oscillatory behaviour preferentially for systems with globally negative feedback.

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ABSTRACT

Gene regulatory networks (GRNs) play an important role in maintaining cellular function by correctly timing key processes such as cell division and apoptosis. GRNs are known to contain similar structural components, which describe how genes and proteins within a network interact - typically by feedback. In many GRNs, proteins bind to gene-sites in the nucleus thereby altering the transcription rate. If the binding reduces the transcription rate there is a negative feedback leading to oscillatory behaviour in mRNA and protein levels, both spatially (e.g. by observing fluorescently labelled molecules in single cells) and temporally (e.g. by observing protein/mRNA levels over time). Mathematical modelling of GRNs has focussed on such oscillatory behaviour. Recent computational modelling has demonstrated that spatial movement of the molecules is a vital component of GRNs, while it has been proved rigorously that the diffusion coefficient of the protein/mRNA acts as a bifurcation parameter and gives rise to a Hopf-bifurcation. In this paper we consider the spatial aspect further by considering the specific location of gene and protein production, showing that there is an optimum range for the distance between an mRNA gene-site and a protein production site in order to achieve oscillations. We first present a model of a well-known GRN, the Hes1 system, and then extend the approach to examine spatio-temporal models of synthetic GRNs e.g. *n*-gene repressilator and activator–repressor systems. By incorporating the idea of production sites into such models we show that the spatial component is vital to fully understand GRN dynamics.

1. Introduction

A gene regulatory network (GRN) can be defined as a collection of DNA segments in a cell which interact with each other indirectly through their RNA and protein products. GRNs lie at the heart of intracellular signal transduction and indirectly control many important cellular functions such as cell division, apoptosis and adhesion. One key class of GRNs is a group of proteins called transcription factors. As the name suggests, in response to a range of signals, transcription factors change the transcription rate of genes, allowing cells to alter the levels of proteins they require at any given time. A GRN is said to contain a negative feedback loop if a gene product inhibits its own production either directly or indirectly, and similarly, is said to contain a positive feedback loop if a gene product enhances its own production either directly or indirectly. In particular, the modification of the transcription of genes by proteins (transcription factors) through negative feedback (down-regulation) is an important component of many gene networks, and such negative feedback systems are known to exhibit oscillations in the levels of the molecules involved. Negative feedback loops are commonly found in diverse biological processes including inflammation, meiosis, apoptosis and the heat shock response (Lahav et al., 2004), where the oscillatory

* Corresponding author.
E-mail address: majc@st-andrews.ac.uk (M.A. Chaplain).

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expression is of particular importance. In addition to their natural occurrence, GRNs have also become an important focus in the emerging field of synthetic biology. Since the pioneering work of Becskei and Serrano (2000) and Elowitz and Leibler (2000), there has been a great deal of interest in synthetic GRNs, both from a practical, experimental viewpoint (Balagadde et al., 2008; Chen et al., 2012; Yordanov et al., 2014) and from a theoretical, modelling viewpoint (Purcell et al., 2010; O'Brien et al., 2012).

Mathematical modelling of GRNs can be traced back 50 years to the seminal paper of Goodwin (1965), followed shortly after by the paper of Griffith (1968). These papers proposed a generic "closed-loop" negative feedback model for a simple mRNA-protein feedback system (which we note is appropriate to model the actual Hes1 protein system, Hirata et al. (2002)). The models were restricted to purely temporal ODEs and oscillatory behaviour was elusive. Mackey and Glass (1977) introduced the idea of incorporating delays into differential equations. Delay-differential equation models for GRNs have been studied extensively for the last two decades, since the early work of Smolen, Baxter and Byrne (e.g. Smolen et al., 1999, 2001, 2002). Of particular interest here is Smolen et al. (1999) where the relation between delays and macromolecular transport was discussed. Specifically, their GRN model used a delay to account for active transport of molecules and showed that while such a model leads to oscillatory behaviour, incorporating molecular diffusion suppressed oscillations. Other more recent models, including models of the Hes1 system, the p53-Mdm2 system and the NF-κB system, also showed that delays were found to provoke oscillatory behaviour (Tiana et al., 2002; Jensen et al., 2003; Lewis, 2003; Monk, 2003; Bernard et al., 2006). Theoretical models of synthetic GRNs (e.g. repressilators) have also been proposed and studied (Purcell et al., 2010; O'Brien et al., 2012), while interest in modelling bacterial operons by Mackey and co-workers (Yildirim and Mackey, 2003; Hilbert et al., 2011; Mackey et al., 2015) has added additional insight.

Early spatial models of theoretical intracellular systems were pioneered in the 1970s by Glass and co-workers (Glass and Kauffman, 1970; Shymko and Glass, 1974) and again in the 1980s by Mahaffy and co-workers (Busenberg and Mahaffy, 1985; Mahaffy, 1988; Mahaffy and Pao, 1984), where the focus was on analysing generic systems with one-dimensional models. ODE models were reconfigured to incorporate a spatial dimension using reaction-diffusion PDEs and steady states and stability were determined with particular attention paid to the geometry of the model. They coined the term "spatial switching" to indicate how the system geometry can lead to different dynamical behaviour. This approach has recently been extended by Naqib et al. (2012). Other spatial models have focussed on the idea of modelling a cell using two (or more) compartments, to account for different processes which occur in the nucleus and cytoplasm (see, for example, Sturrock et al., 2011); certain models incorporate both compartments and delays (e.g. Momiji and Monk, 2008). A two-dimensional spatial model of molecular transport inside a cell was formulated by Cangiani and Natalini (2010) and this general approach was adopted by Sturrock et al. (2011) to formulate and study a spatio-temporal model of the Hes1 GRN considering diffusion of the protein and mRNA. This model was then later extended to account for transport across the nuclear membrane and directed transport via microtubules (Sturrock et al., 2012). Other papers adopting an explicitly spatial approach include those of Szymańska et al. (2014), focussing on the role of transport via the microtubules, and Clairambault and co-workers (Dimitrio et al., 2013; Eliaš and Clairambault, 2014; Eliaš et al., 2014a, 2014b), focussing on the p53 system.

In this paper we focus on the spatial component, by supposing that the different processes within a given GRN occur at specific sites. This approach removes the requirement to consider compartments and instead localises mRNA and protein production. The initial Hes1 model is an extension of the model of Sturrock et al. (2011, 2012) and is inspired by the recent result of Chaplain et al. (2015) where it was proved rigorously that molecular diffusion causes oscillations. We develop and analyse spatio-temporal mathematical models for synthetic GRNs, focussing on the role of diffusion and the spatial location of the gene sites and protein production sites in generating and controlling the oscillatory dynamics.

The paper is structured as follows. In Section 2 we discuss the results of the canonical GRN, the Hes1 system. In Sections 3 and 4 we develop models and present simulation results for three different synthetic GRNs, specifically repressilators and activator–repressors. Discussions, conclusions and directions for future work in this area are given in the final Section 5.

2. The Hes1 system

The Hes1 protein is a member of the family of basic helix-loop-helix (bHLH) transcription factors and is known to repress the transcription of its own gene through direct binding to regulatory sequences in the Hes1 promoter (Hirata et al., 2002). For this reason, it may be termed the *canonical transcription factor* or *canonical gene regulatory network*. It is known that periodically changing levels of Hes1 protein controls embryonic development, specifically in correctly timed somite segmentation (see, for example, Kageyama et al., 2007). Mathematical modelling is particularly well suited to the relatively simple Hes1 system, which is controlled by way of a single negative feedback loop between its mRNA and protein. Of particular interest here is spatial modelling. Sturrock et al. (2011) showed that a two compartment, nucleus-cytoplasm reaction-diffusion model gives rise to oscillatory behaviour, while Ptashnyk and Sturrock (2015) rigorously proved that the diffusion parameter controls whether or not the system oscillates. Here we modify the model used by Ptashnyk and Sturrock (2015) to incorporate sites at which the hes1 mRNA and Hes1 protein will be produced. For the purposes of discussion we will refer to locations of mRNA production as "gene-sites" and protein production as "production sites". We present results for a 1D interval model, however they equally apply to models of the system in other geometries, specifically 2D circular and elliptical and 3D spherical, (more details can be found in Appendix B). We consider the non-dimensional (see Section 2.1 for details of the non-dimensionalisation) form of the 1D model to be:

$$\begin{aligned}\frac{\partial m}{\partial t} &= D\frac{\partial^2 m}{\partial x^2} + \frac{\alpha_m}{1+p^h}\delta^{\varepsilon}_{x_m}(x) - \mu m,\\ \frac{\partial p}{\partial t} &= D\frac{\partial^2 p}{\partial x^2} + \alpha_p m\delta^{\varepsilon}_{x_p}(x) - \mu p,\end{aligned} \tag{1}$$

where $m(x, t)$ and $p(x, t)$ are the concentrations of hes1 mRNA and Hes1 protein, respectively. Initially (and for simplicity) we assume that both mRNA and protein diffuse through the cell with the same constant diffusion coefficient, D, and are subject to degradation (proportional to their concentrations) at the same rate, μ. The protein is translated at a production site located at position x_p, at a rate α_p and proportional to the level of mRNA. The presence of the protein then represses the production of mRNA (modelled by a Hill function with Hill coefficient h) which undergoes transcription at a gene-site located at position x_m, at a rate α_m. As such the Hes1 system consists of a simple negative feedback loop (see Fig. 1 for a simple schematic of the system).

Following (Ptashnyk and Sturrock, 2015) we use a Dirac approximation of the δ-distribution function located at the gene and protein production sites x_i, where $i = \{m, p\}$, such that