Modeling the Hes1 Oscillator in Neural Progenitor Maintenance

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The Hes1 transcription factor regulates the balance between differentiation and the maintenance of progenitors in the developing nervous system. The expression of Hes1 has been shown to be oscillatory within neural progenitors, but at a low steady state in differentiated neurons. Recent experimental results have shown that the micro-RNA miR-9 interacts with Hes1 in a double negative feedback loop, and that accumulating levels of miR-9 can cause oscillations to cease. A mathematical model demonstrates how micro-RNA can terminate oscillations and lead to alternative cell fates. Stochasticity alters both the conditions required to terminate oscillations and the distribution of differentiation events.

Keywords **— Hes1, oscillations, differentiation, miRNA, delay, neurons, progenitors, stochasticity, development**

I. Background

The timing of differentiation is critical to form a brain of the correct shape and cell type diversity. Of particular interest is the Hes gene family of transcription factors, which are key regulators of differentiation and the cell cycle [1].

When Hes genes are absent, neural stem cells will prematurely differentiate and cause a wide range of defects in brain formation [2]. Conversely, overexpression of Hes genes leads to inhibition of neurogenesis and maintenance of neural stem cells. To understand brain development, therefore, it is vital to understand the regulation of Hes genes.

We study the expression of the Hes1 gene, which shows three basic modes of expression within the developing brain. In quiescent stem cells in the boundary regions of the brain, the expression of Hes1 is sustained and high. In proliferating neural progenitor cells, the expression of Hes1 oscillates with a period of around three hours [3]. When neural stem cells differentiate into neurons, oscillations terminate and the expression of Hes1 is low.

Our goal is to understand the gene regulatory mechanisms causing Hes1 to oscillate and eventually reach a low steady-state.

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II. Results

Previous work by the lab has found evidence for the involvement of the micro-RNA miR-9 [4]. Hes1 is a direct target of miR-9, and Hes1 also represses the transcription of both itself and miR-9. It was hypothesized that an accumulation of miR-9 over time could cause oscillations of Hes1 to terminate, eventually triggering differentiation.

A mathematical model is presented, adding miR-9 to a simple model of the Hes1 oscillator with delay processes [5]. The inclusion of miR-9 can bring Hes1 out of an oscillatory state, controlling the timing of differentiation. The model also displays bistability, corresponding to alternative cell fates [6].

Stochastic effects can radically change the conditions required to terminate oscillations [7]. Including stochasticity also has the very important effect of changing the time taken to reach a Hes1-low steady state (differentiation). Understanding stochastic processes is therefore critical to describe timing within neural development.

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