Growth Factor Signal Processing for Cell Proliferation Control

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***Short Abstract* —Through the use of a kinetic model made by connecting a set of five well-characterized models, the signaling cascade beginning with EGF input and ending with the activation of ERK is shown to drive the cell cycle through sustained activation of ERK for high frequency inputs and transient activation of ERK for low frequency inputs, where "high" and "low" mean periods shorter and longer than the time required to complete the cell cycle.**

I. Purpose

UNDERSTANDING the cell how the cell cycle is controlled requires gaining a mechanistic intuition of how the system works. It has been shown that the cell cycle works like a ratchet in that it is made up of irreversible steps [5,10]. Once the cell cycle starts, it cannot stop until it has completed and in order to continue, there has to be a continued 'on' signal.

We have built a kinetic model showing extracellular regulation of the cell cycle by aggregating several established models. The extracellular signal is epidermal growth factor (EGF). The EGF signal binds to its receptor, EGFR and undergoes endocytosis [2]. The signal propagates by activating Ras, which activates Raf, which then leads to activation of ERK [7,8]. ERK, in this model, can be seen as the direct activator of the cell cycle. ERK induces early-response gene (ERG) expression, which in turn promotes delayed-response gene (DRG) expression [11,5]. This ERG-DRG cascade works on sufficiently fast time-scales that ERK activity translates almost directly into synthesis of DRG's effector—Cyclins, which are the limiting reactant in the beginning of the cell cycle [4].

II. Results

When we stimulate the system with a single EGF pulse (sufficiently strong) the cell cycle goes through a single cycle. In this case the cell cycle transit time is long enough for the ERK signal to decay below the cell cycle activation threshold before another cycle begins.

If we space a train of pulses apart longer than the transit time, no memory effects are observed and the cell oscillates once for each pulse. However, if the pulses are closer together than the transit time, the ERK activity is sustained so that the system oscillates at a characteristic frequency—the natural frequency of the cell cycle. Figure 1 illustrates these two modes of cell cycle transit.

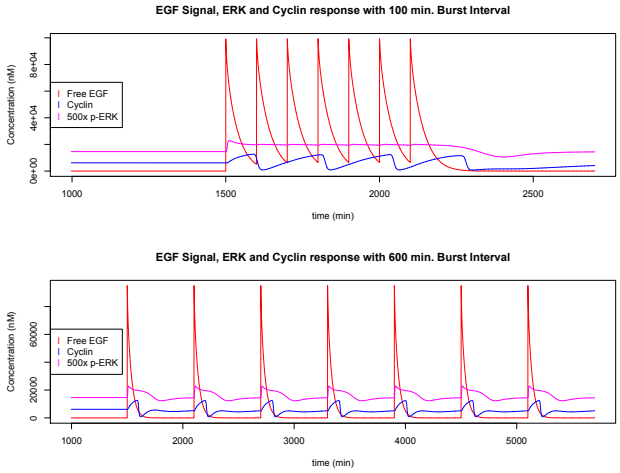

Figure 1: Top: 100 min burst intervals. Bottom: 600 min burst intervals.

III. Conclusion

The model gives a mechanistic understanding of signal propagating through the cell and controlling its reproduction. By simulation over a broad space of signal amplitudes and input frequencies, we characterize how the internal time-scales of the signaling cascade are affected and affect the mode of cell proliferation. In particular, the model illustrates the way ERK activity can filter a high frequency signal input into a single activation signal.

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