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Modeling the cell cycle for discrete-event structures

Kritika Sharma*

Department of Biotechnology, Chandigarh University, Punjab, India

***Corresponding author**: Kritika Sharma, Department of Biotechnology, Chandigarh University, Punjab, India, E-Mail: Kritikaawasthisn1@gmail.com

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Abstract

Computational modeling and the theory of nonlinear dynamical systems allow one to not simply describe the events of the cell cycle, but also to understand why these events occur, just as the theory of gravitation allows one to understand why cannonballs fly in parabolic arcs. The simplest examples of the eukaryotic cell cycle operate like autonomous oscillators. Here, we present the basic theory of oscillatory biochemical circuits in the context of the Xenopus embryonic cell cycle. We examine Boolean models, delay differential equation models, and especially ordinary differential equation (ODE) models. For ODE models, we explore what it takes to get oscillations out of two simple types of circuits (negative feedback loops and coupled positive and negative feedback loops). Finally, we review the procedures of linear stability analysis, which allow one to determine whether a given ODE model and a particular set of kinetic parameters will produce oscillations.

***Keywords:** Computational modeling; Xenopus embryonic cell cycle; Chemical method.*

Introduction

In many eukaryotic cells, the cell cycle proceeds as a sequence of contingent events. A new cell must first grow to a sufficient size before it can begin DNA replication. Then, the cell must complete DNA replication before it can begin mitosis. Finally, the cell must successfully organize a metaphase spindle before it can complete mitosis and begin the cycle again. If cell growth, DNA replication, or spindle assembly is slowed down, the entire cell cycle slows [1].

Although many biological processes seem almost unfathomably complex and incomprehensible, oscillators and clocks are the types of processes that we might have a good chance of not just describing, but also understanding. Accordingly, much effort has gone into understanding how simple cell cycles work in model systems like Xenopus embryos and the fungi S. pombe and S. cerevisiae. This requires the identification of the proteins and genes needed for the embryonic cell cycle and the elucidation of the regulatory processes that connect these proteins and genes [2]. Over the past three decades, enormous progress has been made toward these ends. In each case, the cell cycle is driven by a protein circuit centered on the cyclin-dependent protein kinase CDK1 and the anaphase-promoting complex (APC). The activation of CDK1 drives the cell into mitosis, whereas the activation of APC, which generally lags behind CDK1, drives the cell back out. There are still some missing components and poorly understood connections,

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but overall, the cell-cycle network is fairly well mapped out. But a satisfying understanding of why the CDK1/APC system oscillates requires more than a description of components and connections; it requires an understanding of why any regulatory circuit would oscillate instead of simply settling down into a stable steady state. What types of biochemical circuits can oscillate, and what is required of the individual components of the circuit to permit oscillations? Such insights are provided by the theory of nonlinear dynamics and by computational modeling [3].

Adding a Bistable Trigger

To this point, we have ignored an important part of the scheme, the positive feedback loop (CDK1 activates Cdc25, which in turn activates CDK1) and the double-negative feedback loop (CDK1 inhibits Wee1, which in turn inhibits CDK1). Nevertheless, this is probably a critical part of the network; every eukaryotic species examined so far has at least one identifiable Wee1 homolog, and all eukaryotic species except higher plants have at least one Cdc25 homolog. In addition, genetic studies in S. pombe identified these genes as critical for cell-cycle oscillations, although, surprisingly, they become less important in S. pombe strains engineered to run off a single cyclin/Cdk fusion protein [4]. Biochemical studies in Xenopus egg extracts and gene disruption studies in human HeLa cells also provide evidence that these feedback loops are important for the cell cycle [5]. What do these positive and double-negative feedback loops add to the oscillator?

Conclusion

The Xenopus embryonic cell cycle is driven by a protein circuit that acts like an autonomous oscillator. In this Primer, we set out to explore how oscillations can arise from a protein circuit [6]. We examined three types ofmodels of simple oscillator circuits based on the CDK1/APC system: Booleanmodels, ordinary differential equation models, and delay differential equation models [7]. The discrete character of Boolean models and the time lags introduced into Cell 144, March 18, 2011 ª2011 Elsevier Inc. 883 delay differential equation models make it relatively easy to generate oscillations. For ODE models, it is more difficult to keep the model from settling into a stable steady state. With everything else equal, longer negative feedback loops are easier to get oscillating than shorter ones, and switch-like, ultrasensitive response functions within the negative feedback loop promote oscillations, as well. Adding a positive feedback loop to a negative feedback loop tends to promote oscillations, and oscillators with this bistable trigger have distinct characteristics that might make them particularly suitable for biological systems. Linear stability analysis addresses why one ODE model oscillates and another one does not [8]. Accordingly, we have presented several examples of stability analysis for simple oscillator circuits [9]. For one-ODE systems, linear stability analysis is fairly simple. For two or more ODEs, however, one must make use of matrix algebra manipulations, calculating the eigenvalues of the system at the steady state(s). This takes some effort, but the effort is worth it—it provides us with an understanding of why a circuit does or does not oscillate. In many eukaryotic cells, the cell cycle is driven by a CDK1/ APC circuit that behaves more like a succession of decisions or contingent events rather than an autonomous oscillator. Nevertheless, simple models of the Xenopus oscillator, such as the ones discussed here, provide insight that informs the understanding of more complex cell-cycle circuits [10-13]. Just as positive feedback loops can provide an oscillator circuit with robustness, positive feedback loops can be used to build a succession of reliable switches. We suspect that the link between clock-like cell cycles (like the Xenopus embryonic cycle) and domino-like cell cycles (like the somatic cell cycle) is that they are both constructed out of bistable switches [14].

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