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Computational Modeling of the Cell Cycle

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Abstract

This Teaching Resource provides lecture notes, slides, and a problem set introducing graduate-level students to computational biology through a simple mathematical model of the cell cycle. The model simulates interactions between cyclin B and cyclin-dependent kinase 1, proteins that together form the mitosis-promoting factor (MPF), which initiates the processes leading to mitosis. The lecture begins with a biological background describing the importance of for mitosis, the components of MPF, and the changes in cellular MPF observed during different phases of the cell cycle. The model is compared with newer, more mechanistically detailed models of the same process, which allows for discussion of the insights that can be gained even from simplified models. lecture concludes with a demonstration of how this model can be implemented in the scientific programming language MATLAB and includes a problem set.

Keywords

Dynamical systems; mathematical modeling; mitosis; numerical methods; *Xenopus* oocytes; simulation; computer programming; MATLAB

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Educational Details

Learning Resource Type: Lecture, assignment, digital presentation

Context: Graduate

Intended Users: Teacher, learner

Intended educational use: Learn, plan, teach

Discipline: Biochemistry, bioengineering, biophysics, cell biology, developmental biology, education, physiology, reproductive biology, theoretical biology

Technical Details

Format: PowerPoint (.ppt)

Size: 1.58 MB

Requirements: Microsoft PowerPoint

Format: MATLAB (.m)

Size: 1 KB, 3 KB, 3 KB

Requirements: Mathworks MATLAB

Supplementary Materials

<http://stke.sciencemag.org/cgi/content/full/sigtrans;4/192/tr11/DC1>

Slides. Computational modeling of the cell cycle.

MATLAB code. Three MATLAB files for computational analysis of the cell cycle with ordinary differential equations.

Problem set answer key file is available upon request

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Lecture Notes

The signaling pathways controlling the cell cycle in eukaryotes have been studied intensively for many decades, and the components are now known in great detail. Many of the important advances have been made using model systems, such as oocytes from the South African clawed frog *Xenopus laevis* and the budding yeast *Saccharomyces cerevisiae*. However, the many interlocking loops of activation and inhibition make control of the cell cycle difficult to interpret intuitively. As a result of this complexity, computational modeling has been used to study this system, and several mathematical models have been published (1–8). Although all of these models successfully reproduce certain fundamental features of the cell cycle, they differ greatly from each other in terms of the level of detail and the processes that are simulated.

The lecture begins by defining relevant terms and reviewing biological concepts important for understanding the cell cycle. Mitosis-promoting factor (MPF; also known as maturation-promoting factor or M-phase promoting factor), originally described in experiments performed on extracts from *Xenopus* oocytes, is made up of a molecule of cyclin B bound to a molecule of Cdk1 (cyclin-dependent kinase 1) (Slide 3). When Cdk1 is phosphorylated at Thr¹⁴ and Tyr¹⁵, MPF is in an inactive form, known as “pre-MPF.” Dephosphorylation of these residues by the phosphatase Cdc25 converts pre-MPF into its active form (Slide 5). A rapid increase in active MPF in eukaryotic cells accompanies the transition from G2 to M-phase (Slide 4), and this surge in the cytosolic concentration of MPF ([MPF]) initiates many processes that are required for orderly cell division. The dephosphorylation reaction is autocatalytic so that an initial increase in active MPF increases the rate at which the reaction occurs (Slide 5). MPF also triggers the rapid degradation of cyclin B, decreasing cellular [MPF] and allowing the cell cycle to begin again. As a result of these regulatory reactions, the cell cycle is accompanied by periodic increases and decreases in the abundance of cyclin (Slide 4).

The core of the lecture is the presentation of a mathematical model published by Tyson in 1991 (8) (Slide 6). This relatively simple model allows for a discussion of how to construct models that consist of systems of ordinary differential equations (ODEs), and the results presented in the paper illustrate the biological insights that can be gained through simulations. Tyson's model simulates the following processes: synthesis of cyclin B, binding and unbinding of cyclin B to Cdk1, phosphorylation and dephosphorylation of Cdk1, degradation of cyclin B, and the autocatalytic activation by MPF of the pre-MPF dephosphorylation reaction. The result is a system of six nonlinear ODEs. The lecture discusses a few equations in detail to illustrate that each ODE describes the difference between the rate of appearance and the rate of disappearance of a particular chemical species (Slide 7).

To illustrate the issue of simplicity versus mechanistic detail that arises repeatedly in modeling studies, the strengths and weaknesses of Tyson's 1991 model (8) are presented. This discussion emphasizes aspects of the biological pathways that have become apparent subsequent to the model's publication (Slides 8 to 10), and several details not included in Tyson's original model (8) are mentioned. For instance, autocatalytic activation of the

dephosphorylation reaction is not directly mediated by MPF itself but instead occurs through the phosphatase Cdc25 (Slide 8) (9). In addition, cyclin B degradation does not occur at a constant rate, as assumed by Tyson, but instead is triggered by MPF (Slide 9) (9). Lastly, the Tyson model did not include a role for the protein Wee1 (Slide 10), which is a kinase that phosphorylates Cdk1, which shifts MPF from the active to inactive form (10).

Despite these simplifications, Tyson's essentially phenomenological model generated important insights into cell cycle regulation (Slides 11 to 13). The model exhibited distinct behaviors, which could then be connected to particular biological states and experimental observations. Examples of these model behaviors include the spontaneous oscillations in [MPF] that are analogous to the rapid division cycles that occur in the *Xenopus* oocyte immediately after fertilization (Slide 11). The model also revealed two mechanisms for cessation of oscillations, which represented either meta-phase arrest or the G_0 state of nondividing somatic cells (Slide 12). Additionally, the model showed “excitability” so that under some conditions, [MPF] is low, but a small stimulus that initiates an increase in [MPF] can induce a further surge in [MPF] and trigger a cell division (Slide 13). Because these model behaviors occurred with different combinations of the model's parameters, they could be connected to different biological states and interpreted in this context.

To reinforce the issue of simple versus more complex models, improvements that have been reported in subsequent publications from the same group are discussed (Slides 14 to 18) (3–5, 11). These examples illustrate the gradual evolution that occurs with many mathematical representations of biological processes.

The lecture concludes with information that is required for students to implement the model in a computing language, such as MATLAB (Slides 19 to 21).

Problem Set

Introductory Details

The homework assignment includes two parts, a programming component (Part 1) and a second component that reveals whether the students have gained biological insight (Part 2). For Part 1, the students are provided with a model that solves Tyson's model (8) using Euler's method, and are asked to convert this into a program that uses MATLAB's ODE solvers. Because it is generally quite difficult for students without programming experience to produce such a program de novo, an incomplete program is provided as a template. In Part 2, the students vary parameters to reproduce several of the figures in the original Tyson publication and then interpret the biological meaning of how changing parameters alters the model's response.

The Supplementary Materials include three MATLAB programs: “tyson.m”, which uses Euler's method to solve the system of ODEs; “tyson_ode.m”, which is an incomplete program that sets up a solution using MATLAB's solvers; “dydt_tyson.m”, which is an incomplete function that is called by “tyson_ode.m”.

If “tyson” is typed at the MATLAB prompt, the program will integrate the equations and plot output similar to that shown in figure 3A of Tyson's paper (8).

Student Assignment: Part 1—Programming

Using the working program “tyson.m” as a guide, add lines of MATLAB code to “tyson_ode.m” and “dydt_tyson.m” so that the equations will be integrated when “tyson_ode” is typed at the MATLAB prompt. The locations where lines of MATLAB code need to be added are indicated in the two incomplete files. When this is working, typing “tyson_ode” should generate a plot similar to figure 3A in Tyson's paper (8).

Student Assignment: Part 2—Biological Interpretation

1. Two especially important parameters in this model are k_4 and k_6 . In the Tyson paper (8), figure 2 shows that changes in these parameters lead to qualitatively different model behavior. The control values of these parameters in the model are 180 min^{-1} and 1 min^{-1} , respectively. Keeping k_4 constant at 180 min^{-1} , run the model for different values of k_6 . Either decreasing or increasing k_6 will eventually abolish oscillations. How small does k_6 have to become before oscillations cease? How large does k_6 have to become before oscillations cease?
2. On a single graph, plot [MPF] versus time for $k_4 = 180 \text{ min}^{-1}$ and the following three values of k_6 : 0.2 min^{-1} , 1 min^{-1} , and 5 min^{-1} . Only $k_6 = 1 \text{ min}^{-1}$ should show spontaneous oscillations in [MPF]. Considering the biochemical reactions simulated by the model, why do very small values of k_6 cause oscillations to cease? Why do very large values of k_6 cause oscillations to cease?
3. Although either a large increase or a large decrease in k_6 will abolish spontaneous oscillations, your plot should show that the steady-state concentrations of MPF are different in the two cases. To what different biological states do these different steady levels correspond?

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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