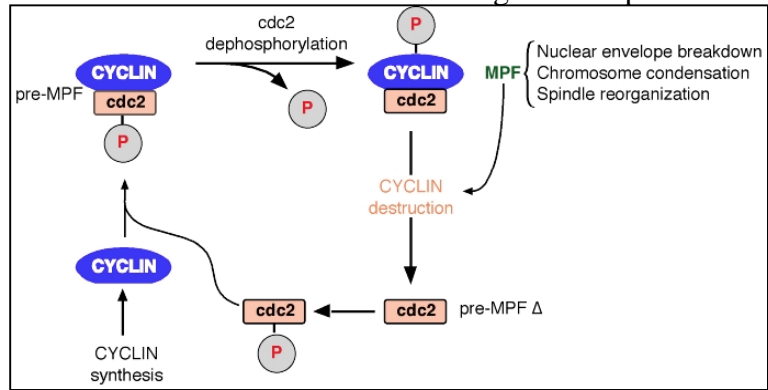


MODELING THE CELL CYCLE

Introduction

One of the most exciting areas of current research in cell biology is the cell cycle. Finally, biologists are beginning to understand the mechanism that drives cells through their repetitive cycles of mitosis and cell division.

Goldbeter (1991) has constructed a very simple model that reproduces some of the qualitative features of the cell cycle. The model is built around a chain of Michaelis-Menten reactions, and so it will give you an opportunity to investigate the consequences of concatenating simple kinetic schemes. The original reprint is on the course web site.



Model

The protein **cyclin** is a key ingredient in the cell cycle. Its periodic buildup and breakdown in the cell parallels the cycle, and may actually drive it. When cyclin exceeds a certain threshold it begins to combine with and activate a protein kinase (called **CDC2 kinase**, not shown) to form a complex called “maturation promoting factor” (MPF), which appears to stimulate mitosis. The CDC2 kinase stimulates degradation of cyclin by activating a **protease**.

Thus the system has a negative feedback: cyclin stimulates its own degradation via MPF and protease. Denote the concentration of cyclin by C, MPF by M, and protease by X. A diagram of the kinetic scheme is shown in

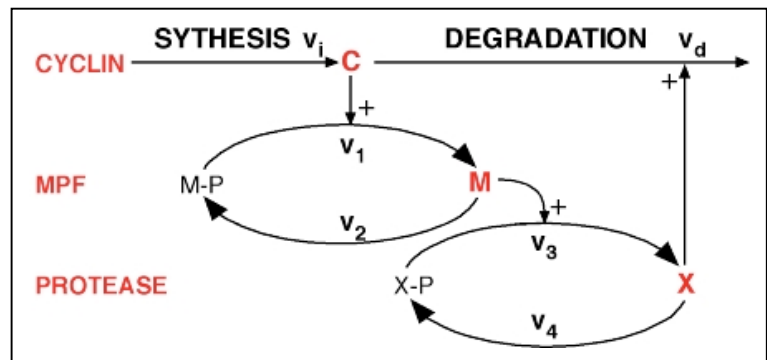


Figure 1.

Figure 1. Model for oscillations in C, M, and X .

Here M-P and X-P represent the phosphorylated (inactive) forms of the enzymes. Remembering that the enzymes are conserved: $E + E-P = \text{constant}$, we can write this scheme as a set of conservation equations of the form: *Rate of reaction = Gain - Loss*, where each term is a Michaelis-Menten hyperbola: $\text{Rate} = V_{\text{max}} \frac{C}{K + C}$. For example, the cyclin equation in difference equation notation is:

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$$\begin{aligned} \frac{dC}{dt} &= \text{Synthesis} - \text{Degradation} \\ &= -0.025 - v_d X \left(\frac{C}{K_d + C} \right) - k_4 C, \quad C(0) = 0.01 \end{aligned}$$

Here are the complete set of equations.

$$\text{CYCLIN} \quad \frac{dC}{dt} = \underbrace{v}_{\text{synthesis}} - \underbrace{v_d X \frac{C}{K_d + C}}_{\text{protease degradation}} - \underbrace{k_4 C}_{\text{spontaneous degradation}} \quad (1)$$

$$\text{MPF} \quad \frac{dM}{dt} = \underbrace{V_{M1} \left[\frac{C}{K_C + C} \right]}_{\text{cyclin-stimulated activation (dephosphorylation)}} \underbrace{\left[\frac{(1-M)}{K_1 + (1-M)} \right]}_{\text{M-M term in the fraction of inactive MPF}} - \underbrace{V_2 \frac{M}{K_2 + M}}_{\text{inactivation (phosphorylation)}} \quad (2)$$

$$\text{PROTEASE} \quad \frac{dX}{dt} = \underbrace{M V_{M3}}_{\text{activation by MPF}} \underbrace{\left[\frac{(1-X)}{K_3 + (1-X)} \right]}_{\text{M-M term in the fraction of inactive protease}} - \underbrace{V_4 \frac{X}{K_4 + X}}_{\text{inactivation}} \quad (3)$$

Table 1 gives *some* of the parameter values.

Exercise

1. Fill in the missing entries in **Table 1**.
2. Use the Fourier Transform button to find the period and frequency
3. Plot the (C, M) phase plane using the parameters in Figure 4 of Goldbeter (1991).
4. Use the Parameter Plot to plot the frequency of oscillations in M vs. v_d . Find the 'bifurcation point' where oscillations begin. Verify this by moving the v_d slider.

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Quantity	Symbol	Value & Units
Maximum velocity of MPF activation	V_{M1}	3
Maximum velocity of MPF inactivation	V_2	1.5
	V_{M3}	1
	V_4	0.5
	K_c	0.5
	K_i (i = 1-4)	0.005
	M_T	4
	v_i	0.025
	v_d	0.25 $\mu\text{M}/\text{min}$
	K_d	0.02 μM
	k_d	0.01 /min
Initial concentration of cyclin	$C(0)$	0.01 μM
Initial concentration of MPF & Protease	$M(0), X(0)$	0.01

Table 1: The actual values of the maximum rates and Michaelis constants of the converter enzymes E_1 and E_2 are obtained by multiplying V_{M1} , V_2 , K_1 , K_2 by $M_T = 4\mu\text{M}$. The parameters for the enzymes are obtained by multiplying V_{M3} , V_4 , K_3 , K_4 by $X_T = 4\mu\text{M}$.

References

- Goldbeter, A. (1991). A minimal cascade model for the mitotic oscillator involving cyclin and cdc2 kinase. *Proc Natl Acad Sci.* 88:9107-11.
- Decroly, O., A. Goldbeter (1982). Birhythmicity, chaos, and other patterns of temporal self-organization in a multiply regulated biochemical system. *Proc. Natl. Acad. Sci.* 79:6917-21.
- Goldbeter, A., D. Koshland (1981). An amplified sensitivity arising from covalent modification in biological systems. *Proc. Natl. Acad. Sci.* 78:6840-44.
- Goldbeter, A., D. Koshland (1982). Sensitivity amplification in biochemical systems. *Qrt. Rev. Biophys.* 15:555-91.
- Goldbeter, A. (1995). "A model for circadian oscillations in the drosophila period protein (PER)." *Proc. R. Soc. Lond.* 261: 319-324.
- A recent paper on circadian oscillations constructed with Madonna™.*
- Goldbeter, A. (1996). *Biochemical Oscillations and Cellular Rhythms*. Cambridge, Cambridge University Press.

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A compendium of models on oscillatory phenomena in biology—most constructed with Madonna™. More recent models are more complicated

Chen KC, Csikasz-Nagy A, Gyorffy B, Val J, Novak B, Tyson JJ. 2000. Kinetic analysis of a molecular model of the budding yeast cell cycle. *Molecular Biology of the Cell* 11(1):369-391.

Sveiczzer A, Csikasz-Nagy A, Gyorffy B, Tyson JJ, Novak B. 2000. Modeling the fission yeast cell cycle: Quantized cycle times in *wee1- cdc25DELTA* mutant cells. *Proceedings of the National Academy of Sciences of the United States of America* 97(14):7865-7870.

Circadian rhythms make good fodder for modeling

Tyson J., Hong C., Thron C., Novak B. 1999. A simple model of circadian rhythms based on dimerization and proteolysis of PER and TIM. *Biophysical Journal* 77(5):2411-2417.