Cell Cycle Vignettes

Cell Cycle Modeling by Differential Equations

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The physiological properties of cells—their growth, division, movement, signaling, metabolism, differentiation, death—are all controlled by gene-protein regulatory networks of considerable complexity. Thanks to the revolutionary advances of molecular genetics in the latter part of the 20th Century, much is known now about the genes and proteins that constitute these networks and about their interactions, as well as the meso-scale topology of particular regulatory networks and the global topology of genome-wide surveys of gene, mRNA and protein interactions. The analysis of genome-wide ('omics') data is still very much dominated by statistical methods, but at the local and meso-scale of network complexity it is possible to build detailed, accurate and predictive models of the dynamics of network behavior by using differential equations.

The applicability of differential equations to modeling network dynamics in general, and cell cycle regulation in particular, is based on the following logic (Tyson et al. 2001). A molecular regulatory network can be described, depending on the level of detail available from experimental investigations, by (1) a system of biochemical reactions or (2) an 'influence' diagram or (3) a hybrid of the two types. These types of descriptions are illustrated in Fig. 1. Realistic networks are, of course, much more complex than the example given. Whether the network is described by chemical *reactions* or *influences* or a *hybrid* of the two, the network diagram is trying to tell us how one biochemical species is affecting the rates of production or removal of another species. As such, the network diagram can be converted into a set of ordinary differential equations (ODEs), one ODE for each time-varying biochemical concentration:

$$\frac{\mathrm{d}[\mathrm{X}_i]}{\mathrm{d}t} = \sum_j P_{ij}\left([\mathrm{X}_{\dots}],[\mathrm{M}_{\dots}],k_j\right) - \sum_l R_{il}\left([\mathrm{X}_{\dots}],[\mathrm{M}_{\dots}],k_l\right) \qquad [1]$$

In this equation, $[\mathrm{X}_i]$ = concentration of species i, P_{ij} = rate of the j-th reaction that produces species i, $[\mathrm{X}_{\dots}]$ = concentrations of the time-varying biochemical species that participate in each of these reactions, $[\mathrm{M}_{\dots}]$ = constant concentrations of the time-invariant biochemical species ('modifiers') that participate in each of these reactions (e.g., the total concentration of the enzyme that catalyzes reaction j), and k_j = the rate constant(s) needed to express the material flux through reaction j. Similarly, R_{il} = rate of the l-th reaction that removes species i, etc.

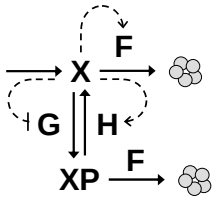

Figure 1. A typical molecular regulatory network. In this diagram, letters denote chemical species (proteins) and solid arrows represent chemical reactions transforming substrate(s) into product(s). A letter sitting next to an arrow denotes the enzyme catalyzing the reaction. Dashed arrows represent 'influences' of one protein on another: barbed arrows denote 'activation' and blunt arrows denote 'inhibition'. The dynamics of this reaction network is represented by the system of five ODEs in Eq. [2].

Regulatory networks like Fig. 1 are sometimes called 'wiring' diagrams, in analogy to the schematic diagrams of electrical devices. Just like the dynamical behavior of an electrical device can be predicted (in practice) from Kirchoff's Laws (ODEs for the voltages at various points in the circuit), so the dynamics of a molecular regulatory network can be predicted (in principle) from ODEs [1]. Unfortunately, the analogy to electrical engineering goes no further. For an electrical device, we can obtain a schematic wiring diagram from the manufacturer, as well as a specification of the numerical values of the parameters that characterize each component (resistances, capacitances, etc.). For the living cell, we must guess the wiring diagram, and we must estimate the rate constants from the very experiments we are trying to explain. In essence, we must 'reverse engineer' the cell's circuitry by performing well-designed experiments to probe the input-output (signal-response) characteristics of the cell under normal and contrived conditions (including mutations which scramble the wiring diagram in controlled ways).

For the many ways that differential equations have been used in molecular and cell biology, see the classic books by Edelstein-Keshet (1988), Murray (1989), Goldbeter (1996), Fall et al. (2002) and Keener and Sneyd (2009).

Wiring diagrams and rate equations

Figure 1, which will serve as our example of modeling by ODEs, can be interpreted as a model of MPF dynamics in a fertilized egg. (See: cell cycle dynamics, bistability and oscillations.) In this example, X = MPF = dimer of Cdk1 and cyclin B, XP = preMPF = phosphorylated (inactive) form of MPF, G = Wee1 = kinase that inactivates MPF, H = Cdc25 = phosphatase that converts preMPF into active MPF, F = APC/Cdc20 = ubiquitin-ligase that labels cyclin B for proteolysis. The production and removal of X and XP are described by chemical reactions (synthesis, degradation, phosphorylation, dephosphorylation), and kinetic equations for the rates of change of X and XP can be written by standard principles of biochemical kinetics:

$$\frac{\mathrm{d}X}{\mathrm{d}t} = k_{\mathrm{sx}} - k_{\mathrm{dx}}X - \frac{k_{\mathrm{g}}GX}{K_{\mathrm{mg}} + X} + \frac{k_{\mathrm{h}}HX_{\mathrm{P}}}{K_{\mathrm{mh}} + X_{\mathrm{P}}}$$
$$\frac{\mathrm{d}X_{\mathrm{P}}}{\mathrm{d}t} = -k_{\mathrm{dx}}X_{\mathrm{P}} + \frac{k_{\mathrm{g}}GX}{K_{\mathrm{mg}} + X} - \frac{k_{\mathrm{h}}HX_{\mathrm{P}}}{K_{\mathrm{mh}} + X_{\mathrm{P}}} \qquad [2a,b]$$

In each case, the rate of a reaction is given either by the law of mass action (for synthesis and degradation reactions) or by the Michaelis-Menten rate law (for the phosphorylation and dephosphorylation reactions). (Which rate law we use for an enzyme-catalyzed reaction depends on whether the enzyme tends to work in its 'linear' regime or in its 'saturated' regime.) Regulation of the enzymes, F, G and H in Fig. 1, are only specified as 'influences': X 'activates' F and H, and X 'inhibits' G. We choose to describe these influences by generic ODEs:

$$\frac{\mathrm{d}F}{\mathrm{d}t} = \lambda_{\mathrm{f}}\left[\Psi(\sigma_{\mathrm{f}} \cdot \{\omega_{\mathrm{f0}} + \omega_{\mathrm{f1}}X\}) - F\right]$$
$$\frac{\mathrm{d}G}{\mathrm{d}t} = \lambda_{\mathrm{g}}\left[\Psi(\sigma_{\mathrm{g}} \cdot \{\omega_{\mathrm{g0}} + \omega_{\mathrm{g1}}X\}) - G\right] \qquad [2c,d,e]$$
$$\frac{\mathrm{d}H}{\mathrm{d}t} = \lambda_{\mathrm{h}}\left[\Psi(\sigma_{\mathrm{h}} \cdot \{\omega_{\mathrm{h0}} + \omega_{\mathrm{h1}}X\}) - H\right]$$

where $\Psi(\xi) = 1/\left(1 + e^{-\xi}\right)$ is a 'soft Heaviside' function; $\Psi(\xi)$ varies smoothly from 0 for ξ << -1 to 0.5 for ξ = 0 to +1 for ξ >> 1. According to Eq. [2c,d,e], F, G and H are continually changing to keep up with the soft Heaviside functions, which are changing in response to the dynamical variable X. In return, the dynamical variables X and X_{P} are changing in response to F, G and H according to Eq. [2a,b]. It would be impossible to keep track of the implications of all these changes in one's head; it is the job of the ODEs to track the variables for us.

Numerical simulation of ODEs: parameter values and initial conditions

Before we can solve the ODEs [2] we must specify numerical values for all the 'parameters' (rate constants, Michaelis constants, ω's and σ's); see Table 1. Usually, these parameters must be estimated from experimental data, but in this example we assign values to illustrate some interesting and physiologically relevant solutions of the ODEs. In addition to parameter assignments, we must also specify 'initial conditions' (values at t = 0) for the five time-varying species: $X(0)$, $X_{\mathrm{P}}(0)$, $F(0)$, $G(0)$, $H(0)$; see Table 2.

With this information, we can now instruct a computer, using the ODEs [2], to take small time steps, $\mathrm{d}t$, and update the values of the dynamical variables:

$$X(t+\mathrm{d}t) = X(t) + \left[k_{\mathrm{sx}} - k_{\mathrm{dx}} X(t) - \frac{k_{\mathrm{g}} G X(t)}{K_{\mathrm{mg}} + X(t)} + \frac{k_{\mathrm{h}} H X_{\mathrm{P}}(t)}{K_{\mathrm{mh}} + X_{\mathrm{P}}(t)} \right] \cdot \mathrm{d}t$$

$$X_{\mathrm{P}}(t+\mathrm{d}t) = X_{\mathrm{P}}(t) + \left[-k_{\mathrm{dx}} X_{\mathrm{P}}(t) + \frac{k_{\mathrm{g}} G X(t)}{K_{\mathrm{mg}} + X(t)} - \frac{k_{\mathrm{h}} H X_{\mathrm{P}}(t)}{K_{\mathrm{mh}} + X_{\mathrm{P}}(t)} \right] \cdot \mathrm{d}t \qquad \text{[3a,b,c,d,e]}$$

etc.

Table 1. Parameter values for the simulations in Figure 2.

$k_{\mathrm{g}} = k_{\mathrm{h}} = 10$		$K_{\mathrm{mg}} = K_{\mathrm{mh}} = 0.05$		$\lambda_{\mathrm{f}} = \lambda_{\mathrm{g}} = \lambda_{\mathrm{h}} = 1$	$\omega_{\mathrm{f1}} = 1$
$\sigma_{\mathrm{g}} = 3$	$\omega_{\mathrm{g0}} = 0.2$	$\omega_{\mathrm{g1}} = -0.7$	$\sigma_{\mathrm{h}} = 3$	$\omega_{\mathrm{h0}} = -0.2$	$\omega_{\mathrm{h1}} = 0.8$
Fig. 2A	Fig. 2B	Fig. 2C	Fig. 2A	Fig. 2B	Fig. 2C
$k_{\mathrm{sx}} = 0.04$	$k_{\mathrm{sx}} = 0.1$	$k_{\mathrm{sx}} = 0.1$	$k_{\mathrm{dx}} = 1$	$k_{\mathrm{dx}} = 1$	$k_{\mathrm{dx}} = 0.5$
$\sigma_{\mathrm{f}} = 20$	$\sigma_{\mathrm{f}} = 20$	$\sigma_{\mathrm{f}} = 5$	$\omega_{\mathrm{f0}} = -0.3$	$\omega_{\mathrm{f0}} = -0.3$	$\omega_{\mathrm{f0}} = -0.4$

Table 2. Initial conditions for the simulations in Figure 2.

	X	X_{P}	F	G	H
Fig. 2A	0.1149	1.5459	0.0241	0.5887	0.4197
Fig. 2B	0.1036	1.0602	0.0181	0.5961	0.4111
Fig. 2C(low)	0.1058	0.9649	0.1868	0.5933	0.4143
Fig. 2C(med)	0.1946	0.526	0.318	0.544	0.471
Fig. 2C(high)	0.3327	0.1472	0.4167	0.4753	0.5495

The computer starts at t = 0, with the given initial conditions, computes the instantaneous rates of change (the functions in […] above), and then uses Eq. [3] to compute the values of the five dynamical variables at t = 0 + dt. The computer then repeats the process to get the values of the dynamical variables at t = 2dt, 3dt, etc. For dt small enough, this procedure gives an accurate numerical solution of the ODEs. Of course, there are more sophisticated and efficient algorithms for solving nonlinear ODEs, but they are all based on the fundamental procedure just described.

In Fig. 2, we present numerical simulations of ODEs [2] for the parameter values in Table 1, with modifications given in the figure legend. For the case in Fig. 2A, the ODEs have a single stable steady state solution. In Fig. 2B the steady state solution is unstable and the system of ODEs exhibits spontaneous oscillations of all the variables. In Fig. 2C, the system exhibits a phenomenon called 'bistability', i.e., two stable steady states separated by an unstable steady state.

Analysis of nonlinear ordinary differential equations

Why does the system of nonlinear ODEs in Eq. [2] show the many different sorts of behavior illustrated in Fig. 2? Might the system show other, qualitatively different sorts

of behavior? For what values of the parameters are each of the types of solutions expected? The answers to these sorts of questions are provided by bifurcation theory, which is described in the vignette 'Analysis of Cell Cycle Dynamics by Bifurcation Theory'.

Parameter estimation

If we have experimental measurements of some of the dynamical variables at a sequence of time points, under a variety of experimental conditions, both natural and contrived (e.g., in mutant cells), then it is sometimes possible to estimate the parameters in a dynamical model (and to test the adequacy of the wiring diagram) by least-squares fitting of numerical simulations of the model to the experimental data. For instance, the curves in Fig. 2B look very much like the measurements of Pomerening et al. (2005; their Fig. 1V). However, even for a modest network such as our example, with five dynamical variables and 18 parameters, fitting simulations to experimental data can be a very difficult task. It requires careful choice of experimental conditions and sophisticated methods of searching the parameter space. A lead-in to this extensive literature is provided by Apgar et al. (2010).

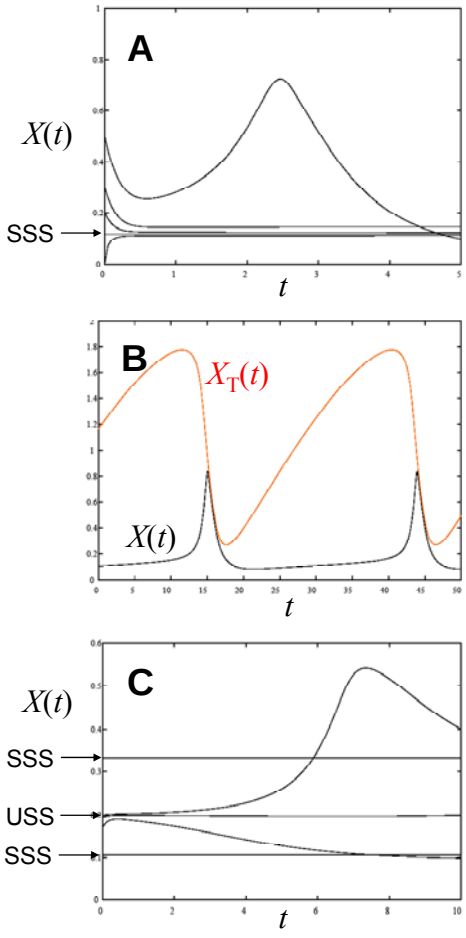

Figure 2. Representative simulations of ODEs [2]. The parameter values and initial conditions for these simulations are given in Tables 1 and 2. (A) A unique stable steady state (sss). Small perturbations away from the steady state return immediately. A larger perturbation, $X(0)$ = 0.5, exhibits a transient pulse of MPF activity before returning to the steady state. This behavior is called 'excitability'. (B) A stable limit cycle oscillation. In addition to $X(t)$ = [MPF], we also plot $X_T(t)$ = $X(t)$ + $X_P(t)$ = [total cyclin]. The period of oscillation is 29 min. Compare to Fig. 1V in Pomerening et al. (2005). (C) Two co-existing stable steady states separated by an unstable steady state (uss).

Alternative modeling strategies

In this chapter, we have discussed modeling by nonlinear ODEs, assuming that the cell is a well-mixed chemical reactor. Surprisingly, in some cases this is not a bad approximation. For example, the time it takes for a typical protein to diffuse across a yeast cell (diameter ~5 μm) is only about 10 s, which is very short compared to the interdivision time (at least 90 min) of a yeast cell. Hence, for models of the yeast cell cycle, the cytoplasm is essentially well-mixed. Of course, one might want to distinguish between nuclear and cytoplasmic compartments, but this situation can be handled with nonlinear ODEs by including fluxes of components into and out of the nucleus.

In other situations, where the time scale is shorter and/or the space scale is larger, one must take into account the coupling of local chemical reactions with molecular diffusion (and possibly vectorial transport processes, e.g., along microtubules). In these cases, the correct modeling approach might be partial differential equations.

In some cases, when very little is known about the underlying biochemistry of a control system, systems biologists prefer to model the system with a Boolean network, an approach described elsewhere in the Encyclopedia of Systems Biology.

Software for dynamic modeling

There are several convenient software packages for modeling molecular regulatory networks with differential equations:

Copasi www.copasi.org

XPP http://www.math.pitt.edu/~bard/xpp/xpp.html

Madonna http://www.berkeleymadonna.com/download.html

Reaction-diffusion modeling with partial differential equations is best done by

Virtual Cell http://www.nrcam.uchc.edu/

References

Apgar JF, Witmer DK, White FM, Tidor B (2010) Sloppy models, parameter uncertainty, and the role of experimental design. Mol Biosyst. 6:890-900.

Edelstein-Keshet L (1988) Mathematical models in biology. Random House, New York.

Ermentrout B (2002) Simulating, analyzing, and animating dynamical systems. SIAM, Philadelphia

Fall CP, Marland ES, Wagner JM, Tyson JJ (2002) Computational cell biology. Springer-Verlag, Berlin

Goldbeter A (1996) Biochemical oscillations and cellular rhythms. Cambridge University Press, Cambridge

Keener J, Sneyd J (2009) Mathematical physiology, 2nd edition. Springer-Verlag, Berlin

Murray JD (1989) Mathematical biology. Springer-Verlag, Berlin

Pomerening JR, Kim SY, Ferrell JE Jr (2005) Systems-level dissection of the cell-cycle oscillator: bypassing positive feedback produces damped oscillations. Cell 122:565-578

Tyson JJ, Chen K, Novak B (2001) Network dynamics and cell physiology. Nat Rev Mol Cell Biol 2:908-916