Control Theory and Systems Biology

edited by Pablo A. Iglesias and Brian P. Ingalls

The MIT Press
Cambridge, Massachusetts
London, England

This book was set in Times New Roman on 3B2 by Asco Typesetters, Hong Kong. Printed and bound in the United States of America.

Library of Congress Cataloging-in-Publication Data

Control theory and systems biology / edited by Pablo A. Iglesias and Brian P. Ingalls.
p. cm.
Includes bibliographical references and index.
ISBN 978-0-262-01334-5 (hardcover : alk. paper) 1. Biological control systems. 2. Control theory.
I. Iglesias, Pablo A., 1964– II. Ingalls, Brian P., 1974–
[DNLM: 1. Biochemical Phenomena. 2. Cell Physiological Processes. 3. Feedback, Biochemical—physiology. 4. Models, Biological. 5. Systems Biology. QU 34 C764 2010]
QH508.C67 2010
571.7—dc22 2009007075

10 9 8 7 6 5 4 3 2 1

1 A Primer on Control Engineering

Brian P. Ingalls and Pablo A. Iglesias

The field of control engineering grew out of the need to analyze and design regulatory mechanisms. To meet this need, a vast array of mathematical tools has been developed. Because of the conceptual similarities between engineering and biological regulatory mechanisms, it is not surprising that these tools are now being used to analyze biochemical and genetic networks. *Control Theory and Systems Biology* brings together some examples of this work. This chapter introduces background material that will be helpful in reading the chapters to follow.

1.1 System Modeling

The current volume addresses the dynamic behavior of biochemical and genetic networks. This time-varying behavior is often left implicit in the cartoon models of biological networks that are standard in the biological literature. Though such models are static, they typically attempt to describe interactions that evolve over time. For example, the activation of a transcription factor does not lead to an immediate increase in the target protein, but instead produces this effect through a sequence of events, each of which unfolds on a particular time scale. Our descriptions of these interactions indicate how the *rate* of a process, such as expression, degradation, phosphorylation, or cleavage, depends on the availability of an affector species, such as a transcription factor, metabolite, or enzyme.

1.2 Differential Equation Description of Biochemical Reaction Networks

The most successful way to describe quantitatively dynamic processes is with models based on differential equations. The simplest such models, consisting of ordinary differential equations (ODEs), can be applied to biochemical networks only under two key assumptions, however.

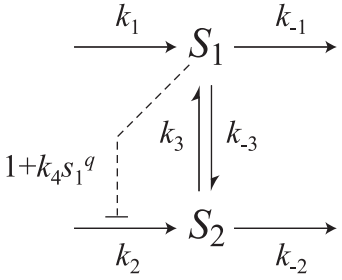

Figure 1.1
Hypothetical biochemical pathway. Molecules of two interacting species, S_1 and S_2, are produced with rates k_1 and k_2 nMh^{-1} and are degraded at rates k_{-1} and k_{-2} h^{-1}. Interconversion between the two species occurs at rates k_3 and k_{-3} nMh^{-1}. Finally, species S_1 inhibits the formation of S_2 (*dashed line*).

The first assumption, called the *continuum hypothesis*, allows us to measure species abundance as a continuously changing concentration rather than a discrete number of molecules. This is usually considered a valid assumption provided the number of molecules is not less than about 1,000 (corresponding to a concentration of about 10 nM in a cell of volume of 0.1 picoliter). If the number drops well below 1,000, it is advisable to use a formalism that allows a discrete measure of the molecule number and that captures the randomness that is significant on this scale. Such stochastic methods are the subject of chapter 2.

The second required assumption is that the reactants find one another immediately and equally, the so-called *well-mixed assumption*. This is valid provided that the time scale of the process under investigation is longer than the time scale of diffusion of its components. This second assumption can be relaxed through the use of partial differential equations, which are introduced in chapter 3.

Under these assumptions, each of the interactions in a cartoon model such as the one illustrated in figure 1.1 can be characterized by an appropriate mathematical formalism (for example, mass-action or Michaelis-Menten kinetics) and these terms can be combined into a description of the rate of change of the abundance (that is, concentration) of the various species in the model.

In general, given a network with n interacting components, we denote their respective concentrations by s_i, for $i = 1, \ldots, n$. We organize these into a vector:

$$\boldsymbol{s}(t) = \begin{bmatrix} s_1(t) \\ \vdots \\ s_n(t) \end{bmatrix}.$$

(In this volume, the shorthand notation $\boldsymbol{s} \in \mathbf{R}^n$ will sometimes be used to indicate that $\boldsymbol{s}$ is a vector with n components.) Given a vector-valued function $\boldsymbol{f} = [f_1 \ldots f_n]^T$

whose components describe the rate of change of the concentration of each species the system dynamics can be described by a differential equation of the form

$$\dot{\boldsymbol{s}}(t) = \frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{s}(t) = \boldsymbol{f}(\boldsymbol{s}(t)). \tag{1.1}$$

(Both the Leibniz $\left(\frac{\mathrm{d}}{\mathrm{d}t}\right)$ and Newtonian "overdot" $(\dot{\boldsymbol{s}})$ notation for time derivative will be used.) The vector $\boldsymbol{s}(t)$ of concentrations is referred to as the *state* of the system and can be interpreted as the system's memory: together with the differential equation (1.1), knowledge of the state at any given time t_0 allows us to determine the behavior of the system for all future time $t \geq t_0$.

Example Consider the biochemical system shown in figure 1.1. Denoting the concentrations of S_1 and S_2 by s_1 and s_2, respectively, the system is described by the following two differential equations:

$$\frac{\mathrm{d}}{\mathrm{d}t}s_1(t) = k_1 + k_3 s_2(t) - (k_{-1} + k_{-3})s_1(t), \tag{1.2a}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}s_2(t) = \frac{k_2}{1 + k_4 s_1^q(t)} + k_{-3}s_1(t) - (k_{-2} + k_3)s_2(t). \tag{1.2b}$$

We can represent this system with

$$\boldsymbol{s} = \begin{bmatrix} s_1 \\ s_2 \end{bmatrix}, \quad \text{and} \quad \boldsymbol{f}(\boldsymbol{s}) = \begin{bmatrix} f_1(s_1, s_2) \\ f_2(s_1, s_2) \end{bmatrix} = \begin{bmatrix} k_1 + k_3 s_2 - (k_{-1} + k_{-3})s_1 \\ \dfrac{k_2}{1 + k_4 s_1^q} + k_{-3}s_1 - (k_{-2} + k_3)s_2 \end{bmatrix}. \qquad \blacksquare$$

In nearly all cases of interest, the function $\boldsymbol{f}$ does not depend linearly on the state $\boldsymbol{s}$, in which case the vector equation (1.1) is known as a set of nonlinear differential equations. Although, in general, it is not possible to obtain explicit solutions to such nonlinear equations, the evolution of the system from particular initial states can be simulated numerically using generic packages such as Matlab or Mathematica, or programs tailored to biological systems (reviewed by Alves et al. 2006). Alternatively, features of the system behavior can be analyzed directly from the differential equations, as will be illustrated below.

The points $\bar{\boldsymbol{s}}$ satisfying

$$\boldsymbol{f}(\bar{\boldsymbol{s}}) = \boldsymbol{0}$$

are *fixed points* of the system and are referred to as *steady states* or *(mathematical) equilibria*. Note that the term "steady state" is also used to describe persistent dynamic behaviors such as limit cycle oscillations, discussed below.

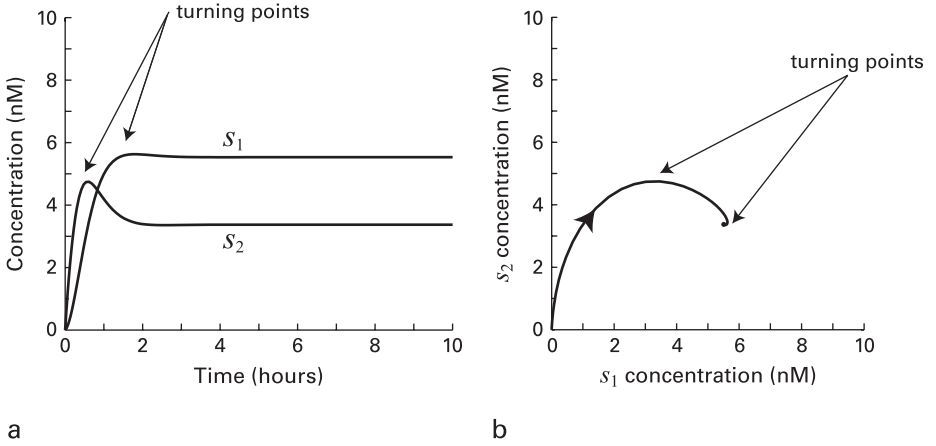

Figure 1.2
Evolution of the system described by equation (1.2). (a) The time-varying nature of the concentrations is emphasized by plotting each species concentration as a function of time, t. (b) The relationship between the concentrations of the two species is emphasized by plotting them in the s_1-s_2 plane. The curve starts at the initial condition and continues until it reaches an equilibrium. The arrowhead indicates progression with time. The turning points are instances where the phase plot changes direction. Parameters used are $k_1 = 1$ nM h^{-1}, $k_{-1} = 1$ h^{-1}, $k_2 = 20$ nM h^{-1}, $k_{-2} = 1$ h^{-1}, $k_3 = 2$ h^{-1}, $k_{-3} = 0.4$ h^{-1}, $k_4 = 0.05$ nM^{-1}, and $q = 2$.

1.2.1 Phase-Plane Analysis

Figure 1.2a shows how system behavior is typically visualized by plotting the concentrations of the two species (s_1 and s_2) as functions of time, which is consistent with an experimental time course. An alternative approach is to plot the time-varying behavior on the s_1-s_2 plane, which is referred to as the *phase plane*. These plots, called *phase portraits* cannot be generated for systems with more than two (or three) species. Nevertheless, the enhanced understanding they provide in these cases leads to valuable insights into more complex networks.

As an example, figure 1.2b shows precisely the same behavior as in figure 1.2a: the system starts from initial condition $(s_1, s_2) = (0, 0)$ and converges to the steady state $(\bar{s}_1, \bar{s}_2) \approx (5.53, 3.37)$; the plot emphasizes the time-varying relationship between the two variables, but de-emphasizes the relationship with the time variable t itself. Indeed, although each point on the curve corresponds to the value $(s_1(t), s_2(t))$ at a particular time instant t, the only time points that can be easily identified are at $t = 0$ (where the curve starts) and the longtime behavior $t \to \infty$ (where the curve ends).

In figure 1.3, the time courses (or *trajectories*) corresponding to a number of different initial conditions are displayed simultaneously. The trajectories begin at different

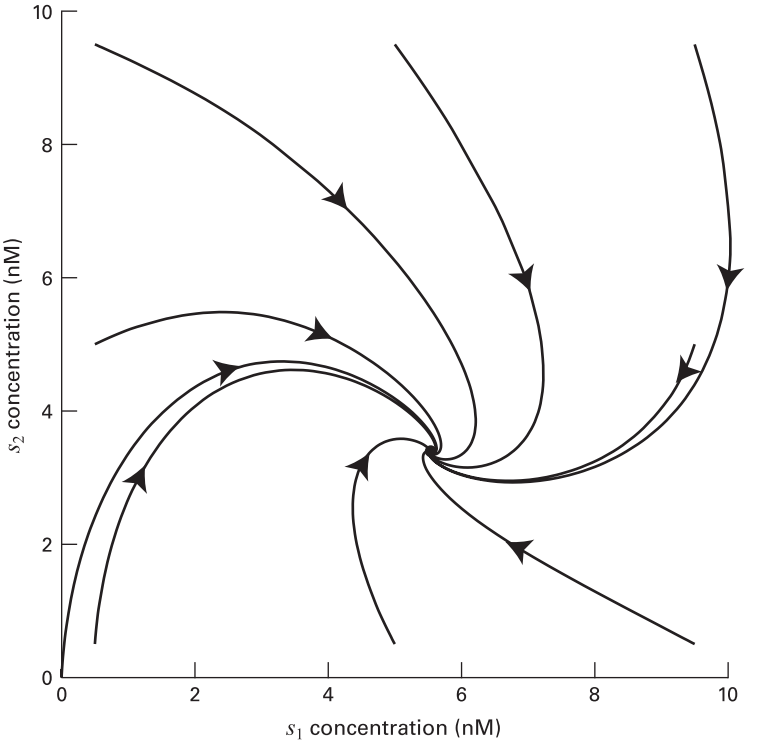

Figure 1.3
Phase-plane plot for the system of figure 1.1. Each trajectory begins at a different initial condition. Note that the trajectories cannot intersect; they can only come together at equilibria.

initial points in the s_1-s_2 plane and all end (in this case) at the steady state $(\bar{s}_1, \bar{s}_2)$. By capturing the behavior of multiple trajectories simultaneously, this single figure provides an overall impression of how the system behaves which would be difficult to achieve with a time-series plot.

An alternative to drawing many trajectories is to use short arrows to indicate the direction of motion at each point. The resulting plot, as shown in figure 1.4, is referred to as a *vector field* (or *direction field*). The trajectories lie parallel to (i.e., tangent to) the vector field at each point, and so can be constructed directly by "connecting the arrows." It is sometime useful to consider the analogy with particles suspended in a flowing fluid. The vector field describes the direction of motion of the fluid. The trajectories are the paths suspended particles would traverse as they are carried along with the flow.

The direction field can be derived directly from the differential equations—no explicit solution is needed. For a generic system involving two species s_1 and s_2,

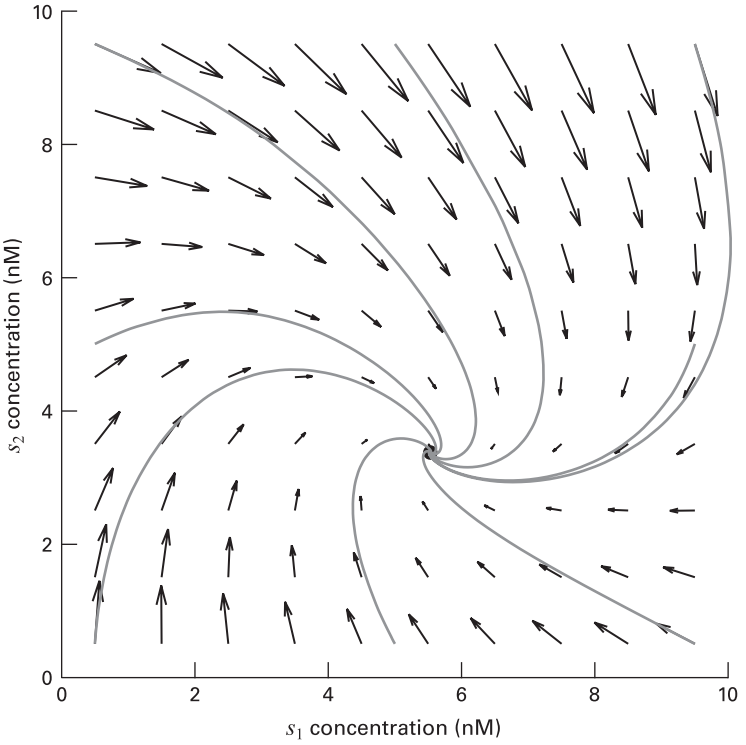

Figure 1.4
Vector field for the system defined by equation (1.2). The trajectories lie parallel to the arrows.

$$\frac{\mathrm{d}}{\mathrm{d}t}s_1(t) = f_1(s_1(t), s_2(t)),$$

$$\frac{\mathrm{d}}{\mathrm{d}t}s_2(t) = f_2(s_1(t), s_2(t)),$$

the slope of the (s_1, s_2) trajectory at any point is

$$\frac{\mathrm{d}s_2}{\mathrm{d}s_1} = \frac{\mathrm{d}s_2/\mathrm{d}t}{\mathrm{d}s_1/\mathrm{d}t} = \frac{f_2(s_1, s_2)}{f_1(s_1, s_2)}.$$

An arrow is drawn with this slope at each point. (If the denominator in this quotient is zero, then the arrow has an infinite slope, meaning that it points straight up or down.)

A key feature of the phase portrait is the set of points at which the trajectories "turn around," that is, change their direction with respect to one of the axes. These

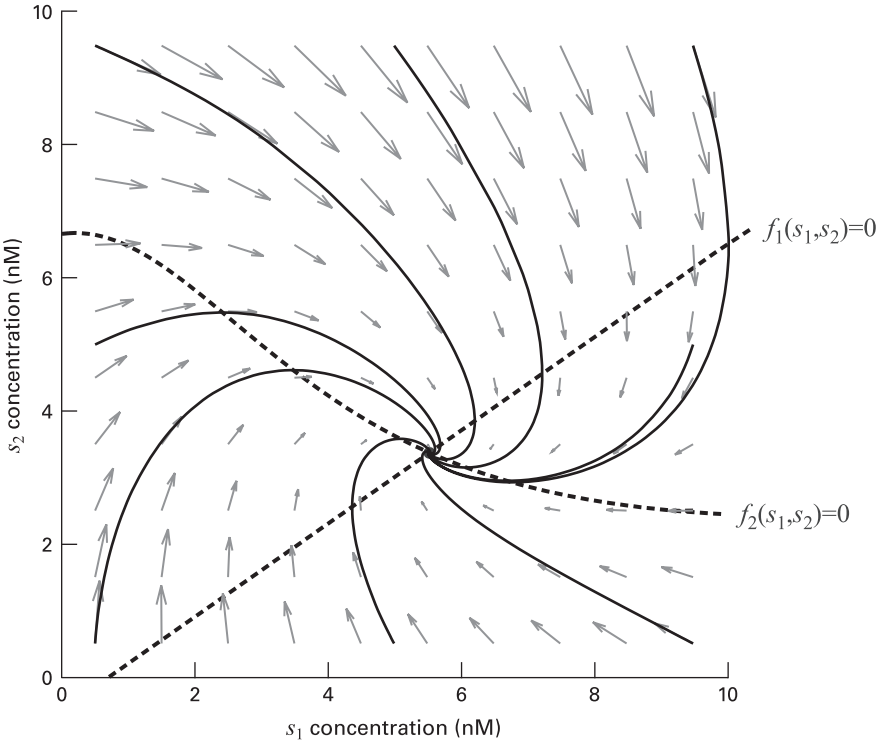

Figure 1.5
Trajectories for the system change direction as they cross the nullclines (*dotted lines*). Note also that the vector field points vertically on the s_1-nullcline and horizontally on the s_2-nullcline.

are the points at which one of the two variables $s_1(t)$ or $s_2(t)$ reaches a maximum or minimum, as shown in figure 1.2a. In this case, the maximum in s_2 occurs at time $t \approx 0.61$ h, at which point the concentrations are $(s_1, s_2) \approx (3.46, 4.75)$. Similarly, a maximum occurs in s_1 at time $t \approx 1.85$ h, at which point the concentrations are $(s_1, s_2) \approx (5.63, 3.42)$. These points can be identified on the same trajectory in the phase plane, as shown in figure 1.2b.

Turning points occur whenever the phase plane trajectory is directed either

1. vertically (vector points up or down): $\frac{\mathrm{d}}{\mathrm{d}t} s_1 = 0$; or
2. horizontally (vector points left or right): $\frac{\mathrm{d}}{\mathrm{d}t} s_2 = 0$.

The set of points (s_1, s_2) where the trajectory is vertical satisfies $f_1(s_1, s_2) = 0$, which defines the s_1-*nullcline* of the system. Likewise, the equation $f_2(s_1, s_2) = 0$ defines the s_2-*nullcline*. Figure 1.5 shows the nullclines for the system described by equation (1.2) along with a few trajectories and the vector field.

It is clear in figure 1.5 that the end point of the trajectories is marked by the intersection of the two nullclines. Note that the points (s_1, s_2) where the nullclines intersect satisfy $f_1(s_1, s_2) = f_2(s_1, s_2) = 0$ and thus are the equilibria of the system.

Because the nullclines can be generated without solving the differential equations, they allow direct insight into the dynamic behavior. This type of shortcut is a recurring theme in the analysis of dynamical systems.

1.3 Linear Systems and Linearization

If the function $\boldsymbol{f}$ in equation (1.1) is linear in $\boldsymbol{s}$, then the system can be written in the form

$$\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{s}(t) = \boldsymbol{A}\boldsymbol{s}(t), \tag{1.3}$$

where $\boldsymbol{A}$ is an $n \times n$ matrix.

The assumption of linearity greatly simplifies the analysis of the system. In particular, analytic expressions for the solution of the differential equations are now available. In this case, the solution takes the form

$$\boldsymbol{s}(t) = e^{\boldsymbol{A}(t-t_0)}\boldsymbol{s}(t_0),$$

where $e^{\boldsymbol{A}}$ is the matrix exponential (Rugh, 1996).

Unfortunately, except for the simplest of systems, linear models are inappropriate for describing biochemical or genetic networks. Nevertheless, linear analysis can be used to understand the behavior of a nonlinear system in regions of the state space that are near a steady state $\bar{\boldsymbol{s}}$, as shown next. We approximate the function $\boldsymbol{f}$ in equation (1.1) by a linear function that coincides with $\boldsymbol{f}$ at the steady state:

$$\boldsymbol{f}(\boldsymbol{s}) \approx \boldsymbol{f}(\bar{\boldsymbol{s}}) + \frac{\partial \boldsymbol{f}}{\partial \boldsymbol{s}}(\boldsymbol{s} - \bar{\boldsymbol{s}}). \tag{1.4}$$

This approximation represents the first two terms in the Taylor series expansion of $\boldsymbol{f}$.

The matrix

$$\boldsymbol{A} = \frac{\partial \boldsymbol{f}}{\partial \boldsymbol{s}}$$

is known as the *Jacobian* of the system. If $\boldsymbol{s}$ (and hence $\boldsymbol{f}$) has n components, then the Jacobian is an $n \times n$ matrix where the i, jth element is the partial derivative of the ith component of $\boldsymbol{f}$ with respect to the jth element of $\boldsymbol{s}$, evaluated at the steady state $\bar{\boldsymbol{s}}$:

$$a_{i,j} = \left.\frac{\partial f_i(\boldsymbol{s})}{\partial s_j}\right|_{\boldsymbol{s}=\bar{\boldsymbol{s}}}.$$

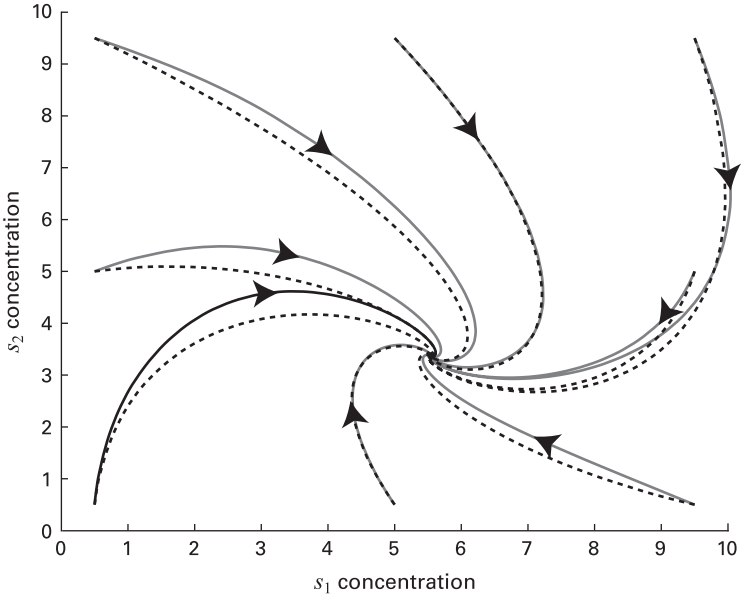

Figure 1.6
Phase portrait around a stable equilibrium for a nonlinear system (*solid lines*) and the linearization (*dotted lines*).

We introduce an auxiliary variable $\boldsymbol{x}(t)$, which represents the deviation of the species concentrations from their steady-state values:

$$\boldsymbol{x}(t) = \boldsymbol{s}(t) - \bar{\boldsymbol{s}}.$$

Then, because

$$\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{x}(t) = \frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{s}(t) - \boldsymbol{0},$$

and $\boldsymbol{f}(\bar{\boldsymbol{s}}) = \boldsymbol{0}$, the system (1.1) can be rewritten as

$$\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{x}(t) = \frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{s}(t) = \boldsymbol{f}(\boldsymbol{s}(t)) \approx \boldsymbol{f}(\bar{\boldsymbol{s}}) + \frac{\partial \boldsymbol{f}}{\partial \boldsymbol{s}}(\boldsymbol{s}(t) - \bar{\boldsymbol{s}}) = \boldsymbol{A}\boldsymbol{x}(t),$$

that is,

$$\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{x}(t) = \boldsymbol{A}\boldsymbol{x}(t). \tag{1.5}$$

This is referred to as the *linearization* of equation (1.1).

The behavior of the linearized system (1.5) can provide considerable information about the nonlinear model (1.1). In particular, if the matrix $\boldsymbol{A}$ has no eigenvalues with zero real part and certain other technical conditions hold, then the behavior of the linear and nonlinear systems agrees whenever the trajectories remain near the equilibrium (Hartman, 1963; see figure 1.6 for an example).

Thus the linearization describes the qualitative behavior of the system when the state variables remain "close" to the equilibrium. Although there are results that give precise bounds on the error made in this approximation, they are generally intractable; we will not pursue them here. Because regulated systems often have the property that the state remains near the equilibrium, this approximation provides the central basis for many of the tools of control engineering.

1.4 Stability

The concept of stability is central to the analysis of dynamical systems. Depending on the particular type of system—for example, whether it is linear or nonlinear, whether it has inputs or not—there are numerous definitions of what it means for a system to be stable. In all cases, however, the general idea is that systems are stable if small perturbations, whether in the initial condition or due to external stimuli, do not give rise to large sustained changes in the behavior of the system.

Turning to stability in the context of the nonlinear system

$$\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{x}(t) = \boldsymbol{f}(\boldsymbol{x}(t)),$$

let us suppose that the system has an equilibrium $\bar{\boldsymbol{s}}$. We say that the equilibrium is *stable* if every initial condition $\boldsymbol{s}_0$ that is near $\bar{\boldsymbol{s}}$ gives rise to trajectories that stay close to the equilibrium. A precise definition of what it means to be close involves so-called δ-ϵ arguments (Khalil, 2002), which we will avoid here.

Note that stability does not specifically require that the trajectory tend to the equilibrium as $t \to \infty$, a separate property known as *attractivity*. When an equilibrium is both stable and attractive, we say that it is *asymptotically stable*. Because, in practice, it is rare for an equilibrium to be stable but not asymptotically stable (the case of *marginal* or *neutral* stability), in the computational biological community the two terms are often used interchangeably. Where an equilibrium is *unstable*, nearby trajectories will diverge from the steady state (figure 1.7).

It should be emphasized that stability is not a property of a system but rather of particular steady states. Nonlinear systems can have multiple equilibria, with varying stability properties (see chapter 7). In general, all linear systems have a single equilib-

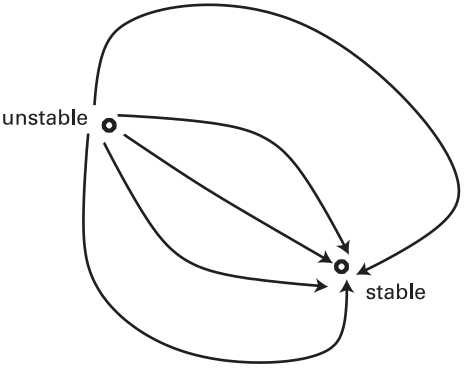

Figure 1.7
Two equilibria, one stable and the other unstable. Trajectories move away from the unstable and toward the stable equilibrium.

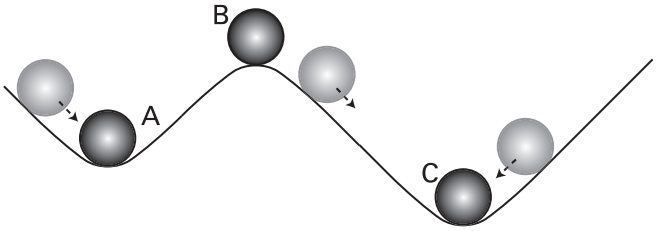

Figure 1.8
Stability and instability of equilibria likened to the behavior of balls on an undulating slope. For balls rolling on the slope depicted here, there are three possible equilibria, corresponding to the valley bottoms (stable) and the top of the hill (unstable). A ball balanced perfectly on the top of the hill (B) will remain there, but the slightest perturbation will cause it to roll away. Conversely, a ball in a valley bottom (A or C), if displaced by a small amount, will return to its resting place.

rium (at the origin) and so the term ''stable system'' is sometimes used to describe a linear system for which this equilibrium is stable.

In a standard analogy, stable and unstable states are likened to the valleys and hill tops of an undulating topography (figure 1.8). The valley bottoms represents stable equilibria: small perturbations will not let a ball escape and, in the presence of friction, the ball will return to a resting state at the bottom of the valley. Alternatively, the peak of a hill represents an unstable equilibrium: any disturbance will make a ball accelerate away from its rest state. A topography with two valleys would correspond to a bistable system. In this case, we can assign to each stable steady state a *basin of attraction*, which is the region in the phase space from which trajectories approach this point. The dividing line between the two is referred to as a *separatrix*.

1.4.1 Determining Stability for Linear Systems

How can we determine the stability of an equilibrium? For simple systems, we could draw the vector field and observe the direction of the arrows. For a more generally applicable method, however, let us first consider the linear case, where n linear differential equations are written in matrix form:

$$\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{x}(t) = \boldsymbol{A}\boldsymbol{x}(t).$$

As mentioned earlier, the solution, given an initial state $\boldsymbol{x}(0) = \boldsymbol{x}_0$, is

$$\boldsymbol{x}(t) = e^{\boldsymbol{A}t}\boldsymbol{x}_0,$$

which can be expanded in the form

$$e^{\boldsymbol{A}t}\boldsymbol{x}_0 = \alpha_1 e^{\lambda_1 t}\boldsymbol{v}_1 + \cdots + \alpha_n e^{\lambda_n t}\boldsymbol{v}_n, \tag{1.6}$$

where the constants α_i depend on the initial condition $\boldsymbol{x}_0$, the λ_i are the *eigenvalues* of the matrix $\boldsymbol{A}$, and the $\boldsymbol{v}_i$ are the associated *eigenvectors*. We have assumed that the matrix $\boldsymbol{A}$ has n distinct eigenvalues, which is typically the case. The main stability results stated here hold in the general case (for more detailed discussions, see Rugh, 1996; Khalil, 2002).

Eigenvalues and Singular Values

The n eigenvalues of an $n \times n$ square matrix provide a valuable summary of the overall matrix structure and are used in a wide array of application areas (Horn and Johnson, 1985). The eigenvalues of a matrix $\boldsymbol{A}$ are the solutions λ of the *characteristic equation* $\det(\lambda \boldsymbol{I} - \boldsymbol{A}) = 0$. In the case of the 2×2 matrix

$$\boldsymbol{A} = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix},$$

the characteristic equation is quadratic:

$$\lambda^2 - (a_{11} + a_{22})\lambda + (a_{11}a_{22} - a_{12}a_{21}).$$

Readers may recall that $a_{11} + a_{22}$ and $a_{11}a_{22} - a_{12}a_{21}$ are the *trace* and *determinant* of the matrix $\boldsymbol{A}$, respectively. Thus, in this case, the eigenvalues can be written explicitly in terms of these two values:

$$\lambda_{1,2} = \frac{1}{2}\left(\mathrm{trace}(\boldsymbol{A}) \pm \sqrt{\mathrm{trace}(\boldsymbol{A})^2 - 4\,\det(\boldsymbol{A})}\right).$$

For larger matrices, the characteristic equation is less tractable, and iterative numerical methods are typically employed to find eigenvalues. Closely related to the notion of eigenvalues are the *singular values*, which also provide a "summary" of a matrix. The singular values of an $n \times m$ matrix $\boldsymbol{A}$ are defined as the square roots of the eigenvalues of the square matrix $\boldsymbol{A}^T\boldsymbol{A}$. Although, in special cases, the singular values of a square matrix coincide with its eigenvalues, they generally provide a different measure of matrix properties. Singular values will be used to address system robustness in chapters 9, 10, and 11.

Stability Criteria

The stability of the linear system depends on the behavior of the time-varying terms $e^{\lambda_i t}$ that appear in the solution (1.6). In general, eigenvalues are complex numbers; thus we write

$$\lambda_k = \sigma_k + j\omega_k,$$

where $j = \sqrt{-1}$. (Note, outside of engineering, the more common notation is $i = \sqrt{-1}$.) Recalling Euler's formula for the exponential of a complex number:

$$e^{(\sigma+\omega j)t} = e^{\sigma t}(\cos(\omega t) + j\,\sin(\omega t)),$$

we see that the term $e^{\lambda_k t}\boldsymbol{v}_k$ will decay to zero asymptotically if and only if the real part of the eigenvalue (σ_k) is strictly less than zero. If this is true for all eigenvalues of $\boldsymbol{A}$, then all solutions tend to zero, and the system is asymptotically stable. In this case the matrix $\boldsymbol{A}$ is called *Hurwitz*. Similarly, we say that the polynomial

$$\lambda^n + a_{n-1}\lambda^{n-1} + \cdots + a_1\lambda + a_0 = 0$$

is Hurwitz if all the roots have negative real parts.

Alternatively, if *any* of the eigenvalues has real part σ_j greater than zero, then some trajectories will grow exponentially, thus the origin is unstable. Finally, in the special case that some of the eigenvalues have real part exactly equal to zero, the origin cannot be asymptotically stable. It may, however, be (neutrally) stable.

1.4.2 Determining Stability for Nonlinear Systems

We now consider the stability of an equilibrium $\bar{\boldsymbol{s}}$ of the nonlinear system

$$\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{s}(t) = \boldsymbol{f}(\boldsymbol{s}(t)). \tag{1.7}$$

In this case, the stability properties of an equilibrium need to be characterized as *local* or *global*. An equilibrium is globally (asymptotically) stable if all trajectories

converge to it, no matter what the initial condition (clearly this can only happen if there is a unique equilibrium), whereas it is locally stable if trajectories must start in some neighborhood of the equilibrium. In the special case of linear systems, global stability is implied by local stability.

To determine the local stability properties of an equilibrium, it is enough to consider the stability properties of the system's linearization. In particular, an equilibrium of equation (1.7) is asymptotically stable if all the eigenvalues of the Jacobian, evaluated at the equilibrium, have negative real part. Conversely, the equilibrium is unstable if the Jacobian has an eigenvalue with positive real part. If the linearization is stable but not asymptotically stable (implying that the Jacobian has eigenvalues on the imaginary axis), then we can draw no conclusion about the stability of the nonlinear system from the linearized analysis.

The characterization of local stability through linearization is known as Lyapunov's indirect method, named after the nineteenth-century Russian mathematician Aleksandr Mikhailovich Lyapunov, who developed many of the early concepts of stability. Lyapunov also provided tests of global stability that can be applied to nonlinear systems. In particular, suppose that a real-valued function $V(\boldsymbol{s})$ exists such that

1. $V(\boldsymbol{s}) \geq 0$ for all $\boldsymbol{s}$ and $V(\boldsymbol{s}) = 0$ if and only if $\boldsymbol{s} = \mathbf{0}$; and

2. $$\frac{\mathrm{d}V(\boldsymbol{s}(t))}{\mathrm{d}t} < 0,$$

that is, the value of V decreases along trajectories, then the equilibrium is locally asymptotically stable. If a third condition is also satisfied:

3. $V(\boldsymbol{s}) \to \infty$ as $\|\boldsymbol{s}\| \to \infty$,

then the equilibrium is globally asymptotically stable.

The function V is known as a *Lyapunov function*. Because energy dissipates through friction, it can be taken as a Lyapunov function when modeling mechanical systems. For biological systems, however, there is no obvious way of choosing a suitable Lyapunov function.

1.5 Oscillatory Behavior

Thus far, our analysis of long-term (asymptotic) behavior has been restricted to fixed-point steady states. We now extend our discussion to systems that give rise to persistent, oscillatory dynamics. Oscillatory systems are commonplace in biology, and there are numerous treatises dealing with them (see, for example, Goldbeter, 1996, and the references therein). As an example, we consider a simple metabolic model, illustrated in figure 1.9. This scheme is motivated by the "turbocharged" posi-

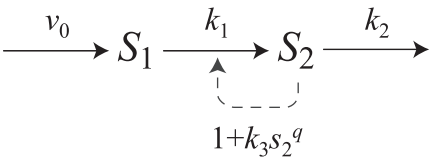

Figure 1.9
System involving positive feedback. Examples of such systems are found in catabolic pathways in which the first step involves coupling of ATP hydrolysis to activation of a substrate. Downstream, conversion of the substrate into product generates a surplus of ATP, which increases the available activated substrate (Teusink et al., 1998).

tive feedback aspect of the glycolytic chain in which the ATP output is used to produce more ATP (Teusink et al., 1998).

The potential for oscillations can be inferred from the model structure: the concentration of species S_2 builds up, causing further buildup until the pool of S_1 is depleted. The S_2 level then crashes until more S_1 is available, and so on. Although this intuitive argument indicates the potential for oscillatory behavior, it cannot predict the conditions under which oscillations will occur.

The equations describing the system are given by

$$\frac{\mathrm{d}}{\mathrm{d}t} s_1(t) = v_0 - k_1 s_1(t)(1 + k_3 s_2^q(t)), \tag{1.8a}$$

$$\frac{\mathrm{d}}{\mathrm{d}t} s_2(t) = k_1 s_1(t)(1 + k_3 s_2^q(t)) - k_2 s_2(t). \tag{1.8b}$$

The system can exhibit stable behavior as shown in figure 1.10: both species concentrations converge to steady state. This same behavior can be observed over a wide range of initial conditions, as shown in the phase portrait, which indicates that there is a single steady state.

Note that the trajectories seem to be spiraling in as they approach the steady state. That behavior, apparent in the damped oscillations seen in the time-domain description, indicates that the system is somehow close to oscillatory behavior. Increasing the nonlinearity in the model leads to the sustained oscillatory behavior seen in figure 1.11a. Considering the accompanying phase portrait in figure 1.11b, we see that the trajectories are attracted to a cyclic track, called a *limit cycle*. When we compare this phase portrait with the one corresponding to the steady state (figure 1.10b), we see that the nullclines' structure has not changed significantly. What has changed is the stability of the single steady state, which is now unstable. For two-dimensional systems, there is a useful result known as the Poincaré-Bendixson theorem which guarantees the existence of a limit cycle in a case like this. With no stable equilibrium points and all trajectories bounded, the trajectories have to go *somewhere*, and a limit

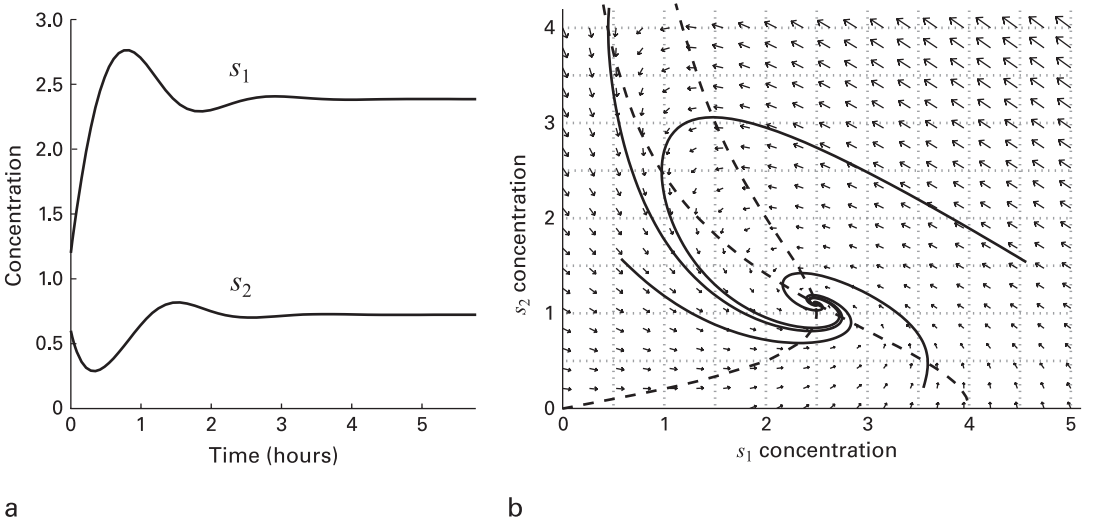

Figure 1.10
Time-domain (a) and phase-plane (b) plot of the system of figure 1.9, described by equation (1.8). Parameter values used are $v_0 = 8$, $k_1 = 1$, $k_2 = 5$, $k_3 = 1$ and $q = 2$.

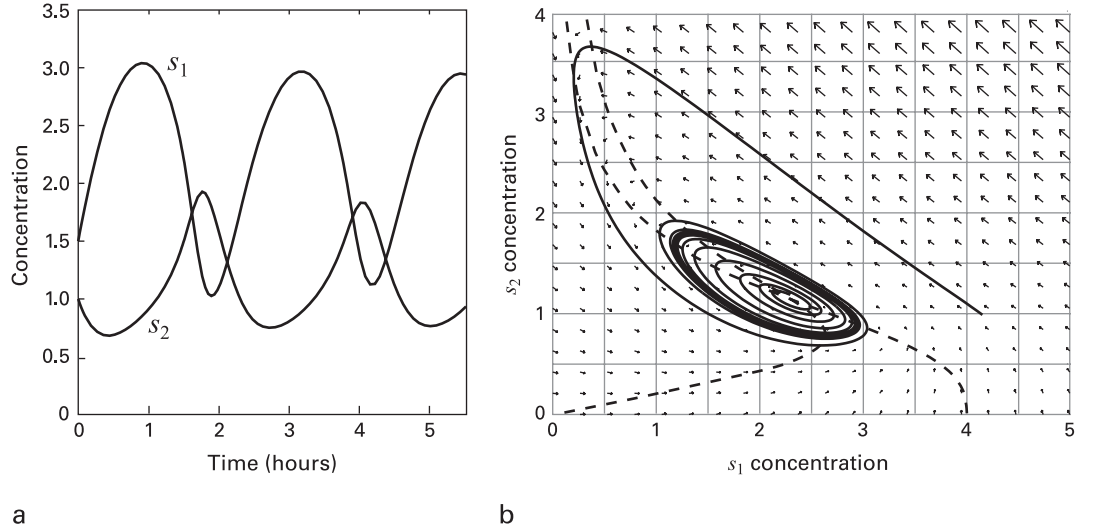

Figure 1.11
Time-domain (a) and phase-plane (b) plot of the system of figure 1.9, described by equation (1.8). The parameter values used are the same as in figure 1.10 except that the feedback strength has been increased to $q = 3$. This increase leads to sustained oscillatory behavior. In the phase plane, this can be seen as a closed curve.

cycle is the only remaining option (Khalil, 2002). Here we also see that the *qualitative* behavior of the system changes as the parameter values shift. The nature of those changes can be understood through bifurcation analysis.

1.6 Bifurcations

An important question when studying dynamical systems is whether the dynamic behavior of the system is retained as the system parameters change. This is of particular interest in biological systems, where the parameters may represent variables such as enzyme concentrations that are likely to vary significantly from one cell to another. When a system's properties do not undergo significant qualitative changes, we say that the system is *robust* or *structurally stable*. Robustness is the topic of chapters 9, 10, and 11. When qualitative changes do occur—for example, a stable equilibrium becomes unstable, or the system acquires a new equilibrium point—the system is said to undergo a *bifurcation*.

1.6.1 Bifurcation Diagrams

One way of studying bifurcations is by plotting the location and nature of the system's equilibria as a function of a parameter. These plots, which correspond to experimental dose-response curves, are known as *continuation diagrams*. Bifurcations occur at the points on a continuation diagram where a major change takes place. The specific value of the parameter where the change occurs is the *bifurcation point*. In these cases, the continuation diagram is known as a *bifurcation diagram*.

Figure 1.12 contains a bifurcation diagram showing the steady state of s_1 in system (1.8) as a function of the parameter q. In addition to the position of the equilibrium, the stability type is indicated by the line style: a stable (attracting) steady state is indicated by the solid line from $q = 1$ to $q \approx 2.86$; an unstable (repelling) fixed point, by the dashed line from that point up until $q = 5$. The value $q \approx 2.86$, at which the stability changes, is the bifurcation point. Recall that stability is dictated by the sign of the real part of the eigenvalues of the linearization of the system. These eigenvalues change as the parameter q changes; their real parts cross over from being negative to being positive at the bifurcation point.

In this particular system, the bifurcation point dictates not only the change in the stability of the fixed point, but also the appearance of a limit cycle. This particular type of bifurcation is known as a *Hopf bifurcation*. For such bifurcations, it is customary to denote the limit cycle by the maximum and minimum values reached in the oscillation (figure 1.13).

Knowledge of the bifurcation structure can be useful in assaying the robustness of system behavior. If the nominal conditions are near a bifurcation point, it is possible that environmental perturbations could push the system into a very different

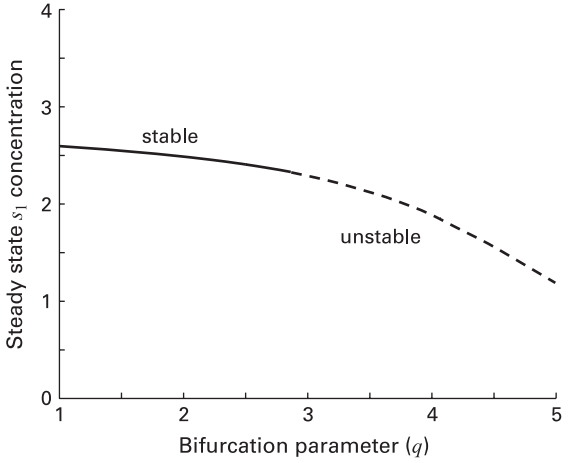

Figure 1.12
Bifurcation diagram for system (1.8), showing the steady state of s_1 as a function of the parameter q. Although one equilibrium exists for all these values of the parameter, the stability of the equilibrium changes at $q \approx 2.86$. For values smaller than this, the equilibrium is stable (*solid line*); for greater values, it is unstable (*dashed line*).

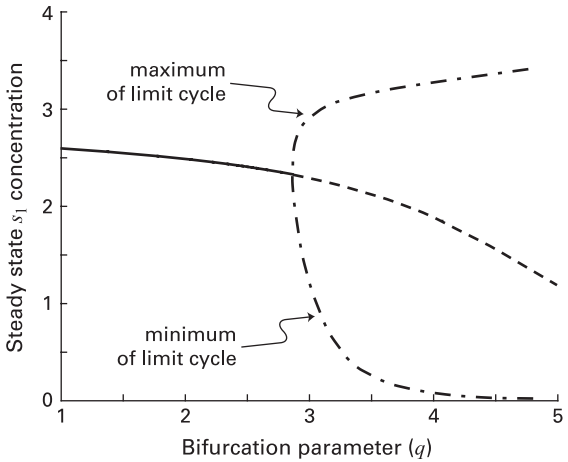

Figure 1.13
Bifurcation diagram for the system in figure 1.9, showing the steady state s_1 as a function of the parameter q and denoting the location and stability of the equilibrium as well as the maximum and minimum values achieved by s_1 during the steady-state oscillations (*dashed-dotted curve*).

behavior. On the other hand, if bifurcations are far away in parameter space, then the nominal behavior may be highly robust to changes in operating conditions.

1.7 Systems with Inputs and Outputs

Thus far, we have considered systems that evolve autonomously, and we have treated the whole state vector in our analysis. In control engineering, it is more common to consider systems that respond to external inputs and provide specific output signals to their environment.

We first consider systems of the form

$$\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{s}(t) = \boldsymbol{f}(\boldsymbol{s}(t), \boldsymbol{u}(t)). \tag{1.9}$$

In this equation, the vector

$$\boldsymbol{u}(t) = \begin{bmatrix} u_1(t) \\ \vdots \\ u_m(t) \end{bmatrix}$$

represents species or other influences that act as external inputs to the system.

In a biological context, the inputs could represent any external parameters over which an experimenter has control or any regulatory signals coming from outside of the process of interest, for example, genetic control of enzyme abundance in a metabolic model. In these contexts, we might ask to what degree the input can influence the system dynamics (addressed in section 1.9.1). Alternatively, the input $\boldsymbol{u}(t)$ could be used to incorporate the effect of external disturbances on model behavior. In this case, the model allows us to analyze the robustness of system behavior in the face of these perturbations.

Additionally, control engineers consider a set of p observable outputs, denoted by

$$\boldsymbol{y}(t) = \begin{bmatrix} y_1(t) \\ \vdots \\ y_p(t) \end{bmatrix}.$$

The choice of output might be dictated by available experimental assays or by which components of the system interact with processes external to the network of interest. An alternative role for the output $\boldsymbol{y}(t)$ is to allow the analysis to focus on a particular aspect of system behavior. That might be the concentration of a particular component species or some function of overall behavior, for example, the flux through a metabolic pathway. For the simplest input-output systems, referred to as

memoryless input-output maps, there is no system state and the output $\boldsymbol{y}$ at time t is given directly by a function of the input $\boldsymbol{u}$ at time t:

$$\boldsymbol{y}(t) = \boldsymbol{h}(\boldsymbol{u}(t)).$$

More generally, the effect of the input is not immediate, and so a dynamic description in which the output is a function of the system states and inputs is required:

$$\boldsymbol{y}(t) = \boldsymbol{h}(\boldsymbol{s}(t), \boldsymbol{u}(t)). \tag{1.10}$$

In this case, equations (1.9) and (1.10) represent a dynamic input-output system. Fixing a specific initial condition (typically at the origin), such systems can be thought of as maps from input signals $\boldsymbol{u}(t)$ to corresponding output signals $\boldsymbol{y}(t)$. In the specific case that the system has only one input ($m = 1$) and one output ($p = 1$) the system is said to be a *single-input, single-output* (SISO) system. Otherwise, the system is referred to as *multiple-input, multiple-output* (MIMO). For simplicity, we will assume that the systems are SISO.

1.7.1 Feedback

Central to control theory is the use of feedback control (figure 1.14). The idea is to arrange for the input variables to depend on the system response. When the input depends directly on the state variables:

$$u(t) = k_s(\boldsymbol{s}(t)),$$

for some suitable function k_s, known as a *control law*, the feedback is referred to as *static state feedback*. It is "state" feedback because the controller has access to the full state vector; and "static" because the feedback is implemented through a memoryless

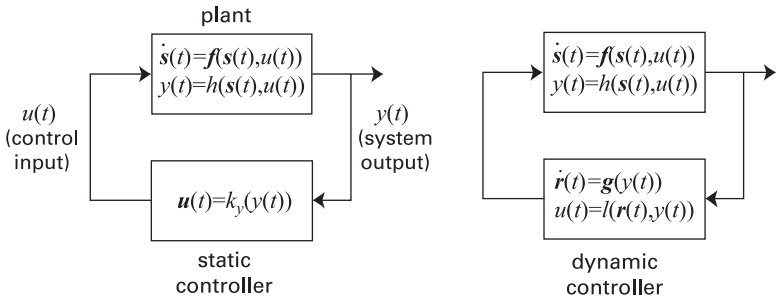

Figure 1.14
Typical feedback control system, consisting of two dynamical systems. One, referred to as the *plant*, is the system to be controlled. The other, known as the *controller*, acts in a feedback loop and is often designed to regulate the complete system. It can be a static (*left*) or a dynamic (*right*) function of the plant output. In biological implementations, the distinction between plant and controller is blurred.

map (i.e., a function). Alternatively, when the control depends only on the system output:

$$u(t) = k_y(y(t)),$$

the feedback is known as static *output feedback*.

In contrast to static feedback, the controller may itself involve an auxiliary dynamic system, which allows it to take into account past behavior of the system (as opposed to only acting on current system values). In this case, the feedback system is described by a vector of control states $\boldsymbol{r}(t)$. When such a feedback depends on output values, it takes the form

$$\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{r}(t) = \boldsymbol{g}(y(t)), \tag{1.11a}$$

$$u(t) = l(\boldsymbol{r}(t), y(t)) \tag{1.11b}$$

and is referred to as *dynamic* output feedback. In this case, the feedback depends on a history of the output signals: the controller state $\boldsymbol{r}(t)$ retains a memory of the output $y(t)$. Incorporating this memory into the control input allows the system to cope with behavior that a direct (static) feedback cannot.

1.7.2 Linear Input-Output Systems

If the function $\boldsymbol{f}$ in equation (1.9) is linear in $\boldsymbol{s}$ and $\boldsymbol{u}$, then the system can be written in the form

$$\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{s}(t) = \boldsymbol{A}\boldsymbol{s}(t) + \boldsymbol{B}\boldsymbol{u}(t). \tag{1.12}$$

Moreover, if the output depends linearly on the state and input, then we write

$$\boldsymbol{y}(t) = \boldsymbol{C}\boldsymbol{s}(t) + \boldsymbol{D}\boldsymbol{u}(t). \tag{1.13}$$

The system defined by equations (1.12) and (1.13) is referred to as a linear, time-invariant (LTI) system ("time-invariant" refers to the fact that the matrices do not change with time). If the system has m inputs, p outputs, and n states, then $\boldsymbol{A}$, $\boldsymbol{B}$, $\boldsymbol{C}$, and $\boldsymbol{D}$ are $n \times n$, $n \times m$, $p \times n$, and $p \times m$, matrices, respectively. The solution to this linear system can be written explicitly in the form

$$\boldsymbol{s}(t) = e^{\boldsymbol{A}(t-t_0)}\boldsymbol{s}(t_0) + \int_{t_0}^{t} e^{\boldsymbol{A}(t-\tau)}\boldsymbol{B}\boldsymbol{u}(\tau)\,\mathrm{d}\tau.$$

Linearization of a nonlinear input-output system follows in the manner described in section 1.3 and is centered at a steady state $\bar{\boldsymbol{s}}$ corresponding to a constant nominal

input $\bar{\boldsymbol{u}}$. In addition to the state $\boldsymbol{x}$ and Jacobian $\boldsymbol{A}$, the linearization also includes the matrix $\boldsymbol{B}$ with i, jth element

$$b_{i,j} = \left.\frac{\partial f_i(\boldsymbol{s}, \boldsymbol{u})}{\partial u_j}\right|_{\boldsymbol{s}=\bar{\boldsymbol{s}}, \boldsymbol{u}=\bar{\boldsymbol{u}}}.$$

In this case, the linearized equation is

$$\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{x}(t) = \boldsymbol{A}\boldsymbol{x}(t) + \boldsymbol{B}\boldsymbol{v}(t), \tag{1.14}$$

where $\boldsymbol{v}(t) = \boldsymbol{u}(t) - \bar{\boldsymbol{u}}$.

Example Let us linearize the system described by equation (1.2). To define an input-output system, we consider the parameter k_2 as the input by setting $u(t) = k_2(t)$ and the concentration of S_2 as output: $y(t) = s_2(t) - \bar{s}_2$. We linearize about the equilibrium with input set to $\bar{u} = 20$ nMh^{-1}. The corresponding steady state is $(\bar{s}_1, \bar{s}_2) \approx (5.53, 3.37)$.

We now compute the Jacobian $\boldsymbol{A} = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix}$:

$$a_{11} = \frac{\partial f_1}{\partial s_1} = -(k_{-1} + k_{-3}), \qquad a_{12} = \frac{\partial f_1}{\partial s_2} = k_3,$$

$$a_{21} = \frac{\partial f_2}{\partial s_1} = -\frac{k_4 \bar{u} q \bar{s}_1^{q-1}}{(1 + k_4 \bar{s}_1^q)^2} + k_{-3}, \qquad a_{22} = \frac{\partial f_2}{\partial s_2} = -(k_{-2} + k_3),$$

and the input matrix $\boldsymbol{B} = \begin{bmatrix} b_1 \\ b_2 \end{bmatrix}$:

$$b_1 = \frac{\partial f_1}{\partial u} = 0, \qquad b_2 = \frac{\partial f_2}{\partial u} = \frac{1}{(1 + k_4 \bar{s}_1^q)}.$$

The output equation has $\boldsymbol{C} = [0 \;\; 1]$ and $\boldsymbol{D} = 0$. ■

1.8 Frequency-Domain Analysis

The longtime (asymptotic) behavior of linear, time-invariant dynamical systems can be elegantly analyzed through an approach that makes use of a parallel, *frequency-domain* description of input and output signals. There are two features of LTI systems that are exploited in this analysis. The first is simply the linear nature of their

input-output behavior that implies an *additive property*: provided the system starts with initial condition $\boldsymbol{x}(0) = \mathbf{0}$ (which corresponds to the nominal steady state of the biochemical network), the output produced by the sum of two inputs is the sum of the outputs produced independently by the two inputs. That is, if input $\boldsymbol{u}_1(t)$ elicits output $\boldsymbol{y}_1(t)$, and input $\boldsymbol{u}_2(t)$ yields output $\boldsymbol{y}_2(t)$, then input $\boldsymbol{u}_1(t) + \boldsymbol{u}_2(t)$ leads to output $\boldsymbol{y}_1(t) + \boldsymbol{y}_2(t)$.

The additive property allows a reductionist approach to the analysis of system response: if a complicated input can be written as a sum of simpler signals, the response to each of these simpler inputs can be addressed separately, and the original response can be found through a straightforward summation. This leads to a satisfactory procedure provided we are able to find a family of "simple" functions with the following two properties: (1) the family has to be "complete" in the sense that an arbitrary signal can be decomposed into a sum of functions chosen from this family; and (2) it must enjoy the property that the asymptotic response of a linear system to inputs chosen from the family is easily characterized. The family of sinusoids (sines and cosines) satisfies both of these conditions. The decomposition of a signal $y(t)$ into a combination of sinusoids is the foundation of *Fourier analysis* (Körner, 1988). This technique allows the description of a signal $y(t)$ in terms of its *Fourier transform* $Y(\omega)$, which provides a record of the frequency content of $y(t)$ and is an alternative characterization of the original function. In essence, the Fourier transform $Y(\omega)$ indicates the coefficients that appear in decomposing the original function $y(t)$ into a "sum" of sinusoids at different frequencies ω. (The sum is really an integral over a continuum of frequencies.)

In theory, the signal $y(t)$ can be recovered from $Y(\omega)$ by an inverse transform (which amounts to summing over the sinusoids). In practice, recovery of a signal from its transform is difficult to achieve. Nevertheless, important aspects of the signal can be gleaned directly from the graph of the transform. In particular, one can determine what sort of variations dominate the signal (for example, low-frequency or high-frequency) by comparing the content at various frequencies. Quickly varying signals have transforms with most of their content at high frequencies, whereas slowly varying functions show primarily low-frequency content. The second crucial property of linear, time-invariant systems is that, as mentioned above, their response to sinusoidal inputs can be easily described. For LTI systems, a sinusoidal input of frequency ω_0:

$$u(t) = \sin(\omega_0 t),$$

generates an output that is, after an initial transient, a sinusoid of the same frequency:

$$y(t) = A(\omega_0)\,\sin(\omega_0 t + \phi(\omega_0)).$$

This longtime response can be characterized by two frequency-dependent functions: $A(\omega_0)$, the amplitude of the oscillatory output, known as the *system gain*; and $\phi(\omega_0)$, the phase of the oscillatory output, referred to as the *phase shift*. As indicated, these depend on the particular frequency ω_0 of the input signal. The particular gain and phase shift that correspond to each frequency can be conveniently described by the assignment of a single complex number $A(\omega)e^{j\phi(\omega)}$ to each frequency ω. This complex-valued function is called the *frequency response* of the system.

1.8.1 The Laplace Transform

Although the Fourier transform provides a valuable description of a signal in terms of its frequency content, the definition is not a useful starting point for calculations. A more general tool, the *Laplace transform* (Körner, 1988), fills that role. The Laplace transform of a signal $y(t)$ is denoted $Y(s)$, where $s = \sigma + j\omega$ is a complex number with real part σ and imaginary part ω. The Fourier transform can be thought of as the special case of the Laplace transform in which $\sigma = 0$, although, in some cases, a function may have a Laplace transform but not have a well-defined Fourier transform (Körner, 1988).

The Transfer Function

For a linear, time-invariant system with zero initial conditions, input $\boldsymbol{u}(t)$, and output $\boldsymbol{y}(t)$, the transfer function is defined in terms of the Laplace transforms of the output $\boldsymbol{Y}(s)$ and the input $\boldsymbol{U}(s)$:

$$\boldsymbol{Y}(s) = \boldsymbol{G}(s)\boldsymbol{U}(s).$$

In the specific case that the system is defined by the linear differential equation (1.12) with output (1.13), the transfer function is given by

$$\boldsymbol{G}(s) = \boldsymbol{C}(s\boldsymbol{I} - \boldsymbol{A})^{-1}\boldsymbol{B} + \boldsymbol{D}. \tag{1.15}$$

This function will, in general, be matrix valued, but it is scalar valued when dealing with SISO systems. The frequency response of the system is the restriction of the transfer function to arguments of the form $s = j\omega$.

The complex-valued frequency response $G(j\omega) = A(\omega)e^{j\phi(\omega)}$ can be plotted in a number of ways. Perhaps the most useful of these visualizations is the *Bode plot*, in which the magnitude and argument of the frequency response are plotted separately (Bode, 1945). The magnitude $A(\omega)$, the system gain, is plotted on a log-log scale, where the gain is measured in decibels (dB) (defined by x dB $= 20 \log_{10} x$). The argument $\phi(\omega)$, the phase shift, appears on a semilog plot, with log frequency plotted against phase in degrees. An example is given in figure 1.15. The frequency-filtering properties of the system can be read directly from the magnitude plot. In this example, the higher-frequency content of an input signal will be attenuated (i.e., filtered)

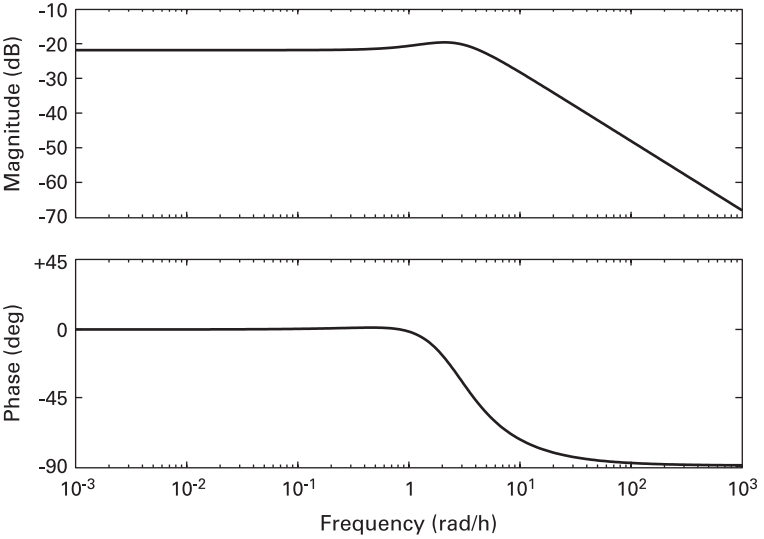

Figure 1.15
Frequency response of system described by equation (1.2), with $u = k_2$ and $y = s_2$. Using the linearization about the equilibrium, we computed the system's Bode magnitude (top) and phase (bottom) plots. From the magnitude plot, it can be seen that the system behaves as a low-pass filter with a cutoff frequency of approximately 1 rad/h.

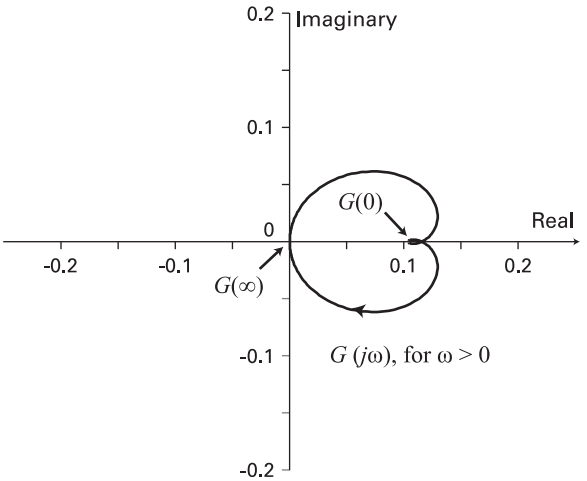

Figure 1.16
Nyquist plot. The frequency response of figure 1.15 can alternatively be represented as a Nyquist plot. The complex values of $G(j\omega)$ are plotted as the frequency ω ranges from $-\infty$ to ∞. The curve's arrowhead indicates the direction of increasing ω. The resulting curve is, in general, symmetric. Moreover, since the values of $G(j\omega)$ tend to zero for large frequencies ($\omega \to \pm\infty$), the plot generates a closed curve in the complex plane. The stability of a system under negative feedback can be determined by the number of times that the open-loop plot encircles the -1 point. In this case, there are no encirclements.

due to the low gain at frequencies above 1 rad/h. An input that consists solely of these high-frequency components (e.g., a highly variable noise signal) may be completely attenuated by the system (i.e., result in near-zero output), whereas other signals will have such highly variable noise filtered out by the system.

An alternative method for visualizing the frequency response is to plot it as a parametrized curve on the complex plane $\omega \mapsto A(\omega)e^{j\phi(\omega)}$. The resulting curve, known as a *Nyquist plot*, provides a valuable tool for addressing the stability of the system when the static output feedback with $k_y(y) = -y$ (called the *unity-feedback* closed loop) is implemented. An example is shown in figure 1.16. The Nyquist stability criterion will be taken up in chapters 9 and 10.

1.9 Controllability and Observability

There are two concepts that, though central to control engineering, are relatively unknown outside the field. Controllability and its counterpart observability deal, respectively, with the relationship between input and state and between state and output. To offer the simplest illustration, we will assume linear systems with one input or one output.

1.9.1 Controllability

Consider the system

$$\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{x}(t) = \boldsymbol{A}\boldsymbol{x}(t) + \boldsymbol{B}u(t), \qquad \boldsymbol{x}(0) = \boldsymbol{x}_0, \tag{1.16}$$

where the state $\boldsymbol{x}(t)$ is an n-dimensional vector.

A system is *controllable* if the control input $u(t)$ is able to drive the state $\boldsymbol{x}(t)$ from any nonzero initial condition to the origin. Thus controllability is a measure of our ability to influence the system's state through $u(t)$. Specifically, we say that the system is "controllable over an interval $[0, t_f]$" if, for any initial condition $\boldsymbol{x}_0$, there exists an input $u(t)$, defined over the interval $[0, t_f]$ such that the solution $\boldsymbol{x}(t)$ of equation (1.16) satisfies $\boldsymbol{x}(t_f) = \boldsymbol{0}$.

Though the definition involves the dynamic behavior of the system, there is a simple algebraic test for controllability of linear, time-invariant systems. It relies only on the matrices $\boldsymbol{A}$ and $\boldsymbol{B}$. In particular, the system (1.16) is controllable over $[0, t_f]$ if and only if the matrix

$$\mathcal{C} = [\boldsymbol{B} \quad \boldsymbol{A}\boldsymbol{B} \quad \cdots \quad \boldsymbol{A}^{n-1}\boldsymbol{B}]$$

is invertible. Alert readers will note that the time interval $[0, t_f]$ does not play a role in the test. Consequently, if a system is controllable over one time interval, it is con-

trollable over any time interval, and the time interval can be dropped. (The time interval plays a significant role if there is a bound on the input values.)

One of the more significant consequences of controllability arises when a linear state-feedback controller is implemented:

$$u(t) = -\boldsymbol{K}\boldsymbol{x}(t). \tag{1.17}$$

In this case, replacing $u(t)$ in equation (1.16) with the control law (1.17) gives rise to the following closed-loop dynamical system:

$$\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{x}(t) = (\boldsymbol{A} - \boldsymbol{B}\boldsymbol{K})\boldsymbol{x}(t), \qquad \boldsymbol{x}(0) = \boldsymbol{x}_0. \tag{1.18}$$

The stability of this system is determined by the eigenvalues of the matrix $\boldsymbol{A} - \boldsymbol{B}\boldsymbol{K}$. It is a remarkable fact that, if the system is controllable, the location of these eigenvalues can be assigned arbitrarily by the appropriate choice of $\boldsymbol{K}$.

1.9.2 Observability

To address observability, we consider systems with a specified output signal, but no input. In particular:

$$\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{x}(t) = \boldsymbol{A}\boldsymbol{x}(t), \qquad \boldsymbol{x}(0) = \boldsymbol{x}_0, \tag{1.19a}$$

$$y(t) = \boldsymbol{C}\boldsymbol{x}(t). \tag{1.19b}$$

The system is *observable* if, based on knowledge of the output $y(t)$ over some time interval, we can discern the state $\boldsymbol{x}$ of the system at the beginning of the interval. Recall that knowledge of the initial condition allows us to determine the state at subsequent times. Specifically, we say that the system (1.19) is observable over the time interval $[0, t_f]$ if any initial state $\boldsymbol{x}_0$ is uniquely determined by the ensuing output $y(t)$ for $t \in [0, t_f]$. As with controllability, an algebraic test can be used to determine observability. In particular, the system (1.19) is observable over $[0, t_f]$ if and only if the matrix

$$\mathcal{O} = \begin{bmatrix} \boldsymbol{C} \\ \boldsymbol{C}\boldsymbol{A} \\ \vdots \\ \boldsymbol{C}\boldsymbol{A}^{n-1} \end{bmatrix} \tag{1.20}$$

is invertible. As with controllability, the test is independent of the specific time interval, which implies that, if a system is observable over one time interval, it is observable over any time interval.

Observability guarantees that one can "look back" along the output signal and determine the state at a previous time. Typically, it is more useful to have real-time knowledge of the system's state. An *observer* is an auxiliary dynamical system that provides an asymptotically correct estimate for the current state. Define the system

$$\frac{\mathrm{d}}{\mathrm{d}t}\tilde{\boldsymbol{x}}(t) = \boldsymbol{A}\tilde{\boldsymbol{x}}(t) + \boldsymbol{L}(y(t) - \boldsymbol{C}\tilde{\boldsymbol{x}}(t)),$$

where the matrix $\boldsymbol{L}$ is yet to be chosen. The state $\tilde{\boldsymbol{x}}$ of the observer serves as an estimate of the state of the system (1.19). Defining the estimation error as

$$\boldsymbol{e}(t) = \boldsymbol{x}(t) - \tilde{\boldsymbol{x}}(t),$$

we see that

$$\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{e}(t) = (\boldsymbol{A} - \boldsymbol{LC})\boldsymbol{e}(t).$$

If this system is stable, then $\boldsymbol{e}(t)$ tends to zero or, equivalently, $\tilde{\boldsymbol{x}}$ tends to $\boldsymbol{x}$. This system will be stable provided that the eigenvalues of $\boldsymbol{A} - \boldsymbol{LC}$ have negative real parts. The matrix $\boldsymbol{L}$ can be chosen arbitrarily. This is analogous to the problem of choosing a control gain $\boldsymbol{K}$ so as to make $\boldsymbol{A} - \boldsymbol{BK}$ stable, considered above. As in that case, if the system is observable, then $\boldsymbol{L}$ can be chosen so that the system is stable. (In fact, there are no constraints on the placement of the eigenvalues of $\boldsymbol{A} - \boldsymbol{LC}$.) When the system equations are subject to stochastic disturbances, the corresponding observer is known as a *filter*. In the specific case that the matrix $\boldsymbol{L}$ minimizes the variance of the estimation error, the observer is known as the *Kalman filter* (Kalman, 1960). An application of the Kalman filter to the analysis of the signaling pathway regulating bacterial chemotaxis can be found in the work of Andrews et al. (2006).