CHAPTER 3

LINEARIZATION AND DEVIATION VARIABLES

Most of the state equations derived in Chapter 2 include nonlinear terms. In general, analytical solutions (i.e., closed-form expressions) are only available for some classes of nonlinear equations. Computer simulations offer the ability to obtain numerical results and to visualize actual process behaviors. In addition, simulations make it possible to test a number of designs and to study the influence of an array of conditions on the process.

Linearization is another tool that can be used to describe a system in the vicinity of certain operating conditions. However, there is a drawback to this approach. The performance of the approximation degrades further away from the linearization point. Some of the advantages of the linear approximation are (1) the local stability of a dynamic system can be analyzed and (2) controllers can be tuned using the approximated solution. This technique is appropriate for situations where the plant does not deviate significantly from a desired operating condition.

3.1 COMPUTER SIMULATIONS

Several simulation software packages have been developed for representing real-world processes and for assessing the effects of a number of factors on system performance. MATLAB® (MathWorks, Inc.) and *Mathematica*® (Wolfram Research, Inc.) are two packages, among others, that can be used to

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simulate biological processes. A working knowledge of governing engineering principles and the ability to visualize dynamic behaviors are equally important to the development of an efficient control strategy.

The first step in process simulation is to derive a mathematical model of the physical system, as discussed in Chapter 2. Most computational tools are only able to numerically solve the differential equations provided by the user. Model parameter values, rate laws, and certain assumptions have to be entered into the program. Other computational software packages, such as Aspen Plus® (Aspen Technology, Inc.), contain a database of pure components and phase equilibrium information for a range of chemicals. Libraries of equipment models are available and allow the user to build very complex systems and run simulations to analyze the nonlinear behavior of these systems. The performance of a controller, based on a linear representation of the plant, can be evaluated using the original process model.

Simulation platforms can be exploited to solve the nonlinear differential equations included in this book. Most graphics, presented in the subsequent chapters, are generated using MATLAB (http://www.mathworks.com/) or *Mathematica* (http://www.wolfram.com/). Since both software resources provide extensive documentation and support information on their websites, instructions on the use of these tools are not provided in the text.

3.2 LINEARIZATION OF SYSTEMS

3.2.1 Function of One Variable

The Taylor series expansion of functions is applied to linearize nonlinear systems. A function $f(x)$ can be approximated by the following expression:

$$f(x) = f(x_0) + \frac{(x-x_0)}{1!}\left(\frac{df}{dx}\right)_{x_0} + \frac{(x-x_0)^2}{2!}\left(\frac{d^2f}{dx^2}\right)_{x_0} + \ldots + \frac{(x-x_0)^n}{n!}\left(\frac{d^nf}{dx^n}\right)_{x_0}, \tag{3.1}$$

where f is continuous on an interval containing the reference point x_0. Equation (3.1) is known as the Taylor series for the function $f(x)$ around $x = x_0$. The linear approximation of $f(x)$ is

$$f(x) \approx f(x_0) + \frac{(x-x_0)}{1!}\left(\frac{df}{dx}\right)_{x_0}. \tag{3.2}$$

The error from the linear approximation has the same order of magnitude as

$$\frac{(x-x_0)^2}{2!}\left(\frac{d^2f}{dx^2}\right)_{x_0}.$$

The expression $(df/dx)_{x_0}$ means the derivative of f evaluated at $x = x_0$.

Example 3.1 Linearize the function $f(x) = x^3 + 1$ around $x_0 = 1$.

Solution The first derivative of f with respect to x is calculated:

$$\frac{df(x)}{dx} = f'(x) = 3x^2. \tag{3.3}$$

The function and its derivative evaluated at $x_0 = 1$ are given by

$$f(1) = 1^3 + 1 = 2; \quad \left(\frac{df}{dx}\right)_{x_0=1} = 3(1)^2 = 3. \tag{3.4}$$

As a result, the linear approximation is

$$\begin{aligned} f(x) &\approx 2 + \frac{(x-1)}{1!} \times 3 \\ f(x) &\approx 2 + 3x - 3 \\ f(x) &\approx 3x - 1. \end{aligned} \tag{3.5}$$

The function and its estimation are plotted in Figure 3.1. It is clear that the linearization produces good results around the reference point.

Example 3.2 Linearize the function $f(x) = 5x^2 + 2x + 2$ around $x_0 = 0$.

Solution The first derivative of f with respect to x is

$$\frac{df(x)}{dx} = f'(x) = 10x + 2. \tag{3.6}$$

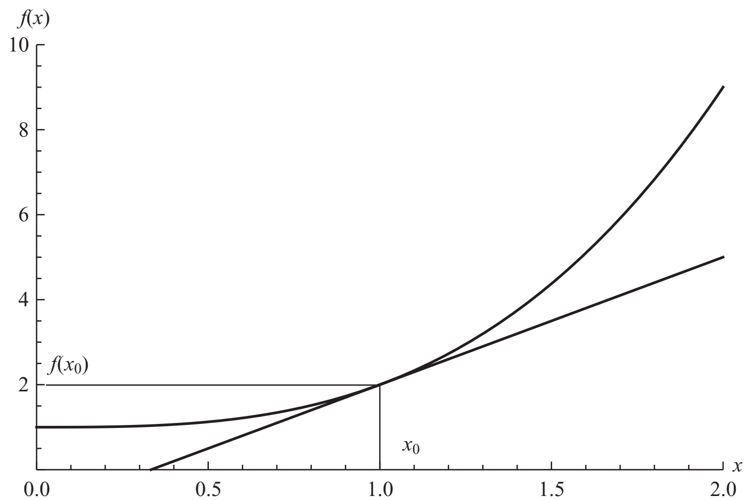

Figure 3.1. Approximation of the function $f(x) = x^3 + 1$ around $x_0 = 1$.

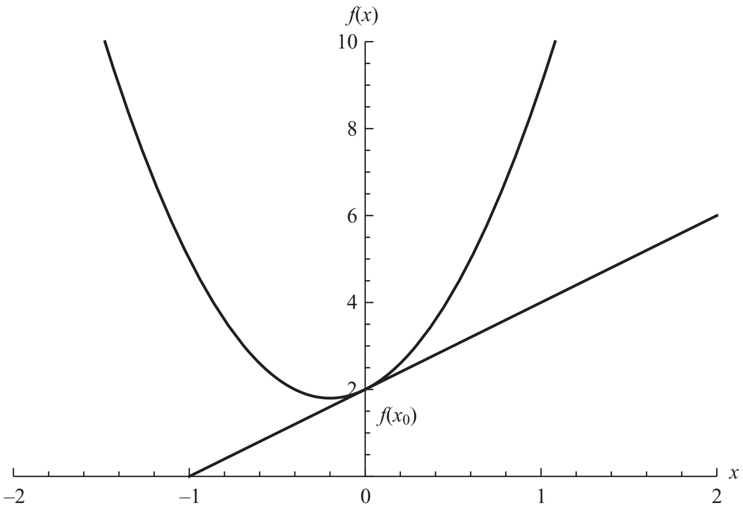

Figure 3.2. Approximation of the function $f(x) = 5x^2 + 2x + 2$ around $x_0 = 0$.

The function and its derivative evaluated at $x_0 = 0$ are given by

$$f(0) = 5(0)^2 + 2(0) + 2 = 2; \quad \left(\frac{df}{dx}\right)_{x_0=0} = 10(0) + 2 = 2. \tag{3.7}$$

As a result, the linear approximation is

$$\begin{aligned} f(x) &\approx 2 + \frac{(x-0)}{1!} \times 2 \\ f(x) &\approx 2 + 2x \\ f(x) &\approx 2(x+1). \end{aligned} \tag{3.8}$$

The function and its linear approximation are plotted in Figure 3.2. Again, the best agreement is achieved near the reference point.

3.2.2 Function of Two or More Variables

For a function of two variables, we have

$$f(x_1, x_2) \approx f(x_{10}, x_{20}) + \frac{(x_1 - x_{10})}{1!}\left(\frac{\partial f}{\partial x_1}\right)_{x_{10},x_{20}} + \frac{(x_2 - x_{20})}{1!}\left(\frac{\partial f}{\partial x^2}\right)_{x_{10},x_{20}}. \tag{3.9}$$

Equation (3.9) can be generalized for n variables:

$$f(x_1, x_2, \ldots, x_n) \approx \begin{cases} f(x_{10}, x_{20}, \ldots, x_{n0}) + \dfrac{(x_1 - x_{10})}{1!}\left(\dfrac{\partial f}{\partial x_1}\right)_{x_{10}, x_{20}, \ldots, x_{n0}} \\ + \dfrac{(x_2 - x_{20})}{1!}\left(\dfrac{\partial f}{\partial x_2}\right)_{x_{10}, x_{20}, \ldots, x_{n0}} + \ldots + \dfrac{(x_n - x_{n0})}{1!}\left(\dfrac{\partial f}{\partial x_n}\right)_{x_{10}, x_{20}, \ldots, x_{n0}} \end{cases}. \tag{3.10}$$

Example 3.3 Linearize the function $f(x, y) = 5x^2y + xy^2 + 1$ around $(x_0, y_0) = (1,1)$.

Solution The first derivative of f with respect to x is

$$\frac{\partial f(x, y)}{\partial x} = \frac{\partial\left(5x^2y + xy^2 + 1\right)}{\partial x} = 10xy + y^2. \tag{3.11}$$

The first derivative of f with respect to y is

$$\frac{\partial f(x, y)}{\partial y} = \frac{\partial\left(5x^2y + xy^2 + 1\right)}{\partial y} = 5x^2 + 2xy. \tag{3.12}$$

The function and its derivatives evaluated at $(x_0, y_0) = (1,1)$ are given by

$$\begin{aligned} f(1,1) &= f(1,1) = 5(1)^2(1) + (1)(1)^2 + 1 = 7; \\ \left(\frac{\partial f}{\partial x}\right)_{(x_0, y_0)=(1,1)} &= 10(1)(1) + (1)^2 = 11; \\ \left(\frac{\partial f}{\partial y}\right)_{(x_0, y_0)=(1,1)} &= 5(1)^2 + 2(1)(1) = 7. \end{aligned} \tag{3.13}$$

Application of Equation (3.9) with $(x_1, x_2) = (x, y)$ gives

$$\begin{aligned} f(x, y) &\approx f(x_0, y_0) + \frac{(x - x_0)}{1!}\left(\frac{\partial f}{\partial x}\right)_{x_0, y_0} + \frac{(y - y_0)}{1!}\left(\frac{\partial f}{\partial y}\right)_{x_0, y_0} \\ f(x, y) &\approx f(1,1) + \frac{(x-1)}{1!}\left(\frac{\partial f}{\partial x}\right)_{(x_0, y_0)=(1,1)} + \frac{(y-1)}{1!}\left(\frac{\partial f}{\partial y}\right)_{(x_0, y_0)=(1,1)} \\ f(x, y) &\approx 7 + (x-1)\times(11) + (y-1)\times(7) \\ f(x, y) &\approx 7 + 11x - 11 + 7y - 7 \\ f(x, y) &\approx 11x + 7y - 11. \end{aligned} \tag{3.14}$$

The function and its linear approximation are plotted in Figure 3.3.

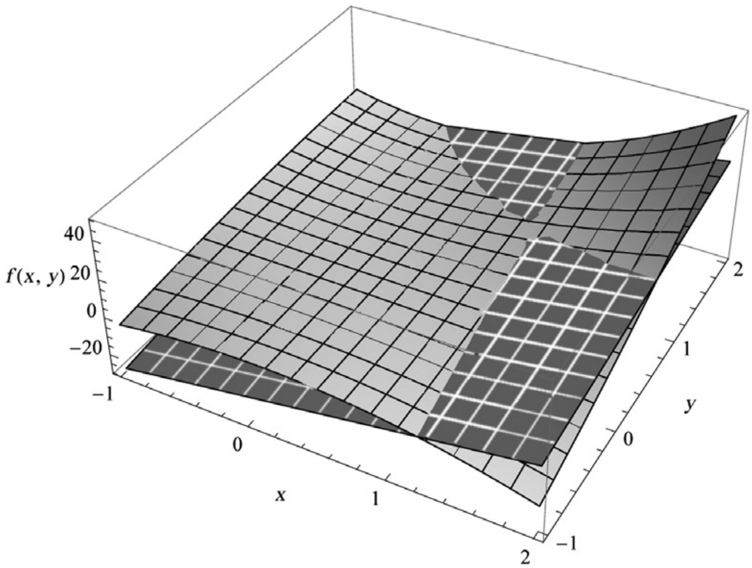

Figure 3.3. Approximation of the function $f(x,y) = 5x^2y + xy^2 + 1$ around $(x_0, y_0) = (1,1)$.

3.2.3 Nonlinear Ordinary Differential Equations (ODEs)

Linearization methods also work for nonlinear ODEs. For example, considering the first-order nonlinear differential equation $dy/dt = f(y, t)$, the linearization technique can be used to obtain an approximate solution: $y(t)$.

Example 3.4 Linearize the differential equation $dy/dt = y^2 - 2y$ around the steady-state point (s).

Solution The steady-state point is obtained by setting $dy/dt = 0$:

$$y^2 - 2y = 0. \tag{3.15}$$

The steady-state points are $y_0 = 2$ and $y_0 = 0$.

(a) When $y_0 = 2$, the first derivative of $f(y) = y^2 - 2y$ with respect to y is

$$\frac{df(y)}{dy} = 2y - 2, \tag{3.16}$$

where f is only a function of y. The function and its derivative evaluated at $y_0 = 2$ are given by

$$f(2) = (2)^2 - 2(2) = 0; \quad \left(\frac{df}{dy}\right)_{y_0=2} = 2(2) - 2 = 2. \tag{3.17}$$

The result for $f(2)$ is not surprising because $y_0 = 2$ is a steady-state value. The linear approximation around $y_0 = 2$ is

$$\begin{aligned} f(y) &\approx 0 + \frac{(y-2)}{1!} \times 2 \\ f(y) &\approx 2y - 4 \\ \frac{dy}{dt} &\approx 2y - 4. \end{aligned} \tag{3.18}$$

As a check, verify that $2y - 4$ has the same value as $y^2 - 2y$ when $y = 2$.

(b) When $y_0 = 0$, the derivative evaluated at $y_0 = 2$ is given by

$$\left(\frac{df}{dy}\right)_{y_0=0} = 2(0) - 2 = -2. \tag{3.19}$$

As a result, the linear approximation around $y_0 = 0$ is

$$\begin{aligned} f(y) &\approx 0 - \frac{(y-0)}{1!} \times 2 \\ f(y) &\approx -2y \\ \frac{dy}{dt} &\approx -2y. \end{aligned} \tag{3.20}$$

since $f(0) = 0$ (steady state). Verify that $-2y$ has the same value as $y^2 - 2y$ when $y = 0$.

Figure 3.4 shows that the linear approximations are very good around the points $y_0 = 2$ and $y_0 = 0$.

Note:

1. The lines $f_1(y) = 2y - 4$ and $f_2(y) = -2y$ are *equations of the tangent lines* to the curve $f(y) = y^2 - 2y$ at the points $y_0 = 2$ and $y_0 = 0$, respectively.
2. Some local properties of the original nonlinear system $dy/dt = y^2 - 2y$ can be analyzed using the linear ODEs $dy/dt \approx 2y - 4$ and $dy/dt \approx -2y$.

Example 3.5 Linearize the differential equation $dy/dt = y^2 - 2y + u$ (where both y and u are functions of t) around the steady-state point: $(u_0, y_0) = (0, 2)$.

Solution The first derivative of $f(y, u) = y^2 - 2y + u$ with respect to y is

$$\frac{\partial f(y)}{\partial y} = 2y - 2. \tag{3.21}$$

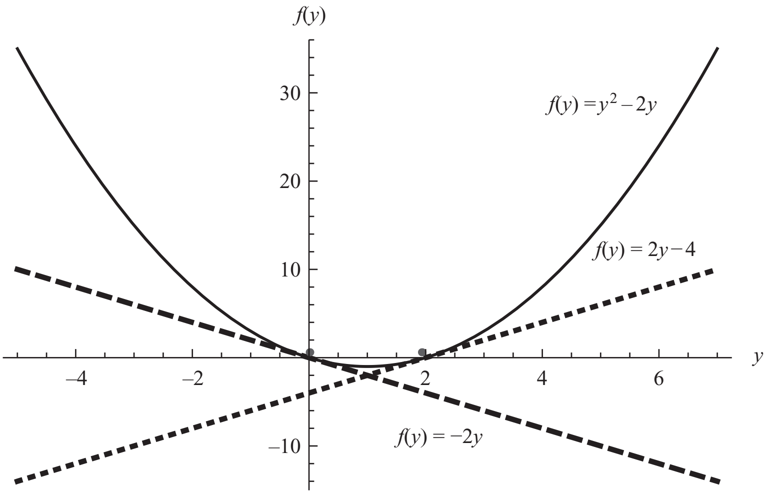

Figure 3.4. Approximation of the function $f(y) = y^2 - 2y$ around the *equilibrium points* $y_0 = 2$ and $y_0 = 0$.

The first derivative of $f(y) = y^2 - 2y + u$ with respect to u is

$$\frac{\partial f(y)}{\partial u} = 1. \tag{3.22}$$

The first derivatives of f evaluated at $u_0 = 0$ and $y_0 = 2$ are given by

$$\begin{aligned} \left(\frac{\partial f}{\partial y}\right)_{(y_0,u_0)=(2,0)} &= 2(2) - 2 = 2 \\ \left(\frac{\partial f}{\partial u}\right)_{(y_0,u_0)=(2,0)} &= 1. \end{aligned} \tag{3.23}$$

Finally, the approximation is

$$\begin{aligned} f(y,u) &\approx f(y_0,u_0) + \frac{(y-y_0)}{1!}\left(\frac{\partial f}{\partial y}\right)_{y_0,u_0} + \frac{(u-u_0)}{1!}\left(\frac{\partial f}{\partial u}\right)_{y_0,u_0} \\ f(y,u) &\approx f(2,0) + \frac{(y-2)}{1!}\left(\frac{\partial f}{\partial y}\right)_{(y_0,u_0)=(2,0)} + \frac{(u-0)}{1!}\left(\frac{\partial f}{\partial u}\right)_{(y_0,u_0)=(2,0)} \\ f(x,y) &\approx 0 + (y-2)\times(2) + (u-0)\times(1) \\ f(x,y) &\approx 2(y-2) + (u-0) \\ \frac{dy}{dt} &\approx 2(y-2) + (u-0). \end{aligned} \tag{3.24}$$

Verify that $f(2, 0) = 0$. If *deviation variables* are defined by $\tilde{y} = y - 2$ and $\tilde{u} = u - 0$ (i.e., *deviation from the equilibrium point*), we have

$$\frac{d\tilde{y}}{dt} \approx 2\tilde{y} + \tilde{u} \tag{3.25}$$

because

$$\begin{aligned} \frac{d\tilde{y}}{dt} &= \frac{d(y-2)}{dt} = \frac{dy}{dt} - \frac{d(2)}{dt} = \frac{dy}{dt} \\ \frac{d\tilde{y}}{dt} &= \frac{dy}{dt}. \end{aligned} \tag{3.26}$$

Deviation variables (i.e., $d\tilde{y}/dt \approx 2\tilde{y} + \tilde{u}$ instead of $dy/dt \approx 2(y-2) + (u-0)$) are frequently preferred in control applications where the focus is placed on how the system deviates from an operating point under the effects of disturbances.

The system $dy/dt = y^2 - 2y + u$ may describe a process with state variable y and input variable u. If we consider the system to be originally at *steady state* at time $t = 0$, a relevant question is: How does y vary with time if the input variable u changes suddenly from $u_0 = 0$ or $\tilde{u}_0 = 0$ to a point (u_{new0} or $\tilde{u}_{\text{new0}}$) in a stepwise fashion (also called *step change*)? Based on the linearization result, the system represented by

$$\frac{dy}{dt} \approx 2(y-2) + (u-0) \quad \text{or} \quad \frac{d\tilde{y}}{dt} \approx 2\tilde{y} + \tilde{u}$$

can be used to approximate the response.

3.2.4 Nonlinear Systems of ODEs

If we consider the following dynamic system:

$$\begin{aligned} \frac{dx_1}{dt} &= f_1(x_1, x_2, \ldots, x_n, u_1, u_2, \ldots, u_m) \\ \frac{dx_2}{dt} &= f_2(x_1, x_2, \ldots, x_n, u_1, u_2, \ldots, u_m) \\ &\vdots \\ \frac{dx_n}{dt} &= f_n(x_1, x_2, \ldots, x_n, u_1, u_2, \ldots, u_m) \end{aligned} \tag{3.27}$$

with n state variables (x_n) and m input variables (u_m), a linear approximation gives

$$\frac{dx_1}{dt} \approx \begin{cases} f_1(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0}) + (x_1 - x_{10})\left(\dfrac{\partial f_1}{\partial x_1}\right)_{(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0})} \\ + (x_2 - x_{20})\left(\dfrac{\partial f_1}{\partial x_2}\right)_{(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0})} + \ldots \\ + (x_n - x_{n0})\left(\dfrac{\partial f_1}{\partial x_n}\right)_{(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0})} \\ + (u_1 - u_{10})\left(\dfrac{\partial f_1}{\partial u_1}\right)_{(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0})} \\ + (u_2 - u_{20})\left(\dfrac{\partial f_1}{\partial u_2}\right)_{(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0})} + \ldots \\ + (u_m - u_{m0})\left(\dfrac{\partial f_1}{\partial u_m}\right)_{(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0})} \end{cases}$$

$$\frac{dx_2}{dt} \approx \begin{cases} f_2(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0}) + (x_1 - x_{10})\left(\dfrac{\partial f_2}{\partial x_1}\right)_{(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0})} \\ + (x_2 - x_{20})\left(\dfrac{\partial f_2}{\partial x_2}\right)_{(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0})} + \ldots \\ + (x_n - x_{n0})\left(\dfrac{\partial f_2}{\partial x_n}\right)_{(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0})} \\ + (u_1 - u_{10})\left(\dfrac{\partial f_2}{\partial u_1}\right)_{(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0})} \\ + (u_2 - u_{20})\left(\dfrac{\partial f_2}{\partial u_2}\right)_{(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0})} + \ldots \\ + (u_m - u_{m0})\left(\dfrac{\partial f_2}{\partial u_m}\right)_{(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0})} \end{cases} \tag{3.28}$$

$$\vdots$$

$$\frac{dx_n}{dt} \approx \begin{cases} f_n(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0}) + (x_1 - x_{10})\left(\dfrac{\partial f_n}{\partial x_1}\right)_{(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0})} \\ + (x_2 - x_{20})\left(\dfrac{\partial f_n}{\partial x_2}\right)_{(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0})} + \ldots \\ + (x_n - x_{n0})\left(\dfrac{\partial f_n}{\partial x_n}\right)_{(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0})} \\ + (u_1 - u_{10})\left(\dfrac{\partial f_n}{\partial u_1}\right)_{(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0})} \\ + (u_2 - u_{20})\left(\dfrac{\partial f_n}{\partial u_2}\right)_{(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0})} + \ldots \\ + (u_m - u_{m0})\left(\dfrac{\partial f_n}{\partial u_m}\right)_{(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0})} \end{cases}$$

Since the linearization is done around the steady state, we have

$$f_i(x_{10}, x_{20}, \ldots, x_{n0}, u_{10}, u_{20}, \ldots, u_{m0}) = f_i(x_{1s}, x_{2s}, \ldots, x_{ns}, u_{1s}, u_{2s}, \ldots, u_{ms}) = 0, \tag{3.29}$$

where the subscript s is used to represent a steady-state point. Using deviation variables leads to

$$\begin{aligned}
\frac{d\tilde{x}_1}{dt} &\approx \begin{array}{l} \tilde{x}_1\left(\dfrac{\partial f_1}{\partial x_1}\right)_P + \tilde{x}_2\left(\dfrac{\partial f_1}{\partial x_2}\right)_P + \ldots + \tilde{x}_n\left(\dfrac{\partial f_1}{\partial x_n}\right)_P \\ +\tilde{u}_1\left(\dfrac{\partial f_1}{\partial u_1}\right)_P + \tilde{u}_2\left(\dfrac{\partial f_1}{\partial u_2}\right)_P + \ldots + \tilde{u}_m\left(\dfrac{\partial f_1}{\partial u_m}\right)_P \end{array} \\
\frac{d\tilde{x}_2}{dt} &\approx \begin{array}{l} \tilde{x}_1\left(\dfrac{\partial f_2}{\partial x_1}\right)_P + \tilde{x}_2\left(\dfrac{\partial f_2}{\partial x_2}\right)_P + \ldots + \tilde{x}_n\left(\dfrac{\partial f_2}{\partial x_n}\right)_P \\ +\tilde{u}_1\left(\dfrac{\partial f_2}{\partial u_1}\right)_P + \tilde{u}_2\left(\dfrac{\partial f_2}{\partial u_2}\right)_P + \ldots + \tilde{u}_m\left(\dfrac{\partial f_2}{\partial u_m}\right)_P \end{array} \\
\frac{d\tilde{x}_n}{dt} &\approx \begin{array}{l} \tilde{x}_1\left(\dfrac{\partial f_n}{\partial x_1}\right)_P + \tilde{x}_2\left(\dfrac{\partial f_n}{\partial x_2}\right)_P + \ldots + \tilde{x}_n\left(\dfrac{\partial f_n}{\partial x_n}\right)_P \\ +\tilde{u}_1\left(\dfrac{\partial f_n}{\partial u_1}\right)_P + \tilde{u}_2\left(\dfrac{\partial f_n}{\partial u_2}\right)_P + \ldots + \tilde{u}_m\left(\dfrac{\partial f_n}{\partial u_m}\right)_P, \end{array}
\end{aligned} \tag{3.30}$$

where P represents the steady-state point $(x_{1s}, x_{2s}, \ldots, x_{ns}, u_{1s}, u_{2s}, \ldots, u_{ms})$. The continuous-time state-space representation of Equation (3.30) is

$$\frac{d\tilde{\mathbf{x}}}{dt} \approx \mathbf{A}\tilde{\mathbf{x}} + \mathbf{B}\tilde{\mathbf{u}} \tag{3.31}$$

with

$$\mathbf{A} = \begin{bmatrix} \left(\dfrac{\partial f_1}{\partial x_1}\right)_P & \left(\dfrac{\partial f_1}{\partial x_1}\right)_P & \cdots & \left(\dfrac{\partial f_1}{\partial x_n}\right)_P \\ \left(\dfrac{\partial f_2}{\partial x_1}\right)_P & \left(\dfrac{\partial f_2}{\partial x_1}\right)_P & \cdots & \left(\dfrac{\partial f_2}{\partial x_n}\right)_P \\ \vdots & \vdots & \vdots & \vdots \\ \left(\dfrac{\partial f_n}{\partial x_1}\right)_P & \left(\dfrac{\partial f_n}{\partial x_1}\right)_P & \cdots & \left(\dfrac{\partial f_n}{\partial x_n}\right)_P \end{bmatrix}, \tag{3.32}$$

$$\mathbf{B} = \begin{bmatrix} \left(\dfrac{\partial f_1}{\partial u_1}\right)_P & \left(\dfrac{\partial f_1}{\partial u_2}\right)_P & \cdots & \left(\dfrac{\partial f_1}{\partial u_m}\right)_P \\ \left(\dfrac{\partial f_2}{\partial u_1}\right)_P & \left(\dfrac{\partial f_2}{\partial u_2}\right)_P & \cdots & \left(\dfrac{\partial f_2}{\partial u_m}\right)_P \\ \vdots & \vdots & \vdots & \vdots \\ \left(\dfrac{\partial f_n}{\partial u_1}\right)_P & \left(\dfrac{\partial f_n}{\partial u_2}\right)_P & \cdots & \left(\dfrac{\partial f_n}{\partial u_m}\right)_P \end{bmatrix}, \tag{3.33}$$

$$\tilde{\mathbf{x}} = \begin{bmatrix} \tilde{x}_1 \\ \tilde{x}_2 \\ \vdots \\ \tilde{x}_n \end{bmatrix} \tag{3.34}$$

and

$$\tilde{\mathbf{u}} = \begin{bmatrix} \tilde{u}_1 \\ \tilde{u}_2 \\ \vdots \\ \tilde{u}_m \end{bmatrix}. \tag{3.35}$$

In addition, if the output equation is defined as

$$\begin{aligned} y_1 &= g_1(x_1, x_2, \ldots, x_n, u_1, u_2, \ldots, u_m) \\ y_2 &= g_2(x_1, x_2, \ldots, x_n, u_1, u_2, \ldots, u_m) \\ &\vdots \\ y_q &= g_q(x_1, x_2, \ldots, x_n, u_1, u_2, \ldots, u_m), \end{aligned} \tag{3.36}$$

it can be shown that

$$\tilde{\mathbf{y}} \approx \mathbf{C}\tilde{\mathbf{x}} + \mathbf{D}\tilde{\mathbf{u}}, \tag{3.37}$$

where

$$\mathbf{C} = \begin{bmatrix} \left(\frac{\partial g_1}{\partial x_1}\right)_P & \left(\frac{\partial g_1}{\partial x_2}\right)_P & \cdots & \left(\frac{\partial g_1}{\partial x_n}\right)_P \\ \left(\frac{\partial g_2}{\partial x_1}\right)_P & \left(\frac{\partial g_2}{\partial x_2}\right)_P & \cdots & \left(\frac{\partial g_2}{\partial x_n}\right)_P \\ \vdots & \vdots & \vdots & \vdots \\ \left(\frac{\partial g_q}{\partial x_1}\right)_P & \left(\frac{\partial g_q}{\partial x_2}\right)_P & \cdots & \left(\frac{\partial g_q}{\partial x_n}\right)_P \end{bmatrix} \tag{3.38}$$

and

$$\mathbf{D} = \begin{bmatrix} \left(\frac{\partial g_1}{\partial u_1}\right)_P & \left(\frac{\partial g_1}{\partial u_2}\right)_P & \cdots & \left(\frac{\partial g_1}{\partial u_m}\right)_P \\ \left(\frac{\partial g_2}{\partial u_1}\right)_P & \left(\frac{\partial g_2}{\partial u_2}\right)_P & \cdots & \left(\frac{\partial g_2}{\partial u_m}\right)_P \\ \vdots & \vdots & \vdots & \vdots \\ \left(\frac{\partial g_q}{\partial u_1}\right)_P & \left(\frac{\partial g_q}{\partial u_2}\right)_P & \cdots & \left(\frac{\partial g_q}{\partial u_m}\right)_P \end{bmatrix} \tag{3.39}$$

The q output variables are

$$\tilde{\mathbf{y}} = \begin{bmatrix} \tilde{y}_1 \\ \tilde{y}_2 \\ \vdots \\ \tilde{y}_q \end{bmatrix}. \tag{3.40}$$

The size of the matrices (called *Jacobian* matrices) are $\mathbf{A}(n \times n)$, $\mathbf{B}(n \times m)$, $\mathbf{C}(q \times n)$, and $\mathbf{D}(q \times m)$. In this notation, the number of rows in a matrix of size $i \times j$ is i and the number of columns is j.

3.3 GLYCOLYTIC OSCILLATION

The glycolytic pathway is used for the degradation of glucose to pyruvate and is employed by all major groups of microorganisms. *Adenosine triphosphate* (ATP, energy currency of the cell) is also produced. The process can be represented by the following equation [1]:

$$\mathrm{C_6H_{12}O_6 + 2NAD^+ + 2ADP + 2P}_i \rightarrow \mathrm{2C_3H_4O_3 + 2ATP + 2NADH + 2H^+} \tag{3.41}$$

Glucose: $C_6H_{12}O_6$
Nicotinamide adenine dinucleotide: NAD^+
Adenosine diphosphate: ADP
Phosphate group: P_i
Pyruvate: $CH_3COCOOH$
Adenosine triphosphate: ATP
Nicotinamide adenine dinucleotide, reduced: NADH
Hydrogen ion: H^+.

Because the reactions occur in the presence or absence of oxygen, the pathway is utilized by yeast in the production of alcohol. The mechanism is usually invoked to illustrate sustained oscillation in a metabolic pathway. A simplified system of two differential equations, involving adenosine diphosphate (normalized concentration x), a glycolytic intermediate, and fructose-6-phosphate (normalized concentration y), is used here to describe the oscillation [2, 3]:

$$\frac{dx}{dt} = -x + \alpha y + x^2 y \tag{3.42}$$

and

$$\frac{dy}{dt} = \beta - \alpha y + x^2 y, \tag{3.43}$$

where α and β are positive numbers. A first step in studying process stability (to be discussed in later chapters) is to linearize the model around an equilibrium point. In this case, the matrix **A** from Equation (3.32) is

$$\mathbf{A} = \begin{bmatrix} \left(\frac{\partial f_1}{\partial x}\right)_{x_s, y_s} & \left(\frac{\partial f_1}{\partial y}\right)_{x_s, y_s} \\ \left(\frac{\partial f_2}{\partial x}\right)_{x_s, y_s} & \left(\frac{\partial f_2}{\partial y}\right)_{x_s, y_s} \end{bmatrix}, \tag{3.44}$$

where

$$f_1(x, y) = -x + \alpha y + x^2 y \tag{3.45}$$

and

$$f_2(x, y) = \beta - \alpha y + x^2 y. \tag{3.46}$$

To calculate the equilibrium points, we set $f_1(x, y) = 0$ and $f_2(x, y) = 0$ to give

$$-x + \alpha y + x^2 y = 0 \tag{3.47}$$

and

$$\beta - \alpha y - x^2 y = 0. \tag{3.48}$$

After adding Equations (3.47) and (3.48), we obtain $x_s = \beta$; y is calculated by replacing x in Equation (3.47):

$$y_s = \frac{\beta}{\alpha + \beta^2},$$

where "s" denotes a steady-state value. The matrix **A** is

$$\mathbf{A} = \begin{bmatrix} -1 + 2x_s y_s & x_s^2 + \alpha \\ -2x_s y_s & -x_s^2 - \alpha \end{bmatrix}. \tag{3.49}$$

Replacing the steady-state point in **A** gives

$$\mathbf{A} = \begin{bmatrix} -1 + \frac{2\beta^2}{\alpha + \beta^2} & \alpha + \beta^2 \\ -\frac{2\beta^2}{\alpha + \beta^2} & -\alpha - \beta^2 \end{bmatrix} = \begin{bmatrix} \frac{-\alpha + \beta^2}{\alpha + \beta^2} & \alpha + \beta^2 \\ -\frac{2\beta^2}{\alpha + \beta^2} & -\alpha - \beta^2 \end{bmatrix}. \tag{3.50}$$

Therefore,

$$\frac{d\tilde{\mathbf{x}}}{dt} \approx \begin{bmatrix} \frac{-\alpha+\beta^2}{\alpha+\beta^2} & \alpha+\beta^2 \\ -\frac{2\beta^2}{\alpha+\beta^2} & -\alpha-\beta^2 \end{bmatrix} \tilde{\mathbf{x}}$$
$$\begin{bmatrix} \frac{d\tilde{x}}{dt} \\ \frac{d\tilde{y}}{dt} \end{bmatrix} \approx \begin{bmatrix} \frac{-\alpha+\beta^2}{\alpha+\beta^2} & \alpha+\beta^2 \\ -\frac{2\beta^2}{\alpha+\beta^2} & -\alpha-\beta^2 \end{bmatrix} \begin{bmatrix} \tilde{x} \\ \tilde{y} \end{bmatrix} \tag{3.51}$$

or

$$\begin{aligned} \frac{d\tilde{x}}{dt} &= \left(\frac{-\alpha+\beta^2}{\alpha+\beta^2}\right)\tilde{x} + \left(\alpha+\beta^2\right)\tilde{y} \\ \frac{d\tilde{y}}{dt} &= \left(-\frac{2\beta^2}{\alpha+\beta^2}\right)\tilde{x} - \left(\alpha+\beta^2\right)\tilde{y} \end{aligned} \tag{3.52}$$

with $\tilde{x} = x - x_s$ and $\tilde{y} = y - y_s$.

3.4 HODGKIN–HUXLEY MODEL

The flow of current through the membrane of a nerve axon can be investigated using the Hodgkin and Huxley (HH) model. This mathematical model was proposed in 1952 to describe the electrical excitation of the squid giant axon [4]. Current is transported through the membrane either by charging the membrane capacity or by transporting ions through resistances connected in parallel with the capacity [4]. Four differential equations are written to describe the model:

$$\begin{aligned} C_{\mathrm{M}}\frac{dV}{dt} &= I_{\mathrm{ext}} - \left[\bar{g}_{\mathrm{Na}} m^3 h (V + V_{\mathrm{E}} - V_{\mathrm{Na}}) + \bar{g}_{\mathrm{K}} n^4 (V + V_{\mathrm{E}} - V_{\mathrm{K}}) + g_I (V + V_{\mathrm{E}} - V_I)\right] \\ \frac{dm}{dt} &= [\alpha_m(V)(1-m) - \beta_m(V)m] \\ \frac{dh}{dt} &= [\alpha_h(V)(1-h) - \beta_h(V)h] \\ \frac{dn}{dt} &= [\alpha_n(V)(1-n) - \beta_n(V)n], \end{aligned} \tag{3.53}$$

where the parameters and variables are

V: membrane potential (mV)
t: time (ms)
m: dimensionless sodium activation
h: dimensionless sodium inactivation
n: dimensionless potassium activation
V_{Na}: equilibrium potential of sodium (mV)
V_K: equilibrium potential of potassium (mV)
V_I: equilibrium potential of leak current (mV)
V_E: induced transmembrane potential (mV)
$\bar{g}_{Na}$: maximum sodium conductance (mmho/cm^2)
$\bar{g}_K$: maximum potassium conductance (mmho/cm^2)
g_I: maximum conductance for the leak current I (mmho/cm^2)
I_{ext}: externally applied current (μA/cm^2)
C_M: membrane capacity per unit area (μF/cm^2).

The parameters $\alpha_m(V)$, $\beta_m(V)$, $\alpha_h(V)$, $\beta_h(V)$, $\alpha_n(V)$, and $\beta_n(V)$ are nonlinear functions of the membrane potential [4]:

$$\begin{aligned}
\alpha_m(V) &= 0.1(25.0-V)/[\exp((25.0-V)/10.0)-1.0] \\
\beta_m(V) &= 4.0\exp(-V/18.0) \\
\alpha_h(V) &= 0.07\exp(-V/20.0) \\
\beta_h(V) &= 1.0/[\exp((-V+30.0)/10.0)+1.0] \\
\alpha_n(V) &= 0.01(10.0-V)/[\exp((10.0-V)/10.0)-1.0] \\
\beta_n(V) &= 0.125\exp(-V/80.0).
\end{aligned} \tag{3.54}$$

This model has been used to study the dynamic behavior of neurons and to reveal oscillatory or nonoscillatory patterns depending on the model parameter values. The state variables are V, m, h, and n; I_{ext} is the input variable. A simpler set of equations that captures the dynamic characteristics of the HH model is the FitzHugh–Nagumo model [3]:

$$\begin{aligned}
\frac{dV}{dt} &= c\left(V+W-\frac{V^3}{3}+I_{ext}\right) \\
\frac{dW}{dt} &= -\frac{1}{c}(V-a+bW),
\end{aligned} \tag{3.55}$$

where W is a recovery parameter corresponding to combined forces that are apt to return the axonal membrane to a resting state [3]. The parameters are subject to the following constraints [5]:

$$1-\frac{2b}{3}<a<1, \quad 0<b<1, \quad b<c^2. \tag{3.56}$$

Consider the following parameters: $a = 0.7$, $b = 0.8$, and $c = 3$; then Equation (3.55) becomes

$$\begin{aligned}\frac{dV}{dt}&=3\left(V+W-\frac{V^3}{3}+I_{\text{ext}}\right)\\ \frac{dW}{dt}&=-\frac{1}{3}(V-0.7+0.8W).\end{aligned} \tag{3.57}$$

To calculate the steady-state values for $I_{\text{ext}} = 0$, Equation (3.57) is written as

$$\begin{aligned}f_1&=3\left(V+W-\frac{V^3}{3}+I_{\text{ext}}\right)=0\\ f_2&=-\frac{1}{3}(V-0.7+0.8W)=0\end{aligned} \tag{3.58}$$

or

$$\begin{aligned}V+W-\frac{V^3}{3}&=0\\ V+0.8W&=0.7.\end{aligned} \tag{3.59}$$

The steady-state points are

$$\begin{aligned}(V_s, W_s, I_{\text{exts}})&=(1.19941, -0.62426, 0)\\ (V_s, W_s, I_{\text{exts}})&=(-0.599704+1.35238i, 1.62463-1.69048i, 0)\\ (V_s, W_s, I_{\text{exts}})&=(-0.599704-1.35238i, 1.62463+1.69048i, 0).\end{aligned} \tag{3.60}$$

Linearization of Equation (3.57) around $(V_s, W_s, I_{exts}) = (1.19941, -0.62426, 0)$ leads to the following $\mathbf{A}$ matrix:

$$\mathbf{A}=\begin{bmatrix}\left(\frac{\partial f_1}{\partial V}\right)_{V_s,W_s,I_{\text{exts}}} & \left(\frac{\partial f_1}{\partial W}\right)_{V_s,W_s,I_{\text{exts}}}\\ \left(\frac{\partial f_2}{\partial V}\right)_{V_s,W_s,I_{\text{exts}}} & \left(\frac{\partial f_2}{\partial W}\right)_{V_s,W_s,I_{\text{exts}}}\end{bmatrix} \tag{3.61}$$

or

$$\mathbf{A}=\begin{bmatrix}3(1-V_s^2) & 3\\ -\frac{1}{3} & -\frac{4}{15}\end{bmatrix}. \tag{3.62}$$

Similarly, the matrix **B** is

$$\mathbf{B} = \begin{bmatrix} \left(\dfrac{\partial f_1}{\partial V}\right)_{V_s, W_s, I_{\text{exts}}} \\ \left(\dfrac{\partial f_2}{\partial W}\right)_{V_s, W_s, I_{\text{exts}}} \end{bmatrix} \tag{3.63}$$

or

$$\mathbf{B} = \begin{bmatrix} 3 \\ 0 \end{bmatrix}. \tag{3.64}$$

After substituting $(V_s, W_s, I_{exts}) = (1.19941, -0.62426, 0)$ into **A** and **B**, we obtain

$$\begin{aligned} \frac{d\tilde{\mathbf{x}}}{dt} &\approx \begin{bmatrix} -1.31574 & 3 \\ -\dfrac{1}{3} & -\dfrac{4}{15} \end{bmatrix} \tilde{\mathbf{x}} + \begin{bmatrix} 3 \\ 0 \end{bmatrix} \tilde{u} \\ \begin{bmatrix} \dfrac{d\tilde{V}}{dt} \\ \dfrac{d\tilde{W}}{dt} \end{bmatrix} &\approx \begin{bmatrix} -1.31574 & 3 \\ -\dfrac{1}{3} & -\dfrac{4}{15} \end{bmatrix} \begin{bmatrix} \tilde{V} \\ \tilde{W} \end{bmatrix} + \begin{bmatrix} 3 \\ 0 \end{bmatrix} \tilde{u}, \end{aligned} \tag{3.65}$$

and finally,

$$\begin{aligned} \frac{d\tilde{V}}{dt} &\approx -1.31574\tilde{V} + 3\tilde{W} + 3\tilde{u} \\ \frac{d\tilde{W}}{dt} &\approx -\frac{1}{3}\tilde{V} - \frac{4}{15}\tilde{W} \end{aligned} \tag{3.66}$$

with $\tilde{V} = V - V_s$, $\tilde{W} = W - W_s$ and $\tilde{u} = I_{\text{ext}} - I_{\text{exts}}$.

3.5 SUMMARY

The concepts of linearization and deviations were introduced. These methods help convert a set of nonlinear equations into a linear system. For a dynamic system, the original process is linearized around a steady-state (or equilibrium) point and can be written in a state-space form that involves Jacobian matrices evaluated at this point. Two examples, the glycolytic pathway and a Hodgkin–Huxley model, were presented to illustrate how to apply the method.

PROBLEMS

3.1. Linearize the function $f(x) = 2x^3 + 3$ around $x_0 = 2$.

3.2. Linearize the function $f(x, y) = xy^3 + 5xy + 3$ around $(x_0, y_0) = (0,1)$.

3.3. Linearize the differential equation

$$A\frac{dh}{dt} = F_{\text{in}} - \beta\sqrt{h}$$

around the steady-state point $F_{\text{in,ss}}$ and h_{ss}.

3.4. Linearize the differential equation

$$\begin{aligned}\frac{dx}{dt} &= y - \alpha\frac{x^2}{x^2+1}\\ \frac{dy}{dt} &= x - y\end{aligned}$$

around the steady-state point (x_0, y_0).

3.5. The dynamic equation for the concentration in a continuous stirred-tank reactor is given by

$$V\frac{dC}{dt} = F_{\text{in}}(C_{\text{in}} - C) - k_0 e^{-E/RT} CV,$$

where F_{in}, V, and C_{in} are constant. The temperature (T) and concentration (C) are state variables. Linearize the differential equation around the steady-state point (C_0, T_0).

3.6. The component balance equations in a continuous enzyme reactor are given by

$$\begin{aligned}V\frac{dS}{dt} &= F_S S_{\text{in}} - F_1 S - r_s V\\ V\frac{dP}{dt} &= -F_1 P + r_P V\\ V\frac{dE}{dt} &= F_E E_{\text{in}} - F_1 E\end{aligned}$$

with

$$\begin{aligned}r_S &= v_{\text{m}}\frac{S}{K_{\text{M}} + S}\\ v_{\text{m}} &= kE\\ r_P &= 2r_S,\end{aligned}$$

where the concentrations of substrate (S), enzyme (E), and product (P) represent the state variables. Linearize the differential equations around the steady-state point (S_0, P_0, E_0). The flows are held constant; the volume is V_0.

3.7. A kinetic model of enzyme catalysis is given by

$$\frac{d\sigma_1}{d\theta} = v_1 - \frac{\sigma_1 \sigma_2^\gamma}{1+\sigma_2^\gamma(1+\sigma_1)}$$

$$\frac{d\sigma_2}{d\theta} = \alpha_2 \left(\frac{\sigma_1 \sigma_2^\gamma}{1+\sigma_2^\gamma(1+\sigma_1)} - \chi_2 \sigma_2 \right),$$

where σ_1 and σ_2 are the relative substrate and product concentrations, respectively. Linearize the differential equations around the steady-state point (σ_{10}, σ_{20}).

3.8. A system describing the concentrations of an activator (x) and an inhibitor (y) is given by (Gierer–Meinhardt model)

$$\frac{dx}{dt} = \rho + \frac{cx^2}{y} - \mu x$$

$$\frac{dy}{dt} = dx^2 - \gamma y.$$

(a) Calculate the steady-state concentrations.

(b) Linearize the differential equations around the steady-state concentrations.

3.9. The cell (C_x) and substrate (C_s) concentrations in a chemostat are described by

$$\frac{dC_x}{dt} = (\mu - D)C_x$$

and

$$\frac{dC_s}{dt} = D(C_{s0} - C_s) - \frac{\mu C_x}{Y_{x/s}},$$

where $Y_{x/s}$ is the yield coefficient. The specific growth rate is

$$\mu = \frac{\mu_{\max} C_s}{K_s + C_s + \dfrac{C_s^2}{K_I}}.$$

Linearize the differential equations around the steady-state point ($C_{x,ss}$, $C_{s,ss}$).

3.10. Redo Problem 3.9 when the specific growth rate is

$$\mu = \frac{\mu_{\max} C_s}{K_s + C_s}\left(1 - \frac{C_s}{C_{sm}}\right)^n.$$

REFERENCES

1. Prescott LM, Harley JP, Klein DA. *Microbiology*, 3rd ed. Dubuque, IA: Wm. C. Brown Publishers, 1996.
2. Sel'kov EE. Self-oscillations in glycolysis. 1. A simple kinetic model. *European Journal of Biochemistry* 1968; 4:79–86.
3. Edelstein-Keshet L. *Mathematical Models in Biology*. New York: Random House, 1988.
4. Hodgkin A, Huxley A. A quantitative description of membrane current and its application to conduction and excitation in nerve. *Journal of Physiology* 1952; 117:500–544.
5. Fitzhugh R. Impulses and physiological states in theoretical models of nerve membrane. *Biophysical Journal* 1961; 1:445–466.