3.2 ANALYSIS OF A LINEAR, OPEN LOOP CONTROL SYSTEM

The methods of linear control theory are probably best presented by considering a specific example which is almost trivially simple but which will introduce techniques that generalize to more complicated problems. We consider Goodwin's model of the control of protein synthesis (Goodwin, 1965; Maynard Smith, 1968). Let $x_1(t)$ be the concentration of messenger RNA (mRNA), x_1, at time t. This messenger directs the synthesis of an enzyme, x_2, whose concentration is denoted by $x_2(t)$. This enzyme catalyzes a reaction producing a product, x_3, of concentration $x_3(t)$. The flow of information is mRNA to enzyme to enzyme product.

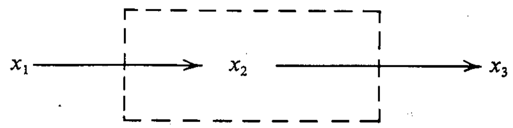

Figure 3.2.1. Diagrammatic representation of the conversion of compound x_1 to x_3 with a single intermediate x_2.

The **input** is the function of time $x_1(t)$. In general the input is a stimulus applied to a control system by an external agency. In this example we suppose that the concentration $x_1(t)$ will be controlled and that the concentration $x_3(t)$, the **output**, will be measured. It is common practice to represent control systems by block diagrams. A block diagram is a graphical representation of the relation between input, output and the components of a system. MacFarlane (1970; Section 3.3) gives the symbol conventions for more complicated systems. While the block

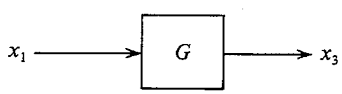

Figure 3.2.2. Block diagram representing the conversion of x_1 to x_3 as an open loop input–output relationship.

diagram is trivial for the example system, the technique is valuable for studying more complicated circuits where block diagrams can identify simpler equivalent circuits and facilitate the transformation of a control system to one that has already been analyzed. The block diagram has evolved into the **signal flow graph**. For a discussion of the well developed flow graph transformation techniques see DiStefano *et al.* (1967, Chapter 8).

The output x_3 depends on x_2, and hence on x_1. Neither x_2 or x_3 regulate their respective synthesis rates; there is no feedback. This is an **open-loop control system**. In the mathematical literature this is also referred to as components in a cascade. This can cause an unfortunate confusion with cascaded enzymatic mechanisms which can include feedback (Savageau, 1976, Chapter 13).

The x_1 to x_3 input–output relation is assumed to be **linear**. This means that the **law of superposition** (compare the discussion following (A.1.39)) is obeyed. Suppose input x_a gives output y_a and input x_b gives output y_b. If input $k_a x_a + k_b x_b$ gives output $k_a y_a + k_b y_b$ for all inputs x_a, x_b, and all constants k_a and k_b, then the system is linear (i.e. it obeys the law of superposition). In constructing a mathematical model of x_1 to x_3 conversion, it is supposed that the rate of enzyme synthesis is directly proportional to mRNA concentration and the synthesis of product x_3 is directly proportional to enzyme concentration. Also it is assumed that x_2 and x_3 leave the reaction system by transport or decomposition at a rate directly proportional to their concentrations. Translating these assumptions into differential equation form gives

$$dx_2(t)/dt = b_1x_1(t) - b_2x_2(t), \qquad dx_3(t)/dt = b_2x_2(t) - b_3x_3(t). \tag{1}$$

Here the initial conditions $x_2(0)$ and $x_3(0)$ are regarded as given, while b_1, b_2 and b_3 are *distinct positive* constants. Clearly this model is an enormous simplification of the truth, since translation actually involves thousands of separate nonlinear reaction steps and since the production of $x_3(t)$ should follow a nonlinear enzymatic rate law. The model should be regarded as a crude first approximation. (It would be possible to eliminate some of the parameters by transforming the problem to nondimensional variables; however, for this simple problem this process is not necessary.) This differential equation is simple enough to be solved explicitly by any of several techniques. The Laplace transform method is chosen because it will be useful in considering more complicated systems. Let $f(t)$ be a real function of time defined for $t>0$; its Laplace transform, $L[f(t)]$, is defined as

◆◆ $$L[f(t)] \equiv \hat{f}(s) \equiv \int_0^\infty \exp(-st)f(t)\,dt. \tag{2}$$

Properties of the Laplace transform

Example 3.2.1. Find the Laplace transform for the step function, ramp input and the exponential.

Solution:
The step function is:

$$f_s(t)=\begin{cases}K & t\geqslant 0\\ 0 & t<0.\end{cases}$$

$$L[f_s(t)]=\hat{f}_s(s)=\int_0^\infty K\exp(-st)\,dt$$

$$=-\frac{K\exp(-st)}{s}\Big|_0^\infty=K/s.$$

The ramp input is

$$f_r(t)=\begin{cases}Kt & t\geqslant 0\\ 0 & t<0.\end{cases}$$

Using the integration by parts formula (A.1.127), we find that

$$L[f_r(t)]=\hat{f}_r(s)=\int_0^\infty Kt\exp(-st)\,dt$$

$$=\frac{K[\exp(-st)](-st-1)}{s^2}\Big|_0^\infty=\frac{K}{s^2}.$$

The exponential input is given by

$$f_e(t)=\begin{cases}\exp(-\alpha t) & t\geqslant 0\\ 0 & t<0.\end{cases}$$

$$L[f_e(t)]=\hat{f}_e(s)=\int_0^\infty \exp(-\alpha t)\exp(-st)\,dt$$

$$=\frac{-1}{s+\alpha}\exp[-(s+\alpha)]t\Big|_0^\infty=\frac{1}{s+\alpha}.$$

In practice one can consult a table of Laplace transforms (Bateman, 1954) and thus avoid performing tiresome integrals. The connection between the Laplace transform and differential equations is established by the following three results (DiStefano *et al.*, 1967).

Example 3.2.2. Show that the Laplace transform is a linear operator.

Solution:
We begin with the definition of a **linear operator** (compare (A.1.39)). An operator G acting on a class of objects $\{x_j\}$ is linear if it obeys the law of superposition, i.e.

$$G(k_ax_a+k_bx_b)=k_aG(x_a)+k_bG(x_b);$$

for all constants k_a and k_b and all objects x_a and x_b in the set $\{x_j\}$.

$$L[k_af_a(t)+k_bf_b(t)]$$

$$=\int_0^\infty (k_af_a(t)+k_bf_b(t))\exp(-st)\,dt$$

$$=k_a\int_0^\infty f_a(t)\exp(-st)\,dt+k_b\int_0^\infty f_b(t)\exp(-st)\,dt$$

$$=k_aL[f_a(t)]+k_bL[f_b(t)],$$

so L is a linear operator.

Example 3.2.3. Demonstrate that the Laplace transform of the derivative of a function is related to the Laplace transform of the function itself by

$$L[df/dt]=sL[f(t)]-f(0).$$

Solution:
This is most easily shown by using integration by parts

$$\int_0^\infty u\,dv=uv\Big|_0^\infty-\int_0^\infty v\,du.$$

$$L[df/dt]=\int_0^\infty \exp(-st)\frac{df}{dt}\,dt$$

$$=\exp(-st)f(t)\Big|_0^\infty+s\int_0^\infty f(t)\exp(-st)\,dt.$$

$$L[df/dt]=sL[f(t)]-f(0).$$

Example 3.2.4. Show that the Laplace transform of the integral of a function is related to the Laplace transform of the function itself by

$$L\left[\int_0^t f(\tau)\,d\tau\right]=\frac{L[f(t)]}{s}.$$

Solution:
Again use integration by parts:

$$\int_0^\infty u\, dv = uv \Big|_0^\infty - \int_0^\infty v\, du.$$

$$u = \exp(-st), \qquad dv = f(t)\, dt, \qquad v = \int_0^t f(\tau)\, d\tau.$$

$$\int_0^\infty \exp(-st) f(t)\, dt = \left\{\exp(-st) \int_0^t f(\tau)\, d\tau\right\} \Big|_0^\infty$$
$$- \int_0^\infty \int_0^t f(\tau)\, d\tau (-s) \exp(-st)\, dt.$$

$$L[f(t)] = s \int_0^\infty \left(\int_0^t f(\tau)\, d\tau\right) \exp(-st)\, dt$$
$$= sL\left[\int_0^t f(\tau)\, d\tau\right].$$

The Laplace transform will now be used to solve the differential equation (3.2.1). Taking the transform of both sides of each equation gives

$$s\hat{x}_2(s) - x_2(0) = b_1\hat{x}_1(s) - b_2\hat{x}_2(s),$$

$$s\hat{x}_3(s) - x_3(0) = b_2\hat{x}_2(s) - b_3\hat{x}_3(s).$$

Using the first equation it is possible to eliminate $\hat{x}_2$ and thus find $\hat{x}_3$ as a function of $\hat{x}_1$. *This demonstrates the principal advantage of the Laplace transform method: a differential equation problem has been reduced to an algebraic manipulation.*

$$\hat{x}_3(s) = \frac{b_1 b_2 \hat{x}_1(s)}{(s+b_2)(s+b_3)} + \frac{b_2 x_2(0)}{(s+b_2)(s+b_3)} + \frac{x_3(0)}{s+b_3}.$$

Input–output relations of this form are particularly common. Functions that can be expressed as the ratio of polynomials are called **rational functions**. If the degree of the denominator is greater than the degree of the numerator, they are termed **proper rational functions**. Having determined $\hat{x}_3(s)$, the next step is to find $x_3(t)$. This requires the inverse Laplace transform, L^{-1}.

$$L^{-1}[\hat{f}(s)] = f(t).$$

Like L, the inverse transform has an integral representation; however, its use requires an understanding of contour integration in the complex plane. The usual practice – using tables – will be followed here. L^{-1} is a linear operator, so the solution $x_3(t)$ naturally divides itself into two parts: one dependent on the input function x_1 and the other dependent on the initial conditions $x_2(0)$ and $x_3(0)$.

$$x_3(t) = L^{-1}[\hat{x}_3(s)]$$
$$= L^{-1}\left[\frac{b_1 b_2 \hat{x}_1(s)}{(s+b_2)(s+b_3)}\right] + L^{-1}\left[\frac{b_2 x_2(0)}{(s+b_2)(s+b_3)} + \frac{x_3(0)}{s+b_3}\right].$$

The contribution to the solution of a linear differential equation that depends on the input function is the **input response** (IR) or the **forced response**. The part that depends on the initial conditions is the **initial condition response** (ICR) or the **free response**.

The initial condition response is particularly simple and is examined first. Recalling that b_2 and b_3 are assumed to be unequal, the usual partial fraction expansion (see Appendix Section A.2) gives:

$$\frac{1}{(s+b_2)(s+b_3)} = \left(\frac{1}{b_3-b_2}\right)\left(\frac{1}{s+b_2}\right) + \left(\frac{1}{b_2-b_3}\right)\left(\frac{1}{s+b_3}\right).$$

Using the linearity of L^{-1} one finds the following restatement of the initial condition response:

$$\mathrm{ICR} = L^{-1}\left[\frac{b_2 x_2(0)}{(s+b_2)(s+b_3)} + \frac{x_3(0)}{s+b_3}\right]$$
$$= L^{-1}\left[\frac{b_2 x_2(0)}{(b_3-b_2)(s+b_2)} + \frac{b_2 x_2(0)}{(b_2-b_3)(s+b_3)} + \frac{x_3(0)}{s+b_3}\right]$$
$$= \frac{b_2 x_2(0)}{b_3-b_2} L^{-1}\left(\frac{1}{s+b_2}\right) + \frac{b_2 x_2(0)}{b_2-b_3} L^{-1}\left(\frac{1}{s+b_3}\right)$$
$$+ x_3(0) L^{-1}\left(\frac{1}{s+b_3}\right).$$

In Example 3.2.1 the Laplace transform of the exponential was derived.

$$L[\exp(-\alpha t)] = 1/(s+\alpha).$$

Applying the inverse Laplace transform to each side of the equation gives

$$\exp(-\alpha t) = L^{-1}L[\exp(-\alpha t)] = L^{-1}[1/(s+\alpha)].$$

The initial condition response can now be stated.

$$\mathrm{ICR} = \frac{b_2 x_2(0)}{b_3-b_2} \exp(-b_2 t) + \frac{b_2 x_2(0)}{b_2-b_3}$$
$$\times \exp(-b_3 t) + x_3(0) \exp(-b_3 t).$$

Note that the ICR tends exponentially to zero. For this reason the ICR is usually neglected by assuming zero initial values for all of the variables. We now state the final value theorem. Using this, it is possible to show that ICR$\to 0$ without explicitly evaluating the inverse of the Laplace transform $\hat{\text{ICR}}(s)$.

Example 3.2.5. Final value theorem.
Let $f(t)$ have Laplace transform $\hat{f}(s)$. Show that if $\lim_{t\to\infty} f(t)$ exists, then

$$\lim_{t\to\infty} f(t) = \lim_{s\to 0} s\hat{f}(s),$$

Solution:
Example 3.2.3 gives

$$L[df/dt] = s\hat{f}(s) - f(0), \qquad \int_0^\infty \frac{df}{dt} \exp(-st)\, dt = s\hat{f}(s) - f(0).$$

Take the limit $s\to 0$ on each side ($\exp(-st)\to 1$):

$$\lim_{s\to 0} \int_0^\infty \frac{df}{dt} \exp(-st)\, dt = \int_0^\infty \frac{df}{dt}\, dt = \lim_{s\to 0} s\hat{f}(s) - f(0),$$

$$f(t)\Big|_0^\infty = \lim_{t\to\infty} f(t) - f(0) = \lim_{s\to 0} s\hat{f}(s) - f(0),$$

$$\lim_{t\to\infty} f(t) = \lim_{s\to 0} s\hat{f}(s).$$

The final value theorem can easily be applied to the initial condition response.

$$\lim_{t\to\infty} \text{ICR}(t) = \lim_{s\to 0} s\hat{\text{ICR}}(s)$$

$$= \lim_{s\to 0} \left[\frac{sb_2 x_2(0)}{(s+b_2)(s+b_3)} + \frac{sx_3(0)}{s+b_3}\right] = 0.$$

Because the initial condition response is short lived, attention is usually directed to the input response. As an example $x_3(t)$ is found for the case where $x_2(0) = x_3(0) = 0$ and $x_1(t)$ is a step function, i.e.

$$x_1(t) = \begin{cases} K & t \geq 0 \\ 0 & t < 0. \end{cases}$$

Since $x_2(0) = x_3(0) = 0$,

$$x_3(t) = L^{-1}\left[\frac{b_1 b_2 \hat{x}_1(s)}{(s+b_2)(s+b_3)}\right].$$

Using Example 3.2.1 we find that $\hat{x}_1(s) = K/s$ so

$$x_3(t) = L^{-1}\left[\frac{b_1 b_2 K}{s(s+b_2)(s+b_3)}\right].$$

Again a partial fraction expansion is used:

$$\frac{1}{s(s+b_2)(s+b_3)} = \frac{1}{b_2 b_3 s} + \frac{1}{b_2(b_2-b_3)(s+b_2)} + \frac{1}{b_3(b_3-b_2)(s+b_3)},$$

$$x_3(t) = \frac{Kb_1}{b_3} L^{-1}\left(\frac{1}{s}\right) + \frac{Kb_1}{b_2-b_3} L^{-1}\left(\frac{1}{s+b_2}\right) + \frac{Kb_1 b_2}{b_3(b_3-b_2)} L^{-1}\left(\frac{1}{s+b_3}\right),$$

$$x_3(t) = \frac{Kb_1}{b_3} + \frac{Kb_1}{b_2-b_3} \exp(-b_2 t) + \frac{Kb_1 b_2}{b_3(b_3-b_2)} \exp(-b_3 t).$$

The solution tends exponentially to a new final state Kb_1/b_3. Again use of the final value theorem would give the limiting value of $x_3(t)$ immediately:

$$\lim_{t\to\infty} x_3(t) = \lim_{s\to 0} s\hat{x}_3(s) = \lim_{s\to 0} \frac{sKb_1 b_2}{s(s+b_2)(s+b_3)} = \frac{Kb_1}{b_3}.$$

Transfer functions, the unit impulse response and stability of linear input–output systems

The definition of the transfer function is best motivated by recalling the simple example where

$$\hat{x}_3(s) = \frac{b_1 b_2 \hat{x}_1(s)}{(s+b_2)(s+b_3)} + \frac{b_2 x_2(0)}{(s+b_2)(s+b_3)} + \frac{x_3(0)}{s+b_3}.$$

The form of input–output relation obtained in the more general cases follows the same pattern

$$\hat{y}(s) = G(s)\hat{x}(s) + \text{terms due to initial conditions},$$

where $y(t)$ is the output and $x(t)$ is the input. For the special case where all initial values are zero

$$\hat{y}(s)/\hat{x}(s) = G(s).$$

Hence the definition: the **transfer function** of a linear system, $G(s)$, is the ratio of the Laplace transform of the output and the input for the special case where all initial conditions are zero. Thus for (1) the transfer function is:

$$G(s) = \frac{b_1 b_2}{(s+b_2)(s+b_3)}. \tag{3}$$

Work in systems analysis is often concerned with the experimental determination of transfer functions. Suppose there was an input $x(t)$ such that $\hat{x}(s)=1$, then $\hat{y}(s)=G(s)$. The input function having this property is the **unit impulse** or **delta function**, $\delta(t)$, which is defined as the rectangular pulse function of height $1/\Delta t$ and width Δt taken in the limit $\Delta t \to 0$.

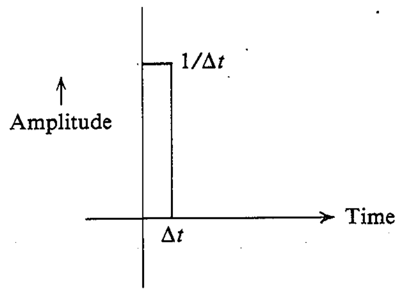

Figure 3.2.3. The rectangular pulse function of width Δt and height $1/\Delta t$. The unit impulse function is the mathematical idealization of a pulse input obtained in the limit $\Delta t \to 0$.

Example 3.2.6. Show that $L[\delta(t)]=1$.

Solution:
Let $u(t)$ be the unit step function. With this the definition of $\delta(t)$ becomes

$$\lim_{\Delta t \to 0}\left[\frac{u(t)-u(t-\Delta t)}{\Delta t}\right].$$

Thus

$$L[\delta(t)]=\int_0^\infty \lim_{\Delta t\to 0}\left[\frac{u(t)-u(t-\Delta t)}{\Delta t}\right]\exp(-st)\,dt$$

$$=\lim_{\Delta t\to 0}\left[\int_0^\infty \frac{u(t)}{\Delta t}\exp(-st)\,dt-\int_0^\infty \frac{u(t-\Delta t)}{\Delta t}\right]\exp(-st)\,dt.$$

The Laplace transform of $u(t)$ is $1/s$ (Example 3.2.1) so the first integral gives $1/(s\Delta t)$. A change in the variable of integration in the second integral gives

$$L[\delta(t)]=\lim_{\Delta t\to 0}\frac{1}{\Delta t}\left[\frac{1}{s}-\frac{\exp(-\Delta ts)}{s}\right].$$

The Taylor series has been defined in (A.1.30). Using this definition, we obtained the Taylor series (A.1.64) for the

exponential function. In particular

$$\exp(-\Delta ts)=1-\Delta ts+\frac{(\Delta ts)^2}{2!}-\frac{(\Delta ts)^3}{3!},$$

so

$$L[\delta(t)]=\lim_{\Delta t\to 0}\frac{1}{\Delta t}\left[\Delta t-\frac{(\Delta t)^2 s}{2!}+\frac{(\Delta t)^3 s^2}{3!}-\ldots\right]=1.$$

Thus the definition of the transfer function can be restated as the Laplace transform of the response to the input $\delta(t)$ for the case of zero initial conditions. $\delta(t)$ is a mathematical idealization but it can be approached experimentally. In actual practice there are more reliable techniques for measuring transfer functions. The response of the example system to an impulse response is determined in Example 3.2.7.

Example 3.2.7. Find the response of the differential equation (3.2.1) to $\delta(t)$ for the case $x_2(0)=x_3(0)=0$.

Solution:

$$\hat{x}_3(s)=\frac{b_1b_2\hat{x}_1(s)}{(s+b_2)(s+b_3)}=\frac{b_1b_2\hat{\delta}(s)}{(s+b_2)(s+b_3)}=\frac{b_1b_2}{(s+b_2)(s+b_3)},$$

$$\hat{x}_3(s)=b_1b_2\left[\left(\frac{1}{b_3-b_2}\right)\left(\frac{1}{s+b_2}\right)+\left(\frac{1}{b_2-b_3}\right)\left(\frac{1}{s+b_3}\right)\right],$$

$$x_3(t)=L^{-1}(\hat{x}_3(s))=\frac{b_1b_2}{b_3-b_2}\exp(-b_2t)+\frac{b_1b_2}{b_2-b_3}\exp(-b_3t).$$

From Example 3.2.7. it is seen that the response to $\delta(t)$ decays. We shall refer to systems with this property as being stable, i.e. a linear system is **stable** if its response to an impulse input $\delta(t)$ approaches zero as time approaches infinity. (The reader is warned that there are several other definitions of stability in the literature; the present definition is essentially equivalent to definitions used elsewhere in this volume.)

A linear system has the Laplace transform representation

$$\hat{y}(s)=G(s)\hat{x}(s)+\hat{\mathrm{ICR}}(s).$$

Usually $\mathrm{ICR}(t)\to 0$ as $t\to\infty$, so the system is stable if

$$L^{-1}[G(s)\hat{\delta}(s)]=L^{-1}[G(s)]\to 0$$

as $t\to\infty$. For most simple systems $G(s)$ can be expressed in the form $G(s)=N(s)/D(s)$ where $D(s)$ is a polynomial. Suppose $D(s)=0$ has roots $r_1\ldots r_n$ (which may be complex, see Appendix Section A.2); then $D(s)=(s-r_1)\ldots(s-r_n)$. In Example 3.2.7, $D(s)=(s+b_2)(s+b_3)$: the roots $-b_2$ and $-b_3$ appear in the solution $x_3(t)$ in exponents $\exp(-b_2t)$ and $\exp(-b_3t)$. Similarly in the more general case roots $r_1 \ldots r_n$ appear in the solution in terms with $\exp(r_1t) \ldots \exp(r_nt)$. The function $\exp(r_jt)$ decays with time only if $\mathrm{Re}(r_j) < 0$. This gives an important result, namely: *a necessary condition for stability is that the roots of $D(s) = 0$ have negative real parts.* The equation $D(s) = 0$ is usually called the **characteristic equation** and its roots $r_1 \ldots r_n$ are the **characteristic roots**. (Sometimes they are referred to as the **eigenvalues of the transfer function**.) The straightforward way of determining the stability of a linear system is to determine explicitly its characteristic roots. Unfortunately this is not usually possible; but there are several techniques for determining the stability properties of characteristic roots without solving the characteristic equation explicitly, e.g. the Routh–Hurwitz criterion and the continued fraction stability criterion. One of the most useful stability tests, the Nyquist criterion, will be presented in the discussion of closed loop feedback systems. Details of other tests can be found in any textbook on control theory.

3.3 FEEDBACK IN LINEAR PATHWAYS

The canonical negative feedback loop

Biologists have now established the broad outline of self-regulation in metabolic control systems, with the elucidation of some simple induction and repression mechanisms that regulate enzyme concentration. The allosteric regulation of enzyme activity has also been investigated. To use the analogy with mechanical control systems, we now understand something about the component parts of the control unit and something about their position in the circuit. The remaining problem – which is always much more difficult – is to understand the time-dependent response to a changing environment and to understand the way in which these 'local' control circuits are coordinated. By definition these are mathematical problems and unfortunately rather difficult ones. The subject will be introduced by considering some examples. Lengthy algebraic manipulations have been included with possibly excessive detail, and, while it could be argued that these details are not of interest to biologists, it is probably true that even a casual understanding of the methods discussed can be gained only by seeing a relatively complicated example worked through carefully.

In Section 3.2 we considered a process where an input in the form of mRNA produced a final product x_3. The rate of forward synthesis of x_3 was unaffected by its concentration (i.e. the process was not controlled). Clearly this is a potentially wasteful system, since, if x_3 was provided by some other source, say an external supply, the synthesis from mRNA and enzyme x_2 would still continue. We know in fact that biochemical processes are usually regulated and, in the case of negative control described in Section 3.1, an increase in x_3 concentration would decrease its net rate of synthesis. To provide a concrete example for mathematical examination, suppose x_3 exerts a negative feedback control at the translational level by inhibiting x_1. Previously the input to the synthesis process represented by transfer function $G(s)$ was $x_1(t)$; now suppose it is $x_1(t) - x_3(t)$. The control loop representation is given in Figure 3.3.1 with