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

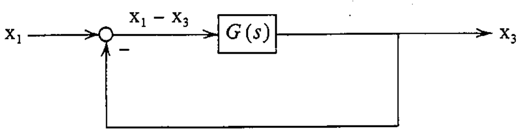

Figure 3.3.1. A specific example of a linear negative feedback system in which output x_3 exerts a negative control on its own synthesis.

$G(s)$ given in (3.2.3). $G(s)$ is referred to as the **direct transfer function** or the **forward transfer function.**

In order to define other concepts that frequently appear in the control literature, two complications will be added to this system: an explicit reference signal and a feedback controller. Often a reference signal y_{ref} equal to the desired output is available. This signal is subtracted from output before it is returned via the feedback loop. The output less the reference signal $(x_3 - y_{\text{ref}})$ is called the **error signal**. Frequently the error signal is modified before being subtracted from the input by a **feedback controller**. The feedback controller, which is also called the **output transducer**, has **feedback transfer function** $K(s)$. The resulting control system is shown in Figure 3.3.2. Circuits of this form are encountered so frequently in the control literature that they have been graced with the adjective canonical.

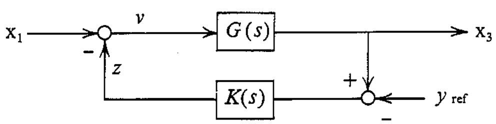

Figure 3.3.2. The canonical negative feedback loop.

Considering the complexity of biochemical control systems, the canonical feedback loop seems a simplistic caricature; however, a surprisingly large number of control systems can be transformed into this configuration. Also, since it is one of the simplest feedback systems it seems the best place to start. In analyzing a system of this kind three properties are examined. Accuracy: does the output follow the requirement specified by the reference signal? Stability: is the system reliable, or are there conditions which result in a radically unacceptable output? Speed: does the control system respond quickly enough to changes in input or reference signals? These questions will now be considered.

Accuracy of a simple linear negative feedback loop

The accuracy of the control loop in Figure 3.3.2 is considered for the following specific realization: the forward transfer function, $G(s)$, is given

by (3.2.3). This transfer function described the forward synthesis process analyzed in Section 3.2. In this example we consider the simplest possible feedback controller which multiplies the feedback signal $(x_3 - y_{\text{ref}})$ by a *positive* constant; giving feedback transfer function $K(s) = k$. The constant k could of course be $k = 1$ in which case the feedback signal is unmodified. Systems where $K(s) = k$ are called **proportional feedback systems**, and k is a gain constant. The **gain** of a control component can be most simply defined as the transmission function of the component when it is a simple multiplier. A more general definition would be the ratio of a change in output to a change in input, i.e. if a change of z units in the input results in a change Kz in the output, then the gain of the process is K. In this more general sense gain can be a very complicated function depending on the form of the input:

$$\text{Gain} = \frac{\Delta\ \text{output}}{\Delta\ \text{input}}.$$

As in Section 3.2 the analysis is conducted in Laplace transform space. Setting initial conditions to zero gives

$$\hat{x}_3(s) = G(s)\hat{v}(s),$$

$$\hat{v}(s) = \hat{x}_1(s) - \hat{z}(s) = \hat{x}_1(s) - k[\hat{x}_3(s) - \hat{y}_{\text{ref}}(s)],$$

$$\hat{x}_3(s) = G(s)\hat{x}_1(s) - kG(s)\hat{x}_3(s) + kG(s)\hat{y}_{\text{ref}}(s).$$

This equation is solved, determining the output transform $\hat{x}_3(s)$:

$$\hat{x}_3(s) = \frac{G(s)}{1 + kG(s)}[\hat{x}_1(s) + k\hat{y}_{\text{ref}}(s)]. \tag{1}$$

In the case of the open loop system, the process was described by the transfer function $G(s)$; here it is described by the **closed loop transfer function** $G(s)/[1 + kG(s)]$.

A control system is accurate if the output closely tracks the reference setting. It is useful to define a function of time called the **offset** as the difference output − reference signal, which for this example would be $[x_3(t) - y_{\text{ref}}(t)]$. The Laplace transform of the offset is

$$\hat{x}_3(s) - \hat{y}_{\text{ref}}(s) = \frac{1}{k}\left[\frac{G(s)\hat{x}_1(s) - \hat{y}_{\text{ref}}(s)}{G(s) + (1/k)}\right].$$

The aim is to have the smallest possible offset. Since superficial examination of this equation suggests that $|\hat{x}_3(s) - \hat{y}_{\text{ref}}(s)|$ appears to approach zero as $k \to \infty$, it would seem that the offset could be decreased by increasing the gain of the feedback loop. Indeed, this is frequently the case and provides a simple and successful method for improving control accuracy. However, if increasing k causes $G(s)+(1/k)$ to approach zero, the offset can rapidly increase; the accuracy of control would dramatically decrease with an increase in gain. This is a specific example of a general phenomenon termed the control–stability conflict (or tightness of control–stability trade-off). We can now see that the problem of accuracy of control is intimately connected with the problem of stability.

Stability of a linear negative feedback loop

The closed loop transfer function (3.3.1) has denominator $1+kG(s)$. If this function has a zero, $s=r_j$ with $\mathrm{Re}\,(r_j)>0$, then $x_3(t)$ contains a growing exponential, because partial fraction expansions of $G\hat{x}_1/(1+kG)$ and $kG\hat{y}_{\mathrm{ref}}/(1+kG)$ give terms $\rho_j/(s-r_j)$ (ρ_j being the expansion coefficient) and hence the inverse transform $\rho_j \exp(r_j t)$. So a necessary condition for the stability of the control system of Figure 3.3.2 is that all of the zeros of $1+kG(s)=0$ have negative real parts. This equation is the characteristic equation of the closed feedback loop and the roots are the characteristic roots.

For the example case, the characteristic equation is simple enough to be solved explicitly.

$$1+kG(s)=1+\frac{kb_1b_2}{(s+b_2)(s+b_3)}=0,$$

$$(s+b_2)(s+b_3)+kb_1b_2=0,$$

$$s^2+(b_2+b_3)s+b_2b_3+b_1b_2k=0, \tag{2}$$

$$2r_{1,2}=-(b_2+b_3)\pm[(b_2+b_3)^2-4(b_2b_3+b_1b_2k)]^{\frac{1}{2}}.$$

The problem is to determine the stability properties of the system not for a single value of feedback gain k but for the entire range of positive values. The plot of the roots r_1 and r_2 in the complex plane as k increases from zero is the **root locus diagram.** For stability, the roots have to be on the left side of the complex plane (i.e. they must have negative real parts). A summary of the basic properties of complex numbers is given in Appendix A.2.

Example 3.3.1. Draw the root locus diagram as a function of k for the system of Figure 3.3.2 for the case $b_1=0.5$, $b_2=1$, $b_3=2$.

Solution:
For these parameter values the two roots are

$$r_1=-\tfrac{3}{2}+[\tfrac{1}{4}-(k/2)]^{\frac{1}{2}}, \qquad r_2=-\tfrac{3}{2}-[\tfrac{1}{4}-(k/2)]^{\frac{1}{2}}.$$

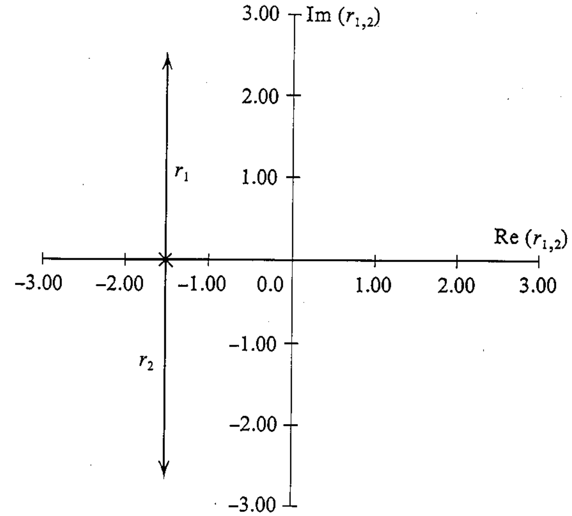

Figure 3.3.3. Root locus diagram for characteristic equation (2) when $b_1=0.5$, $b_2=1$ and $b_3=2$. Arrows indicate the direction of increasing feedback gain, k.

The root locus diagram is simple enough to draw by hand, but following usual practice a simple computer program was written to produce the diagram.

For all positive values of k the roots have negative real parts, so the system appears to be stable. For more complicated systems the root locus method is not completely satisfactory. Usually the characteristic equation cannot be solved explicitly. Also the example produced the root locus diagram for a specific set of parameters b_1, b_2 and b_3; however, this does not generally ensure that it is impossible to find a set of positive b's that give instability. Let us next consider a more powerful technique, the Routh–Hurwitz criterion, which shows that the roots have negative real parts for any set of positive b's and positive k.

If stability is the only concern it is only necessary to show that the characteristic roots all have negative real parts. Thus a test like the Routh–Hurwitz criterion that shows this without actually finding values of r_j's is usually acceptable. In its general case the criterion considers polynomial equations of order n,

$$a_ns^n+a_{n-1}s^{n-1}+\ldots+a_1s+a_0=0,$$

where it is assumed that $a_n>0$. (If this is not the case, divide the equation by -1. Usually one divides through by the coefficient of s^n so that a_n can be taken equal to unity.) The theorem states that all roots have negative real parts if and only if $\Delta_1>0$, $\Delta_2>0,\ldots,\Delta_n>0$, where the Δ's have a rather complicated form. (A summary of the definitions and elementary properties of determinants is given in Appendix A.2.)

$$\Delta_1 = a_{n-1},$$

$$\Delta_2 = \begin{vmatrix} a_{n-1} & a_{n-3} \\ a_n & a_{n-2} \end{vmatrix},$$

$$\Delta_3 = \begin{vmatrix} a_{n-1} & a_{n-3} & a_{n-5} \\ a_n & a_{n-2} & a_{n-4} \\ 0 & a_{n-1} & a_{n-3} \end{vmatrix},$$

$$\Delta_4 = \begin{vmatrix} a_{n-1} & a_{n-3} & a_{n-5} & a_{n-7} \\ a_n & a_{n-2} & a_{n-4} & a_{n-6} \\ 0 & a_{n-1} & a_{n-3} & a_{n-5} \\ 0 & a_n & a_{n-2} & a_{n-4} \end{vmatrix},$$

and so on. If a_{n-r} does not appear in the polynomial equation (or $n-r<0$) then a_{n-r} is set equal to zero. There are several equivalent ways of defining Δ's; this convention has been followed by DiStefano *et al.* (1967).

Example 3.3.2. Use the Routh–Hurwitz criterion to show that the roots of the characteristic equation

$$(s+b_2)(s+b_3)+b_1b_2k=0$$

have negative real parts if k and the b's are positive.

Solution:
In the previous example the root locus was drawn for the special case $b_1=\frac{1}{2}$, $b_2=1$ and $b_3=2$. Now the analysis is performed for arbitrary positive k and positive b's (indicating the value of analytical methods).

$$a_n = a_2 = 1, \qquad a_{n-1} = a_1 = b_2+b_3,$$

$$a_{n-2} = a_0 = b_2b_3 + b_1b_2k.$$

Expressions for Δ_1 and Δ_2 follow from the previous definitions.

$$\Delta_1 = a_{n-1} = a_1 = b_2+b_3.$$

Since b_2 and b_3 are both positive it follows that Δ_1 is positive.

$$\Delta_2 = \begin{vmatrix} a_{n-1} & a_{n-3} \\ a_n & a_{n-2} \end{vmatrix} = \begin{vmatrix} a_1 & 0 \\ a_2 & a_0 \end{vmatrix},$$

$$\Delta_2 = \begin{vmatrix} b_2+b_3 & 0 \\ 1 & b_2b_3+b_1b_2k \end{vmatrix} = (b_2+b_3)(b_2b_3+b_1b_2k).$$

Since each factor in Δ_2 is positive, $\Delta_2>0$. The roots of the closed loop characteristic equation have negative real parts even if the feedback gain is arbitrarily large.

While the Routh–Hurwitz criterion satisfactorily disposed of the problem in Example 3.3.2, some experimentation with the formula for Δ indicates that the method becomes very tedious as the dimension n increases. This is a major drawback for biological work where the dimension is frequently very large. Fortunately the Routh–Hurwitz criterion is complemented by the Nyquist criterion which is often easier to apply to large-dimension systems. An exact statement of the Nyquist theorem requires an understanding of elementary complex analysis. We propose to make a substantial compromise with rigor and attempt to give a purely operational presentation of the methods used by considering again Example 3.3.2. The feedback system in Figure 3.3.2 has a closed loop transfer function

$$\hat{x}_3(s) = \frac{G(s)}{1+kG(s)}(\hat{x}_1(s)+k\hat{y}_{\text{ref}}(s)), \qquad G(s)=\frac{b_1b_2}{(s+b_2)(s+b_3)}. \tag{3}$$

In Figure 3.3.4 the complex function $G(i\omega)$, $i=\sqrt{(-1)}$, is plotted for $\omega=0$ to $\omega=\infty$, for the parameters $b_1=0.5$, $b_2=1$ and $b_3=2$. This curve is the **Nyquist locus.**

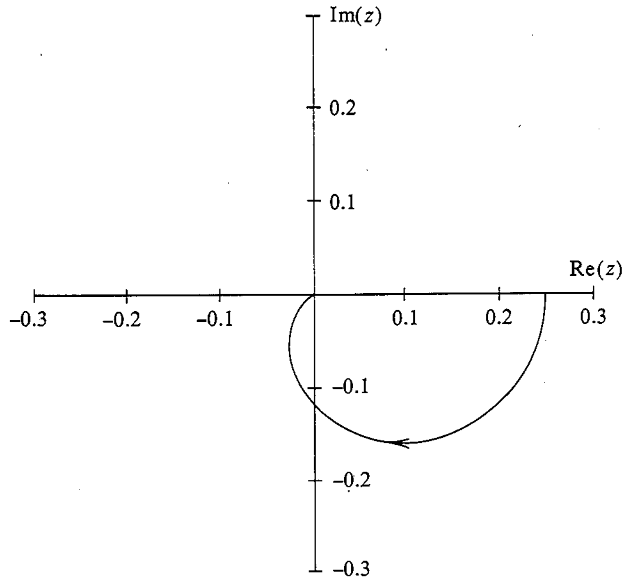

Figure 3.3.4. Nyquist locus, $G(i\omega)$, for the transfer function of equation (3) for $b_1=0.5$, $b_2=1$ and $b_3=2$. The arrow indicates direction of increasing ω.

The Nyquist theorem shows that the characteristic equation has a root with positive real part if and only if the point $-1/k$ is encircled by the Nyquist locus. The difficulty in understanding the criterion centers on the ambiguity of the word 'encircled'. Consider the Nyquist locus and its reflection through the real axis (Figure 3.3.5). The resulting figure is a closed curve with a direction defined by the direction of increasing ω. The interior of the curve is shaded. (If you walk around the boundary of a directed closed curve, your right shoulder is on the inside.) A point is encircled by the Nyquist locus if it is in the shaded region.

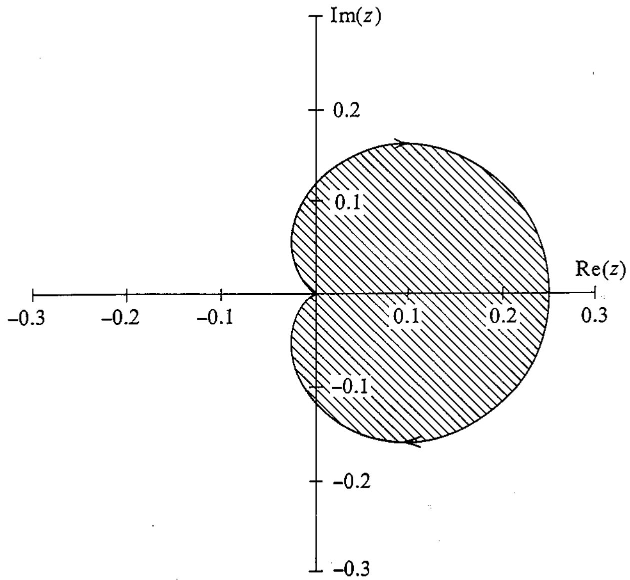

Figure 3.3.5. The Nyquist locus for the transfer function of (3) and its reflection through the real axis with the interior shaded. The arrows indicate direction of increasing ω.

Using the Nyquist locus in Figure 3.3.5 and this definition of encirclement, the stability properties of the loop can be determined.

Example 3.3.3. Using the Nyquist criterion, show that the roots of the characteristic equation of the closed loop transfer function of (3.3.1) have negative real parts when $b_1=0.5$, $b_2=1$ and $b_3=2$ and when k is an arbitrary positive gain constant.

Solution:
Figures 3.3.4 and 3.3.5 show that no point on the negative real axis is encircled by the Nyquist locus. Gain k is a positive real number so $-1/k$ is a negative real number and hence never encircled. The Nyquist criterion demonstrates that the roots of the characteristic equation always have negative real parts.

In this example the Nyquist criterion demonstrated stability for $b_1=0.5$, $b_2=1$, $b_3=2$ and for feedback gain k, while the Routh–Hurwitz criterion showed stability for a completely general set of positive b's. In fact, it is fairly easy to generalize the Nyquist criterion result. This is done in Example 3.3.4.

Example 3.3.4. Using the Nyquist criterion, show that the roots of the characteristic equation (3.3.2) have negative real parts for all positive b_1, b_2, b_3 and positive k.

Solution:
The argument has six steps. (Listing these steps may make the solution seem more complicated than it really is. The reader can convince himself or herself of the simplicity of the method by sketching a few Nyquist loci by hand.)

1. Instability is indicated only if the point $-1/k$ is encircled by the Nyquist locus.
2. k is a positive real number, so $-1/k$ is a negative real number.
3. From steps (1) and (2) instability can occur only if the Nyquist locus encircles some interval of the negative real axis.
4. The Nyquist locus can encircle an interval of the negative real axis only if it intersects the negative real axis.
5. An intersection of $G(\mathrm{i}\omega)$ and the real axis takes place for ω such that Im $G(\mathrm{i}\omega)=0$ (i.e. the imaginary part of $G(\mathrm{i}\omega)$ is zero).
6. If the only solution of Im $G(\mathrm{i}\omega)=0$ is $\omega=0$, then it follows from steps (4) and (5) that the negative real axis is never intersected and thus the system is stable.

$$G(\mathrm{i}\omega)=\frac{b_1b_2}{(b_2+\mathrm{i}\omega)(b_3+\mathrm{i}\omega)}\left[\frac{(b_2-\mathrm{i}\omega)(b_3-\mathrm{i}\omega)}{(b_2-\mathrm{i}\omega)(b_3-\mathrm{i}\omega)}\right],$$

$$G(\mathrm{i}\omega)=\frac{b_1b_2(b_2-\mathrm{i}\omega)(b_3-\mathrm{i}\omega)}{(b_2^2+\omega^2)(b_3^2+\omega^2)}$$

$$=\frac{b_1b_2[-\omega^2+b_2b_3-\mathrm{i}\omega(b_2+b_3)]}{(b_2^2+\omega^2)(b_3^2+\omega^2)},$$

$$\operatorname{Im} G(\mathrm{i}\omega)=\frac{-b_1b_2(b_2+b_3)\omega}{(b_2^2+\omega^2)(b_3^2+\omega^2)}.$$

Using the expression for Im $G(\mathrm{i}\omega)$ it is seen that the equation Im $G(\mathrm{i}\omega)=0$ has only the solution $\omega=0$. The system is stable.

The tightness of control–stability trade-off has been mentioned and it was claimed that increasing feedback gain can cause a loss of stability. The claim is not confirmed by the above example, since the system is stable for arbitrarily large feedback gain, k. The next example shows that this is atypical.

Instability due to high feedback gain

In this control circuit the forward operator describes a three-step chemical reaction.

$$dx_2(t)/dt = b_1x_1(t) - b_2x_2(t),$$

$$dx_3(t)/dt = b_2x_2(t) - b_3x_3(t),$$

$$dx_4(t)/dt = b_3x_3(t) - b_4x_4(t),$$

where b_1, b_2, b_3 and b_4 are positive reaction constants. Assuming initial values are zero, the transfer function of the process is found by taking the Laplace transform of each differential equation.

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

$$s\hat{x}_3(s) = b_2\hat{x}_2(s) - b_3\hat{x}_3(s),$$

$$s\hat{x}_4(s) = b_3\hat{x}_3(s) - b_4\hat{x}_4(s).$$

The second and third equations are used to eliminate $\hat{x}_2(s)$ and $\hat{x}_3(s)$, giving $\hat{x}_4(s)$ as a function of $\hat{x}_1(s)$:

$$\hat{x}_4(s) = \frac{b_1b_2b_3}{(s+b_2)(s+b_3)(s+b_4)}\hat{x}_1(s) = G(s)\hat{x}_1(s). \tag{4}$$

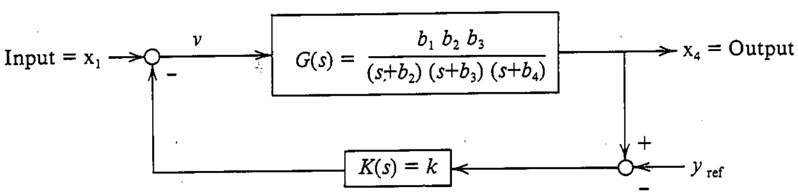

Figure 3.3.6. The canonical control loop in which the forward operator models a three-step chemical reaction and the feedback controller is a gain constant.

As before let us consider proportional feedback where the feedback transfer function is again constant, $K(s) = k$. The same form of closed loop transfer function is obtained.

$$\hat{x}_4(s) = \frac{G(s)}{1+kG(s)}[\hat{x}_1(s) + k\hat{y}_{\text{ref}}(s)].$$

Stability is determined by the roots of the characteristic equation.

$$1 + kG(s) = 1 + \frac{kb_1b_2b_3}{(s+b_2)(s+b_3)(s+b_4)} = 0. \tag{5}$$

Example 3.3.5. Using the Routh–Hurwitz criterion, examine the stability properties of characteristic equation (5) for positive b's and positive feedback gain k.

Solution:
The characteristic equation is

$$s^3 + s^2(b_2+b_3+b_4) + s(b_2b_3+b_2b_4+b_3b_4) + b_2b_3b_4 + kb_1b_2b_3 = 0.$$

$$a_n = a_3 = 1,$$

$$a_{n-1} = a_2 = b_2+b_3+b_4,$$

$$a_{n-2} = a_1 = b_2b_3+b_2b_4+b_3b_4,$$

$$a_{n-3} = a_0 = b_2b_3b_4 + kb_1b_2b_3.$$

Expressions for Δ_1, Δ_2 and Δ_3 must be derived. There is a root with positive real part if (and only if) there is a negative Δ.

$$\Delta_1 = a_{n-1} = a_2 = b_2+b_3+b_4.$$

Since all b's are positive, Δ_1 is positive.

$$\Delta_2 = \begin{vmatrix} a_{n-1} & a_{n-3} \\ a_n & a_{n-2} \end{vmatrix} = \begin{vmatrix} a_2 & a_0 \\ a_3 & a_1 \end{vmatrix} = a_1a_2 - a_0a_3,$$

$$\Delta_2 = (b_2+b_3+b_4)(b_2b_3+b_2b_4+b_3b_4) - b_2b_3b_4 - kb_1b_2b_3,$$

$$\Delta_2 = b_2(b_2b_3+b_2b_4) + (b_3+b_4)(b_2b_3+b_2b_4+b_3b_4) - kb_1b_2b_3.$$

The first two terms are positive; the third is negative. The magnitude of the third term increases with k, so if k is big enough Δ_2 is negative and the system is unstable (tight control (increasing k) causes instability (Δ_2 negative)). The inequality determining the minimum k for *instability* is

$$0 > \Delta_2 = b_2(b_2b_3+b_2b_4) + (b_3+b_4)(b_2b_3+b_2b_4+b_3b_4) - kb_1b_2b_3,$$

$$kb_1b_2b_3 > b_2(b_2b_3+b_2b_4) + (b_3+b_4)(b_2b_3+b_2b_4+b_3b_4),$$

$$k > \frac{b_2(b_2b_3+b_2b_4) + (b_3+b_4)(b_2b_3+b_2b_4+b_3b_4)}{b_1b_2b_3}.$$

The system is unstable if k is greater than the expression on the right, which is defined as k_c (c = critical). Analysis of Δ_3 gives the same result.

$$\Delta_3 = \begin{vmatrix} a_{n-1} & a_{n-3} & a_{n-5} \\ a_n & a_{n-2} & a_{n-4} \\ 0 & a_{n-1} & a_{n-3} \end{vmatrix} = \begin{vmatrix} a_2 & a_0 & 0 \\ a_3 & a_1 & 0 \\ 0 & a_2 & a_0 \end{vmatrix},$$

$$\Delta_3 = a_2 \begin{vmatrix} a_1 & 0 \\ a_2 & a_0 \end{vmatrix} - a_0 \begin{vmatrix} a_3 & 0 \\ 0 & a_0 \end{vmatrix},$$

$$\Delta_3 = a_0(a_1a_2 - a_0a_3).$$

From the characteristic equation, $a_0 = b_2b_3b_4 + kb_1b_2b_3$. Since all of these constants are positive, it follows that a_0 is positive. This means that the sign of Δ_3 is the same as the sign of its second factor:

$$\operatorname{sgn} \Delta_3 = \operatorname{sgn} (a_1a_2 - a_0a_3).$$

But $a_1a_2 - a_0a_3 = \Delta_2$, so

$$\operatorname{sgn} \Delta_2 = \operatorname{sgn} \Delta_3.$$

Thus Δ_3 gives the same stability condition as Δ_2, namely:

$k < k_c$ roots stable (negative real parts);

$k > k_c$ roots unstable (positive real parts).

The special case $k = k_c$ gives pure imaginary roots. This would result in periodic solutions of the differential equation exactly as in the case of simple harmonic motion. However, it must be stressed that linear systems cannot generally successfully model chemical oscillations. The reason can be easily seen using the example. If $k = k_c$ *exactly*, then oscillations result, but there is always noise in any real system so k will move above or below k_c. If k is even an ε above k_c (ε being an *arbitrarily small* positive number), the system is unstable. If k is ε below k_c, the oscillations damp out. The inevitable variation from k_c will destroy periodic motion.

Using the Routh–Hurwitz criterion, it has been shown that increasing feedback gain can cause instability. In Example 3.3.6 this result is reproduced via the Nyquist criterion.

Example 3.3.6. Determine the stability properties of the system of Figure 3.3.6 by the Nyquist criterion for parameters $b_1 = \frac{1}{2}$, $b_2 = 1$, $b_3 = 1.05$ and $b_4 = 1.1$.

Solution:

The Nyquist locus spirals in a counterclockwise direction from $G(0)$.

$$G(0) = b_1b_2b_3/b_2b_3b_4 = b_1/b_4 = 0.4545\ldots.$$

There is an intersection with the negative real axis at $\omega \cong 1.82$. Instability is indicated if $-1/k$ is encircled by the Nyquist locus. The points on the negative real axis between the origin and the intersection of $G(i\omega)$ and the negative real axis correspond to feedback gain that can produce instability. (This is the region marked by the heavy line in Figure 3.3.7.) For $1/k$ small enough

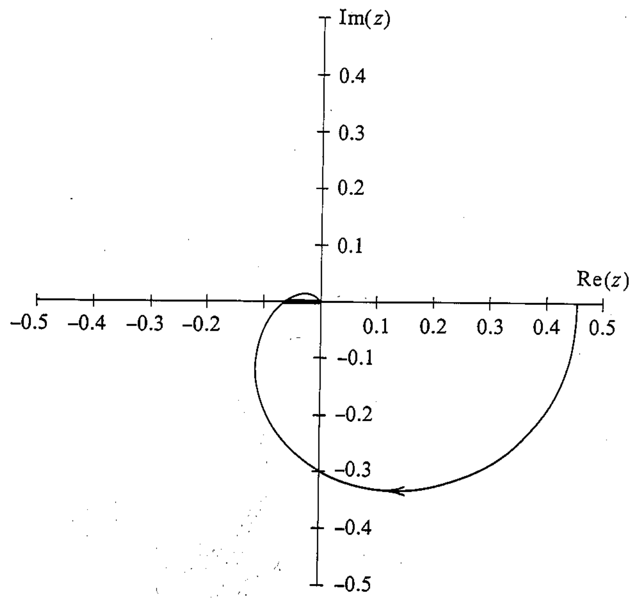

Figure 3.3.7. The Nyquist locus, $G(i\omega)$, for the transfer function of (4) for $b_1 = 0.5$, $b_2 = 1$, $b_3 = 1.05$ and $b_4 = 1.1$. The arrow indicates the direction of increasing ω. The overlined segment of the negative real axis is encircled by the Nyquist locus.

(i.e. k big enough), $-1/k$ is encircled. The point of intersection gives the minimum gain for instability. The intersection occurs at

$$-1/k_c = -0.0568, \qquad k_c = 17.6.$$

This is the same k_c found by the formula of Example 3.3.5.

The three step reaction system gives a useful example of a general control system phenomenon; as the number of separate steps in a process increases, instability becomes more likely. In a five-step reaction scheme, for example, k_c would be smaller and so on. A detailed analysis of this effect is given in Rapp (1976). Similarly a time delay between reaction steps can destabilize a control loop. The destabilizing effect of time delays is briefly considered in Section 3.4.