3.6 NONLINEAR MODELS

Experience suggests that most biological systems are inherently nonlinear and that linear analysis is at best only an approximation which is valid for a possibly restricted range near dynamic equilibrium.

There are two classes of behavior of particular biological importance unique to nonlinear systems: switching and oscillations.

Nonlinear chemical systems can have more than one steady state. The selection of a particular steady state will depend on the parameter values and on the past history of the system. As shown in Section 3.8, it is possible to cause a chemical system to move abruptly from one state to another in response to a small change in a parameter, i.e. the system responds as a switch. Several authors have suggested that switching behavior could provide a basis for cell differentiation or for the transformation from normal to neoplastic growth (Simon, 1965; Grigorov, Polyakova & Chernavskii, 1967; Babloyantz & Nicolis, 1972; van Cauter & Dumont, 1978).

As indicated in Section 3.3, the linear oscillator cannot successfully model biological oscillations which are known to be insensitive to fairly large variations in parameters and initial conditions. A chemical system can oscillate only if it is nonlinear, thermodynamically open and far from equilibrium (Prigogine, 1967, 1969). Biochemical oscillations in positive feedback loops are exemplified by the glycolytic oscillator (Section 4.1). Oscillations in positive feedback loops are intuitively plausible since one would expect that positive feedback could destabilize a steady state. However, since the response of biological systems saturates, the output should ultimately be bounded. A stable oscillation would be the expected 'compromise' in bounded systems with an unstable steady state (for an example see Goldbeter & Segel, 1977). Unforced oscillations (i.e. oscillations that are produced by the system itself and are not due to external periodic forcing) in negative feedback loops seem less likely because the action of the control is to direct the output to the reference signal. Indeed at one time it was commonly supposed that oscillations in negative feedback *biochemical* systems were impossible. However, experience in engineering control systems has indicated that negative feedback systems are quite likely to have stable oscillations unless an effort is made to prevent them. Indeed in Example 3.6.1 it is shown that even very simple negative feedback loops can oscillate.

Example 3.6.1. The Chancellor of the Exchequer Oscillator (so named because the control element always does the right thing but too late and in an extreme way). Consider the control loop in Figure 3.6.1. The object of the control is to hold the value of x to zero. If x becomes negative, then after a time delay, τ, the value of $\dot{x}$ is $+a > 0$, i.e. x will increase and return to zero. If x becomes positive then, after the delay, its derivative is $-b < 0$, so x decreases returning to zero. Thus the negative sign on the return loop appears because the output of the nonlinear control element is $+a$ if $x(t-\tau) < 0$ and $-b$ is $x(t-\tau) > 0$. The component $1/s$ appears because the output of the nonlinearity is equal to $\dot{x}$ and not x. The input is the constant zero, so if oscillations appear it is not as a result of periodic forcing. Suppose that initially $x = 0$ and the nonlinear controller is set at $-b$. The existence of oscillations will be demonstrated by explicitly following the subsequent movement of x and $\dot{x}$ and showing that the system returns to this initial state, i.e. a repeating cycle is established.
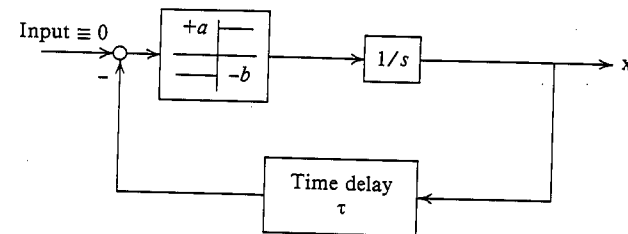

Figure 3.6.1. The Chancellor of the Exchequer Oscillator: the derivative of x is either $+a$ or $-b$. The instability results from the time delay τ. Details are in the text.

Solution:

Initially $x = 0$ and $\dot{x} = -b$; because of the time delay element, x will decrease for a time interval τ. It will then increase and eventually become positive, but again $\dot{x}$ will not change sign until after a delay interval τ; x then decreases to zero reproducing the initial conditions $x = 0$ and $\dot{x} = -b$. Figure 3.6.2 shows the variation of x and its derivative. The argument is made clearer by explicitly calculating the period and amplitude.
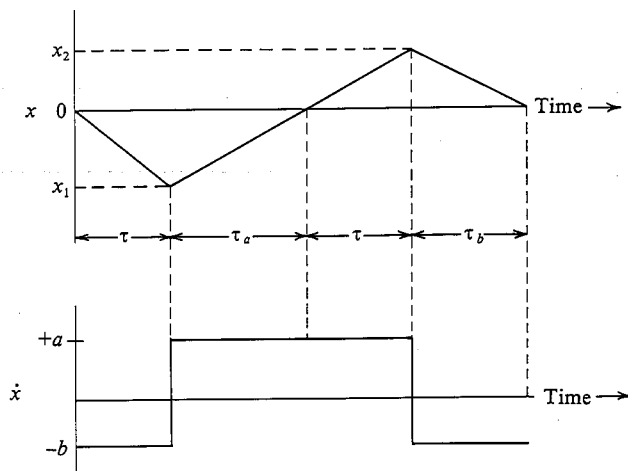
Figure 3.6.2. Transitions in x and its derivative in the control loop of Figure 3.6.1. Initially $x = 0$ and $\dot{x} = -b$. The transition to $\dot{x} = +a$ follows after a time delay τ.

(a) Calculation of x_1.
Start at $x = 0$ and decrease at rate $-b$ for time τ. Thus $x_1 = -\tau b$.

(b) Calculation of τ_a.
Start at $x = -\tau b$ and increase at rate $+a$.

distance $=$ (rate) $\cdot$ (time),   i.e. $\tau b = (a)(\tau_a)$, $\tau_a = \tau b / a$.

(c) Calculation of x_2.
Start at $x = -\tau b$ and increase at rate $+a$.

$x_2 = a\tau$.

(d) Calculation of τ_b.
Start at $x_2 = a\tau$ and decrease at rate $-b$.

$\tau_b = a\tau / b$.

Thus

period $= \tau + \tau_a + \tau + \tau_b = 2\tau + \tau[(b/a) + (a/b)]$,

amplitude $= x_2 - x_1 = \tau(a + b)$.

The system in Example 3.6.1 is clearly an extreme case in having a mechanical plus–minus nonlinearity and in containing an idealized pure delay. However, it does show that oscillations can occur in a negative feedback system that appears always to decrease displacements from a constant reference setting. A model of a biochemical negative feedback system is discussed in Section 3.7.