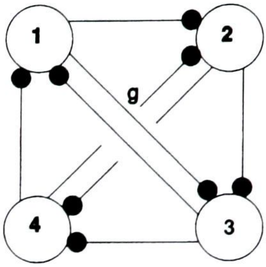

Fig. 4.2 Four-neuron network for respiratory control involving sequential neural disinhibition.

neuron 4, from which it receives inhibition. These interactions are repeated for the other neurons. This is a sequential network that involves inhibition but also disinhibition. To appreciate this, note that inhibition of neurons 2 and 3 by neuron 1 shuts off all inhibition to neuron 4.

To analyze this network and determine the inhibitory strengths that will produce a respiratory oscillation, let us assume that the inhibitory synaptic weights between adjacent neurons are -5 and that each neural response will decay to zero at a rate of -3 in the absence of stimulation. What strength $-g$ must the diagonal inhibition in the network have to generate periodic behavior? The system of four coupled linear neural equations is:

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} E_1 \\ E_2 \\ E_3 \\ E_4 \end{pmatrix} = \begin{pmatrix} -3 & 0 & -g & -5 \\ -5 & -3 & 0 & -g \\ -g & -5 & -3 & 0 \\ 0 & -g & -5 & -3 \end{pmatrix} \begin{pmatrix} E_1 \\ E_2 \\ E_3 \\ E_4 \end{pmatrix} \tag{4.8}$$

Type the A matrix into **Hopf.m** (again using G for the unknown), save this function, and run **Routh_Hurwitz.m**. The program reveals that $G = 3$ will generate an oscillation of the general form:

$$E_k = A\,\mathrm{e}^{-t} + B\,\mathrm{e}^{-11t} + C\cos(5t) + D\sin(5t) \tag{4.9}$$

where $k = 1, 2, 3, 4$. Assuming that t is in seconds the oscillation frequency is $5/(2\pi) = 0.8$ Hz, about right for respiration. Here again the Routh–Hurwitz criterion in Theorem 7 has found a parameter value that produces a neural oscillation. As the first two terms in (4.9) die out with increasing t, the oscillation occurs on a two-dimensional surface in the four-dimensional state space of the system. These examples will generalize to nonlinear neural networks, because Theorem 7 can be employed in conjunction with the Hopf Bifurcation Theorem (see Chapter 8).

4.4 Feedback with delays

A final, very important example of oscillations in neural systems is related to delays in feedback loops. The negative feedback loop between horizontal cells and cones

(Chapter 3) generates an asymptotically stable spiral point. Can this network also produce an oscillation? Consider the very general linear feedback network between an excitatory neuron E and an inhibitory neuron I. The equations are:

$$\frac{\mathrm{d}E}{\mathrm{d}t} = \frac{1}{\tau_E}(-E - aI)$$
$$\frac{\mathrm{d}I}{\mathrm{d}t} = \frac{1}{\tau_I}(-I + bE) \tag{4.10}$$

For $a > 0, \mathrm{b} > 0$, eqn (4.10) describes a negative feedback loop as illustrated in Fig. 1.3. The A matrix is easily be seen to be:

$$\overleftrightarrow{A} = \begin{pmatrix} -1/\tau_E & -a/\tau_E \\ b/\tau_I & -1/\tau_I \end{pmatrix} \tag{4.11}$$

so the eigenvalues are:

$$\lambda = -\frac{1}{2}\left(\frac{1}{\tau_E} + \frac{1}{\tau_I}\right) \pm \frac{\sqrt{(\tau_E - \tau_I)^2 - 4ab\tau_E\tau_I}}{2\tau_E\tau_I} \tag{4.12}$$

As real$(\lambda) < 0$, all solutions to eqn (4.10) must be decaying exponential functions of time, and so oscillations are impossible in this two component feedback loop. The reason for this is that both E and I decay exponentially with their respective time constants, as required for physiological plausibility. (It is, of course, possible to generate oscillations in an idealized second order system such as a spring without any frictional resistance.)

Does this analysis indicate that linear feedback systems can never oscillate? To answer this, suppose that physiological conditions caused a delay (for example, an axonal conduction time delay) in the feedback loop. To represent such a delay exactly in eqn (4.10), however, becomes extremely complex. In fact, differential equations with delays are infinite-dimensional dynamical systems! You can convince yourself of this fact from the following argument. An N-dimensional system requires N initial conditions, one for each variable at time $t = 0$. If there is a delay in the system of say 5 ms, a continuum of values must be specified between $t = -5$ ms and $t = 0$ to specify the initial state of the system. Hence, dynamical systems with true delays become extraordinarily complex, and the interested reader is referred to discussions by Glass and Mackey (1988), MacDonald (1989), and Milton (1996).

As a simplified approach to the problem, suppose we take our cue from the fact that delays increase the dimensionality of a dynamical system. This increase is certainly infinite, but let us be modest and introduce just one additional differential equation to approximate the delay by defining the variable Δ for delay. Before seeing the effect this has on eqn (4.10), let us see how an additional equation alters the response of a single first order equation. Consider therefore:

$$\begin{aligned}\frac{dx}{dt} &= \frac{1}{\tau}(-x+1)\\ \frac{d\Delta}{dt} &= \frac{1}{\delta}(-\Delta+x)\end{aligned} \tag{4.13}$$

where δ will approximate the delay time lag in milliseconds, and the initial conditions $x(0)=0$ and $\Delta(0)=0$. Note that the equation for Δ has been constructed so that $\Delta = x$ in the steady state, a requirement that any delay must meet. The first equation was solved in Chapter 2, and the second can also be solved using Theorem 1 with the results:

$$\begin{aligned}x(t) &= 1 - e^{-t/\tau}\\ \Delta(t) &= 1 - \frac{\tau e^{-t/\tau}}{\tau-\delta} + \frac{\delta e^{-t/\delta}}{\tau-\delta}\end{aligned} \tag{4.14}$$

assuming $\tau \neq \delta$ (the solution involves critical damping otherwise). Now let $\tau = 10$ ms and $\delta = 5$ ms and examine the solutions plotted on the left of Fig. 4.3. It is clear that the response Δ lags behind $x(t)$, which is required of a delay. The figure also plots $x(t)$ with a true 5 ms delay to show that $\Delta(t)$ with $\delta = 5$ ms provides a modest approximation to the delay. If a more accurate approximation is desired, one can always include a chain of additional delay stages in eqn (4.13). For example, with four delay stages one would set $\delta = 1.25$ ms in this case, and the approximation to a true delay is greatly improved as shown on the right side of Fig. 4.3. In the limit of an infinite number of stages our approximation would be exact (see below). Remember, however, that in all computer simulations neural time delays are *de facto* represented by a finite number of stages simply because computers can only calculate a result at a finite number of time points. Thus, computer simulations reduce to embellishments of the delay approximation in eqn (4.13).

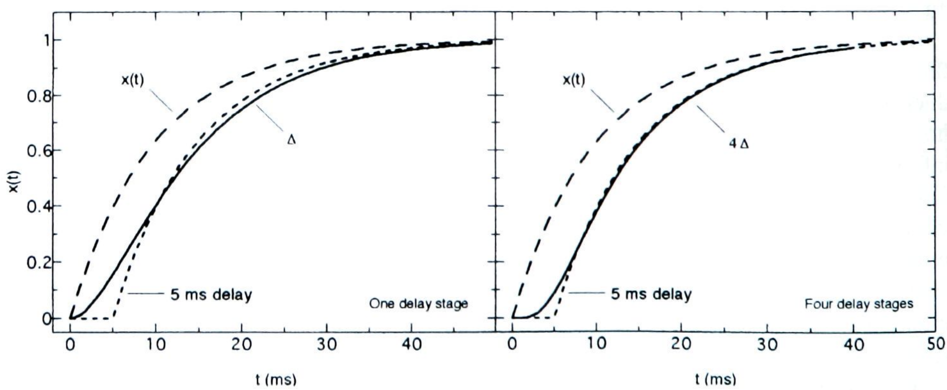

Fig. 4.3 Solid lines plot approximations to a 5 ms time delay by the introduction of one (left) or four (right) additional differential stages Δ as in (4.13). For comparison, an actual 5 ms delay of $x(t)$ (long dashes) is also shown (short dashes). Additional stages increase the accuracy of the approximation.

For most purposes the addition of one or two delay stages in the manner just described will permit a satisfactory approximation of delay effects on dynamics. (As emphasized by MacDonald (1989), however, a very large number of stages is sometimes necessary to explain all aspects of a true time delay.) Let us return to the feedback system in (4.10) and introduce a delay before the inhibition I begins to exert its effect. If we let $a = 2$, $b = 8$, and the time constants be 10 ms and 50 ms for E and I respectively, the equations describing the system become:

$$\begin{aligned}\frac{\mathrm{d}E}{\mathrm{d}t} &= \frac{1}{10}(-E - 2\Delta)\\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \frac{1}{50}(-I + 8E)\\ \frac{\mathrm{d}\Delta}{\mathrm{d}t} &= \frac{1}{\delta}(-\Delta + I)\end{aligned} \tag{4.15}$$

The presence of the delay stage Δ can be represented in a simple neural diagram like Fig. 4.4. Is there any value of the delay time δ that will produce an oscillation? The matrix for (4.15) is:

$$\overleftrightarrow{A} = \begin{pmatrix} -1/10 & 0 & -1/5 \\ 8/50 & -1/50 & 0 \\ 0 & 1/\delta & -1/\delta \end{pmatrix} \tag{4.16}$$

The Routh–Hurwitz criterion in Theorem 7 can be used to solve for δ by entering matrix A into the MatLab function **Hopf.m** (always with G as the unknown), saving this function, and then running **Routh_Hurwitz.m**. You will find that $\delta = 7.61$ ms will cause solutions to (4.15) to be periodic with a frequency of 0.133, which is $0.133/2\pi$ cycles/ms or 21.2 Hz. Thus even a short feedback lag in eqn (4.15) can lead to rapid oscillations. Oscillations caused by delays in neural transmission may well be one cause of the tremors exhibited by patients with multiple sclerosis, a disease in which axonal transmission is known to be slowed down (Beuter *et al.*, 1993). Indeed, Mackey and Milton (1987) coined the term 'dynamical diseases' to refer to physiological systems that become dysfunctional due to alterations such as increased time delays. One cautionary note: not all feedback loops are guaranteed to oscillate for some value of δ in eqn (4.15). Whether an oscillation can occur or not is dependent on the feedback gain as well, an issue

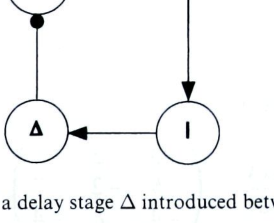

Fig. 4.4 Negative feedback loop with a delay stage Δ introduced between the I and E neurons. The network is described by (4.15).