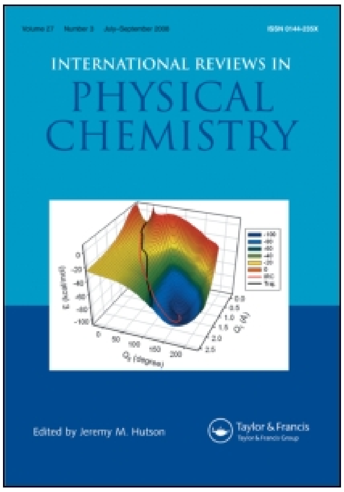

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Delay effects and differential delay equations in chemical kinetics

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Delay effects and differential delay equations in chemical kinetics

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The effects of time lags on the kinetic behaviour of chemical systems are considered. Such lags can result from spatial separation of components of a system, from the introduction of a delayed feedback, or as a way of representing the effects of intermediate steps in a series of reactions. The mathematical apparatus for treating systems with delay is introduced. Then, a number of examples, both experimental and theoretical, are discussed. It is seen that time lags can produce major, qualitative changes in the behaviour of a system, and that it is sometimes possible to reduce significantly the number of variables needed to describe a system if one utilizes differential delay rather than ordinary differential equations.

1. Introduction

The vast majority of studies in chemical kinetics employ sets of coupled, first-order, ordinary differential equations to describe the changes in time of the concentrations of species in the system. These rate equations, commonly derived from the Law of Mass Action, are idealized in a number of ways. They often assume isothermal conditions, yielding polynomial rate laws instead of the transcendental expressions that would result if the temperature were explicitly included as a variable. They constitute an average over microstates, allowing us to employ a relatively small number of bulk concentrations as our dependent variables. They ignore fluctuations, so that we may utilize deterministic equations rather than a stochastic or a master-equation formulation. They usually contain the implicit assumption that the medium is well-mixed with all species uniformly distributed; any spatial gradients would require the inclusion of diffusion terms and the use of partial differential equations. All of these assumptions or approximations are well known, and in all cases chemists have more elaborate techniques at their disposal for treating these effects more exactly should that be desirable.

Another, less widely appreciated idealization in chemical kinetics is that phenomena take place instantaneously, that a change in $[A]$ at time t generates a change in $[B]$ at time t and not at some later time $t+\tau$. If one takes a microscopic view, it is clear that this state of affairs cannot hold. At the very least, a molecular event taking place at point x and time t can affect a molecule at point x' only after a time of the order of $(x-x')^2/2D$, where D is an appropriate diffusion constant. The consequences of this observation at the macroscopic level are not obvious, but as we shall see in the examples below it may sometimes be useful, particularly if the mechanism is not known in detail, to introduce delays explicitly in modelling complex reaction networks.

Since relatively few studies have been undertaken of the effects of including delay in describing chemical kinetics, this article is not a review in the usual sense of summarizing and evaluating a large body of relevant literature in a mature field. The intent here is in part pedagogical, in part proselytizing. I hope to demonstrate to

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chemists that one may gain useful insights into some systems by using a formalism that includes delay effects, that it is worth thinking about these effects in mechanistic terms, and that there exists an accessible mathematical apparatus for dealing with such models. Mathematical biologists have been using delay models extensively for some time (Sharpe and Lotka 1923, May 1973). With the recent surge of interest in nonlinear chemical dynamics (e.g., Field and Burger (1985), Gray and Scott (1990)), the time is ripe for chemists to exploit these techniques as well.

The equations that one uses in treating systems with delay are *functional differential equations*, equations in which the time derivatives of a function depend not simply on the independent variable t, but on some function of t, e.g.

$$\frac{dx(t)}{dt} = -kx[f(t)]. \tag{1.1}$$

More specifically, we shall be dealing with *differential delay* or *differential difference equations*, where the concentrations $x(t)$ may change at rates that depend not only on the present values of the concentrations, but also on their values at earlier times. In other words, the function $f(t)$ in an equation like (1.1) will take the form $f(t) = t - \tau$, where τ is the delay. In the next section, I give a brief survey of the relevant mathematics. The most important material is contained in section 3. There, I summarize a variety of examples that should give the reader a sense of what has been done and of the potential and the power of this point of view. A final section is devoted to possible future directions.

2. Mathematical background

There are several books on the subject of differential delay equations. The recent work by MacDonald (1989) is probably the most accessible for the reader without extensive mathematical background. The earlier work by Bellman and Cooke (1963), while more mathematically oriented, contains a number of useful results. Hale's (1979) review article and several sections of Murray's (1989) excellent treatise on mathematical biology also contain readable treatments of differential delay equations.

2.1. *Differential delay equations*

A differential delay equation (DDE) is one in which the time rate of change of a species depends upon the state of the system at some previous time or times. In the simplest case, we have

$$\frac{dx}{dt} = f[x(t), x(t-\tau)], \tag{2.1}$$

where τ is the time lag or delay. It is, of course, possible to have equations with multiple delays $\tau_1, \tau_2, \ldots$, or even a continuous distribution of delays (MacDonald 1989). Also, one will generally be dealing with coupled systems of equations rather than with a single equation like equation (2.1).

To illustrate the profound effects that introducing delay can have on the nature of the solutions to chemical rate equations, we consider the prototype first-order decay

$$\frac{dx}{dt} = -kx(t). \tag{2.2}$$

We modify equation (2.2) by introducing a delay τ:

$$\frac{dx}{dt} = -kx(t-\tau). \tag{2.3}$$

By rescaling equation (2.3) in terms of the 'reduced time' t/τ, one can show that the properties of the solutions depend only upon the product $k\tau$ and not on the rate constant and time lag individually. We obtain the solutions to equation (2.3) explicitly in the next section. For $k\tau$ sufficiently small, $x(t)$ decays monotonically, though not exactly exponentially, in a manner similar to the non-delayed system. As $k\tau$ is increased, we observe first damped and then growing oscillations, with a single value, $q \equiv k\tau = \pi/2$, for which periodic oscillations occur.

In the table and figure 1, we summarize the behaviour of $x(t)$ as a function of the parameter $k\tau$. Note that the periodic behaviour is structurally unstable: the smallest change in the parameter q leads to a qualitative change in the behaviour. By adding a small nonlinear term, e.g., of the form $-\varepsilon x(t)^3$, to the right-hand side of equation (2.3), one obtains a system that gives structurally stable limit cycle oscillations, illustrated in figure 2, over a range of parameters q (Epstein 1990). Solutions to *linear* sets of coupled differential delay equations can be built up from the fundamental solutions (analogous to exponentials) to equation (2.3).

2.2. *Solution methods*

The analytical treatment of coupled, or even individual, nonlinear DDEs is an even more formidable task than that of solving ordinary differential equations. Nevertheless, it is useful to examine some of the methods available for solving DDEs. The prototype equation (2.3)

$$\frac{dx}{dt} = -qx(t-1), \tag{2.4}$$

in the generic transformed form (2.4) serves as a useful example for illustrating some of these techniques.

2.2.1. *Direct, interval by interval integration*

The most straightforward approach to solving an equation like (2.4) is to attempt to integrate it over an interval equal to the delay time and then to use that solution to integrate equation (2.4) in the next interval, etc. The mere description of this procedure points out a fundamental difference between ordinary and delay differential equations. To solve an ordinary differential equation, one must have the value of the solution (or its derivatives) at n points, where n is the order of the equation. For the first-order equations typically encountered in chemical kinetics, this requirement means that we

Qualitative behaviour of solutions to equation (2.3).

Range of parameter $q = k\tau$	Behaviour of solution $x(t)$
$0 \leqslant q < 1/e$	Monotonic decay to $x=0$
$1/e \leqslant q < \pi/2$	Damped oscillatory decay to $x=0$
$q = \pi/2$	Periodic oscillation, period $= 4\tau$
$q > \pi/2$	Undamped, growing oscillation

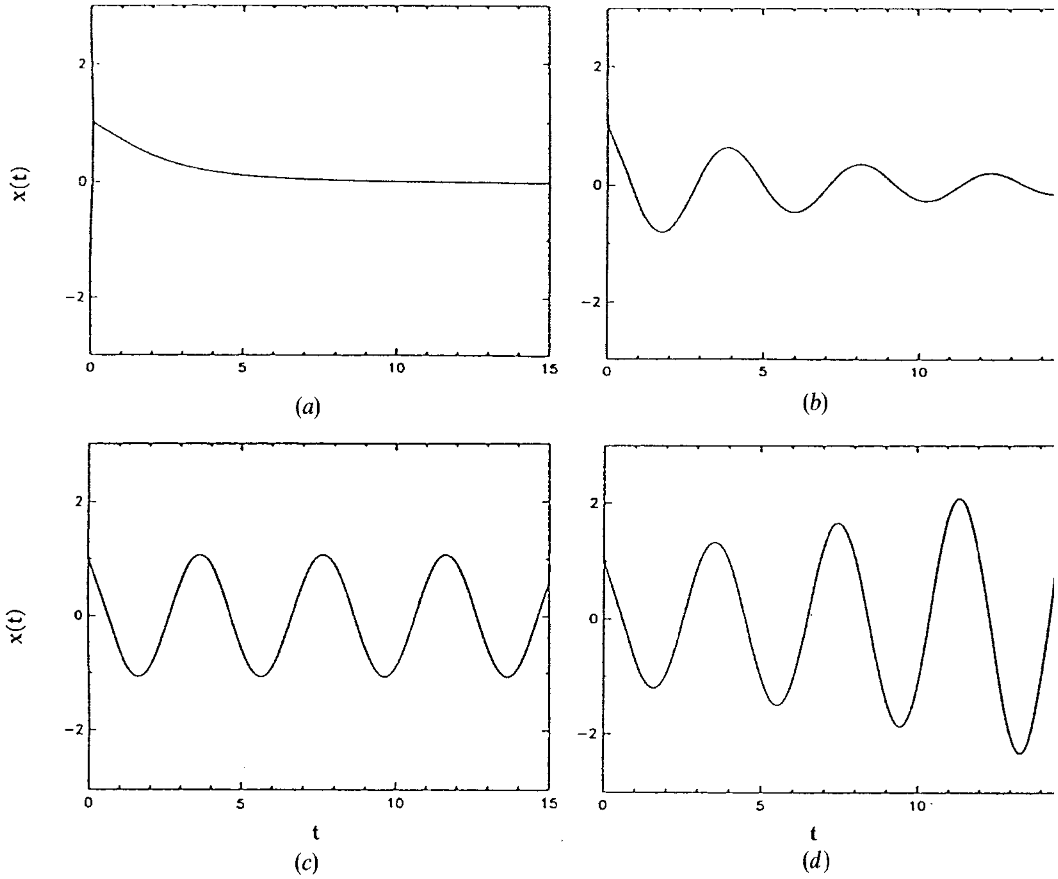

Figure 1. Behaviour of the solution $x(t)$ to equation (2.4) for several values of the parameter q. (*a*) $q=0{\cdot}3$, (*b*) $q=1{\cdot}3$, (*c*) $q=1{\cdot}5708$ $(\pi/2)$, (*d*) $q=1{\cdot}7$.

need to specify all of the concentrations at some initial time, say $t=0$. Solution of a differential delay equation requires the specification of the solution (all concentrations) *on an interval of length* τ, where τ is the delay time. In effect the delay system, even if there is only a single dependent variable, has an infinite number of degrees of freedom, because the solution must be specified at an infinite number of points on the initial interval. For this reason, the variety of dynamical behaviour that can be exhibited by a differential delay equation is far wider than that accessible to the corresponding equation in the absence of delay. For example, even a single nonlinear delay equation can give rise to chaotic solutions, while at least three coupled ordinary differential equations are required for chaos.

Returning to our example (2.4), let us consider the initial condition

$$x(t)=1, \qquad -1\leqslant t<0. \tag{2.5}$$

In the interval $[0,1)$, equation (2.4) becomes

$$\frac{dx}{dt}=-q, \qquad 0\leqslant t<1. \tag{2.6}$$

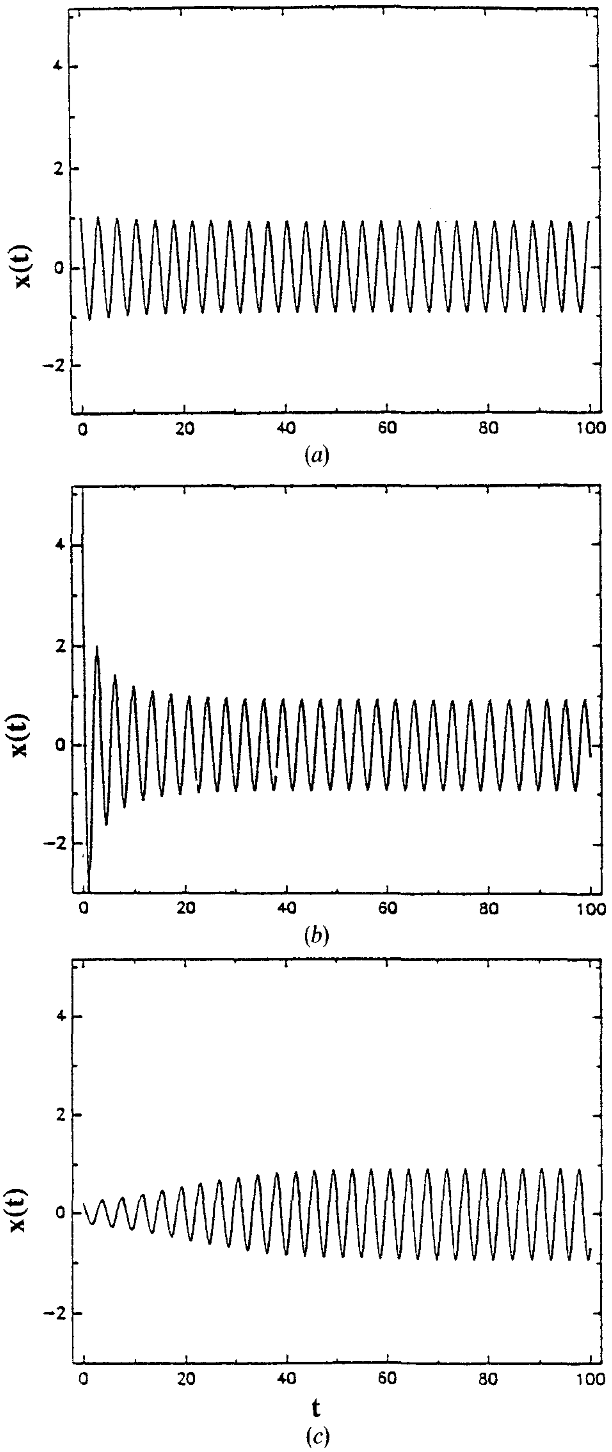

Figure 2. Limit cycle oscillations obtained by adding a small nonlinear term $-\varepsilon x(t)^3$ to the right-hand side of equation (2.4) with $q = 1{\cdot}7$. Note how with the different starting values $x(0) = 1$ (*a*), 5 (*b*), and 0·2 (*c*), the system approaches the limit cycle oscillation with period 3·76 and amplitude 1·87.

This is easily integrated to yield

$$x(t)=-qt+\text{constant},\qquad 0\leqslant t<1. \tag{2.7}$$

By requiring that the solution be continuous at the boundary between intervals, $x=0$, we find that the value of the constant in equation (2.7) must be 1.

Proceeding further, we have

$$x(t)=1-qt,\qquad 0\leqslant t<1, \tag{2.8}$$

$$\frac{\mathrm{d}x}{\mathrm{d}t}=-q+q^2(t-1),\qquad 1\leqslant t<2, \tag{2.9}$$

$$x(t)=-qt+\frac{q^2(t-1)^2}{2}+\text{constant}=1-qt+\frac{q^2(t-1)^2}{2},\qquad 1\leqslant t<2, \tag{2.10}$$

where again the constant in equation (2.10) has been determined by requiring that the solutions (2.8) and (2.10) be continuous at the boundary $t=1$. If we continue in this fashion, we soon observe that the general solution in any interval may be written in the form

$$x(t)=\sum_{m=0}^{n}\frac{(-q)^m}{m!}(t-m+1)^m,\qquad n-1\leqslant t<n, \tag{2.11}$$

or, equivalently

$$x(t)=\sum_{m=0}^{n}\frac{(-q)^m}{m!}(t-m+1)^m\theta(t-m+1). \tag{2.12}$$

2.2.2. *Laplace transform solution*

While the above procedure is a powerful one when it works, there are relatively few systems to which it can be successfully applied. A more generally applicable technique, useful in solving coupled sets as well as individual DDEs, is the Laplace transform. For ordinary differential rate equations, taking the Laplace transform affords sets of polynomial algebraic equations. For DDEs, we obtain transcendental equations.

Let us define, for any function $f(t)$, its Laplace transform $\hat{f}(s)$:

$$\hat{f}(s)=\int_0^\infty f(t)\exp(-st)\,\mathrm{d}t. \tag{2.13}$$

Transforming equation (2.4) with the initial condition $x(0)=1$ yields

$$s\hat{x}(s)-1=-q\left[\hat{x}(s)\exp(-s)+\frac{1}{s}-\frac{\exp(-s)}{s}\right], \tag{2.14}$$

where the last two terms on the right-hand side result from the fact that $x(t)=1$ for $-1\leqslant t<0$. We can solve for $\hat{x}$ to obtain

$$\hat{x}=\frac{1}{s}\frac{\left(1-\frac{q}{s}+\frac{q\exp(-s)}{s}\right)}{1+\frac{q\exp(-s)}{s}}. \tag{2.15}$$

Formal expansion of the denominator on the right-hand side of equation (2.15) as a power series in $q\exp(-s)/s$ yields

$$\hat{x}(s)=\frac{1}{s}+\sum_{m=0}^{\infty}(-q)^{m+1}\exp(-ms)\,s^{m+2}. \tag{2.16}$$

The transform (2.16) is easily inverted term by term to give an expression identical to equation (2.12), which was obtained by direct integration.

2.2.3. *Numerical methods*

Except in special limits, for example in the neighbourhood of equilibrium, most interesting sets of chemical rate equations are analytically intractable; they require numerical integration in order to yield explicit solutions. Sets of chemically significant differential delay equations are *a fortiori* even less likely to afford analytic solutions. While a great deal of progress has been made in recent years in developing numerical methods for treating even very large, stiff sets of ordinary differential equations (ODEs) (Gear 1971, Byrne and Hindmarsh 1987), I am not aware of comparable software readily available for integrating DDEs.

We have had some success with two numerical approaches (Epstein and Luo 1991), one an adaptation of a widely employed package for numerical integration of stiff ODEs, the other specifically developed to treat DDEs. The first method involves an adaptation of the Hindmarsh (1973) implementation of the GEAR program, which employs a backward difference formula with adaptive step size. As additional input for DDEs, we require the length(s) of the time delay(s) and the value(s) of the delayed variable(s) over the initial interval(s). The standard ODE program saves time by stepping the integration through the longest time step compatible with the error specification. In the DDE version, we force the program to compute and store the variables each $\varepsilon\tau$, where ε is a number of the order of 10^{-2} or 10^{-3} and τ is the time delay. The delayed variables are stored in an array, and at each integration step, a test is made to select the appropriate values of the delayed variables to use in computing the derivatives. The array of stored variables is updated at each step. If desired, one can make the procedure more accurate by interpolating the delayed variables from the previously computed stored variables (or one can decrease ε).

A rather different approach utilizes a fourth-order Taylor series approximation to the DDEs. Each interval τ is divided into a large number N of steps, and the non-delayed variables are stored in arrays of length N, while the delayed variables require arrays of length $2N$, the first N of these holding the values for the previous interval. The integration proceeds N steps at a time, moving the solution along by τ units of time. A subroutine must be written that contains explicit expressions for the first through fourth derivatives of each of the variables, obtained by differentiating the original DDEs. Each variable is then calculated by summing the terms in the Taylor series approximation through fourth order. Increasing the number of steps per interval N appears to afford greater improvement in dealing with stiff DDE systems than increasing the order of the Taylor series approximation.

While both of these methods work adequately with systems that are not very stiff in the absence of delay, long delay times τ engender serious numerical difficulties in systems like the Oregonator (Field and Noyes 1974) that display a significant degree of stiffness when $\tau=0$. As interest grows in DDE models, it is likely that more reliable numerical packages will become accessible to kineticists.

2.3. *Linear stability analysis*

A great deal can be learned about the dynamical behaviour of a system of ordinary differential equations by analysing the stability of the steady state(s) of the system. The same is true of systems of DDEs, and the analysis is similar, but more difficult. If the equations are written in the form of equation (2.1), where $\mathbf{f}$ and $\mathbf{x}$ are now considered to be vectors of length m, then a steady state of the system is one in which $\mathbf{x}(t)=\mathbf{x}(t-\tau)$ and all the time derivatives vanish:

$$\mathbf{f}(\mathbf{x}_s, \mathbf{x}_s)=0. \tag{2.17}$$

We are interested in the stability of the steady state $\mathbf{x}_s$ to small perturbations. As in the case of ordinary differential equations, we write

$$\mathbf{x}(t)=\mathbf{x}_s+\boldsymbol{\alpha}\exp(\omega t), \tag{2.18}$$

and substitute equation (2.18) into equation (2.1). We assume that the perturbation amplitude $\boldsymbol{\alpha}$ is small and linearize by dropping terms of second and higher order in $\boldsymbol{\alpha}$. This procedure results in an equation that resembles the familiar secular equation for the eigenvalues ω obtained in linear stability analysis of a set of ODEs. There are, however, some crucial differences.

Linearization of equation (2.18) affords a secular equation of the form

$$\det[\mathbf{J}(\mathbf{x}_s, \mathbf{x}_s)+\mathbf{J}_\tau(\mathbf{x}_s, \mathbf{x}_s)\exp(-\omega\tau)-\omega\mathbf{I}]=0, \tag{2.19}$$

where $\mathbf{I}$ is the identity matrix and we need to define two Jacobian matrices, one with respect to the instantaneous, and one with respect to the delayed concentrations:

$$\mathbf{J}_{ij}(\mathbf{x}_s, \mathbf{x}_s)=\left.\frac{\partial \mathbf{f}_i[\mathbf{x}(t), \mathbf{x}(t-\tau)]}{\partial \mathbf{x}_j(t)}\right|_{\mathbf{x}(t)=\mathbf{x}(t-\tau)=\mathbf{x}_s}, \tag{2.20a}$$

$$\mathbf{J}_{\tau ij}(\mathbf{x}_s, \mathbf{x}_s)=\left.\frac{\partial \mathbf{f}_i[\mathbf{x}(t), \mathbf{x}(t-\tau)]}{\partial \mathbf{x}_j(t-\tau)}\right|_{\mathbf{x}(t)=\mathbf{x}(t-\tau)=\mathbf{x}_s}. \tag{2.20b}$$

As equation (2.19) shows, whenever a derivative is taken with respect to a delayed variable, the resulting term in the Jacobian $\mathbf{J}_\tau$ must be multiplied by a factor $\exp(-\omega\tau)$. For systems without delay that obey Mass Action kinetics, the secular equation yields a polynomial equation of order m that can be solved for the roots $\{\omega_j\}_{j=1,\dots,m}$. With delay, the secular equation is transcendental, and the number of roots ω_j is in general infinite.

Despite the infinite number of roots of equation (2.19), it is often possible to determine analytically whether or not a given steady state $\mathbf{x}_s$ is stable. The problem is equivalent to deciding whether all the roots of an equation of the form

$$g(\omega)+h(\omega)\exp(-\omega\tau)=0, \tag{2.21}$$

where g and h are polynomials of degree $\leqslant m$, lie in the left half of the complex plane. Bellman and Cooke (1963) and MacDonald (1989) each present several general theorems that enable one to test algebraically the stability of a particular steady state. The results for systems of more than two variables are extremely limited, while those for two variables apply only to certain systems, depending upon the signs of the terms in the secular equation.

When there is only a single concentration variable, a powerful theorem due to Hayes (1950) is generally applicable. The theorem is as follows:

All roots of the equation

$$p\exp(z)+q-z\exp(z)=0, \tag{2.22}$$

where p and q are real, have negative real part if and only if

$$p<1, \tag{2.23\,a}$$

and

$$p<-q<(a_1^2+p^2)^{1/2}, \tag{2.23\,b}$$

where a_1 is the root of

$$a=p\tan(a), \tag{2.24}$$

such that $0<a<\pi$. If $p=0$, we take $a_1=\pi/2$.

Equations (2.23) provide three conditions on the steady-state concentration and the parameters that must be fulfilled in order for the steady-state to be stable. Application of equations (2.19) and (2.23) to our prototype DDE (2.3) yields a secular equation

$$-k\exp(-\omega\tau)-\omega=0, \tag{2.25}$$

which, after defining $z=\omega\tau$, and multiplying by $\tau\exp(\omega\tau)$ takes the form of equation (2.22) with $p=0$, $q=-k\tau$. At the unique steady state $\mathbf{x}_s=0$, conditions (2.23 *a*) and the first of (2.23 *b*) are always satisfied, while the second condition (2.23 *b*) implies that, as observed earlier, the steady state is stable if $k\tau<a_1=\pi/2$. For $k\tau>\pi/2$, we have growing oscillations.

MacDonald (1989) proposes a more generally applicable geometric approach to deciding the stability question posed by equation (2.21). He first observes that a change in stability can occur only when a root of equation (2.21) crosses the imaginary axis, i.e., when $\omega=\mathrm{i}\beta$ with β real is a solution of equation (2.21). If we make the substitution $\omega=\mathrm{i}\beta$, we can rearrange equation (2.21) to take the form

$$\frac{-g(\mathrm{i}\beta)}{h(\mathrm{i}\beta)}=\exp(-\mathrm{i}\beta\tau). \tag{2.26}$$

If we know, for example, that the steady state in question is stable in the absence of delay, i.e., for $\tau=0$, then an instability can occur only if there are some real β and positive τ for which equation (2.26) holds. Whether or not this is possible is most easily assessed by a simple geometric construction. As β is increased† from 0 to 2π, the right-hand side of equation (2.26) simply traces out the unit circle in the complex plane. The left-hand side, $-g(\mathrm{i}\beta)/h(\mathrm{i}\beta)$, which MacDonald calls the *ratio curve* $R(\beta)$, will be some other curve in the complex plane. If a bifurcation occurs in which the stability changes, the ratio curve must intersect the unit circle. For our example equation (2.3), the ratio curve is given by $R(\beta)=-\mathrm{i}\beta/k$. As shown in figure 3 (*a*), this curve starts at the origin and then, as β is increased from 0, moves along the negative imaginary axis, intersecting the unit circle at $-\mathrm{i}$. Setting $\exp(-\mathrm{i}\beta\tau)=-\mathrm{i}$ here yields $\beta\tau=\pi/2$, while setting $R(\beta)=-\mathrm{i}$ implies that $\beta=k$. Combining these two results we recover the condition for

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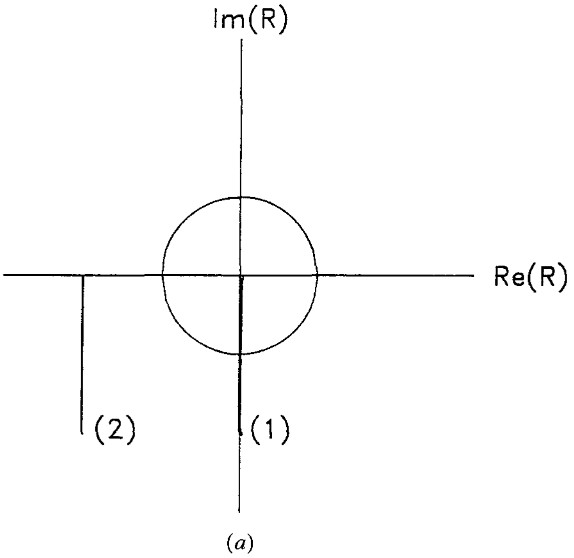
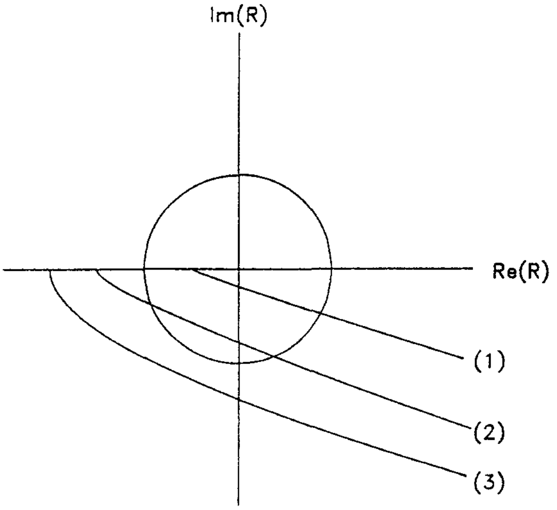
† MacDonald (1989) discusses, the significance of intersections of the ratio curve with higher order ($\beta>2\pi$) circuits of the unit circle.





(*b*)

Figure 3. Geometric construction (MacDonald 1989) for assessing stability of steady states of a DDE. In (*a*) $g(\omega)$ is linear and $h(\omega)$ is constant. Curve 1 shows case of equation (2.3) where stability changes as ratio curve and unit circle intersect. Curve 2 shows case in which the two curves never intersect, so stability is independent of τ. In (*b*), $g(\omega)$ is quadratic and $h(\omega)$ is linear. Curve 1 undergoes a single change in stability as τ is increased. Curve 2 has two changes in stability (e.g., stable→unstable→stable), and curve 3 shows no change in stability with τ.

the change of stability, $k\tau = \pi/2$. Some additional examples of this construction for other equations of the form (2.21) are shown in figure 3.

MacDonald's analysis yields a number of other significant results. For some choices of the functions g and h, it is possible for the ratio curve to cross the unit circle more than once. In such cases, contrary to intuition, the solution may be stable for short delays, unstable in an intermediate range of τ, and then stable again at longer delays (or unstable, then stable, then unstable). There may even be several 'windows of instability' as τ is increased. MacDonald also shows that the period of oscillation immediately after the steady state becomes unstable as τ is varied must exceed τ and is generally $>(3/2)\tau$. If one can show that $|R(\beta)|>1$ for all β, then the ratio curve can never cross the unit circle, so that the stability can never change, and the stability of the system is independent of the delay and can thus be determined for $\tau = 0$.

3. Examples

The significance and potential of differential delay equations in chemical kinetics are best appreciated by considering a number of examples of how delay models have been applied to systems of chemical interest. This section consists of a series of such examples. While it is not meant to be exhaustive, it should give a broad perspective on the sorts of things that one may do with delay models and DDEs.

3.1. *Network thermodynamics*

Katchalsky and collaborators (Oster, Perelson and Katchalsky 1973) have developed an approach to the thermodynamic analysis of complex dynamical systems in which chemical reactions are represented by the charging and discharging of capacitors (products and reactants, respectively) accompanied by the dissipation of free energy in a resistor (the reaction). The generalized capacitances are related to the free energies of the chemical species.

Atlan and Weisbuch (1973) point out that in a dissipative process, electrical or chemical, there is a non-zero time delay between the flow of matter (electrons or molecules) and the concomitant change in potential. Explicit inclusion of this delay within the framework of network thermodynamics leads to an additional resistance, i.e., a purely dissipative term. If the delay is long enough, then an additional inductive term, which may lead to oscillatory behaviour, appears as well. The authors attribute the physical origin of these effects to the time required for mixing after a local concentration change occurs. The magnitude of the time is related to the relaxation time of the reaction. In macromolecules, changes in conformation can increase the delay time significantly, leading to enhanced likelihood of inductance-like effects. While this approach does not appear to have been pursued in the literature, it may provide a useful starting point for connecting the thermodynamic and kinetic approaches to systems involving delays.

3 2. *A sequence of first-order reactions*

In a generalization of the notion of a rate-determining step, Epstein (1990) has shown that a sequence of coupled irreversible first-order reactions is asymptotically equivalent to a smaller set of DDEs involving only the concentrations of the reactant, product and 'bottleneck intermediate' species.

He treats the consecutive reactions

$$A_i \xrightarrow{k_i} A_{i+1}, \qquad i=1,2,\ldots,n-1, \tag{3.1}$$

with initial conditions

$$A_1 = A_0, \tag{3.2a}$$

$$A_i = 0, \qquad i = 2, 3, \ldots, n. \tag{3.2b}$$

The resulting set of rate equations

$$\frac{\mathrm{d}A_1(t)}{\mathrm{d}t} = -k_1 A_1(t), \tag{3.3a}$$

$$\frac{\mathrm{d}A_i(t)}{\mathrm{d}t} = -k_i A_i(t) + k_{i-1} A_{i-1}(t), \qquad i = 2, 3, \ldots, n-1, \tag{3.3b}$$

$$\frac{\mathrm{d}A_n(t)}{\mathrm{d}t} = k_{n-1} A_{n-1}(t), \tag{3.3c}$$

can of course be solved analytically to yield a sum of exponential terms for each of the concentrations. Epstein (1990) shows that after a transient period this solution approaches that of the following, generally smaller set of DDEs:

$$\frac{\mathrm{d}A_1(t)}{\mathrm{d}t} = -k_1 A_1(t), \tag{3.4a}$$

$$\frac{\mathrm{d}A_{\alpha(p)}(t)}{\mathrm{d}t} = -k_{\alpha(p)} A_{\alpha(p)}(t) + k_{\alpha(p-1)} A_{\alpha(p-1)}(t - \tau_{\alpha(p-1)}), \qquad p = 1, 2, \ldots, P, \tag{3.4b}$$

$$\frac{\mathrm{d}A_n(t)}{\mathrm{d}t} = k_{\alpha(P)} A_{\alpha(P)}(t - \tau_{\alpha(P)}). \tag{3.4c}$$

The key to the transformation from the ODEs (3.3) to the DDEs (3.4) lies in defining a subset $\{A_{\alpha(p)}\}_{p=0,1,\ldots,P}$ of *bottleneck intermediates*. These species, each of which is 'rate-determining' for a portion of the reaction sequence, are defined as follows. Let $\alpha(0) = 1$, and let $\alpha(P)$ be the index of that species i such that k_i is the smallest rate constant, i.e.

$$k_{\alpha(P)} = \min(k_i), \qquad i = 1, 2, \ldots, n. \tag{3.5}$$

If k_1 is the smallest rate constant, then $\alpha(P) = 1$, $P = 0$, and there are no bottleneck intermediates. The system is well described by two equations, one, equation (3.4 *a*), for the instantaneous disappearance of A_1, the other, equation (3.4 *c*), for the delayed appearance of A_n, where the delay τ_0 is determined by the mediating effects of all the fast reactions according to equation (3.7) below. If k_1 is not the smallest of the rate constants, then $A_{\alpha(P)}$ is a bottleneck intermediate. It accumulates at some point in the reaction, and the rate of its destruction is rate determining during some portion of the reaction.

Now consider the remaining species for which $i < \alpha(P)$. We choose $\alpha(P-1)$ to be the index of that species whose rate constant is the smallest in this group:

$$k_{\alpha(P-1)} = \min(k_i), \qquad i = 1, 2, \ldots, \alpha(P) - 1. \tag{3.6}$$

Again, if k_1 is the smallest of the remaining rate constants, we are done, $P = 1$, and there is a single bottleneck intermediate. If not, we continue the process until we are left with k_1 as the smallest remaining rate constant. The set of bottleneck intermediates is then complete. The delay times τ_p are given by

$$\tau_p = \frac{1}{k_{\alpha(p)}} \ln\left[\prod_{l=\alpha(p-1)+1}^{\alpha(p)-1} \frac{k_l}{k_l - k_\alpha(p)}\right]. \tag{3.7}$$

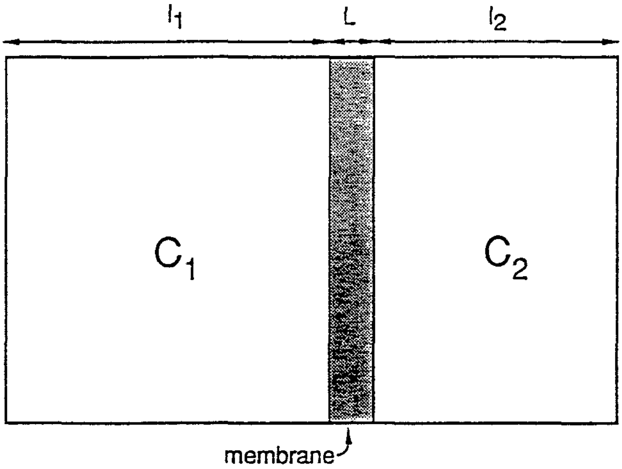


Figure 4. Model experiment involving diffusion through a membrane with associated time delay, equation (3.9) (Epstein 1990). Surface area of the membrane is A.

The DDE model (3.4) reproduces the exponential decay of the reactant A_1, the rise and fall, after a delay, of each of the bottleneck intermediates $A_{\alpha(p)}$, and the delayed buildup of the product A_n, which constitute the essential aspects of the dynamics of the full system represented by equations (3.3). While the model considered here is dynamically trivial, it does suggest the possible utility of an approach based on treating systems with many intermediates in terms of DDE models with just a few key intermediates and delays that incorporate the effects of the non-essential intermediates. The difficulty in implementing such an approach lies in deriving relationships analogous to equation (3.7) between the parameters of the system and the delay times.

Epstein (1990) also considers a model (Allnatt and Jacobs 1968) for nucleation in solid-state reactions that is equivalent to a set of coupled first-order rate equations. He shows that by introducing delays to account for the fact that an n-particle nucleus cannot grow until an $(n-1)$-particle nucleus is formed, the model can be made more physically realistic with relatively little increase in computational effort.

3.3. *Diffusion through a membrane*

Epstein (1990) has introduced a model that dramatically demonstrates the profound effects that delays associated with transport may have on the dynamics of a system *even in the absence of a chemical reaction.* Consider the arrangement shown in figure 4, in which two compartments containing the same species C are connected by a membrane that permits the diffusion of C. Each compartment is assumed to be well stirred and homogeneous, so each is characterized by a single concentration variable, C_i, $i=1,2$. The diffusion constant of C is D; the membrane has cross-sectional area A and length L; and the compartments have lengths l_1 and l_2, respectively.

Fick's First Law of Diffusion gives

$$\frac{\mathrm{d}C_i}{\mathrm{d}t}=\frac{D}{Ll_i}(C_j-C_i), \qquad i,j=1,2, \qquad j\neq i. \tag{3.8}$$

Implicit in equation (3.8) is the assumption that the time required for a molecule of C to cross the membrane is infinitesimal. In reality, this time is non-zero; in fact, there is a distribution of times τ for molecules to cross the membrane. The existence of such time lags is well known, and the mean value of τ for various diffusion geometries is discussed by Crank (1975). Let us for the moment examine a model in which *all* molecules take the same time τ to traverse the membrane. If we solve this problem for a general τ, we can then average the result over an appropriate distribution of time lags.

As a result of taking τ into account, the rate of increase of C_j at time t as a result of diffusion now depends not upon $C_i(t)$ but upon $C_i(t-\tau)$. If we define $q_i = D/Ll_i$, we obtain the DDE version of our instantaneous diffusion model equations (3.8):

$$\frac{\mathrm{d}C_i(t)}{\mathrm{d}t} = q_i[C_j(t-\tau) - C_i(t)], \qquad i,j=1,2, \qquad i \neq j. \tag{3.9}$$

The appropriate initial conditions are†

$$C_i(t) = C_i^0 \exp(-q_i t), \qquad 0 \leqslant t < \tau, \qquad i=1,2. \tag{3.10}$$

Equations (3.9) can be solved analytically (Epstein 1990) in terms of our 'delayed exponentials', equation (2.11). The solutions reveal some remarkable features of the model, two of which are illustrated in figure 5. If the compartments have equal volumes, if τ is large enough, and if the initial concentrations are sufficiently different (figure 5 (*a*)), then the system approaches equilibrium, where $C_1 = C_2 = C$, with damped oscillations. Even more surprising (figure 5 (*b*)), if the volumes of the compartments are sufficiently different, we can start with *equal* concentrations and the system will approach equilibrium in a damped oscillatory fashion.

What is the meaning of the highly counterintuitive and apparently non-physical behaviour? The key lies in the fact that the final equilibrium value of C lies significantly below the starting concentrations in the two compartments. The oscillations occur while the initially empty membrane is filling up. Consider the case of equal initial concentrations with cell 1 much longer than cell 2. In the first interval $[0,\tau)$, the same number of molecules leaves each cell, but, because cell 2 is smaller, its concentration drops further. At time τ, when molecules begin to arrive, the effect is reversed, and the concentration in cell 2 rises more rapidly than that in cell 1. Since molecules are now flowing in both directions, the effect will soon damp out. Calculations of the difference between the initial and final concentrations show that the amount of material 'missing', i.e., remaining in the membrane at equilibrium is proportional to $L/[3(l_1+l_2)+L]$, where we have taken (Crank 1975) $\tau = L^2/6D$.

Readers may find the above result more convincing if they try to picture how the initially equal densities of people in two rooms of very different sizes connected by identical doors through an anteroom will change in time if, when the doors are opened, people move from room to room with equal probability and equal velocity without collisions. It is also reassuring to observe that when the results are averaged over a realistic distribution of τ (which results, among other things, from molecular collisions within the membrane) the oscillations disappear and the concentrations behave monotonically as expected.

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† The diffusion is turned on at $t=0$, so that in the first interval $[0,\tau)$ C flows out of each compartment at a rate q_iC_i, but no C can flow in yet, because there has not been enough time for molecules to cross the membrane.

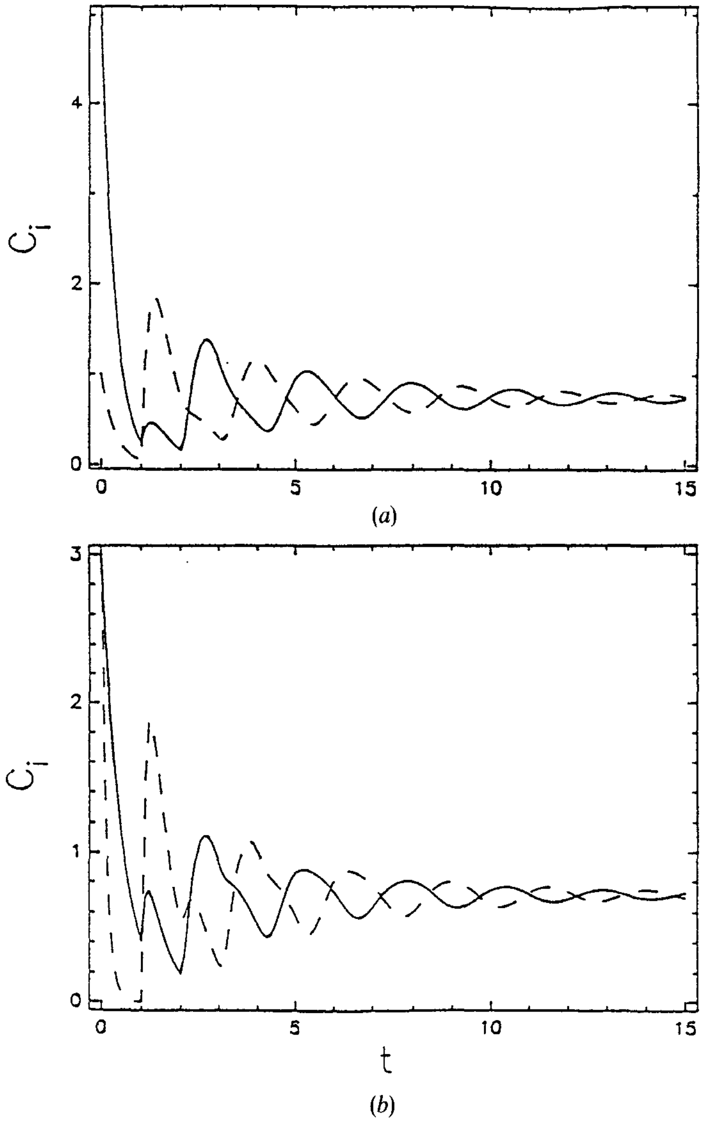


Figure 5. Oscillatory behaviour in the model of diffusion through a membrane shown in figure 4. Solid line is $C_1(t)$, dashed line is $C_2(t)$. (a) Unequal initial concentrations: $q_1 = q_2 = 3$, $C_1(0) = 5$, $C_2(0) = 1$, $\tau = 1$; (b) unequal volumes: $q_1 = 2$, $q_2 = 8$, $C_1(0) = C_2(0) = 3$, $\tau = 1$.

3.4. *A nonlinear system: delayed feedback in an illuminated thermochemical reaction*

The examples considered thus far all involve linear DDEs. While linear systems allow a considerable amount of analysis, they do not possess the rich variety of behaviour exhibited by nonlinear systems. As a first example of a nonlinear delay system, I shall consider a set of experiments and models studied by Ross and coworkers.

When the gas phase reaction

$$S_2O_6F_2 \rightleftarrows 2SO_3F, \qquad (3.11)$$

is illuminated at 488 nm, only the product SO_3F absorbs the light, which is turned into heat. As a result of the heating, the equilibrium shifts to the right, causing more SO_3F to be produced, and increasing further the amount of light absorbed. The reaction thus possesses a positive feedback. If the incident light intensity is slowly varied, the system shows hysteresis between a high-monomer and a low-monomer steady state (Zimmerman and Ross 1984). There is also an unstable steady-state with intermediate monomer concentration.

Zimmerman *et al.* (1984) modify the above system by adding a delayed feedback that causes the instantaneous intensity of the incident light to depend upon the concentration of SO_3F at an earlier time $t-\tau$. The particular relationship they use is

$$\Phi_0(t)=C_1+C_2[1-A(t-\tau)]\Phi_0(t-\tau), \tag{3.12}$$

where Φ_0 is the incident light intensity, C_1 and C_2 are positive constants set by the experimenter, and A is the light absorption of the solution, which can be calculated from $[SO_3F]$ using Beer's Law. The authors then analyse the stability of the resulting delay system.

They find first that the steady states of the modified system are the same as those of the system in the absence of the feeback. What is changed by the delay is the stability of these states. For short delays, the calculations show that the middle steady state, which is unstable, and hence experimentally unobservable in the absence of the feedback, can be stabilized. Schell *et al.* (1984) confirm this prediction experimentally, observing a significant segment of this previously unstable branch.

The phenomenon seen here of a state that is unstable without delay becoming stable for short delays is characteristic of the situation shown in figure 3 (*b*), where the ratio curve crosses the unit circle twice. The second part of the scenario is that at longer delays, the state again becomes unstable, and this is indeed what happens. In addition to the middle state becomining unstable at longer delays, the upper and lower states also become unstable, and the system becomes oscillatory. This behaviour is found both in the model calculations and in the experiments of Zimmerman, Schell and Ross (1984).

In a more detailed theoretical analysis of time delay in rate processes, Schell and Ross (1986) utilize similar models of illuminated thermochemical reactions with delayed feedback to reach a number of interesting conclusions. They observe that such systems, although they possess an infinite number of degrees of freedom as noted above, tend to be strongly contracting, so that they have attractors of relatively low dimension—steady states, periodic orbits, or low-dimensional chaos. The phenomenon of stabilizing an unstable state at short delays is found to be quite general. At longer delays, they observe not only periodic oscillation, but also chaos and hyperchaos (aperiodic behaviour with more than one unstable direction in phase space). These more exotic modes of behaviour result when a delayed feedback is applied to a system which can oscillate periodically in the absence of feedback. They are attributed to memory effects caused by the delay, which repeatedly reinject the system at different points in the neighbourhood of a saddle focus.

3.5. *A simpler example: the cross-shaped phase diagram*

Much of the recent progress in designing chemical oscillators (Epstein *et al.* 1983) has resulted from an algorithm based on a simple two-variable ODE model due to Boissonade and De Kepper (BD) (1980). The primary variable x evolves according to a cubic rate law, leading to bistability and hysteresis. The feedback variable y, for a sufficiently long relaxation time T, provides a delayed feedback that causes the system to become oscillatory. The equations of the model are

$$\frac{dx}{dt} = -(x^3 - \mu x + \lambda) - ky, \tag{3.13a}$$

$$\frac{dy}{dt} = \frac{x-y}{T}. \tag{3.13b}$$

If $T > 1/\mu$, the phase diagram of the system in the k–λ plane shows a characteristic cross shape (dashed lines in figure 6(*a*)), in which two triangular regions each possessing a single stable steady state are separated by regions of bistability and oscillation, all of which meet at the cross point P. If $T < 1/\mu$, only the monostable and bistable regions are present, and no oscillation can occur.

The role of the variable y in equations (3.13) is to generate a delayed feedback that pulls the system toward the line $x = y$. Epstein and Luo suggested that the single DDE (3.14) resulting from eliminating equation (3.13*b*) and replacing $y(t)$ in equation (3.13*a*) by $x(t-\tau)$ should display similar dynamics

$$\frac{dx(t)}{dt} = -[x(t)^3 - \mu x(t) + \lambda] - kx(t-\tau). \tag{3.14}$$

They performed a linear stability analysis of equation (3.14) using equation (2.19) to generate the secular equation

$$-3x_s^2 + \mu - k\exp(-\omega\tau) - \omega = 0. \tag{3.15}$$

Application of the stability conditions in equations (2.23) leads to three equations for the stability of the steady-states x_s. Two of these

$$3x_s^2 - \mu + \frac{1}{\tau} > 0, \tag{3.16}$$

$$3x_s^2 - \mu + k > 0, \tag{3.17}$$

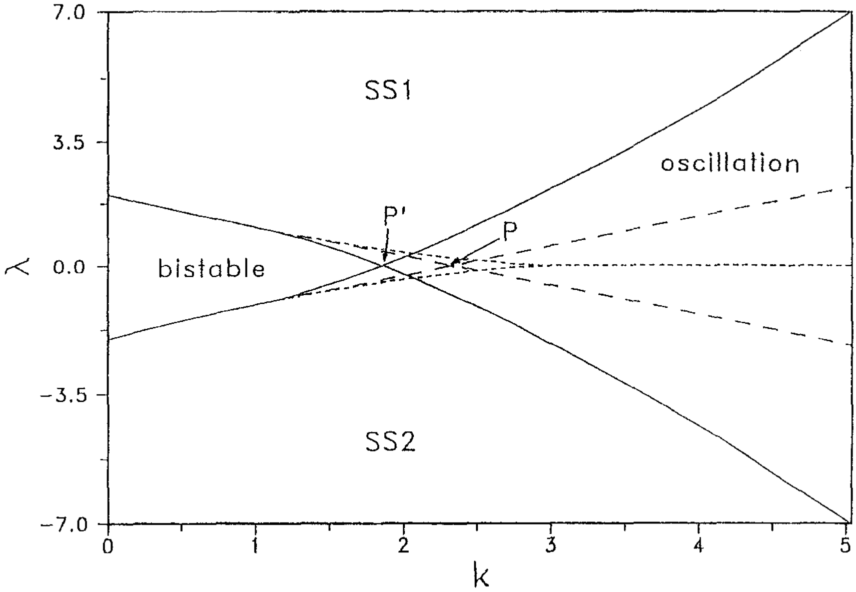
are identical to the conditions for the stability of the steady-states of the standard BD model if we replace the feedback time T in equation (3.13*b*) by the delay time τ in equation (3.14). The third condition

$$\left[(3x_s^2 - \mu)^2 + \left(\frac{a_1}{\tau}\right)^2\right]^{1/2} - k > 0, \tag{3.18}$$

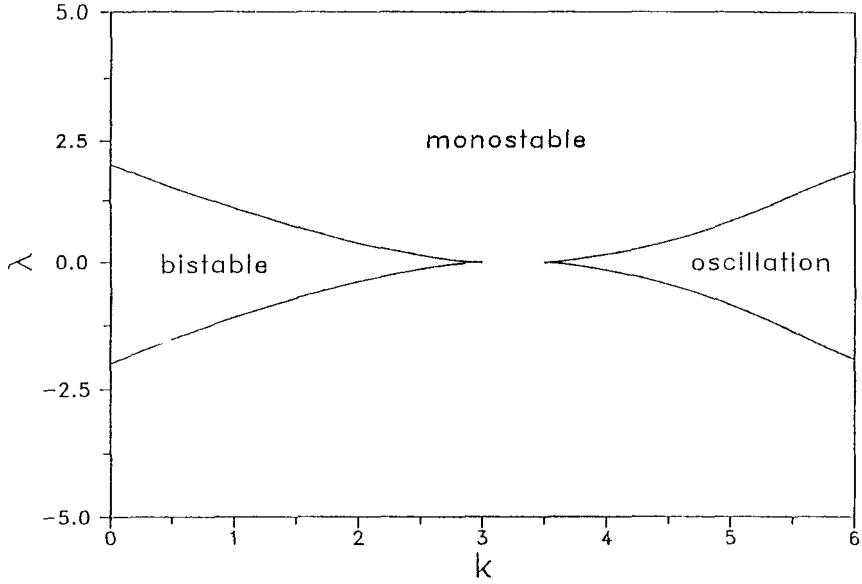
where $0 < a_1 < \pi$ and

$$a_1 = (-3x_s^2 + \mu)\tau \tan a_1, \tag{3.19}$$

is new and makes possible additional regions of instability of the steady-states of equation (3.14). Typical results are summarized in the phase diagrams of figure 6. Figure 6(*a*) illustrates the situation for the case of the usual cross-shaped phase diagram where $\tau > 1/\mu$; the behaviour is qualitatively the same. We have regions of monostability, bistability and oscillation. Now, however, the additional condition (3.18) has caused regions of the parameter space that gave stable steady-states in the BD model to become unstable. The oscillatory parameter range is increased, and the cross point has shifted from P to P′.



(*a*)



(*b*)

Figure 6. Phase diagrams in the k–λ plane obtained from linear stability analysis of the delayed BD model (Epstein and Luo 1991). (*a*) $\mu=3$, $\tau=1$. Dotted line separates regions in which there are one or three steady states. Dashed lines are stability boundaries given by equations (3.16 and 3.17), equivalent to ordinary BD model, equations (3.13) with $T=1$. Solid lines are stability boundary for full DDE model using conditions (3.18) as well. (*b*) $\mu=3$, $\tau=0{\cdot}3$. Only bistable region is found in ordinary BD model. Oscillatory region results from stability condition (3.18).

A more dramatic effect is seen in figure 6(*b*), where we examine the case $\tau < 1/\mu$. Here, the BD model yields only a single wedge-shaped region of bistability surrounded by a much larger region of monostability. In addition to these features, the DDE model possesses a region of oscillatory behaviour at large k and small $|\lambda|$. Recent experiments in our laboratory on the iodate–arsenous acid reaction (Weiner and Epstein, 1991, unpublished) confirm that by adding a delayed feedback to a bistable system that is incapable of autonomous oscillation, one can generate chemical oscillation.

3.6. *The Oregonator*

By far the most widely investigated model in nonlinear chemical dynamics is the Oregonator (Field and Noyes 1974), a set of five pseudoelementary steps that result in three ODEs, which give an excellent qualitative description of much of the dynamics of the classic Belousov–Zhabotinskii chemical oscillator. The model equations are

$$A + Y \rightarrow X, \tag{3.20a}$$

$$X + Y \rightarrow P, \tag{3.20b}$$

$$B + X \rightarrow 2X + Z, \tag{3.20c}$$

$$2X \rightarrow Q, \tag{3.20d}$$

$$Z \rightarrow fY, \tag{3.20e}$$

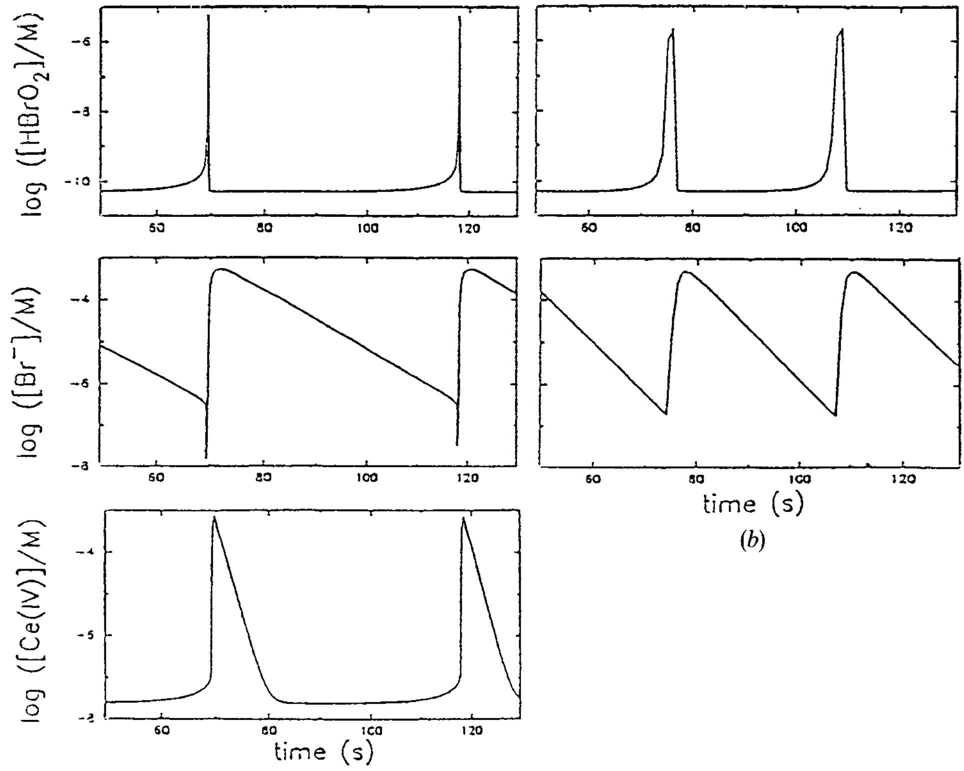
where f is a stoichiometric factor that specifies how many bromide ions are generated for each ceric ion consumed in the reaction, $A = B = \mathrm{BrO_3^-}$ are assumed to be constant, $P = \mathrm{HOBr}$ and $Q = \mathrm{BrO_3^-} + \mathrm{HOBr}$ are inert products, and the variable concentrations are $X = \mathrm{HBrO_2}$, $Y = \mathrm{Br^-}$ and $Z = \mathrm{Ce(IV)}$. Chemically, the role of cerium (Z) is to provide a means of regenerating bromide ion (Y), whose level controls the periodic switching of the reaction between autocatalytic and non-autocatalytic pathways for the consumption of bromous acid (X). In dynamical terms, as we shall see, it is also essential that this feedback generate a delay.

It would seem that there might be conditions under which one could simplify the model (3.20) by combining equations (3.20*c*) and (3.20*e*) into a single step (3.21), thereby eliminating Z and reducing the model to two variables X and Y

$$B + X \rightarrow 2X + fY. \tag{3.21}$$

Field and Noyes (1974) attempted such a reduction, but found that it was impossible to obtain oscillatory behaviour in any such reduced model. Epstein and Luo (1991) reasoned that it might be possible to combine the two steps and maintain oscillatory behaviour if one also incorporated the effects of delay. They examined two 'delayed Oregonator' models consisting of equations (3.20 *a*, *b*, *d*) and (3.21). In the first, the rate of step (3.20 *a*) was taken to be $k_a A Y(t-\tau)$, while all other rates were determined by the Law of Mass Action. In the second model, step (3.20 *a*) had mass action kinetics, but step (3.20 *b*) was given a rate $k_b X(t) Y(t-\tau)$. Thus the first DDE model examines the effect of delay in the bromide feedback on the reaction of bromide with bromate, while the second looks at delay effects on the bromide–bromous acid reaction.

The results obtained were unequivocal. By a combination of linear stability analysis and numerical simulation, we were able to demonstrate that the first model cannot give oscillatory solutions for any values of the rate constants and initial concentrations, while the second model, with an appropriate choice of τ, yields oscillations very similar to those found in the three-variable ODE Oregonator model as shown in figure 7. The



(a)

(b)

Figure 7. Oscillatory behaviour in (*a*) the ordinary Oregonator DDE model of the BZ reaction, and (*b*) the delayed Oregonator (Epstein and Luo 1991) with $\tau = 2$ s as described in the text.

calculation thus shows not only that delay is essential in this system but reveals just where in the mechanism that delay plays its role.

3.7. *Bubble growth and gas evolution oscillators*

Smith and Noyes (1983) have developed a model for the oscillatory evolution of carbon monoxide gas in the Morgan reaction, the dehydration of formic acid by concentrated sulphuric acid. A key element in that model is a consideration of the process by which CO nucleates and forms bubbles. This process is described by a series of rate equations that describe the concentrations of bubbles of different sizes. While the results obtained are encouraging, it was necessary to treat at least 20 different classes of bubbles, and the authors suggest that a more elegant approximate formulation with fewer variables would be desirable. They propose a DDE description in which the change of concentration of dissolved gas $C(t)$ is given by

$$\frac{\mathrm{d}C(t)}{\mathrm{d}t} = \Phi(t) - LFJ_{\mathrm{n}}(t-\tau), \tag{3.22}$$

where L is the number of moles of gas per bubble that escapes the solution, F is the fraction of nuclei that ultimately grow and escape

$$\Phi(t) = k_{\mathrm{c}}[\mathrm{HCOOH}]_0 \exp(-k_{\mathrm{c}}t),$$

is the rate of formic acid dehydration, and J_n is the rate of formation of nuclei. No explicit simulations were carried out with this DDE formulation, but it may be worth pursuing further.

3.8. *The minimal bromate oscillator*

The Belousov–Zhabotinskii reaction (Belousov 1958, Zhabotinskii 1964), the metal ion catalysed reduction of bromate ion by an organic substrate such as malonic acid, is without doubt the most thoroughly studied of the chemical oscillators. The Field–Körös–Noyes (1973) mechanism, proposed nearly two decades ago, has withstood a number of challenges and modifications, and still appears to give an accurate description of the key dynamical aspects of that system. Despite recent progress (Györgyi, Turanyi and Field 1990), the fate of the organic substrate, condensed into the single stoichiometric factor f in equation (3.20 *e*) of the Oregonator model, remains the weakest link in our understanding of the BZ reaction. A modified version of the BZ reaction, in which the organic species is replaced by a flow of bromide ion into a stirred tank reactor (CSTR) has come to be known as the minimal bromate oscillator (MBO) (Orbán, De Kepper and Epstein 1982). This system, consisting of Mn(II), BrO_3^- and Br^- flowed into a CSTR, exhibits the classic cross-shaped phase diagram discussed in Section 3.5, with two regions of monostability, one of bistability and a narrow oscillatory region. Its mechanism (Noyes, Field and Thompson 1971) is probably the best understood of any of the chemical oscillators.

Weiner, Schneider and Bar-Eli (1989) carried out experiments on the MBO in the oscillatory parameter regime with the addition of a delayed feedback introduced by varying the CSTR flow rate at time t as a function of the state of the system at an earlier time $t-\tau$. They found that the period of the oscillation increased and decreased in a 'sawtooth' fashion as the delay τ was introduced.

In a related, but far more detailed study, Chevalier, Freund and Ross (1991) have examined the MBO for parameters that lead to bistability (Geiseler and Bar-Eli 1981) in the absence of delayed feedback. The feedback is introduced by having fixed flows of $MnSO_4$ and $NaBrO_3$ and a variable flow of NaBr with a flow rate given by

$$f_{Br^-}(t)=\kappa\{1+\varepsilon\sin(\omega x(t-\tau)+\phi)\}, \qquad (3.23)$$

where x is the voltage of the bromide-sensitive electrode, κ is the mean flow rate, ε sets the amplitude of the nonlinear feedback, ω is a frequency in concentration space, and Φ is the phase of the feedback. In these experiments, the flow rate was updated according to equation (3.23) every 0·22 s (the sampling time).

The variety of dynamical behaviour observed in this apparently simple system is truly remarkable. As τ is increased, there are Hopf bifurcations to simple periodic behaviour, then period doubling sequences to chaos as well as several types of multistability. One of the most interesting observations, shown in figure 8, is *crisis* (Grebogi, Ott and Yorke 1982), the sudden expansion of the size of a chaotic attractor as a parameter (in this case τ) is varied. This is believed to be the first experimental observation of crisis in a chemical system.

Chevalier *et al.* calculate the correlation dimension (Grassberger and Procaccia 1983) and compare the results with a conjecture (Le Berre, Ressayre, Tallet, Gibbs, Kaplan and Rose 1987) that in chaotic systems with delayed feedback the dimension of the chaotic attractor should be given by τ/δ_f, where δ_f is the correlation time of the delayed feedback. A quantitative comparison with the experimental results shows that in this system τ/δ_f gives an overestimate of the correlation dimension.

Simulations of the MBO system with the delayed feedback of equation (3.23) taken into account give excellent qualitative agreement with the bifurcation sequences observed in the experiments.

3.9. *A model for optical bistability—DDEs and maps*

The single DDE (Ikeda, Daido and Akimoto 1980)

$$\frac{1}{G}\frac{\mathrm{d}X(t)}{\mathrm{d}t} = -X(t)+a-b\sin[X(t-1)], \tag{3.24}$$

has been used in a number of model studies of optically bistable systems. The control parameters a and b depend upon the input voltage, while X represents the output voltage. A simple rescaling ($t \to t/G$) shows that G is the delay time.

Although the behaviour of equation (3.24) is itself of considerable interest, I use it here only to point out a considerable simplification that arises in the limit of very long delay times $G \to \infty$. In that limit, the behaviour of the DDE (3.24) reduces to that of the one-dimensional map (3.25)

$$X_t = a - b\sin X_{t-1}. \tag{3.25}$$

This particular map possesses an extremely rich bifurcation structure, largely because it is a two-parameter, multiple-extremum map, in contrast to the one-parameter, single-extremum maps that are normally studied (Nardone, Mandel and Kapral 1986). The array of analytical techniques that can be brought to bear on the map (3.25) is considerably more powerful than those available for the DDE (3.24). Detailed numerical calculations suggest that the map solutions indeed give an excellent description of the DDE bifurcation structure for large G. Whether this approach is likely to prove useful for other chemical models for realistic values of the delay time (i.e., when is the delay large?) is a question that seems well worth exploring.

3.10. *Biological models*

The number of DDE models of chemical interest is but a small fraction of the number of biologically significant delay models that have been investigated. MacDonald's (1989) book and Murray's (1989) book provide excellent surveys of this work. Here I look briefly at two examples.

Buchholtz and Schneider (1987) have developed a mechanism to describe the transcriptional and translational processes involved in DNA replication during the infection of T3 and T7 bacteriophages. They find that even at 17-step mechanism is inadequate to model the abrupt rise of certain proteins and DNA species, and they conclude that the experimentally observed kinetics is best described by the explicit introduction of lag times. They attribute these delay times to transport processes involving linear diffusion of proteins along macromolecules and they discuss how to estimate the translational and transcriptional delays from experimental data.

The authors conclude that 'the replacement of a time lag by a linear chain of ordinary reaction steps will also produce a steep rise in products where, however, the actual number of reaction steps and their individual rate constants are unknown. Furthermore, multiple reaction steps would make it difficult to achieve a direct correlation between product rise times and the location of the genes'. Thus, as in the treatment of Section 3.2, introduction of delays allows one to eliminate intermediate steps and species. Here one gains the additional advantage that the delay times may be correlated with physical data about the position of genes.

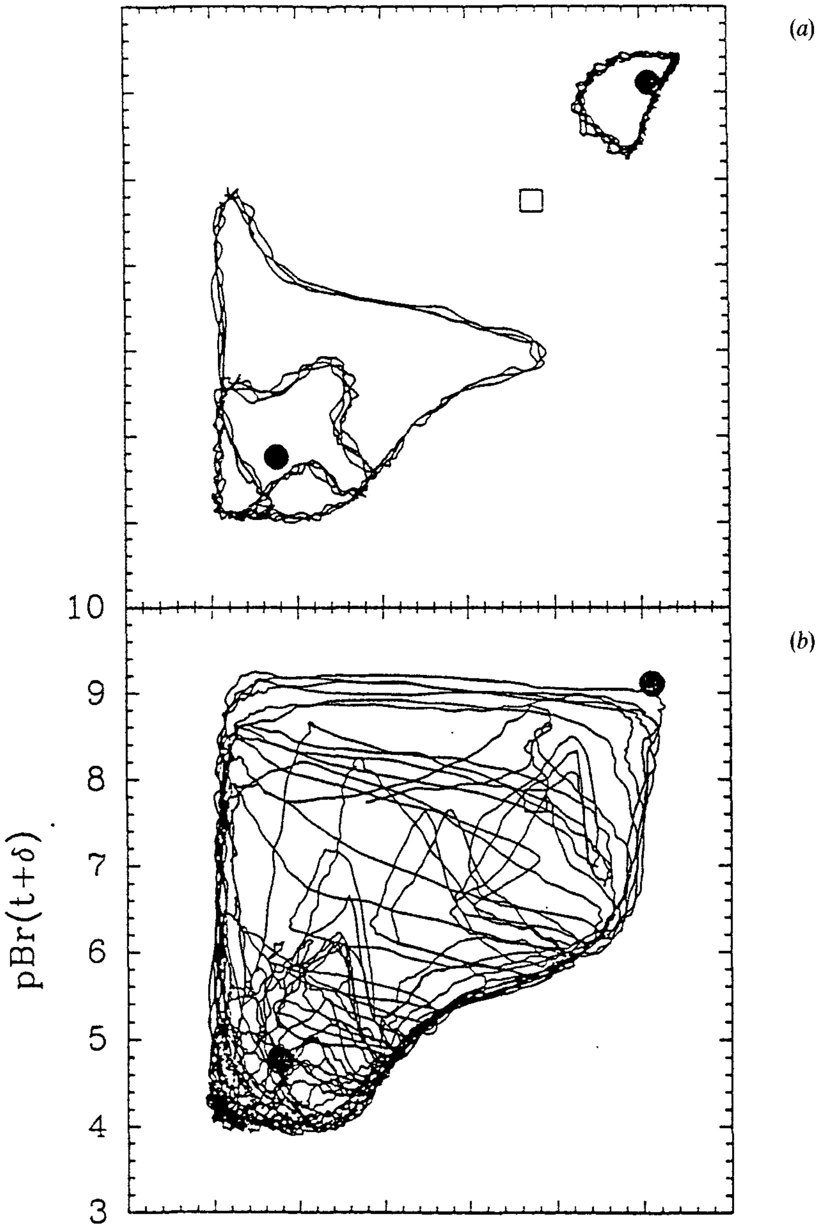


Figure 8. Experimental phase portraits showing crisis (Chevalier *et al.* 1991). Axes represent potential of bromide-sensitive electrode at times t and $t + 32{\cdot}9$ s. $\tau =$ (*a*) 54·925 s, (*b*) 109·85 s. Filled circles represent initially ($\tau = 0$) stable fixed points; empty squares are initially unstable fixed points. As τ is increased, lower attractor collides with unstable fixed point and undergoes sizeable expansion (crisis).

Glass and Mackey (1979) have defined a class of *dynamical diseases*, pathological conditions caused by abnormal temporal organization. One of the best characterized of these conditions is Cheyne–Stokes respiration, a human respiratory ailment in which the ventilation or volume of air taken in regularly increases and decreases, with the periods of low ventilation corresponding to dangerously low or apneic levels. Mackey and Glass (1977) have constructed a delay model for Cheyne–Stokes respiration, which is based on the known physiological features of the respiratory apparatus and which gives excellent agreement with the available clinical data.

Ventilation is controlled by the level of arterial CO_2, $c(t)$. Carbon dioxide is produced at a relatively constant rate by metabolic processes in the body. Since the CO_2 receptors are located in the brain stem and the 'message' about how much air to take in must reach the lungs, there is an inherent time delay τ between any change in c and its effect on the ventilation V. Finally, the ventilation saturates with c; to describe this effect, a Hill function is used to describe the dependence of the ventilation V on c. Incorporating all of these features results in the following equations for the dynamics of the CO_2 level in the blood:

$$V(t)=V_{\max}\frac{c^m(t-\tau)}{a^m+c^m(t-\tau)}, \qquad (3.26\,a)$$

$$\frac{\mathrm{d}c(t)}{\mathrm{d}t}=p-bV(t)c(t)=p-bV_{\max}c(t)\frac{c^m(t-\tau)}{a^m+c^m(t-\tau)}, \qquad (3.26\,b)$$

where $V_{\max}$, the maximum possible ventilation, the Hill parameters a and m and the CO_2 removal coefficient b can all be determined from experimental data. Equation (3.26) possesses a unique positive steady-state. Linear stability analysis reveals that this state is stable when

$$\left.\frac{\mathrm{d}V}{\mathrm{d}c}\right|_{c=c_s}>\frac{p\pi}{2abc_s\tau}, \qquad (3.27)$$

where c_s is the steady-state value of c in equation (3.26 *b*). Equation (3.27) implies that the (healthy) steady-state will become unstable and give way to (pathological) oscillations in ventilation if either the delay time becomes too long or if the dependence of V on c, equation (3.26 *a*), becomes too steep at the steady-state.

4. Future directions

The use of delay models and differential delay equations in chemical kinetics is a subject still in its infancy. While it is always difficult to predict what directions a new area is likely to grow in and how significant those directions may prove to be, it seems worthwhile to close this review by suggesting some aspects of the subject that merit further development.

On the mathematical and computational side, there is a considerable body of theory for dealing with a single differential delay equation. Both the analytical approach to be found in Bellman and Cooke (1963) and the geometrical approach of MacDonald (1989) offer powerful methods for investigating the stability and dynamical behaviour of individual DDEs. Numerical methods for single DDEs are also relatively easily adapted from the corresponding ODE methods. The situation for sets of coupled ODEs is less well developed, and as interest grows in models that require their solution, it seems likely that improved methods will be developed for dealing with such systems. Mathematically, the geometrical approach appears to offer somewhat more promise, at least for systems of moderate size. It may prove more productive, especially in treating larger systems, for numerical analysts to design methods specifically aimed at DDEs rather than to adapt older techniques for treating DDEs.

The notion, presented first in our treatment of sequential first order reactions in Section 3.2 and then in Section 3.8 on the BZ reaction, of using delays both to analyse and to simplify complex reactions with many intermediates, is an attractive one. Chevalier *et al.* (1991) suggest that the imposition of a delayed feedback can be used to determine the elements of the steady-state Jacobian and thus to differentiate among competing mechanisms. Epstein and Luo (1991) take a step in the latter direction by showing at which stage of the BZ reaction the delay in the feedback becomes essential for oscillation. The most difficult part of reducing complex systems by the introduction of delays is to understand how the delay is related to the kinetic parameters (rate constants, concentrations, etc.) of the intermediates being 'hidden' in the delay. The problem is exactly soluble (as many other problems are) for a linear system; one obtains an expression like equation (3.7). For the more interesting nonlinear case, one needs a different approach. Results on the BZ reaction (Epstein and Luo 1991) suggest that the time between the concentration maxima of the intermediate being eliminated and of the species being delayed may be a useful estimate of τ. However, this quantity may not be experimentally accessible. What is needed is an *experimental* approach to assessing the number and magnitude of the time lags in a system.

Experimentally, delayed feedback is a potentially powerful tool for the analysis of dynamical systems. It can be used either to stabilize otherwise unstable steady states (Zimmerman *et al.* 1984) or to cause a steady-state to become unstable, leading to periodic or chaotic behaviour. Presumably, delayed feedback can also be used to stabilize unstable periodic orbits, though this question has not apparently been addressed either experimentally or theoretically. In view of recent interest in using (instantaneous) feedback to make chaotic systems behave periodically (Ott, Grebogi and Yorke 1990), this may be a problem worth exploring further.

Delay systems offer the possibility of creating, with the help of microcomputers, relatively simple, easily controlled 'chemical circuit elements' for studying dynamical systems. One can sample some variable like a concentration or an absorbance at time t and use that reading to affect the system parameters at $t+\tau$.† The delay time τ provides an easily controlled bifurcation parameter that can have profound effects on the dynamics of the system. In my own laboratory, we have recently constructed a simple oscillator from a photochromic reaction and a variable intensity light source by making the light intensity depend upon the composition of the solution at $t-\tau$ (Kagan, Saigh and Epstein, 1991, unpublished). By combining several of these units, it should be possible to construct systems capable of considerable dynamic complexity. The analogy to neural systems, in which impulses must travel from sensory neurons to a central processor and then back to motor neurons with a concomitant transmission delay, is one that may be worh pursuing.

Whatever the path of future development, it seems clear that chemists interested in the dynamical behaviour of complex systems should be aware of the possibilities inherent in models that incorporate delay and of the availability of techniques for treating such models.

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† This is often done unintentionally, but in most (though not all) experiments τ is small enough that its effects may safely be ignored.

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