ISSN 1360–1725

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Numerical Analysis Report No. 343

July 1999

Released on `http://ma.man.ac.uk/~cthbaker`
on October 7th 1999

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A Report on the Use of Delay Differential Equations in Numerical Modelling in the Biosciences

C.T.H.Baker[*], G.A. Bocharov[†] and F.A. Rihan[*]

July 1999

Abstract

We review the application of numerical techniques to investigate mathematical models of phenomena in the biosciences using delay differential equations. We show that there are *prima facie* reasons for using such models: (*i*) they have a richer mathematical framework (compared with ordinary differential equations) for the analysis of biosystems dynamics, (*ii*) they display better consistency with the nature of the underlying processes and predictive results. We now have suitable computational techniques to treat numerically the emerging models for the biosciences.

Keywords Delay differential equations, dynamical systems, biological systems, deterministic and stochastic models, numerical modelling, parameter estimation, optimization.

Contents

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1 Introduction

Retarded functional differential equations (RFDEs),

$$y'(t) = f\left(t, y(t), y(\alpha(t, y(t))), \int_{-\infty}^{t} \mathcal{K}(t, s, y(t), y(s))ds\right), \quad t \geq t_0, \tag{1.1}$$

wherein $\alpha(t, y(t)) \leq t$ and $y(t) = \psi(t),\ t \leq t_0$, form a class of equations which is, in some sense, between ordinary differential equations (ODEs) and time-dependent partial differential equations (PDEs) such as reaction-diffusion equations. RFDEs (1.1) where the integral term is absent are usually called delay differential equations (DDEs) and they assume forms such as $y'(t) = f\left(t, y(t), y(\alpha(t, y(t)))\right)$ with $\alpha(t, y(t)) \leq t$. Neutral delay differential equations (NDDEs) are defined by equations of the form

$$y'(t) = f\left(t, y(t), y(\alpha(t, y(t))), y'(\beta(t, y(t)))\right), \text{ where } \alpha(t, y(t)),\ \beta(t, y(t)) \leq t,$$

although some authors consider only a subset of such equations. The introduction of the "lagging" or "retarded" arguments $\alpha(t, y(t)),\ \beta(t, y(t))$ is to reflect an "after-effect"; consider (as an example of a time-lag) the gestation period in population modelling.

Our concern here is with the role of the numerical analysis of RFDEs in the biosciences. There are three important components to our approach: first, the place of RFDEs in modelling in bioscience (which involves an understanding of the underlying science), second, familiarity with the analytical features of RFDEs, and third, familiarity with the numerics (an ability to obtain insight from numerical analysis, and an awareness of key features in designing or implementing robust codes). Like some other fields of analysis, research on qualitative analysis of RFDEs has profited greatly by choosing test examples from theoretical biology. In order to develop appropriate computational strategies and insight, numerical analysts, especially those producing codes, should classify the various types of problems with delay (there are point delays, distributed delays, state-dependent delays, integrals within or taken over the delay) and it is helpful to follow recent developments in the life sciences to see what problems require further study. Note that the type of RFDEs that occur in the physical sciences or engineering may be different from those that occur in bioscience, and some of our remarks should be modified in the light of differences between the application areas.

Two classical references for DDEs are the books by Bellman & Cooke [21], and Elsgol'ts & Norkin [60]. These are rich sources for analytical techniques and many interesting examples. Kolmanovskii *et al.* [105, 106] gave a rigorous treatment of a wide class of problems. Starting from the first edition, the monograph of Hale [83], (subsequently Hale & Verduyn Lunel [85]) is a standard source on the theory of delay equations. Another substantial monograph is by Diekmann *et al.* [53]. Kuang [107] and R. Banks [18] pay particular attention to problems in population dynamics; the former also looked at neutral equations. Gopalsamy [73] and Györi & Ladas [78] addressed the question of oscillations in delay differential equations. Early books by Cushing [48], Driver [58], Halanay [84], MacDonald [110, 111], May [128], Maynard Smith [129], and Waltman [175] have been very stimulating for the development of the field.

2 Mathematical Models with Delays

Delay equations generate (as do reaction-diffusion equations) infinite-dimensional dynamical systems; in both cases a solution is in general determined by an initial function rather than an initial value. In both cases the "flow" has properties which leads to the existence of limit sets and global attractors. On the other hand, there are clear differences between DDEs and PDEs. Whereas DDEs may appear to somewhat simpler than PDEs. It is possible that PDEs with memory combine the advantages of both types of equation as possible models.

We are concerned with applications in the biosciences, but an early use of DDEs was to describe technical devices, e.g. control circuits. In that context the delay is a measurable physical quantity (for example, the time that the signal takes to travels to the controlled object, the reaction time, and the time that the signal takes to return). There are parallels in the reaction of the body to pain, for example.

In most applications in the life sciences a delay is introduced when there are some hidden variables and processes which are not well understood but are known to cause a time-lag [45, 138]. Thus, a delay may in fact represent a reaction chain or a transport process [64]. We shall see later that the mathematical properties of DDEs justify such approximations. A well-known example is Cheyne-Stokes breathing, discovered in the 19th century: some people show, under constant conditions, periodic oscillations of breathing frequency [113]. This strange phenomenon can be considered to be caused by a delay in the physiological circuit controlling the carbon dioxide level in the blood, caused by cardiac insufficiency.

Delays occur naturally in biological systems, e.g., in the chemostat (a laboratory device [163] for controlling the supply of nutrient to a growing population of micro-organisms). The use of ODEs to model the chemostat carries the implication that changes occur instantaneously. This is a potential deficiency of the ODE model. There are two sources of delays in the chemostat model: delays due to the possibility that the organism stores the nutrient (so that the "free" nutrient concentration does not reflect the nutrient available for growth); and delays due to the cell cycle; see [25], [24], [40], [111] and [141]. However, in some cases, e.g., in simplistic ecological models, it seems that delays have been introduced rather *ad hoc*, thus putting subsequent researchers on the wrong track, as was remarked in [49]; one can suggest that better coordination between the modellers and the biologists would reduce or eliminate this problem.

2.1 Some deterministic equations

Pursing[1] the last theme, we note that Hutchinson [93] was one of the first mathematical modellers to introduce a delay in a biological model, when he modified the classical model of Verhulst to account for hatching and maturation periods. He pointed out that the observed oscillation in some kinds of biological phenomena could be explained by a discrete time delay in the crowding or resource term. He studied the rather simple equation

$$y'(t) = ry(t)\left(1 - \frac{y(t-\tau_\star)}{K}\right), \tag{2.1}$$

where the non-negative parameters r and K are known respectively as the intrinsic growth rate and the environmental carrying capacity, and if $\tau_\star = 0$ we recover the logistic differential equation. In fact, although eqn (2.1) appears at first sight to be simple, the solution can display complicated dynamics.

The incorporation by Hutchinson of the delay in eqn (2.1) allows one to model the appearance of sustained oscillations in a single species population, without any predatory interaction of other species. However, the underlying argument is somewhat questionable [2], and one may ask a number of questions of this model: (*i*) How can it be that the present change in population size depends exactly on the population size of time $\tau_\star$ units earlier? (*ii*) Why does the delay enter the removal term $-y^2/K$ and not the production term y ? The first question has led people, commencing with

[1]The authors are indebted to Prof. Hadeler for his input to this section; see Acknowledgments in Section 7.

[2]There has been a tendency in the "mathematical ecology" literature to introduce delays into existing predator–prey competition models on the basis of rather general arguments that the interacting species somehow rely on resources that have been accumulated in the past. It can be somewhat difficult to separate genuine results for firmly-grounded models from results for those rather arbitrary equations where an "artificial" delay is introduced with no specific justification other than its impact on the solution.

the early work of Volterra [172], to consider more general equations

$$y'(t) = ry(t)\left(1 - \frac{1}{K}\int_{-\tau_\star}^{0} y(t+s)d\sigma(s)\right). \tag{2.2}$$

The second question can be answered by applying the theory of populations structured by age (or structured by size). It is interesting that one can (see [35]) establish a connection between some models of population dynamics using neutral delay differential equations and the widely accepted Lotka-McKendrick model formulated as a hyperbolic PDE. The Sharpe-Lotka-McKendrick model, and its extension due to Gurtin and MacCamy [131],

$$u_t(t,a) + u_a(t,a) + \mu(a,W)u(t,a) = 0, \qquad u(t,0) = \int_0^\infty b(a,W)u(t,a)da, \tag{2.3}$$

provide the standard models in the theory of age-structured populations. Here $u(t,a)$ is the density of the population with respect to age a, the mortality μ and the fertility b depend on age and on some functional W of the population density, traditionally the total population size $W(t) = \int_0^\infty u(t,a)da$. The functions $\mu(a)$ and $b(a)$ have the following typical features: The death function $\mu(a)$ may be large for small a (high infant mortality), then level off to some plateau and finally become large for large a. A maximum age can be incorporated by letting $\mu(a) \to \infty$ for $a \to a^*$, where a^* is some finite value, or by simply discarding individuals with ages $a > a^*$. The birth function $b(a)$ is zero below a certain age, then becomes large in an interval of high fecundity, then returns to zero. This assumption leads to population models in the form of delay equations. Assume that

- (i) there is a maturation age $\tau_\star > 0$, separating juveniles from adults;
- (ii) $\mu(a) = \mu_0 + (\mu_1 - \mu_0)H_{\tau_\star}(a)$;
- (iii) $b(a) = b_1 H_{\tau_\star}(a) + b_2\delta_{\tau_\star}(a)$.

Here $H_\tau(\cdot)$ is the Heaviside function ($H_\tau(\alpha) = 0$ for $\alpha < \tau$, $H_\tau(\alpha) = 1$ for $\alpha \geq \tau$) and the delta function $\delta_{\tau_\star}(\cdot)$ is its generalized derivative. For $t \geq \tau_\star$, the populations of juveniles $U(t) = \int_0^{\tau_\star} u(t,a)da$ and adults $V(t) = \int_{\tau_\star}^\infty u(t,a)da$ satisfy a system of DDEs:

$$\begin{aligned} U'(t) &= b_1V(t) + (b_2-1)(b_1+b_2\mu_1)e^{-\mu_0\tau_\star}V(t-\tau_\star) + \\ &\qquad (b_2-1)\times b_2e^{-\mu_0\tau_\star}V'(t-\tau_\star) - \mu_0U(t), \qquad (2.4)\\ V'(t) &= ((b_1+b_2\mu_1)V(t-\tau_\star) + b_2V'(t-\tau_\star))\,e^{-\mu_0\tau_\star} - \mu_1V(t). \qquad (2.5)\end{aligned}$$

If we have initial data for the partial differential equation $u_0(a)$, and use the corresponding solution $u(t,a)$ to form $U(t)$, $V(t)$, then these two functions do not satisfy the system of eqns (2.4)-(2.5) for $t \in [0,\tau_\star]$, but only for $t \geq \tau_\star$ (after a time interval of length $\tau_\star$ which is, in some sense, needed to "forget" the information contained in the initial data). For $t \in [0,\tau_\star]$, the variables $U(t)$ and $V(t)$ satisfy a non-autonomous system of ODEs

$$U'(t) = b_1V(t) + (b_2-1)u_0(\tau_\star - t)e^{-\mu_0 t} - \mu_0U(t), \tag{2.6}$$

$$V'(t) = u_0(\tau_\star - t)e^{-\mu_0 t} - \mu_1V(t). \tag{2.7}$$

Using eqns (2.5), (2.7), one can compute $V(t)$ without using $U(t)$ (this is not the case if one allows some fertility of juveniles). Eqn (2.5) is a neutral DDE for the adult population. The neutral character of the equation is a consequence of the fertility peak at age $\tau_\star$ and is in no way artificial. If this peak is absent, i.e., $b_2 = 0$, then one gets the standard DDE

$$V'(t) = b_1V(t-\tau_\star)e^{-\mu_0\tau_\star} - \mu_1V(t). \tag{2.8}$$

This equation allows the following interpretation: adults die with rate μ_1 and produce offspring with rate b_1; the offspring enter the equation only at the age of maturity, diminished by a factor $e^{-\mu_0\tau_\star}$, which takes into account juvenile mortality. A similar approach can be applied to yield a nonlinear equation with state-dependent b_1, μ_1. For example, if we assume that the birth and the death coefficients depend on W and we choose $W = V$, then instead of eqn (2.8) we have

$$V'(t) = \Big\{e^{-\mu_0\tau_\star} b_1\big(V(t-\tau_\star)\big)\Big\}V(t-\tau_\star) - \Big\{\mu_1\left(V(t)\right)\Big\}V(t). \tag{2.9}$$

An equation of this form has been used in modelling an oscillating insect population (see [80] for references). A framework for deriving delay models for age-structured populations can be found in [35, 77, 131, 162, 165].

2.2 A stochastic approach

So far we have considered *deterministic* delay models for biological systems. There is increasing evidence that better consistency with some phenomena can be provided if the effects of random processes in the system are taken into account. We refer to some examples in modelling population dynamics [141], blood cell production [117], immune responses [9, 121, 123, 130, 134], and neural control mechanisms: pupil light reflex, human postural sway and visuomotor feedback [26, 109].

Indeed, the random perturbations which are present in the real world imply that deterministic equations are often an idealization. For example, the neurological control systems operate in a noisy environment, and the effect of noise on the nonlinear system dynamics needs to be considered in the analysis of the experimental traces of the state variables (such as, the electro-encephalogram, pupil area, displacement of the finger position in patients with Parkinson's disease). To model the dynamics of biological delay systems under random perturbations, *stochastic* delay differential equations (SDDEs) are used:

$$dY(t) = f(t, Y(t), Y(t-\tau_\star))dt + g(t, Y(t))dW(t), \tag{2.10}$$

Here, the first term on the right is the *drift term* and *incorporates the time lag*; the second term on the right is the *diffusion term*. $W(t)$ is a Wiener process having independent stationary Gaussian increments with $W(0) = 0$, $E\{W(t) - W(0)\} = 0$, $E\{(W(t) - W(s))^2\} = t - s$, $E\{W(t)W(s)\} = \min(t, s)$. There are two common interpretations of (2.10): it can be interpreted in the Itô sense or in the Stratonovich sense according to whether, when it is is reformulated in integral equation form as

$$Y(t) = \int_0^t f(s, Y(s), Y(s-\tau_\star))ds + \int_0^t g(s, Y(s))dW(s), \tag{2.11}$$

the second (stochastic) integral is taken in the Itô sense or in the Stratonovich sense. (If it is taken as a Stratonovich integral it is normal to use the notation $\int_0^t g(s, Y(s)) \circ dW(s)$.)

SDDEs (2.10) take into account the effect of noise via the diffusion term, either in an additive form, when g does not depend on the state $Y(t)$, or otherwise in a multiplicative form. Under certain conditions it can be shown that Equation (2.10) possesses a unique strong solution (we refer to the standard texts on SDDEs [106, 119, 133]). In the definition given above the stochastic differential equation is driven by white noise, where the concept of white noise is an idealization of a real fluctuating signal, requiring no correlation at different time instances. Mathematically speaking, we here have $dW(t) = \xi(t)dt$, where $\xi(t)$ stands for a stationary Gaussian white noise process. Other choices of driving processes, such as Poisson noise or coloured noise (usually modelled by a so-called Ornstein-Uhlenbeck process) are also used and the characteristics (bandwidth, energy, law,..) of the noise involved depend on the real-life phenomenon being modelled.

As noted, there exist two mathematically correct frameworks, namely the Itô and Stratonovich calculus, to deal with (2.11). For additive noise there is no difference between the two interpretations

of stochastic integrals. The choice of the stochastic calculus to be used again depends on the problem that is modelled. However, as it is possible to recast a SDE formulated in one framework to one formulated in the other one, the strengths of both calculi can be used to maximum benefit.

If one argues that in boimathematics the SDEs are generally serving as approximations to stochastic difference equations with autocorrelated noise, the Itô calculus may provide the more useful approximation. The Stratonovich framework may be more appropriate when the white noise can be considered as the limiting case of a smooth real noise process. Further discussions about appropriate modelling can be found in [116] and [169].

A well-documented example of a biological system where noise is an important component is the pupil light reflex, which displays complicated dynamics [109]. Noise is introduced into the reflex at the level of the brain-stem nuclei. The noise correlation time, the system response time and the delay in signal transmission are all of the same order of magnitude, and indicative of coloured noise. The spontaneously occurring aperiodic oscillations in the pupil area were explained with the mathematical model:

$$y'(t) = -\alpha y(t) + c\,\frac{\theta^n}{\theta^n + y^n(t-\tau_\star)} + k, \tag{2.12}$$

by assuming the effect of an additive or multiplicative coloured noise (respectively, $k = \overline{k} + \eta(t)$) or $c = \overline{c} + \eta(t)$). The long-term (compared to the size of the delay) numerical simulations of the SDDE provided the only possible means to establish the assumption of a major role of the noise in the dynamic behaviour. Longtin *et al.* [109] computed numerical approximations to sample trajectories $Y(t)$ using a combination of an integral Euler method for the equation defining the Ornstein-Uhlenbeck process, and a fourth-order Runge-Kutta (RK) method with a linear interpolation formula for the SDDE.

For another example of a SDDE, with the coloured noise entering equations multiplicatively, we refer to the model of neurological diseases suggested in [26], where the noise process is produced with a special electronic generator. The effect of *additive* white noise perturbations on the dynamics of human postural sway was studied in [65], using a scalar SDDE:

$$dY(t) = \alpha Y(t)dt + f(Y(t-\tau_\star))dt + \sqrt{2d}\xi(t)dt. \tag{2.13}$$

With this model and a piecewise constant approximation of f, noise-induced transitions between different limit cycle attractors were observed.

3 Studies of Biological Systems via Delay Models

Some non-stationary phenomena in biology (such as periodic oscillations, or instabilities) can be explained by considering the effects of delays in model systems. Recently, it has been suggested that delays can also have an opposite effect, i.e., they can damp out oscillations; this was shown with models for coupled oscillators under the condition that the delays in mutual interactions exceed a threshold value [152, 164]. It is generally accepted that the presence of delays in biological models is a potent source of instabilities. This can manifest itself as the loss of stability of an otherwise stable steady state if the delay exceeds a certain threshold (related to the dominant time-scale of a system); see [143]. However, there also exists opposing evidence [128] that a time delay can enhance stability, and short delays were shown to stabilize an otherwise unstable dynamical system [141, 143]. We seek to predict the qualitative properties of biological systems (equilibrium states, oscillations, chaotic dynamics, etc.) from the intriguing feature of delay differential equations.

The study of predator-prey systems occupies a considerable portion of the biomathematical literature, and the size of the book [73] reflects this interest. In research papers, the theoretical discussion is frequently complemented by *ad hoc* computational results. We shall be somewhat

selective in the areas of biomathematics that we detail, and in the following subsections we describe qualitative and quantitative studies based on DDEs. The former stem from mathematical analysis. A qualitative investigation informs the numerical analyst as well as the bioscientist but numerical simulation is invaluable for quantitative studies. In turn, the mathematical insight produced by numerical simulation can inform the analytical investigation and can guide the bioscientist both in the design of experiments and in the construction of a theory.

3.1 Qualitative studies

A simple delay model of growth in cell populations is given by the following linear DDE (see, for example, [13])

$$y'(t) = \alpha y(t) + \beta y(t - \tau_\star), \tag{3.1}$$

This equation is widely used as a standard test equation in the analysis of numerical methods for DDEs. The qualitative behaviour of (3.1) is well understood and can be summarized as follows: *the equilibrium solution* $y(t) \equiv 0$ *becomes unstable when the value of the delay exceeds the threshold given by*

$$\tau^{\#} = \frac{\cos^{-1}[-\alpha/\beta]}{\sqrt{\beta^2 - \alpha^2}} \tag{3.2}$$

and a Hopf bifurcation takes place with a period given by $T = \dfrac{2\pi}{\sqrt{\beta^2 - \alpha^2}}$.

For a long time, the delayed logistic equation (2.1) was a subject of qualitative and numerical studies in mathematical biology (see [18, 138, 110, 111] for extended discussions). This solution $y(t)$ converges monotonically to the carrying capacity K for $0 < r\tau_\star < \dfrac{1}{e}$; it converges to K in an oscillatory fashion for $\dfrac{1}{e} < r\tau_\star < \dfrac{\pi}{2}$; it oscillates in a stable limit cycle pattern for $\tau_\star > \dfrac{\pi}{2}$; see [18].

The classical eqn (2.1) assumes (by a simple re-scaling of the variables) the form

$$y'(t) = -\alpha\,(1 + y(t))\,y(t - \tau_\star) \quad (y(t) > 0, \quad t \geq -\tau_\star). \tag{3.3}$$

This equation, known as Wright's equation, has been investigated in number theory in connection with the distribution of primes. In two papers [98, 99], Jones demonstrated how an analytical approach and a computational approach can complement one another.

With $x(t) = \ln\{y(t)\}$, and $f(x) = e^x - 1$, eqn (3.3) can be transformed into the form

$$x'(t) = -\alpha f\left(x(t - \tau_\star)\right). \tag{3.4}$$

In the early 1970's equations of the form (3.4), with $f(0) = 0$, $f'(0) = 1$, $f'(x) > 0$, and some boundedness properties, became the standard equations for qualitative analysis; see Nussbaum [145] and references therein on earlier work. If we extended (3.4) by including a feedback term we arrive at an equation of the form

$$w'(t) = -\nu w(t) + \alpha f\left(w(t - \tau_\star)\right); \tag{3.5}$$

this equation was used to explain bursting in neurons by delays and also used as a model of blood cell dynamics [2, 113, 115]. For this equation, the existence of nontrivial periodic solutions has been shown by Hadeler and Tomiuk [82]. Eqn (3.5) depends on (apart from the delay $\tau_\star$) the two parameters ν and α. By re-scaling the variables and introducing $\varepsilon = 1$, one can cast the problem into the form

$$\varepsilon w'(t) = -w(t) + f\left(w(t - \tau_\star)\right). \tag{3.6}$$

Eqn (3.6) can be viewed as a singular perturbation of the discrete dynamical system $w(t) = f\left(w(t - \tau_\star)\right)$, which for any fixed t is an explicit recurrence relation.

In the standard form of Wright's equation the bifurcation is backward (the 3/2-theorem [144, 173, 174] says that the zero solution is globally stable for $\alpha \in (0, 3/2)$ but unstable for some $\alpha > 0$, $\alpha < \pi/2$). Hence there is an unstable branch of periodic solutions emanating from $x = 0$ at $\alpha = \pi/2$. This branch can be computed by combining a Poincaré-map (with *a priori* unknown period) with Newton's method; see [81]. The unstable branch enters the stable branch at a turning point; in other words, stable and unstable branches start from a saddle-node bifurcation at the turning point. The stable branch continues for increasing α and may undergo secondary bifurcations, depending on the nonlinearity. These secondary bifurcations are typically transcritical, but may be backward and such that new saddle-node bifurcations appear. For certain classes of f in eqn (3.4) the lowest secondary bifurcation has been thoroughly investigated by Dormayer [56], who showed that for an odd right hand side function f: $f(-x) = -f(x)$, there are solutions with period $4\tau_\star$. The underlying connection to embedded discrete dynamical systems leads to results on the existence of periodic solutions and global attractors for general *constant* delay differential equations of the form $y'(t) = f\left(y(t), y(t-\tau_\star)\right)$.

As far as (3.5), with a constant $\tau_\star > 0$, is concerned: for every $\nu \geq 0$, there is a critical α_ν such that the zero solution is stable for $\alpha \in (-\nu, \alpha_\nu)$, and unstable for $\alpha > \alpha_\nu$. For $\tau_\star = 1$ and $\nu = 0$, the critical value is $\alpha_0 = \pi/2$. Thus, for $\alpha > \alpha_\nu$, the constant solution becomes unstable, and a stable periodic solution appears. This transition can also be treated as a Hopf bifurcation.

The occurrence of oscillatory or periodic solutions is of wide interest [100, 73]. He, Zhang & Gopalsamy [88] considered equation of the form

$$y'(t) = y(t) f(t, y(t-\tau_\star)), \tag{3.7}$$

in modelling single species dynamics in a temporally changing environment. If f in eqn (3.7) is a periodic function in t, we can get a periodic solution.

Gopalsamy[3] [74] considered the neutral-delay equation of the form

$$y'(t) + by'(t-\sigma_\star) + ay(t-\tau_\star) = 0. \tag{3.8}$$

He proved that if a, b, τ, and σ are nonnegative constants and $[a/(1+b)](\tau_\star - \sigma_\star)e > 1$, then all bounded solutions of (3.8 are oscillatory. His result was extended to the nonlinear case

$$y'(t) + f(y'(t-\sigma_\star)) + g(y(t-\tau_\star)) = 0, \tag{3.9}$$

where f and g are continuous functions. He proved that under the conditions $yf(y) > 0$ and $yg(y) > 0$ for $y \neq 0, 0 \leq f(x)/x < b \leq 1$, $g(x)/x \geq a > 0$, and $[a/(1+b)](\tau_\star - \sigma_\star)e > 1$, all bounded solutions of (3.9) defined on $[0, \infty)$ are oscillatory.

So far, we have discussed delay equations with constant time-lag $\tau_\star$. In remote control problems it is easy to imagine situations where the delay is not constant but depends in some way on the state of the system. If such state-dependence is introduced, we get a state-dependent DDE, $y'(t) = f\left(y(t - \tau(y(t)))\right)$, where $\tau : \mathbb{R} \to [0, \bar{\tau}]$ is a given function, with some upper bound $\bar{\tau}$. For quite some time the study of its qualitative features was inhibited by the fact that it is difficult to linearize this equation about the zero solution. (If one tries a formal expansion then $y'(t)$, which is still nonlinear in y, appears on the right hand side.) Then it was discovered that for an adaptation of the existence proof for periodic solutions one does not need an exact linearization. One can project the solution on the unstable manifold of the problem with constant lag $\tau_\star(0)$ and still get ejectivity. This approach is presented by Mallet-Paret [118]. Thus, as far as the main branch of periodic solutions is concerned, the equation with state-dependent delay behaves about the same as a constant lag equation.

[3]We remark that we are aware of over 140 papers authored or coauthored by Gopalsamy that relate to delay equations.

In some biological applications the lag is governed by a differential equation (that models adaption to the system state). As an example, one has systems of the form:

$$\begin{aligned} y'(t) = &\quad f\left(y(t-\tau(t))\right) \\ \tau'(t) = &\quad g\left(y(t),\tau(t)\right), \end{aligned}$$

which, with $g(y,\tau) = \tilde{g}(y) - \tau$, have been studied recently in [4].

In an equation like (2.2) it is assumed that the lag has an upper bound. Although infinite lags are biologically unrealistic, it is sometimes mathematically convenient to allow for arbitrarily large lags, as in the RFDE

$$y'(t) = f\left(\int_{-\infty}^{0} y(t+s)d\sigma(s)\right). \tag{3.10}$$

(Equations of this form also appear in the theory of materials with memory.) The global properties of such systems may depend strongly on the chosen state space. A particular class of problems consists of systems of equations where the weight function σ is an exponential polynomial $\sigma(s) = e^{-s}$; these could be reduced to a system of ODEs of the form $y'(t) = f(z(t)), \quad z'(t) = y(t) + z(t)$, where $z(t) = \int_{-\infty}^{0} e^{-s}y(t+s)ds$; see Fargue [66], Wörz-Busekros [177].

It was underlined, in [128], that solutions for distributed delay equations are generally easier to obtain than solutions for discrete delay equations. A variety of analytical forms can be used for the kernel function. If the kernel appears to be a convex combination of gamma distribution functions

$$F_m(t) = \frac{t^{m-1}a^m}{(m-1)!}e^{-at}, \quad a \in \mathbb{R}, m \in \mathbb{N} \tag{3.11}$$

(non-integer m are considered in [86]) then the integro-differential equation is a reducible system and can be transformed to an equivalent system of ODEs through a linear chain trick technique [110, 111]. The delay kernels of this particular form are widely used in biological modelling as they can be represented as ODE models. Consider, as an example,

$$y'(t) = b\int_{-\infty}^{t} y(\sigma)F_m(t-\sigma)d\sigma - cy(t) \tag{3.12}$$

Applying the linear chain trick technique its solution can be obtained with the following ODEs

$$y'(t) = bz_m(t) - cy(t) \tag{3.13}$$

$$z_1'(t) = a\left(y(t) - z_1(t)\right) \tag{3.14}$$

$$z_i'(t) = a\left(z_{i-1}(t) - z_i(t)\right) \tag{3.15}$$

where i runs from 1 to m. The average time lag for the distributed delay model with kernel $F_m(t)$ is related to the parameters of the gamma distribution as $< \tau_\star >= \dfrac{m}{a}$. Distributed delay models with a gamma distribution kernel appear to be quite popular in modelling of the biological processes (see Sec.3.2 for examples in chemostat systems, blood cell production, and virus infections).

We note, in passing, that Arino and Sánchez [5] discuss models of cell population kinetics that can be presented as an "abstract" delay differential equations. Partial differential equations with retarded argument have been recently suggested for population dynamics problems by Mackey and Rudnicki [112] (a first order hyperbolic PDEs), Gourley and Bartuccelli [75], Kolesov and Rozov [103], and Faria [67] (delayed parabolic equations of reaction-diffusion type).

3.2 Quantitative studies

An understanding of biological phenomena implies the ability to predict and control them, and this understanding comes in several related stages: (i) formulation of mathematical models based

on biological first principles, (*ii*) qualitative assessment of the models, (*iii*) numerical analysis and computer simulation and (*iv*) biological interpretation. In the previous subsection we introduced feasible types of delay equations and we now look at their application in the numerical modelling of biological systems.

Mathematical problems in biology are derived under simplifying assumptions, which allow a mathematical representation to be developed. More stringent assumptions lead to a more consistent mathematical model, but one which is in general impossible to investigate explicitly, and it is numerical analysis and computer modelling that allow one to approximate the solutions of mathematically expressed biological problems. Of course, an increase in the complexity of mathematical models should be correlated with the quality and amount of experimental data available, and in studies of living systems this is not always the case. In this respect recent experience in the systematic refinement of mathematical models for HIV infection seems to be quite remarkable [89, 132].

Numerical studies using biomathematical models are undertaken in order to understand the system dynamics, estimate relevant parameters from data, test competing hypotheses, and assess the sensitivity to changes in parameters or variations in data and optimize its performance with the least possible cost. These objectives are associated with an increasing complexity of the numerical procedures.

Numerical modelling with RFDEs has been used for analysis and prediction in various branches of biosciences: ecology, chemostat systems, epidemiology, immunology, compartmental studies, neural networks, to name just few of them. We shall now discuss various situations where we know that numerical simulation has been used to advantage. Typically, the models represent a number of time-dependent state variables, each having a recognized biological interpretation, and a corresponding complexity in the parameters. (There are some data to support the need for such complexity.) Delay models formulated in mathematical biology represent several types of functional differential equations; DDEs, NDDEs, integro-differential equations, threshold-type equations, retarded PDEs and others. Recently, attention has also been given to implicit DDEs, for example $G\left(t, y(t), y(t-\tau_\star), y'(t)\right) = 0$, and to equations involving stochastic variables.

3.2.1 Ecology

Mathematical studies using delay models to study ecology are built upon various generalizations of Volterra's integro-differential system of predator-prey dynamics:

$$\begin{aligned} y_1'(t) &= b_1 y_1 \left(1 - c_{11} y_1 - c_{12} \textstyle\int_0^\infty y_2(t-s) k_1(s) ds\right) \\ y_2'(t) &= b_2 y_2 \left(-1 + c_{21} \textstyle\int_0^\infty y_1(t-s) k_2(s) ds\right) \end{aligned} \tag{3.16}$$

where the $y_1(t)$, $y_2(t)$ represent the populations of the prey and the predator, and the parameters specifying the birth and interaction rates are non-negative[4] (see [48]). These equations can be extended naturally to describe the dynamics of multi-species ecological systems. A recent example using (3.16) is presented in [55], where the stability, direction of bifurcation, period and asymptotic form of the periodic solutions (resulting from a Hopf bifurcation) are studied. The author considerd the case of kernels $k_i(s) = a_i e^{-a_i s}$. Extensive numerical simulations were carried out to investigate the behaviour of the periodic orbits in the parameter region around the stability-instability boundary.

Models incorporating a distributed delay like that in the equation

$$y'(t) = -\alpha y(t) + M_0 \left(\int_{-\infty}^{t-\tau_m} y(s) g(t-s)\, ds \right)$$

[4]There are variations of these equations, including forms with differing limits of integration and forms that incorporate Stieltjes integrals, in the literature.

are used in modelling ecological and chemostat systems, where the delay indicates that the growth of a species depends on the past concentration of nutrients. For early studies of the chemostat see references cited in the book by Smith & Waltman [163] and the recent exposition of delay models given in Wolkowicz *et al.* [180]. We refer to recent work by Ruan & Wolkowicz [158] presenting qualitative and numerical studies of Hopf bifurcation with, the average time delay as a bifurcation parameter. In [180] both discrete and distributed delays were used in computer simulations. The numerical simulations provided evidence that the delays representing the time-lag in the growth of the species as a function of the past concentration of nutrient, enhance the predictions on the transient behaviour, and with distributed delays the models are more realistic and accurate in reproducing the observed dynamics. One can, however, face difficulties in introducing delays in chemostat models as reported in Cunningham and Nisbet [47].

Various classes of differential equations are used as building blocks for increasingly complex models, with a recent example of a mixed model coming from parasitology [36]. To describe the dynamics of the host-parasitoid interaction an age-structured model has been suggested that combines the McKendrick - von Foerster equation (a first order hyperbolic PDE) for the juvenile host population, an ODE for the adult host population and a delay differential equation for the adult parasitoid population. A fixed lag appears in the production term of the parasitoid population. The phenomenon studied concerned the mechanism of oscillations in the populations of hosts and parasitoids. Numerical simulations suggested that there are multiple attractors in much of the parameter space and revealed a range of dynamics that can be produced with the model. Evidence was provided that it is the delayed density dependence in the parasitoid birth rate that can induce the cycles, in addition to the classic Lotka-Volterra consumer-resource cycles. The delayed feedback cycles result from periodic variation in the survival of cohorts through the juvenile class caused by the age-dependent processes.

We note that reaction-diffusion systems with delays in the reaction terms have been used recently in population models, for example the Lotka-Volterra competition system [75]. The distributed delays were approximated by gamma distribution functions ($m = 1, 2$). Parameter domains for instability (stability diagrams) of the spatially-uniform steady state solution were examined by computational means in conjunction with the argument principle. It was found that for fixed lags the stability diagrams have a much more complicated structure than for distributed delays. Another reaction-diffusion parabolic equation with delay was used for modelling the predator-prey system taking into account the migration of the predator and with a delay represents the length of time to mature to adulthood [103].

3.2.2 Epidemiology

Amongst the first to produce a theory of epidemics were Kermack and McKendrick [102]; they used mathematical models to study the spread of infections in populations. In modelling disease transmission the population is usually considered to be subdivided into disjoint epidemiological classes (or compartments) of individuals in relation to the infectious disease, for example: susceptible S, exposed E, infectious I and removed R, individuals. The development of the infection is represented by transitions between these classes. In the epidemiological models the waiting times in the compartments must be specified and the assumption of a constant period of stay of individuals in any of the compartments leads to delay differential equations. We cite some recent examples of delay models using fixed delays to represent the duration of the infectious period in the SIS-model [91], the immune period ($SIRS$-model) [92], or the periods of latency and temporary immunity ($SEIRS$-model) [44]. The case of a distributed duration of the latent period was studied with a distributed delay SIR-model by Beretta and Takeuchi [23]. In epidemic models that seek to take into account the age structure of the population, the lag represents the maturation period [79]. The

major effect of delays in the epidemic models is considered to make them less stable than the analogous models without delays [91]. The characteristics of infection dynamics being examined with the delay models are the existence and stability of the steady states associated with a disease-free situation or with epidemics. To this end one derives analytically the threshold parameters (such as the basic reproductive number) which specify sufficient conditions for asymptotic stability of the steady states or the appearance of periodic solutions. The numerical studies are usually carried out to support analytical results and provide some insight into more general situations which are difficult to treat analytically. It was reported in [72] that the numerical simulations $SEIRS$ model with delay differential equations were performed in XPPAUT [61]. For other references on epidemic models with delays we refer to the recent papers by van der Driessche [171], and by Hethcote and van der Driessche [91].

3.2.3 Immunology

Immunology presents many examples of mathematical models formulated using DDEs starting from simple models of the humoral immune response suggested by Dibrov *et al.* [50] and Marchuk [121]. We refer to [121, 122, 136, 151] as sources for numerous references on delay models formulated in immunology.

Marchuk and associates [9], [10], [30], [32], [101], [121]–[125], [157], [161] developed a hierarchy of immune response models of increasing complexity to account for the various details of the within-host defense responses to pathogens. The delays are used in the functional terms describing the proliferation and differentiation of lymphocytes, and represent the time needed for cells to divide, mature (i.e., express certain genes), or become destined to die. Whereas a basic model of an infectious disease has only one time-lag, more sophisticated mathematical models [121, 161] for viral-bacterial infections in lungs, or for T-cell division incorporate about ten delays. The numerical approaches to assimilation with the models of real data on the within-host immune responses and pathogen dynamics allowed the researchers to quantify a number of relevant parameters of pathogen-host interaction for human infections caused by influenza A [32], hepatitis B viruses [124, 125, 161], bacterial infections in the lung [101, 121, 157], mixed infections [127] and murine LCMV [30, 59] and influenza [121] infections.

We shall summarize the approach of Marchuk and his associates. Motivated by the need to solve constant lag models arising in immunology reliably and efficiently, two adaptive numerical codes were developed [34, 121]; these were based (*i*) on embedded Runge-Kutta-Fehlberg methods of order 4/5 supplemented by the Hermite interpolation, and (*ii*) on Gear's DIFSUB [71], which uses the variable order variable step-size *Adams-Bashforth-Moulton* or *BDF* methods to advance the solution and the Nordsieck interpolation technique to approximate the variables with delays [34, 121].

A typical data set characterizing immune responses can display a large variation in scale but with each datum being equally significant. To fit these types of data sets, the classical "least-squares" minimization of the sum of squared residuals appeared to be inefficient as it gives undue weight to a small change in large data value. The approach based on the log least-squares, i.e., fitting the logarithm of data and model prediction (see eqn (5.2)), improves the tractability of the parameter identification problem. The corresponding functional, providing a metric in $\mathbb{R}^N_+$, was proved to be efficient by other parameter estimation studies in immunology [132, 137].

Fitting of a large scale nonlinear model to data is a difficult task, and a good initial guess for the optimized parameters is of great importance. The parameter estimates can be improved by a sequential process of finding the best-fit parameter values for subsets of the data, where the subsets are obtained by subdividing the observation interval. The decomposition of the original identification problem into a set of simpler optimization subproblems on smaller time intervals is based upon the

precise idea on which processes are active during the smaller observation intervals. As the size of the subintervals increases, the best-fit parameter values can be improved in a step-by-step manner [33, 125]. For some specific issues arising in numerical parameter estimation with delay equations we refer to Sec.5

Another experience of fitting with time-lag equations in immunology is provided by Mohler *et al.* who developed compartmental models for lymphocyte migration [68, 135]. In studies of the compartmentalized systems, the delays represent (*i*) the time that cells reside in a particular compartment, or (*ii*) the transit times through compartments, or (*iii*) the duration of inter-compartmental transfer. The model in [68] was used to match quantitatively the data on lymphocytes in various relevant organs of the immune system; it employs ten constant lags. Experimentalists have the means to observe cell recirculation within the body by radioactive labelling and tracing the dynamics of radioactivity distribution to various organs of the immune system. The problem of interest is how to estimate the lymphocyte intra- and inter-compartment transfer rates using the given data. A combination of compartmental analysis and numerical modelling allowed the parameters representing the directional permeabilities to be estimated; these characterize the flow rates in the various circulatory vessels and organs in different regions of the body. The linear models

$$y'(t) = Ay(t), \quad y'(t) = A(t)y(t), \quad y'(t) = Ay(t) + \sum B_j y(t-\tau_j) \tag{3.17}$$

were employed to model lymphocyte circulation. The fit of the time-delay model was shown to be better than that provided by autonomous and non-autonomous ODE models. The common problem with the linear compartmental models was that they gave a biased fit with a systematic deviation from the data during the initial "response" phase and the "steady state" phase (either overshooting or undershooting). It was established that a non-linear ODE model, with nonlinearities representing a saturation of diffusion-rate-flow into organ from blood at high concentration of lymphocytes in the organ, gives a better approximation to the data than the linear counterparts. This again provides the evidence that an increase in complexity of mathematical models can lead to a better quantitative consistency with real data. Later, a similar linear system of DDEs was suggested to fit the experimental data on lymphocyte trafficking through sub-compartments within a single lymph node [135]. For other compartmental models using delays see Györi & Ladas [78].

The most recent example of constant-lag equations in immunology is the model of humoral immune response to Hemophilus influenza by provided Rundell *et al.* [160]. They take into account the fine structure of the humoral immune response, introduce several time-lags and a dozen variables, and provide an up-to-date framework for the analysis and control of the infection dynamics. The parameter identification problem for the nonlinear model was treated as a sequence of 'reduced' parameter identification problems by splitting the observation interval into a sequence of smaller subintervals (over each of which some reduced subset of parameters and equations are dominant). The design variables included the dosage of bacterial antigen administered, and the interval between immunization.

The pneumonia caused by *H. Influenza* presents a problem for hosts with immune deficiencies, such as AIDS patients. To cure the infection, intravenous treatment with antibiotics is used. In the latter paper, numerical simulations were carried out to investigate the efficacy of several vaccination scenarios aimed to establish a long-lasting protection against the bacteria mediated by the neutralizing antibody. A simple two dimensional predator-prey model, involving populations of bacteria and antibodies, with a delay in the antibody production term, was advanced to determine an optimal strategy for the drug delivery [159]. Numerical experiments with the model established a nonlinear dependence of the protective time period on the interval between immunizations and dosage, and suggested a sufficient strategy to provide two years of protection for a 18 month old child. The numerical approach to the optimal control problem (see Sec.7) allowed the authors to find a control

function-drug treatment regime which demonstrated a shorter recovery time, required 6% less drug administration and 3-times lower peak drug concentration. The model suggested continuous drug administration, as opposed to the standard approach based on periodic dosages. A sensitivity analysis indicated the robustness of the predicted control function with respect to parameter variation, although the range of parameter variation was not specified.

3.2.4 HIV (Human immunodeficiency virus)

The mathematical study of the within-host dynamics of HIV infection has received more attention during recent years than that of other infectious diseases. Estimates with simple models, based on ODEs, of the turnover of virus and infected cells revealed that HIV infection is a highly dynamic process, although the viral load and cell counts in infected patients can be in a quasi-steady state for years. This discovery was a breakthrough in understanding the nature of HIV and AIDS. The estimated value of 6 hrs for the viral half-life is considered, however, to be an upper bound, and the key problem (which is still outstanding) is to get an improved estimate [132]. It was suggested that a model of HIV infection that accounts for detailed aspects of an intracellular delay in virus production should give more accurate estimates. It was shown that adding more realism (associated with an increase in mathematical complexity) to the models by considering a fixed lag modification and, later on, including a distributed delay, could give better accuracy in estimating the viral clearance rate provided detailed patient data are available.

Herz *et al.* have recently shown [89] that explicit consideration of the delay between infection of a cell and the production of new viruses is necessary to estimate reliably the turn-over of HIV and HBV (Hepatitis B Virus) in infected patients. In [132] the approach was further refined by including continuously distributed intra-cellular delays. The delay distribution was assumed to be a gamma distribution. The authors noticed that, although there is no particular biological or mechanistic justification for it, the gamma distribution provides a suitable approximation of bell-shaped distribution curves. In this case the set of integro-differential equations used as a model can be converted into an equivalent set of ordinary differential equations using a linear chain trick technique (see Sec.3.1). The resulting system of ODEs was approximated numerically using a fixed step-size mesh and Euler or fourth order *RK* methods. The increased complexity of the model needs to be supported by clinical data, and the authors examined whether the parameters of the model including the time delay can be reliably estimated from data sets that include realistic levels of noise. Numerical minimization of the log least-squares functional was performed using the Levenberg-Marquardt algorithm with finite difference approximation of the partial derivatives. Parameter estimation results indicate that a number of optimal solutions exist and a good initial guess for the delay is needed in order to obtain more accurate estimates for the viral clearance rate from detailed patient data.

A similar problem of reliable estimates of HIV turnover rate is addressed by Grossman *et al.* [76]. They argue that a realistic model of HIV infection should take into account that infected cells producing the virus die after a certain time lag, rather than decay exponentially. They suggest a set of ODE equations, modelling the cell death as a transition between several sequential phases. This ODE model is equivalent, in view of the linear chain trick technique, to a distributed delay model with a gamma distribution function ($m = 4$).

3.2.5 Physiology

The great potential of simple DDEs in capturing complex dynamics observed in physiological systems was convincingly shown in a series of related works by an der Heiden, Bélair, Glass, Mackey and co-workers [1, 2, 3, 113, 114, 142]. A key element in the models is an assumption that either the rate

of production or the rate of elimination are nonlinear functions of the past state of the following general form

$$f(y_{\tau_\star}) = \frac{y^m(t-\tau_\star)}{\theta + y^n(t-\tau_\star)} \tag{3.18}$$

with $m \leq n$ and $n \geq 1$. DDEs with time-lags appearing in the non-linear terms were used to model (i) the human respiration system and regulation of blood concentration of CO_2 (periodic breathing and prediction of low- and large amplitude oscillations; see [19]); (ii) the production of blood cells (periodic and chaotic regimes); (iii) hormone regulation in the endocrine system (period-doubling bifurcations and chaotic solutions); (iv) recurrent inhibition in neural networks (multiple steady states, periodic solutions and transition to chaos [3]).

Respiratory control represents an important physiological system where delay equations are used to study the control mechanism and unstable patterns of ventilation (see as, examples, the work by Glass and Mackey [113], Revow *et al.* [153], Cooke and Turi [43] and references therein). The delays represent the transport time between the lung and the peripheral and central chemoreceptors. Models of different degrees of complexity have been formulated and the general view is that, due to the complexity of the real system and the presence of multiple delays, the only feasible way to understand the behaviour is through computational means. In [153], a mathematical model of respiratory control in newborn infants is formulated using a dozen nonlinear equations for CO_2 and O_2 concentration in the lung, tissue, heart and large arteries, extracellular fluid and brain (regarded as separate "compartments"). This model is considered as a framework for testing hypotheses on maturation processes in the neonatal respiratory system. A simplified nonlinear delay model considering the dynamics of the arterial CO_2 and O_2 was suggested in [43] and used in the qualitative study of the effect of transport delay on the stability of the unique steady state in the model. When the lag is greater than a certain threshold value, instability takes place and yields irregular patterns in the dynamics of the system.

The study of haematological diseases is a field where *time- and state-dependent* DDEs have been used to formulate physiologically realistic mathematical models. The dynamics of haematopoiesis was modelled with a state-dependent delay model in [117]. The delay variable appears in the equation describing the age at which blood cells die by apoptosis, i.e., by a programmed cell-death process. The modelling efforts were focussed on understanding the origin of periodic haematological diseases. The studies included both a qualitative analysis of a Hopf bifurcation and the estimation of parameters using real-life data. This allowed a quantitative comparison between the data and predictions concerning the period and amplitude of oscillations in the number of erythrocytes and the erythropoietin level. Numerical simulations were used to analyze how the model reproduces the effect of a loss of blood cells (in humans) and the oscillations in erythrocyte number resulting from regular application of auto-antibodies (in rabbits). In both situations, real data were available that allowed adjustment of some relevant parameters, such as the time of maturation and the destruction rate of blood cells.

The same authors recently advanced a mathematical model of granulopoiesis formulated using a non-linear integro-differential equation [87]:

$$y'(t) = -\alpha y(t) + M_0\left(\int_{-\infty}^{t-\tau_m} y(s)g(t-s)\,ds\right), \tag{3.19}$$

where τ_m is the minimal maturation time-lag and the kernel is defined by the gamma distribution function. The production term is assumed to be a monotone decreasing function of its argument, and the slope of this function is a major control parameter (feedback mechanism) determining the stability of the equilibrium state. In numerical simulations the authors made use of a Hill function to represent the function $M_0(\cdot)$ and reported that use of a non-integer value of the parameter m in

the gamma distribution function provides a good fit to typical data sets. The primary objective with this model was to test hypotheses concerning whether the oscillations in blood counts of neutrophils observed in the progress of a disease originate from a loss of stability in the peripheral control system of neutrophil production, rather than in the stem cell compartment. Mathematically, the transition from a normal state to a diseased state can be associated with a loss of stability of the unique steady state in the model (3.19) and a supercritical bifurcation of a periodic solution. An elegant combination of three types of analysis: logical (clinical data and phenomenology), qualitative (local stability and Hopf bifurcation) and numerical, provided the necessary basis to decide between the above hypotheses, on the origin of cyclical neutropenia. Numerical examination of the solution of the model allowed an investigation of whether the relevant characteristics of clinically observed disease (the period and amplitude of oscillations in cell numbers) can be obtained under a systematic variation of parameters, within their physiological ranges. Again, a linear chain trick technique was used to check the numerical approximation scheme for the integro-differential model, since for integer values of the gamma distribution parameter m the model could be represented as an ODE system.

In the modelling of haematopoiesis undertaken by Mackey and co-authors [113, 117], particular attention is always paid to the numerical methods used to produce the solution. The first constant lag models were solved by a predictor-corrector method with a fixed step-size [113]. To check the solution, both smaller step-sizes and a RK scheme were utilized. For the *state-dependent* DDEs arising in erythropoiesis modelling a modified fourth order RK scheme with fixed step-size with a linear interpolation for the delayed variable between grid points [117]. To treat numerically the *integro-differential* equations modelling the dynamics of cyclical neutropenia, the method chosen in [87] was based upon the *trapezoidal* scheme used to advance in time and to evaluate the integral term in the equation. It should be noted that the authors took care to test the accuracy of the resulting numerical method.

3.2.6 Neural networks

The modelling of neural networks (NN) is an important area of application of delay equations. It was Hopfield who, in 1984, introduced a continuous version of the circuit equations for a network of N neurons, represented by saturating voltage amplifiers. The lags in the model of the living nervous system can represent the synaptic processing time or the time it takes for action potential to propagate along axons. In artificial NNs the delays arise from the hardware implementation due to finite switching and transmission times of circuit units. Marcus and Westrevelt were the first to include the delay in Hopfield's equations [126]. Various generalizations of the Hopfield-type NN models with delay have been recently analyzed (see [41], [27], [54], [57], [90], [147] and [181]) A 'standard' delayed Hopfield neural network model is:

$$C_i y_i'(t) = -\frac{y_i(t)}{R_i} + \sum_1^n T_{ij} f_j\left(y_j(t-\tau_j)\right) + I_i, \quad i = 1, ..., N. \tag{3.20}$$

The variable $u_j(t)$ represents the voltage on the input of the ith neuron, the values $C_i > 0,\ R_i > 0$ are certain parameters, τ_j represent the lags, f is a transfer function (assumed to be a sigmoid one with maximum slope at $y = 0$), the values I_i represent the external input and the matrix $T = (T_{ij})$ specifies the network architecture corresponding to the connection strength between neurons.

In some applications of NNs, such as associative memory, it is important that the model admits the existence of many steady states and to that purpose a non-monotone activation function f gives an advantage. The existence of global attractors in signal processing, parallel computing and optimization problems, is of primary importance. The delayed Hopfield models display complicated behaviour, and the origin of instabilities in NNs is in the focus of qualitative and numerical studies. These studies seek to relate the values of the delay, the network structure/connection topology and

the properties of the function f in eqn (3.20) to the stability of steady states, and the emergence of sustained or transient oscillations. Whereas oscillatory patterns observed in the activity of the nervous system are quite natural for the respiration control system, in artificial NNs (that rely on convergence to a steady state) it is important that the real delays do not affect the local or global stability and only minimally change the transient regime. As a general rule, there is a threshold in the value of the lag at which a delay-induced instability occurs and leads to oscillations. The numerical simulations proved to be instructive in understanding complicated dynamics of the NNs as presented in [147]. The authors of the latter paper examined the origin of long-lasting transient oscillations in an excitatory (positive feedback) ring neural network, a closed chain in which each unit is connected unidirectionally to the next one. Ring systems appear, for example, in studies of feedback in systems controlling gene expression. It is suggested that the delay-induced oscillations are long-lasting transients, and according to the proposed mechanism the continuous delayed NNs behaves transiently as a discrete-time network and asymptotically as a continuous-time network without delay. The shorter the duration of charge-discharge time of the neurons, C_i in eqn (3.20), the longer is the duration of oscillations. For the numerical approximation of the model the authors refer to two independent methods: (i) solution of the initial value problem by the Gear predictor-corrector formula adapted to DDEs and (ii) solution of the equivalent integral representation using the trapezoidal formula. We note in passing that the first delayed Hopfield model was treated with an Euler method [126]. A recent model for neural reflex mechanisms [8] is an example of an *implicit* DDE of the type

$$\epsilon y'(t) = -\alpha(\epsilon y'(t))y(t) + f(y(t-\tau_\star)). \tag{3.21}$$

The need for such models is related to the fact that neuromuscular reflexes with retarded negative feedback have different rates depending on the direction of movement. Both the qualitative properties and the numerical analysis of such equations represent a challenge that remains to be addressed.

3.2.7 Cell kinetics

Recently a biochemical model of the cell cycle, modelling the dynamics of concentration of two peptides (cdc2 and cyclin) and their cdc2/cyclin complex, was formulated using delay equations in [38]. The time-lag represents the duration of the transformation of the complex into the active maturation promoting factor (MPF). The cell division is characterized by periodic fluctuations of MPF activity and the level of free cyclin. The effect of various parameters on the stability of the steady state occurring in the model and on Hopf bifurcation were examined both qualitatively and numerically.

Growth of cell populations is a central issue in cell biology and provides a rich source of various types of functional differential equation models. In [39], Byrne considered two ways of modifying the standard model of avascular tumor growth by incorporating a time-delayed factor into the net proliferation rate. Numerical and asymptotic techniques are used to show how the dynamics of the growth of a tumor are affected by including such delay terms. In the first, the time-lag represents the time taken for cells to undergo mitosis. Here the size of the lag does not affect the limiting behaviour of the tumor; it simply modifies the details of its evolution. In the second case, the lag represents the time for changes in the proliferation rate to stimulate compensatory changes in apoptotic cell loss. Here, the delay can alter the tumor's evolution dramatically.

Cell populations are, in general, not homogeneous, i.e., the cells differ in their age, maturity level, activation status, duration of cell cycle, etc. The generic means for modelling structured population dynamics are provided by first order hyperbolic partial differential equations (see Sec. 2.1), describing the dynamics of the density $u(t,a)$ of cells at time t and with the "age" a (representing for example position in the cell cycle). When the cells are initially uniformly distributed over the cell

cycle then an exponential growth would be observed. Cell populations which are made synchronous exhibit a step-like growth. The process of periodic synchronization needs special experimental conditions, and one can model the corresponding external manipulations of cell culture with a delta peak in the birth rate function $b(a)$ at $a = \tau_\star$ ($\tau_\star$ is the period). As it was illustrated in Sec.2, the total cell number $N(t) = \int_0^\infty u(t,a)da$ satisfies, under this assumption, a neutral delay differential equation.

The kinetics of cell division exhibit various dynamic patterns ranging from exponential increase to prolonged step-like growth. *Neutral* DDEs have recently been shown to provide better qualitative and quantitative consistency with the step-like growth patterns (observed under certain experimental conditions in the, so called, synchronous cultures [13]) than ODEs or DDEs with constant time-lag. Using a model formulated as an NDDE some relevant growth parameters of synchronous cultures were estimated, including the fraction of cells that are dividing, the rate of commitment of cells to cell division, the degree of synchronization of cells in the population, and the death rate of cells. The numerical approach deals with a hierarchy of models, parameter estimates obtained from simpler models being used as initial guess in more complex models. Neutral equations were also used [137] to model the division of T-lymphocytes induced by Interleukin-2.

Recently, attention has been paid [112] to the analysis of cell population dynamics using retarded partial differential equations (RPDEs) of hyperbolic type, in which there is a retardation in the time variable:

$$\frac{\partial u(t,a)}{\partial t} + \frac{\partial u(t,a)}{\partial a} = f\left(t, u(t,a), u(t-\tau_\star, h(a))\right) \tag{3.22}$$

with $\tau_\star > 0$ and $h(a) < a$, for $a > 0$. The model considers cell populations with simultaneous proliferation and maturation processes, where the kinetic/reaction terms are dependent on the cell population at a previous time represented by a lag $\tau_\star$ and at a previous maturity level specified by $h(a)$. Models of this type have been advanced to describe the dynamics of the blood production system [154, 155, 156]. So far, little is known about the qualitative behaviour (local and global stability, for example) of the solutions to these equations. Numerical studies proved to be instructive in getting some insight into the possible dynamics of (3.22), with a maturation time-lag as a critical parameter [46, 154, 155, 156]. In particular, evidence has been presented of temporal and spatial oscillatory behaviour of convection and reaction-convection fronts, when the lag, either temporal or related to maturation, exceeds a critical value corresponding to Hopf bifurcation of the reaction equation. The model displayed a variety of regimes: homogeneous and non-stationary modes, homogeneous oscillatory modes, regular and chaotic travelling modes, and pulse and front propagation solutions. The computed dynamics were used to characterize delay-induced instabilities and thresholds for the various regime transitions were identified. It was observed that many of the time-dependent modes of the retarded PDE are directly associated with a limit cycle behaviour in the pure birth–and–death cell population balance equation. The underlying connection to the properties of delay differential equation has been established in [112], they consider the DDE $z' = f\left(t, z(t), z(t-\tau_\star)\right)$ associated with (3.22) and show that the global stability of a solution of the original RPDE can be reduced to the global stability of the corresponding DDE.

4 Numerical Methods for Delay Equations

We shall embark on a brief review of numerical strategies for DDEs. First we remark that some of those undertaking numerical studies of delay equations in biology devise an indirect approach, rather than use purpose-built numerical codes for DDEs; they try to reduce the study to that of a set of ODEs. Thus they eliminate lag-terms from delay differential equations by introducing additional variables on one of the following bases:

(1) *the methods of steps* [21] allows one to represent a DDE equivalently on successive intervals $[0, \tau_\star], [\tau_\star, 2\tau_\star], ..., [(N-1)\tau_\star, N\tau_\star]$ as successive systems of ODEs with increasing dimensions;

(2) a process represented by a delay can be approximated by introducing a number of intermediate stages using an ODE system to mimic the transition through the stages [9, 10, 70, 121];

(3) the effect of the time-lag can be modelled by using "gearing up" variables [52].

We note, however, that the long-term dynamics of DDEs and of approximating finite-dimensional ODEs can differ substantially. There are occasions when (2) (given above) may have appeal, but a familiarity with numerical methods for DDEs will often reap dividends. If a system of DDEs has no closed-form analytical solution, we advocate the application of direct numerical techniques to approximate the solution. Even where there is a closed-form solution, numerical techniques can be of use in forming hypotheses that can subsequently be established theoretically. Numerical methods also have a role when estimating parameters in models (see Sec.5).

We now approach the issue systematically. To orientate the reader, we first consider the numerical solution of an initial-value problem for a system of ordinary differential equations,

$$\mathbf{y}'(t) = \mathbf{g}(t, \mathbf{y}(t)), \quad t \geq t_0; \quad \mathbf{y}(t_0) = \mathbf{y}_0. \tag{4.1}$$

It is usual for numerical algorithms to provide approximate values $\widetilde{\mathbf{y}}(t_i)$ at a sequence of points $(t_0 < t_1 < t_2 < t_3 \cdots < t_N)$ determined by the algorithm using (say) estimates of the local truncation error or of the defect. Supplementary approximations provide *dense output* that defines approximate values $\widetilde{\mathbf{y}}(t)$ (densely defined) for $t \in [t_0, t_N]$. Such ODE methods can be modified, with varying degrees of success, to provide approximate solutions for DDEs. To indicate the principal features, consider the *initial function problem* for the system of DDEs with parameter $\mathbf{p}$:

$$\mathbf{y}'(t) = \mathbf{f}(t, \mathbf{y}(t), \mathbf{y}(t-\tau_\star), \mathbf{p}), \quad t \geq t_0; \quad \mathbf{y}(t) = \boldsymbol{\psi}(t, \mathbf{p}), \quad t \in [t_0 - \tau_\star, t_0], \tag{4.2}$$

in which $\tau_\star > 0$ does not vary with t. To find the solution $\mathbf{y}(t)$ for $t \geq t_0$ one has to specify the initial function $\boldsymbol{\psi}$ on the interval $t \in [t_0 - \tau_\star, t_0]$. (Its exact form depends on the problem and we refer to the discussion of various forms of initial functions in cell growth to [13, 121].) A simplistic approach to solving system (4.2) numerically consists of replacing (4.2) by the 'ODE'

$$\mathbf{y}'(t) = \mathbf{f}(t, \mathbf{y}(t), \widetilde{\mathbf{y}}(t-\tau_\star), \mathbf{p}), \text{ for } t \geq t_n, \quad (\hat{y}(t-\tau_\star) \text{ being supposed known},$$

where we assume that we compute $\widetilde{\mathbf{y}}(t)$ for $t \leq t_n$ using dense-output techniques. At the risk of over-simplification, numerical methods for DDEs (derived in this manner) amount, in essence, to a combination of two basic elements: a method π_q for approximation of delayed variables with order q in the spirit of a dense-output routine, and an ODE-based p-th order method Φ_p to advance the solution with a step-size h_n (on the assumption $\tau_\star > h_n$). This said, a third feature of an adaptive algorithm concerns the control of step-size and adaptation of the formulae or their implementation, and some features of delay equations can seriously affect the reliability and performance of a naive numerical method based on a pair (Φ_p, π_q). In general, the solution to (4.2) is not smooth and has *jump discontinuities* in its i-th derivatives at times $t_i = t_0 + i\tau_\star$, $i \in N^+$. The effect and propagation of the *jump discontinuities* in the derivatives of the solution have to be addressed when adapting any ODE solver to the problem with delays [16]. Theoretical analysis of the convergence and asymptotic error expansion issues of the adapted method (Φ_p, π_q) tells us that we require $q \geq p - 1$ in order to retain (asymptotically) the global convergence order and $(q \geq p)$ the error expansion form characteristic of the ODE method [34].

The scenario outlined above can be modified to provide numerical methods for a wide range of deterministic retarded differential equations. Note that rigorous development of effective numerical techniques for *stochastic* DDEs is a relatively unexplored area requiring further attention from numerical analysts.

Underlying ODE type method	Dormand-Prince (5)4 Runge-Kutta	Continuous Extension	5th order Hermite
Systems of Equations:	Delay, Neutral & Volterra delay	Delays:	State-independent and state-dependent delays
Discontinuity tracking:	An option	Error control:	Step-size control with asymptotically correct estimator of local truncation error
Programming language:	FORTRAN 77	Floating point precision:	Can be increased using the `-dbl` option in some FORTRAN compilers

Table 4.1: Features of `Archi` code.

4.1 DDE solvers

From a modeller's viewpoint, two historical periods in the production of numerical codes for delay equations can be distinguished. During the first period, a number of experimental codes were developed by modellers or numerical analysts. The second period can be characterized by the availability of more sophisticated DDE solvers. The Numerical Algorithms Group (Oxford) supported, in part, the construction of the codes written by Paul (`Archi`) [149] and Willé (`DELSOL`) [179]. The major problems that the designers of such codes try to accommodate are: automatic location or tracking of the discontinuities in the solution or its derivatives, efficient handling of any "stiffness" (if possible), dense output requirements, control strategy for the local and global error underlying the step-size selection, the cost and consistency of interpolation technique for evaluating delayed terms (to name but a few of them).

The earliest, simple, numerical methods for DDEs (4.2) utilized the *Euler* or classical fourth-order *RK* methods with a constant step-size, supplemented with linear interpolation schemes for the retarded terms. Such adaptations provided minimally effective means for solving models numerically: they had no error control, used fixed step-size, and had problems coping with "stiffness" (which is still a challenge).

Numerical analysts are now in a position to cite published algorithms for the numerical solution of DDEs. Recently, numerical analysts have developed a number of professional adaptive solvers (based on *LMM*, *RK* or *collocation* schemes) producing numerical solutions for a wide range of requested tolerances and various classes of problems with delays. The code `Archi` is (see Table 1) based on the successful Dormand & Prince fifth-order *RK* method for ODEs due to Shampine [170] and a fifth-order Hermite interpolant [146]. In addition to `Archi` [149], which is available from the internet, we mention `DDESTRIDE` (Baker, Butcher & Paul [15]), `DELSOL` (Willé and Baker [179]), `DRKLAG6` (Corwin, Sarafyan & Thomson [42]), `SNDDELM` (by Jackiewicz & Lo [97]) and the code of Enright and Hayashi [62].

Other approaches may be found in the literature. Fourth-order *RK* methods and two-point Hermite-type interpolation polynomials were used by Neves [140], and algorithms based on fourth- and seventh-order Runge-Kutta-Fehlberg methods together with Hermite interpolation polynomials were presented by Oberle and Pesch [146]. Thompson [167] developed a code based on a continuously embedded *RK* method of Sarafyan [168]. An algorithm based on a predictor-corrector mode of a one-step collocation method at k Gaussian points has been constructed by Bellen and Zennaro [20]. An explicit *RK* method has been proposed by Paul [148] and Paul and Baker [150].

Some of the authors associated with progress made in the numerics of DDEs are (ordered alphabetically) Arndt, Ascher, Baker, Bellen, Bickart, Bock, Butcher, Corwin, Enright, Feldstein,

in't Hout, Iserles, Jackiewicz, Hayashi, van der Houwen, Neves, Oberle, Oppelstrup, Paul, Pesch, Petzold, Roose, Roth, Sarafyan, Schlöder, Sommeijer, Spijker, Torelli, Thompson, Watanabe, Willé, Zennaro; see [6, 7, 28, 29, 63, 69, 94, 96, 97, 139, 140, 146, 176, 178, 179, 182].

4.2 Stiffness

Several authors have reported difficulties in the numerical modelling of immune processes using delay equations, which they identified as due to "stiffness". Mohler [68] mentioned that an explicit fourth-order *RK* integration method was " inefficient" in treating his constant lag model, whereas Gear's algorithm based on *BDFs* did well. Bocharov *et al.* [34, 125] give examples of a *variable stiffness* problem appearing in modelling the acute immune response. In simulating *hepatitis B* infection, the "stiffness" emerges at about day 110 post infection, and is associated with the increase in sizes of lymphocytes and antibody populations (by a factor of about 10^5) that accelerates the damping of virus and infected cells by the same scale. The *BDF*-based codes performed nicely, whereas the Adams- and explicit *RK* based codes failed to produce a numerical solution after the day indicated because of very small step-sizes required; see Bocharov *et al.* [34].

The recent models of immune responses by Rundell *et al.* [159, 160] also generate apparently stiff computational problems as one can conclude by analyzing the values of parameters being used. Rundell *et al.* used the stiff solver `ode15s` from the SIMULINK collection.

Stiffness is a phenomenon identified in the numerical solution of ODEs, and is variously defined. It is often characterized in terms of the largest and smallest real parts of the zeros of the stability function corresponding to a stable solution. The main symptom of "stiffness" is that one requires a highly stable numerical formula in order to use large step-sizes reliably. The same symptom could be used to identify "stiffness" in the delay case. We refer to a forthcoming report by Baker and Tian for a discussion of stiffness for DDEs.

The application of delay equations to biomodelling is in many cases associated with studies of dynamical phenomena like oscillations, Hopf bifurcations, chaotic behaviour. Recent work on the analysis of the periodic orbits in delay equations and their discretizations based on the *RK* methods showed that the discretizations possess invariant curves when step-sizes are sufficiently small [95]. Further studies of spurious numerical solutions of finite-difference approximations to the delay equations, which can be generated at critical (bifurcation) values of model parameters are needed.

5 Fitting Models and Parameter Estimation

Suppose that the general form of a suitable mathematical model,

$$\begin{aligned} \mathbf{y}'(t) &= f\left(t, \mathbf{y}(t), \mathbf{y}(\alpha(t;\mathbf{p}));\mathbf{p}\right) \qquad (t \geq t_0) \\ \mathbf{y}(t) &= \boldsymbol{\psi}(t,\mathbf{p}) \qquad (t \leq t_0) \end{aligned} \tag{5.1}$$

with solution $\mathbf{y}(t;\mathbf{p})$ is postulated as compatible with a set of (experimental) data, but the values of the parameters $\mathbf{p}$ and their significance in the model are not known. In the simplest case, $\alpha(t;\mathbf{p}) = t - \tau_\star$; see eqn (4.2). The task of parameter estimation for such mathematical models is one of minimizing a suitable objective function $\Phi(\mathbf{p})$ depending on the unknown parameters $\mathbf{p} \in \mathbb{R}^L$ and the observed data $\{\mathfrak{y}_j\}_{j=1}^N$. In the case of delay models (4.2), this can additionally include estimating $\tau_\star$, the position of the initial time point t_0 and the parameters of the initial function $\boldsymbol{\psi}(\cdot,\mathbf{p})$. Possible objective functions are, for example,

$$\Phi(\mathbf{p}) = \sum_{j=1}^{N}\sum_{i=1}^{M}\left[\mathbf{y}^{(i)}(t_j,\mathbf{p}) - \mathfrak{y}_j^{(i)}\right]^2 \text{ or } \Phi(\mathbf{p}) = \sum_{j=1}^{N}\sum_{i=1}^{M}\left[\log\left(\frac{\mathfrak{y}_j^{(i)}}{\mathbf{y}^{(i)}(t_j,\mathbf{p})}\right)\right]^2. \tag{5.2}$$

The first one is the *least squares* (LS) function, and we refer to the second choice as the *log-least squares* (LLS) function. The LLS objective functions provide metrics in $\mathbb{R}_+^M$ and has been used for parameter estimation of immune responses [33, 121, 132, 137].

The *numerical* technique for finding the best-fit parameter values for a given mathematical model and objective function involves solving with high precision the model equations for the current values of the parameters to compute $\Phi(\mathbf{p})$. The parameter values are then adjusted (by a minimization routine, for example `EOUPF` in the `NAG` library, `LMDIF` from `NETLIB` or `FMINS` in `MATLAB`) so as to reduce the value of the objective function (see [13, 14]).

5.1 Problems with parameter estimation in DDEs

One obvious difficulty with such procedures is that solutions of DDEs are not, in general, differentiable with respect to variation of the lag (see Baker and Paul [11], Hartung and Turi [86], and Ladeira [108]). As we noted earlier, *discontinuities* can arise in the solution of a DDE and its derivatives. Such discontinuities, when they come from the initial point $t_0(\mathbf{p})$ and the initial function $\psi(t,\mathbf{p})$, may propagate into $\Phi(\mathbf{p})$ via the solution values $\{y(\zeta_i,\mathbf{p})\}$. From the formulas (in a scalar case)

$$\left(\frac{\partial\Phi(\zeta_i;\mathbf{p})}{\partial p_l}\right)_{\pm} = 2\sum_{j=1}^{N}\left[y(\zeta_j;\mathbf{p})-\mathfrak{y}_j\right]\left(\frac{\partial y(\zeta_j;\mathbf{p})}{\partial p_l}\right)_{\pm}, \tag{5.3}$$

$$\begin{aligned}\left(\frac{\partial^2\Phi(\zeta_j;\mathbf{p})}{\partial p_l\partial p_m}\right)_{\pm\pm} = 2\sum_{j=1}^{N}\Bigg[&\left(\frac{\partial y(\zeta_j;\mathbf{p})}{\partial p_l}\right)_{\pm}\left(\frac{\partial y(\zeta_j;\mathbf{p})}{\partial p_m}\right)_{\pm}\\ &+\left[y(\zeta_j;\mathbf{p})-\mathfrak{y}_j\right]\left(\frac{\partial^2 y(\zeta_j;\mathbf{p})}{\partial p_l\partial p_m}\right)_{\pm\pm}\Bigg].\end{aligned} \tag{5.4}$$

It follows that, unless $\mathfrak{y}_i = y(\zeta_i;\mathbf{p})$, jumps can arise in the first and second partial derivatives of $\Phi(\mathbf{p})$ with respect to p_l, if the first or the second partial derivatives of $y(t,\mathbf{p})$, with respect to p_l, has a jump at $t=\zeta_i$ (one of the data-points). These jumps can propagate into the second derivative of $\Phi(\mathbf{p})$ if the first derivative of $y(t;\mathbf{p})$ with respect to p_l has a jump at one of the data-points $t=\zeta_i$, even when $\mathfrak{y}_i = y(\zeta_i;\mathbf{p})$. For more discussion about these issues we refer to [16]. For correct numerical parameter estimation in DDEs attention has to be given to

- differentiability of the solution $\mathbf{y}(t;\mathbf{p})$ with respect to the parameters $\mathbf{p}$,
- existence and position of the jump discontinuities,
- statistical nature of the observed data-points.

5.2 Analysis of the best fit: uniqueness, bias

A fundamental difference between DDE and ODEs is that solutions corresponding to different initial function data can intersect. Of course, solutions that are computed with different parameters can intersect in both the ODE and DDE case. In the context of the parameter estimation problem, this implies that for a given set of $\{t_j\}_{j=1}^N$ and an arbitrary function $\mathbf{f}$ in (4.2), there is no reason to suppose that there exists a *unique* minimizer $\widehat{\mathbf{p}}$ of $\Phi(\mathbf{p})$. Indeed, it is easy to find examples for non-unique best fit models; one requires only to find solutions for two different parameters that agree at the points $t_1, t_2, \ldots, t_N$. In FIGURE 5.1 we give an example of such a scenario, plotting graphs of the solutions to the Hutchinson equation $y'(t) = y(t)\,(a - y(t-1))\,, \quad t>0$, with $\mathbf{p}=[a]$, and $1 \le a \le 1.6$. Considering its solutions for different a and the same initial function, we find that

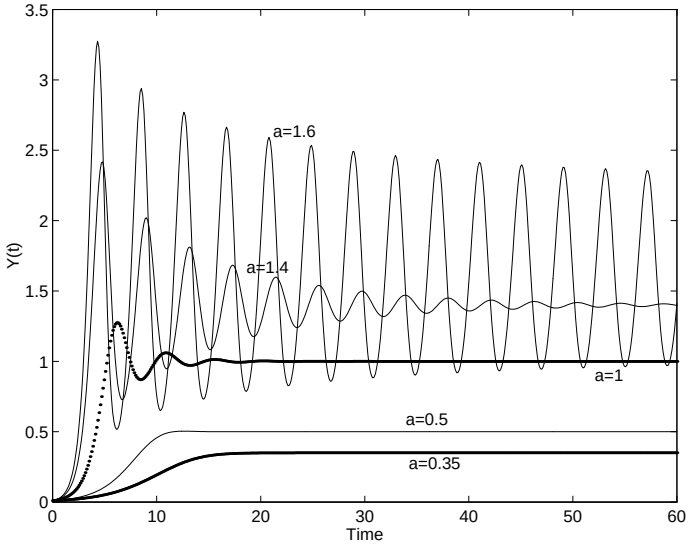

Figure 5.1: Intersection of solutions to the different DDEs can cause non-unique best fit in certain data.

a range of different values of parameter a gives solutions that intersect. If the data correspond to the points of intersection, K is not uniquely determined. The question of what happens as $N \to \infty$ is of theoretical interest but could only be answered with precise assumptions on $\{t_i\}$ and $\mathbf{f}$.

In general, the parameter estimation problem (4.2)&(5.2) is an example of *nonlinear* regression. Difficulties may arise due to the fact that nonlinear regression models differ, in general, from linear regression models in that the LS parameter estimates can be biased, non-normally distributed, and have a variance exceeding the least possible variance. These characteristics depends on the model (as well as the data and the best fit parameters) and it is necessary to assess the nonlinearity effect. To estimate biases of parameter estimates one may take the approach (see [12])

- perturb the solution corresponding to the best-fit parameter $\widehat{\mathbf{p}} \in \mathbb{R}^{\mathbb{L}}$ with normally distributed random errors of mean zero and error variance $\sigma^2 = \dfrac{\Phi(\widehat{\mathbf{p}})}{N-L}$;
- find the new best-fit parameters $\widetilde{\mathbf{p}}$;
- repeat this process a statistically significant number of times and check whether $|\widehat{\mathbf{p}} - mean\{\widetilde{\mathbf{p}}\}| < 0.01|\widehat{\mathbf{p}}|$. (If so, then the LS estimates are not significantly biased, the effect of non-linearity is not significant and the best-fit parameter estimates as well as their standard deviation are confident.)

We give an example of parameter estimation for a simple delay growth model for fission yeast [13]

$$\begin{aligned} y'(t) &= \rho_1 y(t-\tau_\star), \quad t \geq 0, \\ y(t) &= (2.25 y_0 \rho_2/\rho_1)\, E(t+1.5),\ t \in [0,\tau_\star),\ y(0) = y_0, \end{aligned} \tag{5.5}$$

where y_0 stands for the initial number of cells, $E(\cdot)$ is a bell-shaped initial distribution function. Estimated are the components of $\mathbf{p} = [\rho_1, \rho_2, \tau_\star]$. FIGURE 5.2 shows the best-fit solution and the shape of the LS function in the vicinity of the minima. Table 2 presents the analysis of the best-fit.

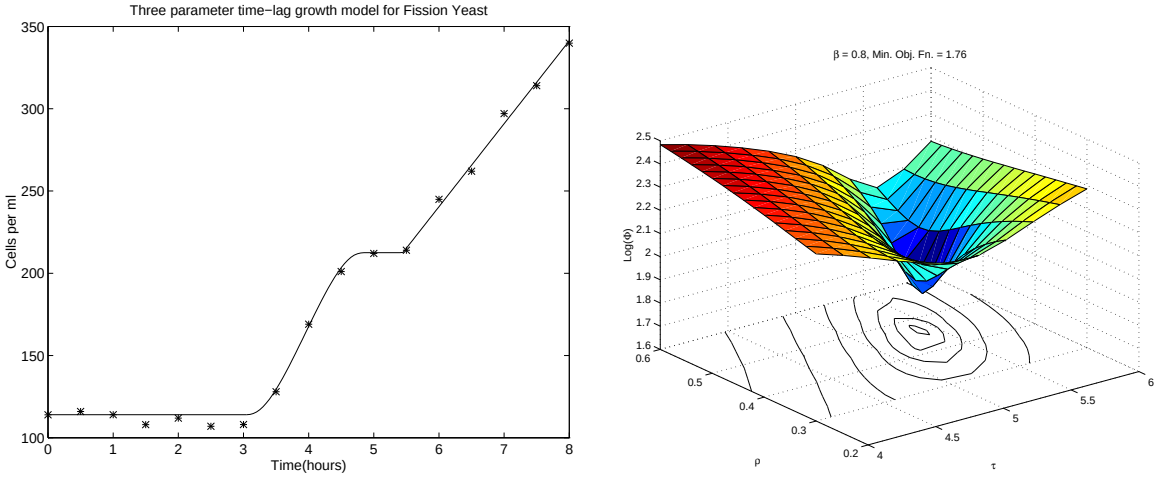

Figure 5.2: a) Shows the best fit solution of time-lag model (5.5) with three parameters, fitted to the observed data. b) Indicates local uniqueness of the best fit and the dependence of Φ on parameters $\tau_\star, \rho_1$.

Best-fit, standard deviation, non-linear biases					
$\hat{\tau}_\star$	σ	$\hat{\rho}_1$	σ	$\hat{\rho}_2$	σ
5.45	0.038	0.443	0.014	0.864	0.019
$\widetilde{\tau_\star}$	NLB($\tau_\star$)	$\widetilde{\rho_1}$	NLB(ρ_1)	$\widetilde{\rho_2}$	NLB(ρ_2)
5.446	0.0066%	0.4426	0.0284%	0.8645	0.0772%

TABLE 2:Best-fit estimates $\hat{p}$, mean of perturbed parameters p and their non-linear biases to the model (5.5), NLB= $(\frac{\hat{p}}{\widetilde{p}} - 1) \times 100\%$.

6 Sensitivity Analysis: direct and adjoint methods for DDEs

Sensitivity analysis of mathematical models is an important tool for assessing their properties. The following types of sensitivity can be investigated:

- sensitivity of the solution $\mathbf{y}(t, \widehat{\mathbf{p}})$ to changes in the parameter values $\widehat{\mathbf{p}}$;
- sensitivity of the parameter estimates $\widehat{\mathbf{p}}$ to variations in the observation data $\{t_j; \mathfrak{y}_j\}_{j=1}^N$;
- sensitivity of biologically meaningful functionals $J(\mathbf{y})$ (see §6.2) that characterize the solution, to variations in parameters.

6.1 Sensitivity coefficients

The first two types of *sensitivity analysis* are examined by *direct methods* and rely upon the computation of the sensitivity coefficients $\mathbf{s}_i(t, \mathbf{p}) = \dfrac{\partial \mathbf{y}(t, \mathbf{p})}{\partial p_i}$, which characterize the effect of small perturbations in the i-th parameter on the solution:

$$\mathcal{A}(\mathbf{y}(t, \widehat{\mathbf{p}}), \widehat{\mathbf{p}})\mathbf{s}_i(t, \widehat{\mathbf{p}}) = \frac{\partial \mathbf{f}}{\partial p_i}, \quad t \geq 0, \quad \mathbf{s}_i(t, \widehat{\mathbf{p}}) = \frac{\partial \psi}{\partial p_i}, \quad t \in [-\tau_\star, 0]. \tag{6.1}$$

The operator $\mathcal{A} \equiv \frac{d}{dt} - \left[\frac{\partial \mathbf{f}}{\partial \mathbf{y}}\right]_t - \left[\frac{\partial \mathbf{f}}{\partial \mathbf{y}_{\tau_\star}}\right]_t \mathcal{D}_{\tau_\star}$, represents the variational system of equations, $[\cdot]_t$ denotes a matrix-function evaluated at time t, and $D_{\tau_\star}$ is a backward shift operator. The overall

sensitivity of the solution $\mathbf{y}(\mathbf{t}, \widehat{\mathbf{p}})$ is given by the matrix-function $\mathbf{S}(t, \mathbf{p}) = \frac{\partial \mathbf{y}(t,\mathbf{p})}{\partial \mathbf{p}}$ evaluated at $\mathbf{p} = \widehat{\mathbf{p}}$. This function characterizes the sensitivity of parameter estimates to small variations in the i-th datum $\mathfrak{y}_j$ via the formula: $\dfrac{\partial \widehat{\mathbf{p}}}{\partial \mathfrak{y}_j} = \left[\sum_{i=1}^{N} \mathbf{S}^T(t_i, \widehat{\mathbf{p}})\mathbf{S}(t_i, \widehat{\mathbf{p}})\right]^{-1} \mathbf{S}(t_j, \widehat{\mathbf{p}})$. Numerical sensitivity analysis by the direct method requires solution of the model equations (4.2) (called the main system) and the variational system (6.1) of $M \times L$ equations taken jointly. This implies that for multiparameter models, numerical methods for *sparse* systems of DDEs would be an advantage. The other issue affecting the performance of numerical codes is the propagation of jumps in the derivatives of solution of the main problem to the system of sensitivity equations. We refer to Baker and Rihan (to appear) for additional details.

6.2 The adjoint equations

Consider, as an example, the quadratic functional and its first-order variation caused by perturbations of the basic parameter set $\widehat{\mathbf{p}}$ (where $\widehat{\mathbf{y}} \equiv \mathbf{y}(t, \widehat{\mathbf{p}})$)

$$J(\widehat{\mathbf{y}}) = \int_0^T \langle \widehat{\mathbf{y}}, \widehat{\mathbf{y}} \rangle dt, \quad \delta J(\widehat{\mathbf{y}}) = 2 \sum_i \int_0^T \langle \widehat{\mathbf{y}}, \mathbf{s}_i(t, \widehat{\mathbf{p}}) \delta p_i \rangle dt, \tag{6.2}$$

where $\mathbf{s}_i(t, \widehat{\mathbf{p}})$ is a solution to (6.1) on $[0, T]$.

The sensitivity of non-linear functionals $J(\mathbf{y})$ can be examined using an approach based on *adjoint equations*; see Marchuk [120, 121]. The linear operator $\mathcal{A}$ in (6.1) acts on some Hilbert space H with domain $\mathcal{D}(\mathcal{A})$. For $\mathcal{A}$ the adjoint operator $\mathcal{A}^*$ can be introduced satisfying the Lagrange identity $\langle \mathcal{A}(\widehat{\mathbf{y}}, \widehat{\mathbf{p}})\mathbf{s}, \mathbf{w} \rangle = \langle \mathbf{s}, \mathcal{A}^*(\widehat{\mathbf{y}}, \widehat{\mathbf{p}})\mathbf{w} \rangle$, where $\langle \cdot, \cdot \rangle$ is an inner product in H, $\mathbf{s} \in \mathcal{D}(\mathcal{A})$, $\mathbf{w} \in \mathcal{D}(\mathcal{A}^*)$. Using the solution $\mathbf{w}(t)$ of the adjoint problem

$$\mathcal{A}^*(\widehat{\mathbf{y}}, \widehat{\mathbf{p}})\mathbf{w} \equiv -\frac{d\mathbf{w}(t)}{dt} - \left[\frac{\partial \mathbf{f}}{\partial \mathbf{y}}\right]_t^T \mathbf{w}(t) - \left[\frac{\partial \mathbf{f}}{\partial \mathbf{y}_{\tau_\star}}\right]_{t+\tau_\star}^T \mathbf{w}(t + \tau_\star) = \mathbf{y}(t, \widehat{\mathbf{p}}),$$
$$0 \le t \le T, \quad \mathbf{w}(t) = 0, t \in [T, T + \tau_\star], \tag{6.3}$$

the variation of $J(\mathbf{y})$ takes the form $\delta J = \sum_{i=1}^{L} 2 \int_0^T \langle \mathbf{w}, \frac{\partial \mathbf{f}}{\partial p_i} \delta p_i \rangle dt$. Thus, instead of solving an $M \times L$-dimensional system of sensitivity equations within a direct approach to the sensitivity analysis, one needs to solve, only once, the evolutionary problem for the main system and the adjoint problem, each being of dimension M.

The approach above was used (see [31], [121]) to analyze the sensitivity of functionals for delay models of influenza and hepatitis, each having about 10 ($= M$) state variables and 50 ($= L$) parameters including 5 time-lags. DIFSUB adapted for constant-lag DDEs [34], was used to perform the numerical integration of the forward and backward (adjoint) evolutionary problems. Computational results indicate that the numerical sensitivity analysis of complex systems using the adjoint equations requires careful selection of codes for DDEs with particular attention to the following issues: (*i*) the adjoint problem inherits the jump discontinuities of the forward problem so the smoothness of the matrix-function $\mathcal{A}^*$ decreases as t approaches t_0; (*ii*) the stiffness properties of the main and adjoint problems are opposite and in general, both display variable stiffness behaviour; (*iii*) adaptive codes generate different step-size sequences for the main and adjoint problems and $\mathbf{y}(t)$ has to be re-evaluated on every integration step of the adjoint problem; therefore, numerical schemes that produce 'cheap' interpolation techniques (dense output) would give an advantage.

7 Optimal Control Using Delay Models

Although there are many problems in the biosciences that can be addressed within an optimal control framework for systems of DDEs (epidemics, harvesting, chemostat, treatment of diseases, physiological control, vaccination) the amount of real-life experience [17, 104, 159] is quite small. The general formulation of an optimal control problem (OCP) for delay system is as follows:
For a system with the state vector $\mathbf{y}(t, \mathbf{u})$ *governed by a DDE find a control function* $\mathbf{u}(t)$*, defined on* $[-\tau_u, T]$*, that gives a minimum to the objective functional* $J_0(\mathbf{u})$*, where*

$$\mathbf{y}'(t) = \mathbf{f}(t, \mathbf{y}(t), \mathbf{y}(t-\tau_y), \mathbf{u}(t), \mathbf{u}(t-\tau_u)), \quad 0 \le t \le T, \tag{7.1}$$

$$J_0(\mathbf{u}) = \Phi_0(\mathbf{y}(T)) + \int_0^T F_0(t, \mathbf{y}(t), \mathbf{y}(t-\tau_y), \mathbf{u}(t), \mathbf{u}(t-\tau_u))dt \tag{7.2}$$

subject to corresponding initial functions for the state and control vectors. Additional equality or inequality constraint(s) can be imposed in terms of functionals $J_i(\mathbf{u})$. The Pontryagin maximum principle and the Bellman dynamic programming method are two frameworks for solving OCP. For the computational treatment of time-delayed optimal control problems we refer to monographs by Banks [17], Kolmanovskii *et al.* [104], Teo *et al.* [166]. OCPs using DDEs were studied in connection with immune responses to infections.

In [37], delay models of the immune responses were used to find the optimal control regimes of unfavourable disease outcomes. The objective functional was expressed in terms of the virus population size, either at a given final time $t = T$, i.e., $J_0(u) = (Virus(T))$, or a cumulative virus amount over $[0, T]$; in this case $J_0(u) = \int_0^T Virus(t)dt$. Specific features of the studies [37] are: (i) delays appear only in state variables; (ii) linear scalar control functions appearing additively or multiplicatively in one equation (for the virus) were considered; (iii) unconstrained problems were treated. An original algorithm using non-classical variations of the control function was developed: the system of model equations and the adjoint problem were solved by an adaptation of a fourth/fifth order *RK* method with Hermite interpolation for the delayed terms. The control function was approximated by a set of piecewise constant functions on a uniform mesh with the step-size being an integer fraction of the delay. Control improvement was an iterative procedure using a constructive form of necessary optimality conditions and spike variations of the current control function.

A humoral immune response model was considered in a recent paper [159] on determining optimal intravenous drug delivery in AIDS patients. The objective was to find a control strategy that minimizes the total drug administered, subject to the constraint that the patient recovers. The control function, appearing non-linearly in the equations, was obtained numerically by applying convex minimization techniques based on linear matrix inequalities (LMI), with the time-lag being approximated by a fourth-order Bessel filter. The nonlinearities were addressed by transforming the non-linear model to a linear-fractional representation. Gear's algorithm in SIMULINK was adapted to solve the DDEs and the LMI toolbox from MATLAB was used to compute the optimizer.

We refer in passing to another example of a control problem with delay models inspired by recently proposed nonconventional approach to the anti-HIV drug administration [22]. A cohort of drug loaded red blood cells (RBC) with density function $u(t, a)$ at time t and age $a \in R_+$ is injected at time $t = 0$ into a patient. The cells with age $a \ge a^*$ ($a^* > 120$ days), called the senescent cells, are phagocytosed by macrophages thus causing the drug to be absorbed. This process of drug delivery can not be described by standard mathematical models in pharmacokinetics. The authors propose a delay model which for the dynamics of (i) senescent loaded RBC (x_1), (ii) macrophages which are digesting the RBC (x_2) and free for phagocytosis (x_3), (iii) macrophages that can phagocytose senescent RBC (x_3) (that is they are not engaged at the moment t the digesting the RBC), and (iv)

the average drug concentration in macrophages (x_4). The drug has therapeutic effect as long as x_4 satisfies: $0 < m \leq x_4(t) < M$ over a certain interval $t \in [t_1, t_2]$. The time-lag represents the digestion time, which can be described as a fixed or a distributed delay. The initial age distribution of the RBC can be experimentally preassigned, i.e., $u(0, a) = \phi(a),\ a \geq 0$ is a controllable characteristic, and only a fraction α of the total cell number $\int_0^{+\infty} u(t, a)da$ are senescent cells. This function appears additively as a control function in the equation for x_1. The OCP for the delay model of the drug treatment is: *Choose the control function* $\phi(a)$ *in the interval* $[0, a^*]$ *and the parameter* α *such that* $\Delta t = t_2 - t_1 \rightarrow \max$*, subject to (i)* $x_4(t) < M$ *for all* $t > 0$*, (ii) the condition that* $u_0 = \int_0^{a^*} \phi(a)da/(1-\alpha), u_0 \in [n_1, n_2]$*, be minimum.* A qualitative analysis of the problem suggests that one searches for a constant age distribution function as a solution to it.

The numerical approach to general nonlinear OCP for DDEs still remains a relatively unexplored area and further research is needed to provide biomodellers with user-friendly adaptive packages.

Acknowledgments

Professor Baker acknowledges related support from EPSRC, the London Mathematical Society and the University of Manchester Research Support Fund. Professor Bocharov was supported by the Alexander von Humboldt-Stiftung, Germany during a visit to the group of Professor K.P. Hadeler at Tübingen; Section 1, and parts of the introduction to Section 2 and of subsections 2.1, 3.1 in particular reflect input (private communication) from Professor Hadeler during this visit, which is most appreciated. Fathalla Rihan acknowledges the support from the Egyptian Government. The comments by colleagues of the authors (in particular Dr Buckwar and Dr Paul at Manchester) are also gratefully acknowledged; any imperfections are, however, the responsibility of the authors.

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