Available at www.MATHEMATICSWEB.ORG
POWERED BY SCIENCE @ DIRECT•

Journal of Computational and Applied Mathematics 151 (2003) 445–462

JOURNAL OF COMPUTATIONAL AND APPLIED MATHEMATICS

www.elsevier.com/locate/cam

Sensitivity analysis for dynamic systems with time-lags

Fathalla A. Rihan

Department of Mathematics, University of Manchester, Oxford Rd., Manchester M13 9PL, UK

Received 3 January 2002

Abstract

Many problems in bioscience for which observations are reported in the literature can be modelled by suitable functional differential equations incorporating time-lags (other terminology: delays) or memory effects, parameterized by scientifically meaningful constant parameters $\mathbf{p}$ or/and variable parameters (for example, control functions) $\mathbf{u}(t)$. It is often desirable to have information about the effect on the solution of the dynamic system of perturbing the initial data, control functions, time-lags and other parameters appearing in the model. The main purpose of this paper is to derive a general theory for sensitivity analysis of mathematical models that contain time-lags. In this paper, we use *adjoint equations* and *direct methods* to estimate the sensitivity functions when the parameters appearing in the model are not only constants but also variables of time. To illustrate the results, the methodology is applied numerically to an example of a delay differential model.

Keywords: Sensitivity function; Delay differential equation; Time-lag; Control function

1. Introduction

In many biological applications, mathematical models have an optimal control framework for systems of delay differential equations (DDEs) [3–5,8,11,12,14,22]. We can find such examples in epidemiology, chemostatics, treatment of diseases, physiological control, etc., where complex systems include transportation delays in state and in control variables.

There are many results on sensitivity analysis of models without delay (see, e.g., [7,10,13,23]); however, there are few results on sensitivity analysis for time-lag systems. A knowledge of how the state variable can vary with respect to small variations in the initial data, parameters (or constant

E-mail address: frihan@ma.man.ac.uk (F.A. Rihan).

0377-0427/03/$ - see front matter © 2003 Published by Elsevier Science B.V.
PII: S0377-0427(02)00659-3

lags) appearing in the model, and the control functions can yield insights into the behaviour of the model and can actually assist the modelling process. Sensitivity analysis may provide some guidelines for the reduction of complex models by indicating those variables and parameters that determine the essential behaviour of the system and hence must be retained in any simpler model. For example, if it can be seen that a particular parameter has no effect on the solution, it may be possible to eliminate it, at some stages, from the modelling process.

In this paper we consider models that include variable and constant parameters. We discuss two different methods to estimate: (i) general sensitivity coefficients for the constant parameters appearing in the model, and (ii) functional derivative sensitivity coefficients for the variable coefficients such as initial and control functions. The approaches that we shall consider are the variational method (in Section 3) and the direct method (in Section 4). n the variational approach, the sensitivity coefficients are calculated based on introducing adjoint variables to solve state and adjoint equations. The direct method is based on considering all parameters as constants and then the sensitivity coefficients are estimated by solving a variational system simultaneously with the original system.

2. The problem

Let us consider a class of systems modelled by DDEs of the form

$$\mathbf{y}'(t) = \mathbf{f}(t, \mathbf{y}(t), \mathbf{y}(t-\tau), \mathbf{u}(t), \mathbf{u}(t-\sigma), \mathbf{p}), \quad 0 \leqslant t \leqslant T, \tag{1a}$$

$$\mathbf{y}(t) = \Psi(t, \mathbf{p}), \quad t \in [-\tau, 0), \quad \mathbf{y}(0) = \mathbf{y}_0 \in \mathbb{R}^n, \tag{1b}$$

$$\mathbf{u}(t) = \Phi(t), \quad t \in [-\sigma, 0), \quad \mathbf{u}(0) = \mathbf{u}_0 \in \mathbb{R}^m, \tag{1c}$$

where the vector function $\mathbf{f}$ on the right-hand side is sufficiently smooth with respect to each arguments; $\mathbf{y}(t) \in \mathbb{R}^n$, $\mathbf{y}(t-\tau) \in \mathbb{R}^{n'}$, $\mathbf{u}(t) \in \mathbb{R}^m$, $\mathbf{u}(t-\sigma) \in \mathbb{R}^{m'}$, $\mathbf{p} \in \mathbb{R}^r$, and $\tau \in \mathbb{R}^{r'}$ and $\sigma \in \mathbb{R}^{r''}$ are positive constant lags (r', $r'' \leqslant r$, $n' \leqslant n$, $m' \leqslant m$). $\Psi(t)$ and $\Phi(t)$ are given continuous functions. We note that $\mathbf{u}(t)$ in (1a) can be viewed as a control variable, defined on $[-\sigma, T]$, that gives a minimum to the objective functional

$$J(\mathbf{u}) = F_0(\mathbf{y}(T)) + \int_0^T F_1(t, \mathbf{y}(t), \mathbf{y}(t-\tau), \mathbf{u}(t), \mathbf{u}(t-\sigma), \mathbf{p})\, \mathrm{d}t, \tag{2}$$

where F_0 and F_1 are continuous functionals.

We also note that the system model involves both lags in the state variable $\mathbf{y}(t)$ and the control variable $\mathbf{u}(t)$. In this paper, we are concerned to estimate the sensitivity functions for system (1a)–(1c) rather than with the computational aspects of optimal control problems. (For the computational treatment of time-delayed optimal control problems we refer to the monographs in [3,12].)

In order to examine the effects of parameter uncertainty on a model, it is necessary to test the sensitivity of the predicted model responses to numerical values of the parameters. In this way, possible deficiencies in the model can be revealed if, for example, small changes in a parameter from its nominal value result in large, improbable changes in patterns of model prediction. Equally, sensitivity analysis can indicate the most informative data points for a specific parameter. We start our analysis with the definitions of sensitivity functions of a dynamic system, including constant and variable parameters, as follows:

Definition 1. For the given DDEs (1a)–(1c):

(1) The sensitivity coefficients, when the parameters are constants, are defined by the partial derivatives

$$S_{ij}(t) = \frac{\partial y_i(t)}{\partial \alpha_j}, \tag{3}$$

where α_j represent the parameters p_j, the constant lags τ_j or the initial values $y_j(0)$. Then the total variation in $y_i(t)$ due to small variations in the parameters α_j is such that

$$\delta y_i(t) = \sum_j \frac{\partial y_i(t)}{\partial \alpha_j}\,\delta\alpha_j + \mathrm{O}(|\alpha|^2). \tag{4}$$

Thus Eq. (3) estimates the sensitivity of the state variable to small variations in the parameters α_j.

(2) The functional derivative sensitivity coefficients, when the parameters are functions of time, are defined by

$$\beta_{ij}(t,t^*) = \frac{\partial y_i(t^*)}{\partial u_j(t)}, \qquad t < t^*. \tag{5}$$

Then the total variation in $y_i(t^*)$ due to any perturbation in the parameters $u_j(t)$ is, denoted by $\delta y_i(t^*)$, such that

$$\delta y_i(t^*) = \int_0^{t^*} \frac{\partial y_i(t^*)}{\partial u_j(t)}\,\delta u_j(t)\,\mathrm{d}t, \quad t < t^*. \tag{6}$$

Thus the functional derivative sensitivity density function $\partial y_i(t^*)/\partial u_j(t)$ measures the sensitivity of $y_i(t)$ at location t^* to variation in $u_j(t)$ at any location $t < t^*$. It is then noted that the sensitivity density functions inherently contain and provide more information than the sensitivity coefficients.

2.1. Adjoint equations

Adjoint equations have been used, in [15,16], to study sensitivity analysis of nonlinear functionals $J(\mathbf{y})$ depending on the solution to the delay differential models

$$\mathbf{y}'(t) = \mathbf{f}(t, \mathbf{y}(t), \mathbf{y}(t-\tau), \mathbf{p}), \quad t \geqslant t_0; \qquad \mathbf{y}(t) = \boldsymbol{\psi}(t,\mathbf{p}), \quad t \in [t_0 - \tau, t_0]. \tag{7}$$

He considered the quadratic functional and its first-order variation caused by perturbations of the basic parameter set $\mathbf{p}$ (where $\mathbf{y} \equiv \mathbf{y}(t,\mathbf{p})$):

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

where $\mathbf{s}_i(t,\mathbf{p})$ is a solution of the sensitivity equation

$$\mathscr{A}(\mathbf{y}(t,\mathbf{p}),\mathbf{p})\mathbf{s}_i(t,\mathbf{p}) = \frac{\partial \mathbf{f}}{\partial p_i}, \quad t \geqslant 0, \qquad \mathbf{s}_i(t,\mathbf{p}) = \frac{\partial \boldsymbol{\psi}}{\partial p_i}, \quad t \in [-\tau, 0]. \tag{8}$$

The operator

$$\mathscr{A} \equiv \frac{\mathrm{d}}{\mathrm{d}t} - \frac{\partial \mathbf{f}(t)}{\partial \mathbf{y}} - \frac{\partial \mathbf{f}(t+\tau)}{\partial \mathbf{y}_\tau} D_\tau,$$

where $\mathbf{f}(t)$ denotes the value of $\mathbf{f}$ at time t, $\mathbf{y}_\tau = \mathbf{y}(t-\tau)$, and D_τ is a backward shift operator. The linear operator $\mathscr{A}$ in (8) acts on some Hilbert space H with domain $\mathscr{D}(\mathscr{A})$. Given $\mathscr{A}$, the adjoint operator $\mathscr{A}^*$ can be introduced satisfying the Lagrange identity $\langle \mathscr{A}(\mathbf{y},\mathbf{p})\mathbf{s},\mathbf{w}\rangle = \langle \mathbf{s}, \mathscr{A}^*(\mathbf{y},\mathbf{p})\mathbf{w}\rangle$, where $\langle\cdot,\cdot\rangle$ is an inner product in H, $\mathbf{s}\in\mathscr{D}(\mathscr{A})$, $\mathbf{w}\in\mathscr{D}(\mathscr{A}^*)$. Using the solution $\mathbf{w}(t)$ of the adjoint problem

$$\mathscr{A}^*(\mathbf{y},\mathbf{p})\mathbf{w}(t) \equiv -\frac{\mathrm{d}\mathbf{w}(t)}{\mathrm{d}t} - \frac{\partial \mathbf{f}^{\mathrm{T}}(t)}{\partial \mathbf{y}}\mathbf{w}(t) - \frac{\partial \mathbf{f}^{\mathrm{T}}(t+\tau)}{\partial \mathbf{y}_\tau}\mathbf{w}(t+\tau) = \mathbf{y}(t,\mathbf{p}),$$
$$0 \leqslant t \leqslant T, \quad \mathbf{w}(t) = 0, \; t\in[T, T+\tau], \tag{9}$$

enables one to estimate the first-order variation of $J(\mathbf{y})$, due to perturbations of the parameters p_i, via the formula

$$\delta J(\mathbf{y}) = \sum_{i=1}^{r} 2\int_0^T \left\langle \mathbf{w}, \frac{\partial \mathbf{f}}{\partial p_i}\delta p_i \right\rangle \mathrm{d}t = \sum_{i=1}^{r} \frac{\partial J}{\partial p_i}\delta p_i, \tag{10}$$

where

$$\frac{\partial J}{\partial p_i} \equiv 2\int_0^T \left\langle \frac{\mathbf{w}, \partial \mathbf{f}}{\partial p_i} \right\rangle \mathrm{d}t$$

is the gradient of the functional with respect to the parameters.

In order to estimate the sensitivity of the functional $J(\mathbf{y})$ to variations in all parameters appearing in model (7), we need to solve this system model together with the adjoint problem (9) (see Section 5). In the next section, we extend the use of adjoint equations to investigate the sensitivity analysis for more general system (1a)–(1c) including constant and variable parameters.

3. Variational approach

In this section, we use adjoint equations to formulate systematically formulae for the sensitivities of the state variable to small variations in the initial data, delays, parameters, and the control function appearing in the model. Then the main object here is to derive equations for the sensitivity coefficients $\partial y_i(t)/\partial \alpha_j$ and the sensitivity density functions $\partial y_i(t^*)/\partial u_j(t)$.

Theorem 1. *If* $\mathbf{W}(t)$ *is an n-dimensional adjoint function which satisfies the differential equation*

$$\mathbf{W}'(t) \equiv \frac{\mathrm{d}\mathbf{W}(t)}{\mathrm{d}t} = -\frac{\partial \mathbf{f}^{\mathrm{T}}(t)}{\partial \mathbf{y}}\mathbf{W}(t) - \frac{\partial \mathbf{f}^{\mathrm{T}}(t+\tau)}{\partial \mathbf{y}_\tau}\mathbf{W}(t+\tau), \quad t \leqslant t^*,$$
$$\mathbf{W}(t) = 0, \quad t > t^*; \qquad \mathbf{W}(t^*) = [0,\ldots,0,1_{ith},0,\ldots,0]^{\mathrm{T}}, \tag{11}$$

then:

(i) *The sensitivity coefficients for the DDEs* (1a)–(1c) *can be expressed by the formulae*

$$\frac{\partial y_i(t^*)}{\partial \mathbf{y}_0} = \mathbf{W}(0), \tag{12a}$$

$$\frac{\partial y_i(t^*)}{\partial \mathbf{p}} = \int_0^{t^*} \mathbf{W}^{\mathrm{T}}(t)\,\frac{\partial \mathbf{f}}{\partial \mathbf{p}}\,\mathrm{d}t, \quad t \leqslant t^*, \tag{12b}$$

$$\frac{\partial y_i(t^*)}{\partial \tau} = -\int_{-\tau}^{t^*-\tau} \mathbf{W}^{\mathrm{T}}(t+\tau)\,\frac{\partial \mathbf{f}(t+\tau)}{\partial \mathbf{y}_\tau}\,\mathbf{y}'(t)\,\mathrm{d}t, \tag{12c}$$

$$\frac{\partial y_i(t^*)}{\partial \sigma} = -\int_{-\sigma}^{t^*-\sigma} \mathbf{W}^{\mathrm{T}}(t+\sigma)\,\frac{\partial \mathbf{f}(t+\sigma)}{\partial \mathbf{u}_\sigma}\,\mathbf{u}'(t)\,\mathrm{d}t. \tag{12d}$$

(ii) *The functional derivative sensitivity coefficients can also be expressed by*

$$\frac{\partial y_i(t^*)}{\partial \Psi(t)} = \frac{\partial \mathbf{f}^{\mathrm{T}}(t+\tau)}{\partial \mathbf{y}}\,\mathbf{W}(t+\tau), \quad t \in [-\tau, 0), \tag{13a}$$

$$\frac{\partial y_i(t^*)}{\partial \Phi(t)} = \frac{\partial \mathbf{f}^{\mathrm{T}}(t+\sigma)}{\partial \mathbf{u}_\sigma}\,\mathbf{W}(t+\sigma), \quad t \in [-\sigma, 0), \tag{13b}$$

$$\frac{\partial y_i(t^*)}{\partial \mathbf{u}(t)} = \frac{\partial \mathbf{f}^{\mathrm{T}}}{\partial \mathbf{u}}\,\mathbf{W}(t) + \frac{\partial \mathbf{f}^{\mathrm{T}}(t+\sigma)}{\partial \mathbf{u}_\sigma}\,\mathbf{W}(t+\sigma), \quad t \in (0, t^*]. \tag{13c}$$

Proof. For simplicity in Eq. (1a), we write

$$\mathbf{f}(t, \mathbf{y}, \mathbf{y}_\tau, \mathbf{u}, \mathbf{u}_\sigma, \mathbf{p}) = \mathbf{f}(t, \mathbf{y}(t), \mathbf{y}(t-\tau), \mathbf{u}(t), \mathbf{u}(t-\sigma), \mathbf{p}).$$

Small variations in the initial data, control, and system parameters cause a perturbation in the system state in (1a)–(1c). Then small variations $\delta\Psi$, $\delta\Phi$, $\delta\mathbf{y}_0$, $\delta\mathbf{u}$, $\delta\mathbf{p}$, $\delta\tau$ and $\delta\sigma$ result in a variation $\delta\mathbf{y}$ which satisfies (for first order) the equation

$$\begin{aligned}\delta\mathbf{y}'(t) = {} & \frac{\partial \mathbf{f}}{\partial \mathbf{y}}\,\delta\mathbf{y}(t) + \frac{\partial \mathbf{f}}{\partial \mathbf{y}_\tau}\,\delta\mathbf{y}(t-\tau) + \frac{\partial \mathbf{f}}{\partial \mathbf{u}}\,\delta\mathbf{u}(t) + \frac{\partial \mathbf{f}}{\partial \mathbf{u}_\sigma}\,\delta\mathbf{u}(t-\sigma) + \frac{\partial \mathbf{f}}{\partial \mathbf{p}}\,\delta\mathbf{p} \\ & + \frac{\partial \mathbf{f}}{\partial \mathbf{y}}\,\frac{\partial \mathbf{y}(t-\tau)}{\partial \tau}\,\delta\tau + \frac{\partial \mathbf{f}}{\partial \mathbf{u}}\,\frac{\partial \mathbf{u}(t-\sigma)}{\partial \sigma}\,\delta\sigma,\end{aligned} \tag{14a}$$

$$\delta\mathbf{y}(t) = \delta\Psi(t), \quad t \in [-\tau, 0); \quad \delta\mathbf{y}(0) = \delta\mathbf{y}_0 \in \mathbb{R}^n, \tag{14b}$$

$$\delta\mathbf{u}(t) = \delta\Phi(t), \quad t \in [-\sigma, 0). \tag{14c}$$

If we multiply both sides of (14a) by $\mathbf{W}^{\mathrm{T}}(t)$ (the transpose of the function $\mathbf{W}(t)$) and integrate both sides with respect to t over the interval $[0, t^*]$, we obtain

$$\mathbf{W}^{\mathrm{T}}(t^*)\delta\mathbf{y}(t^*) - \mathbf{W}^{\mathrm{T}}(0)\delta\mathbf{y}(0) - \int_0^{t^*} \mathbf{W}'^{\mathrm{T}}(t)\delta\mathbf{y}(t)\,\mathrm{d}t$$

$$= \int_0^{t^*} \mathbf{W}^{\mathrm{T}}(t)\left[\frac{\partial \mathbf{f}}{\partial \mathbf{y}}\,\delta\mathbf{y}(t) + \frac{\partial \mathbf{f}}{\partial \mathbf{y}_\tau}\,\delta\mathbf{y}(t-\tau)\right]\mathrm{d}t$$
$$+ \int_0^{t^*} \mathbf{W}^{\mathrm{T}}(t)\left[\frac{\partial \mathbf{f}}{\partial \mathbf{u}}\,\delta\mathbf{u}(t) + \frac{\partial \mathbf{f}}{\partial \mathbf{u}_\sigma}\,\delta\mathbf{u}(t-\sigma)\right]\mathrm{d}t$$
$$+ \int_0^{t^*} \mathbf{W}^{\mathrm{T}}(t)\left[\frac{\partial \mathbf{f}}{\partial \mathbf{p}}\,\delta\mathbf{p} + \frac{\partial \mathbf{f}}{\partial \mathbf{y}_\tau}\,\frac{\partial \mathbf{y}(t-\tau)}{\partial \tau}\,\delta\tau + \frac{\partial \mathbf{f}}{\partial \mathbf{u}_\sigma}\,\frac{\partial \mathbf{u}(t-\sigma)}{\partial \sigma}\,\delta\sigma\right]\mathrm{d}t. \tag{15}$$

Eq. (15), after some manipulations, can be rewritten in the form

$$\mathbf{W}^{\mathrm{T}}(t^*)\delta\mathbf{y}(t^*) - \mathbf{W}^{\mathrm{T}}(0)\delta\mathbf{y}(0)$$
$$= \int_{-\tau}^{0} \mathbf{W}^{\mathrm{T}}(t+\tau)\,\frac{\partial \mathbf{f}(t+\tau)}{\partial \mathbf{y}_\tau}\,\delta\Psi(t)\,\mathrm{d}t$$
$$+ \int_0^{t^*-\tau}\left[\mathbf{W}'(t) + \frac{\partial \mathbf{f}^{\mathrm{T}}}{\partial \mathbf{y}}\,\mathbf{W}(t) + \frac{\partial \mathbf{f}^{\mathrm{T}}(t+\tau)}{\partial \mathbf{y}_\tau}\,\mathbf{W}(t+\tau)\right]^{\mathrm{T}}\delta\mathbf{y}(t)\,\mathrm{d}t$$
$$+ \int_{t^*-\tau}^{t^*}\left[\mathbf{W}'(t) + \frac{\partial \mathbf{f}}{\partial \mathbf{y}}\,\mathbf{W}(t)\right]^{\mathrm{T}}\delta\mathbf{y}(t)\,\mathrm{d}t + \int_{-\sigma}^{0} \mathbf{W}^{\mathrm{T}}(t+\sigma)\,\frac{\partial \mathbf{f}(t+\sigma)}{\partial \mathbf{u}_\sigma}\,\delta\Phi(t)\,\mathrm{d}t$$
$$+ \int_0^{t^*-\sigma}\left[\mathbf{W}^{\mathrm{T}}(t)\,\frac{\partial \mathbf{f}}{\partial \mathbf{u}} + \mathbf{W}^{\mathrm{T}}(t+\sigma)\,\frac{\partial \mathbf{f}(t+\sigma)}{\partial \mathbf{u}_\sigma}\right]\delta\mathbf{u}(t)\,\mathrm{d}t + \int_{t^*-\sigma}^{t^*} \mathbf{W}^{\mathrm{T}}(t)\,\frac{\partial \mathbf{f}}{\partial \mathbf{u}}\,\delta\mathbf{u}(t)\,\mathrm{d}t$$
$$+ \int_0^{t^*} \mathbf{W}^{\mathrm{T}}(t)\,\frac{\partial \mathbf{f}}{\partial \mathbf{p}}\,\delta\mathbf{p}\,\mathrm{d}t - \int_{-\tau}^{t^*-\tau} \mathbf{W}^{\mathrm{T}}(t+\tau)\,\frac{\partial \mathbf{f}(t+\tau)}{\partial \mathbf{y}_\tau}\,\mathbf{y}'(t)\delta\tau\,\mathrm{d}t$$
$$- \int_{-\sigma}^{t^*-\sigma} \mathbf{W}^{\mathrm{T}}(t+\sigma)\,\frac{\partial \mathbf{f}(t+\sigma)}{\partial \mathbf{u}_\sigma}\,\mathbf{u}'(t)\delta\sigma\,\mathrm{d}t, \quad t \leqslant t^*. \tag{16}$$

Under the assumptions given in (11) the above equation takes the form

$$\delta y_i(t^*) = \mathbf{W}^{\mathrm{T}}(0)\delta\mathbf{y}(0) + \int_{-\tau}^{0} \mathbf{W}^{\mathrm{T}}(t+\tau)\,\frac{\partial \mathbf{f}(t+\tau)}{\partial \mathbf{y}_\tau}\,\delta\Psi(t)\,\mathrm{d}t$$
$$+ \int_{-\sigma}^{0} \mathbf{W}^{\mathrm{T}}(t+\sigma)\,\frac{\partial \mathbf{f}(t+\sigma)}{\partial \mathbf{u}_\sigma}\,\delta\Phi(t)\,\mathrm{d}t$$
$$+ \int_0^{t^*}\left[\mathbf{W}^{\mathrm{T}}(t)\,\frac{\partial \mathbf{f}}{\partial \mathbf{u}} + \mathbf{W}^{\mathrm{T}}(t+\sigma)\,\frac{\partial \mathbf{f}(t+\sigma)}{\partial \mathbf{u}_\sigma}\right]\delta\mathbf{u}(t)\,\mathrm{d}t$$
$$+ \int_0^{t^*} \mathbf{W}^{\mathrm{T}}(t)\,\frac{\partial \mathbf{f}}{\partial \mathbf{p}}\,\delta\mathbf{p}\,\mathrm{d}t - \int_{-\tau}^{t^*-\tau} \mathbf{W}^{\mathrm{T}}(t+\tau)\,\frac{\partial \mathbf{f}(t+\tau)}{\partial \mathbf{y}_\tau}\,\mathbf{y}'(t)\delta\tau\,\mathrm{d}t$$
$$- \int_{-\sigma}^{t^*-\sigma} \mathbf{W}^{\mathrm{T}}(t+\sigma)\,\frac{\partial \mathbf{f}(t+\sigma)}{\partial \mathbf{u}_\sigma}\,\mathbf{u}'(t)\delta\sigma\,\mathrm{d}t, \quad t \leqslant t^* \tag{17}$$

or

$$\delta y_i(t^*) = \mathbf{W}^{\mathrm{T}}(0)\delta\mathbf{y}(0) + \int_0^{t^*} \mathbf{W}^{\mathrm{T}}(t)\,\frac{\partial \mathbf{f}}{\partial \mathbf{p}}\,\delta\mathbf{p}\,\mathrm{d}t$$
$$- \int_{-\tau}^{t^*-\tau} \mathbf{W}^{\mathrm{T}}(t+\tau)\,\frac{\partial \mathbf{f}(t+\tau)}{\partial \mathbf{y}_\tau}\,\mathbf{y}'(t)\delta\tau\,\mathrm{d}t - \int_{-\sigma}^{t^*-\sigma} \mathbf{W}^{\mathrm{T}}(t+\sigma)\,\frac{\partial \mathbf{f}(t+\sigma)}{\partial \mathbf{u}_\sigma}\,\mathbf{u}'(t)\delta\sigma\,\mathrm{d}t$$
$$+ \int_{-\tau}^{0} \mathbf{W}^{\mathrm{T}}(t+\tau)\,\frac{\partial \mathbf{f}(t+\tau)}{\partial \mathbf{y}_\tau}\,\delta\Psi(t)\,\mathrm{d}t + \int_{-\tau}^{0} \mathbf{W}^{\mathrm{T}}(t+\sigma)\,\frac{\partial \mathbf{f}(t+\sigma)}{\partial \mathbf{u}_\sigma}\,\delta\Phi(t)\,\mathrm{d}t$$
$$+ \int_0^{t^*} \left[\mathbf{W}^{\mathrm{T}}(t)\,\frac{\partial \mathbf{f}}{\partial \mathbf{u}} + \mathbf{W}^{\mathrm{T}}(t+\sigma)\,\frac{\partial \mathbf{f}(t+\sigma)}{\partial \mathbf{u}_\sigma}\right] \delta\mathbf{u}(t)\,\mathrm{d}t, \quad t \leqslant t^*. \tag{18}$$

Functional derivative sensitivity coefficients, for constant parameters, are equivalent to the partial derivative sensitivity coefficients defined by (3). When $\delta\mathbf{y}(0) \to 0$, $\delta\mathbf{p} \to 0$, $\delta\tau \to 0$, and $\delta\sigma \to 0$, we, respectively, obtain the sensitivity coefficients (12a)–(12d) from the first four terms of Eq. (18). Then the first part of Theorem 1 is proved.

From the definition of the functional derivative sensitivity coefficients in (6), we then obtain formulae (13a)–(13c) from the last three terms of Eq. (18). Thus, the second part of Theorem 1 is proved. □

4. Direct approach

If we take all the parameters appearing in the system model (1a)–(1c) to be constants, then sensitivity analysis, in this case, may just entail finding the partial derivatives of the solution with respect to each parameter.

We denote by $\mathbf{S}(t)$ the $n \times \tilde{n}$ matrix $\mathbf{S}(t,\alpha)$ of the sensitivity functions

$$\mathbf{S}(t) \equiv \mathbf{S}(t,\alpha) := \left[\frac{\partial y^i(t,\alpha)}{\partial \alpha_j}\right]_{\substack{i=1,\dots,n \\ j=1,\dots,\tilde{n}}}, \qquad \tilde{n} = r + r'.$$

If we introduce the notation $\{\partial/\partial\alpha\}^{\mathrm{T}}$, the matrix of *sensitivity functions* takes the form

$$\mathbf{S}(t,\alpha) \equiv \left\{\frac{\partial}{\partial\alpha}\right\}^{\mathrm{T}} \mathbf{y}(t,\alpha) \in \mathbb{R}^{n\times\tilde{n}}. \tag{19}$$

Its ith column is

$$S_i(t,\alpha) = \left[\frac{\partial y_i(t,\alpha)}{\partial \alpha_1}, \frac{\partial y_i(t,\alpha)}{\partial \alpha_2}, \dots, \frac{\partial y_i(t,\alpha)}{\partial \alpha_{\tilde{n}}}\right]^{\mathrm{T}}.$$

Thus $S_i(t,\alpha)$ is a vector whose components denote the sensitivity of the solution $y_i(t,\alpha)$ of the model to small variations in the parameters α_j, $j = 1,2,\dots,\tilde{n}$.

Theorem 2. $\mathbf{S}(t)$ *satisfies the DDE*

$$\mathbf{S}'(t) = \mathbf{J}(t)\mathbf{S}(t) + \mathbf{J}_\tau(t)\mathbf{S}(t-\tau) + \mathbf{B}(t), \quad t \geqslant 0, \tag{20}$$

where

$$\mathbf{J}(t) := \frac{\partial}{\partial \mathbf{y}} \mathbf{f}(t, \mathbf{y}, \mathbf{y}_\tau, \mathbf{u}, \mathbf{u}_\sigma; \mathbf{p}) \in \mathbb{R}^{n\times n} \tag{21a}$$

$$\mathbf{J}_\tau(t) := \frac{\partial}{\partial \mathbf{y}_\tau} \mathbf{f}(t, \mathbf{y}, \mathbf{y}_\tau, \mathbf{u}, \mathbf{u}_\sigma; \mathbf{p}) \in \mathbb{R}^{n\times r'}; \tag{21b}$$

$$\mathbf{B}(t) := \frac{\partial}{\partial \alpha} \mathbf{f}(t, \mathbf{y}, \mathbf{y}_\tau, \mathbf{u}, \mathbf{u}_\sigma; \mathbf{p}) \in \mathbb{R}^{n\times \tilde{n}}. \tag{21c}$$

Proof. Assuming appropriate differentiability of $\mathbf{y}(t,\alpha)$ with respect to α, we have

$$\mathbf{y}(t, \alpha + \delta\alpha) = \mathbf{y}(t,\alpha) + \sum_{j=1}^{\tilde{n}} \frac{\partial \mathbf{y}(t,\alpha)}{\partial \alpha_j} \delta\alpha_j + \mathrm{O}(\|\delta\alpha\|^2),$$

or using (19),

$$\delta\mathbf{y}(t,\alpha) = \mathbf{S}(t,\alpha)\delta\alpha + \mathrm{O}(\|\delta\alpha\|^2).$$

Thus, the $n \times \tilde{n}$ matrix $\mathbf{S}(t,\alpha)$ may be regarded as the *local* sensitivity of the solution $\mathbf{y}(t,\alpha)$ to small variations in α. (The term *local* refers to the fact that these sensitivities describe the system around a given set of values for the parameters α.)

By differentiating Eqs. (1a)–(1c) with respect to the vector of parameters α we obtain the variational system

$$\begin{aligned} \mathbf{S}'(t,\alpha) &= \frac{\partial \mathbf{f}}{\partial \mathbf{y}}(t, \mathbf{y}, \mathbf{y}_\tau, \mathbf{u}, \mathbf{u}_\sigma; \mathbf{p})\mathbf{S}(t,\alpha) + \frac{\partial \mathbf{f}}{\partial \mathbf{y}_\tau}(t, \mathbf{y}, \mathbf{y}_\tau, \mathbf{u}, \mathbf{u}_\sigma; \mathbf{p})\mathbf{S}(t-\tau,\alpha) \\ &\quad + \frac{\partial \mathbf{f}}{\partial \alpha}(t, \mathbf{y}, \mathbf{y}_\tau, \mathbf{u}, \mathbf{u}_\sigma; \mathbf{p}), \quad t \geqslant 0, \\ \mathbf{S}'(t,\alpha) &= \frac{\partial \Psi(t,\alpha)}{\partial \alpha}, \quad t \leqslant 0. \end{aligned} \tag{22}$$

Our result follows. □

To estimate the sensitivity functions $\mathbf{S}(t)$, we then have to solve the $n \times \tilde{n}$ sensitivity equations (20) together with the original system (1a)–(1c). We should mention here, solving such systems can be a difficult and costly numerical problem when the number of states and parameters is large, or when the sensitivities must be computed repeatedly; see Section 5.

Remark 1. We apply the direct method to the linear DDE model

$$\begin{aligned} y'(t,\alpha) &= p_1 y(t,\alpha) + p_2 y(t-\tau,\alpha) + p_3 u(t), \quad t \geqslant 0, \\ y(t,\alpha) &= \psi(t,\alpha), \quad t \leqslant 0, \end{aligned} \tag{23}$$

as an example. Here $\alpha = [p_1, p_2, p_3, \tau]^{\mathrm{T}}$. The equations for $\mathbf{S}(t)$ cannot be solved in isolation; they require the solution $y(t)$. We obtain, in the present model, a system of *neutral delay differential* *equations* (NDDEs) expressed as

$$\mathbf{x}'(t,\alpha) = \mathbf{A}\mathbf{x}(t,\alpha) + \mathbf{B}\mathbf{x}(t-\tau,\alpha) + \mathbf{C}\mathbf{x}'(t-\tau,\alpha) + \mathbf{D}(t), \quad t > 0,$$
$$\mathbf{x}(t,\alpha) = \Psi(t,\alpha), \quad t \in [-\tau, 0], \tag{24}$$

where

$$\mathbf{A} = \begin{bmatrix} p_1 & 0 & 0 & 0 & 0 \\ 1 & p_1 & 0 & 0 & 0 \\ 0 & 0 & p_1 & 0 & 0 \\ 0 & 0 & 0 & p_1 & 0 \\ 0 & 0 & 0 & 0 & p_1 \end{bmatrix}, \quad \mathbf{B} = \begin{bmatrix} p_2 & 0 & 0 & 0 & 0 \\ 0 & p_2 & 0 & 0 & 0 \\ 1 & 0 & p_2 & 0 & 0 \\ 0 & 0 & 0 & p_2 & 0 \\ 0 & 0 & 0 & 0 & p_2 \end{bmatrix},$$

$$\mathbf{C} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -p_2 \end{bmatrix},$$

$$\mathbf{D}(t) = \begin{bmatrix} p_3 u(t) \\ 0 \\ 0 \\ u(t) \\ 0 \end{bmatrix}, \quad \mathbf{x}(t,\alpha) = \begin{bmatrix} y(t,\mathbf{p}) \\ s_{p_1}(t,\alpha) \\ s_{p_2}(t,\alpha) \\ s_{p_3}(t,\alpha) \\ s_\tau(t,\alpha) \end{bmatrix}, \quad \text{and} \quad \Psi(t,\alpha) = \begin{bmatrix} \psi(t,\alpha) \\ \frac{\partial}{\partial p_1}\psi(t,\alpha) \\ \frac{\partial}{\partial p_2}\psi(t,\alpha) \\ \frac{\partial}{\partial p_3}\psi(t,\alpha) \\ \frac{\partial}{\partial \tau}\psi(t,\alpha) \end{bmatrix}.$$

Here $s_{\alpha_i} \equiv \partial y(t,\alpha)/\partial\alpha_i$, and some terms $(\partial/\partial\alpha_i)\psi(t,\alpha)$ are nonvanishing in the case where the initial function ψ depends nontrivially upon p_1, p_2, p_3 and τ.

5. Numerical method for sensitivity equations and adjoint problems

The numerical method, that we applied here, for solving the DDEs (1a)–(1c) or (20) is based upon the use of a one-step *continuous* Runge–Kutta method for solving *delay* and *neutral* differential equations. This method, implemented in `Archi` code [18], is based on the Dormand and Prince explicit fifth-order Runge–Kutta method for ODEs [9], due to Shampine [21], and fifth-order Hermite interpolant [17]. We may refer to [1,19] for remarks on the design and analysis of numerical methods for DDEs and NDDEs.

The adjoint problem is formulated as the initial value problem for the system of adjoint equations (9) or (11), where the right-hand side is determined by the solution $\mathbf{y}(t)$ of the original problem.

The original delay differential system (1a)–(1c) is then solved numerically forward in time with positive integration step from t_0 to $t_0 + T$, and the adjoint system is solved backward in time with negative integration step from $t_0 + T$ to t_0. The solution of the original system (1a)–(1c) on the interval $[t_0, t_0 + T]$ results in the set of values $\{t_n, \tilde{y}_n\}$ in the grid points of an irregular grid of integration which are used while solving the adjoint problem form the right-hand side of system (11). We may note that the grid points of integration algorithms are not the same for the original and adjoint problems. Therefore, we can use an interpolation (such as a continuous extension formula or a Hermite interpolant) to estimate the solution of the original problem at nonmesh points. For more discussion about numerical treatment of DDEs, we may refer to [19].

While solving the DDEs such as (1a)–(1c), we should take into account the existence of discontinuity points for the derivatives of the solutions. In other words, if the solution $\mathbf{y}(t)$ is not smoothly linked to the initial function $\Psi(t,\alpha)$ at the initial point t_0, jumps may arise in the derivatives of $\boldsymbol{y}(t)$. (To be precise, this occurs when $\Psi'(t_0) \neq \mathbf{f}(t_0, \mathbf{y}(t_0), \mathbf{y}(t-\tau), \mathbf{u}(t))$.) Such jumps spread forward along the integration interval. The location of such discontinuities is determined by the delayed argument $t-\tau$. Therefore, the set of discontinuity points for the DDEs (1a)–(1c) of the first p derivatives of a solution is $\{t_0 + j\tau\}_{j=0}^{p+1}$, and for the adjoint problem is the join $\{t_0 + j\tau\}_{j=0}^{p+1} \cup \{t_0 + T - j\tau\}_{j=0}^{p+1}$. We may note that the solution of the original problem becomes smoother as t increases toward the end point T and then the smoothness of the solution of the adjoint problem decreases from p at the point $t_0 + p\tau$ to 1 at the point t_0. For further discussion about this issue, we refer to [2].

6. Numerical results

In this section, we apply the results obtained in the above sections to an example of linear DDE:

$$
\begin{aligned}
&y'(t) = p_1 y(t) + p_2 y(t-\tau) + p_3, \quad t \geqslant 0, \\
&y(t) = \psi(t), \quad t \in [-\tau, 0].
\end{aligned} \tag{25}
$$

We have chosen this model because it has many applications in cell growth dynamics, as the behaviour of its solution (for particular parameters) is consistent with the step-like growth pattern; see [6,19,20]. A knowledge of how the solution can vary with respect to small changes in the initial data or the parameters can yield insights into the behaviour of the model and can assist the modelling process. The observation interval is often divided into subintervals each of which could be informative about a specific parameter. Knowledge of these intervals is not only important for understanding the role of the model, but also for an enhanced experiment design for estimating selected parameters. Thus, sensitivity functions can allow one to assess qualitatively which data points have the most effect on a particular parameter.

According to the above analysis, we wish to find (analytically and numerically) the sensitivity density function $\partial y(t^*)/\partial\psi(t)$ (where $t \leqslant t^*$) and the sensitivity coefficients $\partial y(t)/\partial\alpha$. The sensitivity coefficients (for constant parameters) can be obtained by using both the variational and direct methods. However, the functional derivative sensitivity coefficients can only be computed by using the variational method.

First, we apply the variational approach:

In (25) $\alpha=[p_1,p_2,p_3,\tau]^{\mathrm{T}}$ and the control is chosen to be $u(t)=p_3=1$. The adjoint equation for this case is

$$\begin{aligned} &W'(t)=-p_1W(t)-p_2W(t+\tau), \quad t\leqslant t^*,\\ &W(t)=0, \quad t>t^*; \quad W(t^*)=1. \end{aligned} \tag{26}$$

The analytical solution of the adjoint equation (26) is as follows:

(i) $0<t^*\leqslant\tau$,

$$W(t)=\mathrm{e}^{-p_1(t-t^*)}, \quad t\leqslant t^*. \tag{27}$$

(ii) $\tau<t^*\leqslant 2\tau$,

$$W(t)=\begin{cases}\mathrm{e}^{-p_1(t-t^*)}-p_2(t-t^*+\tau)\mathrm{e}^{-p_1(t-t^*+\tau)}, & 0<t\leqslant t^*-\tau,\\ \mathrm{e}^{-p_1(t-t^*)}, & t^*-\tau<t\leqslant t^*.\end{cases} \tag{28}$$

(Here $W(t+\tau)=0$ for $t^*-\tau<t\leqslant t^*$ and $W(t+\tau)=\mathrm{e}^{-p_1(t-t^*+\tau)}$ for $0<t\leqslant t^*-\tau$.)

The solution of the DDE (25), with an initial function $\psi(t)=0$ with $t\leqslant 0$, is

$$y(t)=\begin{cases}\xi(\mathrm{e}^{p_1t}-1), & 0<t\leqslant\tau,\\ \xi^2p_2-\xi+\xi\mathrm{e}^{p_1t}+\xi p_2(t-\tau-\xi)\mathrm{e}^{p_1(t-\tau)}, & \tau<t\leqslant 2\tau,\end{cases} \tag{29}$$

where $\xi=1/p_1$.

Thus, the functional derivative sensitivity density function to the initial function, by using (13a), becomes

(i) $0<t^*\leqslant\tau$,

$$\frac{\partial y(t^*)}{\partial\psi(t)}=p_2W(t+\tau)=\begin{cases}p_2\mathrm{e}^{-p_1(t-t^*+\tau)}, & -\tau<t\leqslant t^*-\tau,\\ 0, & t^*-\tau<t\leqslant 0.\end{cases} \tag{30}$$

(ii) $\tau<t^*\leqslant 2\tau$,

$$\frac{\partial y(t^*)}{\partial\psi(t)}=\begin{cases}p_2\mathrm{e}^{-p_1(t-t^*+\tau)}-p_2^2(t-t^*+2\tau)\mathrm{e}^{-p_1(t-t^*+2\tau)}, & -\tau<t\leqslant t^*-2\tau,\\ p_2\mathrm{e}^{-p_1(t-t^*+\tau)}, & t^*-2\tau<t\leqslant 0.\end{cases} \tag{31}$$

On the other hand, the functional derivative sensitivity density sensitivity function to the control variable $u(t)$, as depicted in (13c), becomes

$$\frac{\partial y(t^*)}{\partial u(t)}=W(t). \tag{32}$$

The sensitivity function of $y(t)$ to the constant parameter p_1, by using (12b), takes the form

$$\frac{\partial y(t^*)}{\partial p_1} = \int_0^{t^*} W(t)\,\frac{\partial f}{\partial p_1}\,\mathrm{d}t = \begin{cases} \xi^2 + \xi(t^* - \xi)\mathrm{e}^{p_1 t^*}, & 0 < t^* \leqslant \tau, \\ I_1 + I_2, & \tau < t^* \leqslant 2\tau, \end{cases} \tag{33}$$

where

$$\begin{aligned} I_1 &= \int_0^{t^*-\tau} W(t)\,\frac{\partial f}{\partial p_1}\,\mathrm{d}t \\ &= \xi(t^* - \tau)\mathrm{e}^{p_1 t^*} + \xi^2(\mathrm{e}^{p_1\tau} - \mathrm{e}^{p_1 t^*}) + \frac{1}{2}\,\xi p_2(t^* - \tau)^2\mathrm{e}^{p_1(t^*-\tau)} \\ &\quad - \xi^2 p_2(t^* - \tau)\mathrm{e}^{p_1(t^*-\tau)} - \xi^3 p_2(1 - \mathrm{e}^{p_1(t^*-\tau)}) \end{aligned} \tag{34}$$

and

$$I_2 = \int_{t^*-\tau}^{t^*} W(t)\,\frac{\partial f}{\partial p_1}\,\mathrm{d}t = I_1 + \xi^2 + \xi(t^* - \xi)\mathrm{e}^{p_1 t^*}. \tag{35}$$

The sensitivity of $y(t)$ to the parameter p_3 is given by

$$\begin{aligned} \frac{\partial y(t^*)}{\partial p_3} &= \int_0^{t^*} W(t)\,\frac{\partial f}{\partial p_3}\,\mathrm{d}t, \\ &= \begin{cases} \xi(\mathrm{e}^{p_1 t^*} - 1), & 0 < t^* \leqslant \tau, \\ \xi^2 p_2 - \xi + \xi\mathrm{e}^{p_1 t^*} + \xi p_2(t^* - \tau - \xi)\mathrm{e}^{p_1(t^*-\tau)}, & \tau < t^* \leqslant 2\tau. \end{cases} \end{aligned} \tag{36}$$

It is clear that $\partial y(t^*)/\partial p_3 = y(t^*)$, as it is satisfying Eq. (25).

By using (12c), we obtain the sensitivity coefficient of $y(t)$ to the constant parameter τ as

$$\begin{aligned} \frac{\partial y(t^*)}{\partial \tau} &= -\int_{-\tau}^{t^*-\tau} W(t+\tau)\,\frac{\partial f(t+\tau)}{\partial y_\tau}\,y'(t)\,\mathrm{d}t \\ &= \begin{cases} 0, & 0 < t^* \leqslant \tau, \\ -p_2(t^* - \tau)\mathrm{e}^{p_1(t^*-\tau)}, & \tau < t^* \leqslant 2\tau. \end{cases} \end{aligned} \tag{38}$$

Numerical results, using the variational approach, are presented in Figs. 1–6. Fig. 1 plots the analytical solution of DDE (25) in the interval $[0, 2\tau]$. Figs. 2 and 3 show the sensitivity of the state variable to the initial function, $\partial y(t^*)/\partial\psi(t)$ $(t < t^*)$ as a function of t for (i) $0 < t^* \leqslant \tau$ and (ii) $\tau < t^* \leqslant 2\tau$, respectively. For case (i), $\partial y(t^*)/\partial\psi(t)$ is positive and increases monotonically in the interval $[-\tau, t^* - \tau]$ and attains maximum value at $t = t^* - \tau$ and vanishes for $t^* - \tau < t \leqslant 0$. In case (ii), $\partial y(t^*)/\partial\psi(t)$ monotonically increases and then decreases to attain the minimum at $t = t^* - 2\tau$. We note that $t = t^* - 2\tau$ is the time when the initial data stop to affect the state delay in the system dynamic. The functional derivative sensitivity density function $\partial y(t^*)/\partial u(t)$ is shown in Fig. 4 as a function of t for $t^* = 2\tau$.

Fig. 5 shows the plot of the sensitivity coefficient $\partial y(t)/\partial p_1$. We note that $\partial y(t)/\partial p_1$ is positive and increases as t increases. Fig. 6 shows the sensitivity of the state variable to the lag τ, $\partial y(t)/\partial\tau$. We note that $\partial y(t)/\partial\tau$ is negative, and as expected $y(t)$ is very sensitive to a change in τ in the

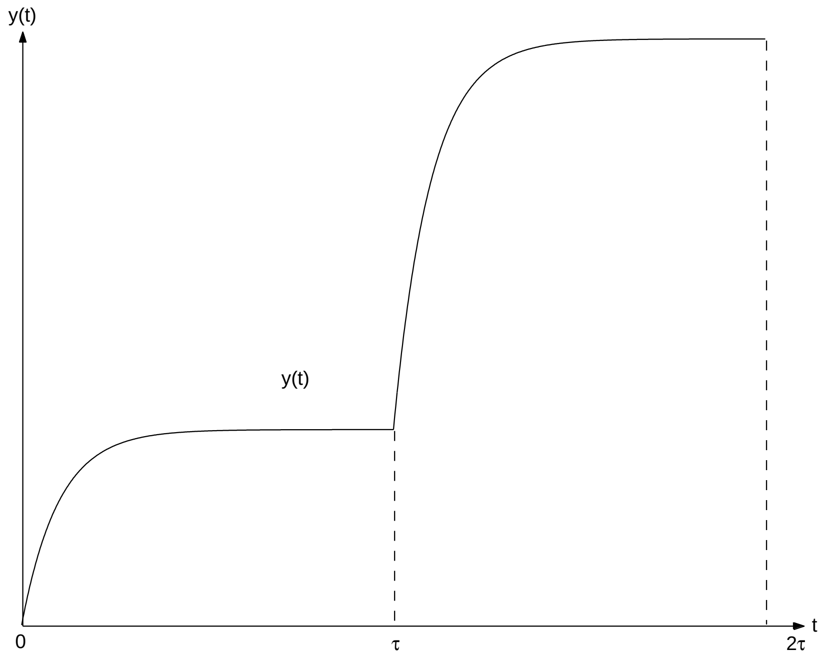

Fig. 1. Analytical solution of DDE (25) in the interval $0 \leqslant t \leqslant 2\tau$ with $p_1 = -2$, $p_2 = 4$, and $p_3 = 1$.

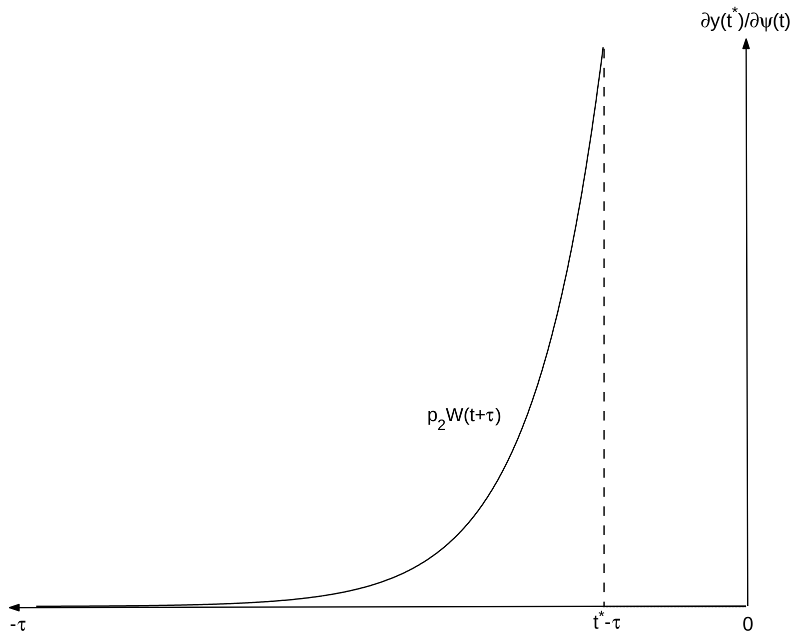

Fig. 2. Functional derivative sensitivity density function $\partial y(t^*)/\partial\psi(t)$, (30), when $0 < t^* \leqslant \tau$.

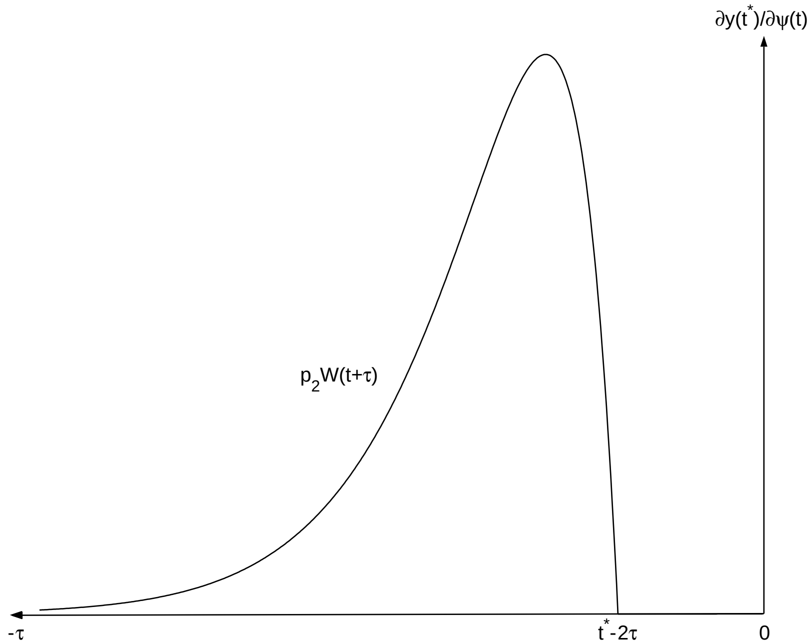

Fig. 3. Functional derivative sensitivity density function $\partial y(t^*)/\partial\psi(t)$, (31), when $\tau < t^* \leqslant 2\tau$.

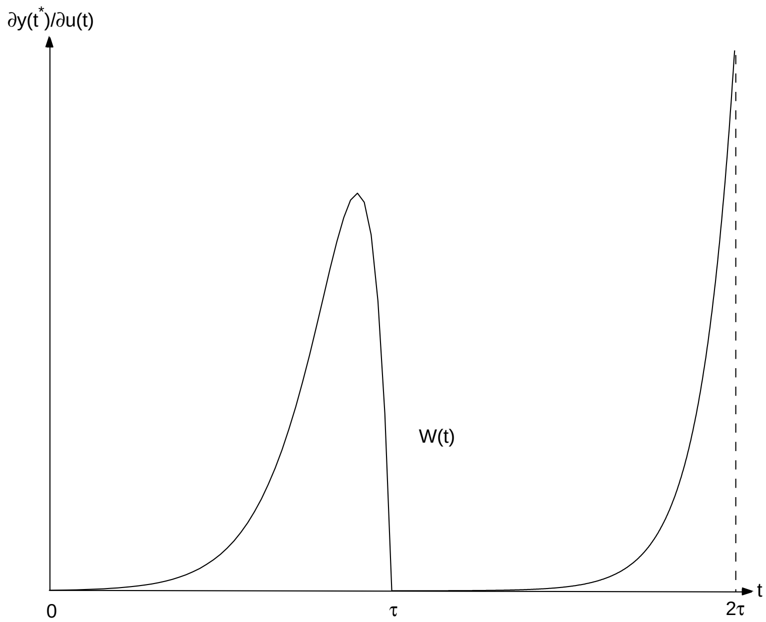

Fig. 4. Functional derivative sensitivity density function $\partial y(t^*)/\partial u(t)$, (32), for $t^* = 2\tau$.

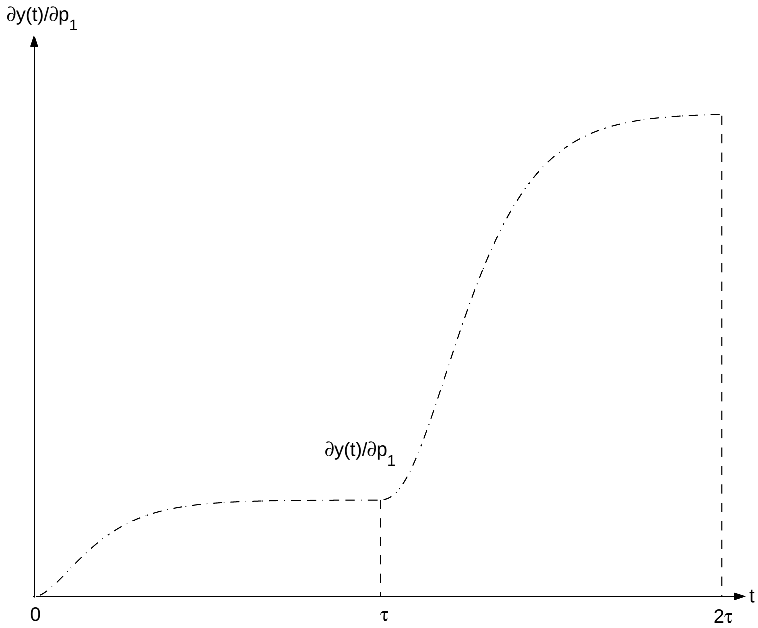

Fig. 5. Sensitivity function $\partial y(t)/\partial p_1$, (33).

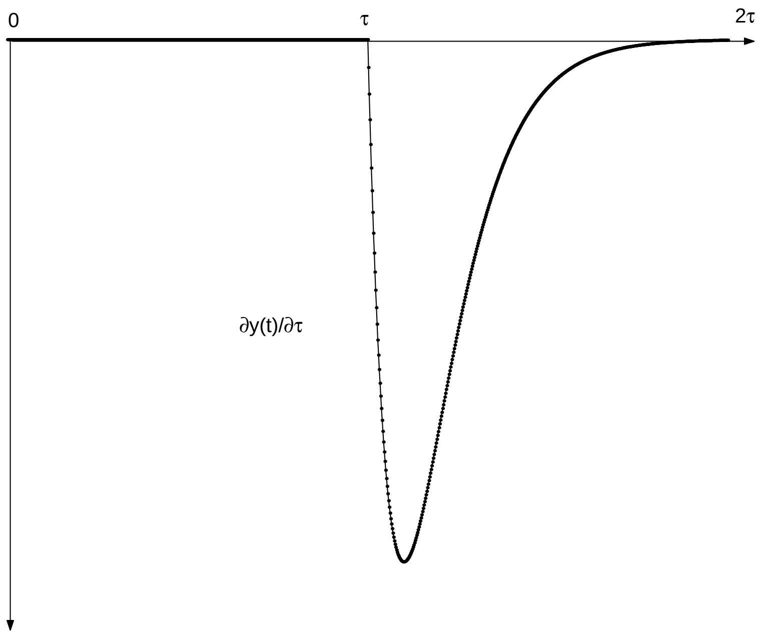

Fig. 6. Sensitivity function $\partial y(t)/\partial \tau$, (38).

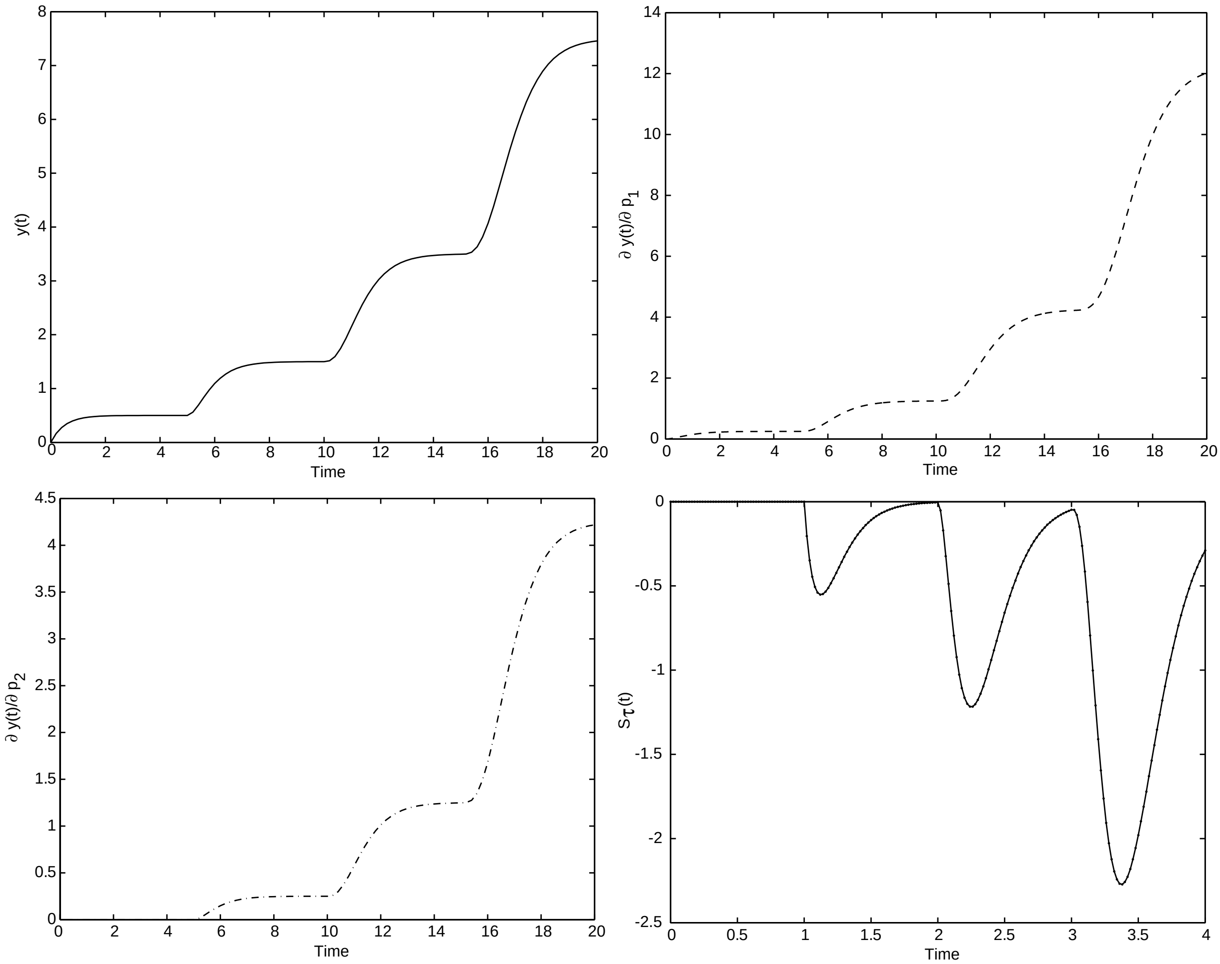

Fig. 7. Numerical results for (25). The first graph (from the left to right, up to down) plots the numerical solution. The second shows the sensitivity function $\partial y(t)/\partial p_1$, the third $\partial y(t)/\partial p_2$, and the fourth $\partial y(t)/\partial \tau$.

time interval $\tau < t \leqslant 2\tau$ and is insensitive to changes in the constant lag τ in the time interval $[0, \tau]$. The plots have a kink at $t = \tau$ as a result of existence of the delay in the system state.

Second, if we apply *the direct approach* in the example being considered (25), we can simply use the results obtained in Remark 1 to get a variational system of NDDEs in the unknown functions of the sensitivity coefficients. We solve this system numerically, as discussed in the previous section, using `Archi` code [18] together with the original equations. The numerical results are displayed in Fig. 7. We note that this approach provides the same results provided by the variational approach.

7. Conclusion

In this paper, we have investigated the sensitivity of model solutions due to perturbing the parameters appearing in delay differential systems, using variational and direct approaches. The theory is applied to a linear DDE. Either of the two approaches is capable, in principle, of providing the same information concerning the system. It has been shown that adjoint equations need to be solved to estimate the sensitivity coefficients via the variational approach. In models consisting parameters that are varying or temporally varying, the functional derivative sensitivity coefficients can only be computed by using the variational method. The direct method is based only on considering all parameters as constants (those independent of time or location) and then the sensitivity coefficients are estimated by solving a variational system simultaneously with the original system. The variational approach can provide a rigorous sensitivity measure that gives a precise interpretation of the results, because sensitivity density functions contain more information than the sensitivity coefficients.

We have discussed how the sensitivity analysis can be used to evaluate which parameters have a significant effect on uncertainty. Sensitivity functions of the solution $y(t)$ for the given DDE model are shown in Figs. 2–6 (by using the variational approach) and in Fig. 7 (by using the direct method). These functions are useful in simulation studies for assessing the sensitivity of the solutions with respect to assigned model parameters. We have seen how the sensitivity functions enable one to assess the relevant time intervals for the identification of specific parameters and improve the understanding of the role played by specific model parameters in describing experimental data. We noted, for example, from Figs. 6 and 7, that the experimental points in the subinterval $[\tau, 2\tau]$ are informative data points for the estimation of parameter τ, while the state variable is insensitive to a change in the constant parameter τ through the time interval $[0, \tau]$. The oscillation accompanied by the sensitivity of $y(t)$ to τ (in Fig. 7) means that the solution is sensitive to changes in the parameter τ and this parameter plays an important role in the model.

Acknowledgements

The author is most grateful to Professor C.T.H. Baker for his valuable comments and numerous suggestions concerning the content of the paper.

References

[1] C.T.H. Baker, Retarded differential equations, J. Comput. Appl. Math. 125 (2000) 309–355.

[2] C.T.H. Baker, C.A. Paul, D.R. Willé, Issues in the numerical solution of evolutionary delay differential equations, Adv. Comput. Math. 3 (1995) 171–196.

[3] H.T. Banks, Modelling and Control in Biosciences, in: Lecture Notes in Biomathematics, Vol. 6, Springer, Berlin, 1975.

[4] J.J. Batzel, H.T. Tran, Stability of the human respiratory control system. I. Analysis of a two-dimensional delay state-space model, J. Math. Biol. 41 (1) (2000) 45–79.

[5] J.J. Batzel, H.T. Tran, Stability of the human respiratory control system. II. Analysis of a three-dimensional delay state-space model, J. Math. Biol. 41 (1) (2000) 80–102.

[6] G.A. Bocharov, F.A. Rihan, Numerical modelling in biosciences using delay differential equations, J. Comput. Appl. Math. 125 (2000) 183–199.

[7] C. Büskens, H. Maurer, SQP-methods for solving optimal control problems with control and state constraints: adjoint variables, sensitivity analysis and real-time control, J. Comput. Appl. Math. 120 (1–2) (2000) 85–108.

[8] P.C. Das, N.K. Patel, S.S. Prabhu, Determination of the optimal initial function and the parameters in a system described by delay-differential equations, J. Optim. Theory Appl. 40 (4) (1983) 583–593.

[9] J.R. Dormand, P.J. Prince, Family of embedded Runge–Kutta formulae, J. Comput. Appl. Math. 6 (1980) 19–26.

[10] L. Eno, J.G. Beumee, H. Rabitz, Sensitivity analysis of experimental data, Appl. Math. Comput. 16 (1985) 153–163.

[11] V.B. Kolmanovskii, A. Myshkis, Applied Theory of Functional Differential Equations, MIA Vol. 85, Kluwer, Dordrecht, 1992.

[12] V.B. Kolmanovskii, L.E. Shaikhet, Control of Systems with Aftereffect, in: Translations of Mathematical Monographs, Vol. 157, AMS, Providence, RI, 1993.

[13] J.R. Leis, M.A. Kramer, The simultaneous solution and sensitivity analysis of systems of described by ordinary differential equations, ACM. Trans. Math. Software 14 (1988) 45–60.

[14] J.M. Mahaffy, Genetic control models with diffusion and delays, Nonlinearity in biology and medicine (Los Alamos, NM, 1987), Math. Biosci. 90 (1–2) (1988) 519–533.

[15] G.I. Marchuk, Adjoint Equations and Analysis of Complex Systems, MIA Vol. 295, Kluwer Academic Publishers, Dordrecht, 1994.

[16] G.I. Marchuk, Mathematical Modelling of Immune Response in Infectious Diseases, MIA Vol. 395, Kluwer Academic Publishers, Dordrecht, 1997.

[17] H.J. Oberle, H.J. Pesch, Numerical treatment of delay differential equations by Hermite interpolation, Numer. Math. 37 (1981) 235–255.

[18] C.A.H. Paul, A user-guide to `Archi`—an explicit Runge–Kutta code for solving delay and neutral differential equations and parameter estimation problems, MCCM Report No. 283, University of Manchester, 1997 (available at: http://www.ma.man.ac.uk/MCCM/MCCM.html).

[19] F.A. Rihan, Numerical treatment of delay differential equations in bioscience, Ph.D. Thesis, University of Manchester, 2000.

[20] F.A. Rihan, C.A.H. Paul, G.A. Bocharov, C.T.H. Baker, Modelling and analysis of cell proliferation. II Identification, discrimination & sensitivity of models, J. Math. Biol., in preparation.

[21] L.F. Shampine, Quadrature and Runge–Kutta formulas, Appl. Math. Comput. 2 (1976) 161–171.

[22] K.L. Teo, G.J. Goh, K.H. Wong, A Unified Computational Approach to Optimal Control Problems, in: Pitman Monographs and Surveys in PAM, Vol. 55, Longman Scientific and Technical, London, 1991.

[23] K. Thomaseth, C. Cobelli, Generalized sensitivity in physiological system identification, Ann. Biomed. Engrg. 27 (1999) 607–616.