Chapter 6
Sensitivity Analysis of Delay Differential Equations

6.1 Introduction

Delay differential equations can be used to model many problems in biosciences and are parameterized by meaningful constant parameters p or/and variable parameters (e.g., control functions) $u(t)$. 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 chapter is to derive a general theory for the sensitivity analysis of mathematical models that contain time-lags. In this chapter, we use *adjoint equations* and *direct methods* to estimate the sensitivity functions when the parameters that appear 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.

Many studies in the sensitivity analysis of models without delay have been done (see, e.g., [1–4]); 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 lags) appearing in the model, and the control functions can yield insights into the behavior of the model and can actually assist the modeling process. Sensitivity analysis may provide some guidelines for the reduction of complex models by indicating those variables and parameters that determine the essential behavior 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 modeling process.

In this chapter, we evaluate sensitivity functionals of DDEs with constant and variable parameters. We estimate general sensitivity coefficients for the constant parameters appearing in the model, and functional derivative sensitivity coefficients for variable coefficients such as initial and control functions. We utilize variational method in Sect. 6.3 and direct method in Sect. 6.4. In the variational approach, the

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sensitivity coefficients are calculated based on the introduction of adjoint variables to solve state and adjoint equations. The direct methods are based on consideration of all parameters as constants and then the sensitivity coefficients are estimated by solving a variational system simultaneously with the original system. We also investigate the sensitivity of the best estimates to small noise in the data/observations in Sect. 6.5.

6.2 Sensitivity Functions

Let us consider a class of systems modeled by DDEs of the form [5]

$$\mathbf{y}'(t) = \mathbf{f}(t, \mathbf{y}(t), \mathbf{y}(t-\tau), \mathbf{u}(t), \mathbf{u}(t-\sigma), \mathbf{p}), \quad 0 \le t \le T, \tag{6.1a}$$

$$\mathbf{y}(t) = \Psi(t, \mathbf{p}), \quad t \in [-\tau, 0), \quad \mathbf{y}(0) = \mathbf{y}_0 \in \mathbb{R}^n \tag{6.1b}$$

$$\mathbf{u}(t) = \Phi(t), \quad t \in [-\sigma, 0), \quad \mathbf{u}(0) = \mathbf{u}_0 \in \mathbb{R}^m, \tag{6.1c}$$

where the vector function $\mathbf{f}$ in the right-hand side is sufficiently smooth with respect to each of arguments; and $\mathbf{y}(t) \in \mathbb{R}^n$, $\mathbf{y}(t-\tau) \in \mathbb{R}^{n'}$, $\mathbf{u}(t) \in \mathbb{R}^m$, $\mathbf{u}(t-\sigma) \in \mathbb{R}^{m'}$, $\mathbf{p} \in \mathbb{R}^r$, and $\tau \in \mathbb{R}^{r'}$ and $\sigma \in \mathbb{R}^{r''}$ are positive constant lags (r', $r'' \le r$, $n' \le n$, $m' \le m$). $\Psi(t)$ and $\Phi(t)$ are given continuous functions. We note that $\mathbf{u}(t)$ in (6.1a) can be viewed as a control variable, defined on $[-\sigma, T]$, which gives a minimum to the objective functional

$$J(\mathbf{u}) = F_0(\mathbf{y}(T)) + \int_0^T F_1(t, \mathbf{y}(t), \mathbf{y}(t-\tau), \mathbf{u}(t), \mathbf{u}(t-\sigma), \mathbf{p})dt, \tag{6.2}$$

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 chapter, we estimate the sensitivity functions for the system (6.1a)–(6.1c) rather than the computational aspects of optimal control problems. (For the computational treatment of time-delayed optimal control problems, refer to the monograph by Kolmanovskii et al. [6].)

To examine the effect 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 manner, possible deficiencies in the model can be revealed if, e.g., 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 6.1 For the given DDEs (6.1a)–(6.1c):

1. The sensitivity functions, when the parameters are constants, are defined by the partial derivatives

$$S_{ij}(t) = \frac{\partial y_i(t)}{\partial \alpha_j}, \tag{6.3}$$

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

$$\delta y_i(t) = \sum_j \frac{\partial y_i(t)}{\partial \alpha_j}\delta\alpha_j + O(|\alpha|^2). \tag{6.4}$$

Thus, Eq. (6.3) estimates the sensitivity of the state variable to small variations in parameters α_j.

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

$$\beta_{ij}(t, t^*) = \frac{\partial y_i(t^*)}{\partial u_j(t)}, \qquad t < t^*. \tag{6.5}$$

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

$$\delta y_i(t^*) = \int_0^{t^*} \frac{\partial y_i(t^*)}{\partial u_j(t)}\delta u_j(t)dt, \qquad t < t^*. \tag{6.6}$$

Thus, the functional derivative sensitivity density function $\frac{\partial y_i(t^*)}{\partial u_j(t)}$ 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.

6.2.1 Adjoint Equations

Adjoint equations have been used by Marchuk [7, 8] to study sensitivity analysis of non-linear functionals $J(\mathbf{y})$ depending on the solution of the delay differential models:

$$\mathbf{y}'(t) = \mathbf{f}(t, \mathbf{y}(t), \mathbf{y}(t-\tau), \mathbf{p}), \quad t \geq t_0; \quad \mathbf{y}(t) = \psi(t, \mathbf{p}), \; t \in [t_0 - \tau, t_0]. \tag{6.7}$$

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

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

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

$$\mathcal{A}(\mathbf{y}(t, \mathbf{p}), \mathbf{p})\mathbf{s}_i(t, \mathbf{p}) = \frac{\partial \mathbf{f}}{\partial p_i}, \quad t \geq 0, \quad \mathbf{s}_i(t, \mathbf{p}) = \frac{\partial \psi}{\partial p_i}, \quad t \in [-\tau, 0]. \tag{6.8}$$

The operator $\mathcal{A} \equiv \frac{d}{dt} - \frac{\partial \mathbf{f}(t)}{\partial \mathbf{y}} - \frac{\partial \mathbf{f}(t+\tau)}{\partial \mathbf{y}_\tau} D_\tau$, 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 $\mathcal{A}$ in (6.8) acts on some Hilbert space H with domain $\mathcal{D}(\mathcal{A})$. Given $\mathcal{A}$, the adjoint operator $\mathcal{A}^*$ can be introduced satisfying the Lagrange identity $\langle \mathcal{A}(\mathbf{y}, \mathbf{p})\mathbf{s}, \mathbf{w} \rangle = \langle \mathbf{s}, \mathcal{A}^*(\mathbf{y}, \mathbf{p})\mathbf{w} \rangle$, 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

$$\mathcal{A}^*(\mathbf{y}, \mathbf{p})\mathbf{w}(t) \equiv -\frac{d\mathbf{w}(t)}{dt} - \frac{\partial \mathbf{f}^T(t)}{\partial \mathbf{y}} \mathbf{w}(t) - \frac{\partial \mathbf{f}^T(t+\tau)}{\partial \mathbf{y}_\tau} \mathbf{w}(t+\tau) = \mathbf{y}(t, \mathbf{p}),$$
$$0 \leq t \leq T, \quad \mathbf{w}(t) = 0, \ t \in [T, T+\tau] \tag{6.9}$$

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

$$\delta J(\mathbf{y}) = \sum_{i=1}^{r} 2 \int_0^T \left\langle \mathbf{w}, \frac{\partial \mathbf{f}}{\partial p_i} \delta p_i \right\rangle dt = \sum_{i=1}^{r} \frac{\partial J}{\partial p_i} \delta p_i, \tag{6.10}$$

where $\frac{\partial J}{\partial p_i} \equiv 2 \int_0^T \left\langle \mathbf{w}, \frac{\partial \mathbf{f}}{\partial p_i} \right\rangle dt$ is the gradient of the functional with respect to the parameters.

To estimate the sensitivity of the functional $J(\mathbf{y})$ to variations in all parameters appearing in the model (6.7), we need to solve this system model together with the adjoint problem (6.9). In the next section, we extend the use of adjoint equations to investigate the sensitivity analysis for a more general system (6.1a)–(6.1c), including constant and variable parameters.

6.3 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 $\dfrac{\partial y_i(t)}{\partial \alpha_j}$ and the sensitivity density functions $\dfrac{\partial y_i(t^*)}{\partial u_j(t)}$.

Theorem 6.1 *If* $\mathbf{W}(t)$ *is an n-dimensional adjoint function that satisfies the differential equation*

$$\begin{aligned}\mathbf{W}'(t) \equiv \frac{d\mathbf{W}(t)}{dt} &= -\frac{\partial \mathbf{f}^T(t)}{\partial \mathbf{y}}\mathbf{W}(t) - \frac{\partial \mathbf{f}^T(t+\tau)}{\partial \mathbf{y}_\tau}\mathbf{W}(t+\tau), \quad t \le t^*, \\ \mathbf{W}(t) &= 0, \quad t > t^*; \qquad \mathbf{W}(t^*) = [0, \ldots, 0, 1_{ith}, 0 \ldots, 0]^T,\end{aligned} \tag{6.11}$$

then

1. *The sensitivity coefficients for the DDEs (6.1a)–(6.1c) can be expressed by the formulae*

$$\frac{\partial y_i(t^*)}{\partial \mathbf{y}_0} = \mathbf{W}(0), \tag{6.12a}$$

$$\frac{\partial y_i(t^*)}{\partial \mathbf{p}} = \int_0^{t^*} \mathbf{W}^T(t)\frac{\partial \mathbf{f}}{\partial \mathbf{p}}dt, \quad t \le t^*, \tag{6.12b}$$

$$\frac{\partial y_i(t^*)}{\partial \tau} = -\int_{-\tau}^{t^*-\tau} \mathbf{W}^T(t+\tau)\frac{\partial \mathbf{f}(t+\tau)}{\partial \mathbf{y}_\tau}\mathbf{y}'(t)dt, \tag{6.12c}$$

$$\frac{\partial y_i(t^*)}{\partial \sigma} = -\int_{-\sigma}^{t^*-\sigma} \mathbf{W}^T(t+\sigma)\frac{\partial \mathbf{f}(t+\sigma)}{\partial \mathbf{u}_\sigma}\mathbf{u}'(t)dt. \tag{6.12d}$$

2. *The functional derivative sensitivity coefficients can also be expressed by*

$$\frac{\partial y_i(t^*)}{\partial \Psi(t)} = \frac{\partial \mathbf{f}^T(t+\tau)}{\partial \mathbf{y}}\mathbf{W}(t+\tau), \quad t \in [-\tau, 0) \tag{6.13a}$$

$$\frac{\partial y_i(t^*)}{\partial \Phi(t)} = \frac{\partial \mathbf{f}^T(t+\sigma)}{\partial \mathbf{u}_\sigma}\mathbf{W}(t+\sigma), \quad t \in [-\sigma, 0) \tag{6.13b}$$

$$\frac{\partial y_i(t^*)}{\partial \mathbf{u}(t)} = \frac{\partial \mathbf{f}^T}{\partial \mathbf{u}}\mathbf{W}(t) + \frac{\partial \mathbf{f}^T(t+\sigma)}{\partial \mathbf{u}_\sigma}\mathbf{W}(t+\sigma), \quad t \in (0, t^*]. \tag{6.13c}$$

Proof For simplicity in Eq. (6.1a), 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 (6.1a)–(6.1c). 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 $\delta\mathbf{y}$ that satisfies (for first order) the equation

$$\delta\mathbf{y}'(t) = \frac{\partial\mathbf{f}}{\partial\mathbf{y}}\delta\mathbf{y}(t) + \frac{\partial\mathbf{f}}{\partial\mathbf{y}_\tau}\delta\mathbf{y}(t-\tau) + \frac{\partial\mathbf{f}}{\partial\mathbf{u}}\delta\mathbf{u}(t) + \frac{\partial\mathbf{f}}{\partial\mathbf{u}_\sigma}\delta\mathbf{u}(t-\sigma) + \frac{\partial\mathbf{f}}{\partial\mathbf{p}}\delta\mathbf{p} + \frac{\partial\mathbf{f}}{\partial\mathbf{y}}\frac{\partial\mathbf{y}(t-\tau)}{\partial\tau}\delta\tau + \frac{\partial\mathbf{f}}{\partial\mathbf{u}}\frac{\partial\mathbf{u}(t-\sigma)}{\partial\sigma}\delta\sigma, \tag{6.14a}$$

$$\delta\mathbf{y}(t) = \delta\Psi(t), \quad t \in [-\tau, 0); \quad \delta\mathbf{y}(0) = \delta\mathbf{y}_0 \in \mathbb{R}^n, \tag{6.14b}$$

$$\delta\mathbf{u}(t) = \delta\Phi(t), \quad t \in [-\sigma, 0). \tag{6.14c}$$

If we multiply both sides of (6.14a) by $\mathbf{W}^T(t)$ (the transpose of the function $\mathbf{W}(t)$) and integrate both sides with respect to t over the interval $[0, t^*]$, we obtain

$$\begin{aligned}
&\mathbf{W}^T(t^*)\delta\mathbf{y}(t^*) - \mathbf{W}^T(0)\delta\mathbf{y}(0) - \int_0^{t^*}\mathbf{W}'^T(t)\delta\mathbf{y}(t)dt = \\
&\int_0^{t^*}\mathbf{W}^T(t)\left[\frac{\partial\mathbf{f}}{\partial\mathbf{y}}\delta\mathbf{y}(t) + \frac{\partial\mathbf{f}}{\partial\mathbf{y}_\tau}\delta\mathbf{y}(t-\tau)\right]dt + \\
&\int_0^{t^*}\mathbf{W}^T(t)\left[\frac{\partial\mathbf{f}}{\partial\mathbf{u}}\delta\mathbf{u}(t) + \frac{\partial\mathbf{f}}{\partial\mathbf{u}_\sigma}\delta\mathbf{u}(t-\sigma)\right]dt + \\
&\int_0^{t^*}\mathbf{W}^T(t)\left[\frac{\partial\mathbf{f}}{\partial\mathbf{p}}\delta\mathbf{p} + \frac{\partial\mathbf{f}}{\partial\mathbf{y}_\tau}\frac{\partial\mathbf{y}(t-\tau)}{\partial\tau}\delta\tau + \frac{\partial\mathbf{f}}{\partial\mathbf{u}_\sigma}\frac{\partial\mathbf{u}(t-\sigma)}{\partial\sigma}\delta\sigma\right]dt.
\end{aligned} \tag{6.15}$$

Equation (6.15), after some manipulations, can be rewritten in the form

$$\begin{aligned}
&\mathbf{W}^T(t^*)\delta\mathbf{y}(t^*) - \mathbf{W}^T(0)\delta\mathbf{y}(0) = \int_{-\tau}^{0}\mathbf{W}^T(t+\tau)\frac{\partial\mathbf{f}(t+\tau)}{\partial\mathbf{y}_\tau}\delta\Psi(t)dt \\
&+ \int_0^{t^*-\tau}\left[\mathbf{W}'(t) + \frac{\partial\mathbf{f}^T}{\partial\mathbf{y}}\mathbf{W}(t) + \frac{\partial\mathbf{f}^T(t+\tau)}{\partial\mathbf{y}_\tau}\mathbf{W}(t+\tau)\right]^T\delta\mathbf{y}(t)dt \\
&+ \int_{t^*-\tau}^{t^*}\left[\mathbf{W}'(t) + \frac{\partial\mathbf{f}}{\partial\mathbf{y}}\mathbf{W}(t)\right]^T\delta\mathbf{y}(t)dt + \int_{-\sigma}^{0}\mathbf{W}^T(t+\sigma)\frac{\partial\mathbf{f}(t+\sigma)}{\partial\mathbf{u}_\sigma}\delta\Phi(t)dt \\
&+ \int_0^{t^*-\sigma}\left[\mathbf{W}^T(t)\frac{\partial\mathbf{f}}{\partial\mathbf{u}} + \mathbf{W}^T(t+\sigma)\frac{\partial\mathbf{f}(t+\sigma)}{\partial\mathbf{u}_\sigma}\right]\delta\mathbf{u}(t)dt + \int_{t^*-\sigma}^{t^*}\mathbf{W}^T(t)\frac{\partial\mathbf{f}}{\partial\mathbf{u}}\delta\mathbf{u}(t)dt \\
&+ \int_0^{t^*}\mathbf{W}^T(t)\frac{\partial\mathbf{f}}{\partial\mathbf{p}}\delta\mathbf{p}dt - \int_{-\tau}^{t^*-\tau}\mathbf{W}^T(t+\tau)\frac{\partial\mathbf{f}(t+\tau)}{\partial\mathbf{y}_\tau}\mathbf{y}'(t)\delta\tau dt \\
&- \int_{-\sigma}^{t^*-\sigma}\mathbf{W}^T(t+\sigma)\frac{\partial\mathbf{f}(t+\sigma)}{\partial\mathbf{u}_\sigma}\mathbf{u}'(t)\delta\sigma dt, \quad t \le t^*.
\end{aligned} \tag{6.16}$$

Under the assumptions given in (6.11), the above equation takes the form

$$\delta y_i(t^*) = \mathbf{W}^T(0)\delta\mathbf{y}(0) + \int_{-\tau}^{0} \mathbf{W}^T(t+\tau)\frac{\partial\mathbf{f}(t+\tau)}{\partial\mathbf{y}_\tau}\delta\Psi(t)dt$$
$$+ \int_{-\sigma}^{0} \mathbf{W}^T(t+\sigma)\frac{\partial\mathbf{f}(t+\sigma)}{\partial\mathbf{u}_\sigma}\delta\Phi(t)dt$$
$$+ \int_{0}^{t^*} \left[\mathbf{W}^T(t)\frac{\partial\mathbf{f}}{\partial\mathbf{u}} + \mathbf{W}^T(t+\sigma)\frac{\partial\mathbf{f}(t+\sigma)}{\partial\mathbf{u}_\sigma}\right]\delta\mathbf{u}(t)dt$$
$$+ \int_{0}^{t^*} \mathbf{W}^T(t)\frac{\partial\mathbf{f}}{\partial\mathbf{p}}\delta\mathbf{p}dt - \int_{-\tau}^{t^*-\tau} \mathbf{W}^T(t+\tau)\frac{\partial\mathbf{f}(t+\tau)}{\partial\mathbf{y}_\tau}\mathbf{y}'(t)\delta\tau dt$$
$$- \int_{-\sigma}^{t^*-\sigma} \mathbf{W}^T(t+\sigma)\frac{\partial\mathbf{f}(t+\sigma)}{\partial\mathbf{u}_\sigma}\mathbf{u}'(t)\delta\sigma dt, \quad t \le t^*; \tag{6.17}$$

or

$$\delta y_i(t^*) = \mathbf{W}^T(0)\delta\mathbf{y}(0) + \int_{0}^{t^*} \mathbf{W}^T(t)\frac{\partial\mathbf{f}}{\partial\mathbf{p}}\delta\mathbf{p}dt$$
$$- \int_{-\tau}^{t^*-\tau} \mathbf{W}^T(t+\tau)\frac{\partial\mathbf{f}(t+\tau)}{\partial\mathbf{y}_\tau}\mathbf{y}'(t)\delta\tau dt - \int_{-\sigma}^{t^*-\sigma} \mathbf{W}^T(t+\sigma)\frac{\partial\mathbf{f}(t+\sigma)}{\partial\mathbf{u}_\sigma}\mathbf{u}'(t)\delta\sigma dt$$
$$+ \int_{-\tau}^{0} \mathbf{W}^T(t+\tau)\frac{\partial\mathbf{f}(t+\tau)}{\partial\mathbf{y}_\tau}\delta\Psi(t)dt + \int_{-\tau}^{0} \mathbf{W}^T(t+\sigma)\frac{\partial\mathbf{f}(t+\sigma)}{\partial\mathbf{u}_\sigma}\delta\Phi(t)dt$$
$$+ \int_{0}^{t^*} \left[\mathbf{W}^T(t)\frac{\partial\mathbf{f}}{\partial\mathbf{u}} + \mathbf{W}^T(t+\sigma)\frac{\partial\mathbf{f}(t+\sigma)}{\partial\mathbf{u}_\sigma}\right]\delta\mathbf{u}(t)dt, \quad t \le t^*. \tag{6.18}$$

Functional derivative sensitivity coefficients, for constant parameters, are equivalent to the partial derivative sensitivity coefficients defined by (6.3). 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 (6.12a)–(6.12d) from the first four terms of Eq. (6.18). Then, the first part of Theorem 6.1 is proved.

From the definition of the functional derivative sensitivity coefficients in (6.6), we then obtain the formulae (6.13a)–(6.13c) from the last three terms of Eq. (6.18). Thus, the second part of Theorem 6.1 is proved.

6.4 Direct Approach

If we take all the parameters appearing in the system model (6.1a)–(6.1c) 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

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

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

$$\mathbf{S}(t,\alpha) \equiv \left\{\frac{\partial}{\partial\alpha}\right\}^{\mathrm{T}}\mathbf{y}(t,\alpha) \in \mathbb{R}^{n\times\tilde{n}}. \tag{6.19}$$

Its ith column is

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

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, $j = 1, 2, \ldots, \tilde{n}$.

Theorem 6.2 $\mathbf{S}(t)$ *satisfies the* DDE*:*

$$\mathbf{S}'(t) = \mathbf{J}(t)\mathbf{S}(t) + \mathbf{J}_\tau(t)\mathbf{S}(t-\tau) + \mathbf{B}(t), \quad t \geq 0, \tag{6.20}$$

where

$$\mathbf{J}(t) := \frac{\partial}{\partial\mathbf{y}}\mathbf{f}(t,\mathbf{y},\mathbf{y}_\tau,\mathbf{u},\mathbf{u}_\sigma;\mathbf{p}) \in \mathbb{R}^{n\times n} \tag{6.21a}$$

$$\mathbf{J}_\tau(t) := \frac{\partial}{\partial\mathbf{y}_\tau}\mathbf{f}(t,\mathbf{y},\mathbf{y}_\tau,\mathbf{u},\mathbf{u}_\sigma;\mathbf{p}) \in \mathbb{R}^{n\times r'}; \tag{6.21b}$$

$$\mathbf{B}(t) := \frac{\partial}{\partial\alpha}\mathbf{f}(t,\mathbf{y},\mathbf{y}_\tau,\mathbf{u},\mathbf{u}_\sigma;\mathbf{p}) \in \mathbb{R}^{n\times\tilde{n}}. \tag{6.21c}$$

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

$$\mathbf{y}(t,\alpha+\delta\alpha) = \mathbf{y}(t,\alpha) + \sum_{j=1}^{\tilde{n}} \frac{\partial\mathbf{y}(t,\alpha)}{\partial\alpha_j}\delta\alpha_j + O(\|\delta\alpha\|^2), \quad \text{or, using (6.19),}$$

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

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 equations (6.1a)–(6.1b) with respect to the vector of parameters α, we obtain the variational system

$$\mathbf{S}'(t,\alpha) = \frac{\partial \mathbf{f}}{\partial \mathbf{y}}(t,\mathbf{y},\mathbf{y}_\tau,\mathbf{u},\mathbf{u}_\sigma;\mathbf{p})\mathbf{S}(t,\alpha) + \frac{\partial \mathbf{f}}{\partial \mathbf{y}_\tau}(t,\mathbf{y},\mathbf{y}_\tau,\mathbf{u},\mathbf{u}_\sigma;\mathbf{p})\mathbf{S}(t-\tau,\alpha)$$
$$+\frac{\partial \mathbf{f}}{\partial \alpha}(t,\mathbf{y},\mathbf{y}_\tau,\mathbf{u},\mathbf{u}_\sigma;\mathbf{p}) \qquad t \geq 0,$$
$$\mathbf{S}'(t,\alpha) = \frac{\partial \Psi(t,\alpha)}{\partial \alpha}, \qquad t \leq 0.$$

Our result is as follows. □

To estimate the sensitivity functions $\mathbf{S}(t)$, we must solve the $n \times \tilde{n}$ sensitivity Eq. (6.20) together with the original system (6.1a)–(6.1c). We should mention here that 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.

Remark 6.1 We apply the direct method to the linear DDE model:

$$\begin{aligned} y'(t,\alpha) &= p_1 y(t,\alpha) + p_2 y(t-\tau,\alpha) + p_3 u(t), \quad t \geq 0 \\ y(t,\alpha) &= \psi(t,\alpha), \quad t \leq 0, \end{aligned} \tag{6.22}$$

as an example. Here $\alpha = [p_1, p_2, p_3, \tau]^T$. The equations for $S(t)$ 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

$$\begin{aligned} \mathbf{x}'(t,\alpha) &= \mathbf{A}\mathbf{x}(t,\alpha) + \mathbf{B}\mathbf{x}(t-\tau,\alpha) + \mathbf{C}\mathbf{x}'(t-\tau,\alpha) + \mathbf{D}(t), \quad t > 0, \\ \mathbf{x}(t,\alpha) &= \Psi(t,\alpha), \quad t \in [-\tau, 0], \end{aligned} \tag{6.23}$$

where

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

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

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

6.5 Sensitivity of Optimum Parameter $\widehat{p}$ to Data

To compute $\frac{\partial \widehat{\mathbf{p}}}{\partial \mathbf{Y}_j}$, the sensitivity of the parameter estimate $\widehat{\mathbf{p}}$ to the observed data $\mathbf{Y}_j$, assume that the unweighted objective function

$$\Phi(\mathbf{p}) \equiv \Phi(\mathbf{p}, \mathbf{Y}) := \sum_i \left[y(t_i, \mathbf{p}) - \mathbf{Y}_i \right]^2 \tag{6.24}$$

is smooth as a function of $\mathbf{p}$ in the neighborhood of the optimal parameter $\widehat{\mathbf{p}}$. Then we have

$$\frac{\partial}{\partial p_k} \Phi(\mathbf{p}, \mathbf{Y}) = 2 \sum_i \left[y(t_i, \mathbf{p}) - \mathbf{Y}_i \right] \frac{\partial y(t_i, \mathbf{p})}{\partial p_k}, \tag{6.25}$$

$$\frac{\partial^2}{\partial p_l \partial p_k} \Phi(\mathbf{p}, \mathbf{Y}) = 2 \sum_i \frac{\partial y(t_i, \mathbf{p})}{\partial p_l} \frac{\partial y(t_i, \mathbf{p})}{\partial p_k} + 2 \sum_i \left[y(t_i, \mathbf{p}) - \mathbf{Y}_i \right] \frac{\partial^2 y(t_i, \mathbf{p})}{\partial p_l \partial p_k}. \tag{6.26}$$

To minimize the objective function (6.24), the right-hand side of Eq. (6.25) vanishes at $\mathbf{p} = \widehat{\mathbf{p}}$ (where $\widehat{\mathbf{p}} \equiv \widehat{\mathbf{p}}(\mathbf{Y})$); therefore,

$$\sum_i [y(t_i, \widehat{\mathbf{p}}(\mathbf{Y})) \mathbf{Y}_i] s_k(t_i, \widehat{\mathbf{p}}(\mathbf{Y})) = 0. \tag{6.27}$$

Now, the left-hand side of Eq. (6.27) is a function of $\widehat{\mathbf{p}}$ and $\mathbf{Y}$; differentiating both sides with respect to $\mathbf{Y}_j$ yields, for $k = 1, \ldots, L$,

$$\sum_{i=1}^{N} \sum_{l=1}^{L} \left[s_k(t_i, \widehat{\mathbf{p}}) s_l(t_i, \widehat{\mathbf{p}}) + \left[y(t_i, \widehat{\mathbf{p}}) - \mathbf{Y}_i \right] r_{lk}(t_i, \widehat{\mathbf{p}}) \right] \frac{\partial \widehat{p}_l}{\partial \mathbf{Y}_j} = s_k(t_j, \widehat{\mathbf{p}}). \tag{6.28}$$

If we assume that $y(t_i, \widehat{\mathbf{p}})$ is close to the observed value $\mathbf{Y}_i$, so that the second term in the left-hand side of Eq. (6.28) can be neglected, then the above system can be approximated by

$$\sum_{i=1}^{N} \sum_{l=1}^{L} s_k(t_i, \widehat{\mathbf{p}}) s_l(t_i, \widehat{\mathbf{p}}) \frac{\partial \hat{p}_l}{\partial \mathbf{Y}_j} \approx s_k(t_j, \widehat{\mathbf{p}}), \quad k = 1, \ldots, L,$$

or

$$\sum_{i=1}^{N} s_k(t_i, \widehat{\mathbf{p}}) \Big(\sum_{l=1}^{L} s_l(t_i, \widehat{\mathbf{p}}) \frac{\partial p_l}{\partial \mathbf{Y}_j} \Big) \approx s_k(t_j, \widehat{\mathbf{p}}), \quad k = 1, \ldots, L. \tag{6.29}$$

This equation can be written in a compact form:

$$\Big[\sum_{i=1}^{N} \mathbf{s}(t_i, \widehat{\mathbf{p}})\mathbf{s}^{\mathrm{T}}(t_i, \widehat{\mathbf{p}})\Big]\frac{\partial \widehat{\mathbf{p}}}{\partial bfY_j} \approx \mathbf{s}(t_j, \widehat{\mathbf{p}}). \tag{6.30}$$

Then, the sensitivity of the best-fit parameter estimate $\widehat{\mathbf{p}}$ to observations $\mathbf{Y}_j (j = 1, 2, \ldots, N)$ can be estimated by

$$\frac{\partial \widehat{\mathbf{p}}}{\partial \mathbf{Y}_j} \approx \Big[\mathfrak{B}(\widehat{\mathbf{p}})\Big]^{-1} \mathbf{s}(t_j, \widehat{\mathbf{p}}), \tag{6.31}$$

where $\mathbf{s}$ is $L \times 1$ vector and $\mathfrak{B}(\widehat{\mathbf{p}}) := \Big[\sum_{i=1}^{N} \mathbf{s}(t_i, \widehat{\mathbf{p}})\mathbf{s}^{T}(t_i, \widehat{\mathbf{p}})\Big]$ is a $L \times L$ nonsingular matrix.

A desirable property of the model is that the sensitivity of the parameter estimate to the observation $\frac{\partial \widehat{\mathbf{p}}}{\partial \mathbf{Y}_j}$ should be small to minimize the effect of observation noise on the parameter estimate. Equation (6.31) suggests that increasing $\mathbf{s}(t, \widehat{\mathbf{p}})$ (the sensitivity of the state variable with respect to the unknown parameter) decreases the sensitivity of the parameter estimation to observation.

6.5.1 Standard Deviation of Parameter Estimates

We can use the sensitivity coefficients $(s_i,\ i = 1, \ldots, L)$ to determine the covariance matrix $[\varsigma_{ij}]$ of the estimates as follows [9]:

$$\begin{bmatrix} \varsigma_{11} & \varsigma_{12} & \cdots & \varsigma_{1L} \\ \varsigma_{21} & \varsigma_{22} & \cdots & \varsigma_{2L} \\ \varsigma_{31} & \varsigma_{32} & \cdots & \varsigma_{3L} \\ \cdot\cdot & \cdot\cdot & \cdots & \cdot\cdot \\ \varsigma_{R1} & \varsigma_{R2} & \cdots & \varsigma_{LL} \end{bmatrix} = 2\frac{\Phi(\widehat{\mathbf{p}})}{N - L}\left[H(\widehat{\mathbf{p}})\right]^{-1},$$

where $(N - L)$ is the number of degrees of freedom and $H(\widehat{\mathbf{p}})$ is the Hessian matrix of the objective function $\Phi(\widehat{\mathbf{p}})$. Using the notation $\frac{\partial}{\partial \mathbf{p}}$ and $\frac{\partial}{\partial \mathbf{p}^T}$, the Hessian matrix can be written in the form

$$H(\widehat{\mathbf{p}}) = \left[\frac{\partial^2}{\partial \mathbf{p} \partial \mathbf{p}^{\mathrm{T}}} \Phi(\widehat{\mathbf{p}})\right].$$

This matrix can be approximated, in terms of (6.26) and using the sensitivity coefficients, as

$$H(\widehat{\mathbf{p}}) \approx \widetilde{H}(\widehat{\mathbf{p}}) := 2\left[\sum_{k=1}^{N} s_i(t_k, \widehat{\mathbf{p}}) s_j(t_k, \widehat{\mathbf{p}})\right]_{i,j=1,\ldots,L}.$$

Hence, the standard deviations for the parameter estimates are the quantities $\sigma_i \equiv \sigma(\hat{p}_i) = \sqrt{\varsigma_{ii}}$ $(i = 1, \ldots, L)$.

6.5.2 Non-linearity and Indications of Bias

We remarked earlier that percentage *bias* in the values of the parameter estimates is a good indicator of the quantitative effect of non-linearity [10]. To examine the *biases* in the values of the parameter estimates due to the non-linearity of the parameters, we proceed as follows:

(1) Perturb the obtained solution of the model corresponding to the best-fit parameters $\widehat{\mathbf{p}}$ with normally distributed random errors of zero mean and variance (see [9]):
$$s^2 = \frac{\Phi(\widehat{\mathbf{p}})}{N - L}.$$
(2) Find new best-fit parameters $\widetilde{\mathbf{p}}$ to the perturbed data from (1).
(3) Repeat this process a large number of times (500, or preferably 1000 times) to generate a statistically significant estimate of the mean value of $\widetilde{\mathbf{p}}$.
(4) If the *relative biases* satisfy the relation
$$\|\widehat{\mathbf{p}} - mean\{\widetilde{\mathbf{p}}\}\| < 0.01\|\widehat{\mathbf{p}}\|,$$
then the effect of non-linearity is not regarded as significant and the experimenter can have confidence in the parameter estimates and their standard deviations.

In other words, if the LS estimator of a non-linear regression model is only *slightly biased* (the relative biases $<1\%$) with a distribution close to that of a normal distribution and with a variance only slightly in excess of the minimum variance bound, it seems reasonable to consider the estimator as behaving *close to a linear* regression model. If, on the other hand, the LS estimator has a large non-linear bias, with a distribution far from normal and variance greatly in excess of the minimum variance bound, the non-linear regression model might be far from a linear model in its behavior. For more details about the non-linearity effect and issues related to parameter estimations, refer to [9–12].

6.6 Numerical Results

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

$$\begin{aligned} y'(t) &= p_1 y(t) + p_2 y(t-\tau) + p_3, \quad t \geq 0, \\ y(t) &= \psi(t), \quad t \in [-\tau, 0]. \end{aligned} \tag{6.32}$$

We have chosen this model because it has many applications in cell-growth dynamics, as the behavior of its solution (for particular parameters) is consistent with the step-like growth pattern; see [12]. 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 behavior of the model and can assist the modeling 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 qualitatively assess which data points have the most effect on a particular parameter.

According the above analysis, we wish to find (analytically and numerically) the sensitivity density function $\dfrac{\partial y(t^*)}{\partial \psi(t)}$ (where $t \leq t^*$) and the sensitivity coefficients $\dfrac{\partial y(t)}{\partial \alpha}$. The sensitivity coefficients (for constant parameters) can be obtained by using both 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 (6.32), $\alpha = [p_1, p_2, p_3, \tau]^T$ and the control is chosen to be $u(t) = p_3 = 1$. The adjoint equation for this case is

$$\begin{aligned} W'(t) &= -p_1 W(t) - p_2 W(t+\tau), \quad t \leq t^*, \\ W(t) &= 0, \quad t > t^*; \quad W(t^*) = 1. \end{aligned} \tag{6.33}$$

The analytical solution of the adjoint Eq. (6.33) is as follows:

(1) $0 < t^* \leq \tau$

$$W(t) = e^{-p_1(t-t^*)}, \quad t \leq t^*, \tag{6.34}$$

(2) $\tau < t^* \leq 2\tau$

$$W(t) = \begin{cases} e^{-p_1(t-t^*)} - p_2(t - t^* + \tau)e^{-p_1(t-t^*+\tau)}, & 0 < t \leq t^* - \tau, \\ e^{-p_1(t-t^*)}, & t^* - \tau < t \leq t^*. \end{cases} \tag{6.35}$$

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

The solution of the DDE (6.32), with an initial function $\psi(t) = 0$ with $t \leq 0$, is

$$y(t) = \begin{cases} \xi(e^{p_1 t} - 1), & 0 < t \leq \tau, \\ \xi^2 p_2 - \xi + \xi e^{p_1 t} + \xi p_2(t - \tau - \xi)e^{p_1(t-\tau)}, & \tau < t \leq 2\tau, \end{cases} \tag{6.36}$$

where $\xi = \dfrac{1}{p_1}$.

Thus, the functional derivative sensitivity density function to the initial function, by using (6.13a), becomes

(1) $0 < t^* \le \tau$

$$\frac{\partial y(t^*)}{\partial \psi(t)} = p_2 W(t+\tau) = \begin{cases} p_2 e^{-p_1(t-t^*+\tau)}, & -\tau < t \le t^* - \tau, \\ 0, & t^* - \tau < t \le 0. \end{cases} \tag{6.37}$$

(2) $\tau < t^* \le 2\tau$

$$\frac{\partial y(t^*)}{\partial \psi(t)} = \begin{cases} p_2 e^{-p_1(t-t^*+\tau)} - p_2^2(t - t^* + 2\tau)e^{-p_1(t-t^*+2\tau)}, & -\tau < t \le t^* - 2\tau, \\ p_2 e^{-p_1(t-t^*+\tau)}, & t^* - 2\tau < t \le 0. \end{cases} \tag{6.38}$$

On the other hand, the sensitivity functional to the control variable $u(t)$, as depicted in (6.13c), becomes

$$\frac{\partial y(t^*)}{\partial u(t)} = W(t). \tag{6.39}$$

The sensitivity function of $y(t)$ to the constant parameter p_1, by using (6.12b), takes the form

$$\frac{\partial y(t^*)}{\partial p_1} = \int_0^{t^*} W(t)\frac{\partial f}{\partial p_1}dt = \begin{cases} \xi^2 + \xi(t^* - \xi)e^{p_1 t^*}, & 0 < t^* \le \tau, \\ I_1 + I_2, & \tau < t^* \le 2\tau, \end{cases} \tag{6.40}$$

where

$$\begin{aligned} I_1 &= \int_0^{t^*-\tau} W(t)\frac{\partial f}{\partial p_1}dt \\ &= \xi(t^* - \tau)e^{p_1 t^*} + \xi^2(e^{p_1\tau} - e^{p_1 t^*}) + \frac{1}{2}\xi p_2(t^* - \tau)^2 e^{p_1(t^*-\tau)} \\ &\quad -\xi^2 p_2(t^* - \tau)e^{p_1(t^*-\tau)} - \xi^3 p_2(1 - e^{p_1(t^*-\tau)}), \end{aligned} \tag{6.41}$$

and

$$I_2 = \int_{t^*-\tau}^{t^*} W(t)\frac{\partial f}{\partial p_1}dt = I_1 + \xi^2 + \xi(t^* - \xi)e^{p_1 t^*}. \tag{6.42}$$

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

$$\frac{\partial y(t^*)}{\partial p_3} = \int_0^{t^*} W(t)\frac{\partial f}{\partial p_3}dt \tag{6.43}$$

$$= \begin{cases} \xi(e^{p_1 t^*} - 1), & 0 < t^* \leq \tau \\ \xi^2 p_2 - \xi + \xi e^{p_1 t^*} + \xi p_2(t^* - \tau - \xi)e^{p_1(t^*-\tau)}, & \tau < t^* \leq 2\tau \end{cases} \tag{6.44}$$

It is clear that $\frac{\partial y(t^*)}{\partial p_3} = y(t^*)$, as it is satisfying Eq. (6.32).

By using (6.12c), we obtain the sensitivity coefficient of $y(t)$ to the constant parameter τ as

$$\frac{\partial y(t^*)}{\partial \tau} = -\int_{-\tau}^{t^*-\tau} W(t+\tau)\frac{\partial f(t+\tau)}{\partial y_\tau}y'(t)dt$$

$$= \begin{cases} 0, & 0 < t^* \leq \tau, \\ -p_2(t^* - \tau)e^{p_1(t^*-\tau)}, & \tau < t^* \leq 2\tau, \end{cases} \tag{6.45}$$

Numerical results using the variational approach are presented in Figs. 6.1, 6.2, 6.3, 6.4, 6.5, and 6.6. Figure 6.1 plots the analytical solution of DDE (6.32) in the interval $[0,2\tau]$. Figures 6.2 and 6.3 show the sensitivity of the state variable to the initial function $\frac{\partial y(t^*)}{\partial \psi(t)}$ $(t < t^*)$ as a function of t for (i) $0 < t^* \leq \tau$ and (ii) $\tau < t^* \leq 2\tau$, respectively. For case (i), $\frac{\partial y(t^*)}{\partial \psi(t)}$ is positive and increases monotonically in the interval $[-\tau, t^* - \tau]$ and attains maximum value at $t = t^* - \tau$ and vanishes for $t^* - \tau < t \leq 0$. In case (ii), $\frac{\partial y(t^*)}{\partial \psi(t)}$ 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 stops to affect the state delay in the system dynamic. The functional

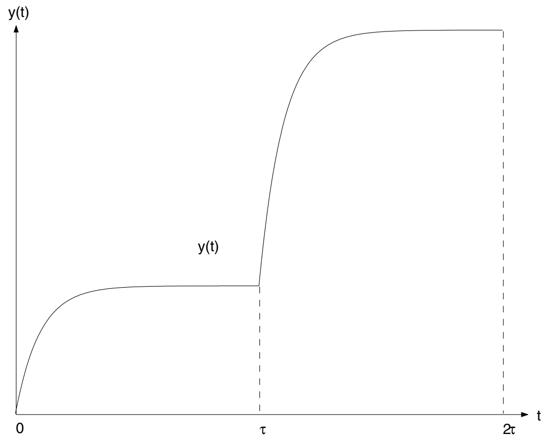

Fig. 6.1 Analytical solution of DDE (6.32) in the interval $0 \leq t \leq 2\tau$ with $p_1 = -2$, $p_2 = 4$, and $p_3 = 1$

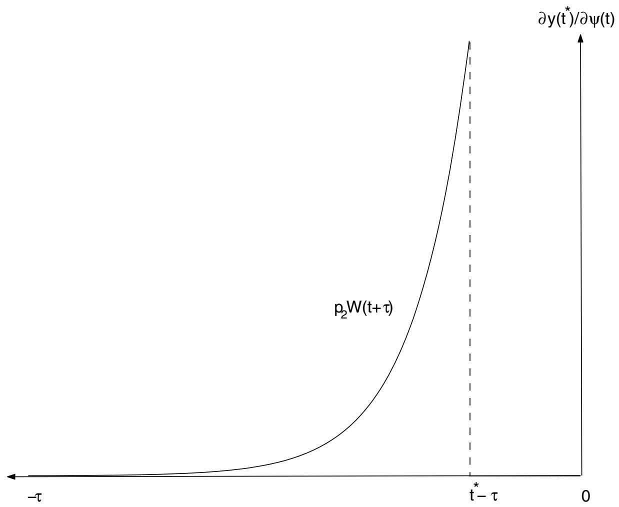

Fig. 6.2 Functional derivative sensitivity density function $\frac{\partial y(t^*)}{\partial \psi(t)}$, (6.37), when $0 < t^* \le \tau$

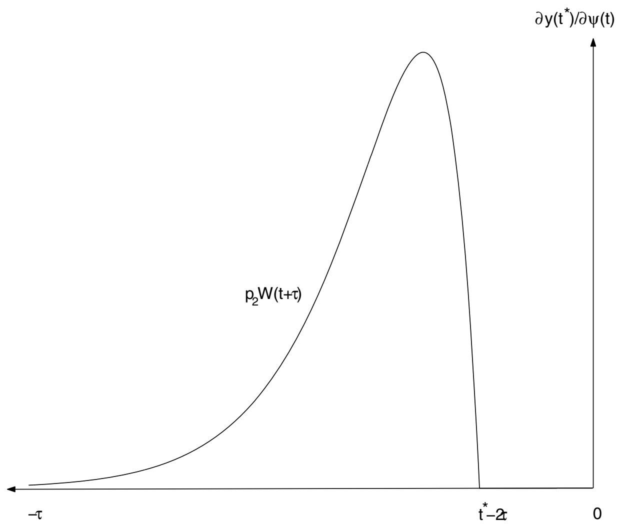

Fig. 6.3 Functional derivative sensitivity density function $\frac{\partial y(t^*)}{\partial \psi(t)}$, (6.38), when $\tau < t^* \le 2\tau$

derivative sensitivity density function $\dfrac{\partial y(t^*)}{\partial u(t)}$ is shown in Fig. 6.4 as a function of t for $t^* = 2\tau$.

Figure 6.5 shows the plot of the sensitivity coefficient $\dfrac{\partial y(t)}{\partial p_1}$. We note that $\dfrac{\partial y(t)}{\partial p_1}$ is positive and increases as t increases. Figure 6.6 shows the sensitivity of the state

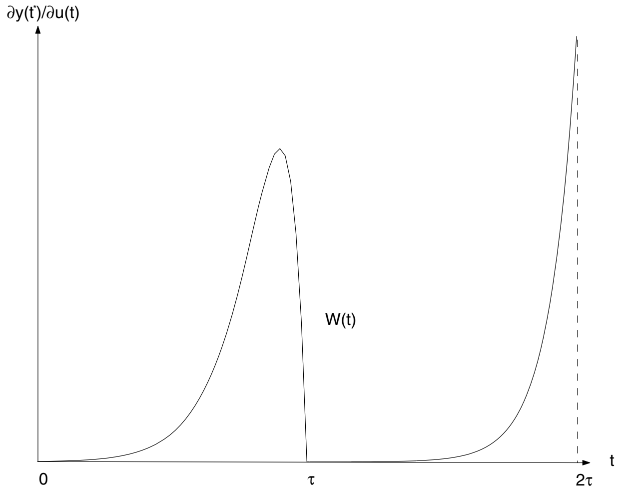

Fig. 6.4 Functional derivative sensitivity density function $\frac{\partial y(t^*)}{\partial u(t)}$, (6.39), for $t^* = 2\tau$

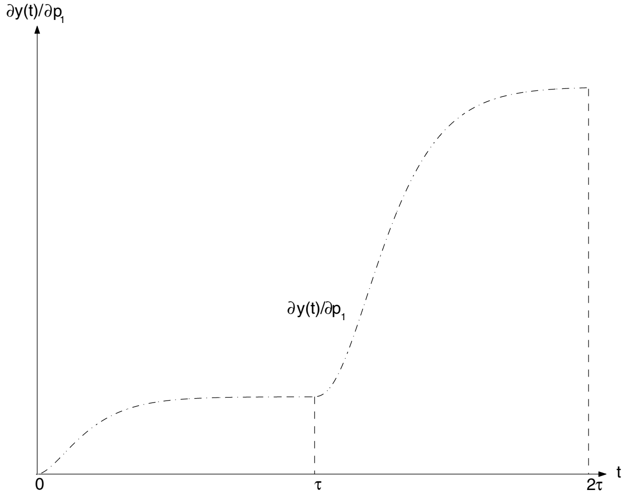

Fig. 6.5 Sensitivity function $\frac{\partial y(t)}{\partial p_1}$, (6.40)

variable to lag τ, $\dfrac{\partial y(t)}{\partial \tau}$. We note that $\dfrac{\partial y(t)}{\partial \tau}$ is negative and, as expected, $y(t)$ is very sensitive to changes in τ in the time interval $\tau < t \leq 2\tau$ 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.

• Secondly, if we apply *the direct approach* in the example being considered (6.32), we can simply use the results obtained in Remark 6.1 to obtain a variational

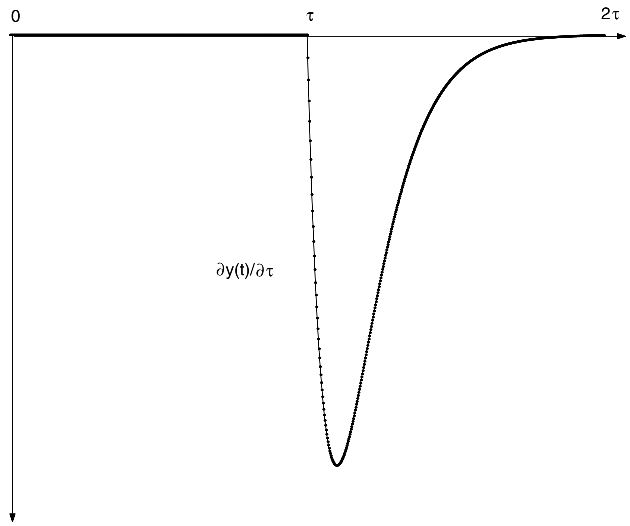

Fig. 6.6 Sensitivity function $\frac{\partial y(t)}{\partial \tau}$, (6.45)

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 [13] together with the original equations. The numerical results are displayed in Fig. 6.7. We note that this approach provides the same results provided by the variational approach.

6.7 Concluding Remarks

In this chapter, we have investigated the sensitivity of model solutions by 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 of parameters that are varying or temporally varying, the functional derivative sensitivity coefficients can only be computed via 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.

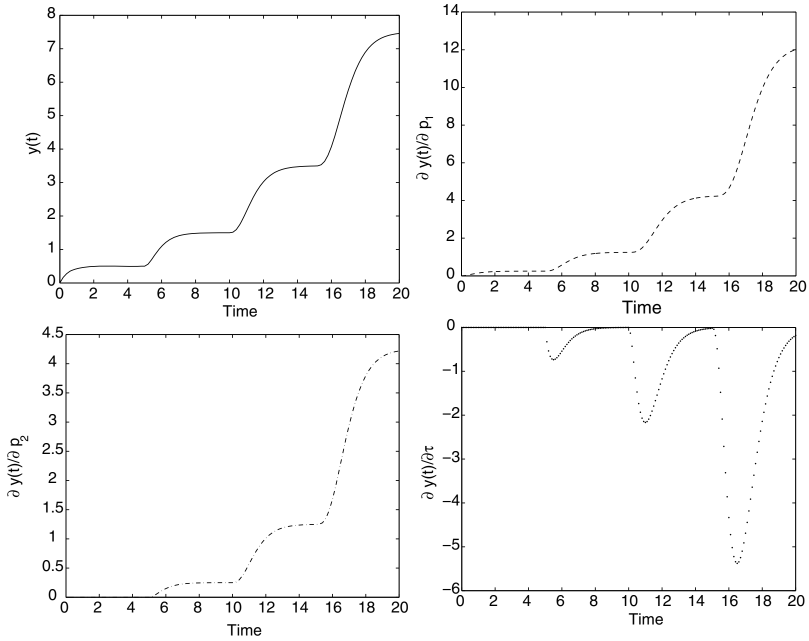

Fig. 6.7 Numerical results for (6.32). The first graph (from left to right, up to down) plots the numerical solution. The second shows the sensitivity function $\frac{\partial y(t)}{\partial p_1}$, the third $\frac{\partial y(t)}{\partial p_2}$, and the fourth $\frac{\partial y(t)}{\partial \tau}$

We have discussed how 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. 6.2, 6.3, 6.4, 6.5, and 6.6 (by using the variational approach), and in Fig. 6.7 (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, e.g., from Figs. 6.6 and 6.7, 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. 6.7) indicates that the solution is sensitive to changes in the parameter τ, and this parameter plays an important role in the model.

In the next chapter, we extend the analysis to study stochastic delay differential equations (SDDEs) which play a prominent role in many application areas including biology, epidemiology, and population dynamics. SDDEs mostly can offer a more sophisticated insight through physical phenomena than their deterministic counterparts do.

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