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Adjoint Sensitivity Analysis of Neutral Delay Differential Models[1]

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Abstract: In this short paper, we investigate sensitivity and robustness of neutral delay differential models to small perturbations in the parameters that occur in the models, using variational approach. The technique provides a guidance for the modelers to determine the most informative data for a specific parameter. It may also help modelers to select the best fit model to the observations.

Keywords: Adjoint; Neutral delay differential equations; Sensitivity; Time-lag

Mathematics Subject Classification: 93A13; 93A30; 34K05; 34K28; 34K40; 45G15; 47N60; 65Y20; 65L2.

1 Introduction

Sensitivity analysis is crucial both in the modeling phase and in the interpretation of model predictions. It contributes to model development, model calibration, model validation, reliability and robustness analysis, decision-making under uncertainty, and model reduction. Sensitivity analysis is concerned with the study of the relationship between infinitesimal changes in the model parameters and changes in model output. As an example, biological and physical problems are often subject to disturbance or perturbations in the system data. It is quite usual for a model to display very high sensitivity to small variations in some parameters, while displaying robustness to variations in other parameters; See [7, 8, 9, 10, 11, 12].

A *retarded functional differential equation* (RFDE) describes a system where the rate of change of state is determined by the present and the past states of the system. If the rate of change of the state depends on its own values as well, the system is called a *neutral functional differential equations* (NFDEs). When only discrete values of the past have influence on the present rate of change of state, the corresponding mathematical model is either *delay differential equation* (DDE) or *neutral differential equation* (NDDE). The theory of RFDEs is of both theoretical and practical interest, as they provide a powerful model of many phenomena in applied sciences such as physics, biology, economics, control theory and so on. The work reported in [1, 2, 3, 4, 5, 11, 13, 14]

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indicates the scope for applications of RFDEs in bioscience. The authors remark, therein, how delay differential equations have, prospectively, more interesting dynamics than equations that lack memory effects; in consequence they provide potentially more flexible tools for modelling.

A knowledge of how the model predictions can vary to small changes in their parameters and initial conditions; and how a particular parameter is affected by small variations in the observations can yield insights into the behavior of the model and assist the modelling process. There are two main approaches for sensitivity analysis: "direct approach" (using various numerical methods [2, 12, 14]) and "variational approach" (or adjoint method). 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; See [12].

Consider the predictive model of a system of NDDEs, parameterized by $\mathbf{p} \in \mathbb{R}^L$, of the form

$$\begin{array}{rcl} \mathbf{y}'(t) & = & \mathbf{f}(t, \mathbf{y}(t), \mathbf{y}(t-\tau), \mathbf{y}'(t-\tau); \mathbf{p}), \quad t \in [0, T], \\ \mathbf{y}(t) & = & \boldsymbol{\psi}(t, \mathbf{p}), \quad \mathbf{y}'(t) = \boldsymbol{\psi}'(t, \mathbf{p}) \equiv \boldsymbol{\phi}(t, \mathbf{p}), \quad t \in [-\tau, 0]. \end{array} \tag{1}$$

In (1), we assume that the vector function $\mathbf{f}$ is sufficiently smooth with respect to each arguments; $\mathbf{y}(t) \in \mathbb{R}^M$, $\mathbf{p} \in \mathbb{R}^L$, and τ is positive constant lag, which may have to be identified as a parameter. $\boldsymbol{\psi}(t)$, is a given continuous function. The value $\psi'(t_0)$ is the left-hand derivative $\psi'_-(t_0)$ and the value $\psi'(t_0-\tau)$ is the right-hand derivative, $\psi'_+(t_0-\tau)$.

In the following two sections, we extend the work of [12] to provide accurate sensitivity analysis to (1), using variational approach.

2 Sensitivity of model predictions to parameter estimates

Of considerable importance in assessing the model (1), is the sensitivity of the model solution $\mathbf{y}(t, \mathbf{p})$ to small variations in the parameter $\mathbf{p}$. For example, if it can be observed that a particular parameter p_j has no effect on the solution, it may be possible to eliminate it, at some stage, from the modelling process. Adjoint sensitivity analysis involves integration of the original differential equations forward in time followed by integration of the so-called adjoint equations backward in time; See [8, 11, 12] for details.

2.1 Adjoint method for sensitivity analysis

We provide here a *variational approach* to derive general sensitivity coefficients for minor changes in the parameters, time delays, and initial data in NDDEs. Use of this approach gives an expression for the sensitivity functions in terms of the solution of an adjoint equation. Variational approach has been used in [6, 8, 10, 11, 12] to investigate the qualitative behaviour of the solution of a dynamic system of DDEs due to small variations in the parameters occur in the model. Here, we extend the analysis to include a dynamic system described by a system of NDDEs.

In view of the preceding remarks, we desire to compute the sensitivity of the state variable $\mathbf{y}(t, \mathbf{p})$ to small variations in the parameters which occur in the NDDE (1). The familiar first-order sensitivity functions for constant parameters α, are defined by the partial derivatives $S_{ij}(t^*) = \partial y_i(t^*)/\partial \alpha_j$, where α_j represent the parameters p_j, the constant lags τ 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

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

The functional derivative sensitivity coefficients, however, when the parameters are functions of time such as the initial function $\boldsymbol{\psi}(t, \mathbf{p})$, are defined by $\beta_{ij}(t, t^*) = \partial y_i(t^*)/\partial \alpha_j(t)$ (where $t < t^*$).

Then the total variation in $y(t^*)$ due to any perturbation in $\alpha(t)$ is denoted by $\delta y(t^*)$, such that:

$$\delta y_i(t^*) = \int_0^{t^*} \frac{\partial y(t^*)}{\partial \alpha_j(t)} \delta\alpha_j(t)dt, \qquad t < t^*. \tag{3}$$

The functional derivative sensitivity density function $\partial y_i(t^*)/\partial\alpha_j(t)$ measures the sensitivity of $y_i(t)$ at location t^* to variation in $\alpha_j(t)$ at any location $t < t^*$.

For simplicity, in equation (1), we write $\mathbf{f}(t) = \mathbf{f}(t, \mathbf{y}(t), \mathbf{y}(t-\tau), \mathbf{y}'(t-\tau), \mathbf{p})$, and $\boldsymbol{\psi}(t) = \boldsymbol{\psi}(t, \mathbf{p})$. Then the linearized system associated to (1) due to small variations $\delta\boldsymbol{\psi}$, $\delta\boldsymbol{\phi}$, $\delta\mathbf{y}_0$, $\delta\mathbf{p}$, and $\delta\tau$ that result in a variation $\delta\mathbf{y}$ satisfies the equations

$$\delta\mathbf{y}'(t) = \frac{\partial\mathbf{f}(t)}{\partial\mathbf{y}}\delta\mathbf{y}(t) + \frac{\partial\mathbf{f}(t)}{\partial\mathbf{y}_\tau}\delta\mathbf{y}_\tau + \frac{\partial\mathbf{f}(t)}{\partial\mathbf{y}'_\tau}\delta\mathbf{y}'_\tau + \frac{\partial\mathbf{f}(t)}{\partial\mathbf{p}}\delta\mathbf{p} + [\frac{\partial\mathbf{f}(t)}{\partial\mathbf{y}_\tau}\frac{\partial\mathbf{y}(t-\tau)}{\partial\tau} + \frac{\partial\mathbf{f}(t)}{\partial\mathbf{y}'_\tau}\frac{\partial\mathbf{y}'(t-\tau)}{\partial\tau}]\delta\tau, \tag{4}$$
$$\delta\mathbf{y}(t) = \delta\boldsymbol{\psi}(t),\ \delta\mathbf{y}'(t) = \delta\boldsymbol{\phi}(t) \quad t \in [-\tau, 0); \quad \delta\mathbf{y}(0) = \delta\mathbf{y}_0 \in \mathbb{R}^M. \tag{5}$$

Since the sensitivity equations are always linear, then we can express the sensitivity functions in terms of the solution of an adjoint equation throughout the following theorem.

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

$$\begin{aligned} \mathbf{W}'(t) &= -A(t)^T\mathbf{W}(t) - B(t)^T\mathbf{W}(t+\tau) + C(t)^T\mathbf{W}'(t+\tau), t \le t^*, \\ \mathbf{W}(t) &= \mathbf{W}'(t) = 0, \quad t > t^*; \quad \mathbf{W}(t^*) = [0,\ldots,0,1_{ith},0\ldots,0]^T, \mathbf{W}'(t^*) = 0, \end{aligned} \tag{6}$$

then the functional derivative sensitivity functions of NDDEs (1) can be expressed by the formulae

$$\frac{\partial y_i(t^*)}{\partial\mathbf{y}_0} = \mathbf{W}(0), \tag{7}$$
$$\frac{\partial y_i(t^*)}{\partial\mathbf{p}} = \int_0^{t^*} \mathbf{W}^T(t)D(t)dt, \quad t \le t^*, \tag{8}$$
$$\frac{\partial y_i(t^*)}{\partial\tau} = -\int_{-\tau}^{t^*-\tau} \mathbf{W}^T(t+\tau)\left[B(t+\tau)\mathbf{y}'(t) + C(t+\tau)\mathbf{y}''(t)\right]dt, \tag{9}$$
$$\frac{\partial y_i(t^*)}{\partial\boldsymbol{\psi}(t)} = A(t+\tau)\mathbf{W}(t+\tau), \quad t \in [-\tau, 0) \tag{10}$$

where $A(t) = \frac{\partial}{\partial\mathbf{y}}\mathbf{f}(t,\mathbf{y}(t),\mathbf{y}(t-\tau),\mathbf{y}'(t-\tau),\mathbf{p})$, $B(t) = \frac{\partial}{\partial\mathbf{y}_\tau}\mathbf{f}(t,\mathbf{y}(t),\mathbf{y}(t-\tau),\mathbf{y}'(t-\tau),\mathbf{p})$, $C(t) = \frac{\partial}{\partial\mathbf{y}'_\tau}\mathbf{f}(t,\mathbf{y}(t),\mathbf{y}(t-\tau),\mathbf{y}'(t-\tau),\mathbf{p})$ *and* $D(t) = \frac{\partial}{\partial\mathbf{p}}\mathbf{f}(t,\mathbf{y}(t),\mathbf{y}(t-\tau),\mathbf{y}'(t-\tau),\mathbf{p})$.

Proof: If we multiply both sides of (4) by $\mathbf{W}^T(t)$ (the transpose of the function $\mathbf{W}(t)$) and then integrate the both sides with respect to t over the interval $[0, t^*]$, we obtain

$$\mathbf{W}^T(t^*)\delta\mathbf{y}(t^*) - \mathbf{W}^T(0)\delta\mathbf{y}(0) - \int_0^{t^*}\mathbf{W}'^T(t)\delta\mathbf{y}(t)dt = \int_0^{t^*}\mathbf{W}^T(t)\left[\frac{\partial\mathbf{f}(t)}{\partial\mathbf{y}}\delta\mathbf{y}(t) + \frac{\partial\mathbf{f}(t)}{\partial\mathbf{y}_\tau}\delta\mathbf{y}_\tau + \frac{\partial\mathbf{f}(t)}{\partial\mathbf{y}'_\tau}\delta\mathbf{y}'_\tau\right]dt +$$
$$\int_0^{t^*}\mathbf{W}^T(t)\left[\frac{\partial\mathbf{f}(t)}{\partial\mathbf{p}}\delta\mathbf{p} + \frac{\partial\mathbf{f}(t)}{\partial\mathbf{y}_\tau}\frac{\partial\mathbf{y}(t-\tau)}{\partial\tau}\delta\tau + \frac{\partial\mathbf{f}(t)}{\partial\mathbf{y}'_\tau}\frac{\partial\mathbf{y}'(t-\tau)}{\partial\tau}\delta\tau\right]dt. \tag{11}$$

This equation, after some manipulations, can be rewritten in the form

$$\begin{aligned}
\mathbf{W}^T(t^*)\delta\mathbf{y}(t^*) - \mathbf{W}^T(0)\delta\mathbf{y}(0) &= \int_{-\tau}^{0} \mathbf{W}^T(t+\tau)\left[\frac{\partial\mathbf{f}(t+\tau)}{\partial\mathbf{y}_\tau}\delta\boldsymbol{\psi}(t) + \frac{\partial\mathbf{f}(t+\tau)}{\partial\mathbf{y'}_\tau}\delta\boldsymbol{\phi}(t)\right]dt \\
&+ \int_{0}^{t^*-\tau}\left[\mathbf{W}'(t) + \frac{\partial\mathbf{f}(t)^T}{\partial\mathbf{y}}\mathbf{W}(t) + \frac{\partial\mathbf{f}^T(t+\tau)}{\partial\mathbf{y}_\tau}\mathbf{W}(t+\tau) - \frac{\partial\mathbf{f}^T(t+\tau)}{\partial\mathbf{y'}_\tau}\mathbf{W}'(t+\tau)\right]^T\delta\mathbf{y}(t)dt \\
&- \mathbf{W}^T(0)\frac{\partial\mathbf{f}(t)}{\partial\mathbf{y'}_\tau}\delta\mathbf{y}_\tau(0) + \int_{t^*-\tau}^{t^*}\left[\mathbf{W}'(t) + \frac{\partial\mathbf{f}(t)}{\partial\mathbf{y}}\mathbf{W}(t)\right]^T\delta\mathbf{y}(t)dt + \int_{0}^{t^*}\mathbf{W}^T(t)\frac{\partial\mathbf{f}(t)}{\partial\mathbf{p}}\delta\mathbf{p}dt \\
&- \int_{-\tau}^{t^*-\tau}\mathbf{W}^T(t+\tau)\left[\frac{\partial\mathbf{f}(t+\tau)}{\partial\mathbf{y}_\tau}\mathbf{y}'(t) + \frac{\partial\mathbf{f}(t+\tau)}{\partial\mathbf{y'}_\tau}\mathbf{y}''(t)\right]\delta\tau dt, \quad t \le t^*. \qquad (12)
\end{aligned}$$

We now make use of the relations (6) to get

$$\begin{aligned}
\delta y_i(t^*) &= \mathbf{W}^T(0)\delta\mathbf{y}(0) + \int_{0}^{t^*}\mathbf{W}^T(t)\frac{\partial\mathbf{f}(t)}{\partial\mathbf{p}}\delta\mathbf{p}dt - \\
&\int_{-\tau}^{t^*-\tau}\mathbf{W}^T(t+\tau)\left[\frac{\partial\mathbf{f}(t+\tau)}{\partial\mathbf{y}_\tau}\mathbf{y}'(t) + \frac{\partial\mathbf{f}(t+\tau)}{\partial\mathbf{y'}_\tau}\mathbf{y}''(t)\right]\delta\tau dt - \\
&\mathbf{W}^T(0)\frac{\partial\mathbf{f}(t)}{\partial\mathbf{y'}_\tau}\delta\mathbf{y}_\tau(0) + \int_{-\tau}^{0}\mathbf{W}^T(t+\tau)\left[\frac{\partial\mathbf{f}(t+\tau)}{\partial\mathbf{y}_\tau}\delta\boldsymbol{\psi}(t) + \frac{\partial\mathbf{f}(t+\tau)}{\partial\mathbf{y'}_\tau}\delta\boldsymbol{\phi}(t)\right]dt, \quad t \le t^*. \qquad (13)
\end{aligned}$$

When $\delta\mathbf{y}(0) \to 0$, $\delta\mathbf{p} \to 0$, and $\delta\tau \to 0$ we obtain, respectively, the sensitivity coefficients (7)-(9) from the first three terms of equation (13). From the definition of the functional derivative sensitivity coefficients in (3), we then obtain the formulae (10) from the last term of equation (13). This finishes the proof. □

2.2 Illustrative example

We apply the results obtained in the above analysis to the scalar linear NDDE model:

$$\begin{aligned}
y'(t) &= \rho_0 y(t) + \rho_1 y(t-\tau) + \rho_2 y'(t-\tau), \quad t \ge 0, \\
y(t) &= \psi(t),\ y'(t) = \psi'(t), \quad t \in [-\tau, 0], \quad y(0) = y_0.
\end{aligned} \qquad (14)$$

We desire to find, analytically, the sensitivity functions $\dfrac{\partial y(t^*)}{\partial\psi(t)}$ & $\dfrac{\partial y(t^*)}{\partial\alpha_i}$ $(t \le t^*)$, where $\alpha = [\rho_0, \rho_1, \rho_2, y_0, \tau]^T$.

The adjoint equation for this case is

$$\begin{aligned}
W'(t) &= -\rho_0 W(t) - \rho_1 W(t+\tau) + \rho_2 W'(t+\tau), \quad t \le t^*, \\
W(t) &= 0, \quad t > t^*; \quad W(t^*) = 1.
\end{aligned} \qquad (15)$$

The analytical solution of the adjoint Eq (15) is as follows:

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

$$W(t) = e^{-\rho_0(t-t^*)}, \quad t \le t^*, \qquad (16)$$

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

$$W(t) = \begin{cases} e^{-\rho_0(t-t^*)} - b(t-t^*+\tau)e^{-\rho_0(t-t^*+\tau)}, & 0 < t \le t^*-\tau, \\ e^{-\rho_0(t-t^*)}, & t^*-\tau < t \le t^*. \end{cases} \qquad (17)$$

Here $b = (\rho_1 + \rho_0\rho_2)$, $W(t+\tau) = 0$ for $t^* - \tau < t \le t^*$ and $W(t+\tau) = e^{-\rho_0(t-t^*+\tau)}$ for $0 < t \le t^* - \tau$.

The solution of the NDDE (14), with an initial function $\psi(t) = y_m$ ($\psi'(t) = 0$) for $t \le 0$, is

$$y(t) = \begin{cases} ae^{\rho_0 t} - y_m\xi, & 0 < t \le \tau, \\ ae^{\rho_0 t} - [y_m\xi - ab(t-\tau) + y_m\xi^2]e^{\rho_0(t-\tau)} + y_m\xi^2, & \tau < t \le 2\tau, \end{cases} \tag{18}$$

where $a = (y_0 + y_m\xi)$, and $\xi = \dfrac{\rho_1}{\rho_0}$.

Thus the functional derivative sensitivity density function to the initial function, by using (10), becomes:

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

$$\frac{\partial y(t^*)}{\partial \psi(t)} = \rho_1 W(t+\tau) = \begin{cases} \rho_1 e^{-\rho_0(t-t^*+\tau)}, & -\tau < t \le t^* - \tau, \\ 0, & t^* - \tau < t \le 0. \end{cases} \tag{19}$$

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

$$\frac{\partial y(t^*)}{\partial \psi(t)} = \begin{cases} \rho_1 e^{-\rho_0(t-t^*+\tau)} - \rho_1 b(t - t^* + 2\tau)e^{-\rho_0(t-t^*+2\tau)}, & -\tau < t \le t^* - 2\tau, \\ \\ \rho_1 e^{-\rho_0(t-t^*+\tau)}, & t^* - 2\tau < t \le 0. \end{cases} \tag{20}$$

While the sensitivity function of $y(t)$ to the initial condition $y(0)$, that given by the formula (7), is

$$\frac{\partial y(t^*)}{\partial y(0)} = W(0) = \begin{cases} e^{\rho_0 t^*}, & 0 < t^* \le \tau, \\ e^{\rho_0 t^*} + b(t^* - \tau)e^{\rho_0(t^*-\tau)}, & \tau < t^* \le 2\tau. \end{cases} \tag{21}$$

The sensitivity function of $y(t)$ to the constant parameter $\rho_0(\equiv \dfrac{1}{\eta})$, by using (8), takes the form:

$$\frac{\partial y(t^*)}{\partial \rho_0} = \int_0^{t^*} W(t)\frac{\partial F}{\partial \rho_0}dt = \begin{cases} (at^* - y_m\xi\eta)e^{\rho_0 t^*} + y_m\xi\eta, & 0 < t^* \le \tau, \\ \mathbf{I}, & \tau < t^* \le 2\tau, \end{cases} \tag{22}$$

where

$$\begin{aligned} \mathbf{I} \;=\; & \int_0^{t^*-\tau} W(t)\frac{\partial F}{\partial \rho_0}dt + \int_{t^*-\tau}^{t^*} W(t)\frac{\partial F}{\partial \rho_0}dt = (at^* - y_m\xi\eta)e^{\rho_0 t^*} - 2y_m\xi^2\eta - \\ & \big[[y_m\xi - ab(t^*-\tau) + y_m\xi^2 + a\rho_2 - by_m\xi\eta](t^*-\tau) - y_m\xi\eta - 2y_m\xi^2\eta\big]e^{\rho_0(t^*-\tau)} \end{aligned} \tag{23}$$

(Similarly, we can deduce $\partial y(t^*)/\partial\rho_1$ & $\partial y(t^*)/\partial\rho_2$.) By using (9), we obtain the sensitivity of $y(t)$ to small perturbations in the time-lag parameter τ as:

$$\begin{aligned} \frac{\partial y(t^*)}{\partial \tau} &= -\int_{-\tau}^{t^*-\tau} W(t+\tau)\left[\frac{\partial \mathbf{f}(t+\tau)}{\partial \mathbf{y}_\tau}\mathbf{y}'(t) + \frac{\partial \mathbf{f}(t+\tau)}{\partial \mathbf{y}'_\tau}\mathbf{y}''(t)\right]dt \\ &= \begin{cases} 0, & 0 < t^* \le \tau, \\ -\rho_0 ab(t^*-\tau)e^{\rho_0(t^*-\tau)}, & \tau < t^* \le 2\tau, \end{cases} \end{aligned} \tag{24}$$

with $a = (y_0 + y_m\xi)$ and $b = (\rho_1 + \rho_0\rho_2)$.

We notice from the above formula that, as expected, $y(t)$ is sensitive to a change in τ in the time interval $\tau < t \le 2\tau$ and is insensitive to changes in the constant lag τ in the time interval [0, τ]. The plots (see Fig. 1) have a kink at $t = \tau$ due to the existence of the delay in the system. We may also remark from Eq (18), that if $y_0 \ne y_m$, then $\partial y(t_i)/\partial\tau$ has a jump at $t_i = \tau$.

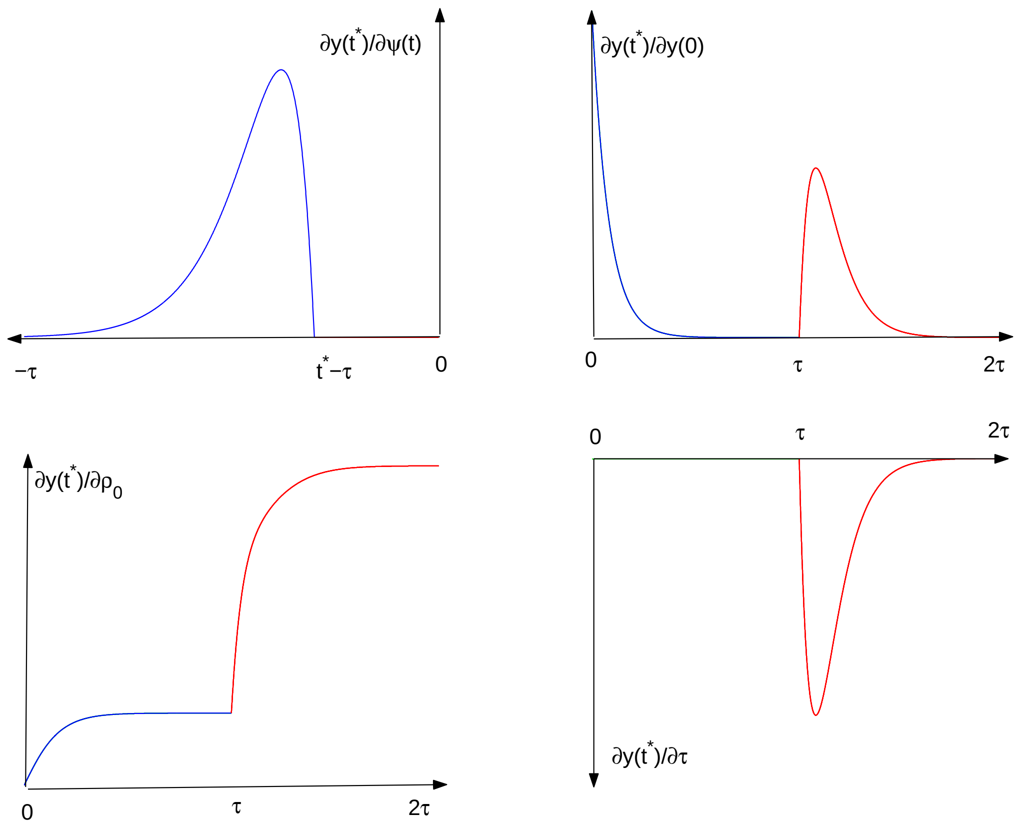

Figure 1: Shows general sensitivity functions, $\partial y(t^*)/\partial\psi(t)$, $\partial y(t^*)/\partial y_0$, $\partial y(t^*)/\partial\rho_0$, $\partial y(t^*)/\partial\tau$, for NDDE (14).

3 Discussion and concluding remarks

Modeling with NDDE represents an active area of research and there is a link between stability/conditioning and sensitivity of a solution to perturbation in the problem. The term *stability* is frequently used by numerical analysts to describe the propagation of errors in an evolutionary problem when initial values are perturbed. However, the term *conditioning* is often used to indicate the magnitude of the sensitivity of a solution to perturbation in the problem.

In this paper, we have proposed an accurate method to analytically investigate the behavior of the model predictions due to small changes in the parameters occurring in NDDE models, using adjoint method. We have discussed how the sensitivity analysis can be used to evaluate which parameters have a significant effect on uncertainty. Sensitivity functions clearly demonstrate the measure of the importance of the input parameters. We have remarked how these functions enable one to assess the relevant time intervals for the identification of specific parameters and enhance the understanding of the role played by specific model parameters in describing experimental data. The oscillation accompanied by $S_\tau(\equiv \partial y(t^*)/\partial\tau)$, as an example, means that the solution of the models is sensitive to changes in the parameter τ and this parameter plays a significant role in the model.

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