

An Inverse Problem for Delay Differential Equations: Parameter Estimation, Nonlinearity, Sensitivity

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Abstract: This article presents the theoretical framework to solve inverse problems for Delay Differential Equations (DDEs). Given a parameterized DDE and experimental data, we estimate the parameters appearing in the model, using least squares approach. Some issues associated with the inverse problem, such as nonlinearity and discontinuities which make the problem more ill-posed, are studied. Sensitivity and robustness of the models to small perturbations in the parameters, using variational approach, are also investigated. The sensitivity functions may provide guidance for the modelers to determine the most informative data for a specific parameter, and select the best fit model. The consistency of delay differential equations with bacterial cell growth is shown by fitting the models to real observations.

Keywords: Biological systems - DDEs - Nonlinearity - Parameter estimation - Sensitivity analysis - Time-lags

1 Introduction

Delay differential equations (DDEs) are a class of differential equations that have received considerable attention and been shown to model many real life problems, traditionally formulated by systems of ordinary differential equations (ODEs), more naturally and more accurately. Such class of DDEs are widely used for analysis and predictions of systems with memory such as population dynamics, epidemiology, immunology, physiology, neural networks and systems with memory [1,2,3,4,5]. In ODEs, the unknown function and its derivatives are evaluated at the same time instant. However, in a DDE the evolution of the system at a certain time instant, depends on the state of the system at an earlier time. The delay can be related to the duration of certain hidden processes like the stages of the life cycle, the time between infection of a cell and the production of new viruses, the duration of the infectious period, the immune period, and so on; See [6,7,8,9,10].

Identification of unknown parameters in DDEs, using least squares estimator or maximum likelihood estimation, has been studied and addressed by many authors (see, e.g., [11,12,13,14,15,16,17]). In these approaches, the dynamical system is simulated using initial guesses for the parameters, first. Then, the model

predictions are compared with measured data and an optimization algorithm updates the parameters. The challenging problems related to parameter estimation in nonlinear problems (such as ODEs or DDEs) are numerous. One of the most important issues is the unpredictable and inevitable existence of noise in measurements. Some parameters are very sensitive to noise which can make their estimation difficult and sometimes even impossible. Another difficulty results from the nonlinearity of the most relevant ODE/DDE models, which complicates the adoption of most optimization techniques. Moreover, parameter estimation for systems of DDEs is more challenging due to frequent discontinuities in the solution caused by the delay terms. It is often desirable to have information about the effect of nonlinearity of the parameters. Nonlinear regression models differ from linear regression models in that, given the usual assumption of an independent and identically distributed normal stochastic term, linear models give rise to unbiased, normally distributed, minimum variance estimators; Whereas nonlinear regression models have these properties only asymptotically (when the sample size becomes very large) [18, Chap.2].

Sensitivity analysis, of a particular DDE model, is a most important tool for investigating the quantitative (or qualitative) influence of perturbing the parameters (or the

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data) on the model. The objective of a sensitivity analysis is to determine systematically the effect of uncertain parameters on system solutions and the effect of the noisy data on the accuracy to which parameters may be determined; see [19,20,21,22,23]. There are different approaches to find the sensitivity functions. Rihan [19] derives a general theory for sensitivity analysis of DDE models by using adjoint equations and direct methods to estimate the sensitivity equations with variable and constant parameters, respectively. Zivaripiran [20] develops a systematic collection of tools related to DDE simulations, sensitivity analysis and parameter estimation. The kinetic preprocessor (KPP) numerical library is a comprehensive set of software tools for direct and adjoint sensitivity analysis [21]. Another approach which can be used to evaluate sensitivity equations is automatic differentiation [23].

The goal of this paper is to develop a unified framework for parameter estimation for both ODEs and DDEs. In Section 2, we address this problem using an ordinary/logarithmic least squares (OLS) method to find the best fit parameters. Some related issues, such as nonlinearity and discontinuities, are discussed in Sections 3 & 4. In Section 5, we provide the variation of parameters technique to study sensitivity analysis and evaluate the sensitivity functions due to small perturbations in the parameters. Numerical simulations and applications to cell growth dynamics are given in Section 6. We then give discussion and remarks in Section 7.

2 Parameter Estimation with DDEs

Parameter identification problem, to estimate the values of the parameters which appear in model equations, is considered as an inverse problem. We assume that we have observed our system and collected data; we then wish to determine the unknown parameters by fitting the model equations to the data. Consider a general form of predictive DDE model

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

This model is parameterized by $\mathbf{p} \in \mathbb{R}^L$ which are estimated using a given set of observations, $\{t_j; Y_j^i\}_{j=1}^N$. We assume that, in (1), the vector function \mathbf{f} is sufficiently smooth with respect to each arguments; $\mathbf{y}(t) \in \mathbb{R}^M$, $\mathbf{y}(t - \tau) \in \mathbb{R}^{M'}$, $\mathbf{p} \in \mathbb{R}^L$, and $\tau \in \mathbb{R}^{L'}$ is positive constant lag, which may have to be identified as a parameter ($L' \leq L$, $M' \leq M$). $\boldsymbol{\psi}(t)$ is given continuous function. If \mathbf{f} includes $\mathbf{y}'(t - \tau)$, the equation is called *neutral delay differential equation* (NDDE). Our concern is to fit the given data to the system of DDEs (1). The model-fitting problem is then select a value or a set values for \mathbf{p} for which the function $\mathbf{y}(t; \hat{\mathbf{p}})$ provides a 'best' fit, at arguments $t = t_j$, to the given set $\{Y_{ij}\}_{j=1}^N$ ($1 \leq i \leq M$). The key part in fitting a model to data is the formulation

of the objective function to be optimized that depends on the stochastic features of the errors in the data [13].

We assume that the data \mathbf{Y}_i satisfy the following observation equation

$$Y_{ij} = y_j(t_i) + \sigma_j \varepsilon_{ij} \quad (2)$$

where $\sigma_j > 0$ measures the variance of the noise associated with the j th component and is related to the scale of the expected magnitude of the j th component, $|Y_j(t)|$. The ε_{ij} are independent and standard Gaussian distributed random variables. The principle of maximum-likelihood yields an appropriate cost function which should be minimized with respect to the parameters \mathbf{p} to yield an approximation, $\hat{\mathbf{p}}$ to the true value. We define the cost function or objective function by

$$\Phi(\mathbf{P}) = \sum_{i=1}^M \varepsilon_i^T \omega_i(\sigma) \varepsilon_i \equiv \frac{1}{N} \sum_{i=1}^M \sum_{j=1}^N \frac{[y_j(t_i; \mathbf{p}) - Y_{ij}]^2}{2\sigma_j^2}. \quad (3)$$

We seek $\hat{\mathbf{p}}$ that satisfies

$$\Phi(\hat{\mathbf{p}}) =: \min_{\mathbf{p}} \Phi(\mathbf{p}) \equiv \max_{\mathbf{p}} \mathcal{L}(\mathbf{p}). \quad (4)$$

where $\mathcal{L}(\mathbf{p}) = [\exp(-\varepsilon_{ij}^2/2\sigma_j^2)]/\sqrt{2\pi\sigma_j^2}$ is the likelihood function; See [13].

If we adapt the Log Least Squares (LLS) approach, the objective function may take the form

$$\Phi_L(\mathbf{p}) = \frac{1}{N} \sum_{i=1}^M \sum_{j=1}^N [\log y_j(t_i, \mathbf{p}) - \log Y_{ij}]^2 / 2\sigma_j^2. \quad (5)$$

The choice of LLS in model-fitting problem may decrease the exponential nonlinearity of model predictions with respect to \mathbf{p} . (It is assumed that $y^j(t_i, \mathbf{p}) > 0$.) Another significant feature of the LLS approach is that small relative changes in large data values can be unduly weighted.

The methods for minimizing $\Phi(\mathbf{p})$ are iterative in nature. We start with a given point \mathbf{p}_1 known as the initial guess, and proceed to generate a sequence of points $\mathbf{p}_2, \mathbf{p}_3, \dots$ which we hope that they converge to the point $\hat{\mathbf{p}}$ at which $\Phi(\hat{\mathbf{p}})$ is minimum. (The computation of \mathbf{p}_{i+1} is called the i th iteration.) In practice, one terminates the sequence after a finite number k of iterations, and one accepts \mathbf{p}_k as an approximation to $\hat{\mathbf{p}}$. The vector

$$\boldsymbol{\delta}_i = \mathbf{p}_{i+1} - \mathbf{p}_i \quad (6)$$

is called the i th step. We wish each step to bring us closer to the minimum. Since we do not know where the minimum is, we cannot test for this condition directly. In a sense, however, we may consider the i th step to have "improved" our situation if

$$\Phi_{i+1} < \Phi_i, \quad (7)$$

where $\Phi_j = \Phi(\mathbf{p}_j)$ ($j = 1, 2, \dots$). We call the i th step *acceptable* if equation (7) holds. An iterative method is acceptable if all the steps of its procedures are acceptable. We shall only consider acceptable methods. The methods we consider are then based on following scheme:

1. Set $i = 1$. An initial guess \mathbf{p}_1 must be provided.
2. The model solution values $\{\mathbf{y}(t_j, \mathbf{p}_1)\}$ are obtained numerically.
3. Determine a vector \mathbf{v}_i (see Theorem 1) in the direction of the proposed i th step.
4. Determine a scalar ρ_i such that the step

$$\delta_i = \rho_i \mathbf{v}_i$$

is acceptable. That is, we take

$$\mathbf{p}_{i+1} = \mathbf{p}_i + \rho_i \mathbf{v}_i \tag{8}$$

and require that ρ_i be chosen so that equation (7) holds.

5. Test whether the termination criterion

$$|\mathbf{p}_{i+1,j} - \mathbf{p}_{i,j}| \leq \varepsilon_j \quad (j = 1, 2, \dots, L),$$

where $\mathbf{p}_{i,j}$ is the j th component of \mathbf{p}_i . If not, increase i by one and return to step 3. Otherwise, accept \mathbf{p}_{i+1} as the value of $\hat{\mathbf{p}}$.

2.1 Acceptability

Consider the i th iteration of a minimization procedure. Suppose we strike out from \mathbf{p}_i along some direction \mathbf{v} , generating the ray

$$\mathbf{p}(\rho) \equiv \mathbf{p}_i + \rho \mathbf{v}, \quad (\rho \in \mathbb{R}).$$

Along this ray, the objective function varies as ρ is changed, thus becoming a function of ρ alone. We designate this function

$$\Psi_{iv}(\rho) \equiv \Phi(\mathbf{p}(\rho)) = \Phi(\mathbf{p}_i + \rho \mathbf{v}),$$

its derivative is given by

$$d\Psi_{iv}/d\rho = (\partial\Phi/\partial\mathbf{p})^T (\partial\mathbf{p}/\partial\rho) = (\partial\Phi/\partial\mathbf{p})^T \mathbf{v}.$$

The gradient vector of $\Phi(\mathbf{p})$ is $\partial\Phi/\partial\mathbf{p} := \mathbf{q}(\mathbf{p})$. Denoting by \mathbf{q}_i the gradient vector evaluated at $\mathbf{p} = \mathbf{p}_i$, we have

$$\Psi'_{iv} \equiv d\Psi_{iv}/d\rho|_{\rho=0} = \mathbf{q}_i^T \mathbf{v}.$$

In the sequel, we assume $\mathbf{q}_i \neq 0$.

The quantity Ψ'_{iv} is called the *directional derivative* of Φ relative to \mathbf{p}_i . If $\Psi'_{iv} < 0$, then $\Phi(\mathbf{p})$ decreases in value when one starts moving away from \mathbf{p}_i in the direction of \mathbf{v} . Therefore, if ρ is sufficiently small positive number, the step $\rho \mathbf{v}$ is acceptable. On the other hand, if $\Psi'_{iv} \geq 0$, there may not exist any positive value of ρ for which $\rho \mathbf{v}$ is an acceptable step. We call \mathbf{v} an *acceptable direction* if $\Psi'_{iv} < 0$.

Theorem 1. A direction \mathbf{v} is acceptable if and only if there exists a positive definite matrix R such that $\mathbf{v}_i = -R\mathbf{q}_i$.

For the proof; see Bard [13].

Therefore the basic equation of the i th iteration in any gradient method is

$$\mathbf{p}_{i+1} = \mathbf{p}_i - \rho_i R_i \mathbf{q}_i \tag{9}$$

and various gradient method differ in the manner of choosing the R_i and ρ_i . If $\rho_i = 1$ and $R_i = H_i^{-1}$ (where $H := \partial^2\Phi(\mathbf{p})/\partial\mathbf{p}\partial\mathbf{p}^T$, is the Hessian matrix), then equation (9) defines the i th iteration of Newton (or Newton-Raphson) method.

2.2 Convergence

Suppose $\Phi(\mathbf{p})$ is smooth as a function of \mathbf{p} in the neighbourhood of the optimal parameter $\hat{\mathbf{p}}$, and let Φ_i denote the value of $\Phi(\mathbf{p}_i)$. If we select (at each iteration) an acceptable point, then the sequence $\{\Phi_i\} \equiv \{\Phi_0, \Phi_1, \Phi_2, \dots\}$ is monotone decreasing. If the values of the objective function possess a lower bound, and the sequence $\{\mathbf{p}_i\}$ is bounded, then this sequence must converge to a limit Φ_∞ . It follows from the assumption of continuity of Φ that $\Phi(\mathbf{p}_\infty) = \Phi_\infty$, where \mathbf{p}_∞ is any limit point of $\{\mathbf{p}_i\}$. In all practical cases, the sequence $\{\mathbf{p}_i\}$ is either unbounded (and has more than one limit point), or converges to a point \mathbf{p}_∞ . The rate of convergence, however, may be so slow that the sequence appears non-convergent.

A *stationary point* of the objective function is one at which $\mathbf{q}(\mathbf{p}) = 0$. If \mathbf{p}_i is stationary, i.e., $\mathbf{q}_i = 0$, then equation (9) shows that all $\mathbf{p}_j (j \geq i)$ coincide with \mathbf{p}_i . Convergence to the true minimum can be guaranteed only if it can be shown that the objective function has no other stationary points. In order to get a true minimum, the initial guess of the parameter values should be sufficiently close to the global minimum; See Figure 4 that shows the pairwise plots of parameter estimates.

3 Nonlinearity of Model Predictions

When the predictions are governed by differential equation models, then the *LS* approach (even for models linear in their parameters) generally leads to a nonlinear minimization problem. This nonlinearity comes from a combination of the quadratic transformation $[\cdot]^2$, the ratios scaling function $F(\cdot)$ and the solution function $y(t, \mathbf{p})$ of the mathematical model formulated as a parameter-dependent differential system. The nonlinearity of the fitness function $\Phi(\mathbf{p})$ with respect to \mathbf{p} can lead to several local minima. To decrease this nonlinearity of $\Phi(\mathbf{p})$, the function F should be selected with this behaviour of $y(t, \mathbf{p})$ in mind.

To illustrate the above ideas, we consider the simplest case of the linear ODE model: $y'(t) = py(t)$. Let the model be exactly related to the observed process, and let p^* be the “true” parameter i.e., observations are described by $Y(t) = y_0 e^{p^*t}$. The solution of the model for a perturbed p value is $y_0 e^{pt}$ (with $y(0) = y_0$). Then the classical residual of *LS* approach leads to the nonlinear minimization problem for p :

$\Phi(\mathbf{p}) = \sum_{j=1}^M y_0^2 (e^{pt_j} - e^{\hat{p}t_j})^2$, and the relative distance *LS* approach results in the problem:

$\Phi(\mathbf{p}) = \sum_{j=1}^M (e^{(p-\hat{p})t_j})^2$. Selecting the scaling function

$F(\cdot)$ as the logarithm formula (5), decreases the exponential nonlinearity of model predictions with respect to \mathbf{p} . With this choice, one arrives at the following minimization problem: $\Phi(\mathbf{p}) = \sum_{j=1}^M (p - \hat{p})^2 t_j^2$. The last formulation is the common linear *LS* problem corresponding to the linear ODE model, $y'(t) = py(t)$.

The real situations may become much more complicated due to inexactness of models, nonlinearity of the differential system, noisy observation data, and non-exponential behaviour of the solution. Nevertheless, the LS criterion for relative distance can be scaled by a logarithmic transformation,

$$\Phi(\mathbf{p}) = \frac{1}{N} \sum_{i=1}^M \sum_{j=1}^N \left[\log \left(\frac{Y_{ij}}{y_j(t_i; \mathbf{p})} \right) \right]^2 / 2\sigma_j^2.$$

The percentage *bias* in the values of the parameter estimates is a good indicator of the quantitative effect of nonlinearity [18]. To examine the *biases* in the values of the parameter estimates, due to the nonlinearity of the parameters, we proceed as follows:

- (i) Perturb the obtained solution of the model, corresponding to the best-fit parameters $\hat{\mathbf{p}}$ with normally distributed random errors of zero mean and variance (see [13]),

$$s^2 = \frac{\Phi(\hat{\mathbf{p}})}{N-L}.$$

- (ii) Find new best-fit parameters $\tilde{\mathbf{p}}$ to the perturbed data from (i).
 (iii) Repeat this process a large number of times (500 or preferably 1000 times) sufficiently often to generate a statistically significant estimate of the mean value of $\tilde{\mathbf{p}}$.
 (iv) If the *relative biases* satisfy the relation,

$$\|\hat{\mathbf{p}} - \text{mean}\{\tilde{\mathbf{p}}\}\| < 0.01 \|\hat{\mathbf{p}}\|,$$

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; see Tables 2 & 5.

In other words, if the LS estimator of a nonlinear 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 nonlinear regression model might be far from a linear model in its behaviour. For more details about the nonlinearity effects and issues related parameter estimations, we may refer to [24]. Figure 4 shows the degree of the closeness of those models to a linear regression behaviour.

4 Discontinuities Associated with the Time-Delay

One obvious difficulty with such parameter estimation problem is (from both the practical and the theoretical

viewpoints) that solutions of DDEs are not generally differentiable with respect to the lag τ . In addition, some discontinuities can arise and propagate in the solution of DDE. Such discontinuities, when arising from the initial point $t_0(\mathbf{p})$ (and the initial function $\psi(t, \mathbf{p})$), may propagate into $\Phi(\mathbf{p})$ via the solution $y(t, \mathbf{p})$, if it has a jump at one of the data points $\{\zeta_i\}$. Let us explain this further: We have

$$\left(\frac{\partial \Phi(t_i; \mathbf{p})}{\partial p_l} \right)_{\pm} = -2 \sum_{i=1}^M [Y(t_i) - y(t_i; \mathbf{p})] \left(\frac{\partial y(t_i; \mathbf{p})}{\partial p_l} \right)_{\pm} \quad (10)$$

$$\left(\frac{\partial^2 \Phi(t_i; \mathbf{p})}{\partial p_l \partial p_m} \right)_{\pm\pm} = 2 \sum_{i=1}^M \left[\left(\frac{\partial y(t_i; \mathbf{p})}{\partial p_l} \right)_{\pm} \left(\frac{\partial y(t_i; \mathbf{p})}{\partial p_m} \right)_{\pm} - [Y(t_i) - y(t_i; \mathbf{p})] \left(\frac{\partial^2 y(t_i; \mathbf{p})}{\partial p_l \partial p_m} \right)_{\pm\pm} \right]; \quad (11)$$

$$\frac{\partial}{\partial \tau} y(t_i - \tau; \mathbf{p}) = -y'(t_i - \tau; \mathbf{p}). \quad (12)$$

Then from equations (10), (11) and (12) that, unless $Y(t_i) = y(t_i; \mathbf{p})$, jumps can arise in the first or the second partial derivative of $\Phi(\mathbf{p})$, with respect to p_l , if the first or the second partial derivatives of $y(t, \mathbf{p})$ with respect to p_l has a jump at $t = t_i$ (one of the data-points). These jumps can propagate into the second derivative of $\Phi(\mathbf{p})$ if the first derivative of $y(t; \mathbf{p})$, with respect to p_l , has a jump at one of the data-points $t = t_i$ even when $Y(t_i) = y(t_i; \mathbf{p})$. Jumps can also arise in the derivatives of $\Phi(\mathbf{p})$ if the lag τ is considered as a parameter to be estimated and the derivative of $y(t; \mathbf{p})$ (with respect to t) has a jump at one of the data points. For more discussion about these issues, we refer to [25].

As a result of the above remarks, we see that parameter estimation in DDEs (1) mainly depends on:

1. differentiability of the solution, $y(t; \mathbf{p})$, of the DDEs with respect to the parameter \mathbf{p} ;
2. the existence and uniqueness of the solution y which depends on the initial function ψ and the parameter \mathbf{p} ;
3. existence and position of the jump discontinuity points depending on τ ;
4. the statistical nature of the observed data-points $\{t_i, Y(t_i)\}_{i=1}^M$.

One can also establish the connection between jumps in the derivatives of $y(t; \mathbf{p})$, with respect to t , and the partial derivatives (in $\Phi(\mathbf{p})$) of $y(t; \mathbf{p})$ with respect to some p_l . Let us rewrite, the scalar case of, (1) in the form:

$$\begin{aligned} y'(t, \mathbf{p}) &= f(t, y(t, \mathbf{p}), y(\sigma(t), \mathbf{p}); \mathbf{p}), \quad t \geq t_0, \\ y(t, \mathbf{p}) &= \psi(t; \mathbf{p}), \quad t \leq t_0 \end{aligned} \quad (13)$$

where $\sigma(t) = t - \tau$. Differentiating both sides of (13) with respect to p_l , gives the variational system of the form:

$$\begin{aligned} \frac{d}{dt} y_l(t; \mathbf{p}) &= \frac{\partial f}{\partial y(t, \mathbf{p})} (t, y(t, \mathbf{p}), y(\sigma(t), \mathbf{p}); \mathbf{p}) \frac{\partial y(t, \mathbf{p})}{\partial p_l} + \\ &\quad \frac{\partial f}{\partial y(\sigma(t), \mathbf{p})} (t, y(t, \mathbf{p}), y(\sigma(t), \mathbf{p}); \mathbf{p}) y'(\sigma(t), \mathbf{p}) \times \\ &\quad \frac{\partial \sigma(t)}{\partial p_l} + \frac{\partial f}{\partial p_l} (t, y(t, \mathbf{p}), y(\sigma(t), \mathbf{p}); \mathbf{p}), \quad (14) \\ y_l(t; \mathbf{p}) &= \psi_l(t; \mathbf{p}), \quad t \leq t_0, \end{aligned}$$

where $y_i(t; \mathbf{p}) \equiv \frac{\partial y_i(t; \mathbf{p})}{\partial p_i}$. Note that equations (13) and (14), together, give a system of *neutral* delay differential equations (NDDEs). It is clear that the jumps in the solution of this system are intimately related to the jumps in the derivatives $y(t, \mathbf{p})$ with respect to t in the delay differential system. Such jumps can spread forward along the integration interval.

In the case of state-dependent DDEs, the problem may become more complicated. In this case, Hartung and Turi [26] gave in the following theorem sufficient conditions of differentiability of the solutions with respect to the parameters:

Theorem 2. *In case of state-dependent DDEs ($\tau = \tau(t, y(t); \mathbf{p})$), the derivatives of $\Phi(\mathbf{p})$, in (10)-(11), and $y'_i(t; \mathbf{p})$ in (14) are exist if:*

- A1- $f(t, u, v; \mathbf{p})$ is: (i) continuous, (ii) locally-Lipschitz continuous in u, v and \mathbf{p} , and (iii) continuously-differentiable with respect to u, v and \mathbf{p} .
- A2- $\tau(t, \psi; \mathbf{p})$ is: (i) continuous, (ii) locally-Lipschitz continuous in ψ and \mathbf{p} , (iii) continuously differentiable with respect to t, ψ and \mathbf{p} , and (iv) the derivatives $\frac{\partial \tau}{\partial t}, \frac{\partial \tau}{\partial \psi}, \frac{\partial \tau}{\partial \mathbf{p}}$ are locally-Lipschitz continuous in ψ and \mathbf{p} .
- A3- $\psi(t; \mathbf{p})$ is: (i) continuous, (ii) locally-Lipschitz continuous in \mathbf{p} , and (iii) continuously differentiable with respect to t , and \mathbf{p} .

Now we discuss how can the parameters uncertainty affect the model state/populations?

5 Sensitivity Analysis

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. In this Section, we provide the approach of variation of parameter to evaluate the analysis of sensitivity for DDEs.

The *variational approach* is to derive, analytically, general sensitivity coefficients for minor changes in the parameters, time delays, and initial data in the model. The 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 Rihan [19,27] to investigate the qualitative behaviour of the solution of a dynamic system of DDEs due to small variations in the parameters that appear in the model. 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 DDE (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

$$\delta y_i(t) = \sum_j \frac{\partial y_i(t)}{\partial \alpha_j} \delta \alpha_j + O(|\alpha|^2). \tag{15}$$

The functional derivative sensitivity coefficients, however, when the parameters are functions of time such as the initial function, 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:

$$\delta y_i(t^*) = \int_0^{t^*} \frac{\partial y_i(t^*)}{\partial \alpha_j(t)} \delta \alpha_j(t) dt, \quad t < t^*. \tag{16}$$

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

$$\begin{aligned} \mathbf{f}(t) &= \mathbf{f}(t, \mathbf{y}(t), \mathbf{y}(t-\tau), \mathbf{p}); \quad A^*(t) = \frac{\partial}{\partial \mathbf{y}} \mathbf{f}(t, \mathbf{y}(t), \mathbf{y}(t-\tau), \mathbf{p}); \\ B^*(t) &= \frac{\partial}{\partial \mathbf{y}_\tau} \mathbf{f}(t, \mathbf{y}(t), \mathbf{y}(t-\tau), \mathbf{p}); \quad D^*(t) = \frac{\partial}{\partial \mathbf{p}} \mathbf{f}(t, \mathbf{y}(t), \mathbf{y}(t-\tau), \mathbf{p}). \end{aligned} \tag{17}$$

Theorem 3. *If $\mathbf{W}(t)$ is an n -dimensional adjoint function which satisfies the differential equation*

$$\begin{aligned} \mathbf{W}'(t) &= -A^*(t)^T \mathbf{W}(t) - B^*(t)^T \mathbf{W}(t+\tau), \quad t \leq t^*, \\ \mathbf{W}(t) &= \mathbf{W}'(t) = 0, \quad t > t^*; \\ \mathbf{W}(t^*) &= [0, \dots, 0, 1_{ith}, 0, \dots, 0]^T, \quad \mathbf{W}'(t^*) = 0, \end{aligned} \tag{18}$$

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

$$\frac{\partial y_i(t^*)}{\partial \mathbf{y}_0} = \mathbf{W}(0), \tag{19a}$$

$$\frac{\partial y_i(t^*)}{\partial \mathbf{p}} = \int_0^{t^*} \mathbf{W}^T(t) D^*(t) dt, \quad t \leq t^*, \tag{19b}$$

$$\frac{\partial y_i(t^*)}{\partial \tau} = - \int_{-\tau}^{t^*-\tau} \mathbf{W}^T(t+\tau) [B^*(t+\tau) \mathbf{y}'(t)] dt, \tag{19c}$$

$$\frac{\partial y_i(t^*)}{\partial \psi(t)} = A^*(t+\tau) \mathbf{W}(t+\tau), \quad t \in [-\tau, 0]. \tag{19d}$$

Proof. See Rihan (2010).

The standard deviations of the estimates are then evaluated by using the sensitivity functions, as indicated the following Remark.

Remark. We can use the sensitivity coefficients ($s_i, i = 1, \dots, L$) to determine the covariance matrix $[\zeta_{ij}]$, of the estimates, as follows [13]:

$$\begin{bmatrix} \zeta_{11} & \zeta_{12} & \dots & \zeta_{1L} \\ \zeta_{21} & \zeta_{22} & \dots & \zeta_{2L} \\ \zeta_{31} & \zeta_{32} & \dots & \zeta_{3L} \\ \dots & \dots & \dots & \dots \\ \zeta_{R1} & \zeta_{R2} & \dots & \zeta_{LL} \end{bmatrix} = 2 \frac{\Phi(\hat{\mathbf{p}})}{N-L} [H(\hat{\mathbf{p}})]^{-1},$$

where $(N - L)$ is the number of degree of freedom and $H(\hat{\mathbf{p}})$ is the Hessian matrix of the objective function $\Phi(\hat{\mathbf{p}})$. The Hessian matrix can be written in the form

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

This matrix can be approximated, using the sensitivity coefficients, as:

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

The standard deviations for the parameter estimates are the quantities

$$\sigma_i \equiv \sigma(\hat{p}_i) = \sqrt{\tilde{H}_{ii}} \quad (i = 1, \dots, L). \quad (20)$$

6 Fitting Models to Cell Growth Data

In this Section, we fit a general form of linear NDDE

$$\begin{aligned} y'(t) &= \rho_0 y(t) + \rho_1 y(t - \tau) + \rho_2 y'(t - \tau), \quad t \geq 0, \\ y(t) &= \psi(t), \quad y'(t) = \psi'(t), \quad t \in [-\tau, 0], \quad y(0) = y_0 \end{aligned} \quad (21)$$

to experimental data of cell growth, using nonlinear least squares described above. Two representative examples of a non-monotone cell growth are provided by the *in vitro* system of synchronized *Tetrahymena pyriformis* cells [28] and *E.coli* cells [29]. We demonstrate how a mathematical model of cell growth that incorporated a time-lag in the cell division phase provides both a qualitatively and quantitatively consistency with the reality. Cell population is an ensemble of individual cells, all of which contribute in a different way to the overall observed behaviour [30]. The heterogeneity of dividing cell populations can be described by a wide range of phenotypic and/or physical characteristics, *e.g.*, the doubling time, the position in the cell cycle. Various proliferation assays are used to quantify the turnover of growing cell populations. Cell growth kinetics is affected by the cellular heterogeneity with respect to the division rate, initial position in the cell cycle, etc. Broadly heterogeneous cell populations display an exponential net growth pattern (for as long as the necessary resources are available), whereas initially synchronized cell cultures with a low variability in their division characteristics show, for some time, a non-monotone step-like growth until they reach a 'steady exponential growth'.

One possible meaning of the parameters of (21) is given in Table 1, that $\tau > 0$ the average cell-division time; $\rho_0 < 0$ the rate of cell-death in culture; and ρ_1 the rate of commitment to cell-division process; and ρ_2 is the gradual dispersal of synchronization of cell-division ($\rho_2 = 2$ implies pure synchronization). The fitting of the parametric growth models to the given experimental data of Tables 4 & 5 is obtained using the a Matlab program and Archi code [31]. Nonlinear least square fits require suitable starting values for the parameter values to be estimated.

Table 1: One biological interpretation of the parameters in the model (21).

Notation	Biological interpretation	Units
$\tau > 0$;	average cell-division time	min
$-\rho_0 \geq 0$	rate of cell-death	min ⁻¹
$\rho_1 \geq 0$	rate of commitment to cell-division	min ⁻¹
$0 \leq \rho_2 \leq 2$	gradual dispersal of synchronization ($\rho_2 = 2$ implies perfect synchronization)	

Table 2: Parameter estimates, STD $\sigma(\cdot)$, Errors and their nonlinear biases (NLB) of the growth model (22) that best fits data of Table 4.

Parameter estimates for <i>Tetrahymena pyriformis</i> growth model					
Model	ρ_0	ρ_1	ρ_2	τ	$\ Err\ _2$
Parameters	-0.0518	0.1054	-	96.33	34.41
$\sigma(\cdot)$	0.0034	0.0082	-	0.0168	
NLB(\cdot)	0.0103%	0.0612%	-	0.0220%	

Example 1. We use the published data on the population size of *Tetrahymena pyriformis* functions of time given Table 4 and Figure 1 to estimate the parameters appearing in the DDE model

$$\begin{aligned} y'(t) &= \rho_0 y(t) + \rho_1 y(t - \tau), \quad t \geq 0, \\ y(t) &= \psi(t), \quad t \in [-\tau, 0], \quad y(0) = y_0. \end{aligned} \quad (22)$$

We adopt the LS approach (3) to fit the observations to model (22) to evaluate the unknown parameters of the model. We consider here a uniform initial function $\psi(t) = 25$ for $t \in [-\tau, 0)$, and initial value $y(0) = 50$. The graph of Figure 1 displays model prediction for the best fit parameters given in Table 2. Prescott (1959) [28] measured the *generation times*¹ of a population of *Tetrahymena pyriformis* cells under uniform conditions. The distribution of generation times in the cell population was displayed for a subpopulation of new born cells at a given time from the *synchronized* cell population, all of age zero. The mean generation time $\tilde{\tau}$ was 111 min, which is close to the estimated value of the best fit, $\tau = 96.33$; see Table 2. The *biases* in the values of of the parameter, due to the nonlinearity, NLB(\cdot), of the parameters, are estimated and displayed in Table 2 as we proceed in Section 3. A Matlab program and Archi code are used to estimate the parameters and simulate the best-fit solutions.

¹ *Generation time*, that varies from cell to cell, is defined as the age at which a cell divides, where age is time measured from birth of a cell.

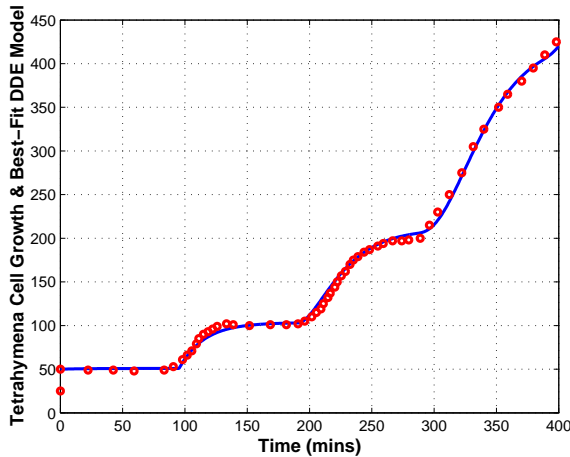


Fig. 1: The circles, Y_i , represents the data for growth of a population of $Y_0 = 50$ of newborn cells of *Tetrahymena pyriformis*. This data represents the multiplication of 25 cells in perfect division synchrony at first population doubling. The line, $y(t, p)$, shows the prediction of the perfect model that based on the DDE (22), with $y(0) = 50$, $y(t) = 25$ for $t < 0$, and best fit parameters given in Table 2. The initially synchronized cell population becomes desynchronized over time.

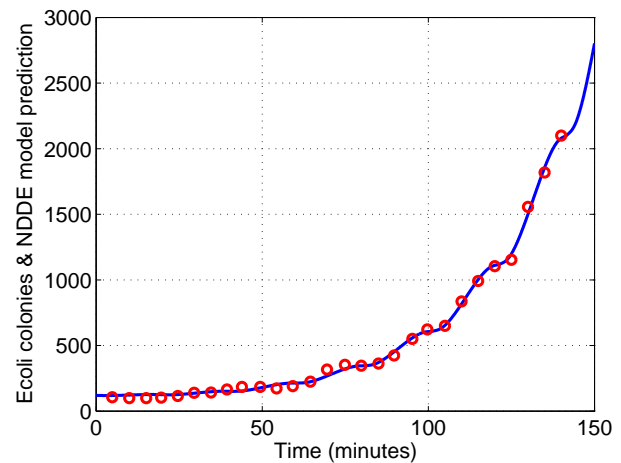


Fig. 3: Shows the data for synchronous *E. coli* growth (based on [29, Fig.4]) & Best-fit model of NDDE $y'(t) = \rho_0 y(t) + \rho_1 y(t - \tau_{cell}) + \rho_2 y'(t - \tau_{cell})$.

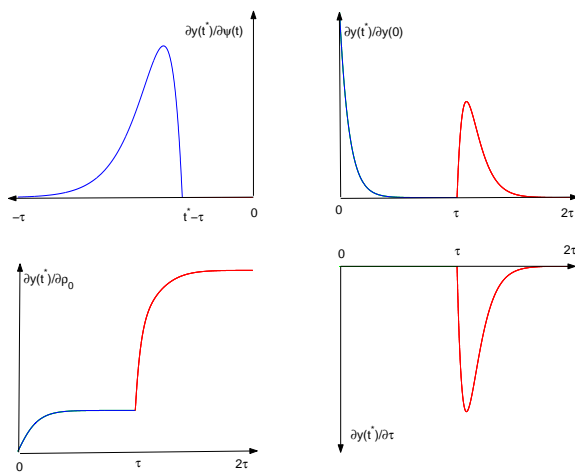


Fig. 2: Shows general sensitivity functions, $\frac{\partial y(t^*)}{\partial \psi(t)}$, $\frac{\partial y(t^*)}{\partial y_0}$, $\frac{\partial y(t^*)}{\partial \rho_0}$, and $\frac{\partial y(t^*)}{\partial \tau}$, for the NDDE (21).

Sensitivity functions $\frac{\partial y(t^*)}{\partial \psi(t)}$ and $\frac{\partial y(t^*)}{\partial \alpha_i}$ ($t \leq t^*$), where $\alpha = [\rho_0, \rho_1, y_0, \tau]^T$ are estimated using the analysis of

Section 5. The adjoint equation of system (22) is

$$\begin{aligned} W'(t) &= -\rho_0 W(t) - \rho_1 W(t + \tau), \quad t \leq t^*, \\ W(t) &= 0, \quad t > t^*; \quad W(t^*) = 1. \end{aligned} \tag{23}$$

The analytical solution of the adjoint Eq (23) is then

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

$$W(t) = e^{-\rho_0(t-t^*)}, \quad t \leq t^*, \tag{24}$$

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

$$W(t) = \begin{cases} e^{-\rho_0(t-t^*)} - \rho_1(t-t^* + \tau)e^{-\rho_0(t-t^* + \tau)}, & 0 < t \leq t^* - \tau, \\ e^{-\rho_0(t-t^*)}, & t^* - \tau < t \leq t^*. \end{cases} \tag{25}$$

Here $W(t + \tau) = 0$ for $t^* - \tau < t \leq t^*$ and $W(t + \tau) = e^{-\rho_0(t-t^* + \tau)}$ for $0 < t \leq t^* - \tau$.

The analytical solution of the DDE (22), with an initial function $\psi(t) = y_m$, is

$$y(t) = \begin{cases} ae^{\rho_0 t} - y_m \xi, & 0 < t \leq \tau, \\ ae^{\rho_0 t} - [y_m \xi - a\rho_1(t - \tau) + y_m \xi^2]e^{\rho_0(t - \tau)} + y_m \xi^2, & \tau < t \leq 2\tau, \end{cases} \tag{26}$$

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

Thus the functional derivative sensitivity density function to the initial function, by using (19d), becomes:

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

$$\frac{\partial y(t^*)}{\partial \psi(t)} = \rho_1 W(t + \tau) = \begin{cases} \rho_1 e^{-\rho_0(t-t^* + \tau)}, & -\tau < t \leq t^* - \tau, \\ 0, & t^* - \tau < t \leq 0. \end{cases} \tag{27}$$

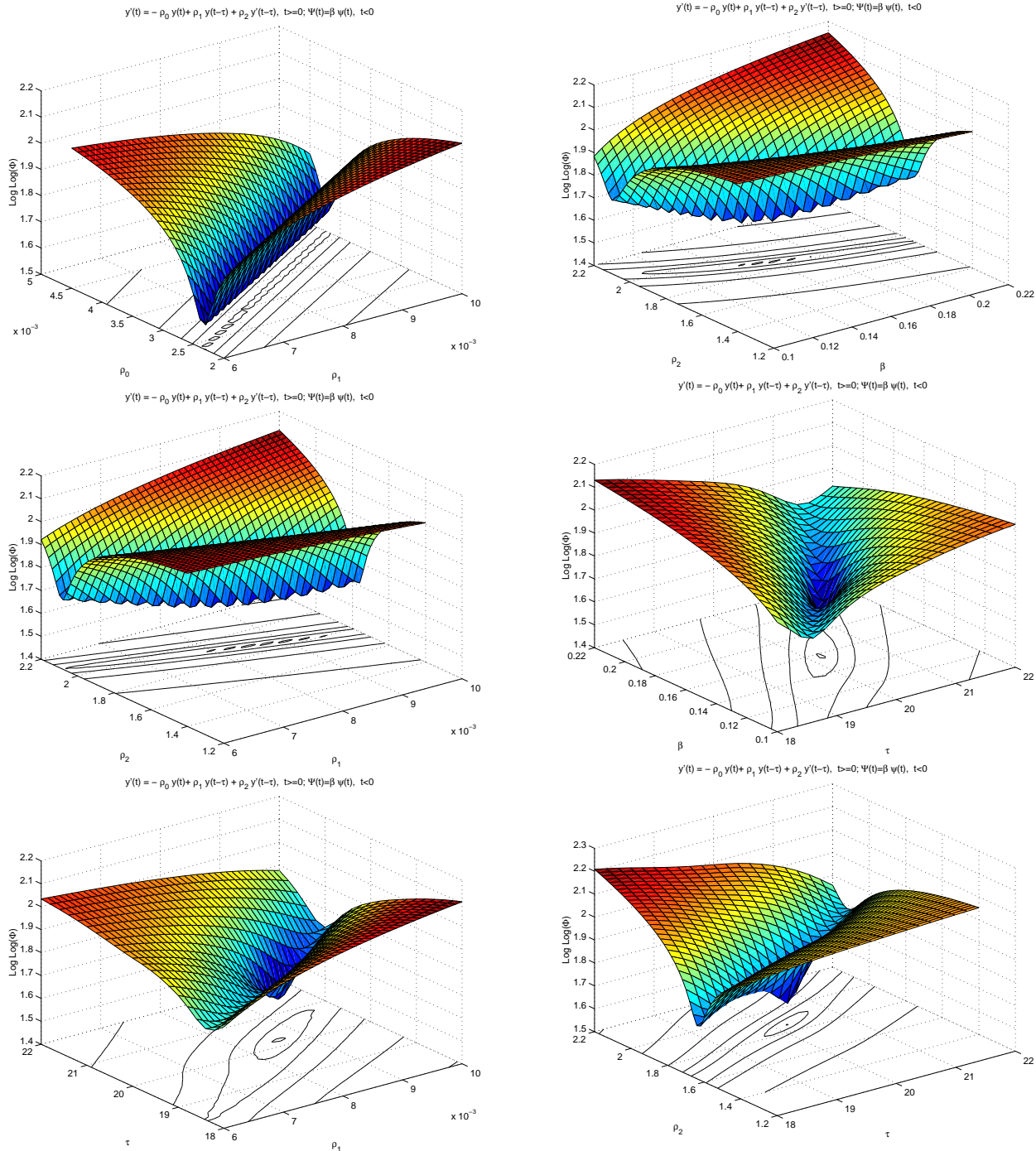


Fig. 4: Pairwise plots of parameter estimates and $\Phi(\mathbf{p})$, in five parameters neutral delay model. For each graph, contours indicate the correlation of the parameter with each other and the inference region of least square estimate. Closeness of the contour to an ellipse, indicates the small degree of nonlinearity of the model to the data.

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

$$\frac{\partial y(t^*)}{\partial \psi(t)} = \begin{cases} \rho_1 e^{-\rho_0(t-t^*+\tau)} - \\ \rho_1 b(t-t^*+2\tau) e^{-\rho_0(t-t^*+2\tau)}, & -\tau < t \leq t^* - 2\tau, \\ \rho_1 e^{-\rho_0(t-t^*+\tau)}, & t^* - 2\tau < t \leq 0. \end{cases} \quad (28)$$

While the sensitivity function of $y(t)$ to the initial condition $y(0)$, that given by the formula (19a), is

$$\frac{\partial y(t^*)}{\partial y(0)} = W(0) = \begin{cases} e^{\rho_0 t^*}, & 0 < t^* \leq \tau, \\ e^{\rho_0 t^*} + b(t^* - \tau)e^{\rho_0(t^* - \tau)}, & \tau < t^* \leq 2\tau. \end{cases} \quad (29)$$

The sensitivity function of $y(t)$ to the constant parameter $\rho_0 (\equiv \frac{1}{\eta})$, by using (19b), takes the form:

$$\frac{\partial y(t^*)}{\partial \rho_0} = \int_0^{t^*} W(t) \frac{\partial F}{\partial \rho_0} dt = \begin{cases} (at^* - y_m \xi \eta) e^{\rho_0 t^*} + y_m \xi \eta, & 0 < t^* \leq \tau, \\ \mathbf{I}, & \tau < t^* \leq 2\tau, \end{cases} \quad (30)$$

where

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

In the same manner, we can deduce $\partial y(t^*)/\partial \rho_1$ & $\partial y(t^*)/\partial \rho_2$. By using (19c), we obtain the sensitivity of $y(t)$ to small perturbations in the time-lag parameter τ as:

$$\frac{\partial y(t^*)}{\partial \tau} = - \int_{-\tau}^{t^* - \tau} W(t + \tau) \left[\frac{\partial \mathbf{f}(t + \tau)}{\partial \mathbf{y}_\tau} \mathbf{y}'(t) + \frac{\partial \mathbf{f}(t + \tau)}{\partial \mathbf{y}'_\tau} \mathbf{y}''(t) \right] dt = \begin{cases} 0, & 0 < t^* \leq \tau, \\ -\rho_0 \rho_1 a(t^* - \tau) e^{\rho_0(t^* - \tau)}, & \tau < t^* \leq 2\tau, \end{cases} \quad (31)$$

with $a = (y_0 + y_m \xi)$.

We also use formula (20) to estimate the standard deviation STD $\sigma(\cdot)$ of the parameters, which are also displayed in Table 2.

Figure 1 displays the best fit model (22) to the observed experiment dat given in the Table 4. We notice from the formula (31) that, as expected, $y(t)$ is sensitive to a change 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 (see Figure 2) have a kink at $t = \tau$ due to the existence of the delay in the system. Thereafter, attention has to be directed to the objective function when τ is a parameter to be estimated.

Example 2. In this example, we consider a synchronous culture of *E.coli* that exhibits prolonged step-like growth [29] given in Table 5 and Figure 3. The cell population is initially homogeneous and synchronized and becomes desynchronized over time. The term ‘synchronous’ refers to the fact that the cells in the culture are homogeneous and synchronized [32]. We assume that: (i) All the cells have the same division time. (ii) All the cells divide simultaneously. (iii) There is prolonged initial step-like growth. (iv) The initial number, y_0 , of *E.coli* colonies is an unknown which can be specified as a parameter to be

Table 3: Parameter estimates, STD, Errors and their nonlinear biases (NLB) for E.coli growth model (21) that best fits data of Table 5.

Parameter estimates for E.coli growth model					
Model	ρ_0	ρ_1	ρ_2	τ	$\ Err\ _2$
Par.	-0.0257	0.0504	1.6847	20.2719	160.16
$\sigma(\cdot)$	0.0038	0.0082	0.02062	0.0868	
NLB(\cdot)	0.070%	0.050%	0.006%	0.042%	

estimated or can be estimated by backwards continuation of the data.

Consider the NDDE model (21). The parameter ρ_2 has a natural interpretation, so the neutral delay term is inviting for qualitative reasons. For the observed data given in Table 5, the numerical values of parameter estimates, and their standard deviations and nonlinear biases, are given in Table 3. Figure 3 displays the best fit model (21) to the observations 5. While, Figure 4 shows the pairwise plots of the parameters. The regular behaviour of the contours (such as ellipses) indicates whether the model-data combinations are not badly nonlinear in the five-parameter time-lag model. In addition, the contours in Figure 4, indicate the degree of the closeness of those models to a linear regression behaviour.

The numerical simulations in this paper have been performed using Matlab Program and Archi code [31] with the current values of the parameters to calculate the corresponding objective function $\Phi(\mathbf{p})$. The parameter values are adjusted by the minimization routine E04USF² from NAG library; See [8].

7 Discussion and Conclusion

In this paper, we provided the theoretical and numerical frameworks for parameter identification in DDEs. We discussed some issues related issues associated with inverse problem such as discontinuities due to the presence of time-delays, nonlinearity of the problem and sensitivity of the model. We adopted two mathematical models of cell growth that incorporated a time-lag in the cell division phase. The models are qualitatively and quantitatively contestant in fitting certain reported data. The use of DDE/NDDE models gives a direct estimate of some relevant growth parameters of synchronous cultures such as (i) the cell-division time, (ii) the fraction of cells that are dividing, (iii) the rate of commitment of cells to

² E04USF is designed to minimize an arbitrary smooth sum of squares function subject to constraints (which may include simple bounds on the variables, linear constraints and smooth nonlinear constraints) using a sequential quadratic programming (SQP) method.

Table 4: Data for growth of a population of ciliates (*Tetrahymena pyriformis*) (See Fig 2 in Prescott (1959)).

Time(mins)	0.0	22.2	42.5	59.2	83.3	90.7	98.1	101.8	105.5	109.2	111.1
Cell no.	50	49	49	48	49	53	61	66	71	79	85
Time(mins)	114.8	118.5	122.2	125.9	133.3	138.8	151.8	168.5	181.4	190.7	196.2
Cell no.	90	93	96	99	102	101	100	101	101	102	105
Time(mins)	201.8	205.5	209.2	211.1	214.8	216.6	220.3	222.2	225.5	228.8	232.5
Cell no.	110	115	119	125	132	137	144	150	157	162	170
Time(mins)	235.1	238.8	243.7	248.1	254.8	259.2	266.6	274	279.6	288.8	296.2
Cell no.	175	179	184	187	191	194	197	197	198	200	215
Time(mins)	302.9	312.2	322.2	331.4	339.9	351.8	359	370.3	379.6	388.8	398.1
Cell no.	230	250	275	305	325	350	365	380	395	410	425

Table 5: Observed data of *E.coli* colonie growth [29, Fig.4]. A synchronous culture of *E.coli* K12 λ F⁻ cells was prepared by loading 2×10^{10} cells from an exponential culture into a 15ml tube. The cells were then centrifuged at 2500g for 20 minutes and the top 2% of cells suspended in fresh growth medium.

Observed data of the growth of <i>E.coli</i> colonies										
Time(mins)	4.85	9.96	15.1	19.6	24.6	29.5	34.6	39.4	43.9	49.2
Cells per ml	10.6	99	99	103	115	140	142	165	185	185
Time(mins)	54.3	59.2	64.5	69.5	74.9	79.8	85.0	89.7	95.2	99.7
Cells per ml	173	190	224	317	353	346	363	424	551	623
Time(mins)	105.0	110.0	115.0	120.0	125.0	130.0	135.0	140.0		
Cells per ml	650	836	992	1105	1153	1556	1818	2100		

cell division, (iv) the degree of synchronization of cells in the population, and (v) the death rate of cells.

The estimated parameters are slightly biased with the relative biases $< 1\%$ which means that the model-data combination are not badly nonlinear; See Tables 2 & 3. An increase in the number of model parameters reduces bias in the data fit. However, small data sets do not support models with many parameters since the increase in the number of parameters to be estimated. In Figure 4, the closeness of graph of $\Phi(\mathbf{p})$ to a paraboloid indicates the degree of nonlinearity of the model-data set combination.

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 kinks at $t = \tau$ in the Figure 2 are due to the existence of the time-delay in the system.

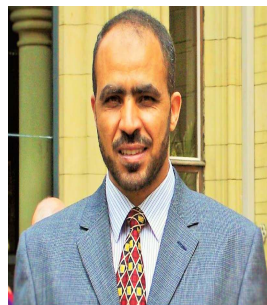
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