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Numerical Modelling of Biological Systems with Memory using Delay Differential Equations

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Abstract: This is a review article, to show the consistency of delay differential equations with biological systems with memory, in which we present a class of mathematical models with time-lags in immunology, physiology, epidemiology and cell growth. We also incorporate optimal control parameters into a delay model to describe the interactions of the tumour cells and immune response cells with external therapy. We then study parameter estimations and sensitivity analysis with delay differential equations. Sensitivity analysis is an important tool for understanding a particular model, which is considered as an issue of stability with respect to structural perturbations in the model. We introduce a variational method to evaluate sensitivity of the state variables to small perturbations in the initial conditions and parameters appear in the model. The presented numerical simulations show the consistency of delay differential equations with biological systems with memory. The displayed results may bridge the gap between the mathematics reserach and its applications in biology and medicine.

Keywords: DDEs, Hamiltonian; Epidemiology; Immunology; Immuno-chemotherapy; Physiology; Optimal control; Parameter estimation; RK-methods; Sensitivity; Tetrahymena; Time-lags

1 Introduction

Mathematical modelling with delay differential equations (DDEs) is widely used for analysis and predictions in various areas of the life sciences, e.g., population dynamics, epidemiology, immunology, physiology, neural networks. The time delays in these models take into account a dependence of the present state of the modelled system on its past history. 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.

An Initial Value Problem (IVP) takes the form:

$$y'(t) = f(y(t),t), \quad \text{where} \quad y(t_0) = y_0 \tag{1}$$

where $y \in \mathscr{R}^N$. We see that, at time t, the system is completely defined by the state of the system, $y(t)$, at time t. (In other words, everything is instantaneously known.) Much work has been done in developing efficient techniques for solving these types of problem. However, in real life, things are rarely so instantaneous; There is usually a propagation delay before the effects are felt. This situation can be modelled using a DDE

$$y'(t) = f(y(t),y(t-\tau_1),y(t-\tau_2),\ldots,y(t-\tau_d),t),\ t \geq t_0 \tag{2}$$

where all of the delay terms, τ_i, are assumed to be none negative functions of the current time t. τ_i could be constant, or variable as functions of t or even the state y. Because of these delay terms it is no longer sufficient to supply an initial value, at time $t = t_0$, to completely define the problem. Instead, it is necessary to define the history of the state vector, $y(t)$, sufficiently far enough back in time from t_0 to ensure that all of the delayed state terms, $y(t-\tau_i)$, are always well defined. Thus, it is necessary to supply an initial state profile of the form:

$$y(t) = \psi(t),\ t_0 - \tau_{max} \leq t < t_0, \text{ and } y(t_0) = y_0. \tag{3}$$

It should be noted that $\psi(t_{0-})$ need not be the same as y_0. This immediately introduces the possibility of a discontinuity in the state, $y(t)$. We refer to [1,2,3,4,5,6,4,7,8,9], and references therein, for the scope of DDEs in bioscience and related issues.

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In the present paper, we show 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 biological systems with memory. This paper is organized as follows: Section 2 displays the role of delay differential models in dynamic diseases. Section 3 provides a delay differential model for tumour-immune response and control with chemo–immunotherapy. Section 4 introduces a general approach of least squares approach for parameter estimations with DDEs. Section 5 introduces a variational approach to investigate the sensitivity of the models to minor changes in the parameters, with applications with cell bacterial growth of Tetrahymena pyriformis. Section 7 presents some available software for DDEs.

2 Delay Models in Dynamic Diseases

In many applications in the life sciences, a delay is introduced when there are some hidden variables and processes which are not well understood but are known to cause a time-lag [10]. Thus, the delays or lags may in fact represent a reaction chain or a transport process, gestation times, incubation periods, transport delays, or can simply lump complicated biological processes together, accounting only for the time required for these processes to occur. A well-known example is Cheyne-Stokes respiration (or periodic breathing), discovered in the 19th century: some people show, under constant conditions, periodic oscillations of breathing frequency [11]. This strange phenomenon is apparently due to a delay caused by cardiac insufficiency in the physiological circuit controlling the carbon dioxide level in the blood. Delays also occur naturally in the chemostat (a laboratory device for controlling the supply of nutrients to a growing population [12]). We shall see in this section that the mathematical properties of DDEs justify such approximations.

2.1 Immunology

The Immune System (IS) is a complex network of cells and signals that have evolved to respond to the presence of pathogens (such as bacteria, virus and fungi) and protect the body from cancer cells. IS basically works by keeping track of all substances normally found in the body. Any new substance in the body that the IS does not recognize raises an alarm, causing the IS to attack it. Substances that cause an IS response are called ”antigens”. The IS can lead to destruction of anything containing antigens, such as pathogens or cancer cells. Pathogens have substances on their outer surfaces such as certain proteins that are not normally found in the human body. The IS sees these foreign substances as antigens. Cancer cells are also different from normal cells in the body and they have unusual substances on their outer surfaces. However, the IS is much better at recognizing and attacking pathogens (harmful germs) than cancer cells. This is due to the fact that pathogens are very different from normal human cells and are often easily seen as foreign, but cancer cells and normal cells have fewer clear differences. This leads us to the fact that the IS may not always recognize cancer cells as foreign.

However, the response of an immune system cannot be represented correctly without the hereditary phenomena being taken into account: cell division, differentiation, etc. (the time needed for immune cells to divide, mature, or die). Therefore, delay differential equations have a particularly important role to play in understanding the dynamics and tracking viral infections and immune populations over time. Recently, many mathematical models for virus dynamics [13,14,15] explicitly consider delay terms to represent the needed time between the infection of a cell and the production of new viruses of HIV (Human Immunodeficiency Virus) in infected patients.

The simple mathematical model of immune response employed by Marchuk [16] describes the interaction of viruses, $V(t)$; antibodies, $F(t)$; plasma cells, $C(t)$; and the relative characteristic of the affected organ, $m(t)$, of a person infected by a viral disease. This model is formulated as a system of four nonlinear DDEs:

$$\begin{aligned} V'(t)&=\big(p_1-p_2F(t)\big)V(t),\\ C'(t)&=\xi(m)p_3F(t-\tau)V(t-\tau)-p_5\big(C(t)-C^*\big),\\ F'(t)&=p_4\big(C(t)-F(t)\big)-p_8F(t)V(t),\\ m'(t)&=p_6V(t)-p_7m(t), \end{aligned} \tag{4}$$

with $t\geq 0$ and $\xi(m)$ is defined by

$$\xi(m)=\begin{cases} 1 & if\ m\leq 0.1,\\ (1-m)\frac{10}{9} & if\ 0.1\leq m\leq 1. \end{cases}$$

The *first equation* describes the change in the number of antigen in an organizm (it is a Volterra-Lotka like predator-prey equation). The *second equation* describes the creation of new plasma cells with time-lag due to infection (in the absence of infection, the second term creates an equilibrium at $C(t)=C^*$). The *third equation* models the balance of the number of antibody reacting with antigens: the generation of antibodies from plasma cells is described by $p_4C(t)$ and their decrease due to aging is described by $(-p_4F(t))$ and binding with antigens by $(-p_8F(t)V(t))$. The relative characteristic $m(t)$ of damaging organizm is given by the *fourth equation* of which the first term expresses the degree of damage to an organ and the second term describes the recuperation due to the recovery activity of the organizm. Finally, the definition of $\xi(m)$ expresses the fact that the creation of plasma cells slows down when the organizm is damaged by the viral infection.

The model (4) has been used to study the relationships between the pathogen and the host immune system

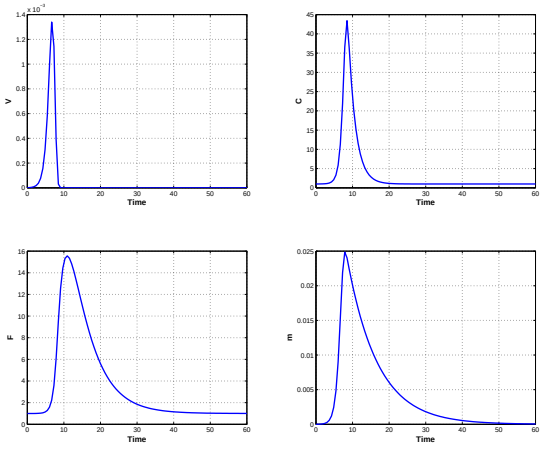

Fig. 1: Numerical simulations of model (4) for $\tau = 0.5$ and $p_1 = 2$, $p_2 = 0.8$, $p_3 = 10^4$, $p_4 = 0.17$, $p_5 = 0.5$, $p_6 = 10$, $p_7 = 0.12$ and $p_8 = 8$.

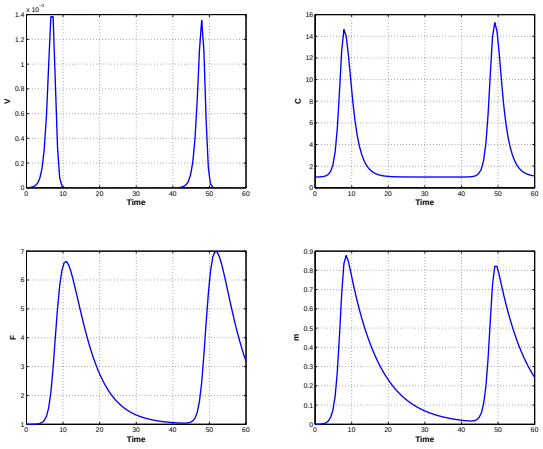

Fig. 2: Simulations of model (4) with the same parameters of Figure 1 except for $p_6 = 300$. The graphs illustrate the periodic outbreak of the disease.

parameters determining the stability of various steady states. It can also be used to underly the basic types of infectious disease dynamics: subclinical, acute with recovery, chronic and lethal, or predicting the results of external manipulations with the immune system. In other words, this model allows us, by changing the coefficients $p_1, p_2 \ldots, p_8$, to model all sorts of behaviour of stable health, unstable health, acute form of a disease, chronic form etc. (see Marchuk [16]). One of the stationary solutions of (4), that describes the healthy state of an organizm, is

$$V(t) = 0,\ C(t) = C^*,\ F(t) = F^* = C^*,\ \text{and}\ m(t) = 0.$$

FIGURES 1 & 2 show the solutions of the model (4) (with different parameters) for $\tau = 0.5$, with initial values:

$$V(0) = 0.5 \times 10^{-6},\ C(0) = 1,\ F(0) = 1 \text{ and } m(0) = 0;$$

and with initial functions:

$$V(t) = \max(0, 10^{-6} + t),\ F(t) = 1, \quad t \leq 0.$$

It may also be noted, from the graphs, that there is either a complete recovery, as in FIGURE 1, or periodic outbreak of the disease, as shown in FIGURE 2 .

Marchuk and his associates [16] developed a hierarchy of immune response models of increasing complexity to account for the various details of defence responses to pathogens. The delays are used in the functional terms describing the proliferation and differentiation of lymphocytes, and represent the time needed for cells to divide, mature (i.e., express certain genes), or to die. Whereas the basic model of an infectious disease has only one time-lag, more sophisticated mathematical models for viral-bacterial infections in lungs, or T-cell division incorporate about ten delays; see [17]. Another example of generic time-lag equations in immunology is provided by Mohler *et al.* [18] who developed compartmental models for lymphocyte migration. The delays represent the time that cells reside in a particular compartment, or the transit times through compartments, or the duration of inter-compartmental transfer.

Mathematical modeling of tumour-immune interactions is also very complex and has a long history e.g. [19,20,21,22,23,24,25]. Kuznetsov *et al.* [26] model the interactions of cytotoxic T lymphocyte (CTL) response and the growth of an immunogenic tumour. In recent contributions of [27,28,29,30], the authors take into account the penetration of the tumour cells by the effector cells, which simultaneously causes the inactivation of effector cells. [31] consider the effects of time delay on the two-dimensional system which represents the basic model of the immune response. They study variations of the stability of the fixed points due to time delay and the possibility for the occurrence of the chaotic solutions. Forys and Kolev [32] propose and study the role of time delay in solid avascular tumour growth. They study a delay model in terms of a reaction-diffusion equation and mass conservation law. Two main processes are taken into account i.e. proliferation and apoptosis. Yafia [33] analyzed an interaction between the proliferating and quiescent cells tumour with a single delay. He showed the occurrence of Hopf bifurcation as the delay crosses some critical value [34,35,36,37].

We just consider a very simple delayed tumour-immune competition model, without treatments

[38]

$$\begin{aligned}\frac{dE(t)}{dt} &= \sigma + \omega E(t-\tau)T(t-\tau) - \delta\bar{E}(t),\\ \frac{dT(t)}{dt} &= \bar{\alpha}(1-\bar{\beta}\bar{T}(t))T(t) - nE(t)T(t),\end{aligned} \tag{5}$$

with given initial functions

$$E(t) = \psi_1(t),\ T(t) = \psi_2(t), t \in [-\tau, 0),\ E(0), T(0) > 0. \tag{6}$$

It is easy to show that if $\omega > 0$, and $\alpha\delta > \sigma$, then the system (5)-(6) has two steady states: $\mathscr{E}_0 \equiv (\frac{\sigma}{\delta}, 0)$ (tumour-free steady state) and $\mathscr{E}_+ \equiv (E^*, T^*)$ (endemic steady state), where $E^* = \dfrac{-\alpha(\beta\delta-\omega)+\sqrt{\Delta}}{2\omega}$, $T^* = \dfrac{-\alpha(\beta\delta+\omega)-\sqrt{\Delta}}{2\alpha\beta\omega}$ with $\Delta := \alpha^2(\beta\delta-\omega)^2 + 4\alpha\beta\sigma\omega > 0$.

Theorem 1. *Under the condition that (i) $\omega > 0$ and (ii) $\alpha\delta > \sigma$, then the steady state $\mathscr{E}_0$ is a asymptotically stable for all $\tau \geq 0$. However the steady state $\mathscr{E}_+$ is asymptotically stable when $\tau = 0$ under the same conditions and (iii) β be close enough to* 0.

The delay time τ plays an important role in stability of the system (5), (6).

Theorem 2. *Under the hypotheses that $\omega > 0$, $\alpha\delta > \sigma$, and β be close enough to* 0*, there exist τ_n , $n = 0, 1, \ldots$ such that (i) $\mathscr{E}_+$ is asymptotically stable for $\tau < \tau_0$ and unstable for $\tau > \tau_0$; (ii) System (5)-(6) undergoes a Hopf bifurcation at $\mathscr{E}_+$ when $\tau = \tau_n$, where*

$$\tau_n = \frac{1}{\nu_0}\arccos\frac{q(\nu_0^2 - r) - \beta s\nu_0^2}{s^2\nu_0^2 + q^2} + \frac{2n\pi}{\nu_0}, \tag{7}$$

and

$$\nu_0^2 = \frac{1}{2}(s^2 - p^2 + 2r) + \frac{1}{2}\sqrt{(s^2 - p^2 + 2r)^2 - 4(r^2 - q^2)},$$

where $p = \delta + \alpha\beta T^*$, $r = \alpha\beta\delta T^*$, $s = -\omega T^*$, and $q = \alpha\omega T^*(1 - 2\beta T^*)$.

Numerical simulations of (5)-(6) are given in Figure 3. (For the proof of Theorem 1 & Theorem 2, I refer to [30, 39].)

2.2 Physiology

The great potential of simple DDEs for capturing complex dynamics observed in physiological systems, was shown in a series of related works by an der Heiden, Mackey *et al.* [40,11]. Delay differential equations were used to model unstable patterns of (i) the human respiratory system and regulation of blood concentration of CO_2 (periodic breathing and prediction of low- and large-amplitude oscillations), (ii) the production of blood cells (periodic and chaotic regimes), and (iii) hormone regulation in the endocrine system (period-doubling bifurcations and chaotic solutions); see [41].

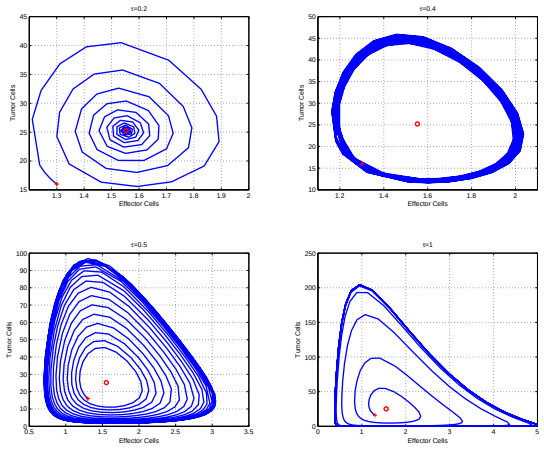

Fig. 3: Numerical simulation of model (5), with $\sigma = 0.1181$, $\omega = 0.01184$, $\delta = 0.3747$, $\alpha = 1.636$, $\beta = 0.002$ with $\tau = 0.2,\ 0.4,\ 0.5,\ 1$. The steady state (E^*, T^*) is table when $\tau < \tau_0 := 0.3854 =$ (the critical delay); and unstable when $\tau \geq \tau_0$ and a bifurcation of a periodic solution from $(E^*, T^*) = (1.5535\ ,\ 25.2260)$ occurs.

The following model is concerned with the regulation of hematopoiesis, the formation of blood cell elements in the body. For example white and red blood cells, platelets and so on are produced in the bone marrow from where they enter the blood stream. When the level of oxygen in the blood decreases this leads to a release of a substance which in turn causes an increase in the release of the blood elements from the marrow. There is thus a feedback from the blood to the bone marrow.

As an illustrative example, let $c(t)$ be the concentration of cells (the population species) in the circulating blood. We assume that the cells are lost (=die) at a rate proportional to their concentration, that is like $\gamma c(t)$, where the parameter γ has dimensions $(day)^{-1}$. After the reduction in cells in the blood stream there is about a 6 day delay before the marrow release further cells to replenish the deficiency (see [11]). We thus assume that the flux λ of cells into the blood stream depends on the cell concentration at an earlier time, namely, $c(t-\tau)$, where τ is the delay. Such assumptions suggest a model equation of the form

$$\frac{dc(t)}{dt} = \lambda c(t-\tau) - \gamma c(t).$$

Glass & Mackey [42] proposed a possible replacement in the form of the non-linear delay differential equation

$$\begin{aligned}\frac{dc(t)}{dt} &= \frac{\lambda a^m c(t-\tau)}{a^m + c^m(t-\tau)} - \gamma c(t), \quad t \geq 0,\\ c(t) &= \alpha, \quad t \leq 0,\end{aligned} \tag{8}$$

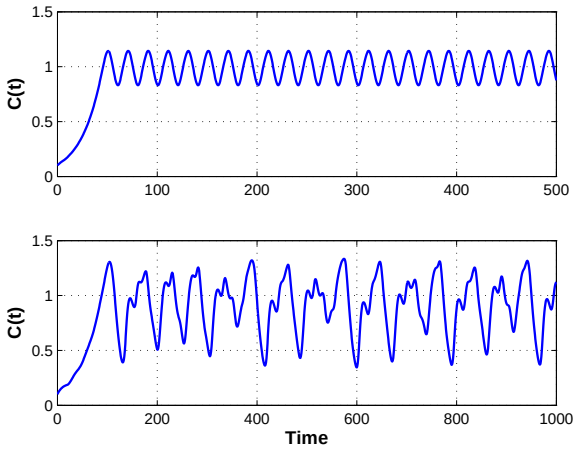

Fig. 4: (top) shows the numerical solution of (8) with parameter values $\alpha = 0.1$, $\gamma = 0.1$ days^{-1}, $\lambda = 0.2$ days^{-1}, $m = 10$ and $\tau = 6$ days; (bottom) shows the numerical simulation with the same parameter values as in (a) except an increase in the delay to $\tau = 20$ days.

where λ, a, m, g, τ, and α are positive constants. Graphs in FIGURE 4 show the numerical solutions of (8) for two values of the delay time τ.

2.3 Epidemiology

Epidemics have ever been a great concern of human kind, since the impact of infectious diseases on human and animal is enormous, both in terms of suffering and social and economic consequences. This concern is now increased, specially when new swine flu viruses H1N1[1] [43] and recently H5N1 have sparked a deadly outbreak in some countries and spread into other parts of the world. Mathematical modeling is an essential tool in studying a diverse range of such diseases. The basic elements for the description of infectious diseases have been considered by three epidemiological classes: $S(t)$ that measures the *susceptible*[2] portion of population, $I(t)$ the *infected*[3], and $R(t)$ the *removed*[4] ones. It was natural to assume that the number of newly infected people per time unit is proportional to the product $S(t)I(t)$. It was also assumed that the number of newly removed persons is proportional to the infected ones, and the total population is a constant $N = S + I + R$ (except death from the disease). Kermack-McKendrick [44] thus arrived at the *SIR* model:

$$S'(t) = -\beta S(t)I(t),\ I'(t) = \beta S(t)I(t) - \alpha I(t),\ R'(t) = \alpha I(t). \tag{9}$$

Here β is the number of contacts between an average infective and the population per unit time (pairwise rate of infection), and α is the fraction of the population which leaves the inflective class (removal rate of infectives). The qualitative analysis is displayed as follows: If $S(0) < \alpha/\beta$, then $I(t)$ is a decreasing function which tends to 0, and $S(t)$ is also decreasing and tends to a constant level greater than 0. However, If $S(0) > \alpha/\beta$, $S(t)$ is also decreasing and tends to a constant level greater than 0, but $I(t)$ will first increase in a time period $(0, T_0)$, then decrease and tends to 0 after T_0.

Define a dimensionless quantity $\mathscr{R}_0 = \beta S(0)/\alpha$, that is a threshold quantity. If we introduce a small number of infectives $I(0)$ into the a susceptible population, then an epidemic will occur if $\mathscr{R}_0 > 1$. As an example, the solution (with all constants equal to one) of (9) (with initial values $S(0) = 5, I(0) = 0.1, R(0) = 0$) is plotted in FIGURE 5. We note that an epidemic breaks out, and everybody finally becomes "removed" and nothing further happens.

To prevent an epidemic, we reduce $\mathscr{R}_0 = \dfrac{\beta S(0)}{\alpha}$, and maximize the immunization by reducing $I(0)$ and transferring $S(t)$ to $R(t)$ (removed ones). Suppose that p percent of population is successfully immunized, then $S(0)$ is replaced by $(1-p)S(0)$, then $p > 1 - \dfrac{\alpha}{\beta S(0)}$. (For practical study to estimate the epidemiological parameters, I refer to [45,43].)

From the above model, we note that the occurrence of an epidemic depends solely on the number susceptibles, the transmission rate, and recovery rate. In other words, the initial number of infectives plays no role in whether or not there is an epidemic. Other considerations, such as vital dynamics (births and deaths), length of immunity, the incubation period of the disease, and disease induced mortality can all have large influences on the course of an outbreak.

2.3.1 Development of SIR model (9)

The nonautonomous phenomenon occurs mainly due to the seasonal variety, which makes the population behave periodically [46,47]. To investigate this kind of phenomenon, in the model, the coefficients should be periodic functions, then the system is called periodic system. Many communicable diseases have this characteristic.

Assume that the immunized people become susceptible again, say after time τ_1 (say, $\tau_1 = 10$) (see

[1] Influenza viruses are defined by two different protein components, known as antigens, on the surface of the virus. They are spike-like features called haemagglutinin (H) and neuraminidase (N) components.

[2] Susceptible: who are not yet infected

[3] Infected: who are infected at time t and are able to spread the disease by contact with susceptible

[4] Removed: who have been infected and then removed from the possibility of being infected again or spreading (Methods of removal: isolation or immunization or recovery or death)

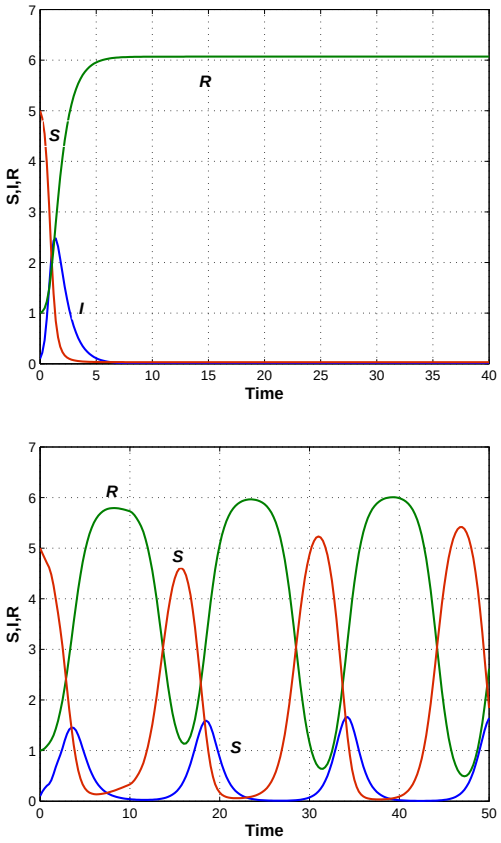

Fig. 5: The left banner shows the solution of the SIR model (9) that illustrate the spread of an infection disease in a population. However, the right banner shows the solution of model (10) with time delays that displays periodic outbreak of the disease.

[48,49]). If we also introduce an incubation period, τ_2, between exposure to infection and becoming infected (say, $\tau_2 = 1$), we can arrive at the model

$$\begin{aligned} S'(t) &= -\beta S(t)I(t-\tau_2) + \gamma I(t-\tau_1), \quad t \geq 0, \\ I'(t) &= \beta S(t)I(t-\tau_2) - \alpha I(t), \quad t \geq 0, \\ R'(t) &= \alpha I(t) - \gamma I(t-\tau_1), \quad t \geq 0. \end{aligned} \tag{10}$$

The solutions of (10) are shown (with initial functions $[S(t),I(t),R(t)]^T = [5,0.1,1]^T$ for $t \leq 0$) in FIGURE 5; we note a periodic outbreak of the disease.

2.3.2 Development of model (10)

If the model allows for a loss of immunity that causes recovered individuals to become susceptible again, we may also consider the more general nonautonomous SIRS epidemic model, with variable periodic coefficients, with distributed delays

$$\begin{aligned} S'(t) =& \Lambda(t) - \beta(t)S(t)\int_0^\infty k(\tau)I(t-\tau)d\tau - \\ & \mu_1(t)S(t) + \xi(t)R(t), \\ I'(t) =& \beta(t)S(t)\int_0^\infty k(\tau)I(t-\tau)d\tau - (\mu_2(t)+\alpha(t))I(t), \\ R'(t) =& \alpha(t)I(t) - (\mu_3(t)+\xi(t))R(t). \end{aligned} \tag{11}$$

Here $N(t) = S(t)+I(t)+R(t)$ denotes the total number of the population at time t. The function $\Lambda(t)$ is the growth rate of the population; function $\beta(t)$ is the daily contact rate, that is the average number of contacts per day; functions $\mu_1(t)$, $\mu_2(t)$, and $\mu_3(t)$ are the instantaneous pro capita mortality rates of susceptible, infective and recovered population, respectively; functions $\alpha(t)$ and $\xi(t)$ are the instantaneous pro capita rates of leaving the infection stage and removed stage, respectively. $k(\tau)$ is the fraction of vector population in which the time taken to become infectious is τ, is assumed to be a nonnegative function on $[0,\infty)$ and satisfies $\int_0^\infty k(\tau)d\tau = 1$ and $\int_0^\infty \tau k(\tau)d\tau < \infty$.

To analyze the dynamics of the models, numerical methods are necessary, as analytical studies can only provide limited results. We next introduce some reliable computational techniques to solve numerically the emerging delay differential models in biosciences.

3 Optimal Control with Delay Models

We mention here that there are many problems in biosciences (such as epidemics, harvesting, chemostat, treatment of diseases, physiological control, vaccination) which can be addressed within an optimal control framework for systems of DDEs [50,51,52,53]. However, the amount of real experience that exists with optimal control problems (OCPs) is still small.

The DDE (2) can be converted into an optimal control problem by adding an $m-$dimensional control term $u(t)$

$$y'(t) = f(y(t),y(t-\tau_1),y(t-\tau_2),\ldots,y(t-\tau_d),u(t),t) \tag{12}$$

and a suitable objective functional (measure): $J_0(u)$

$$\begin{aligned} &\text{Maximize } J_0(u) = \Phi_0(\mathbf{y}(T)) + \\ &\int_0^{t_f} \mathscr{F}(y(t),y(t-\tau_1),y(t-\tau_2),\ldots,y(t-\tau_d),u(t),t)dt, \end{aligned} \tag{13}$$

and subject to control constraint $a \leq u(t) \leq b$, and state constant $y(t) \leq c$, where a and b are the lower and upper bounds. The integrand, $\mathscr{F}(:)$ is called the Lagrangian of objective functional which is continuous in $[0,t_f]$. Additional equality or inequality constraint(s) can be imposed in terms of $J_i(\mathbf{u})$.

OCPs using DDEs were studied in connection with immune responses to infections. In [54], delay model with optimal control is used to describe the interactions

between HIV, CD4+ T cells, and cell-mediated immune response. Both the treatment and the intracellular delay are incorporated into the model in order to improve therapies to cure HIV infection. The optimal controls represent the efficiency of drug treatment in inhibiting viral production and preventing new infections.

A humoral immune response model was considered in the paper [52] on determining optimal intravenous drug delivery in AIDS patients. The objective was to find a control strategy that minimizes the total drug administered subject to the constraint that patient recovers. In this paper, we present a delay differential model with optimal control that describes the interactions of the tumour cells and immune response cells with external therapy. The optimal control variables are also incorporated to identify the best treatment strategy and block producing new tumour cells with minimum side effects, by keeping the number of normal cells above 75% of its carrying capacity. Assume that $E(t)$ represents effector cells population, such as CD8$^+$T cells and $T(t)$ is the tumour cells population. The authors in [38] provide a competing model in terms a system of DDEs, in which we add extra variables namely chemotherapy variable, $u(t)$, normal cells, $N(t)$ and two control variables $v(t)$ and $w(t)$. We also assume a homogeneity of the tumour cells, then the model takes the form

$$\begin{aligned}
\frac{dE(t)}{dt} &= \sigma + \frac{\rho E(t-\tau)T(t-\tau)}{\eta + T(t-\tau)} - \mu E(t-\tau)T(t-\tau) - \\
&\quad \delta E(t) - a_1(1-e^{-u})E(t) + w(t)s_1, \\
\frac{dT(t)}{dt} &= r_2 T(t)(1-\beta T(t)) - nE(t)T(t) - \\
&\quad c_1 N(t)T(t) - a_2(1-e^{-u(t)})T(t), \\
\frac{dN(t)}{dt} &= r_3 N(t)(1-\beta_2 N(t)) - c_2 T(t)N(t) - \\
&\quad a_3(1-e^{-u(t)})N(t), \\
\frac{du(t)}{dt} &= v(t) - d_1 u(t).
\end{aligned} \tag{14}$$

The general goal is to keep the patient healthy while killing the tumour. Since our model takes into account the toxicity of the drug to all types of cells, our control problem consists of determining the variables $v(t)$ and $w(t)$ that will maximize the amount of effector cells and minimize the number of tumour cells and the cost of the control with the constraint that we do not kill too many normal cells. Therefore, our objective is to maximize the functional (see [55])

$$J(v,w) = \int_0^{t_f} \left(E - T - \left[\frac{B_v}{2}[v(t)]^2 + \frac{B_w}{2}[w(t)]^2 \right] \right) dt, \tag{15}$$

where where B_u, B_w are, respectively, the weight factors that describe the patient's acceptance level of chemotherapy and immunotherapy with a constraint

$$k(E,T,N,u,E_\tau,T_\tau,v) = N - 0.75 \geq 0, \quad 0 \leq t \leq t_f. \tag{16}$$

We are seeking optimal control pair (v^*, w^*) such that

$$J(v^*, w^*) = \max\{J(v,w) : (v,w) \in W\}, \tag{17}$$

where W is the control set defined by

$$\begin{aligned}
W = &\{(v,w) : (v,w) \text{ piecewise continuous, such that} \\
&0 \leq v(t) \leq v_{max} < \infty, ; 0 \leq w(t) \leq w_{max} < \infty, \forall t \in [0, t_f]\}.
\end{aligned} \tag{18}$$

The existence of optimal controls $v^*(t)$ and $w^*(t)$ for this model is guaranteed by standard results in Optimal Control Theory [56]. Necessary conditions that the controls must satisfy are derived via Pontryagins Maximum Principle. The optimal control problem given by expressions (14)-(18) is equivalent to that of minimizing the Hamiltonian $\mathscr{H}$:

$$\begin{aligned}
\mathscr{H}(t,E,T,E_\tau,T_\tau,u,v,w,\lambda) &= E - T - \frac{B_v}{2}[v(t)]^2 - \\
&\frac{B_w}{2}[w(t)]^2 + \lambda_1 \frac{dE}{dt} + \lambda_2 \frac{dT}{dt} + \lambda_3 \frac{dN}{dt} + \lambda_4 \frac{du}{dt} + \gamma k
\end{aligned} \tag{19}$$

and $\gamma \geq 0$ with $\gamma(t)k(t) = 0$, where

$$\gamma = \begin{cases} 1 & \text{if } N(t) \leq 0.75, \\ 0 & \text{otherwise} \end{cases}$$

A standard application of Pontryagins Maximum Principle [57] leads to the following result:

Theorem 3. *There exists an optimal pair $v^*(t)$ and $w^*(t)$ and corresponding solutions E^*, T^*, N^* and $u*$ and that minimizes $J(u(t),w(t))$ over Ω. The explicit optimal controls are connected to the existence of continuous specific functions λ_i for $i = 1,2,3,4$ satisfying the adjoint system*

$$\begin{aligned}
\lambda_1'(t) &= -1 + \lambda_1(t)\left[\delta + a_1(1-e^{-u^*})\right] + \\
&\quad \lambda_2(t) n T^* + \lambda_1(t+\tau)\chi_{[0,t_f-\tau]}\left[\mu T^* - \frac{\rho T^*}{\eta + T^*}\right], \\
\lambda_2'(t) &= 1 + \lambda_2\left[-r_2 + 2r_2\beta T^* + nE^* + c_1 N^* + a_2(1-e^{-u^*})\right] + \\
&\quad \lambda_3 c_2 N^* + \chi_{[0,t_f-\tau]}\lambda_1(t+\tau)\left[\frac{\rho E^* T^*}{(\eta+T^*)^2} - \frac{\rho E^*}{\eta + T^*} + \mu E^*\right], \\
\lambda_3'(t) &= \lambda_2 c_1 T^* - \lambda_3\left(r_3 - 2r_3\beta_2 N^* - c_2 T^* - a_3(1-e^{-u^*})\right) - \gamma, \\
\lambda_4'(t) &= -\lambda_1(t) a_1 e^{-u^*} E^* + \lambda_2(t) a_2 e^{-u^*} T^* + \lambda_3(t) a_3 e^{-u^*} N^* + \lambda_4(t) d_1,
\end{aligned} \tag{20}$$

with transversality conditions

$$\lambda_i(t_f) = 0, \ i = \{1,2,3,4\} \ \text{and} \ \chi_{[0,t_f-\tau]} = \begin{cases} 1 & \text{if } t \in [0, t_f - \tau], \\ 0 & \text{otherwise.} \end{cases} \tag{21}$$

Furthermore, the following properties hold

$$v^* = \min\left(v_{max}, \frac{\lambda_4}{B_v}\right), \quad w^* = \min\left(w_{max}, \frac{\lambda_1 s_1}{B_w}\right). \tag{22}$$

The numerical simulations leading to the approximation of the optimal controls, are carried out using forward and backward Euler methods. Starting with

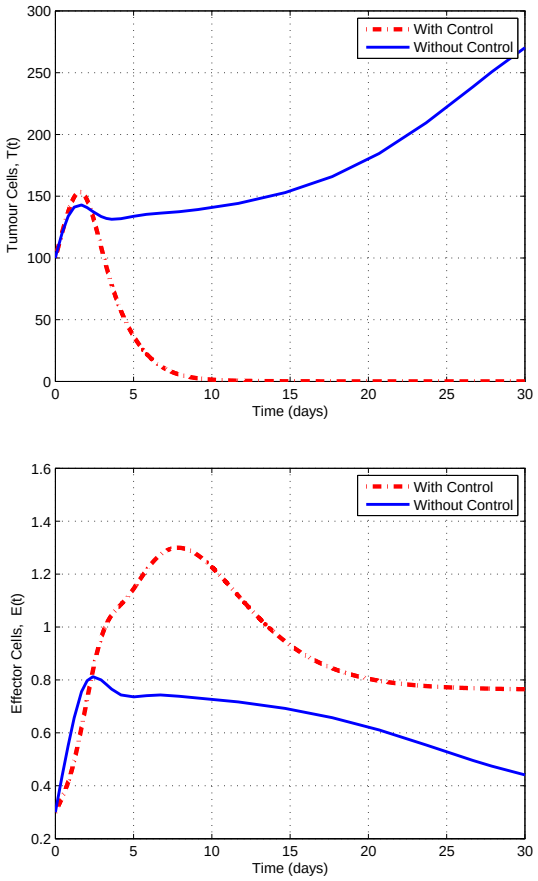

Fig. 6: Simulations of the tumour cells population of system (14), before and after the imuno-chemotherapy treatments with controls. It shows that the tumour cells population can be eradicated in day 10.

an initial guess for the value of the controls on the time interval $[0,t_f]$, we solve the state system with controls (14) using forward Euler. Next, the adjoint system is solved using the solutions of the state system and the transversality conditions (20) backward in time. It has been shown from Figure 6 that the tumour cells can be eradicated at day 10. The numerical simulations show the rationality of the model presented, which in some degree meets the natural facts.

4 Parameter Estimation with DDEs

Consider even a predictive DDE model of *neutral* type, parameterized by $\mathbf{p}\in\mathbb{R}^L$ which are estimated using a given set of observations,

$$\begin{aligned}&\mathbf{y}'(t)=\mathbf{f}(t,\mathbf{y}(t),\mathbf{y}(t-\tau),\mathbf{y}'(t-\tau);\mathbf{p}),\quad t\in[0,T],\\&\mathbf{y}(t)=\psi(t,\mathbf{p}),\quad \mathbf{y}'(t)=\phi(t,\mathbf{p}),\quad t\in[-\tau,0].\end{aligned}\tag{23}$$

In (23), 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 ($L'\le L$, $M'\le M$). $\psi(t)$ and $\phi(t)$ are given continuous functions.

Suppose that N observations, $\{t_j;Y_j^i\}_{j=1}^N$, have been obtained. We are concerned with applying to these data a system of NDDEs (23). The model-fitting problem is then select a value or a set values for $\mathbf{p}$ for which the function $\mathbf{y}(t;\widehat{\mathbf{p}})$ provides a 'best' fit, at arguments $t=t_j$, to the given set $\{Y_j^i\}_{j=1}^N$ ($1\le i\le M$). 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 [58].

There is a variety of methods for regression analysis and interpretation of statistical properties of estimation schemes [59,60]. The discussion here will be based on the use of *weighted least squares* (WLS) or a *log-least squares* (LLS) approach for finding the best-fit parameter values to observed data in the NDDE models. When determining the best fit by the WLS process, we suppose that the unknown parameter $\widehat{\mathbf{p}}$ is the value of $\mathbf{p}$ minimizing the weighted objective function:

$$\Phi_W(\mathbf{p})=\sum_{i=1}^{M}\sum_{j=1}^{N}\left[y^i(t_j,\mathbf{p})-Y_j^i\right]^2 w_{ij},\tag{24}$$

where $\mathbf{w}_j$ are the weights (possibly related to the accuracy of the data points)[5]. When $\mathbf{w}_j=1$, this is the method of unweighted or *ordinary least squares* (OLS).

If we adapt the LLS approach, the objective function may take the form

$$\Phi_L(\mathbf{p})=\sum_{i=1}^{M}\sum_{j=1}^{N}\left[\log y^i(t_j,\mathbf{p})-\log Y_j^i\right]^2.\tag{25}$$

The choice of LLS in model-fitting problem may decrease the exponential nonlinearity of model predictions with respect to $\mathbf{p}$. (It will be assumed that $y^i(t_j,\mathbf{p})>0$.) Another significant feature of the LLS approach is that small relative changes in large data values can be unduly weighted. For comparing between different formulae of objective functions, we refer to Sheiner *et al.* (1985). (The optimum parameter $\widehat{\mathbf{p}}$ is taken to be the value such that $\Phi(\widehat{\mathbf{p}})\le\Phi(\mathbf{p})$, for all physically meaningful values of $\mathbf{p}$ and $\widehat{\mathbf{p}}$.)

When the predictions are governed by models of the form (23), then the *least squares* (LS) approach (even for models linear in their parameters) usually leads to a nonlinear minimization problem, since the cost function is no longer quadratic. Numerical algorithms for nonlinear LS approach are generally iterative procedures for searching the parameter estimates and require initial starting values. An obvious difficulty is that there is the possibility of the iterative scheme converging to a local

[5] The choice of the values $\mathbf{w}_j$ is best based on knowledge of the relative precision of the $\mathbf{Y}_j$.

minimum, or not converging at all, rather than achieving the desired global minimum. Thus, an appropriate choice of the objective function is a significant factor in determining the ease of solving the parameter estimation problem [61].

Given a set of experimental data, $\{Y_j\}_{j=1}^{N}$, the technique for finding the best-fit parameter values for a given mathematical model and objective function consists of the following steps: (*i*) Provide an initial guess $\mathbf{p_0}$ for the parameter estimates; (*ii*) Solve the model equations, using `Archi` code [62] with the current values of the parameters and calculate the corresponding objective function $\Phi(\mathbf{p})$; (*iii*) The parameter values are then adjusted (by the minimization routine, for example `E04USF`[6] from `NAG` library; (*iv*) When no further reduction in the value $\Phi(\mathbf{p})$ is possible, the best fit parameter values have been found; (*v*) Determine whether the chosen set of parameter values is acceptable (and meaningful) or unacceptable by comparing the objective function value to a given criterion for the objective function or the estimates [38].

Note that $\Phi(\mathbf{p})$ can have several local minima and that a good code and/or good starting initial parameter values can be of great assistance, both in accelerating the minimization process and finding the global minimum. Local minimum can also be avoided by repeating the iterative scheme for a variety of different initial estimates of parameter vector. We should also draw attention to the fact that, even if the right hand side of (23) and the initial functions are smooth functions, a discontinuity in the first time derivative of the solution appears at time t_0 and is propagated through the time. The higher derivatives become smoother as time increases. Additional jumps can arise due to discontinuities in the initial functions. These discontinuities propagate into partial derivative of $\Phi(\mathbf{p})$ with respect to p_i, via solution values $\mathbf{y}(t,\mathbf{p})$. Thus, for correct numerical parameter estimates in DDEs or NDDEs attention should be paid to the position of the jumps and the differentiability of state variable with respect to the time-lag τ.

5 Sensitivity Analysis

Of considerable importance in assessing the model (23), 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 variational of parameter to evaluate the analysis of sensitivity for DDEs or NDDEs.

The *variational approach* is to derive, analytically, general sensitivity coefficients for minor changes in the parameters, time delays, and initial data in the model. 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 (2003) 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. Rihan (2010) extended the approach to include a dynamic system described by a system of NDDEs.

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 (23). 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

$$\delta y_i(t)=\sum_j \frac{\partial y_i(t)}{\partial \alpha_j}\delta\alpha_j+O(|\alpha|^2). \tag{26}$$

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:

$$\delta y_i(t^*)=\int_0^{t^*}\frac{\partial y(t^*)}{\partial\alpha_j(t)}\delta\alpha_j(t)dt,\qquad t<t^*. \tag{27}$$

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 (23), we write

$$\mathbf{f}(t)=\mathbf{f}(t,\mathbf{y}(t),\mathbf{y}(t-\tau),\mathbf{y}'(t-\tau),\mathbf{p}). \tag{28a}$$

$$A^*(t)=\frac{\partial}{\partial\mathbf{y}}\mathbf{f}(t,\mathbf{y}(t),\mathbf{y}(t-\tau),\mathbf{y}'(t-\tau),\mathbf{p}). \tag{28b}$$

$$B^*(t)=\frac{\partial}{\partial\mathbf{y}_\tau}\mathbf{f}(t,\mathbf{y}(t),\mathbf{y}(t-\tau),\mathbf{y}'(t-\tau),\mathbf{p}). \tag{28c}$$

$$C^*(t)=\frac{\partial}{\partial\mathbf{y}'_\tau}\mathbf{f}(t,\mathbf{y}(t),\mathbf{y}(t-\tau),\mathbf{y}'(t-\tau),\mathbf{p}). \tag{28d}$$

$$D^*(t)=\frac{\partial}{\partial\mathbf{p}}\mathbf{f}(t,\mathbf{y}(t),\mathbf{y}(t-\tau),\mathbf{y}'(t-\tau),\mathbf{p}). \tag{28e}$$

Theorem 4.*If* $\mathbf{W}(t)$ *is an n-dimensional adjoint function which satisfies the differential equation*

$$\begin{aligned}\mathbf{W}'(t)&=-A^*(t)^T\mathbf{W}(t)-B^*(t)^T\mathbf{W}(t+\tau)+\\&\qquad C^*(t)^T\mathbf{W}'(t+\tau),\quad t\le t^*,\\\mathbf{W}(t)&=\mathbf{W}'(t)=0,\quad t>t^*;\\\mathbf{W}(t^*)&=[0,\dots,0,1_{ith},0\dots,0]^T,\mathbf{W}'(t^*)=0,\end{aligned} \tag{29}$$

[6] `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 1: Parameter estimates for the growth model (31) that best fits data of Figure 7.

ρ_0	ρ_1	τ	$\|Error\|_2$
- 0.0518	0.1054	95.33	34.41

then the functional derivative sensitivity functions of NDDEs (23) can be expressed by the formulae

$$\frac{\partial y_i(t^*)}{\partial \mathbf{y}_0} = \mathbf{W}(0), \tag{30a}$$

$$\frac{\partial y_i(t^*)}{\partial \mathbf{p}} = \int_0^{t^*} \mathbf{W}^T(t) D^*(t) dt, \quad t \le t^*, \tag{30b}$$

$$\frac{\partial y_i(t^*)}{\partial \tau} = -\int_{-\tau}^{t^*-\tau} \mathbf{W}^T(t+\tau)\left[B^*(t+\tau)\mathbf{y}'(t) + C^*(t+\tau)\mathbf{y}''(t)\right] dt, \tag{30c}$$

$$\frac{\partial y_i(t^*)}{\partial \psi(t)} = A^*(t+\tau)\mathbf{W}(t+\tau), \quad t \in [-\tau, 0). \tag{30d}$$

*Proof.*See Rihan (2010).

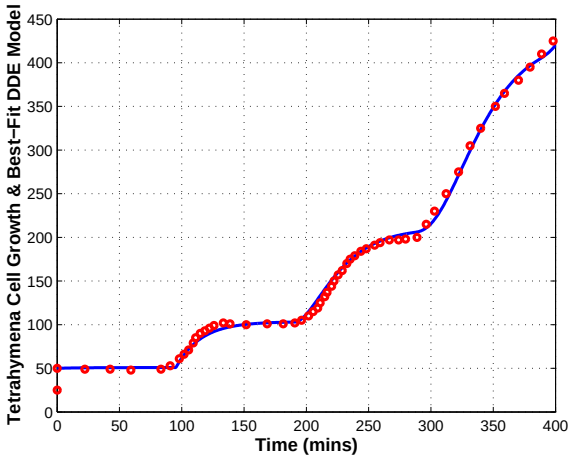

Fig. 7: The circles, Y_i, represents the data for growth of a population of $Y_0 = 50$ of newborn cells of *Tetrahymena pyriformis*. This data represents the multiplication of 25 cells in perfect division synchrony at first population doubling. The line, $y(t,p)$, shows the prediction of the perfect model that based on the NDDE (31), with $y(0) = 50$, $y(t) = 25$ for $t < 0$, and best fit parameters given in Table 1. The initially synchronized cell population becomes desynchronized over time.

5.1 Application to cell growth problem

We apply the above analysis to fit a time-lag model to the growth of a population of Tetrahymena pyriformis (where the experimental data is given in the Figure 7), and evaluate its sensitivity functions.

The cells in the culture of Tetrahymena pyriformis (displayed in Fig. 7) are initially homogeneous and synchronized. This synchronized cell population becomes desynchronized over time. The total observed population as function of time of 50 cells which at time $t = 0$ are newborn is shown in Fig. 7. According to the above analysis, we can model this growth by a parameterized linear NDDE

$$\begin{aligned} &y'(t) = \rho_0 y(t) + \rho_1 y(t-\tau) + \rho_2 y'(t-\tau), \quad t \ge 0, \\ &y(t) = \psi(t),\ y'(t) = \psi'(t), \quad t \in [-\tau, 0], \quad y(0) = y_0. \end{aligned} \tag{31}$$

One possible meaning of the parameters of (31) is 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). We adopt the Log Least Squares Approach (25) to fit model (31) to the observations given in Figure 7 to estimate the unknown parameters. 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 7 displays model prediction for the best fit parameters given in Table 1. Prescott (1959) [63] measured the *generation times*[7] 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 $\widetilde{\tau}$ was 111 min, which is close to estimated value of the best fit, $\tau = 96.33$; see Table 1.

We apply the analysis of Section 3 to find analytically the sensitivity functions $\frac{\partial y(t^*)}{\partial \psi(t)}$ & $\frac{\partial y(t^*)}{\partial \alpha_i}$ $(t \le t^*)$, where $\alpha = [\rho_0, \rho_1, \rho_2, y_0]^T$. In (31) $\alpha = [\rho_0, \rho_1, \rho_2, y_0, \tau]^T$. The adjoint equation for this case is

$$\begin{aligned} &W'(t) = -\rho_0 W(t) - \rho_1 W(t+\tau) + \rho_2 W'(t+\tau),\ t \le t^*, \\ &W(t) = 0, \quad t > t^*; \quad W(t^*) = 1. \end{aligned} \tag{32}$$

The analytical solution of the adjoint Eq (32) is as follows:

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

$$W(t) = e^{-\rho_0(t-t^*)}, \quad t \le t^*, \tag{33}$$

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

$$W(t) = \begin{cases} e^{-\rho_0(t-t^*)} - b(t-t^*+\tau)e^{-\rho_0(t-t^*+\tau)}, & 0 < t \le t^* - \tau, \\ e^{-\rho_0(t-t^*)}, & t^* - \tau < t \le t^*. \end{cases} \tag{34}$$

[7] *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.

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 (31), with an initial function $\psi(t)=y_m$ ($\psi'(t)=0$), is

$$y(t)=\begin{cases} ae^{\rho_0 t}-y_m\xi, & 0<t\le\tau,\\ ae^{\rho_0 t}-[y_m\xi-ab(t-\tau)+ & \\ \quad y_m\xi^2]e^{\rho_0(t-\tau)}+y_m\xi^2, & \tau<t\le 2\tau, \end{cases} \tag{35}$$

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 (30d), becomes:

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

$$\frac{\partial y(t^*)}{\partial\psi(t)}=\rho_1 W(t+\tau)=\begin{cases}\rho_1 e^{-\rho_0(t-t^*+\tau)}, & -\tau<t\le t^*-\tau,\\ 0, & t^*-\tau<t\le 0.\end{cases} \tag{36}$$

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

$$\frac{\partial y(t^*)}{\partial\psi(t)}=\begin{cases}\rho_1 e^{-\rho_0(t-t^*+\tau)}- & \\ \rho_1 b(t-t^*+2\tau)e^{-\rho_0(t-t^*+2\tau)}, & -\tau<t\le t^*-2\tau,\\ \rho_1 e^{-\rho_0(t-t^*+\tau)}, & t^*-2\tau<t\le 0.\end{cases} \tag{37}$$

While the sensitivity function of $y(t)$ to the initial condition $y(0)$, that given by the formula (30a), is

$$\frac{\partial y(t^*)}{\partial y(0)}=W(0)=\begin{cases} e^{\rho_0 t^*}, & 0<t^*\le\tau,\\ e^{\rho_0 t^*}+b(t^*-\tau)e^{\rho_0(t^*-\tau)}, & \tau<t^*\le 2\tau.\end{cases} \tag{38}$$

The sensitivity function of $y(t)$ to the constant parameter $\rho_0(\equiv\dfrac{1}{\eta})$, by using (30b), takes the form:

$$\frac{\partial y(t^*)}{\partial\rho_0}=\int_0^{t^*}W(t)\frac{\partial F}{\partial\rho_0}dt=$$
$$\begin{cases}(at^*-y_m\xi\eta)e^{\rho_0 t^*}+y_m\xi\eta, & 0<t^*\le\tau,\\ \mathbf{I}, & \tau<t^*\le 2\tau,\end{cases} \tag{39}$$

where

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

(Similarly, we can deduce $\partial y(t^*)/\partial\rho_1$ & $\partial y(t^*)/\partial\rho_2$.) By using (30c), we obtain the sensitivity of $y(t)$ to small perturbations in the time-lag parameter τ as:

$$\frac{\partial y(t^*)}{\partial\tau}=$$
$$-\int_{-\tau}^{t^*-\tau}W(t+\tau)\left[\frac{\partial\mathbf{f}(t+\tau)}{\partial\mathbf{y}_\tau}\mathbf{y}'(t)+\frac{\partial\mathbf{f}(t+\tau)}{\partial\mathbf{y}'_\tau}\mathbf{y}''(t)\right]dt$$
$$=\begin{cases}0, & 0<t^*\le\tau,\\ -\rho_0 ab(t^*-\tau)e^{\rho_0(t^*-\tau)}, & \tau<t^*\le 2\tau,\end{cases} \tag{40}$$

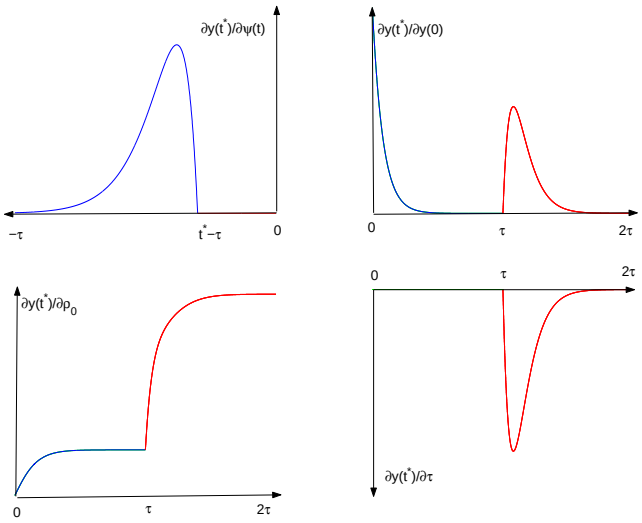

Fig. 8: Shows general sensitivity functions, $\partial y(t^*)/\partial\psi(t)$, $\partial y(t^*)/\partial y_0$, $\partial y(t^*)/\partial\rho_0$, and $\partial y(t^*)/\partial\tau$, for the NDDE (31).

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

We notice from the formula (40) 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 $[0,\ \tau]$. The plots (see FIG. 8) have a kink at $t=\tau$ due to the existence of the delay in the system. We may also remark from Eq (35), that if $y_0\neq y_m$, then $\partial y(t_i)/\partial\tau$ has a jump at $t_i=\tau$. Thereafter attention has to be directed to the objective function when τ is a parameter to be estimated.

6 DDE Solvers and Available Softwares

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

The earliest, simple, numerical methods for DDEs (2) utilized the *Euler* or classical fourth-order *RK* methods

with a constant step-size, supplemented with linear interpolation schemes for the retarded terms. Such adaptations provided minimally effective means for solving models numerically: they had no error control, used fixed step-size, and had problems coping with "stiffness". Numerical analysts are now in a position to cite published algorithms for the numerical solution of DDEs. Several packages and software are available for the numerical integration and/or the study of bifurcations in delay differential equations. Here is a short list for available software:

-Archi (Paul [62]) simulates a large class of functional differential equations.
-DDE23 (Shampine, S. Thompson [64]) simulates retarded differential equations with several fixed discrete delays.
-RADAR5 (Guglielmi, Hairer [65]) simulates stiff problems, including differential-algebraic and neutral delay equations with constant or state-dependent (eventually vanishing) delay.
-DKLAG6 (Thompson [66]) simulates retarded and neutral differential equations with state dependent delays.
-MIDDE (Rihan,*et al.* [67]) simulates stiff and non-stiff delay differential equations & Volterra delay integro-differential equations, using mono-implicit RK methods.
–BIFDD (Hassard [68]) (Fortran 77) normal form analysis of Hopf bifurcations of differential equations with several fixed discrete delays.
–DDE-BIFTOOL (Engelborghs [69]) (MatLab) allows computation and stability analysis of steady state solutions, their fold and Hopf bifurcations and periodic solutions of differential equations with several fixed discrete delays.

For further study of some related issues to the numerical treatments of DDEs, we refer to [6, 70].

7 Concluding Remarks

In this paper, we provided a set of delay differential equations in biosciences. Delay differential equations exhibit much more complicated dynamics than ordinary differential equations since a time delay could cause a stable equilibrium to become unstable and cause the populations to fluctuate. One requires realistic mathematical models that should be quantitatively and qualitatively consistent with the biological phenomena and experimental data. We have seen that delay models of real-phenomena have more interesting dynamics than equations that lack memory-effects. The numerical results show that the optimal treatment strategies reduce the tumour cells load and increase the effector cells after few days of therapy. The numerical simulations show the rationality of the model presented, which in some degree meets the natural facts.

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 literature on this subject is very broad and we cannot quote many interesting papers, as an exhaustive list of references is not possible in this short entry.

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