A PARAMETER SENSITIVITY METHODOLOGY IN THE CONTEXT OF HIV DELAY EQUATION MODELS

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ABSTRACT. A sensitivity methodology for nonlinear delay systems arising in one class of cellular HIV infection models is presented. Theoretical foundations for a typical sensitivity investigation and illustrative computations are given.

1. INTRODUCTION

1.1. **Background.** Over the past several years, the use of mathematical models as an aid in understanding features of HIV and other virus infection dynamics has been substantial. Several papers published in the mid nineties provided strong evidence for the high rate of HIV-1 replication and clearance in infected individuals [16, 37, 51]. By the end of the decade, the general consensus was that *in vivo*, on the order of 10^{10} virions are assembled and cleared every day [25, 35, 39]. In many of these papers, the viral clearance rate c was identified by modeling the disease pathogenesis with a system of deterministic differential equations, numerically calculating a solution, and then fitting the results with experimental data (using a nonlinear least squares (NLS) approach), e.g., see [35, 37, 39]. The existence of such a high replication/clearance rate implies a high mutation rate, thus indicating that pharmacological mono-therapy will ultimately fail, since the virus can rapidly manifest a resistance to any one drug. More importantly, this knowledge directly contributed to the current practice of simultaneously administering multiple drugs to HIV positive individuals in an effort to counteract the high mutation rate of the virus.

Following its success in helping to identify this significant feature of the HIV pathogenesis, the use of mathematical modeling and parameter identification in the study of HIV experienced a dramatic increase. In particular, in the wake of the publication of [37], there were papers covering everything from additional and/or alternative compartment formulations [7, 21, 27, 28, 32, 38, 41, 52, 56, 57] to arguments for and against the use of delay differential equations in modeling the *eclipse phase* [12, 13, 15, 24, 26, 29, 30, 31] (including those that addressed the solution stability [30, 31, 44]). Moreover, in the context of delay equations, many of these papers focused heavily on the inter-relationship between the parameters describing the drug efficacy η, the length of the eclipse phase τ, the infected T-cell death rate δ, and the virion clearance rate c [12, 15, 24, 26, 29, 30, 31, 44]. The purpose of this paper is to illustrate our approach, which allows one to develop new

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insights into HIV pathogenesis by utilizing a mathematical tool not typically associated with conventional NLS techniques. Indeed, there is a precedence for this approach, as is evidenced by previous papers within the HIV modeling literature that make use of stochastic analysis and inference [18, 45, 46, 49, 54, 58], control theory [19, 53], and nonlinear analysis [14, 50]. Note that the above survey is not intended to be comprehensive, as there already exist thorough reviews of the field presented in [33, 34, 36].

For *any* system of differential equations designed to model real world phenomena, whether it be biological, chemical, or physical, a common goal is to understand the manner in which the system's constitutive parameters influence its solution. These parameters (such as δ above) are designed to correspond to aspects of the phenomena under investigation (e.g., HIV pathogenesis), and thus it is desirable to predict how changes in the parameters will affect the solution. Indeed, there are several papers in the HIV modeling field which focus heavily on the topic (good examples include [41, 43]). One way to address this question is to perform a *sensitivity analysis*, a mathematical tool developed in the context of modern control theory and commonly used in mechanical, aerospace, electrical, and structural engineering. The precursor of this technique can be traced back to an 1833 electrostatics experiment designed to measure the inductance of certain metals [8]. However, significant activity in this area only arose in the middle part of this century, concomitant with the development of modern control theory in the late 1930's. In our analysis, we will employ the *semirelative* sensitivity function, though there are other possibilities, such as the *logarithmic* sensitivity function advocated by Bode in his book on electrical network analysis [5]. We direct the interested reader to the following introductory texts [10, 11], advanced texts [20, 47, 48, 55], and surveys of the field [1, 9]. We also note that the sensitivity analysis described in this paper should not be confused with the statistical technique of the same name and based on Latin Hypercube Sampling [4, 17].

1.2. **Approach.** The first step in the sensitivity analysis is to derive the *sensitivity equations* by formally taking derivatives (with respect to a parameter of interest) on both sides of the original equation(s). The solution to this new system (assuming for the moment it is well-posed) contains information regarding the sensitivity of the original system to perturbations in the chosen parameter (around some *a priori* fixed value of that parameter). Hereafter we will refer to the solution to the sensitivity equations as a *sensitivity function.*

To illustrate the sensitivity procedure, we will examine an HIV population system with compartments described in [3], summarized in Table 1, and denoted by the vector $x = (V, A, C, T)^T$. In this case (see [3] for details), our system of distributed delay differential equations is

$$\begin{aligned} \dot{x}(t) &= L(x(t), x_t) + f_1(x(t)) + f_2(t) \qquad \text{for } 0 \leq t \leq t_f \\ (x(0), x_0) &= (\Phi(0), \Phi) \in \mathbb{R}^4 \times \mathscr{C}(-r, 0; \mathbb{R}^4)\,, \end{aligned} \tag{1.1}$$

where r and t_f are finite, x_t denotes the function $\theta \mapsto x(t+\theta)$, $\theta \in [-r, 0]$, and for $(\eta, \phi) \in \mathbb{R}^4 \times \mathscr{C}(-r, 0; \mathbb{R}^4)$,

$$
\begin{aligned}
L(\eta,\phi) &= \begin{bmatrix} -c & 0 & n_C & 0 \\ 0 & r_v-\delta_A & 0 & 0 \\ 0 & 0 & r_v-\delta_C & 0 \\ 0 & 0 & 0 & r_u-\delta_u \end{bmatrix} \eta + n_A \left[\delta_{(1,2)}\right]_{(4,4)} \int_{-r}^{0} \phi(\theta) dP_1(\theta) \\
&\quad + \gamma\left(\left[\delta_{(3,2)}\right]_{(4,4)} - \left[\delta_{(2,2)}\right]_{(4,4)}\right) \int_{-r}^{0} \phi(\theta) dP_2(\theta)\,, \\
f_1(\eta) &= \begin{bmatrix} -p\eta_1\eta_4 \\ -\delta(\sum_{i=2}^4 \eta_i)\eta_2 + p\eta_1\eta_4 \\ -\delta(\sum_{i=2}^4 \eta_i)\eta_3 \\ -\delta(\sum_{i=2}^4 \eta_i)\eta_4 - p\eta_1\eta_4 \end{bmatrix}, \\
f_2(t) &= [0,0,0,S]^T \ , \ 0 \le t \le t_f\,.
\end{aligned}
$$

Here the compartments in x and the parameters (including the probability distributions P_1, P_2) given in the vector $q = (c, r_v, r_u, n_A, n_C, \delta, \delta_A, \delta_C, \delta_u, \gamma, p, P_1, P_2, S)^T$ are all described in [3]. A full and thorough sensitivity analysis could include not only derivatives with respect to the scalar parameters (e.g., γ or δ_A), but also Fréchet derivatives with respect to the delay distributions (e.g., P_1 or P_2). The following sections include discussions regarding the well-posedness of the sensitivity equations and an example numerical simulation as well as an interpretation of the results.

Notation	*Description*
V	Infectious viral population
A	Acutely infected cells
C	Chronically infected cells
T	Uninfected or target cells

TABLE 1. *in vitro* model compartments

2. THEORY

For those interested in the mathematical considerations, this section contains theoretical foundations for the well-posedness of the sensitivity equations. While the results presented here are important because they legitimize our study of these equations, understanding the techniques in the proofs are not essential to appreciating the simulations and results presented in Section 3. Therefore, those readers who wish to skip the details in this section may do so with little loss in understanding the formal aspects of sensitivity analyses.

For our illustrative discussions, we will only consider distributions P_1, P_2 that are both differentiable and parameterizable by a mean μ and a standard deviation σ (i.e., for $i = 1, 2$, $p_i(\theta) = \frac{\partial}{\partial\theta}P_i(\theta)$ and $P_i(\theta) = P_i(\theta; \mu_i, \sigma_i)$ for $\theta \in [-r, 0]$). Moreover, we further assume that the resulting densities p_i are $\mathscr{C}^1$ in μ_i and σ_i, respectively. To illustrate a sensitivity analysis, let us fix the forms of the distributions P_1, P_2 and consider for $t \in [-r, t_f]$, the derivative of $x(t; \mu_1)$ with respect to μ_1 (where μ_1 is the parameter corresponding to the mean of p_1). If we let $(\eta,\phi) \in \mathbb{R}^4 \times \mathscr{C}(-r,0;\mathbb{R}^4)$, $t \in [0,t_f]$, $\mu_1 > 0$, then from results established in [6], we note that $\mathscr{F}(t,\eta,\phi,\mu_1) = L(\eta,\phi;\mu_1) + f_1(\eta) + f_2(t)$ is $\mathscr{C}^1$ in t, η, ϕ, and μ_1 under smoothness assumptions (detailed in [3]) on $\mathscr{F}$, L, f_1, and f_2. For our specific case, to prove that the derivative of x with respect to μ_1 exists and is continuous in t, we will make use of the following lemma.

Lemma 2.1. *There exists a solution to*

$$\begin{aligned} \dot{y}(t) &= g_1(x(t;\mu_1);y(t)) + g_2(\mu_1;y_t) + g_3(x_t(\mu_1),\mu_1;1) \qquad \textit{for } 0 \le t \le t_f \\ (y(0),y_0) &= (\Psi(0),\Psi) \in \mathbb{R}^4 \times \mathscr{C}(-r,0;\mathbb{R}^4)\,, \end{aligned} \tag{2.1}$$

for $x(t;\mu_1)$ the solution to (1.1), and where for $\mu,\xi \in \mathbb{R}$, $\eta,\zeta \in \mathbb{R}^4$, $\phi,\psi \in \mathscr{C}(-r,0;\mathbb{R}^4)$,

$$\begin{aligned} g_1(\eta;\zeta) &= M_\eta \zeta\,, \\ g_2(\mu;\psi) &= n_A \left[\delta_{(1,2)}\right]_{(4,4)} \int_{-r}^{0} \psi(\theta) p_1(\theta;\mu,\sigma_1) d\theta \\ &\quad + \gamma(\left[\delta_{(3,2)}\right]_{(4,4)} - \left[\delta_{(2,2)}\right]_{(4,4)}) \int_{-r}^{0} \psi(\theta) p_2(\theta;\mu_2,\sigma_2) d\theta \\ g_3(\phi,\mu;\xi) &= n_A \left[\delta_{(1,2)}\right]_{(4,4)} \int_{-r}^{0} \phi(\theta) (\frac{\partial}{\partial \mu_1} p_1(\theta;\mu,\sigma_1))(\xi) d\theta\,, \end{aligned}$$

and where

$$M_\eta = \begin{bmatrix} -c - p\eta_4 & 0 & n_C & -p\eta_1 \\ p\eta_4 & r_v - \delta_A - \delta(2\eta_2 + \eta_3 + \eta_4) & -\delta\eta_2 & -\delta\eta_2 + p\eta_1 \\ 0 & -\delta\eta_3 & r_v - \delta_C - \delta(\eta_2 + 2\eta_3 + \eta_4) & -\delta\eta_3 \\ -p\eta_4 & -\delta\eta_4 & -\delta\eta_4 & r_u - \delta_u - \delta(\eta_2 + \eta_3 + 2\eta_4) - p\eta_1 \end{bmatrix}.$$

Proof: On the right side of (2.1), the function $g_1 + g_2 + g_3$ satisfies both the differentiability condition (Lemma 4.1) and the global Lipschitz condition (Lemma 4.2) from [3]. Following the reasoning in the proof of Theorem 4.5 in the same reference, by defining a convergent sequence of successive approximations, it can then easily be shown that a solution exists and is unique.

Remark 2.2. Note that Lemma 2.1 guarantees the existence of a solution to a system of equations with a *general* initial condition Ψ. Recall that in equation (1.1), the initial condition Φ is independent of μ_1 and thus the next step will be to argue that system (2.1) combined with the trivial initial condition $\Psi = 0$ comprises the sensitivity equations.

Theorem 2.3. *For the solution x of (1.1), x has a derivative with respect to the parameter μ_1 and for $\mu_1 = \mu > 0$, this derivative $v(t) = \frac{\partial}{\partial \mu_1} x(t;\mu)$ satisfies (2.1) with the initial condition $(\Psi(0),\Psi) = (0,0) \in \mathbb{R}^4 \times \mathscr{C}(-r,0;\mathbb{R}^4)$.*

Proof: To prove the existence of a derivative of x with respect to the parameter μ_1, we fix μ_1 at $\mu > 0$, let $\varepsilon \in \mathbb{R}$ be a perturbation of μ, and for all $t \in [-r,t_f]$, define

$$h(t,\mu,\varepsilon) = x(t;\mu+\varepsilon) - x(t;\mu)\,.$$

The overall structure of the proof is thus to show that

$$\frac{\partial}{\partial \mu_1} x(t;\mu) = \lim_{|\varepsilon|\to 0} \frac{h(t,\mu,\varepsilon)}{\varepsilon}$$

exists and is continuous for $t \in [-r, t_f]$. We begin by considering h

$$\begin{aligned} h(t,\mu,\varepsilon) &= \int_0^t \{\mathscr{F}(s, x(s;\mu+\varepsilon), x_s(\mu+\varepsilon), \mu+\varepsilon) - \mathscr{F}(s, x(s;\mu), x_s(\mu), \mu)\}\, ds \\ &= \int_0^t \{\mathscr{F}(s, x(s;\mu+\varepsilon), x_s(\mu+\varepsilon), \mu+\varepsilon) - \mathscr{F}(s, x(s;\mu), x_s(\mu+\varepsilon), \mu+\varepsilon) \\ &\quad + \mathscr{F}(s, x(s;\mu), x_s(\mu+\varepsilon), \mu+\varepsilon) - \mathscr{F}(s, x(s;\mu), x_s(\mu), \mu+\varepsilon) \\ &\quad + \mathscr{F}(s, x(s;\mu), x_s(\mu), \mu+\varepsilon) - \mathscr{F}(s, x(s;\mu), x_s(\mu), \mu)\}\, ds\,. \end{aligned}$$

According to the Mean Value Theorem [23], we have

$$\begin{aligned} h(t,\mu,\varepsilon) &= \int_0^t \int_0^1 \{D_x\mathscr{F}(s, x(s;\mu) + s'h(s,\mu,\varepsilon), x_s(\mu+\varepsilon), \mu+\varepsilon)(h(s,\mu,\varepsilon)) \\ &\quad + D_{x_t}\mathscr{F}(s, x(s;\mu), x_s(\mu) + s'h_s(\mu,\varepsilon), \mu+\varepsilon)(h_s(\mu,\varepsilon)) \\ &\quad + D_{\mu_1}\mathscr{F}(s, x(s;\mu), x_s(\mu), \mu + s'\varepsilon)(\varepsilon)\}\, ds' ds\,, \end{aligned}$$

where $D_x\mathscr{F}$, $D_{x_t}\mathscr{F}$, $D_{\mu_1}\mathscr{F}$ are the Fréchet derivatives of $\mathscr{F}$ with respect to its second, third, and fourth arguments respectively. Since $\mathscr{F}$ is $\mathscr{C}^1$ in all its arguments, we then know that there exists linear functions $\Delta^1_{s',\varepsilon}$, $\Delta^2_{s',\varepsilon}$, $\Delta^3_{s',\varepsilon}$ (each parameterized by s' and ε) such that

$$\begin{aligned} h(t,\mu,\varepsilon) &= \int_0^t \int_0^1 \Big\{D_x\mathscr{F}(s, x(s;\mu), x_s(\mu), \mu)(h(s,\mu,\varepsilon)) + \Delta^1_{s',\varepsilon}(h(s,\mu,\varepsilon)) \\ &\quad + D_{x_t}\mathscr{F}(s, x(s;\mu), x_s(\mu), \mu)(h_s(\mu,\varepsilon)) + \Delta^2_{s',\varepsilon}(h_s(\mu,\varepsilon)) \\ &\quad + D_{\mu_1}\mathscr{F}(s, x(s;\mu), x_s(\mu), \mu)(\varepsilon) + \Delta^3_{s',\varepsilon}(\varepsilon)\Big\}\, ds' ds\,, \end{aligned}$$

where $|\Delta^1_{s',\varepsilon}|, |\Delta^2_{s',\varepsilon}|, |\Delta^3_{s',\varepsilon}| \to 0$ uniformly in s' as $|\varepsilon| \to 0$. Thus for $s \in [0,t]$, $\nu, \xi \in \mathbb{R}$, $\eta, \zeta \in \mathbb{R}^4$, $\phi, \psi \in \mathscr{C}(-r, 0; \mathbb{R}^4)$, and g_1, g_2, g_3 as defined in Lemma 2.1,

$$\begin{aligned} D_x\mathscr{F}(s,\eta,\phi,\nu)(\zeta) &= g_1(\eta;\zeta) \\ D_{x_t}\mathscr{F}(s,\eta,\phi,\nu)(\psi) &= g_2(\nu;\psi) \\ D_{\mu_1}\mathscr{F}(s,\eta,\phi,\nu)(\xi) &= g_3(\phi,\nu;\xi)\,. \end{aligned}$$

Then the equation for h is

$$
\begin{aligned}
h(t,\mu,\varepsilon) \quad = \quad & \int_0^t \{g_1(x(s;\mu);h(s,\mu,\varepsilon)) + g_2(\mu;h_s(\mu,\varepsilon)) + g_3(x_s(\mu),\mu;\varepsilon)\}\,ds \\
& + \int_0^t \int_0^1 \left\{\Delta^1_{s',\varepsilon}(h(s,\mu,\varepsilon)) + \Delta^2_{s',\varepsilon}(h_s(\mu,\varepsilon)) + \Delta^3_{s',\varepsilon}(\varepsilon)\right\} ds'ds\,.
\end{aligned}
$$

Moreover, since g_1, g_2, g_3 are all linear in their last arguments, the equation for h can be used to obtain

$$
\begin{aligned}
\leq \quad & \max_{\tau\in[t-r,t]} \int_0^\tau \left\{ \left| g_1(x(s;\mu);\,\cdot\,) + \int_0^1 \left|\Delta^1_{s',\varepsilon}\right| ds' \right| |h(s,\mu,\varepsilon)| \right. \\
& + \left| g_2(\mu;\,\cdot\,) + \int_0^1 \left|\Delta^2_{s',\varepsilon}\right| ds' \right| \|h_s(\mu,\varepsilon)\| \\
& \left. + \left| g_3(x_s(\mu),\mu;\,\cdot\,) + \int_0^1 \left|\Delta^3_{s',\varepsilon}\right| ds' \right| |\varepsilon| \right\} ds\,,
\end{aligned}
$$

where $\|\cdot\|$ is the ∞-norm on $[t-r,t]$. Thus for constants $K_1, K_2 > 0$, we know that

$$
\|h_t(\mu,\varepsilon)\| \quad \leq \quad K_1 \int_0^t \|h_s(\mu,\varepsilon)\|\,ds + K_2 t_f\,|\varepsilon|\ ,
$$

and a simple application of Gronwall's inequality implies that

$$
\|h_t(\mu,\varepsilon)\| \quad \leq \quad K_2\,|t_f|\,|\varepsilon| \exp(K_1 t_f)\,, \tag{2.2}
$$

which will be useful in the next step.

Now, if we divide both sides of the equation for h by ε so that

$$
\begin{aligned}
\frac{h(t,\mu,\varepsilon)}{\varepsilon} \quad = \quad & \int_0^t \left\{ g_1(x(s,\mu);\frac{h(s,\mu,\varepsilon)}{\varepsilon}) + g_2(\mu;\frac{h_s(\mu,\varepsilon)}{\varepsilon}) + g_3(x_s(\mu),\mu;\frac{\varepsilon}{\varepsilon}) \right\} ds \\
& + \int_0^t \int_0^1 \left\{ \Delta^1_{s',\varepsilon}(\frac{h(s,\mu,\varepsilon)}{\varepsilon}) + \Delta^2_{s',\varepsilon}(\frac{h_s(\mu,\varepsilon)}{\varepsilon}) + \Delta^3_{s',\varepsilon}(\frac{\varepsilon}{\varepsilon}) \right\} ds'ds\,,
\end{aligned}
$$

we note that the form of the integrand is strikingly similar to the right side of the equation in (2.1). For equation (2.1), we denote the solution generated using $\mu_1 = \mu$ and initial condition $(\Psi(0),\Psi) = (0,0) \in \mathbb{R}^4 \times \mathscr{C}(-r,0;\mathbb{R}^4)$ as $v(t)$ for $t \in [-r,t_f]$. Moreover, we claim that this solution v is equal to the limit of h/ε as $|\varepsilon| \to 0$.

By Lemma 2.1, we know that v exists and is continuous for $t \in [-r,t_f]$. Clearly v and h/ε are identically zero for $t \in [-r,0]$ for all $\varepsilon > 0$, and thus we consider for $t \in [0,t_f]$

$$
\begin{aligned}
\left| v(t) - \frac{h(t,\mu,\varepsilon)}{\varepsilon} \right| \quad \leq \quad & \left\| v_t - \frac{h_t(\mu,\varepsilon)}{\varepsilon} \right\|_\infty \\
\leq \quad & \max_{\tau\in[t-r,t]} \left| \int_0^\tau \left\{ g_1(x(s,\mu);v(s) - \frac{h(s,\mu,\varepsilon)}{\varepsilon}) + g_2(\mu;v_s - \frac{h_s(\mu,\varepsilon)}{\varepsilon}) \right. \right. \\
& \left. + g_3(x_s(\mu),\mu;1-\frac{\varepsilon}{\varepsilon}) \right\} ds - \int_0^\tau \int_0^1 \left\{ \Delta^1_{s',\varepsilon}(\frac{h(s,\mu,\varepsilon)}{\varepsilon}) \right. \\
& \left. \left. + \Delta^2_{s',\varepsilon}(\frac{h_s(\mu,\varepsilon)}{\varepsilon}) + \Delta^3_{s',\varepsilon}(\frac{\varepsilon}{\varepsilon}) \right\} d\tau ds \right|
\end{aligned}
$$

$$\begin{aligned}
&\leq \max_{\tau\in[t-r,t]}\left\{\int_0^\tau \left\{|g_1(x(s,\mu);\,\cdot)|\left|v(s)-\frac{h(s,\mu,\varepsilon)}{\varepsilon}\right|\right.\right.\\
&\qquad +|g_2(\mu;\,\cdot)|\left\|v_s-\frac{h_s(\mu,\varepsilon)}{\varepsilon}\right\|_\infty+|g_3(x_s(\mu),\mu;\,\cdot)|\,|0|\\
&\qquad \left.\left.+\int_0^1\left\{\left|\Delta^1_{s',\varepsilon}\right|\left|\frac{h(s,\mu,\varepsilon)}{\varepsilon}\right|+\left|\Delta^2_{s',\varepsilon}\right|\left\|\frac{h_s(\mu,\varepsilon)}{\varepsilon}\right\|_\infty+\left|\Delta^3_{s',\varepsilon}\right|\,|1|\right\}ds'\right\}ds\right\}\\
&\leq \int_0^t\left(|g_1(x(s,\mu);\,\cdot)|+|g_2(\mu;\,\cdot)|\right)\left\|v_s-\frac{h_s(\mu,\varepsilon)}{\varepsilon}\right\|_\infty ds+\\
&\qquad +\int_0^t\int_0^1\left\{\left|\Delta^1_{s',\varepsilon}\right|\left|\frac{h(s,\mu,\varepsilon)}{\varepsilon}\right|+\left|\Delta^2_{s',\varepsilon}\right|\left\|\frac{h_s(\mu,\varepsilon)}{\varepsilon}\right\|_\infty+\left|\Delta^3_{s',\varepsilon}\right|\,|1|\right\}ds'ds\,.
\end{aligned}$$

By equation (2.2), we know that

$$\begin{aligned}
\left\|v_t-\frac{h_t(\mu,\varepsilon)}{\varepsilon}\right\|_\infty &\leq \int_0^t\left\{|g_1(x(s,\mu);\,\cdot)|+|g_2(\mu;\,\cdot)|\right\}\left\|v_s-\frac{h_s(\mu,\varepsilon)}{\varepsilon}\right\|_\infty ds+\\
&\quad +\int_0^t\int_0^1 K_2\,|t_f|\exp(K_1t_f)\left\{\left|\Delta^1_{s',\varepsilon}\right|+\left|\Delta^2_{s',\varepsilon}\right|\right\}\frac{|\varepsilon|}{|\varepsilon|}+\left|\Delta^3_{s',\varepsilon}\right|\,|1|\,ds'ds\\
&\leq K_1\int_0^t\left\|v_s-\frac{h_s(\mu,\varepsilon)}{\varepsilon}\right\|_\infty ds\\
&\quad +t_f\int_0^1\left\{K_2t_f\exp(K_1t_f)\left\{\left|\Delta^1_{s',\varepsilon}\right|+\left|\Delta^2_{s',\varepsilon}\right|\right\}+\left|\Delta^3_{s',\varepsilon}\right|\right\}ds'\\
&\leq K_1\int_0^t\left\|v_s-\frac{h_s(\mu,\varepsilon)}{\varepsilon}\right\|_\infty ds+K_3(t_f)\int_0^t\left\{\left|\Delta^1_{s',\varepsilon}\right|+\left|\Delta^2_{s',\varepsilon}\right|+\left|\Delta^3_{s',\varepsilon}\right|\right\}ds'\,,
\end{aligned}$$

where $K_3(t_f)=t_f\max\{K_2t_f\exp(K_1t_f),1\}$. By Gronwall's inequality, we then have that

$$\left|v(t)-\frac{h(t,\mu,\varepsilon)}{\varepsilon}\right| \quad\leq\quad K_3(t_f)\int_0^1\left\{\left|\Delta^1_{s',\varepsilon}\right|+\left|\Delta^2_{s',\varepsilon}\right|+\left|\Delta^3_{s',\varepsilon}\right|\right\}ds'e^{K_1t_f}\,.$$

Since $|\Delta^1_{s',\varepsilon}|,|\Delta^2_{s',\varepsilon}|,|\Delta^3_{s',\varepsilon}|\to 0$ uniformly in s' as $|\varepsilon|\to 0$, we can then conclude that for $t\in[-r,t_f]$, $h/\varepsilon\to v$ as $|\varepsilon|\to 0$. Therefore, the partial derivative of x with respect to μ_1 (evaluated at $\mu_1=\mu>0$) exists and satisfies (2.1) with the initial condition $(\Psi(0),\Psi)=(0,0)\in\mathbb{R}^4\times\mathscr{C}(-r,0;\mathbb{R}^4)$, which completes the proof.

Remark 2.4. The line of reasoning presented here in Lemma 2.1 and Theorem 2.3 concerns the existence and continuity (in t) of the derivative of a solution to (1.1) with respect to the specific parameter μ_1. Similar arguments (with minimal changes to g_3) establish the existence and continuity (in t) of derivatives with respect to μ_2, σ_1, and σ_2. For the parameters that appear in (1.1) as linear coefficients, g_1 and g_2 are slightly altered (dependent upon the parameter under consideration), while $g_3\equiv 0$. However, these differences do not change the conclusion that the derivative of the solution $x(t)$ (with respect to any parameter appearing on the right side of (1.1)) exists and is continuous in time. One can also establish differentiability of solutions with respect to discrete delays (i.e., when P_1 or P_2 is a Dirac measure) and well-posedness of the appropriate sensitivity equations. The arguments, while in the spirit of those given above, are however somewhat more tedious and will not be given here.

3. ANALYSIS AND RESULTS

In this section we examine some applications of the theory developed in Section 2. All of the simulations presented in this section were done using Matlab software originally developed in [3] for the purpose of simulating systems of Abstract Evolution Equations (AEE's) that are linear in the delay (e.g., system (1.1)). As can be inferred from equation (2.1), in order to solve sensitivity equations, one needs the solution x of the original system. Therefore, we use the calculated solution from [3] with parameters $q^* \in Q_{ad}$ (the space of admissible parameters) identified by minimizing the cost

$$J(q) = \frac{1}{10}\sqrt{\sum_{i=1}^{10}(X(t_i;q) - \widehat{X}_i)^2}\,, \tag{3.1}$$

over $q \in Q_{ad}$ and where $\widehat{X} = \{\widehat{X}_i\}$ is the data from [40] taken at times $\{t_i\}$. However, we are not able to compute the exact solution x and thus (as described in [3, 6]) we minimize

$$J^N(q) = \frac{1}{10}\sqrt{\sum_{i=1}^{10}(X^N(t_i;q) - \widehat{X}_i)^2}\,, \tag{3.2}$$

where $x^N = (V^N, A^N, C^N, T^N)$ is an appropriate approximation to x and N is an integer describing the accuracy of the numerical simulation such that $\lim_{N\to\infty} x^N(t;q) = x(t;q)$. The numerical scheme (also described in [3, 6]) is such that as $N \to \infty$, a minimizer q^{N*} to (8) converges to q^*, a minimizer to (8). Both the experimental results and the numerical best fit solution x^N (using parameters q^{N*} from Table 2) are depicted in Figure 3.1.

Parameter	Value	Units
n_A	0.112	hours^{-1}
n_C	0.011	hours^{-1}
γ	$9E-4$	hours^{-1}
δ_A	0.078	hours^{-1}
δ_C	0.025	hours^{-1}
δ_u	0.017	hours^{-1}
δ	$1E-12$	(cell hours)$^{-1}$
p	$1.3E-6$	(cell hours)$^{-1}$
μ_1	-22.8	hours
μ_2	-26	hours

TABLE 2. Optimal *in vitro* model parameter values.

By Theorem 2.3, we can legitimately consider the derivative of both sides of (1.1) with respect to any appropriate parameter. We first consider the derivative of $x(t)$ with respect to μ_1 at $\mu_1 = \mu$

$$\begin{aligned} \tfrac{d}{d\mu_1}\dot{x}(t;\mu) &= \tfrac{d}{d\mu_1}L(x(t;\mu), x_t(\mu);\mu) + \tfrac{d}{d\mu_1}f_1(x(t;\mu)) + \tfrac{d}{d\mu_1}f_2(t) \qquad \text{for } 0 \le t \le t_f \\ \tfrac{d}{d\mu_1}(x(0,\mu), x_0(\mu)) &= \tfrac{d}{d\mu_1}(\Phi(0),\Phi) \in \mathbb{R}^4 \times \mathscr{C}(-r,0;\mathbb{R}^4)\,. \end{aligned} \tag{3.3}$$

If we denote $v(t) = \frac{d}{d\mu_1} x(t;\mu)$ (for some specific value of $\mu_1 = \mu > 0$), we obtain the sensitivity equations

$$(3.4)\qquad \begin{aligned} \dot{v}(t) &= g_1(x(t;\mu); v(t)) + g_2(\mu; v_t) + g_3(x_t(\mu), \mu; 1) \qquad \text{for } 0 \le t \le t_f \\ (v(0), v_0) &= (0,0) \in \mathbb{R}^4 \times \mathscr{C}(-r, 0; \mathbb{R}^4)\,, \end{aligned}$$

where g_1, g_2, g_3 are as defined in Lemma 2.1. As before, due to the complexity of the right side of (3.4), we cannot solve exactly for the solution $v(t)$. Moreover, we do not have x which appears in the terms g_1 and g_3; we only have an approximation x^N to x. Therefore, we must propose a viable numerical scheme to calculate an approximation v^N to solutions of (3.4), with x replaced by x^N such that $\lim_{N\to\infty} v^N = v$.

Hence we consider v^N an approximate solution to (3.4) with $x = x^N$ in the coefficients. This is a linear nonautonomous system of the form

$$(3.5)\qquad \begin{aligned} \dot{v}^N(t) &= \mathscr{A}^N(t) v^N(t) + g_2(v_t^N) + g_3(x_t^N) \qquad \text{for } 0 \le t \le t_f \\ \left(v^N(0), v_0^N\right) &= (0,0) \in \mathbb{R}^4 \times \mathscr{C}(-r, 0; \mathbb{R}^4)\,, \end{aligned}$$

where N is fixed, x^N is given, and $\mathscr{A}^N$ maps $\mathbb{R}^4 \times \mathscr{C}(-r,0;\mathbb{R}^4)$ to $\mathbb{R}^4$. Note that this is a special case of the systems treated in [3], where existence and uniqueness are guaranteed. To obtain convergence of v^N to v (the unique solution to (3.4)), we turn to [2]. A straightforward extension of the theory presented in [2] to treat nonautonomous linear systems such as (3.5) will yield, (under the approximation scheme described in [3]), the desired convergence.

If we were to plot simulations of (3.4) (or actually, the approximate solutions defined by (3.5)), interpretations of these plots would suggest specific effects that changes in μ_1 would have on the solution x. Moreover, if we were to also perform the analogous derivation for the infection rate p, a plot of that sensitivity function would depict the effect that changes in p

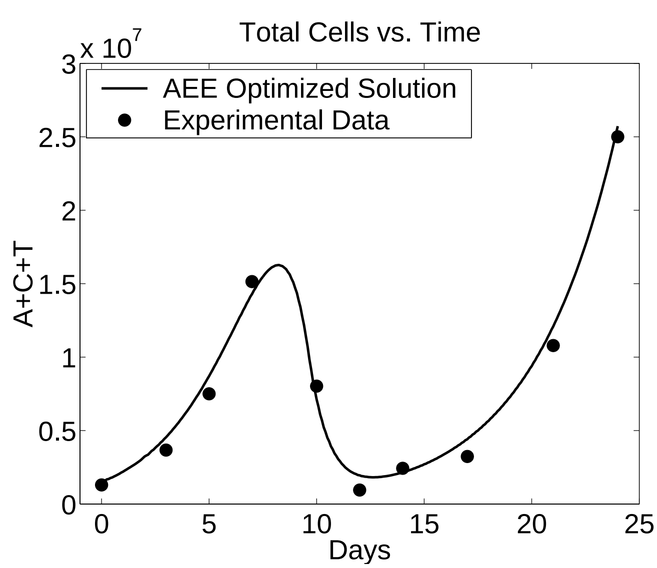

FIGURE 3.1. Data from [40] and best fit simulation x^N of (1.1).

would have on x. Since μ_1 and p differ in their units, the sensitivity functions for μ_1 and p would also have different units, thus rendering any comparison meaningless. We turn to the sensitivity analysis literature to resolve this issue. To enable a comparison of the effects that parameters with different units have on the solution, we simply multiply by the parameter under consideration, e.g., $(\frac{\partial}{\partial\mu_1}x_1(t;\mu), \frac{\partial}{\partial\mu_1}x_2(t;\mu), \frac{\partial}{\partial\mu_1}x_3(t;\mu), \frac{\partial}{\partial\mu_1}x_4(t;\mu)) \cdot \mu$. This form of the sensitivity function is known as the *semirelative* or *semilogarithmic* or *unnormalized* sensitivity function [10, 11]. Moreover, this form is actually the differential of x with respect to μ_1 at μ in the direction μ

$$D_{\mu_1}x_i(t;\mu)[\mu] = (\frac{\partial}{\partial\mu_1}x_i(t;\mu)) \cdot \mu$$

for $i = 1, 2, 3, 4$. With this weighting, we now have the tools to rank the parameters with regard to their influence over the solution.

Figure 3.2 depicts the approximation v^N of the solution v to the (3.4) (at $\mu = -22.8$), with each compartment multiplied by μ. It is important to realize that while the y-axis in Figure 3.2 has units of cells or virions respectively, it should still be thought of as a plot reflecting changes in the state with respect to changes in μ_1. In other words, we interpret the upper-left plot of Figure 3.2 to suggest that for a (positive) change in the mean delay, the virion compartment V will be dramatically smaller just before day 10 and then larger around day 12 (relative to $V(t;-22.8)$). Likewise for a change in μ_1, the acutely infected cell compartment A will be slightly smaller around day 9 and dramatically larger around day 10 (relative to $A(t;-22.8)$). All the plots depicted in Figure 3.2 suggest that there will be dramatic changes in the solution for changes in μ_1, and indeed Figure 3.3 supports this claim (as well as the specific predictions suggested by the interpretation of Figure 3.2). For this simulation, it is important to note that there is practically no indication that the solution x will exhibit any sensitive to μ_1 until around day 5. In other words, for simulations on a short time interval (i.e., $t \in [-r, 120]$ hours), one could easily conclude that the solution x is insensitive to μ_1 (in the neighborhood of $\mu_1 = \mu = -22.8$ hours).

As another example, let us consider the solution parameterized with respect to the infection rate p, i.e., $x(t) = x(t;p)$. Thus the derivative of (1.1) with respect to p at $\tilde{p} = 1.3 \times 10^{-6}$ is

$$\begin{aligned} \tfrac{d}{dp}\dot{x}(t;\tilde{p}) &= \tfrac{d}{dp}L(x(t;\tilde{p}), x_t(\tilde{p})) + \tfrac{d}{dp}f_1(x(t;\tilde{p}),\tilde{p}) + \tfrac{d}{dp}f_2(t) \qquad \text{for } 0 \le t \le t_f \\ \tfrac{d}{dp}(x(0,\tilde{p}), x_0(\tilde{p})) &= \tfrac{d}{dp}(\Phi(0), \Phi) \in \mathbb{R}^4 \times \mathscr{C}(-r, 0; \mathbb{R}^4)\,. \end{aligned} \tag{3.6}$$

As mentioned in the last part of Section 2, the sensitivity equations with respect to different parameters will be slightly different than (3.4), but unique solutions still exist and are continuous (for each system of sensitivity equations). Figures 3.5 and 3.4 depict the semirelative sensitivity functions for p and μ_2, respectively . A comparison of the scales on the vertical axis in Figure 3.2 versus the axis in Figures 3.5 and 3.4 suggests that changes in μ_1 have a more significant influence in the solution x than changes in μ_2 or p (and in one of the compartments by over four orders of magnitude). This result coincides nicely with one of the primary conclusions from [3], in which we concluded that when fitting the data, adding the second

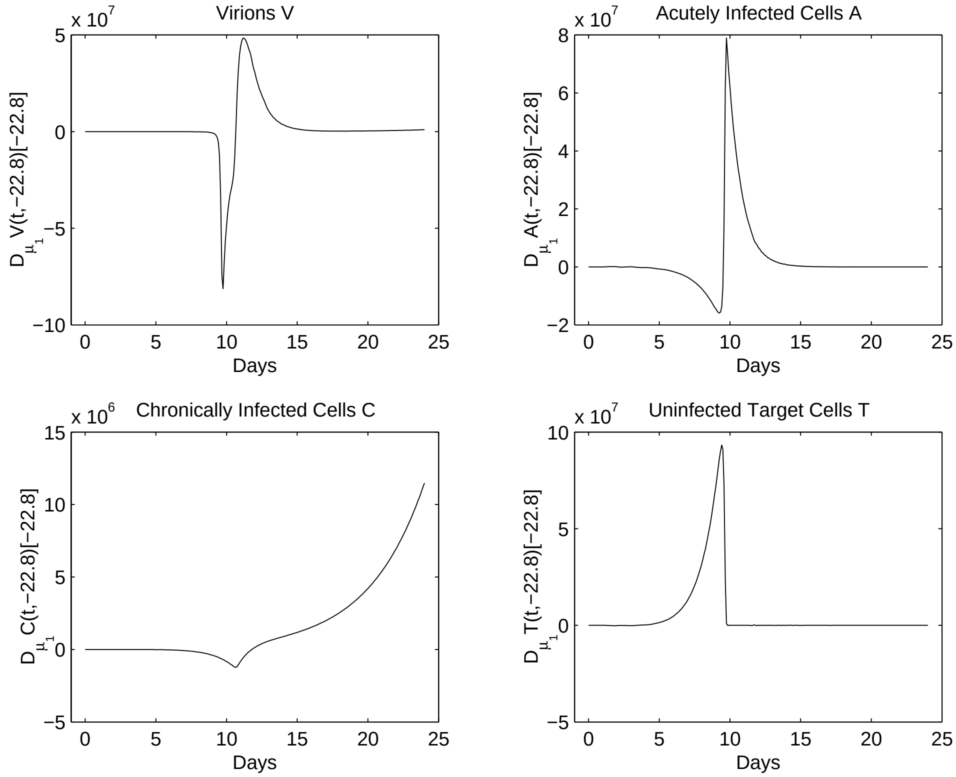

FIGURE 3.2. Simulation of the semirelative sensitivity solution with respect to μ_1 at $\mu_1 = \mu = -22.8$.

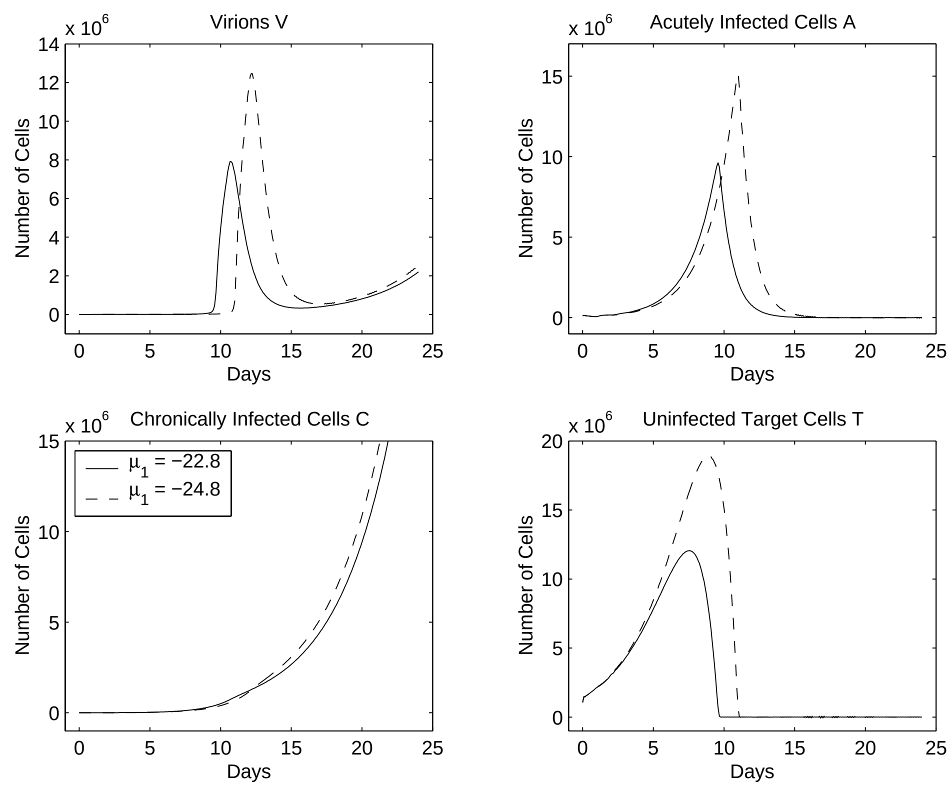

FIGURE 3.3. Simulations of $x^N(t; -24.8)$ and $x^N(t; -22.8)$.

delay between than acute and chronic infection was not as significant as inclusion of the delay between viral infection and viral production.

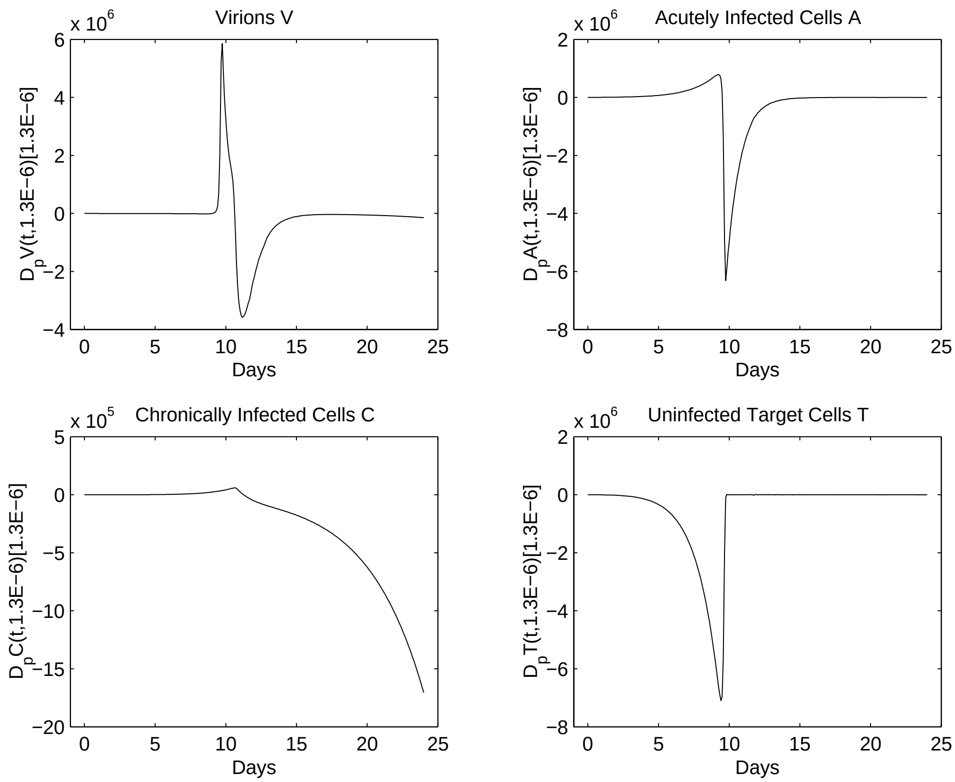

FIGURE 3.4. Simulation of semirelative sensitivity solution with respect to the infection rate p for $\tilde{p} = 1.3 \times 10^6$.

Now that we have established the framework for calculating semirelative sensitivity functions, let us consider how to rank the influence that changes in the individual parameters have upon the solution x. Clearly, there are many options, but for simplicity, we will rank the parameters according to the magnitude of the ∞-norm, e.g., for the virion compartment and the sensitivity with respect to δ_A, we consider

$$\max_{t\in[0,t_f]} |D_{\delta_A} V(t; 0.0776)\,[0.0776]|\ .$$

To illustrate our reasoning, we will focus on just the virion compartment V. Of the parameters over which we performed our NLS in [3], the chosen metric was largest for the parameters μ_1, n_A, δ_A, and δ_u. Figure 3.6 depicts (for the compartment V), the absolute values of the semirelative sensitivity functions with respect to μ_1, n_A, δ_A, and δ_u, for $t \in [8.5, 15]$ (the domain where there is the most activity in the sensitivity functions). The interpretation of this figure strongly suggests that δ_A and n_A have the strongest influence over the solution in the virion compartment (in the chosen ∞-norm). Therefore, for the use of equation (1.1) (as a model to simulate HIV pathogenesis), both the viral production rate and the death rate for acutely infected cells (n_A and δ_A respectively) should be given top priority when choosing which parameters to determine with a high degree of accuracy. In other words, these parameters play an important role in the model and obtaining good values for them is more important to the system response than good values for other parameters to which solutions are less sensitive.

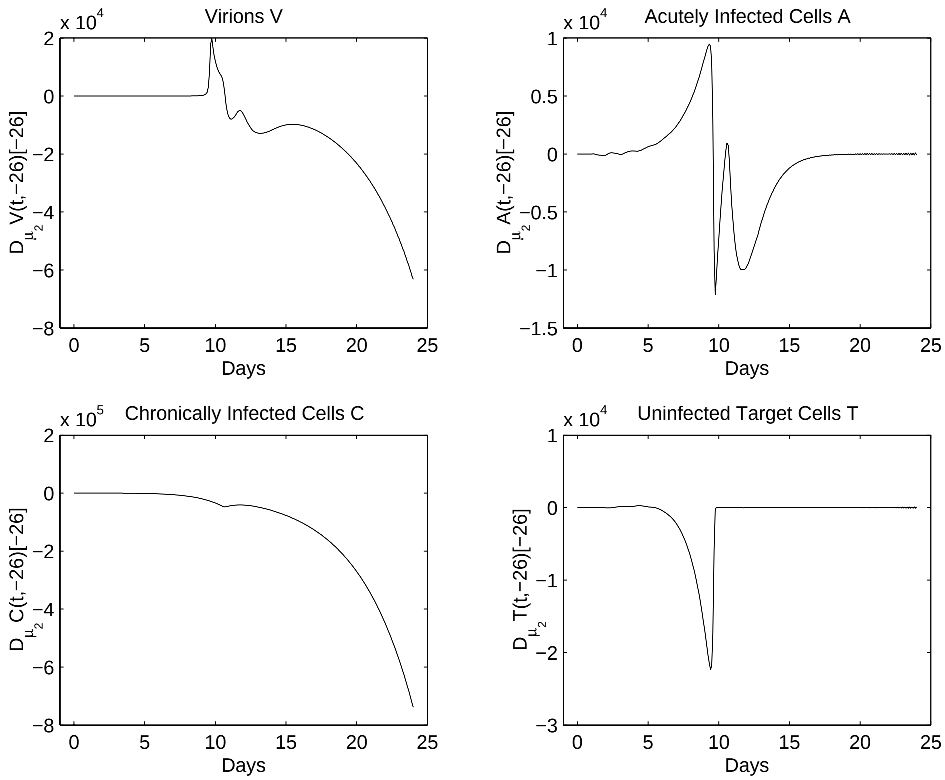

FIGURE 3.5. Simulation of semirelative sensitivity solution with respect to the mean delay between acute and chronic infection μ_2 for $\tilde{\mu}_2 = -26$.

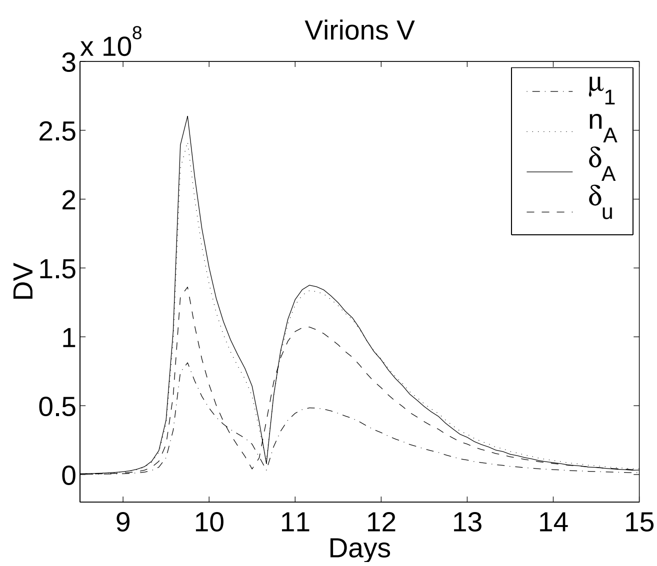

FIGURE 3.6. Absolute value of simulations of semirelative sensitivity solutions for several parameters (V compartment only).

4. Concluding Remarks

As discussed in Section 1.1, the taking of a derivative (with respect to parameters) of the equations governing a system is not a new idea and indeed has been around (in some form) for at least 170 years. Within control theory and engineering applied to physical systems, the forms of the fundamental mathematical models often are, for the most part, relatively well established and not so open to debate. For example, in some investigations, it may not be fruitful to question the significance of the viscosity parameter in the Navier-Stokes equations (although sensitivity of flow patterns to viscosity is sometimes very important, see [42]). However, the constitutive parameters and forms of the mathematical models employed in the biological sciences are frequently not as well agreed upon, and indeed (as is evidenced by the literature) open to considerable debate. Since the current approach to sensitivity was originally developed in the context of control theory, the cited literature is (understandably) biased toward that field; a considerable proportion of the papers are devoted to analyzing the sensitivity of transfer functions and eigenvalues. Thus the application of mathematically rigorous sensitivity analyses to dynamical systems designed to model biological phenomena does not seem to be common practice. Indeed, many sensitivity studies often involve copious simulations. As such, there are many possibilities that have not been fully examined.

In the analysis presented in this paper, we only considered first derivatives of the components. In theory, we could have examined derivatives with respect to multiple parameters $\frac{\partial^2 x}{\partial n_A \partial \delta_A}$ (joint sensitivities), an analysis of which could be used to ascertain the independent identifiability of parameters. We could have also taken a derivative with respect to the initial conditions, which (as is intuitive) would suggest the influence of the initial conditions over the solution (this can be extremely useful in certain biological investigations). Finally, we could have considered the derivative of the least squares functional (3.1)with respect to a parameter (as was explored in [22]), which could then be used as part of a jacobian in an optimization algorithm (as part of a parameter estimation scheme).

The process of taking the derivative of a system with respect to a parameter is usually not an exceedingly challenging task and it is important to remember that the sensitivity function only reveals the local behavior (since it is a derivative) around the fixed parameter value. However, this idea can yield useful insights into the solution of complex systems (even those with nonlinearities and delays) such as (1.1). Effectively, the technique of using simulation sensitivity functions presented in this paper is a more efficient (and mathematically rigorous) way to attain insight into a system than manually adjusting a parameter and observing the effect on the solution through massive simulation efforts.

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