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EIGENVALUES AND SENSITIVITY ANALYSIS FOR A MODEL OF HIV-1 PATHOGENESIS WITH AN INTRACELLULAR DELAY

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ABSTRACT

During the past decade significant research has been aimed at better understanding for human immunodeficiency virus type 1 (HIV-1), and the use of mathematical modeling to interpret experimental results has made a significant contribution. However, time-delays, which play a critical role in various biological models, are still not amenable to many traditional analysis methods. In this paper, we apply a recently developed approach using the Lambert W function to handle the time delay in a HIV-1 pathogenesis dynamic model. Dominant eigenvalues in the infinite eigenspectrum of these time-delay systems are obtained and used to understand the effects of the parameters of the model on the immune system. Also, the result is extended to analyze the sensitivity of the eigenvalues with respect to the parameters in the HIV-1 model. The research makes it possible to know which parameters are more influential than others, and the obtained information is used to investigate the HIV-1 dynamic system analytically.

INTRODUCTION

During the past decade, a number of mathematical models for human immunodeficiency virus type 1 (HIV-1) based on systems of differential equations have been developed. These models combined with experimental results, have yielded important insights into HIV-1 pathogenesis [1–5]. This success in modeling the HIV-1 pathogenesis dynamics has led to various analyses [6–9], and helped in designing better therapy regimes.

To account for the time between viral entry into a target cell and the production of new virus particles, models that include time-delays have been introduced [10–12]. Models of HIV-1 infection that include intracellular delays are more accurate representations of the biology and change the estimated values of kinetic parameters when compared to models without delays [9]. Also, it was shown that allowing for time delays in the model better predicts viral load data when compared to models with no time delays [7, 13, 14].

In dynamical systems, roots of the characteristic equation contain a wealth of information about the system. However, the principal difficulty in studying delay differential equations (DDEs) results from their special transcendental character: delay problems always lead to an infinite spectrum of frequencies. Therefore, DDEs are often solved using numerical methods, asymptotic solutions, and graphical approaches, and time-delay systems are still not amenable to many methods from control theory [15]. Due to the complexity of DDEs, many scientists do not include them in their models. However, many biological processes have inherent delays and including them may lead to additional insights in the study of complicated biological processes [9].

Recently, based on the concept of the Lambert W function, an analytic approach to obtain the complete solution of systems of delay differential equations has been developed by Asl and Ulsoy [16] and Corless et al. [17] and extended to more general cases by Yi et al. [18]. For systems of DDEs, which have infinite number of eigenvalues, the rightmost ones among them have relatively high significance. The matrix Lambert W function provides an expression for the rightmost eigenvalues of systems of DDEs in terms of parameters of the systems and the results have been applied to solve various problems of DDEs [19].

In this paper, dominant eigenvalue analysis, its sensitivity

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with respect to parameters in the model of HIV-1 dynamics are studied. For this research, we apply the matrix Lambert W function approach to investigate analytically the HIV-1 pathogenesis model with an intracellular delay. Eigenvalues of the delayed systems are obtained and used i) to analyze the effects of time-delay on the stability and decay rate of viral load, ii) to determine the stability of patients. Also, via sensitivity of the eigenvalues with respect to parameters, the effects of parameters are studied. The approach presented in this paper for HIV-1 dynamics can be used to deal with time-delay terms in many other pathogenesis models (e.g., hepatitis B viral dynamics [20] and tuberculosis [21]).

TIME-DELAY SYSTEM FOR HIV-1

HIV-1 Pathogenesis Dynamic Model with an Intracellular Delay

The HIV-1 pathogenesis dynamic models have been used to interpret experimental results for complex immune systems. Research on relations between parameters in the models and their impact on the immune system has been reported in the literature (see, e.g., [1, 5]) and have made a significant contribution during the past decade. When intracellular delay is included, the models of HIV-1 infection provide more accurate representations of the biology, and allowing for time delays in the model enables it to better predict viral load data. One of the delay models, where it is assumed that the generation of virus producing cells at time t is due the infection of target cells at time $t-h$, consists of systems of coupled delay differential equations, given by [12]:

$$\begin{aligned} \frac{dT^*(t)}{dt} &= \beta T_0 V_I(t-h) - \delta T^*(t) \\ \frac{dV_I(t)}{dt} &= (1-n_p) N \delta T^*(t) - c V_I(t) \\ \frac{dV_{NI}(t)}{dt} &= n_p N \delta T^*(t) - c V_{NI}(t) \end{aligned} \tag{1}$$

where t is the elapsed time since treatment was initiated (i.e., $t = 0$ is the time of onset of the drug effect), and T^* is the concentration of productively infected T-cells. The state variables V_I and V_{NI} represent the plasma concentrations of virions in the infectious pool (produced before the drug effect) and in the non-infectious pool (produced after the drug effect), respectively. In (1), it is assumed HIV-1 infects target cell T-cells with a rate β and causes them to become productively infected T-cells, T^*. Time-delay, h, in Eq. (1) results from the time between initial viral entry into a cell and subsequent viral production, and is termed "intracellular delay". In this model, c is the rate for virion clearance; δ is the rate of loss of the virus-producing cell; N is the number of new virions produced per infected cell during its lifetime; T_0 is the target T-cell concentration; n_p represents the drug efficacy of a protease inhibitor, a drug that inhibits the cleaving of viral polyproteins and renders newly produced virions non-infectious, V_{NI}. The term $(1-n_p)$ represents the level of leakiness of a protease inhibitor and if $n_p = 1$, the protease inhibitor is 100% effective and no infectious virus particles are produced. The parameters in (1) have been estimated by applying the models to data from drug perturbation experiments [14]. For the research presented in this paper, the parameter set for patient 103, which is given in Table 1, is used [14]. Viral load, $V_I + V_{NI}$, had been collected from patient 103 after administration (600 mg twice daily) of a potent inhibitor (Ritonavir) of HIV-1 protease. For detailed study, refer to [22] on the experiment and the data.

Table 1. Estimated parameter values from one (patient 103) of the 5 patients studied in [14]

Name	Description	Value	Reference
T_0	Target T-cell concentration	408 $cells\ mm^{-3}$	[23]
h	Intracellular delay	0.91 $days$	[12]
δ	Death rate of an infected T-cell	$1.57/day$	[22]
c	Clearance rate of virus	$4.3/day$	[22]
N	Bursting term for viral production after lysis	480 $virions/cells$	[22]
n_p	Protease inhibitor efficacy	0.7	[5]
β	Viral infectivity rate	$\frac{c}{NT_0}$	[23]

The characteristic equation of the system in Eq. (1) is derived as

$$H(\lambda) = \left\{ \lambda^2 + (\delta + c)\lambda + \delta c - (1-n_p)\delta N \beta T_0 e^{-\lambda h} \right\} (\lambda + c) \tag{2}$$

And from the roots of Eq. (2), the eigenvalues, λ, of the system (1) are obtained. Due to the term, $e^{-\lambda h}$, Eq. (2) becomes infinite-dimensional and, thus, an infinite number of roots satisfy the equation. The principal difficulty in studying DDEs results from this special transcendental character, and the determination of this spectrum requires numerical, asymptotic, and graphical approaches [15]. Computing, analyzing, and controlling the infinite eigenspectrum are not as straightforward as for systems of ordinary differential equations (ODEs). Instead, for the time delay systems in Eq. (1), it is crucial to compute and analyze the dominant eigenvalues. To do that, we will apply the Lambert W function-based approach [18], which is introduced in the next subsection.

Lambert W Function-based Approach and Rightmost Eigenvalues

The analysis of eigenvalues has practical importance because the eigenvalues of the system (1) tell us about the stability and, thus, can provide information about the patient's viral dynamics. The eigenvalues of linear time-invariant (LTI) systems of DDEs with a single delay as in Eq. (1) can be obtained by using the Lambert W function-based approach [18]. Consider a

LTI system of DDEs with a single constant delay, h

$$\begin{array}{ll} \dot{\mathbf{x}}(t) = \mathbf{A}\mathbf{x}(t) + \mathbf{A_d}\mathbf{x}(t-h) + \mathbf{B}\mathbf{u}(t) & t > 0 \\ \mathbf{x}(t) = \mathbf{g}(t) & t \in [-h, 0) \\ \mathbf{x}(t) = \mathbf{x}_0 & t = 0 \end{array} \tag{3}$$

where $\mathbf{A}$ and $\mathbf{A_d}$ are $n \times n$ matrices, and $\mathbf{x}(t)$ is an $n \times 1$ state vector, $\mathbf{B}$ is an $n \times r$ matrix, $\mathbf{u}(t)$, an $r \times 1$ vector, is a function representing the external excitation, and $\mathbf{g}(t)$ and $\mathbf{x}_0$ are a specified preshape function and an initial point respectively defined in the Banach space of continuous mappings [24]. The existence and uniqueness of the solution to Eq. (3) has been proven in [24]. The system in Eq. (1) is expressed in the form of Eq. (3) with the coefficients

$$\mathbf{A} = \begin{bmatrix} -\delta & 0 & 0 \\ (1-n_p)N\delta & -c & 0 \\ n_p N\delta & 0 & -c \end{bmatrix}, \quad \mathbf{A_d} = \begin{bmatrix} 0 & \beta T_0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \tag{4}$$

and the initial conditions $\mathbf{g}(t) = \mathbf{x}_0 = \{T_{ss}^* \quad Vss \quad 0\}^T$

In [18], the total (free and forced) solution to (3) was derived using the matrix Lambert W function-based approach and is given by

$$\mathbf{x}(t) = \underbrace{\sum_{k=-\infty}^{\infty} e^{\mathbf{S}_k t}\mathbf{C}_k^I}_{\text{free}} + \underbrace{\int_0^t \sum_{k=-\infty}^{\infty} e^{\mathbf{S}_k (t-\xi)}\mathbf{C}_k^N \mathbf{B}\mathbf{u}(\xi) d\xi}_{\text{forced}} \tag{5}$$

where

$$\mathbf{S}_k = \frac{1}{h}\mathbf{W}_k(\mathbf{A_d} h \mathbf{Q}_k) + \mathbf{A}. \tag{6}$$

The coefficient $\mathbf{C}_k^I$ in (5) is a function of $\mathbf{A}$, $\mathbf{A_d}$, h and the preshape function, $\mathbf{g}(t)$ and the initial point, $\mathbf{x}_0$, while $\mathbf{C}_k^N$ is a function of $\mathbf{A}$, $\mathbf{A_d}$, h and does not depend on $\mathbf{g}(t)$ or $\mathbf{x}_0$. The numerical and analytical methods for computing $\mathbf{C}_k^I$ and $\mathbf{C}_k^N$ were developed respectively in [16] and [18]. Conditions for convergence of the infinite series in (5) have been studied in [24–26]. The following equation based on the Lambert W function is used to solve for the unknown matrix $\mathbf{Q}_k$ in (6)

$$\mathbf{W}_k(\mathbf{A_d} h \mathbf{Q}_k) e^{\mathbf{W}_k(\mathbf{A_d} h \mathbf{Q}_k) + \mathbf{A}h} = \mathbf{A_d} h \tag{7}$$

The solution to Eq. (7), $\mathbf{Q}_k$, is obtained numerically, for a variety of initial conditions, e. g., using the *fsolve* function in Matlab. The matrix Lambert W function, $\mathbf{W}_k(\mathbf{H}_k)$, is complex valued, with a complex argument, $\mathbf{H}_k$, and has an infinite number of branches for $k = -\infty, \cdots, -1, 0, 1, \cdots, \infty$, and satisfies the definition, $\mathbf{W}_k(\mathbf{H}_k) e^{\mathbf{W}_k(\mathbf{H}_k)} = \mathbf{H}_k$ [17]. The principal ($k = 0$) and other ($k \neq 0$) branches of the Lambert W function can be calculated analytically [17], or using commands already embedded in the various commercial software packages, such as Matlab, Maple, and Mathematica.

Note that the solution in terms of the Lambert W function has an analytical form expressed in terms of the parameters, $\mathbf{A}$, $\mathbf{A_d}$ and h, of the DDE in (3). Hence, one can determine how the parameters are involved in the solution and, furthermore, how each parameter affects each eigenvalue [27], [28]. Also, each eigenvalue is distinguished by k, which indicates the branch of the Lambert W function. The solution to DDEs in terms of the Lambert W function is analogous to that of systems of ODEs in terms of the state transition matrix and, thus, has been applied to analysis and control of time-delay systems as detailed in [19].

For systems of DDEs as in Eq. (3), it is difficult to determine the rightmost, thus dominant, eigenvalues in the infinite eigenspectrum. However, this is important, as the rightmost eigenvalues determine system stability. If we compute a finite set of eigenvalues from the infinite eigenspectrum, it is difficult to draw conclusion about stability, because we cannot be sure that the rightmost eigenvalue is included in that set. It has been proven that the root obtained using the principal branch (k = 0) of the Lambert W function always determines the stability of the system using monotinicity of the real part of the function with respect to its branch k for the scalar case, [29]. Such a proof can readily be extended to systems of DDEs where $\mathbf{A}$ and $\mathbf{A_d}$ are simultaneously triangularizable and, thus, commute with each other [30]. Although such a proof is not available in the case of the general matrix-vector DDEs, if the coefficient matrix $\mathbf{A_d}$ does not have repeated zero eigenvalues, then, we have observed the same behavior in all the examples we have considered. If $\mathbf{A_d}$ has repeated zero eigenvalues, the rightmost eigenvalues is obtained by using the principal branch ($k = 0$) or $k = \pm 1$. Consequently, an important advantage of the solution approach based on the Lambert W function, is that the stability of the system can be determined based only on the finite number of branches, $k = -1, 0, 1$, instead of the infinite eigenspectrum, $k = -\infty, \cdots, -1, 0, 1, \cdots, \infty$. In the next section, this approach presented in the section is applied to the model of HIV-1 dynamics with an intracellular delay in (1).

RIGHTMOST EIGENVALUE ANALYSIS

For the model of HIV-1 in (1), the stability of a patient's immune system and the viral decline rate can be expressed with the eigenvalues of the system and, thus, its analysis is interesting from the practical point of view. In this section, the eigenvalues are obtained by using the approach introduced in the previous section and the results are discussed.

Delay Effects on Rightmost Eigenvalues

Introducing a discrete delay in a system of DDEs changes the structure of the solution as seen in (5), which has the form of an infinite series with an infinite eigenspectrum. Figure 1 shows

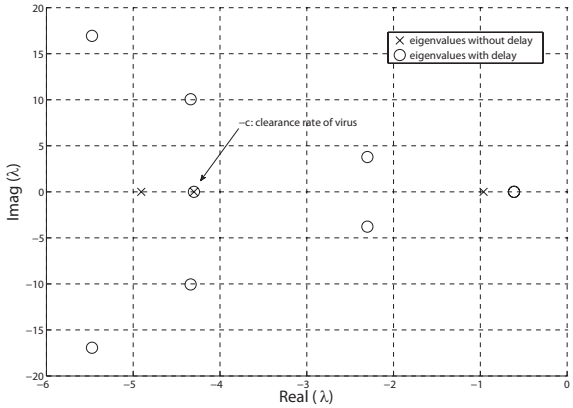

Figure 1. Change of eigenvalues by introduction of delay to the HIV-1 model: the rightmost eigenvalue shifted towards the imaginary axis. Also the time delay leads to imaginary parts of the eigenvalues and, thus, to oscillations in the response.

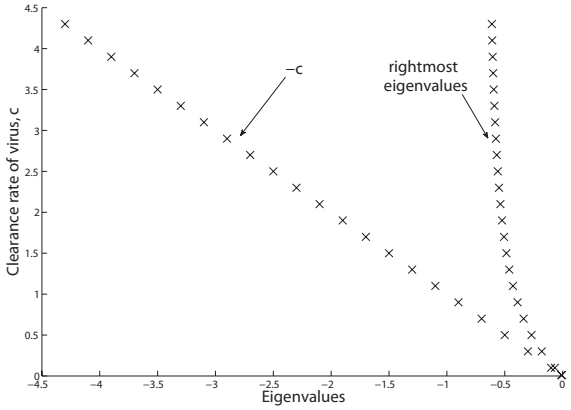

Figure 2. As the clearance rate, c, declines, the rightmost eigenvalues, which are on the interval between $-c$ and the origin, moves toward to the right and, thus, the system becomes less stable.

the change of the eigenspectrum by introducing a delay to the HIV-1 model. If the system in Eq. (1) has no time-delay, all of the eigenvalues of the system are real (shown by the x mark). However, as seen in Fig. 1, the time-delay leads to imaginary parts of the eigenvalues (shown by the o mark) and to oscillations in the response. In the literature [12], time delays, when used in population dynamic models, have been shown to create fluctuations in population size. Without difficulty, from Eq. (2) it can be shown that one of the eigenvalues is always $-c$, regardless of the value of the time delay, h, as seen in Fig. 1. Also, there exists one real eigenvalue of the system (1) on the interval between $-c$ and the origin [12]. In our model of HIV-1, introduction of a time-delay makes the rightmost eigenvalues move to the right (i.e., less stable). This can be confirmed using an eigenvalue sensitivity analysis, which is introduced in the next section, as well as direct computation using the matrix Lambert W function as shown in Fig. 1. Because the eigenvalues of the HIV-1 model describe the viral decline rate, via the eigenvalues change in Fig. 1, it is confirmed that the delay reduces the long-term rate of decline of the viral load [12].

Also, depending on the parameters of the system, the stability can be determined via the rightmost eigenvalues. In Fig. 1, the system has one real rightmost eigenvalue of the system (1) on the interval between $-c$ and the origin. As the value of c declines, this rightmost eigenvalues moves toward to the origin and, thus, the system becomes less stable (see Fig. 2). This will be discussed more in detail via sensitivity analysis in the next section.

Mutation, Drug Efficacy and Eigenvalues

Over the last decade, a number of potent drugs that inhibit HIV-1 replication in vivo have been developed. Treatment regimes involving a combination of three or more different drugs can lead to a decline in viral load by several orders of magnitude. Although research is finding more drugs to combat HIV-1 infection, the virus is continuously evolving to be resistant against these newly developed drugs. The high error rate in reverse transcription process of viral RNA into DNA, combined with the continual viral replication of HIV-1, leads to the emergence of mutant strains of HIV-1 that are drug resistant [31]. Most models for HIV-1 assume either a perfect drug or an imperfect drug with a less than 100%, but constant, efficacy. In reality, the effect of antiviral treatment appears to change over time, due to i) pharmacokinetic variation, ii) fluctuating adherence, and iii) the emergence of drug resistant mutations [32]. Among them, drug resistance is a major concern in the treatment of some human infectious disease, especially, HIV-1. If strains that are resistant to the drug increase, then patients can become infected with the resistant virus, causing therapy to be ineffective [33]. The result is a continuously varying efficacy of drug action. Accounting for this varying efficacy may be particularly important in recent clinical studies [34]. The efficacy can be expressed as a function of time (see, e.g., [32] and the references therein).

Although combination therapy can result in sustained suppression of viral load in many patients, it is not effective in all patients and fails after the emergence of drug-resistant strains. Hence, although finding new drugs to fight HIV is important for improving our chances for success, it is equally important to devise therapy regimes that minimize the chance of drug resistance emerging [35]. To do this, we need more detailed information about the status of patients and stability of the immune system of the patients with HIV-1. Figure 3 shows the movement of the rightmost eigenvalue of the system with respect to drug efficacy. The rightmost eigenvalue moves toward the imaginary axis as the drug efficacy, n_p, decreases, and the status of the patient becomes less stable. This result tells us about the stability of the patient's immune system, and one can monitor the status of the

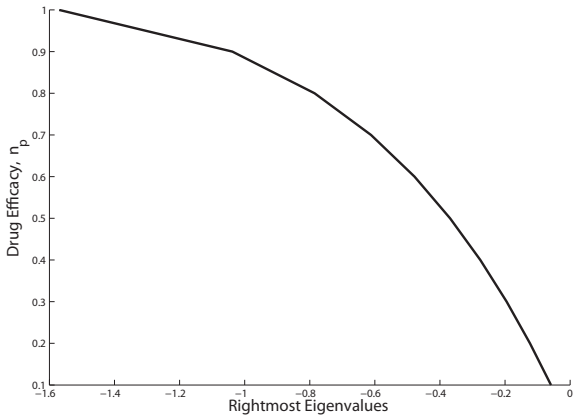

Figure 3. Movement of the rightmost eigenvalues w.r.t drug efficacy: The rightmost eigenvalue moves to the imaginary axis as the drug efficacy, n_p decreases, and the status of the patient becomes less stable.

immune system. Consequently, as time goes, the drug efficacy declines and the rightmost eigenvalue becomes larger and moves toward the imaginary axis (Fig. 3). Therefore, to sustain suppression of the viral load for AIDS patients, proactive switching and alternation of antiretroviral drug regimens is required [36].

Previously, the total viral load, $V_I + V_{NI}$, has been established as the primary prognostic indicator of progression to AIDS [31], and the status of a patient's immune system is determined only in terms of viral load. However, the differences in parameters lead to widely varying conclusions about HIV pathogenesis [13]. Depending on the parameters involved in the system, such as δ and c, the viral load predictions can vary widely. Therefore, it would be more desirable to determine the stability of the immune system from the eigenvalues of the system, which is a function of the parameters involved in the model of HIV-1, in addition to the total viral load. Switching drugs too early risks poor adherence to a new drug regimen and may prematurely exhaust the limited number of remaining salvage therapies. Otherwise, switching too late leads to accumulation of mutations which leads to failure (i.e., viral rebound) [31]. The eigenvalue movement corresponding to the change of drug efficacy over time in Fig. 3 provides information about stability of the immune system for patients with HIV-1, and therapy regimes to sustain suppression of virus load continuously.

SENSITIVITY ANALYSIS

In this section, eigenvalue and response sensitivity analysis with respect to parameters is considered. For systems of differential equations designed to model real systems, such as biological, chemical, or physical, one of the main goals is to understand the manner in which the parameters interact with properties of the systems, such as stability, dynamics, and response. These parameters are designed to correspond to aspects of the phenomena under investigation (e.g., productively infected T-cell death rate, δ, and clearance rate, c, in the HIV-1 pathogenesis dynamics). Thus, it is desirable to predict how changes in the parameters will affect the system's properties: response and eigenvalues. Some previous work on this topic for the HIV-1 model can be found in literature (see, e.g., [6], [8], [37] and the references therein).

Sensitivity analysis for eigenvalue and response, which has been developed in the context of modern control theory, can provide a mathematical tool for the model given by Eq. (1). The improved understanding the models can then help to design better experiments and develop better treatment regimes. Also, the interpretation of the results of sensitivity analysis for complex models makes it possible to understand which parameters have a greater influence on the response and/or eigenvalues. These parameters play an important role in the model and obtaining good estimates for them is critical especially when compared to other parameters to which solutions are less sensitive [6].

Many alternative models exist to describe HIV dynamics, and while they may show acceptable accuracy in data fitting with estimated parameters, one needs to show which model is actually "better". To do so, we are applying methods, such as model selection [7] and model sensitivity [8] to verify which model is more reasonable. Therefore, sensitivity analysis is necessary for validating a model.

HIV: Eigenvalue Sensitivity

Sensitivity of the rightmost eigenvalues analysis reveals an understanding of the interactions of parameters with properties of systems, such as stability or movement behavior of state variables. Although a stability analysis was carried out using a random sampling method to identify which parameters are important in determining stability for systems of ODEs in [37], the study on eigenvalue sensitivity analysis for HIV-1 model with a time delay is presented here for the first time. The analytical expression for sensitivity of the rightmost eigenvalues can be derived by differentiating both sides of the characteristic equation (2) with respect to a parameter, say q, i.e.,

$$\frac{\partial H(\lambda)}{\partial q} = C(\lambda)\frac{\partial \lambda}{\partial q} + D(\lambda) = 0 \Rightarrow \frac{\partial \lambda}{\partial q} = -\frac{D(\lambda)}{C(\lambda)} \qquad (8)$$

For example, the resulting sensitivity for the clearance rate of virus, c, the time delay, h, productively infected T-cell death rate, δ, and for drug efficacy, n_p is given in Eqs. (9-12).

With the parameter set in Table 1, the rightmost eigenvalues, λ_{rm}, of the system (1) from the previous section is (see Fig. 1)

$$\lambda_{rm} = -0.6118 \qquad (13)$$

Then, by applying this rightmost eigenvalue and the parameter set in Table 1, the eigenvalue sensitivity is obtained from Eqs.

$$\frac{\partial\lambda}{\partial c} = -\frac{2\lambda^2+(2\delta+2c)\lambda+2\delta c-(\lambda+c)(1-n_p)\delta e^{-\lambda h}-(1-n_p)\delta c e^{-\lambda h}}{3\lambda^2+2(2c+\delta)\lambda+(2\delta c+c^2)-(1-n_p)\delta c e^{-\lambda h}-(\lambda+c)(1-n_p)\delta c e^{-\lambda h}(-h)} \tag{9}$$

$$\frac{\partial\lambda}{\partial h} = \frac{(\lambda+c)\left\{\eta e^{-\lambda h}(-\lambda)\right\}}{3\lambda^2+(2c+\delta)2\lambda+(2\delta c+c^2)+\eta e^{-\lambda h}(-1+(\lambda+c)h)} \tag{10}$$

$$\frac{\partial\lambda}{\partial\delta} = -\frac{\lambda^2+2c\lambda+c^2-(\lambda+c)(1-n_p)ce^{-\lambda h}}{3\lambda^2+2(2c+\delta)\lambda+(2\delta c+c^2)-(1-n_p)\delta c e^{-\lambda h}-(\lambda+c)(1-n_p)\delta c e^{-\lambda h}(-h)} \tag{11}$$

$$\frac{\partial\lambda}{\partial n_p} = -\frac{(\lambda+c)\delta c e^{-\lambda h}}{3\lambda^2+2(2c+\delta)\lambda+(2\delta c+c^2)-(1-n_p)\delta c e^{-\lambda h}-(\lambda+c)(1-n_p)\delta c e^{-\lambda h}(-h)}. \tag{12}$$

(9-12) as

$$\begin{aligned}\frac{\partial\lambda_{rm}}{\partial h} &= 0.4495, \quad \frac{\partial\lambda_{rm}}{\partial c} = -0.0173,\\ \frac{\partial\lambda_{rm}}{\partial\delta} &= -0.1828, \frac{\partial\lambda_{rm}}{\partial n_p} = -1.4983.\end{aligned} \tag{14}$$

The signs determine whether small increase in a parameter will increase or decrease the rightmost eigenvalue. If the sensitivity with respect to a parameter is positive, the small increase in parameter makes the rightmost eigenvalues shift toward the right and, thus, the system becomes more unstable, and vice versa. As mentioned in the previous section (see Fig. 1), an increase of delay destabilizes the system (sign of $\partial\lambda/\partial h$ is positive). For the other parameters, the sensitivities have negative signs, which means increases in the parameters stabilize the immune system and make the viral load decay faster. This can be inferred from the dynamics of Eq. (1): δ is the death rate of infected cells, which produce virus, and c is the clearance rate of virus. The sensitivity with respect to the clearance rate, c, of virus is relatively small, which means its effect on the stability of the immune system is not so significant compared to other ones. Also, because one infected T-cell produces N new virions, we can infer that the impact of variation in δ may have greater impact on the system than that of c, which explains why the magnitude of $\partial\lambda/\partial\delta$ is larger than that of $\partial\lambda/\partial c$. In this way, the impact of each parameter on the system is analyzed via the signs and the magnitudes. Also, as mentioned before, the parameters with high sensitivity should be given top priority when choosing which parameters to determine with a high degree of accuracy in estimating model parameters from data.

To carry out parameter estimation for HIV-1 models as in (1), one needs to specify a variance of each parameter in prior distribution [32]. Previously (e.g., in [32], [38], etc.), if enough reliable information is available for some of the parameters, then small variances have been used, and vice versa. In such studies, the same variance has been given for c and δ, because enough prior information is available for both parameters. However, if sensitivity is analyzed as seen in (14), it is recommended to differentiate their variances more delicately depending on the sensitivity results, in order that a model may not be too sensitive to a specific parameter. By combining prior information and sensitivity analysis, more accurate estimation of parameters can be performed.

Eigenvalue Sensitivity and Response Sensitivity

In [8], another type of sensitivity called response sensitivity was applied to the system (1). The response sensitivity analysis provides first-order estimates of the effect of parameter variations on the solutions. For the analysis, one need to solve the state equation and a linear time-varying sensitivity equation simultaneously numerically, for example, using the delay differential equation solver *dde23* in Matlab. Considering the magnitudes and the signs, the result of a response sensitivity analysis presented in [8] shows good agreement with the eigenvalues sensitivities as in (14). The study in [8] showed that the response sensitivity with respect to the time delay has a positive slope; on the other hand, the slopes of the response sensitivity with respect to c and δ are negative. Also, the absolute value of the response sensitivity with respect to c is smaller than that with respect to δ. Those coincide well with the results in (14). For rough comparison purposes, the response can be expressed in terms of the rightmost eigenvalues and the initial condition as

$$V(t) \approx e^{\lambda t} V_0 \tag{15}$$

Taking derivatives of both sides with respect to a parameter yields

$$\underbrace{\frac{\partial V(t)}{\partial\rho}}_{\substack{\text{Response}\\ \text{Sensitivity}}} \approx e^{\lambda t} V_0 \quad \underbrace{\frac{\partial\lambda}{\partial\rho}}_{\substack{\text{Eigenvalue}\\ \text{Sensitivity}}} \quad t \tag{16}$$

Table 2. Two different types of sensitivity for HIV-1 model: eigenvalue sensitivity and response sensitivity.

	Response sensitivity	Eigenvalue sensitivity
Application to HIV-1 Model	Studied in [8]	New in this paper
Objective	Effects of parameters on Response	Effects of parameters on Eigenvalues
Method	Numerical integration (e.g., *dde23* in Matlab)	Analytical derivation (see, e.g., Eqs. (9-12))
Result Comparison	Show similar patterns in magnitudes and signs: for rough estimation, see Eq. (17)	
Future Application	Useful in designing the optimal feedback control [39]	Useful in designing the feedback control via eigenvalue assignment [28]

Then, Eq. (16) is divided by Eq. (15) to yield

$$\underbrace{\frac{\frac{\partial V(t)}{\partial \rho}}{V(t)}}_{\substack{\text{Normalized}\\ \text{Response}\\ \text{Sensitivity}}} \approx \underbrace{\frac{\partial \lambda}{\partial \rho}}_{\substack{\text{Eigenvalue}\\ \text{Sensitivity}}} \times t \tag{17}$$

As seen in the approximation in Eq. (17), the normalized response sensitivity is proportional to the product of eigenvalue sensitivity and time. Even though a rough approximation, this would be helpful in grasping the concept about the relation between two different sensitivity approaches. Response sensitivity is a combined function of zero sensitivity and eigenvalue sensitivity [39]. Therefore, for higher than first order systems of DDEs, it is not easy to derive an explicit relation between two sensitivities. However, Eq. (17) provides a good approximate relationship between them.

Using the eigenvalue sensitivities in (14), without integrating all state variables with respect to parameters of system as presented in [8], one can determine which parameter has the greatest influence on the system. This is achieved by comparing the magnitudes and signs of the eigenvalue sensitivity as in (14).

CONCLUSIONS AND FUTURE WORK

In this study, we considered the model of HIV-1 pathogenesis with an intracellular delay. Because the model is represented by a system of DDEs, traditional approaches are not amenable to its analysis. Utilizing a recently developed Lambert W function-based approach, the eigenvalues of the time-delay model of HIV-1 pathogenesis are obtained. Furthermore, the approach is used to analyze changes in the eigenvalues of the HIV-1 model as a time delay is introduced. An increase in delay destabilizes the HIV system (see Fig. 1), and the result is confirmed via sensitivity analysis with respect to the time-delay, h (i.e., sign of $\partial\lambda/\partial h$ is positive). The movement of the rightmost eigenvalues with respect to the drug efficacy in the model is studied. Using the eigenvalues of the HIV-1 model, the stability of the patients' immune system can be monitored. For example, corresponding to the change in drug efficacy due to mutation of the virus, the rightmost eigenvalues moves toward the right and the immune system of the patient becomes less stable (see Fig. 3). Because each patient has different parameter set, the eigenvalues of the immune system can indicate progression to AIDS more accurately than just total viral load, $V_I + V_{NI}$.

Sensitivity analysis was carried out with the rightmost eigenvalues obtained by using the Lambert W function. Sensitivities with respect to the parameters tell us about the impact of variation of parameters on the immune system with HIV-1 by their signs and magnitudes. For some parameters, the sensitivities have negative signs, which means an increase of the parameters stabilizes the immune system, and vice versa. Also, depending on the roles of the parameters, the magnitudes of sensitivities are different (e.g., c and δ). This sensitivity analysis can be used for various purposes, such as improved estimation of parameters and model validation. Eigenvalues sensitivity with respect to each parameter of the system is expressed analytically in terms of the parameter, and shows good agreement with the response sensitivity result in [8]. Unlike the response sensitivity approach, where integrates all state variables for parameters of the system numerically over time, the eigenvalue sensitivity analysis is achieved analytically as in Eqs. (9-12).

Future work, based on the results presented in this paper, may allow drug therapy design via the feedback control based on the Lambert W function [28] to be implemented with incomplete measurements and to minimize the expected effects of measurement error. For that, the controllability and observability analysis [40] for HIV-1 model with a time delay is being studied by authors. Also, a similar approach can be applied to models for hepatitis B virus (HBV) infections [20] and other viral dynamic models. One of the main goals for this research is to find more efficient and reliable therapy regimes.

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REFERENCES

[1] Perelson, A. S. "Modelling viral and immune system dynamics". *Nat. Rev. Immunol.,* **2**(1).

[2] Adams, B. M., Banks, H. T., Davidian, M., Kwon, H. D., Tran, H. T., Wynne, S. N., and Rosenberg, E. S. "HIV

dynamics: Modeling, data analysis, and optimal treatment protocols". *J. Comput. Appl. Math.,* **184**(1), pp. 10–49.

[3] Kirschner, D., and Webb, G. F. "A model for treatment strategy in the chemotherapy of aids". *Bull. Math. Biol.,* **58**(2), pp. 367–390.

[4] Nowak, M. A., Bonhoeffer, S., Shaw, G. M., and May, R. M. "Anti-viral drug treatment: Dynamics of resistance in free virus and infected cell populations". *J. Theor. Biol.,* **184**(2), pp. 205–219.

[5] Perelson, A. S., and Nelson, P. W. "Mathematical analysis of HIV-1 dynamics in vivo". *SIAM Review,* **41**(1), pp. 3–44.

[6] Banks, H. T., and Bortz, D. M. "A parameter sensitivity methodology in the context of HIV delay equation models". *J. Math. Biol.,* **50**, pp. 607–625.

[7] Bortz, D. M., and Nelson, P. W. "Model selection and mixed-effects modeling of HIV infection dynamics". *Bull. Math. Biol.,* **68**(8), pp. 2005–2025.

[8] Bortz, D. M., and Nelson, P. W. "Sensitivity analysis of a nonlinear lumped parameter model of HIV infection dynamics". *Bull. Math. Biol.,* **66**(5), pp. 1009–1026.

[9] Nelson, P. W., and Perelson, A. S. "Mathematical analysis of delay differential equation models of HIV-1 infection". *Math. Biosci.,* **179**(1), pp. 73–94.

[10] Herz, A. V. M., Bonhoeffer, S., Anderson, R. M., May, R. M., and Nowak, M. A. "Viral dynamics in vivo: Limitations on estimates of intracellular delay and virus decay". *Proc. Nat. Acad. Sci. USA,* **93**(14), pp. 7247–7251.

[11] Mittler, J. E., Sulzer, B., Neumann, A. U., and Perelson, A. S. "Influence of delayed viral production on viral dynamics in HIV-1 infected patients". *Math. Biosci.,* **152**(2), pp. 143–163.

[12] Nelson, P. W., Murray, J. D., and Perelson, A. S. "A model of HIV-1 pathogenesis that includes an intracellular delay". *Math. Biosci.,* **163**(2), pp. 201–215.

[13] Ciupe, M. S., Bivort, B. L., Bortz, D. M., and Nelson, P. W. "Estimating kinetic parameters from HIV primary infection data through the eyes of three different mathematical models". *Math. Biosci.,* **200**(1), pp. 1–27.

[14] Nelson, P. W., Mittler, J. E., and Perelson, A. S. "Effect of drug efficacy and the eclipse phase of the viral life cycle on estimates of HIV viral dynamic parameters". *J. AIDS,* **26**(5), pp. 405–412.

[15] Richard, J. P. "Time-delay systems: an overview of some recent advances and open problems". *Automatica,* **39**(10), pp. 1667–1694.

[16] Asl, F. M., and Ulsoy, A. G. "Analysis of a system of linear delay differential equations". *J. Dyn. Syst. Meas. Control,* **125**(2), pp. 215–223.

[17] Corless, R. M., Gonnet, G. H., Hare, D. E. G., Jeffrey, D. J., and Knuth, D. E. "On the Lambert W function". *Adv. Comput. Math.,* **5**(4), pp. 329–359.

[18] Yi, S., Nelson, P. W., and Ulsoy, A. G. "Survey on analysis of time delayed systems via the Lambert W function". *Dyn. Contin. Discret. Impuls. Syst. Ser. A-Math Anal.,* **14**(S2), pp. 296–301.

[19] Yi, S., Nelson, P. W., and Ulsoy, A. G., 2008. "Analysis and control of time delayed systems via the Lambert W function". In Proceedings of 2008 IFAC, Seoul, Korea (accepted).

[20] Ciupe, S. M., Ribeiro, R. M., Nelson, P. W., Dusheiko, G., and Perelson, A. S. "The role of cells refractory to productive infection in acute hepatitis b viral dynamics". *Proc. Natl. Acad. Sci. USA,* **104**(12), pp. 5050–5055.

[21] Marino, S., Beretta, E., and Kirschner, D. E., 2007. "The role of delays in innate and adaptive immunity to intracellular bacterial infection". *Math. Biosci. Eng.,* **4**(2), pp. 261–286.

[22] Perelson, A. S., Neumann, A. U., Markowitz, M., Leonard, J. M., and Ho, D. D. "HIV-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time". *Science,* **271**(5255), pp. 1582–1586.

[23] Ho, D. D., Neumann, A. U., Perelson, A. S., Chen, W., Leonard, J. M., and Markowitz, M. "Rapid turnover of plasma virions and cd4 lymphocites in HIV-1 infection". *Nature,* **373**(6510), pp. 123–126.

[24] Hale, J. K., and Lunel, S. M. V. *Introduction to functional differential equations*. Springer-Verlag, New York.

[25] Banks, H. T., and Manitius, A. "Projection series for retarded functional differental equations with applications to optimal control problems". *J. Differ. Equ.,* **18**(2), pp. 296–332.

[26] Lunel, S. M. V. *Exponential type calculus for linear delay equations*. Centrum voor Wiskunde en Informatica, Amsterdam, The Netherlands.

[27] Yi, S., Nelson, P. W., and Ulsoy, A. G. "Delay differential equations via the matrix Lambert W function and bifurcation analysis: Application to machine tool chatter". *Math. Biosci. Eng.,* **4**(2), pp. 355–368.

[28] Yi, S., Nelson, P. W., and Ulsoy, A. G. "Eigenvalue assignment via the Lambert W function for control for time-delay systems". *J. Vib. Control (in press)*.

[29] Shinozaki, H., and Mori, T. "Robust stability analysis of linear time-delay systems by Lambert W function: Some extreme point results". *Automatica,* **42**(10), pp. 1791–1799.

[30] Radjavi, H., and Rosenthal, P. *Simultaneous triangularization*. Springer, New York.

[31] D'Amato, R. M., D'Aquila, R. T., and Wein, L. M. "Management of antiretroviral therapy for HIV infection: Analyzing when to change therapy". *Manage. Sci.,* **46**(9), pp. 1200–1213.

[32] Huang, Y. X., Rosenkranz, S. L., and Wu, H. L. "Modeling HIV dynamics and antiviral response with consideration of time-varying drug exposures, adherence and phenotypic sensitivity". *Math. Biosci.,* **184**(2), pp. 165–186.

[33] Wodarz, D., and Lloyd, A. L. "Immune responses and the emergence of drug-resistant virus strains in vivo". *Proc. R. Soc. Lond. B,* **271**, pp. 1101–1109.

[34] Dixit, N. M., and Perelson, A. S. "Complex patterns of

viral load decay under antiretroviral therapy: influence of pharmacokinetics and intracellular delay". *J. Theoretical Biology,* **226**(1), pp. 95–109.

[35] Wodarz, D., and Nowak, M. A. "HIV therapy: Managing resistance". *Proc. Natl. Acad. Sci. USA,* **97**(15), pp. 8193–8195.

[36] Martinez-Picado, J., Negredo, E., Ruiz, L., Shintani, A., Fumaz, C. R., Zala, C., Domingo, P., Vilaro, J., Llibre, J. M., Viciana, P., Hertogs, K., Boucher, C., D'Aquila, R. T., and Clotet, B. "Alternation of antiretroviral drug regimens for HIV infection - a randomized, controlled trial". *Ann. Intern. Med.,* **139**(2), pp. 81–89.

[37] Rong, L. B., Feng, Z. L., and Perelson, A. S., 2007. "Emergence of HIV-1 drug resistance during antiretroviral treatment". *Bull. Math. Biol.,* **69**, pp. 2027–2060.

[38] Wu, H. L., Huang, Y. X., Acosta, P., Rosenkranz, S. L., Kuritzkes, D. R., Eron, J. J., Perelson, A. S., and Gerber, J. G. "Modeling long-term HIV dynamics and antiretroviral response - effects of drug potency, pharmacokinetics, adherence, and drug resistance". *J. AIDS,* **39**(3), pp. 272–283.

[39] Rosenwasser, Y., and Yusupov, R. *Sensitivity of automatic control systems*. CRC Press, Boca Raton, Fla.

[40] Yi, S., Nelson, P. W., and Ulsoy, A. G. "Controllability and observability of systems of linear delay differential equations via the matrix Lambert W function". *IEEE Trans. Autom. Control,* **53**(3), pp. 854–860.