Precision in the Specification of Ordinary Differential Equations and Parameter Estimation in Modelling Biological Processes

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Abstract

The chapter describes some of the benefits and challenges associated with mathematical modeling using differential equations to describe non-linear time varying processes in the study of HIV and Hepatitis B etiology and treatment. Emphasis is placed on opportunities for statistical input and collaboration with mathematician in development and implementation of mathematical modelling.

Keywords: longitudinal data, nonlinear regression, ordinary differential equations, parameter estimation.

1 Introduction

In recent years the use of differential equations to describe the dynamics of within host viral infections, most frequently HIV-1 or Hepatitis B or C dynamics, has become quite common. The pioneering work described in [9, 27, 20, 19] provided estimates of both the HIV-1 viral clearance rate, $c$, and infected cell turnover rate, $\delta$, and revealed that while it often takes years for HIV-1 infection to progress to AIDS, the virus is replicating rapidly and continuously throughout these years of apparent latent infection. In addition, at least two compartments of viral producing cells that decay at different rates were identified. Estimates of infected cell decay and viral clearance
rates dramatically changed the understanding of HIV replication, etiology, and pathogenesis. Since that time, models of this type have been used extensively to describe and predict both in vivo viral and/or immune system dynamics and the transmission of HIV throughout a population. However, there are both mathematical and statistical challenges associated with models of this type and the goal of this chapter is to describe some of these as well as offer possible solutions or options. In particular statistical aspects associated with parameter estimation, model comparison and study design will be described. Although the models developed by Perelson et al. [20, 19] are relatively simple and were developed nearly 20 years ago, these models will be used in this chapter to demonstrate concepts in a relatively simple setting. In the first section, a statistical approach for model comparison is described using the model developed in [19] as the null hypothesis model for formal statistical comparison to an alternative model. In the next section, the concept of the mathematical sensitivity matrix and it’s relationship to the Fisher Information Matrix will be described, and will be used to demonstrate how to evaluate parameter identifiability in ODE models. The next section demonstrates how to determine what types of additional data are required to address the problem of non-identifiable parameters in ordinary differential equation models. Examples are provided to demonstrate these concepts. The chapter ends with some recommendations.

Throughout the remainder of this chapter, the term compartments refers to the time varying states in a system of ordinary differential equations (ODEs) and parameters to refer to the constants (either known or unknown) in the vector field which defines the specific system of ODE’s. The following notation will be used. The \( m \) states of an ODE with time \( t \) as independent variable will be described by \( \mathbf{X}(t) = X_1(t), \ldots, X_m(t) \) with a (possibly unknown) parameter vector \( \Theta = (\theta_1, \ldots, \theta_p) \) and vector field, \( f \), which describes the system. The general system of ODE’s is described as:

\[
\frac{d\mathbf{X}}{dt} = f(\mathbf{X}, \Theta), \quad \mathbf{X}(0) = \mathbf{X}_0
\]  

Given the true states \( \mathbf{X}(t) \), one then observes noisy data from one or more of the states

\[
\mathbf{Y}(t_j) = \mathbf{X}(t_j) + \epsilon(t_j),
\]

for \( j = 1, 2, \ldots, n \), where \( \epsilon(t_j) \) is the measurement error assumed to be independently and identically distributed with zero mean.

2 Model Mis-specification and Statistical Model Comparison

As described in the introduction Highly Active Anti-Retroviral Therapy (HAART) produced dramatic reduction of viral loads in HIV-1 infected children and adults. Soon after HAART was introduced, estimates of decay rates of viral RNA and infected cell populations were obtained using mathematical models [9, 27, 20, 19], and estimates of the time on treatment required to eradicate viral infection were made. Many researchers have used these models to measure the biphasic decline of HIV-1 infected cell compartments in adults [18, 17, 29] and children [15, 16] and discuss the possibility of viral eradication after two or more years of therapy. However, it is now obvious that even after many years of successful treatment, ongoing viral replication persists in at least one population of CD4+ T-cells in peripheral blood [30, 21]. In addition, interruption of therapy is generally associated with rapid rebound of virus [17, 4, 7], indicating that viral infection has not been eradicated as predicted. Finally, intermittent episodes of detectable viremia, or “blips”
in viral load are sometimes observed in patients who otherwise have been successfully treated with HAART to establish viral loads below the level of detection. Thus it has become clear that HIV continues to replicate in most individuals long after the times initially estimated for eradication based on the biphasic model developed by Perelson [19]. Since that time, much has been learned about the reservoirs responsible for this persistent infection. These include reactivation of replication competent provirus in latently infected cells which has been shown to persist for long after virus is successfully suppressed [30, 21, 6, 3, 5], failing efficacy of the treatment regimen, and possibly most important, hidden reservoirs of productively infected cells in various compartments other than peripheral blood mononuclear cells. Most of these hypothesis assume that the original models developed by Ho, Wei, and Perelson [9, 27, 20, 19] are correct, and the reason eradication was not achieved is that additional sources of viral replication were overlooked. In order to accommodate longer and longer periods of viral persistence, many researchers continue to add additional linearly (on the log scale) compartments with differing constant decay rates. Indeed, previous estimates of time to eradication of infected cells were based on the assumption that the per capita rates of decay were constant over time. However, it seems unlikely that a single, constant decay rate for an infected cell population is maintained throughout the time course used in estimates of eradication of infected cell populations, especially when no aspects of the immune response or homeostasis are included in the model. In this section a model which contains “density dependent” per capita decay rates for HIV infected cells is considered as an alternative to the Perelson bi-phasic decay model is formulated and compared to the Perelson model via statistical inference; treating the Perelson model as the “null hypothesis”. Additional details on the approach can be found in [11].

Assuming constant per capita decay rates, the decline (or growth) of a population is exponential, and depends on the size of the population in a linear way, i.e., the decay in the population is proportional (via a constant) to the size of the population, and can be described with linear differential equations. In a density-dependent decay model, this proportionality is variable: the per capita decay rate depends on the size of the population, resulting in a model described by non-linear differential equations which governs the population dynamics. Population dynamics models of this type are often used in population biology [12] as an alternative to long-term exponential growth or decay: density dependent homeostatic mechanisms are described for lymphocyte populations in mice [23] and humans [4, 8, 10]; time dependent decay of a single infected cell compartment was suggested as a possible alternative explanation for the biphasic decay pattern observed in HIV-1 decline by [15] and [1].

In order to assess the accuracy of the assumption of simple exponential decay of infected cell populations, a parameterized model for HIV-1 plasma RNA decline after HAART was developed [11]. In this model, a single parameter can be tested with statistical methods to determine if density-dependent decay is a factor in the biphasic pattern that has been observed in HIV-1 RNA decay after treatment. Incorporating the density-dependent decay mechanism for both the short-lived and long-lived infected cells described in [19] can dramatically alter conclusions about the rate at which infected cells are decaying and the associated estimates of time to eradication of both short-lived and long-lived infected cells. This model also has parameters which can be tested to determine if, in addition to density-dependent decay, more than one population of infected cells is contributing to the overall population of viral RNA. The possibility that only one population of infected cells is contributing to the total viral load in the presence of density dependent decay was suggested in [15] and [1], i.e. that what has previously been described as biphasic decay is the result of density-dependent decay of this single population.
It should be noted that the alternative model evaluated is designed to test the assumption of simple exponential decay of infected cell populations, and does not specify the mechanisms; possible mechanisms include differential activity by the immune system or natural cellular homeostasis responsible for this nonlinear decay. Data used for analysis was collected from HIV-1 infected children initiating treatment with HAART consisting of at least three agents at least one of which was a protease inhibitor. Blood samples were taken prior to starting therapy and at multiple time-points afterwards, with data collected so that both first and second phase decay could be estimated. Adherence to the prescribed drug regimen was assessed by direct observation and parent interviews. These data have been presented previously [16, 11] where additional details on study design and methods are provided.

The following model for decay of HIV-1 RNA after initiation of HAART is used to test the assumption of constant log linear decay of infected cell compartments. Here, $X$ represents the population of short-lived infected cells, $Y$ the population of long-lived infected cells, and $V$ the population of HIV-1 RNA.

$$\frac{dX}{dt} = -\delta X^r$$

(3)

$$\frac{dY}{dt} = -\mu Y^r$$

(4)

$$\frac{dV}{dt} = p_x X + p_y Y - cV$$

(5)

These equations extend the model described in [19] by allowing for density-dependent decay of infected cell populations. Note that the right-hand sides of equations (3) and (4) can be written as $(\delta X^{r-1}) X$ and $(\mu Y^{r-1}) Y$ respectively so that the per capita decay rate for the short-lived infected cells is $\delta X^{r-1}$ and for long-lived infected cells is $\mu Y^{r-1}$. If $r$ is not equal to one, the per capita decay rate of these two populations depends on the density of the decaying population. Note that if the parameter $r$ is equal to one, this model reduces to the model presented in [19] which is referred to as the constant decay model for viral decay after initiation of HAART. The parameter $p_x$ represents the contribution to the viral RNA population from short-lived infected cells and $p_y$ represents the contribution to the viral RNA population from long-lived infected cells. To test whether or not density-dependent decay is a factor in the decline of the infected cell populations $X$ and $Y$ the primary hypotheses of interest is $H_0 : r = 1$. Other relevant estimates and tests are whether $p_x = 0$ and $p_y = 0$, i.e. whether at least two populations of infected cells contribute to the total viral load, and whether $\delta = 0$ and $\mu = 0$, i.e. whether there is significant decay in the infected cell populations which are producing viral RNA in the presence of density dependant decay.

To obtain the model solutions for plasma viremia, short- and long-lived infected cells, we solved equations (3) and (4) under the assumption that $r \neq 1$ to obtain

$$X(t) = \left[ \delta \ast (r - 1) \ast t + x_0^{1-r} \right]^{\frac{1}{1-r}}$$

(6)

$$Y(t) = \left[ \mu \ast (r - 1) \ast t + y_0^{1-r} \right]^{\frac{1}{1-r}}$$

and substituted these solutions into equation (5) to obtain

$$\frac{dV}{dt} = p_x \left[ \delta \ast (r - 1) \ast t + x_0^{1-r} \right]^{\frac{1}{1-r}} + p_y \left[ \mu \ast (r - 1) \ast t + y_0^{1-r} \right]^{\frac{1}{1-r}} - cV$$

(7)
If $r = 1$ the solutions to (3) and (4) are simple first order exponential decay curves and the model is identical to the one presented in [19]. Equations (6) describe the model-predicted densities of short-lived infected and long-lived infected cells after drug therapy and the solution of (7) describes the model-predicted plasma viremia density after drug therapy. We used numerical solutions to (7) in the Marquart non-linear least squares algorithm to estimate $\delta$, $\mu$, $r$, $p_x$, and $p_y$. All analyses allowed used observed initial viral load, and both infected cell populations for each child; assuming that, conditional on initial viral load and infected cell compartments, the viral load trajectories are independent and conducted various diagnostics to verify this assumption. Profile bootstrap methods were used to calculate the 95% confidence intervals for the parameters of interest. Additional details on methods for parameters estimation and inference, as well as other details of the study design and methods can be found on [16, 11].

The estimates of time to eradication of the short-lived infected and long-lived infected cell populations under the density-dependent decay model were obtained by using equations (6) with the estimated parameters to determine the time required for the initial populations to decay to one infected cell. For the constant decay model, we used first-order exponential trajectories for the infected cell populations.

Data from all six children was used to fit both the density-dependent and constant models. The estimates of $\delta$, $\mu$, $r$, $p_x$, and $p_y$ from the density-dependent and constant decay models and associated 95% confidence intervals are shown in Table 1. For all but one child (Child 4) the confidence interval for the estimate of the parameter $r$ does not contain one, indicating that density-dependent decay plays a role in the decline of infected cell populations after initiation of treatment in this data set. In other words, the assumption of simple exponential decay for both short- and long-lived infected cells is violated for the data we analyzed. Also $p_x$ and $p_y$, the viral production rates for short-lived and long-lived infected cells, are both significantly different than zero, indicating that at least two populations of infected cells are contributing to the viral pool in the presence of density-dependent decay. Finally, our estimates of both $\delta$ and $\mu$, the decay coefficients for the short-lived and long-lived infected cell populations, are both significantly different than zero for all but one child using the constant decay model. In contrast, the estimated coefficient, $\mu$, is not significantly different than zero for 5 of the 6 children suggesting that there may be no overall decline in the long-lived infected cell compartment. Both the estimated density-dependent and constant decay model trajectories along with the observed plasma viremia data are shown in Figure 1. Projections based on the constant and density-dependent decay models for time to viral eradication (viral load < 1 copy) are shown in Figures 2A and 2B for Child 1. The estimated time to eradication of short lived cells for that child under the constant decay model was 56 days while that time was 271 days based on the density dependent decay model. For the long-lived infected cell population the estimated time to eradication based on the constant decay model was 1.2 years. In contrast, that estimate as 5.2 years based on the density dependent decay model.

The statistical analysis presented here rejects the constant decay model for infected cells developed by Perelson in [19] in favor of the density dependent decay model for this data set. The qualitative conclusions are quite different. In the constant decay model, both short- and long-lived infected cells are predicted to be eradicated within a few years. In the density dependent decay model, the decay parameter for long-lived infected cells is not significantly different than zero for 5 out of the 6 children evaluated so that the long-lived cell population may not be eradicated at all. If that population is decaying, the estimate of time to eradication is significantly longer, in some cases by many years, than the original estimates obtained by Perelson.
Table 1: Parameter Estimates from Constant and Density-Dependent Decay Models with 95% Parametric Bootstrap Confidence Intervals.

<table>
<thead>
<tr>
<th>Child</th>
<th>$\delta$</th>
<th>$\mu$</th>
<th>$p_x$</th>
<th>$p_y$</th>
<th>$r$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.0172</td>
<td>0.00243</td>
<td>80.3</td>
<td>7.81</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>(0.00037 to 186)</td>
<td>(-0.0001 to 0.0265)</td>
<td>(79.4 to 2,993,371)</td>
<td>(0.00287 to 305)</td>
<td>(0.01 to 0.56)</td>
</tr>
<tr>
<td>2</td>
<td>0.236</td>
<td>0.00672</td>
<td>146</td>
<td>1.02</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>(0.00156 to 0.682)</td>
<td>(0.00002 to 0.0160)</td>
<td>(128 to 959)</td>
<td>(0.361 to 3.14)</td>
<td>(0.02 to 0.50)</td>
</tr>
<tr>
<td>3</td>
<td>0.00616</td>
<td>-0.00001</td>
<td>484</td>
<td>0.76</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>(0.00160 to 0.193)</td>
<td>(-0.00022 to 0.00618)</td>
<td>(402 to 2038)</td>
<td>(0.00001 to 22.2)</td>
<td>(0.17 to 0.67)</td>
</tr>
<tr>
<td>4</td>
<td>0.0106</td>
<td>0.00023</td>
<td>202</td>
<td>1.16</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>(0.00006 to 0.257)</td>
<td>(-0.00 to 0.0112)</td>
<td>(0.837 to 4898)</td>
<td>(0.02 to 3.15)</td>
<td>(-0.00246 to 0.59)</td>
</tr>
<tr>
<td>5</td>
<td>0.00356</td>
<td>-0.00003</td>
<td>520</td>
<td>0.0671</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>(0.00138 to 0.0132)</td>
<td>(-0.00008 to 0.00028)</td>
<td>(457 to 1380)</td>
<td>(0.00099 to 0.77)</td>
<td>(0.24 to 0.45)</td>
</tr>
<tr>
<td>6</td>
<td>0.252</td>
<td>0.0265</td>
<td>816</td>
<td>163</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>(0.00320 to 158)</td>
<td>(0.00001 to 0.0860)</td>
<td>(588 to 5,382,581)</td>
<td>(1.09 to 1733)</td>
<td>(0.01 to 0.55)</td>
</tr>
</tbody>
</table>

This is example is provided in order to emphasize the need to carefully evaluate assumptions and compare models with formal statistical procedures. Like all statistical analysis, it is not the case that we conclude the density dependent decay model is the correct model; in fact it almost certainly is not. However, we are able to reject the Perelson constant decay model in favor of the density dependent decay model indicating that additional work with careful attention to model assumptions is needed in order to build and validate a model before using it to make predictions.

3 Model Parameter Identifiability and Study Design

Although the work in [27, 9] had enormous impact in identifying the rapid dynamics of within host viral viral dynamics, 68% confidence intervals were reported in [9] for the cell-free viral RNA clearance rate, $c$, since 95% intervals were too large to be meaningful. This suggested that “information” about the parameter $c$ is very limited based on the observations of viral load used to estimate that
parameter. In other words, observed viral load is not “sensitive” to the viral clearance parameter, $c$, in the model used in that work.

Similarly, Lewin et al [13] used measurements of hepatitis B viral load after treatment with potent antiviral therapy and a mathematical model that included parameters for the death rate of infected cells, $\delta$, the clearance of free virion, $c$, and two parameters, $\epsilon$ and $\eta$ representing drug efficacy at different points in the viral replication cycle to evaluate complex decay profiles after treatment for hepatitis B infection. In that work, they were unable to estimate the efficacy parameter, $\eta$, which represents the efficacy of drug therapy in preventing new cells from becoming infected. They conducted their estimation of the remaining three parameters by setting $\eta = 0.5$ and repeating the analysis with $\eta = 0$ and $\eta = 1$. They found very little difference in the resulting estimates of $c$, $\delta$, and $\epsilon$ in all three analyses, suggesting that hepatitis B viral load is not “sensitive” to the parameter $\eta$ in the model used in their work.

This inability to accurately estimate certain parameters is well known in a variety of fields. In numerical linear algebra, when not all parameters can be estimated from the available data the model is referred to as “ill-posed” (if no unique solution exists) or “ill-conditioned” (if solutions are unstable) [25]. In the study of differential equations, parameters are referred to as “sloppy” or “stiff”, depending on whether their uncertainty is large or require small step sizes to be accurately estimated from the data, respectively; see, e.g., [24, 26, 22]. In statistics, the parameters which cannot be estimated from the available data are referred to as being non-identifiable.

In the mathematical differential equations literature, sensitivity analysis is a widely used approach to provide guidance on which observations and at what time points measurements should be obtained in order to provide the most precise estimates of individual model parameters. Specifically, sensitivity analysis evaluates which compartments in a system of ODE's are sensitive to changes in a specific parameter in the system by calculating the rate of change of the compartment with respect to the parameter (over time), thereby providing information about times at which compartments are most sensitive (i.e. vary the most with respect to) a specific parameter in the system. Unfortunately, sensitivity analysis is a univariate method, and it is not clear how to evaluate sensitivity when one wants to estimate two or more parameters simultaneously, e.g., estimation of HIV or Hepatitis B viral clearance and infected cell decay parameters.

A powerful statistical tool for simultaneous parameter estimation is the Fisher Information Matrix (FIM), which has been well described in the statistical literature. However, the properties of ODE system are not widely studied in the statistical literature while the mathematical literature generally does not focus on the concepts of identifiability and inference for ODE parameter estimates. Fortunately, there is a simple relationship between sensitivity analysis and the Fisher Information Matrix. This insight allows matrix characteristics of the FIM to be explored by evaluating the corresponding characteristics of the simpler matrix derived from sensitivity analysis, which will be referred to as the sensitivity matrix. As a consequence, a combination of sensitivity analysis and the FIM can be used to determine how data should be collected in order to ensure the stable estimation of specific parameters in systems of ODEs. That is, these two tools can be used in combination for study design by identifying which model compartments, and at which time points within these compartments, observations should be measured in order to precisely estimate parameters of interest.
3.1 The Sensitivity Matrix

In the differential equations literature, traditional sensitivity analysis involves analysis of the derivative of $X(t)$ with respect to a single parameter $\theta$ over time. Specifically, the sensitivity function $\frac{\partial X}{\partial \theta}(t)$, quantifies the effect of variations of the parameter $\theta$ on the time course of model outcome(s). In addition to other useful properties, the sensitivity functions provide information about time points at which measurements from compartments or states described by the differential equations are most informative for the estimation of the specific parameter $\theta$, since it identifies time points at which measurements are most "sensitive" to the specific parameter $\theta$.

The sensitivity function(s) for a system of differential equations with respect to a single parameter, $\theta$, can be calculated by noting that the sensitivity function $\frac{\partial X}{\partial \theta}(t)$ satisfies the differential equation

$$\frac{d}{dt}\left(\frac{\partial X}{\partial \theta}\right) = \frac{\partial f}{\partial X}(X(t, \theta); \theta) \frac{\partial X}{\partial \theta} + \frac{\partial f}{\partial \theta}(X(t, \theta); \theta).$$

This allows one numerically calculate the sensitivity function $\frac{\partial X}{\partial \theta}(t)$ as the solution to this differential equation even if there are no closed forms for $X(t)$.

For ease of notation throughout the rest of this subsection and the following two subsection, it is assumed that $X$ refers to a single state system from which observations $Y$ are obtained. The extension to the case where data are collected from multiple states is straight forward and follows the ideas described here with somewhat more complicated notation. This will be revisited in section 3.4 where adding data from additional compartments to improve parameter identifiability and estimation precision is described.

When there are multiple parameters $\Theta = (\theta_1, \ldots, \theta_p)$ to be estimated and the compartment $X(t)$ is observed at time $t = t_1, \ldots, t_n$, the sensitivity matrix is defined as:

$$J(\Theta) = \begin{pmatrix}
\frac{\partial X(t_1, \theta)}{\partial \theta_1} & \ldots & \frac{\partial X(t_n, \theta)}{\partial \theta_1} \\
\vdots & \ddots & \vdots \\
\frac{\partial X(t_1, \theta)}{\partial \theta_p} & \ldots & \frac{\partial X(t_n, \theta)}{\partial \theta_p}
\end{pmatrix},$$

which is a $p \times n$ matrix ($p \times (m \times n)$ matrix when data is observed from all the $m$ states of the system) of time varying functions. Note that each row of $J(\Theta)$ includes the values of the sensitivity function $\frac{\partial X(t, \theta)}{\partial \theta_i}$ at observed time $t = t_1, \ldots, t_n$. Hence, by looking at each row of $J(\Theta)$ separately, one will know when is the most informative time to sample from the compartment $X$ described by that row in order to estimate a specific parameter, $\theta_i$ individually.

Unfortunately, in practice, one usually needs to estimate the unknown parameters $\Theta = (\theta_1, \ldots, \theta_p)$ simultaneously. In this case, it will not be suitable to look at the sensitivity functions $\frac{\partial X(t, \theta)}{\partial \theta_i}$ (other than to eliminate parameters that cannot be estimated from data from a specific compartment) because this will not explain how the model variations would affect the simultaneous estimation of parameters. Without additional tools, it is unclear how to use the sensitivity matrix $J(\Theta)$ to evaluate which of a collection of parameters can estimated simultaneously given the available data or to design the time points at which measurements are most informative for simultaneously estimating multiple parameters $\Theta$. 

8
3.2 The Fisher Information Matrix

The Fisher information matrix is well known in statistics and can be combined with sensitively analysis to understand the the simultaneous estimation of multiple parameters. Based on the observed value $Y_i$’s, the least square estimates (LSE) of $\Theta = (\theta_1, \ldots, \theta_p)$ is defined to be

$$\hat{\Theta} = \arg \min_{\Theta} \sum_{j=1}^{n} (Y_j - X(t_j, \Theta))^2,$$

The LSE estimate $\hat{\Theta}$ is the maximum likelihood estimate (MLE) if the error terms $\epsilon(t_j)$ in (2) are independent and identically distributed as $N(0, \sigma^2)$. Under this setting, the log-likelihood function is given by

$$\log L(\Theta) = -\frac{1}{2\sigma^2} \sum_{j=1}^{n} (Y_j - X(t_j, \Theta))^2 - \log(\sqrt{2\pi}\sigma)^n,$$

and the corresponding score function by

$$\frac{\partial \log L(\Theta)}{\partial \Theta} = \frac{1}{\sigma^2} \sum_{j=1}^{n} (Y_j - X(t_j, \Theta)) \frac{\partial X(t_j, \Theta)}{\partial \Theta}.$$

If $Y_j - X(t_j, \Theta)$ is a real-valued random variable and $\frac{\partial X(t_j, \Theta)}{\partial \Theta}$ is a $p \times 1$ vector, the Fisher information matrix is given by

$$\mathcal{I}(\Theta) = \frac{1}{\sigma^2} \sum_{j=1}^{n} \left( \frac{\partial X(t_j, \Theta)}{\partial \Theta} \right) \left( \frac{\partial X(t_j, \Theta)}{\partial \Theta} \right)^T. \quad (9)$$

By the Cramer-Rao inequality, for any unbiased estimator $\hat{\Theta} = (\hat{\theta}_1, \ldots, \hat{\theta}_p)$ of $\Theta = (\theta_1, \ldots, \theta_p)$,

$$\text{Var}(\hat{\Theta}) = [\mathcal{I}(\Theta)]^{-1},$$

is positive semidefinite. If the lower bound is sharp, then in order to minimize $\text{Var}(\hat{\theta}_1), \ldots, \text{Var}(\hat{\theta}_p)$, we need to minimize all diagonal elements of the matrix $[\mathcal{I}(\Theta)]^{-1}$.

3.3 Combining the Sensitivity Matrix and Fisher Information Matrix

To establish the relationship between Fisher information matrix $\mathcal{I}(\Theta)$ in (9) and sensitivity matrix $J(\Theta)$ in (8) define a $p \times 1$ vector

$$v_j = \frac{\partial X(t_j, \Theta)}{\partial \Theta}. \quad (10)$$

Then the sensitivity matrix $J(\Theta)$ in (8) can be rewritten as

$$J(\Theta) = (v_1, v_2, \ldots, v_n)$$

where the vectors $v_j$ form the columns of $J(\Theta)$. Similarly, the Fisher information matrix $\mathcal{I}(\Theta)$ in (9) can be rewritten as

$$\mathcal{I}(\Theta) = \frac{1}{\sigma^2} \sum_{j=1}^{n} v_j v_j^T.$$
Hence, we have
\[ I(\Theta) = \frac{1}{\sigma^2} J(\Theta)(J(\Theta))^T. \]

Based on this relationship, it is easy to derive

- \( I(\Theta) \) in invertible (i.e., \( \text{rank}(I(\Theta)) = p \)) if and only if \( \text{rank}(J(\Theta)) = p \).

- The smallest eigenvalue of \( I(\Theta) \) is proportional to
  \[
  \min_{u \in \mathbb{R}^p: ||u|| = 1} ||(J(\Theta))^T u||^2 = \min_{u \in \mathbb{R}^p: ||u|| = 1} \sum_{j=1}^n (v_j^T u)^2.
  \]

Therefore, in order to evaluate parameter identifiability and obtain the most precise estimates of the parameters \( \Theta \), one should collect measurements at times \( t_1, t_2, \ldots, t_n \) such that

\[
\min_{u \in \mathbb{R}^p: ||u|| = 1} \left[ \sum_{i=1}^n (v_i^T u)^2 \right] \text{ is maximized,}
\]

where \( v_i \) is defined in (10).

### 3.4 Study Design: Impact of New Compartment or Time Points

As pointed out by Wu et al. [28] for the models described in [20], the information contained the total viral load measurements \( V \) is not sufficient for identifying both the viral clearance rate \( c \) and infected cell turnover rate \( \delta \). However, knowing the concentration of infectious virions \( V_I \) provides sufficient additional information to identify all parameters. To understand this, the FIM again provides insight on how additional measurements from a new compartment can provide the sufficient information. This example will be explored in further detail in Section 4.2.

In general, assume that measurements of \( Y = X(t, \Theta) + \epsilon \) from a single compartment of a system of ODEs are observed with the goal of estimating a collection of parameters \( \Theta \) in the ODE model. Define \( p \times 1 \) vectors, \( v_j \), as described in (10) and the \( p \times n \) sensitivity matrix \( J_1(\Theta) = (v_1, v_2, \ldots, v_n) \). The \( p \times p \) FIM is

\[ I_1(\Theta) = \frac{1}{\sigma^2} \sum_{j=1}^n v_j v_j^T = \frac{1}{\sigma^2} J_1(\Theta)(J_1(\Theta))^T. \]

As noted in Section 3.2, the smallest eigenvalue of \( I_1(\Theta) \) is proportional to

\[
\min_{u \in \mathbb{R}^p: ||u|| = 1} ||(J_1(\Theta))^T u||^2 = \min_{u \in \mathbb{R}^p: ||u|| = 1} \sum_{j=1}^n (v_j^T u)^2.
\]

Hence, if \( v_1, \ldots, v_n \) are nearly linearly dependent, then the smallest eigenvalue of \( I_1(\Theta) \) may be close to zero (so \( I_1(\Theta) \) may be poorly conditioned), and thus the diagonal elements of \( I_1^{-1}(\Theta) \) could be very large, so that the variance of the estimates of \( \Theta \) are very large.

Now suppose we take observations from new compartment \( Y^*(t) = X^*(t, \Theta) + \epsilon^*(t) \). Define

\[
v_j^* = \frac{\partial X^*(t_j, \Theta)}{\partial \Theta}, \quad j = 1, 2, \ldots, n_1
\]
then adding observations from the new compartment $Y^*(t)$ will lead to new sensitivity matrix
\[ J_2(\Theta) = (v_1, v_2, \ldots, v_n, v_1^*, v_2^*, \ldots, v_{n_1}^*) , \]
a $p \times (n + n_1)$ matrix, and leads to new Fisher information matrix
\[ I_2(\Theta) = \frac{1}{\sigma^2} \left( \sum_{j=1}^n v_jv_j^T + \sum_{j=1}^{n_1} v_j^*v_j^{*T} \right) = \frac{1}{\sigma^2} J_2(\theta)(J_2(\theta))^T . \]
If the span of the $v_j^*$’s is orthogonal or nearly orthogonal to the span of the original $v_j$’s then the smallest eigenvalues of $I_2(\Theta)$ can be significantly larger than that of $I_1(\Theta)$, implying that adding observations from the new compartment $X^*$ (as demonstrated in (12) and (13) can significantly improve the estimate of $\Theta$. The sensitivity matrices for each compartment of the system of ODE’s can be evaluated to as guide to determine which states or compartments are sensitive to the parameter(s) of interest.

4 Examples

This section contains examples on the combined use of sensitivity analysis and the Fisher information matrix in order to determine which parameters can be estimated from a given set of data or to design studies to insure that all parameters will identifiable. Both examples demonstrate how to use sensitivity analysis to determine which additional compartments should be used to generate observations for analysis in order to eliminate problems of lack of identifiability and improve precision when parameters are poorly estimated.

4.1 Model Parameter Identifiability: Lumped Parameters

As a simple example to illustrate the use of sensitivity analysis and the FIM to evaluate parameter identifiability, suppose the observations
\[ Y(t) = X(t) + \epsilon , \]
where $X(t) = X(t, g(\theta_1, \theta_2, \theta_3, \ldots, \theta_p)$, where the function $g$ does not depend on $t, \theta_3, \ldots, \theta_p$. The question is whether we can estimate the lumped parameters $\theta_1, \theta_2$, based on the observations $Y$. Intuition suggests that the answer is no, but it is useful to formalize this using the FIM and sensitivity matrix. In this case, note that
\[ \frac{\partial X}{\partial \theta_i} = \frac{\partial X}{\partial g} \frac{\partial g}{\partial \theta_i} , \text{ for } i = 1, 2. \]
Thus for the sensitivity matrix $J(\Theta)$ in (8), its first two rows are linearly dependent, and $\text{rank}(J(\Theta)) < p$. Hence the Fisher information matrix $I(\Theta)$ in (9) has rank less than $p$ and so is not invertible. This implies that we cannot estimate $\theta_1, \theta_2, \ldots, \theta_p$ simultaneously based on the observed values $Y$. 

11
4.2 Models for Viral Decay of HIV After Treatment

As described above, 68% confidence intervals were reported in [20] for the cell-free viral RNA clearance rate, $c$, since 95% intervals were too large to be meaningful. This suggested that “information” about the parameter $c$ is very limited based on the observations of viral load used to estimate that parameter. In [20], the following system of differential equation systems are used to describe viral decay after treatment. Before treatment,\[ \begin{align*}
\frac{dT^*}{dt} &= kTV - \delta T^* \\
\frac{dV}{dt} &= N\delta T^* - cV,
\end{align*} \tag{14} \]
where $T^*$ is the infected cells, and $V$ is the viral RNA. The parameter $k$ denotes the viral infectivity, $T$ the uninfected target cells, $N$ the burst size and $c$ the viral clearance rate. After the treatment \[ \begin{align*}
\frac{dT^*}{dt} &= kTV_I - \delta T^* \\
\frac{dV_I}{dt} &= -cV_I \\
\frac{dV_{NI}}{dt} &= N\delta T^* - cV_{NI},
\end{align*} \tag{15} \]
where $V_I$ and $V_{NI}$ denote the infectious and non-infectious viral RNA, respectively.

It is assumed that the system is at quasi steady state before the treatment and the parameter $T$, the uninfected target cells, remains constant $T_0$. In other words, the initial values for the system (15) are given by $T^*(0) = T_0^*$, $V_I(0) = V_0$ and $V_{NI}(0) = 0$, where $(T_0^*, V_0)$ are the values for the steady state of the system (14).

When measured in a clinical setting, the observed viral load data are a combination of infectious and non-infectious viral load, so that $V(t) = V_I(t) + V_{NI}(t)$ provides the model for the mean structure of the observed data, $(v_0, \ldots, v_n)$ at sampling times $(t_0, \ldots, t_n)$ for a single patient. A standard approach to estimating $c$ and $\delta$ from the observed data is to use nonlinear least squares. Specifically, the solution $V(t) = V_I(t) + V_{NI}(t)$ to (15) can be obtained either with analytic or numerical techniques, and $c$ and $\delta$ can be estimated by minimizing \[ \sum_{j=1}^{n} \left( \log(v_j) - \log(V(t_j, c, \delta)) \right)^2 \tag{16} \]
with respect to $c$ and $\delta$. In this case, log transformation serves to satisfy the assumption that viral load measurements follow a log-normal distribution so that (16) is the maximum likelihood estimator for $c$ and $\delta$.

In order to evaluate the precision of joint estimation of $c$ and $\delta$ from data on total viral load, we simulated data from each of the three compartments, $V_{NI}$, $V_I$, and $T^*$ using $c = 3$ and $\delta = 0.5$ in the model described in [20] and (15). Figure 3 shows the simulated data with the estimated values $\hat{c} = 3.586$ and $\hat{\delta} = 0.456$, based on nonlinear least squares (16), and the corresponding the model solution for total viral load, $V(t) = V_I(t) + V_{NI}(t)$.

In Figure 4 the contours of the likelihood surfaces or cost function for joint estimation of $c$ and $\delta$ based on the simulated total viral load (infectious plus noninfectious) data are shown. These
contours indicate that data on total viral load are sufficient for estimating the infected cell turnover rate \( \delta \) but will not provide reasonable precision for estimation of viral viral clearance rate \( c \), as indicated by the curved “ridge” in the c-axis of the joint estimation surface. While the parameter \( c \) can be estimated from total viral load, this “ridge” indicates that estimation is not likely to be very precise. Simulated data with additional time points did not significantly change the properties of the likelihood surface for joint estimation of \( c \) and \( \delta \) (data not shown) indicating that the addition of data on total viral load at additional time points will not provide substantially more precise estimates for the parameter \( c \).

In order to evaluate why data on total viral load is not sufficient for estimating the viral clearance rate \( c \) based on the model (14) we calculated the sensitivity functions for total viral load \( V(t) = V_I(t) + V_{NI}(t) \) as defined by (14) with respect to \( c \) and \( \delta \), \( V_c \) and \( V_\delta \) respectively. The results are shown in Figure 5. Figure 5A shows why precise estimation of the parameter \( c \) from total viral load is difficult. While not truly non-identifiable, the sensitivity equation, \( V_c \) is quite flat, although not exactly zero, indicating that while \( c \) is technically identifiable from total viral load, that compartment is not very sensitive to small changes in \( c \) so that precise estimation of \( c \) from data on total viral load can not be achieved with much precision. Conversely, Figure 5B shows the sensitivity of total viral load to the parameter \( \delta \), \( V_\delta(t) \). Total viral load is much more sensitive to small changes in \( \delta \) and so \( \delta \) can be estimated with reasonable precision from total viral load.

When estimating parameters in a system of ODEs, collecting data at additional time points from a single state is only one option for adding data to improve precision of parameter estimates. Collecting data from other states represented in the system is another options which is considered here. Sensitivity analysis can help guide the choice of both compartment from which to sample and times at which data should be a sampled. Sensitivity analysis of the infected cell compartment, \( T^*(t) \) has properties similar to the total viral load. That is, based on the model (14), \( T^*(t) \) is not sensitive to \( c \) but is sensitive to \( \delta \) (analysis not shown). However, in Figure 5 we show the sensitivity of: C) infectious viral load with respect to viral clearance rate \( c \), D) infectious viral load with respect to the parameter \( \delta \). Figure 5C suggests that observing data on infectious viral load will significantly improve precision in the estimation of the viral clearance parameter \( c \). Figure 5D confirms that the infectious cell clearance rate, \( \delta \), is not identifiable from data on infectious viral load, which is obvious since the model for infectious viral load, \( V_I(t) = V_0 e^{-c t} \), does not depend on the parameter \( \delta \).

Based on the sensitivity analysis, we expect that using observed data on both the total viral load and infectious viral load in combination with nonlinear regression and model equations for \( V(t) \) and \( V_I(t) \) will improve precision in estimates of the viral clearance parameters \( c \). When using data from more than one compartment, nonlinear regression is conducted in a manner similar to the procedure used for a single compartment, e.g., minimizing (16) over \( c \) and \( \delta \). When data from more than one compartment is available for parameter estimation, minimization of

\[
\sum_{j=1}^{n} \left[ \frac{(\log(v_j) - \log(V(t_j, c, \delta)))^2}{\sigma_V} + \frac{(\log(v_{Ij}) - \log(V_I(t_j, c, \delta)))^2}{\sigma_{V_I}} \right]
\]

with respect to \( c \) and \( \delta \) provides the maximum likelihood estimates for these parameters assuming a log normal distribution for both total viral load and infectious viral load with measurement errors \( \sigma_V \) and \( \sigma_{V_I} \).
Table 2: Expected variance from Fisher Information for joint estimation of $c$ and $\delta$.

<table>
<thead>
<tr>
<th></th>
<th>$c$</th>
<th>$\delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V$ only</td>
<td>1.94</td>
<td>0.05</td>
</tr>
<tr>
<td>$V_I$ only</td>
<td>0.01</td>
<td>NA</td>
</tr>
<tr>
<td>$V$ and $T^*$</td>
<td>0.3</td>
<td>0.01</td>
</tr>
<tr>
<td>$V$ and $V_I$</td>
<td>0.01</td>
<td>0.0002</td>
</tr>
<tr>
<td>$T^*$ only</td>
<td>0.65</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Figure 6 shows contours of the likelihood surface for joint estimation of $c$ and $\delta$ (based on simulated data) using data from: (A) the total (infectious+noninfectious) viral load compartments $V(t) = V_I(t) + V_{NI}(t)$ and (B) total and the infectious viral load compartments $V_I(t)$. Note the difference in the change in scale on the horizontal axis for the parameter $c$. As expected, based on the sensitivity analysis, adding data from the infectious viral load compartment dramatically improves the precision in estimation of the viral clearance rate $c$ (Figure 5B). Contours of the likelihood surface for estimation of $c$ and $\delta$ using simulated data from the infected cell compartment and total viral load were examined and do not improve precision in estimation of $c$ (Results not shown). While the infectious viral load compartment carries most of the “information” on the parameter $c$ for the model (14), the infected cell turnover rate $\delta$ is not identifiable from infectious viral load alone, and so observation on either total viral load or infected cell densities are needed in combination with measurements of infectious viral load to estimate both $c$ and $\delta$ with reasonable precision.

A complete description of the expected variance from Fisher Information for joint estimation of $c$ and $\delta$ from individual and combination of compartments is shown in Table 2.

5 Discussion

As described in the introduction, mathematical models have had tremendous impact on the field of HIV and viral dynamics in helping to understand the etiology of the disease and response to treatment. ODE models have been used extensively to evaluate a variety of aspects related to viral and immune-response dynamics. They have also been applied to predict the spread of epidemics of infectious diseases, and in some cases have been relatively successful provided the time period of evaluation is short. ODE models, however, can be extremely sensitive to the assumptions and so careful attention to the mathematical details is required in interpreting their predictions. In a recent high profile example, mathematical models incorrectly predicted the magnitude of the 2014/15 Ebola epidemic [2]. Similarly, recent conclusions about a hidden reservoir in the lymph system that prevents viral eradication were put forth in terms of a highly complex ODE model [14], yet no aspects of immune response were included and all compartments assumed constant decay, both of which can drastically alter the dynamics. Models of these types are common, but too often little attention is given to validating model assumptions and the various aspects of parameter estimation.

This chapter has emphasized the need for careful evaluation of any ODE model since the predictions of these models can be very sensitive to the underlying assumptions. Statistical testing
and model validation are important prior to making conclusions about the dynamics being modeled. Here we demonstrated how a very slight change to a model’s form—e.g., changes in parameter values resulting in a change in the form of the model, or the compartments measured—can result in dramatically altered predictions. In our example, when a constant decay rate is replaced by a density-dependant decay rate, the predicted time to eradication of infected cells is vastly changed. The statistical analysis conducted rejected the constant decay rate model in favor of the density dependent decay rate model in the data analyzed. It has recently been shown that many other factors (not modeled here) contribute to the inability of potent therapy to eradicate infection and, indeed, this example is not intended to provide an accurate model for time to viral eradication. Rather, it demonstrate the type of investigation, including the formal statistical testing of one model against another, that is needed when using mathematical models to describe any phenomena.

This chapter also discussed the concept of parameter identifiability and its relationship to model-state sensitivity to parameters. The primary conclusion is that for a given structure of an ODE system, it may not be possible to estimate a particular parameter even while fully observing data from that state. Or, a particular parameter may be estimated with very poor precision using observations from a given state. In the former case, no number of additional observation will allow the estimation of that parameter: in order to obtain an estimate, data from additional states of the system must be obtained. In the later case, additional observations from the particular state may aid precision, but observations from other states can dramatically improve the precision of the estimate.

In summary, understanding the sensitivity and validity of model specification are a crucial components in the application of dynamical systems to population-based studies. In this direction, there are many opportunities to improve the performance of ODE models in the areas of viral dynamics and epidemiological transmission dynamics. The development of new methods as well as the rigorous application of tools from other disciplines will improve our statistical understanding of parameter estimates, their inference and potentially even estimation and inference for the entire functional form that defines an ODE model.

References


Figure 1: Total body plasma HIV-1 RNA by days since start of treatment for children with fitted trajectories from the density dependent and constant decay models. Solid lines indicate fitted model trajectories from the density dependent decay model and dashed lines indicate fitted model trajectories from the constant decay model.
Figure 2: Projected short-lived (Panel A) and long lived (Panel B) infected cell populations for Child 1. Solid lines indicate fitted model trajectories from the density dependent decay model and dashed lines indicate fitted model trajectories from the constant decay model.

Figure 3: Data simulated with mean specified by total viral load \((V_{NI}(t) + V_I(t))\).
Data used: Total viral load: \( V = V_I + V_{NI} \)

Figure 4: Contours of the likelihood function for joint estimation of \( c \) and \( \delta \) based on observed simulated viral load

Figure 5: Sensitivity equation \( V_C \) (Panel A), \( V_\delta \) (Panel B), \( V_{IC} \) (Panel C) and \( V_{I\delta} \) (Panel D)
Figure 6: Contours of the likelihood function for joint estimation of $c$ and $\delta$ based on observed A. total viral load and infected cells. B. total viral load and infectious viral load. Estimates of $c$ and $\delta$ are shown with *.