

Parameter Selection Methods in Inverse Problem Formulation

H. T. Banks¹ and Ariel Cintrón-Arias^{1,2}

Center for Research in Scientific Computation
Center for Quantitative Sciences in Biomedicine
Department of Mathematics

¹North Carolina State University
Raleigh, NC 27695-8212

and

²Department of Mathematics and Statistics
East Tennessee State University
Johnson City, TN 37614-0663

February 1, 2010

Abstract

We discuss methods for *a priori* selection of parameters to be estimated in inverse problem formulations (such as Maximum Likelihood, Ordinary and Generalized Least Squares) for dynamical systems with numerous state variables and an even larger number of parameters. We illustrate the ideas with an in-host model for HIV dynamics which has been successfully validated with clinical data and used for prediction.

Key Words: Parameter selection, inverse problems, sensitivity, Fisher Information Matrix, HIV models.

1 Introduction

There are many topics of great importance and interest in the areas of modeling and inverse problems which are properly viewed as essential in the use of mathematics and statistics in scientific inquiries. A brief, noninclusive list of topics include the use of traditional sensitivity functions (TSF) and generalized sensitivity functions (GSF) in experimental design (what type and how much data is needed, where/when to take observations) [9, 10, 11, 16, 56], choice of mathematical models and their parameterizations (verification, validation, model selection and model comparison techniques) [7, 12, 13, 17, 21, 22, 24, 25, 41], choice of statistical models (observation process and sampling errors, residual plots for statistical model verification, use of asymptotic theory and bootstrapping for computation of standard errors, confidence intervals) [7, 14, 30, 31, 54, 55], choice of cost functionals (MLE, OLS, WLS, GLS, etc..) [7, 30], as well as parameter identifiability and selectivity. There is extensive literature on each of these topics and many have been treated in surveys in one form or another ([30] is an excellent monograph with many references on the statistically related topics) or in earlier lecture notes [7].

We discuss here an enduring major problem: selection of which model parameters can be readily and reliably (with quantifiable uncertainty bounds) estimated in an inverse problem formulation. This is especially important in many areas of biological modeling where often one has large dynamical systems (many state variables), an even larger number of unknown parameters to be estimated and a paucity of longitudinal time observations or data points. As biological and physiological models (at the cellular, biochemical pathway or whole organism level) become more sophisticated (motivated by increasingly detailed understanding - or lack thereof - of mechanisms), it is becoming quite common to have large systems (10-20 or more differential equations), with a plethora of parameters (25-100) but only a limited number (50-100 or fewer) of data points per individual organism. For example, we find models for the cardiovascular system [16, Chapter 1] (where the model has 16 state variables and 22 parameters) and [50, Chapter 6] (where the model has 22 states and 55 parameters), immunology [48] (8 states, 24 parameters), metabolic pathways [32] (8 states, 35 parameters) and HIV progression [8, 43]. Fortunately, there is a growing recent effort among scientists to develop quantitative methods based on sensitivity, information matrices and other statistical constructs (see for example [9, 10, 11, 23, 28, 37, 38, 59]) to aid in identification or parameter estimation formulations. We discuss here one approach using sensitivity matrices and asymptotic standard errors as a basis for our developments. To illustrate our discussions, we will use a recently developed in-host model for HIV dynamics which has been successfully validated with clinical data and used for prediction [4, 8].

The topic of system and parameter identifiability is actually an old one. In the context of parameter determination from system observations or output it is at least forty years old and has received much attention in the peak years of linear system and control theory in the investigation of observability, controllability and detectability [6, 18, 19, 33, 39, 44, 46, 52, 53]. These early investigations and results were focused primarily on

engineering applications, although much interest in other areas (e.g., oceanography, biology) has prompted more recent inquiries for both linear and nonlinear dynamical systems [5, 15, 29, 35, 42, 47, 58, 59, 60, 61].

1.1 A Mathematical Model for HIV Progression with Treatment Interruption

We summarize and use as an illustrative example one of the many dynamic models for HIV progression found in an extensive literature (e.g., see [1, 2, 3, 4, 8, 20, 26, 49, 51, 57] and the many references therein). For our example model, the dynamics of in-host HIV are described by the interactions between uninfected and infected type 1 target cells (T_1 and T_1^*) (CD4⁺ T-cells), uninfected and infected type 2 target cells (T_2 and T_2^*) (such as macrophages or memory cells, etc.), infectious free virus V_I , and immune response E (cytotoxic T-lymphocytes CD8⁺) to the infection. This model, which was developed and studied in [1, 4] and later extended in subsequent efforts (e.g., see [8]), is essentially one suggested in [26], but includes an immune response compartment and dynamics as in [20]. The model equations are given by

$$\begin{aligned}
\dot{T}_1 &= \lambda_1 - d_1 T_1 - (1 - \bar{\epsilon}_1(t)) k_1 V_I T_1 \\
\dot{T}_2 &= \lambda_2 - d_2 T_2 - (1 - f \bar{\epsilon}_1(t)) k_2 V_I T_2 \\
\dot{T}_1^* &= (1 - \bar{\epsilon}_1(t)) k_1 V_I T_1 - \delta T_1^* - m_1 E T_1^* \\
\dot{T}_2^* &= (1 - f \bar{\epsilon}_1(t)) k_2 V_I T_2 - \delta T_2^* - m_2 E T_2^* \\
\dot{V}_I &= (1 - \bar{\epsilon}_2(t)) 10^3 N_T \delta (T_1^* + T_2^*) - c V_I \\
&\quad - (1 - \bar{\epsilon}_1(t)) 10^3 k_1 T_1 V_I - (1 - f \bar{\epsilon}_1(t)) 10^3 k_2 T_2 V_I \\
\dot{E} &= \lambda_E + \frac{b_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_b} E - \frac{d_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_d} E - \delta_E E,
\end{aligned} \tag{1}$$

together with an initial condition vector $(T_1(0), T_1^*(0), T_2(0), T_2^*(0), V_I(0), E(0))^T$.

The differences in infection rates and treatment efficacy help create a low, but non-zero, infected cell steady state for T_2^* , which is compatible with the idea that macrophages or memory cells may be an important source of virus after T-cell depletion. The populations of uninfected target cells T_1 and T_2 may have different source rates λ_i and natural death rates d_i . The time-dependent treatment factors $\bar{\epsilon}_1(t) = \epsilon_1 u(t)$ and $\bar{\epsilon}_2(t) = \epsilon_2 u(t)$ represent the effective treatment impact of a reverse transcriptase inhibitor (RTI) (that blocks new infections) and a protease inhibitor (PI) (which causes infected cells to produce non-infectious virus), respectively. The RTI is potentially more effective in population 1 (T_1, T_1^*) than in population 2 (T_2, T_2^*), where the efficacy is $f \bar{\epsilon}_1$, with $f \in [0, 1]$. The relative effectiveness of RTIs is modeled by ϵ_1 and that of PIs by ϵ_2 , while the time-dependent treatment function $0 \leq u(t) \leq 1$ represents therapy levels drug level, with $u(t) = 0$ for fully off and $u(t) = 1$, for fully on. Although HIV treatment is nearly always administered as combination therapy, the model allows the possibility of monotherapy, even for a limited period of time, implemented by considering separate treatment functions $u_1(t), u_2(t)$ in the

treatment factors.

As in [1, 4], for our numerical investigations we consider a log-transformed and reduced version of the model. This transformation is frequently used in the HIV modeling literature because of the large differences in orders of magnitude in state values in the model and the data and to guarantee non-negative state values as well as because of certain probabilistic considerations (for further discussions see [4]). This results in the nonlinear system of differential equations

$$\frac{dx_1}{dt} = \frac{10^{-x_1}}{\ln(10)} (\lambda_1 - d_1 10^{x_1} - (1 - \bar{\epsilon}_1(t))k_1 10^{x_5} 10^{x_1}) \quad (2)$$

$$\frac{dx_2}{dt} = \frac{10^{-x_2}}{\ln(10)} ((1 - \bar{\epsilon}_1(t))k_1 10^{x_5} 10^{x_1} - \delta 10^{x_2} - m_1 10^{x_6} 10^{x_2}) \quad (3)$$

$$\frac{dx_3}{dt} = \frac{10^{-x_3}}{\ln(10)} (\lambda_2 - d_2 10^{x_3} - (1 - f\bar{\epsilon}_1(t))k_2 10^{x_5} 10^{x_3}) \quad (4)$$

$$\frac{dx_4}{dt} = \frac{10^{-x_4}}{\ln(10)} ((1 - f\bar{\epsilon}_1(t))k_2 10^{x_5} 10^{x_3} - \delta 10^{x_4} - m_2 10^{x_6} 10^{x_4}) \quad (5)$$

$$\frac{dx_5}{dt} = \frac{10^{-x_5}}{\ln(10)} ((1 - \bar{\epsilon}_2(t))10^3 N_T \delta (10^{x_2} + 10^{x_4}) - c 10^{x_5} - (1 - \bar{\epsilon}_1(t))\rho_1 10^3 k_1 10^{x_1} 10^{x_5} - (1 - f\bar{\epsilon}_1(t))\rho_2 10^3 k_2 10^{x_3} 10^{x_5}) \quad (6)$$

$$\frac{dx_6}{dt} = \frac{10^{-x_6}}{\ln(10)} \left(\lambda_E + \frac{b_E(10^{x_2} + 10^{x_4})}{(10^{x_2} + 10^{x_4}) + K_b} 10^{x_6} - \frac{d_E(10^{x_2} + 10^{x_4})}{(10^{x_2} + 10^{x_4}) + K_d} 10^{x_6} - \delta_E 10^{x_6} \right) \quad (7)$$

where the changes of variables are defined by

$$T_1 = 10^{x_1}, T_1^* = 10^{x_2}, T_2 = 10^{x_3}, T_2^* = 10^{x_4}, V_I = 10^{x_5}, E = 10^{x_6}. \quad (8)$$

We note that this model contains six state variables and 22 (in general, unknown) system parameters given by

$$\theta_2 = (\lambda_1, d_1, \epsilon_1, k_1, \lambda_2, d_2, f, k_2, \delta, m_1, m_2, \epsilon_2, N_T, c, \rho_1, \rho_2, \lambda_E, b_E, K_b, d_E, K_d, \delta_E).$$

A list of the model parameters along with units of these model parameters are given below in Table 1.

The initial conditions for equations (2)–(7) are denoted by $x_i(t_0) = x_i^0$, for $i = 1, \dots, 6$. We will also consider the initial conditions as unknowns and we use the following notation for the vector of parameters and initial conditions:

$$\theta = (\theta_1, \theta_2)$$

where

$$\theta_1 = (x_1^0, x_2^0, x_3^0, x_4^0, x_5^0, x_6^0)^T.$$

Table 1: Parameters for the HIV model.

| Parameter | Units | Description |
|--------------|--|--|
| λ_1 | $\frac{\text{cells}}{\text{ml day}}$ | Target cell type 1 production rate |
| d_1 | $\frac{1}{\text{day}}$ | Target cell type 1 death rate |
| ϵ_1 | — | Target cell type 1 treatment efficacy |
| k_1 | $\frac{\text{ml}}{\text{virions day}}$ | Target cell type 1 infection rate |
| λ_2 | $\frac{\text{cells}}{\text{ml day}}$ | Target cell type 2 production rate |
| d_2 | $\frac{1}{\text{day}}$ | Target cell type 2 death rate |
| f | — | Treatment efficacy reduction in target cell type 2 |
| k_2 | $\frac{\text{ml}}{\text{virions day}}$ | Target cell type 2 infection rate |
| δ | $\frac{1}{\text{day}}$ | Infected cell death rate |
| m_1 | $\frac{\text{ml}}{\text{cells day}}$ | Type 1 immune-induced clearance rate |
| m_2 | $\frac{\text{ml}}{\text{cells day}}$ | Type 2 immune-induced clearance rate |
| ϵ_2 | — | Target cell type 2 treatment efficacy |
| N_T | $\frac{\text{virions}}{\text{cell}}$ | Virions produced per infected cell |
| c | $\frac{1}{\text{day}}$ | Virus natural death rate |
| ρ_1 | $\frac{\text{virions}}{\text{cell}}$ | Average number of virions infecting a type 1 cell |
| ρ_2 | $\frac{\text{virions}}{\text{cell}}$ | Average number of virions infecting a type 2 cell |
| λ_E | $\frac{\text{cells}}{\text{ml day}}$ | Immune effector production rate |
| b_E | $\frac{1}{\text{day}}$ | Maximum birth rate for immune effectors |
| K_b | $\frac{\text{cells}}{\text{ml}}$ | Saturation constant for immune effector birth |
| d_E | $\frac{1}{\text{day}}$ | Maximum death rate for immune effectors |
| K_d | $\frac{\text{cells}}{\text{ml}}$ | Saturation constant for immune effector death |
| δ_E | $\frac{1}{\text{day}}$ | Natural death rate for immune effectors |

As reported in [1, 4], data to be used with this model in inverse or parameter estimation problems typically consisted of monthly observations over a 3 year period (so approximately 36 longitudinal data points per patient) for the states $T_1 + T_1^*$ and V . While this inverse problem is relatively “small” compared to many of those found in the literature, it is still represents a nontrivial estimation challenge and is more than sufficient to illustrate the ideas and methodology we discuss in this presentation. Other difficult aspects (censored data requiring use of the Expectation Maximization algorithm as well as use of residual plots in attempts to validate the correctness of choice of corresponding statistical models introduced and discussed in the next section) of such inverse problems are discussed in the review chapter [7] and will not be pursued here.

2 Statistical Models for the Observation Process

One has errors in any data collection process and the presence of this error is reflected in any parameter estimation results one might obtain. To understand and treat this, one usually specifies a *statistical model* for the observation process in addition to the *mathematical model* representing the dynamics. To illustrate ideas here we use ordinary least squares (OLS) consistent with an error model for absolute error in the observations. For a discussion of other frameworks (maximum likelihood in the case of known error distributions, generalized least squares appropriate for relative error models) see [7]. Here the OLS estimation is based on the mathematical model for in-host HIV dynamics described above. The observation process is formulated assuming there exists a vector $\theta_0 \in \mathbb{R}^p$, referred to as the *true parameter vector*, for which the model describes the log-scaled total number of CD4⁺ T-cells (uninfected and infected) exactly. It is also reasonably assumed that each of n longitudinal observations $\{Y_i\}_{i=1}^n$ is affected by random deviations from the true underlying process. That is, if the mathematical model output is denoted by

$$z(t_i; \theta_0) = \log_{10} \left(10^{x_1(t_i; \theta_0)} + 10^{x_2(t_i; \theta_0)} \right), \quad (9)$$

then the statistical model for the scalar observation process is

$$Y_i = z(t_i; \theta_0) + \mathcal{E}_i \quad \text{for } i = 1, \dots, n. \quad (10)$$

The errors \mathcal{E}_i are assumed to be random variables satisfying the following assumptions:

- (i) the errors \mathcal{E}_i have mean zero, $E[\mathcal{E}_i] = 0$;
- (ii) the errors \mathcal{E}_i have finite common variance, $\text{var}(\mathcal{E}_i) = \sigma_0^2 < \infty$;
- (iii) the errors \mathcal{E}_i are independent (i.e., $\text{cov}(\mathcal{E}_i, \mathcal{E}_j) = 0$ whenever $i \neq j$) and identically distributed.

Assumptions (i)–(iii) imply that the mean of the observation is equal to the model output, $E[Y_i] = z(t_i; \theta_0)$, and the variance in the observations is constant in time, $\text{var}(Y_i) = \sigma_0^2$.

The estimator $\theta_{OLS} = \theta_{OLS}^n$ minimizes

$$\sum_{i=1}^n [Y_i - z(t_i; \theta)]^2. \quad (11)$$

From [54] we find that under a number of regularity and sampling conditions, as $n \rightarrow \infty$, θ_{OLS} is approximately distributed according to a multivariate normal distribution, i.e.,

$$\theta_{OLS}^n \sim \mathcal{N}_p(\theta_0, \Sigma_0^n), \quad (12)$$

where $\Sigma_0^n = \sigma_0^2 [n\Omega_0]^{-1} \in \mathbb{R}^{p \times p}$ and

$$\Omega_0 = \lim_{n \rightarrow \infty} \frac{1}{n} \chi^n(\theta_0)^T \chi^n(\theta_0). \quad (13)$$

Asymptotic theory requires existence of this limit and non-singularity of Ω_0 . The $p \times p$ matrix Σ_0^n is the covariance matrix, and the $n \times p$ matrix $\chi^n(\theta_0)$ is known as the *sensitivity matrix* of the system, and is defined as

$$\chi_{ij}^n(\theta_0) = \left. \frac{\partial z(t_i; \theta)}{\partial \theta_j} \right|_{\theta=\theta_0} \quad 1 \leq i \leq n, \quad 1 \leq j \leq p. \quad (14)$$

If $g \in \mathbb{R}^6$ denotes the right-side of Equations (2)–(7), then numerical values of $\chi^n(\theta)$ are readily calculated, for a particular θ , by solving

$$\frac{dx}{dt} = g(t, x(t; \theta); \theta) \quad (15)$$

$$\frac{d}{dt} \frac{\partial x}{\partial \theta} = \frac{\partial g}{\partial x} \frac{\partial x}{\partial \theta} + \frac{\partial g}{\partial \theta}, \quad (16)$$

from $t = t_0$ to $t = t_n$. One could alternatively solve for the sensitivity matrix using difference quotients (usually less accurately) or by using automatic differentiation software (for additional details on sensitivity matrix calculations see [7, 9, 27, 28, 34, 36]).

The estimate $\hat{\theta}_{OLS} = \hat{\theta}_{OLS}^n$ is a realization of the estimator θ_{OLS} , and is calculated using a realization $\{y_i\}_{i=1}^n$ of the observation process $\{Y_i\}_{i=1}^n$, while minimizing (11) over θ . Moreover, the estimate $\hat{\theta}_{OLS}$ is used in the calculation of the sampling distribution for the parameters. The error variance σ_0^2 is approximated by

$$\hat{\sigma}_{OLS}^2 = \frac{1}{n-p} \sum_{i=1}^n [y_i - z(t_i; \hat{\theta}_{OLS}^n)]^2, \quad (17)$$

while the covariance matrix Σ_0^n is approximated by

$$\hat{\Sigma}_{OLS}^n = \hat{\sigma}_{OLS}^2 \left[\chi(\hat{\theta}_{OLS}^n)^T \chi(\hat{\theta}_{OLS}^n) \right]^{-1}. \quad (18)$$

As discussed in [7, 30, 54] an approximate for the sampling distribution of the estimator is given by

$$\theta_{OLS} = \theta_{OLS}^n \sim \mathcal{N}_p(\theta_0, \Sigma_0^n) \approx \mathcal{N}_p(\hat{\theta}_{OLS}^n, \hat{\Sigma}_{OLS}^n). \quad (19)$$

Asymptotic standard errors can be used to quantify uncertainty in the estimation, and they are calculated by taking the square roots of the diagonal elements of the covariance matrix $\hat{\Sigma}_{OLS}^n$, i.e.,

$$SE_k(\hat{\theta}_{OLS}^n) = \sqrt{(\hat{\Sigma}_{OLS}^n)_{kk}}, \quad k = 1, \dots, p. \quad (20)$$

3 Subset Selection Algorithm

The focus of our presentation here is how one chooses *a priori* (i.e., *before* any inverse problem calculations are carried out) which parameters and initial conditions can be readily estimated with a typical longitudinal data set. That is, from the parameters θ_2 and initial conditions θ_1 , which components of $\theta = (\theta_1, \theta_2)$ yield a subset of readily identifiable parameters and initial conditions? We illustrate an algorithm, developed recently in [28], to select parameter vectors that can be estimated from a given data set using an ordinary least squares inverse problem formulation (similar ideas apply if one is using a relative error statistical model and generalized least squares formulations). The algorithm searches all possible parameter vectors and selects some of them based on two main criteria: (i) full rank of the sensitivity matrix, and (ii) uncertainty quantification by means of asymptotic standard errors. Prior knowledge of a nominal set of values for all parameters along with the observation times for data (but not the values of the observations) will be required for our algorithm. Before describing the algorithm in detail and illustrating its use, we provide some motivation underlying the steps which involve the sensitivity matrix χ of (14) and the Fisher Information Matrix $\mathcal{F} = \chi^T \chi$.

Ordinary least squares problems involve choosing $\Theta = \theta_{OLS}$ to minimize the difference between observations Y and model output $z(\theta)$, i.e., minimize $|Y - z(\theta)|$ (here we use $|\cdot|$ for the Euclidean norm in \mathbb{R}^n). Replacing the the model with a first order linearization about θ_0 , we then wish to minimize

$$|Y - z(\theta_0) - \nabla_{\theta} z(\theta_0)[\theta - \theta_0]|.$$

If we use the statistical model $Y = z(\theta_0) + \mathcal{E}$ and let $\delta\theta = \theta - \theta_0$, we thus wish to minimize

$$|\mathcal{E} - \chi(\theta_0)\delta\theta|,$$

where $\chi = \nabla_{\theta} z$ is the $n \times p$ sensitivity of (14). This is a standard optimization problem [45, Section 6.11] whose solution can be given using the pseudo inverse χ^{\dagger} defined in terms of minimal norm solutions of the optimization problem and satisfying $\chi^{\dagger} = (\chi^T \chi)^{\dagger} \chi^T = \mathcal{F}^{\dagger} \chi^T$. The solution is

$$\delta\Theta = \chi^{\dagger} \mathcal{E}$$

or

$$\Theta = \theta_0 + \chi^{\dagger} \mathcal{E} = \theta_0 + \mathcal{F}^{\dagger} \chi^T \mathcal{E}.$$

If \mathcal{F} is invertible, then the solution (to first order) of the OLS problem is

$$\Theta = \theta_0 + \mathcal{F}^{-1} \chi^T \mathcal{E}. \tag{21}$$

From these calculations, we see that the rank of χ and the conditioning (or ill-conditioning) of \mathcal{F} play a significant role in solving OLS inverse problems. Observe that the error (or noise) \mathcal{E} in the data will in general be amplified as the ill-conditioning of \mathcal{F} increases. We

further note that the $n \times p$ sensitivity matrix χ is of full rank p if and only if the $p \times p$ Fisher matrix \mathcal{F} has rank p , or equivalently, is nonsingular. These underlying considerations have motivated a number of efforts (e.g., see [9, 10, 11]) on understanding the conditioning of the Fisher matrix as a function of the number n and longitudinal locations $\{t_i\}_{i=1}^n$ of data points as a key indicator for well-formulated inverse problems and as a tool in optimal design, especially with respect to computation of uncertainty (standard errors, confidence intervals) in parameter estimates.

Thus we use an algorithm which first seeks sub-vectors of the parameter vector θ for which the corresponding sensitivity matrix has full rank and then use the normalized diagonals of the covariance matrix (the coefficients of variation) to rank the parameters among the resulting sub-vectors according to their potential for reliability in estimation.

In view of the comments above (which are very *local* in nature—both the sensitivity matrix and the Fisher Information Matrix are local quantities), one should be pessimistic about using these quantities to obtain any *nonlocal* selection methods or criteria for estimation. Indeed, for nonlinear complex systems, it is easy to argue that questions related to some type of global parameter identifiability are not fruitful questions to be pursuing.

As we have stated above, to apply the parameter subset selection algorithm we require prior knowledge of nominal variance and nominal parameter values. These nominal values of σ_0 and θ_0 are needed to calculate the sensitivity matrix, the Fisher matrix and the corresponding covariance matrix defined in (18). For our illustration here, we use the variance and parameter estimates obtained in [1, 4] for Patient # 4 as nominal values. In problems for which no prior estimation has been carried out, one must use knowledge of the observation process error and some knowledge of viable parameter values that might be reasonable with the model under investigation.

More precisely, here we assume the error variance is $\sigma_0^2 = 1.100 \times 10^{-1}$, and assume the following nominal parameter values (for description and units see Table 1): $x_1^0 = \log_{10}(1.202 \times 10^3)$, $x_2^0 = \log_{10}(6.165 \times 10^1)$, $x_3^0 = \log_{10}(1.755 \times 10^1)$, $x_4^0 = \log_{10}(6.096 \times 10^{-1})$, $x_5^0 = \log_{10}(9.964 \times 10^5)$, $x_6^0 = \log_{10}(1.883 \times 10^{-1})$, $\lambda_1 = 4.633$, $d_1 = 4.533 \times 10^{-3}$, $\epsilon_1 = 6.017 \times 10^{-1}$, $k_1 = 1.976 \times 10^{-6}$, $\lambda_2 = 1.001 \times 10^{-1}$, $d_2 = 2.211 \times 10^{-2}$, $f = 5.3915 \times 10^{-1}$, $k_2 = 5.529 \times 10^{-4}$, $\delta = 1.865 \times 10^{-1}$, $m_1 = 2.439 \times 10^{-2}$, $m_2 = 1.3099 \times 10^{-2}$, $\epsilon_2 = 5.043 \times 10^{-1}$, $N_T = 1.904 \times 10^1$, $c = 1.936 \times 10^1$, $\rho_1 = 1.000$, $\rho_2 = 1.000$, $\lambda_E = 9.909 \times 10^{-3}$, $b_E = 9.785 \times 10^{-2}$, $K_b = 3.909 \times 10^{-1}$, $d_E = 1.021 \times 10^{-1}$, $K_d = 8.379 \times 10^{-1}$, and $\delta_E = 7.030 \times 10^{-2}$.

In Figure 1 we depict the log-scaled longitudinal observations (data) on the number of CD4⁺ T-cells, $\{y_i\}$, and the model output evaluated at the estimate (the nominal parameter values described above), $z(t_i; \hat{\theta}_{OLS})$, for Patient #4 in [1, 4].

Given the vector

$$\theta = (\theta_1, \theta_2) \in \mathbb{R}^{28},$$

for initial conditions plus system parameters, we will consider sub-vectors, by partitioning into fixed and active (those to possibly be estimated) parameters. It is assumed the fol-

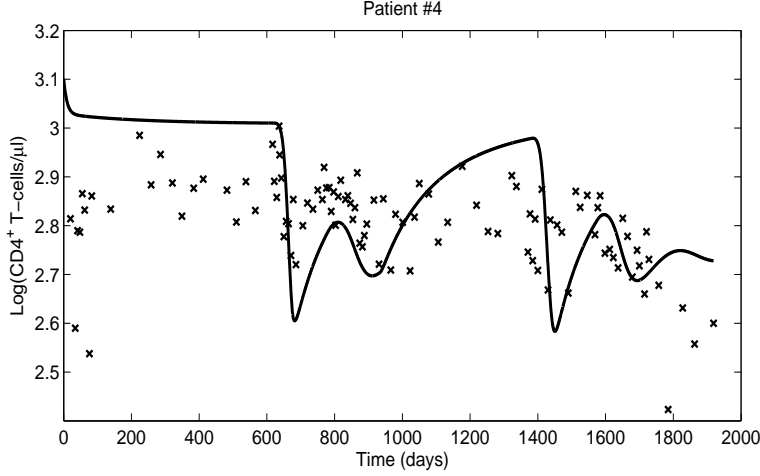


Figure 1: Log-scaled data $\{y_i\}$ of Patient 4 CD4⁺ T-cells (represented as ‘x’), and model output $z(t; \hat{\theta}_{OLS})$ (represented by the solid curve) evaluated at parameter estimates obtained in [1, 4].

lowing entries are always fixed at known values provided in [1, 4]: x_3^0 , x_4^0 , x_6^0 , ρ_1 , and ρ_2 . In other words, we will calculate sub-vectors from the \mathbb{R}^{23} vector

$$q = (x_1^0, x_2^0, x_5^0, \lambda_1, d_1, \epsilon_1, k_1, \lambda_2, d_2, f, k_2, \delta, m_1, m_2, \epsilon_2, N_T, c, \lambda_E, b_E, K_b, d_E, K_d, \delta_E)^T. \quad (22)$$

For every fixed value of p , such that $p = 2, 3, \dots, 22$, there are two partitions of interest: one with p active parameters, and the other one with $23 - p$ fixed parameters. For example, when $p = 22$ one of twenty three possible partitions is the following: fix x_1^0 and consider

$$(x_2^0, x_5^0, \lambda_1, d_1, \epsilon_1, k_1, \lambda_2, d_2, f, k_2, \delta, m_1, m_2, \epsilon_2, N_T, c, \lambda_E, b_E, K_b, d_E, K_d, \delta_E)^T \in \mathbb{R}^{22},$$

as a vector with active parameters. In the implementation of this subset selection algorithm, we carry out the calculation of all possible vectors by using binary matrices with twenty eight columns, such that every row has zeros for entries that are fixed, and ones for those that are active. In the example above, the binary row is (recall that x_3^0 , x_4^0 , x_6^0 , ρ_1 , and ρ_2 are fixed throughout)

$$(0, 1, 0, 0, 1, 0, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 0, 0, 1, 1, 1, 1, 1, 1).$$

For a fixed value of p the set

$$S_p = \{\theta \in \mathbb{R}^p \mid \theta \text{ is a sub-vector of } q \in \mathbb{R}^{23} \text{ defined in equation (22)}\} \quad (23)$$

collects all the possible active parameter vectors in \mathbb{R}^p .

We define the set

$$\Theta_p = \{\theta \mid \theta \in \mathcal{S}_p \subset \mathbb{R}^p, \text{rank}(\chi(\theta)) = p\}, \quad (24)$$

where $\chi(\theta)$ denotes the $n \times p$ sensitivity matrix. By construction, the elements of Θ_p are parameter vectors that give sensitivity matrices with independent columns.

The next step in the selection procedure involves the calculation of standard errors (uncertainty quantification) using the asymptotic theory (see (20)). For every $\theta \in \Theta_p$, we define a vector of *coefficients of variation* $\nu(\theta) \in \mathbb{R}^p$ such that for each $i = 1, \dots, p$,

$$\nu_i(\theta) = \frac{\sqrt{(\Sigma(\theta))_{ii}}}{\theta_i},$$

and

$$\Sigma(\theta) = \sigma_0^2 [\chi(\theta)^T \chi(\theta)]^{-1} \in \mathbb{R}^{p \times p}.$$

The components of the vector $\nu(\theta)$ are the ratios of each standard error for a parameter to the corresponding nominal parameter value. These ratios are dimensionless numbers warranting comparison even when parameters have considerably different scales and units (e.g., N_T is on the order of 10^1 , while k_1 is on the order of 10^{-6}). We then define the *selection score* as

$$\alpha(\theta) = |\nu(\theta)|,$$

where $|\cdot|$ is the norm in \mathbb{R}^p . A selection score $\alpha(\theta)$ near zero indicates lower uncertainty possibilities in the estimation, while large values of $\alpha(\theta)$ suggest that one could expect to find substantial uncertainty in at least some of the components of the estimates in any parameter estimation attempt.

We summarize the steps of the algorithm as follows:

1. **All possible active vectors.** For a fixed value of $p = 2, \dots, 22$, fix $23-p$ parameters to nominal values, and then calculate the set \mathcal{S}_p , which collects all the possible active parameter vectors in \mathbb{R}^p :

$$\mathcal{S}_p = \{\theta \in \mathbb{R}^p \mid \theta \text{ is a sub-vector of } q \in \mathbb{R}^{23} \text{ defined in equation (22)}\}.$$

2. **Full rank test.** Calculate the set Θ_p as follows

$$\Theta_p = \{\theta \mid \theta \in \mathcal{S}_p \subset \mathbb{R}^p, \text{rank}(\chi(\theta)) = p\}.$$

3. **Standard error test.** For every $\theta \in \Theta_p$ calculate a vector of coefficients of variation $\nu(\theta) \in \mathbb{R}^p$ by

$$\nu_i(\theta) = \frac{\sqrt{(\Sigma(\theta))_{ii}}}{\theta_i},$$

for $i = 1, \dots, p$, and $\Sigma(\theta) = \sigma_0^2 [\chi(\theta)^T \chi(\theta)]^{-1} \in \mathbb{R}^{p \times p}$. Calculate the selection score as $\alpha(\theta) = |\nu(\theta)|$.

4 Results and Discussion

Results of the subset selection algorithm with the HIV model of Section 1.1 are given in Table 2. Parameter vectors, condition numbers (ratio of largest to smallest singular value [40]), and values of the selection score are displayed for $p = 11$. The third column of Table 2 displays selection score values from smallest (top) to largest (bottom). For the sake of clarity we only display five out of one million parameter vectors chosen by the selection algorithm. The selection score values range from 2.374×10^0 to 1.910×10^4 for the one million parameter vectors selected when $p = 11$.

Table 2: Parameter vectors obtained with subset selection algorithm for $p = 11$. For each parameter vector $\theta \in \Theta_p$ the sensitivity matrix condition number $\kappa(\chi(\theta))$, and the selection score $\alpha(\theta)$ are displayed.

| Parameter vector, θ | Condition number, $\kappa(\chi(\theta))$ | Selection score, $\alpha(\theta)$ |
|--|--|-----------------------------------|
| $(x_1^0, x_5^0, \lambda_1, d_1, \epsilon_1, \lambda_2, d_2, k_2, \delta, \epsilon_2, c)$ | 1.895×10^5 | 2.374×10^0 |
| $(x_1^0, x_5^0, \lambda_1, d_1, \epsilon_1, \lambda_2, d_2, k_2, \delta, \epsilon_2, N_T)$ | 1.899×10^5 | 2.375×10^0 |
| $(x_1^0, x_5^0, \lambda_1, d_1, \epsilon_1, k_1, \lambda_2, d_2, k_2, \delta, \epsilon_2)$ | 1.193×10^8 | 2.384×10^0 |
| $(x_1^0, x_2^0, \lambda_1, d_1, \epsilon_1, \lambda_2, d_2, k_2, \delta, \epsilon_2, c)$ | 1.480×10^5 | 2.405×10^0 |
| $(x_1^0, x_2^0, \lambda_1, d_1, \epsilon_1, \lambda_2, d_2, k_2, \delta, \epsilon_2, N_T)$ | 1.479×10^5 | 2.406×10^0 |

In [1, 4], the authors estimate the parameter vector

$$\theta = (x_1^0, x_2^0, x_5^0, \lambda_1, d_1, \epsilon_1, k_1, \epsilon_2, N_T, c, b_E) \in \mathbb{R}^{11}.$$

The selection algorithm chooses most of these parameters. For instance, the sub-vector $(x_1^0, \lambda_1, d_1, \epsilon_1, \epsilon_2)$ appears in every one of the top five parameter vectors displayed in Table 2. However, the sub-vector (x_1^0, x_2^0, x_5^0) along with b_E are never chosen among the top five parameter vectors. Even so, use of the subset selection algorithm discussed here (had it been available) might have proved valuable in the efforts reported in [1, 4].

In Figure 2(a) we depict the selection score as a function of the number of parameters. For each fixed value of p , one hundred values are displayed, corresponding to the parameter vectors with the smallest one hundred selection score values. Figure 2(a) suggests that parameter vectors with more than thirteen parameters ($13 \leq p \leq 18$) might be expected to have large uncertainty when estimated from observations, because the selection score ranges from 1.110×10^1 to 5.353×10^2 . Figure 2(b) is a semilog plot of Figure 2(a), i.e., it displays the natural logarithm of the selection score as a function of the number of parameters. Figure 2(b) also depicts the regression line, which fits the natural logarithm of the selection score. From this linear regression we conclude the selection score α grows exponentially

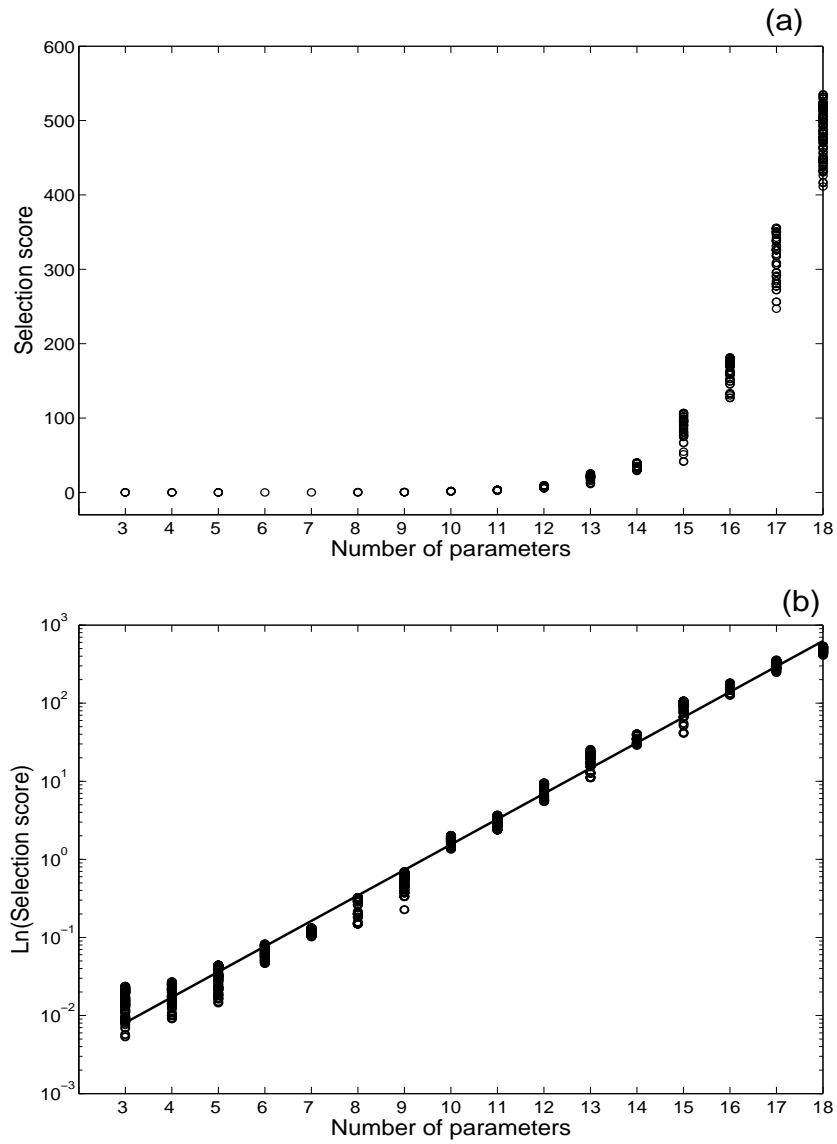


Figure 2: (a) Selection score versus the number of parameters p . (b) Natural logarithm of selection score (circles) and regression line versus number of parameters p . For each fixed value of p , the smallest 100 values of the selection score are displayed.

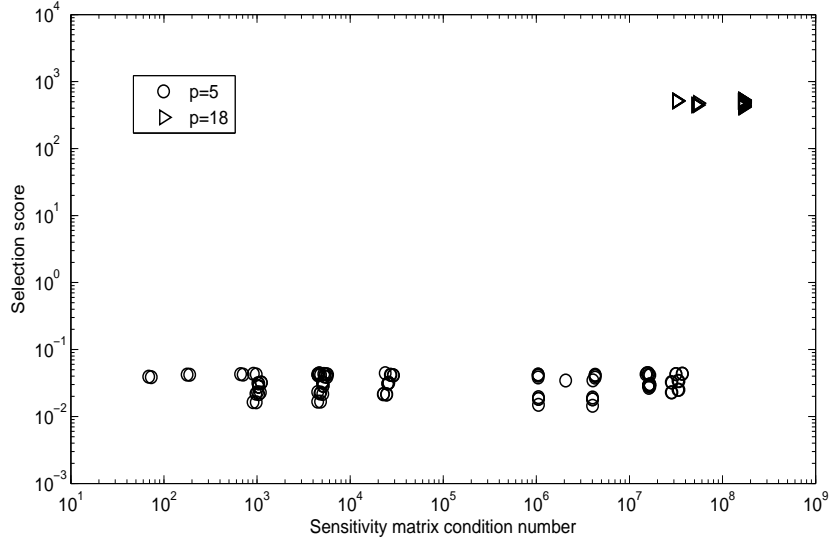


Figure 3: Selection score $\alpha(\theta)$ versus condition number $\kappa(\chi(\theta))$, where $\theta \in \mathbb{R}^p$, for $p = 5$ (circles) and $p = 18$ (triangles). Both axes are in logarithmic scale. The smallest hundred values of the selection score are depicted for each value of p .

with the number of parameters to be estimated. More precisely, for $3 \leq p \leq 18$, we find

$$\alpha \equiv \alpha(p) = C e^{0.75p}, \quad (25)$$

where $C = 8.52 \times 10^{-4}$.

In Figure 3 we graph (in logarithmic scales) the smallest one hundred selection score values $\alpha(\theta)$ versus the sensitivity matrix condition number $\kappa(\chi(\theta))$, with $\theta \in \mathbb{R}^p$, for $p = 5$ (circles) and $p = 18$ (triangles). The condition number $\kappa(\chi(\theta))$ is defined as the ratio of the largest to smallest singular value [40] of the sensitivity matrix $\chi(\theta)$. It is clear from Figure 3 that the selection score drops dramatically from $p = 18$ to $p = 5$, which is suggestive of a reduction in uncertainty quantification for these scenarios. However, the conditioning of the sensitivity matrix does not exhibit this decaying feature. Some values of $\kappa(\chi(\theta))$ are within the same ballpark, $10^7 \leq \kappa(\chi(\theta)) \leq 10^8$ for $p = 5$ and $p = 18$, while other $\kappa(\chi(\theta))$ values for $p = 5$ range considerably from 6.9×10^1 to 4.3×10^6 .

Table 3: Coefficient of variation (CV), defined as the ratio of standard error divided by estimate, for two parameter vectors.

| Parameter | CV for $p = 18$ | CV for $p = 5$ |
|--------------|-----------------------|-----------------------|
| x_1^0 | 8.99×10^0 | 2.84×10^{-3} |
| x_2^0 | 3.04×10^2 | — |
| x_5^0 | 1.20×10^2 | — |
| λ_1 | 5.17×10^{-2} | 7.32×10^{-3} |
| d_1 | 5.84×10^{-2} | — |
| ϵ_1 | 9.29×10^{-3} | 3.64×10^{-4} |
| λ_2 | 3.66×10^0 | — |
| d_2 | 4.30×10^0 | — |
| f | 1.30×10^1 | — |
| k_2 | 4.76×10^0 | — |
| m_1 | 1.42×10^2 | — |
| ϵ_2 | 3.55×10^0 | 1.25×10^{-2} |
| N_T | 8.05×10^0 | — |
| c | 8.98×10^0 | 6.88×10^{-3} |
| λ_E | 9.97×10^1 | — |
| d_E | 4.15×10^1 | — |
| K_d | 1.61×10^2 | — |
| δ_E | 6.37×10^1 | — |

In Table 3 we examine the effect that removing parameters from an estimation has in uncertainty quantification. The coefficient of variation (CV) is defined as the ratio of the standard error to the estimate for each parameter. In Table 3 two cases are considered: $p = 18$, where $\theta = (x_1^0, x_2^0, x_5^0, \lambda_1, d_1, \epsilon_1, \lambda_2, d_2, f, k_2, m_1, \epsilon_2, N_T, c, \lambda_E, d_E, K_d, \delta_E)$, and $p = 5$, where $\theta = (x_1^0, \lambda_1, \epsilon_1, \epsilon_2, c)$. There are substantial improvements in uncertainty quantification. For instance, the reduction of CV for ϵ_2 , going from 3.55×10^0 to 1.25×10^{-2} , implies the standard error is 355% of the estimate for $p = 18$, while it reduces to 1.25% of the estimate when $p = 5$. For the parameter c , it is observed that the standard error reduces from being 898% to less than 1% of the estimate. A similar remarkable improvement is also seen for x_1^0 , with a standard error equal to 899% of the estimate for $p = 18$, dropping to less than 1% for $p = 5$. The improvement in uncertainty quantification is related to going from the upper right corner of Figure 3 into the lower left corner. On one hand, the condition number and selection score for $\theta = (x_1^0, x_2^0, x_5^0, \lambda_1, d_1, \epsilon_1, \lambda_2, d_2, f, k_2, m_1, \epsilon_2, N_T, c, \lambda_E, d_E, K_d, \delta_E)$, are 1.664×10^8 , and 411.022, respectively. On the other hand, the condition number and selection score for $\theta = (x_1^0, \lambda_1, \epsilon_1, \epsilon_2, c)$ are 979.532, and 1.630×10^{-2} , respectively.

5 Concluding Remarks

As we have noted, inverse problems for complex system models containing a large number of parameters are difficult. There is great need for quantitative methods to assist in posing inverse problems that will be well formulated in the sense of the ability to provide parameter estimates with quantifiable small uncertainty estimates. We have introduced and illustrated use of such an algorithm that requires prior local information about ranges of admissible parameter values and initial values of interest along with information on the error in the observation process to be used with the inverse problem. These are needed in order to implement the sensitivity/Fisher matrix based algorithm.

Because sensitivity of a model with respect to a parameter is fundamentally related to the ability to estimate the parameter, and because sensitivity is a local concept, we observe that the pursuit of a global algorithm to use in formulating parameter estimation or inverse problems is most likely a quest that will go unfulfilled.

Acknowledgements

This research was supported in part by Grant Number R01AI071915-07 from the National Institute of Allergy and Infectious Diseases and in part by the Air Force Office of Scientific Research under grant number FA9550-09-1-0226. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIAID, the NIH or the AFOSR.

References

- [1] B.M. Adams. Non-parametric parameter estimation and clinical data fitting with a model of HIV infection. Ph.D. Thesis, North Carolina State University, Raleigh, 2005.
- [2] B.M. Adams, H.T. Banks, M. Davidian, H. Kwon, H.T. Tran, S.N. Wynne and E.S. Rosenberg, HIV dynamics: modeling, data analysis, and optimal treatment protocols, *J. Comp. and Appl. Math.*, **184** (2005), 10–49.
- [3] B.M. Adams, H.T. Banks, H.T. Tran and H. Kwon, Dynamic multidrug therapies for HIV: optimal and STI control approaches, *Math. Biosci. and Engr.*, **1** (2004), 223–241.
- [4] B.M. Adams, H.T. Banks, M. Davidian and E.S. Rosenberg, Model fitting and prediction with HIV treatment interruption data, CRSC-TR05-40, NCSU, October, 2005; *Bull. Math. Biol.*, **69** (2007), 563–584.
- [5] D.T. Anh, M.P. Bonnet, G. Vachaud, C.V. Minh, N. Prieur, L.V. Duc and L.L. Anh, Biochemical modeling of the Nhue River (Hanoi, Vitenam): practical identifiability analysis and parameter estimation, *Ecol. Model.*, **193** (2006), 182–204.

- [6] K.J. Astrom and P. Eykhoff, System identification—A survey, *Automatica*, **7** (1971), 123–162.
- [7] H.T. Banks, M. Davidian, J.R. Samuels and K.L. Sutton, An inverse problem statistical methodology summary, Center for Research in Scientific Computation Technical Report CRSC-TR08-1, NCSU, January, 2008; in *Mathematical and Statistical Estimation Approaches in Epidemiology*, (eds. G. Chowell, et. al.), Springer, New York, 2009, pp. 249–302.
- [8] H.T. Banks, M. Davidian, S. Hu, G. M Kepler and E. S. Rosenberg, Modeling HIV immune response and validation with clinical data, CRSC-TR07-09, March, 2007; *J. Biological Dynamics*, **2** (2008), 357–385.
- [9] H.T. Banks, S. Dediu and S.E. Ernstberger, Sensitivity functions and their uses in inverse problems, *CRSC Technical Report*, CRSC-TR07-12, NCSU, July, 2007; *J. Inverse and Ill-posed Problems*, **15** (2007), 683–708.
- [10] H.T. Banks, S. Dediu, S.L. Ernstberger, F. Kappel, Generalized sensitivities and optimal experimental design, Center for Research in Scientific Computation Technical Report CRSC-TR08-12, NCSU, September, 2008, Revised, November, 2009; *J. Inverse and Ill-posed Problems*, submitted.
- [11] H. T. Banks, S. L. Ernstberger and S. L. Grove, Standard errors and confidence intervals in inverse problems: sensitivity and associated pitfalls, *J. Inverse and Ill-posed Problems*, **15** (2007), 1–18.
- [12] H. T. Banks and B. G. Fitzpatrick, Inverse problems for distributed systems: statistical tests and ANOVA, LCDS/CCS Rep. 88-16, July, 1988, Brown University; *Proc. International Symposium on Math. Approaches to Envir. and Ecol. Problems*, Springer Lecture Note in Biomath., **81** (1989), 262–273.
- [13] H. T. Banks and B. G. Fitzpatrick, Statistical methods for model comparison in parameter estimation problems for distributed systems, CAMS Tech. Rep. 89-4, September, 1989, University of Southern California; *J. Math. Biol.*, **28** (1990), 501–527.
- [14] H.T. Banks, K. Holm and D. Robbins, Standard error computations for uncertainty quantification in inverse problems: Asymptotic theory vs. bootstrapping, Center for Research in Scientific Computation Technical Report CRSC-TR09-13, NCSU, June, 2009; Revised August, 2009; *Arabian Journal for Science and Engineering: Mathematics (AJSE-Mathematics)*, submitted.
- [15] H.T. Banks and J.R. Samuels, Jr., Detection of cardiac occlusions using viscoelastic wave propagation, CRSC-TR08-23, December, 2008; *Advances in Applied Mathematics and Mechanics*, **1** (2009), 1–28.

- [16] J. J. Batzel, F. Kappel, D. Schneditz and H. T. Tran, *Cardiovascular and Respiratory Systems: Modeling, Analysis and Control*, Frontiers in Applied Mathematics **FR34**, SIAM, Philadelphia, 2006.
- [17] E.J. Bedrick and C.L. Tsai, Model selection for multivariate regression in small samples, *Biometrics*, **50** (1994), 226–231.
- [18] R. Bellman and K.M. Astrom, On structural identifiability, *Math. Biosci.*, **7** (1970), 329–339.
- [19] R. Bellman and R. Kalaba, *Quasilinearization and Nonlinear Boundary Value Problems*, American Elsevier, New York, 1965.
- [20] S. Bonhoeffer, M. Rembiszewski, G.M. Ortiz and D.F. Nixon, Risks and benefits of structured antiretroviral drug therapy interruptions in HIV-1 infection, *AIDS*, **14** (2000), 2313–2322.
- [21] H. Bozdogan, Model selection and Akaike’s Information Criterion (AIC): The general theory and its analytical extensions, *Psychometrika*, **52** (1987), 345–370.
- [22] H. Bozdogan, Akaike’s Information Criterion and recent developments in information complexity, *Journal of Mathematical Psychology*, **44** (2000), 62–91.
- [23] M. Burth, G.C. Verghese and M. Vélez-Reyes, Subset selection for improved parameter estimation in on-line identification of a synchronous generator, *IEEE T. Power Syst.*, **14** (1999), 218–225.
- [24] K. P. Burnham and D.R. Anderson, *Model Selection and Multimodel Inference: A Practical Information-Theoretic Approach*, Springer, Berlin Heidelberg New York, 2002.
- [25] K. P. Burnham and D.R. Anderson, Multimodel inference: Understanding AIC and BIC in model selection, *Sociological Methods and Research*, **33** (2004), 261–304.
- [26] D.S. Callaway and A.S. Perelson, HIV-1 infection and low steady state viral loads, *Bulletin of Mathematical Biology*, **64** (2001) 29–64.
- [27] A. Cintrón-Arias, C. Castillo-Chávez, L.M.A. Bettencourt, A.L. Lloyd and H.T. Banks, The estimation of the effective reproductive number from disease outbreak data, Tech Rep CRSC-TR08-08, NCSU, April, 2008; *Math. Biosci. Engr.*, **6** (2009), 261–283.
- [28] A. Cintrón-Arias, H.T. Banks, A. Capaldi and A.L. Lloyd, A sensitivity matrix based methodology for inverse problem formulation, Tech Rep CRSC-TR09, NCSU, April, 2009; *J. Inverse and Ill-posed Problems*, **17** (2009), 545–564.

- [29] C. Cobelli and J. J. DiStefano III, Parameter and structural identifiability concepts and ambiguities: a critical review and analysis, *Am. J. Physiol.* **239** (1980), R7–R24.
- [30] M. Davidian and D.M. Giltinan, *Nonlinear Models for Repeated Measurement Data*, Chapman & Hall, Boca Raton, 1995.
- [31] B. Efron and R.J. Tibshirani, *An Introduction to the Bootstrap*, Chapman & Hall / CRC, Boca Raton, 1998.
- [32] H.W. Engl, C. Flamm, P. Kügler, J. Lu, S. Müller and P. Schuster, Inverse problems in system biology, *Inverse Problems*, **25** (2009), 123014(51pp).
- [33] P. Eykhoff, *System Identification: Parameter and State Estimation*, Wiley & Sons, New York, 1974.
- [34] M. Eslami, *Theory of Sensitivity in Dynamic Systems: an Introduction*, Springer-Verlag, New York, NY, 1994.
- [35] N.D. Evans, L.J. White, M.J. Chapman, K.R. Godfrey and M.J. Chappell, The structural identifiability of the susceptible infected recovered model with seasonal forcing, *Math. Biosci.*, **194** (2005), 175–197.
- [36] M. Fink, myAD: fast automatic differentiation code in MATLAB, 2006; <http://gosh.gmxhome.de/>
- [37] M. Fink, A. Attarian and H. Tran, Subset selection for parameter estimation in an HIV model, *Proc. Applied Math. and Mechanics*, **7** (2008), 1121501–1121502.
- [38] M. Fink, J. J. Batzel and H. Tran, A respiratory system model: parameter estimation and sensitivity analysis, *Cardiovasc Eng.*, **8** (2008), 120–134.
- [39] K. Glover and J.C. Willems, Parametrizations of linear dynamical systems: Canonical forms and identifiability, *IEEE Trans. Automat. Contr.*, **AC-19** (1974), 640–645.
- [40] G.H. Golub and C.F. Van Loan, *Matrix Computations*, Johns Hopkins University Press, Baltimore, 1996.
- [41] C.M. Hurvich and C.L. Tsai, Regression and time series model selection in small samples, *Biometrika*, **76** (1989), 297–307.
- [42] A. Holmberg, On the practical identifiability of microbial growth models incorporating Michaelis-Menten type nonlinearities, *Math. Biosci.*, **62** (1982), 23–43.
- [43] L.E. Jones and A.S. Perelson, Opportunistic infection as a cause of transient viremia in chronically infected HIV patients under treatment with HAART, *Bull. Math. Biol.*, **67** (2005), 1227–1251.

- [44] R.E Kalman, Mathematical description of linear dynamical systems, *SIAM J. Control*, **1** (1963), 152–192.
- [45] D. G. Luenberger, *Optimization by Vector Space Methods*, John Wiley & Sons, New York, NY, 1969.
- [46] A.K. Mehra and D.G. Lainiotis, *System Identification*, Academic Press, New York, 1976.
- [47] I.M. Navon, Practical and theoretical aspects of adjoint parameter estimation and identifiability in meteorology and oceanography, *Dyn. Atmospheres and Oceans*, **27** (1997), 55–79.
- [48] P. Nelson, N. Smith, S. Cuipe, W. Zou, G. S. Omenn and M. Pietropaolo, Modeling dynamic changes in type 1 diabetes progression: Quantifying β -cell variation after the appearance of islet-specific autoimmune responses, *Math. Biosci. Eng.*, **6** (2009), 753–778.
- [49] M.A. Nowak and C.R.M. Bangham, Population dynamics of immune responses to persistent viruses, *Science*, **272** (1996), 74–79.
- [50] J. T. Ottesen, M. S. Olufsen and J. K. Larsen, *Applied Mathematical Models in Human Physiology*, Monographs on Mathematical Modeling and Computation, **MM09**, SIAM, Philadelphia, 2004.
- [51] A.S. Perelson and P.W. Nelson, Mathematical analysis of HIV-1 dynamics in vivo, *SIAM Review*, **41** (1999), 3–44.
- [52] J.G. Reid, Structural identifiability in linear time-invariant systems, *IEEE Trans. Automat. Control*, **22** (1977), 242–246.
- [53] A.P. Sage and J.L. Melsa, *System Identification*, Academic Press, New York, 1971.
- [54] G.A.F. Seber and C.J. Wild, *Nonlinear Regression*, John Wiley & Sons, Chichester, 2003.
- [55] J. Shao and D. Tu, *The Jackknife and Bootstrap*, Springer-Verlag, New York, 1995.
- [56] K. Thomaseth and C. Cobelli, Generalized sensitivity functions in physiological system identification, *Ann. Biomed. Eng.*, **27**(5) (1999), 607 – 616.
- [57] D. Wodarz and M.A. Nowak, Specific therapy regimes could lead to long-term immunological control of HIV, *Proc. National Academy of Sciences*, **96** (1999), 14464–14469.

- [58] L.J. White, N.D. Evans, T.J.G.M. Lam, Y.H. Schukken, G.F. Medley, K.R. Godfrey and M.J. Chappell, The structural identifiability and parameter estimation of a multispecies model for the transmission of mastitis in diary cows, *Math. Biosci.*, **174** (2001), 77–90.
- [59] H. Wu, H. Zhu, H. Miao and A.S. Perelson, Parameter identifiability and estimation of HIV/AIDS dynamics models, *Bull. Math. Biol.*, **70** (2008), 785–799.
- [60] X. Xia and C.M. Moog, Identifiability of nonlinear systems with application to HIV/AIDS models, *IEEE T. Automat. Contr.*, **48** (2003), 330–336.
- [61] H. Yue, M. Brown, F. He, J. Jia and D.B. Kell, Sensitivity analysis and robust experimental design of a signal transduction pathway system, *Int. J. Chem. Kinet.*, **40** (2008), 730–741.