Parameter Selection and Verification Techniques Based on Global Sensitivity Analysis Illustrated for an HIV Model

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Abstract

We consider parameter selection and verification techniques for models having one or more parameters that are noninfluential in the sense that they minimally impact model outputs. We illustrate these techniques for a dynamic HIV model but note that the parameter selection and verification framework is applicable to a wide range of biological and physical models. To accommodate the nonlinear input to output relations, which are typical for such models, we focus on global sensitivity analysis techniques, including those based on partial correlations, Sobol indices based on second-order model representations, and Morris indices, as well as a parameter selection technique based on standard errors. A significant objective is to provide verification strategies to assess the accuracy of those techniques, which we illustrate in the context of the HIV model.

1 Introduction

Biological and physical models commonly have tens to hundreds of inputs – comprised of parameters, discretized spatially-varying coefficients, initial or boundary conditions, or exogenous forces – many of which have minimal influence on model responses. This necessitates the development of robust analysis techniques to establish subsets or subspaces of influential parameters or inputs. This challenge is exacerbated for models such as neutronics equations, which can have 10^6 inputs, of which only 50-100 are considered influential. The need for robust parameter selection techniques is further motivated by the following objectives: (i) determine those inputs that can be uniquely estimated from measured data; (ii) establish the robustness or fragility of models with respect to certain parameter sets; (iii) simplify models by fixing insensitive inputs; and (iv) guide experimental design by ascertaining parameter subsets or subspaces that have the greatest impact on parameter or response sensitivity.

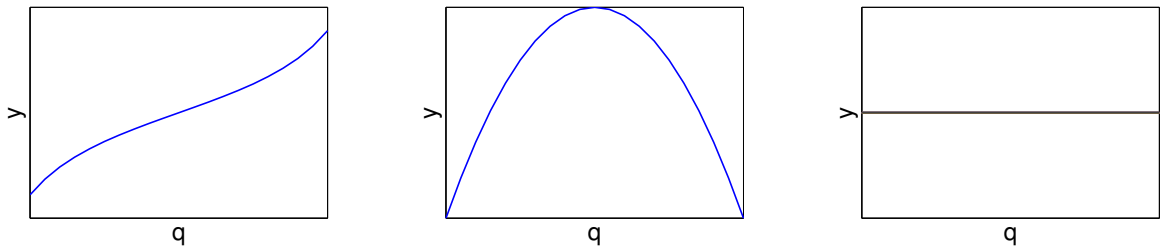
To establish notation and terminology, we consider the nonlinear input-output relation

$$y = f(q)$$

where $q = [q_1, \ldots, q_p]$ denotes the model inputs – e.g., parameters, initial or boundary conditions – and f denotes the mathematical model. For this discussion, we consider real-valued responses $y \in \mathbb{R}^1$.

A significant goal of input or parameter selection techniques is to establish subsets or subspaces of inputs or parameters that can be uniquely identified from data or that strongly influence model responses. Such subsets can be characterized by the concepts of identifiable and influential parameter sets.

The concept of *identifiability* is classical and can be defined as follows. The parameters $q = [q_1, \ldots, q_p]$ are identifiable at q^* if $f(q) = f(q^*)$ implies that $q = q^*$ for all admissible $q \in \mathbb{Q}$. The parameters q are identifiable with respect to a space $\mathcal{I}(q)$, termed the identifiable subspace, if this holds for all $q^* \in I(q)$.



(a) (b) (c)

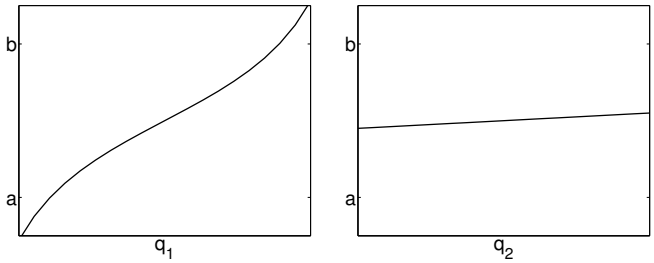
Figure 1: Illustration of $y = f(q)$ for (a) identifiable, (b) unidentifiable and (c) noninfluential parameters q.

Hence identifiable parameters can be uniquely determined from observations. An example of identifiable and nonidentifiable parameters are illustrated in Figure 1 (a) and (b).

Influential parameter spaces are sometimes defined differently in various disciplines. We define the parameter set $q = [q_1, \ldots, q_p]$ to be *noninfluential* on the space $\mathcal{NI}(q)$ if $f(q) - f(q^*) < \varepsilon$ for all q and $q^* \in \mathcal{NI}(q)$. The space $\mathcal{I}(q)$ of influential parameters is defined to be the orthogonal component of $\mathcal{NI}(q)$. Noninfluential parameters, like nonidentifiable parameters, can be fixed for model calibration and uncertainty propagation. Hence, the space of noninfluential parameters is a subspace of the space of nonidentifiable parameters. An example of a noninfluential parameter is illustrated in Figure 1 (c). Furthermore, parameter q_1 is more influential than parameter q_2 if changes in q_1 affect greater changes in y than changes in q_2 do. See Figure 2 for an example of highly and minimally influential parameters. We will quantify the degree of influence using global sensitivity analysis.

For linearly parameterized problems $y = Aq$, it is shown in Chapter 6 of [20] that deterministic and parametrized QR or SVD algorithms can be used to determine subspaces of influential parameters. For the nonlinearly parametrized problems, one typically resorts to global sensitivity analysis or active subspace techniques.

In this paper, we focus on global sensitivity analysis and subset selection based on standard errors to determine subsets $q^s = \{q_1^s, \ldots, q_p^s\} \subset q = \{q_1, \ldots, q_p\}$ of influential parameters. This differs from subspace selection techniques – typically based on QR or SVD algorithms with inputs randomly selected from the admissible input space – which can include linear combinations of inputs [2, 11, 20]. The comparison of active input subspaces with the subset established here for the HIV model constitutes future research.



(a) (b)

Figure 2: Illustration of influential parameters where q_1 is more influential than q_2.

1.1 HIV Model, Inputs and Responses

We illustrate the parameter selection and verification strategies in the context of an HIV model presented in [5] to understand mechanisms regarding the disease dynamics and to develop optimal treatment strategies. The model's predictive capability has been verified using data from patients who underwent a clinical study involving structured treatment interruptions. The system of ODE modeling the HIV disease in [5] is given by

$$
\begin{aligned}
\dot{T_1} &= -d_1 T_1 - (1-\xi_1(t))k_1 V_I T_1 - \gamma_T T_1 + p_T\left(\frac{a_T V_I}{V_I+K_V}+a_A\right)T_2 \\
\dot{T_1^*} &= (1-\xi_1(t))k_1 V_I T_1 - \delta T_1^* - mE_1 T_1^* - \gamma_T T_1^* + p_T\left(\frac{a_T V_I}{V_I+K_V}+a_A\right)T_2^* \\
\dot{T_2} &= \lambda_T \frac{K_s}{V_I+K_s} - \gamma_T T_1 - d_2 T_2 - (1-f\xi_1(t))k_2 V_I T_2 - \left(\frac{a_T V_I}{V_I+K_V}+a_A\right)T_2 \\
\dot{T_2^*} &= \gamma_T T_1^* + (1-f\xi_1(t))k_2 V_I T_2 - d_2 T_2^* - \left(\frac{a_T V_I}{V_I+K_V}+a_A\right)T_2^* \\
\dot{V_I} &= (1-\xi_2(t))10^3 N_T \delta T_1^* - cV_I - 10^3[(1-\xi_1(t))\rho_1 k_1 T_1 + (1-f\xi_1(t))\rho_2 k_2 T_2]V_I \\
\dot{V_{NI}} &= \xi_2(t)10^3 N_T \delta T_1^* - cV_{NI} \\
\dot{E_1} &= \lambda_E + \frac{b_{E_1} T_1^*}{T_1^*+K_{b1}}E_1 - \frac{d_E T_1^*}{T_1^*+K_d}E_1 - \delta_{E1}E_1 - \gamma_E \frac{T_1+T_1^*}{T_1+T_1^*+K_\gamma}E_1 + \frac{p_E a_E V_I}{V_I+K_V}E_2 \\
\dot{E_2} &= \gamma_E \frac{T_1+T_1^*}{T_1+T_1^*+K_\gamma}E_1 + \frac{b_{E2}K_{b2}}{E_2+K_{b2}}E_2 - \delta_{E2}E_2 - \frac{a_E V_I}{V_I+K_V}E_2
\end{aligned}
\tag{1}
$$

with initial conditions $[T_1(0), T_1^*(0), T_2(0), T_2^*(0), V_I(0), V_{NI}(0), E_1(0), E_2(0)]$. Here, T_1 and T_1^* respectively denote uninfected and infected activated (antigen-specific) CD4+ T-cells. Uninfected resting, i.e., not activated, CD4+ T-cells are denoted by T_2 and infected resting CD4+ T-cells are denoted by T_2^*. Infectious free virus is denoted by V_I; this is the virus that is capable of infecting other cells in the plasma. On the other hand, V_{NI} denotes non-infectious free virus, which is yielded inactive by protease inhibitors. HIV-specific effector CD8+ T-cells are denoted by E_1 and HIV-specific memory CD8+ T-cells are denoted by E_2. The compartments of the model are depicted in Figure 3.

Several terms in the model (1) are based on the law of mass action, so that the rate of change in population size is proportional to the population size. The terms $-d_1 T_1$ and $\gamma_T T_1$ in $\dot{T}_1$ are examples of mass action terms. Other terms are based on Michaelis-Menten kinetics, in which the rate saturates at a maximum. An example of this type is $\frac{a_T V_I}{V_I+K_V}$, which is the activation of infected HIV specific resting CD4+ T-cells with a_T being the maximum activation rate. The term $\frac{\lambda_T K_S}{V_I+K_S}$ in the differential equation for $\dot{T}_2^*$ accounts for the source rate of naive CD4+ T-cells. In the equation for $\dot{E}_1$, $\frac{b_{E1}T_1^*}{T_1^*+K_{b1}}E_1$ and $-\frac{d_E T_1^*}{T_1^*+K_d}E_1$ respectively represent dynamic effects that activated, infected CD4+ T-cells have on the effector CD8+ T-cells when

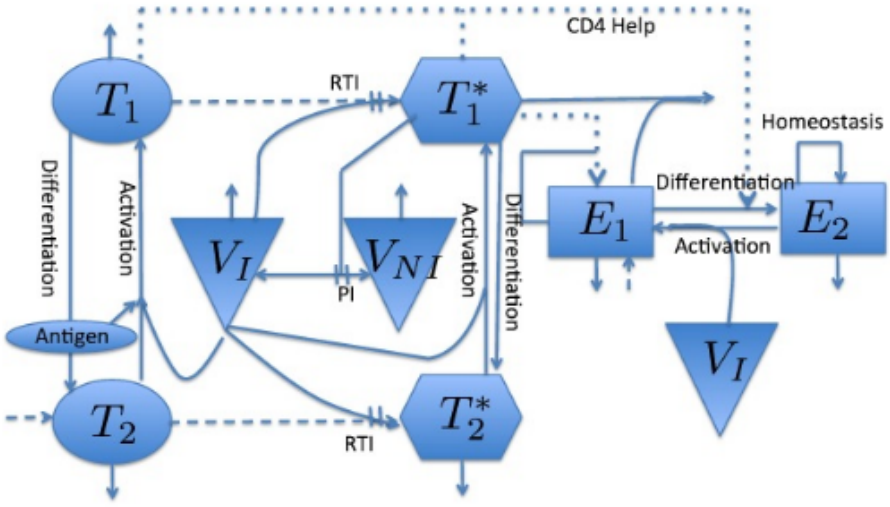


Figure 3: The compartments of HIV model (1).

Parameter	Explanation
δ	Viral produced lysis rate of T_1^*
d_2	T_2 and T_2^* natural death rate
δ_{E2}	Death rate of E_2
m	Rate of removal by cell lysis of T_1^* from the system by E_1
γ_T	Rate at which T_1 and T_1^* differentiate into T_2 and T_2^* , respectively
c	Natural clearance rate of V_I and V_{NI}
δ_{E1}	Constant death rate of E_1
γ_E	Source term for E_1
k_2	Production rate of T_2^* due to encounters between T_2 and V_I that is less than k_1
ρ_1	Rate of removal of V_II through successful infection of T_1
ρ_2	Rate of removal of V_I through successful infection of T_2
d_1	Natural death rate of T_1
ϵ_2	Relative effectiveness of protease inhibitor (PI)
a_A	Activation rate of T_2 and $_2^*$ by non-HIV antigen
ϵ_1	Relative effectiveness of reverse transcriptase inhibitor (RTI)
p_T	Net proliferation of T_1 and T_1^* due to clonal expansion and programmed contraction
p_E	Net proliferation of E_1 due to clonal expansion and programmed contraction
k_1	Production rate of T_1^* from encounters between T_1 and V_I
N_T	Number of RNA copies produced during the process of T_1^* lysis
a_T	Maximum activation rate of T_2 and T_2^*
f	Efficacy of treatment $0 \leq f \leq 1$
λ_E	Constant differentiation of E_2 into E_1
K_V	Half-saturation constant of virus

Table 1: Description of parameters in the model (1).

$K_{b1} < K_d$ and $b_{E1} < b_E$. Also in this differential equation, $\frac{p_E a_E V_I}{V_I + K_V} E_2$ represents the activation of memory CD8+ T-cells into effector CD8+ T-cells. In the differential equation for $\dot{E}_2$, $\frac{E_1(T_1+T_1^*)}{T_1+T_1^*+K_\gamma}$ has an essential role that activated CD4+ T-cells play in the generation of memory CD8+ T-cells, whereas $\frac{b_{E2}K_{b2}E_2}{E_2+K_{b2}}$ and $\delta_{E2}E_2$ are homeostatic regulation terms in E_2.

The parameters in the HIV model (1) are described in Table 1 and nominal values for parameters and initial conditions reported in [3] are compiled in Table 2. The functions $\xi_1 = \epsilon_1 u(t)$ and $\xi_2 = \epsilon_2 u(t)$ represent the impact of the treatment. Here, ϵ_1 is the effectiveness of the reverse transcriptase inhibitor (RTI), whereas ϵ_2 is the effectiveness of the protease inhibitor (PI). Also, $u(t)$ is the HAART drug level, where $u(t) = 1$ when the patient is on treatment, and $u(t) = 0$ when the patient is off treatment. Parameters such as ϵ_1 and ϵ_2, along with many others, can not be directly measured and hence must be estimated through a fit to data.

Among these parameters, however, some do not influence model outputs. These parameters must be identified via parameter selection prior to parameter estimation. Isolating these noninfluential parameters allows us to reduce the parameter dimensions for model calibration and focus on estimating those parameters that can be uniquely determined from the data.

Based on results from [3], we focus on the 15 parameters and initial conditions

$$q = [\lambda_T, d_1, \epsilon_1, k_1, a_T, \epsilon_2, N_T, b_{E2}, a_E, p_E, a_A, p_T, T_1(0), T_1^*(0), T_2(0)] \tag{2}$$

whose values tend to be patient specific. Here, the input dimensions is $p = 15$. The associated random variable, considered for global sensitivity analysis, is denoted by Q. Also, we denoted the admissible input space of biologically feasible parameters and initial conditions by $\mathbb{Q}$. The lower and upper bounds for each parameter, where $q_i \in [\ell b_i, ub_i]$, is summarized in Table 3. For more details of the terms and parameters, see [3, 5].

As detailed in [5], data was collected from patients, in a clinical trial, who underwent anti-retroviral therapy (ART) and had at least one ART interruption. The total CD4+ T-cell count/micro L-blood ($T_1 +$

$\lambda_T = 3.2543$	$d_1 = 0.1317$	$\epsilon_1 = 0.5241$	$k_1 = 4.8200\text{e-}5$
$a_T = 2.3198\text{e-}4$	$\epsilon_2 = 0.7149$	$N_T = 79.26$	$b_{E2} = 0.34554$
$a_E = 1.5332\text{e-}2$	$p_E = 1.0294$	$a_A = 8.07\text{e-}5$	$p_T = 5.531$
$\gamma_T = 3.792\text{e-}4$	$d_2 = 3.096\text{e-}3$	$f = 0.5068$	$k_2 = 2.005\text{e-}9$
$\delta = 0.2095$	$m = 1.127\text{e-}3$	$c = 5.818$	$\lambda_E = 9.9930\text{e-}4$
$b_{E1} = 3.885\text{e-}2$	$K_{b1} = 2.488\text{e-}2$	$d_E = 6.278\text{e-}2$	$K_d = 0.12$
$\delta_{E1} = 5.967\text{e-}2$	$K_{b2} = 86.97$	$\gamma_E = 5.154\text{e-}4$	$K_\gamma = 1.357$
$K_V = 14.79$	$\delta_{E2} = 1.450\text{e-}3$	$K_s = 2.789\text{e+}4$	$T_1(0) = 12.135$
$T_1^*(0) = 5.8604\text{e-}4$	$T_2(0) = 823.59$	$T_2^*(0) = 7.521\text{e-}3$	$V_I(0) = 3.571\text{e+}3$
$V_{NI}(0) = 3.571\text{e+}3$	$E_1(0) = 6.821\text{e-}2$	$E_2(0) = 0.6909$	

Table 2: Nominal values of parameters and initial conditions from [3].

$T_1^* + T_2 + T_2^*$) as well as total RNA copies/mL-plasma ($V_I + V_{NI}$) were recorded during this process.

For global sensitivity analysis, we require a scaler response. At the same time, we are interested in how parameters affect the model output for the feasible input as well for the entire duration of therapy. For these reasons, we choose our scalar model response to be

$$f(q) = \int_0^{1500} T_1(t;q) + T_1^*(t;q) + T_2(t;q) + T_2^*(t;q)\ dt + \int_0^{1500} V_I(t;q) + V_{NI}(t;q)\ dt.$$

To test the parameter selection techniques, we generate synthetic data using the mean values from the model calibration performed in [5], which are summarized in Table 2. The model is solved numerically using `ode15s` in MATLAB.

1.2 Previous Work and Paper Organization

Whereas global sensitivity analysis techniques for parameter selection have not previously been investigated for this dynamic HIV model, certain techniques have been used to analyze other biological models.

Readers are referred to [10] for a case study illustrating the use of sensitivity analysis for a rice model, and [13, 23] for examples of parameter selection in computational and systems biology. The subset selection developed in [4, 6, 9] is applied to the HIV model (1) in [3] and we compare our sensitivity-based parameter subsets to those of [3] in Section 4.

In Section 2, we illustrate the difference between local and global sensitivity analysis using a simple portfolio model. In Section 3, we discuss four different techniques for parameter selection. We start with Partial Correlation [1], which quantifies the linear effects of parameters on the model response. Secondly, we discuss Sobol indices, which are variance-based methods based on a second-order Sobol decomposition. For the HIV example, we discuss the limited accuracy of this decomposition and its affect on parameter selection. Thirdly, we summarize Morris indices using a screening method that ranks parameters in the order of importance. Finally, we discuss the parameter subset selection algorithm discussed in [3]. In Section 4, we present our results of applying parameter selection techniques to the HIV model. We interpret the sensitivity indices from each method and provide a comparison for identifying influential parameters. We present verification techniques to illustrate that non-influential parameters should not affect the model

	λ_T	d_1	ϵ_1	k_1	a_T	ϵ_2	N_T	b_{E2}
ℓb_i	3.1	0.11	0.43	4.0e-5	2.0e-4	0.63	65	0.28
ub_i	3.5	0.15	0.6	5.5e-5	2.7e-4	0.78	85	0.45
	a_E	p_E	a_A	p_T	$T_1(0)$	$T_1^*(0)$	$T_2(0)$	
ℓb_i	1.40e-3	0.85	6.5e-5	5	10.5	5.0e-4	720	
ub_i	1.75e-3	1.3	9.0e-5	6.5	13.5	7.0e-4	950	

Table 3: The lower and upper bounds of parameters, $q_i \in [\ell b_i, ub_i]$, for $i = 1, \ldots, 15$.

output when fixed at nominal values. Finally, we provide comprehensive implications of parameter selection techniques on the HIV model.

2 Global Sensitivity Motivation

There are two types of sensitivity analysis: local versus global. In literature, sensitivity analysis often refers to the local sensitivity analysis, which is typically computed by evaluating the derivative of the response with respect to inputs at nominal input values. On the other hand, global sensitivity analysis considers the effect of parameters over the entire range of input values. Global sensitivity analysis is also used to ascertain how uncertainty in model outputs is apportioned to uncertainties in model inputs; see [17, 19, 20, 21] for details.

We note that global sensitivity techniques rank the relative impact of influential inputs or parameters. Further tests are required to establish that least influential parameters are non-influential in the sense defined in Section 1.

To illustrate the difference between local sensitivity analysis and global sensitivity analysis, we begin by considering the linear portfolio model

$$Y = c_1 Q_1 + c_2 Q_2 \tag{3}$$

considered in [19, 20]. Here, the random variable Y is the return for the investment and $Q_1 \sim N(0, \sigma_1^2)$ and $Q_2 \sim N(0, \sigma_2^2)$ represent hedged portfolios, where c_1 and c_2 are the amounts invested in each portfolio. In this example, we take $c_1 = 2$, $c_2 = 1$, $\sigma_1 = 1$ and $\sigma_2 = 3$. The fact that $\sigma_2 > \sigma_1$ implies that the second portfolio is more volatile than the first. The scatterplots of 1000 joint realizations of q_1, q_2 and y in Figure 4 indicate that Q_2 has more influence on Y than Q_1. Hence, globally, Y is more sensitive to Q_2 than Q_1.

However, the local sensitivity $s_i = \frac{\partial Y}{\partial Q_i}$ for $i = 1, 2$ yields $s_1 = 2$ and $s_2 = 1$, indicating that q_1 is more sensitive. This reflects the amounts invested in the two portfolio rather than the effects of their volatility of the return. Hence the local sensitivity does not incorporate the nonlinear uncertainty structure over the global admissible parameter space nor the effect of parameter variability on the response.

In our HIV example, we are interested in how parameters affect the model response in the entire parameter space, rather than at some nominal parameter values. For this reason, we use global sensitivity analysis as a parameter selection technique and isolate influential parameters from noninfluential parameters. In the next section, we discuss three methods of parameter selection based on global sensitivity analysis and one method based on standard errors.

3 Parameter Selection Methods

The first of the four parameter selection methods that we discuss is termed the Partial Correlation, or Pearson's Correlations. This method quantifies the linear effect of parameters on the model response. Secondly, we detail the use of Sobol indices based on a variance-based, second-order Sobol decomposition. As an initial step, we examine and verify the accuracy of the second-order expansions. Thirdly, we consider the Morris screening method. We note that this method provides a mechanism of ranking parameters but does

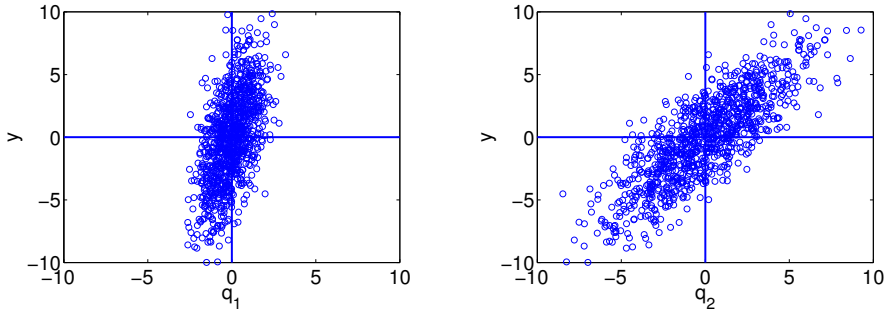


Figure 4: Scatterplots of 1000 joint realizations of y versus (a) q_1 and (b) q_2.

not necessarily quantify their relative importance. Finally, we summarize the parameter subset selection detailed in [3]. This method quantifies the importance of parameters by comparing a dimensionless ratio of standard error and mean for each parameter.

3.1 Partial Correlation

We begin by computing partial correlations as detailed in [1]. For two random variables X and Y, the covariance is given by

$$\text{cov}(X,Y) = \mathbb{E}[(x - \mathbb{E}(X))(Y - \mathbb{E}(Y))] = \mathbb{E}(XY) - \mathbb{E}(X)\mathbb{E}(Y).$$

The partial correlation is then given by

$$\rho_{XY} = \frac{\text{cov}(X,Y)}{\sigma_X \sigma_Y}. \tag{4}$$

The partial correlation quantifies the degree to which two random variables are correlated. For example, $\rho_{XY} = 0$ indicates that X and Y are not correlated. We note that it does not imply that the two random variables are independent since (4) only quantifies linear dependencies between parameters. On the other hand, $\rho_{XY} = \pm 1$ indicates a linear algebraic relation between the variables, in which case they are not jointly identifiable. Values greater than 0.5 generally indicate significant correlations. However, one must study the parameters with partial correlation values less than 0.5 for possible confounding factors or nonlinearities before determining insignificant.

For the HIV example, $X = Q_i$ denotes the random variable for the i^{th} parameter, and Y is the random variable representing the model response. The partial correlation then quantifies the degree of linear correlation between a parameter q_i and model response y. We compute the correlation

$$\rho_{q_i y} = \frac{\sum_j ((q_i)_j - \bar{q_i})(y_j - \bar{y})}{\sqrt{\sum_j ((q_i)_j - \bar{q_i})^2 \sum_k (y_k - \bar{y})^2}},$$

where $\bar{q_i}$ and $\bar{y}$ are the means of q_i and y, respectively. The number of function evaluations required to compute the partial correlation using M Monte Carlo evaluations for p parameters is then $M \times p$.

For this method, variables with large partial correlations are considered more influential on the response than those yielding small values of $\rho_{Q_i Y_i}$. For the portfolio model (3), this would reflect the results shown in Figure 4, which indicate that Q_2 is more influential than Q_1.

3.1.1 Partial Correlation Results

The partial correlation values are computed for the model (1) using $M = 2000$ function evaluations per parameter. The result is plotted in Figure 5 to provide visual comparison for the overall input-output correlation. Since we are interested in the magnitude of correlation values, the negative correlation values are also shown in the positive direction.

The result indicates that N_T is most correlated to the model response. Also, p_T and k_1 are more correlated to the model response than other variables. On the other hand, two of the initial conditions, $T_1(0)$ and $T_1^*(0)$ are not correlated to the model response, implying that they have minimum influence.

3.2 Sobol Indices

To construct Sobol indices, we assume that parameters have been mapped to $[0,1]$ and that $q \sim \mathcal{U}[0,1]^p$. Details regarding the construction of Sobol indices for general densities are provided in [20].

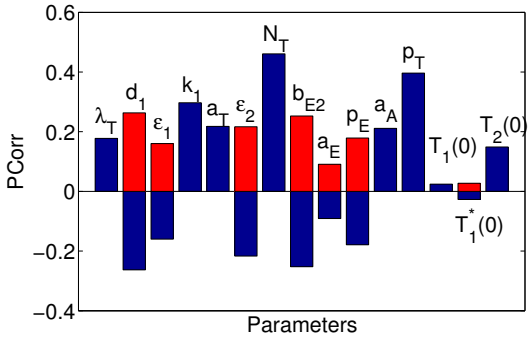


Figure 5: Partial correlation of the scalar response to the input parameters.

3.2.1 Sobol Decomposition

Sobol indices are based on a second-order High Dimensional Model Representation (HDMR) or Sobol representation

$$f(q) \approx f_0 + \sum_{i=1}^{p} f_i(q_i) + \sum_{1 \le i < j \le p} f_{ij}(q_i, q_j). \tag{5}$$

Since the representation (5) is not unique, additional conditions are imposed to ensure the uniqueness of component functions f_i and f_{ij}. As detailed in [14, 16, 20, 21], each component function is uniquely specified by minimizing the functional

$$\mathcal{J} = \int_{\Gamma^p} \left[f(q) - \left(f_0 + \sum_{i}^{p} f_i(q_i) + \cdots + \sum_{i_1 < \cdots < i_s} f_{i_1,\cdots,i_s} q_{i_1}, \cdots, q_{i_s}) \right) \right]^2 dq$$

subject to

$$\int_{\Gamma} f_{i_1,\ldots,i_s}(q_{i_1}, \ldots, q_{i_s})\ dq_{i_k} = 0$$

for $k = 1, \ldots, s$ and $s = 1, \ldots, p$.

The component functions are given by

$$f_i = \int_{\Gamma^{p-1}} f(q)\ dq_{\sim i} \tag{6}$$

$$f_{ij} = \int_{\Gamma^{p-2}} f(q)\ dq_{\sim i,j} \tag{7}$$

where $\Gamma^k = [0,1]^k$ for a positive integer k and the notation $dq_{\sim i}$ denotes $dq_1, \ldots, dq_{i-1}, dq_{i+1}, \ldots, dq_p$.

The variance-based method employs the expansion (5) to quantify the contribution of each parameter to the variance of response. As detailed in [20], the total variance of response Y is given by

$$D = \mathrm{var}(Y) = \int_{\Gamma} f^2(q) dq - f_0^2$$

where f_0 is the mean response given by

$$f_0 = \int_{\Gamma} f(q) dq.$$

The total variance can be expressed as a sum of variances due to first-order and second-order parameter interactions by expressing D as

$$D = \sum_{i=1}^{p} D_i + \sum_{1 \le i < j \le p} D_{ij}$$

where

$$\begin{aligned} D_i &= \int_\Gamma f_i^2(q_i)\ dq_i \\ D_{ij} &= \int_{\Gamma^2} f_{ij}^2(q_i, q_j)\ dq_i\ dq_j. \end{aligned}$$

The Sobol indices are then defined to be

$$S_i = \frac{D_i}{D},\ S_{ij} = \frac{D_{ij}}{D},\ i, j, = 1, \ldots, p.$$

Here S_i are often called the importance measures or first-order sensitivity indices, and they measure the contribution of the parameter q_i on the response variance. A large value of S_i implies stronger influence of parameter q_i on the response variance. Similarly, S_{ij} measures the contribution of parameter interactions between q_i and q_j on the response variance. Since the computation of first- and second- order sensitivity indices requires $p + \frac{p(p-1)}{2}$ model responses, we instead consider the total sensitivity indices

$$S_{T_i} = S_i + \sum_{j=1}^{p} S_{ij}$$

which quantify the total effect of the parameter q_i on the response [20].

3.2.2 Statistical Interpretation

The Sobol indices, along with the expansion terms and partial variances, have expectation or variance interpretations. Let

$$\begin{aligned} \mathbb{E}(Y|q_i) &= \int_{\Gamma^{p-1}} f(q)\ dq_{\sim i} \\ \mathbb{E}(Y|q_i, q_j) &= \int_{\Gamma^{p-2}} f(q)\ dq_{\sim \{ij\}} \end{aligned}$$

denote the expected response when q_i and q_i, q_j are fixed. The component functions are

$$\begin{aligned} &f_0 = \mathbb{E}(Y) \\ &f_i(q_i) = \mathbb{E}(Y|q_i) - f_0 \\ &f_{ij}(q_i, q_j) = \mathbb{E}(Y|q_i, q_j) - f_i(q_i) - f_j(q_j) - f_0. \end{aligned}$$

As detailed in [20],

$$D_i = \mathrm{var}[\mathbb{E}(Y|q_i)]$$

and hence

$$S_i = \frac{\mathrm{var}[\mathbb{E}(Y|q_i)]}{\mathrm{var}(Y)}.$$

Similarly, using the equality

$$D_{ij} = \mathrm{var}[\mathbb{E}(Y|q_i, q_j)] - \mathrm{var}[\mathbb{E}(Y|q_i)] - \mathrm{var}[\mathbb{E}(Y|q_j)],$$

the total sensitivity index has the variance interpretation

$$S_{Ti} = 1 - \frac{\mathrm{var}[\mathbb{E}(Y|q_{\sim i})]}{\mathrm{var}(Y)} = \frac{\mathbb{E}[\mathrm{var}(Y|q_{\sim i})]}{\mathrm{var}(Y)}. \tag{8}$$

The interpretation of $\mathbb{E}(Y|q_i)$ and $\mathrm{var}[\mathbb{E}(Y|q_i)]$ is illustrated in Figure 6 from the portfolio example in Section 2; see also Chapter 15 of [20]. The conditional expectations for fixed q_1 and q_2 are the average values of Y along vertical slices. Again, we see that mean of response for fixed values of q_2 has more variance than that for fixed values of q_1.

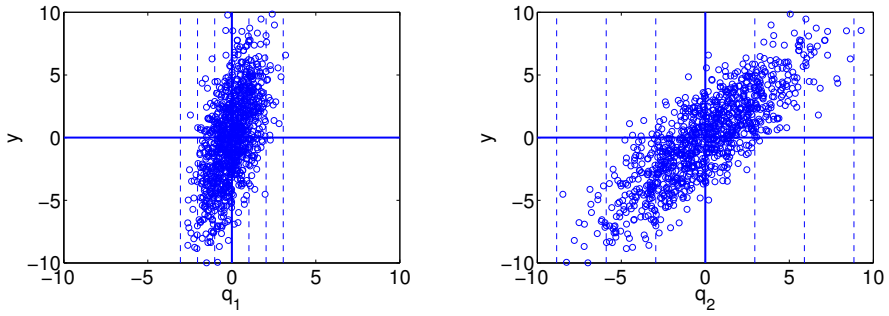


Figure 6: Response for fixed values of (a) q_1 and (b) q_2 illustrating $\mathbb{E}(Y|q_i)$ and $\text{var}[\mathbb{E}(Y|q_i)]$.

3.2.3 Sobol Indices Algorithm

Since the computation of the Sobol indices requires high-dimensional integration, the indices are approximated numerically. If one uses M Monte Carlo evaluations to approximate the mean $\mathbb{E}(Y|q_i)$ and repeats the procedure M times to approximate the variance $\text{var}[\mathbb{E}(Y|q_i)]$, a total of M^2 evaluations will be required to evaluate a single index. The total number of function evaluations required is M^2p, which is computationally prohibitive for a large parameter dimensions p. This motivated the author of [17] to provide a more efficient algorithm to compute Sobol indices that reduces the required evaluations to $M(p+2)$, based on Sobol's original approach in [21]. The algorithm was further improved by the authors of [18, 22] and is summarized here.

Algorithm

1. Create two sample matrices A and B

$$A = \begin{bmatrix} q_1^1 & \dots & q_i^1 & \dots & q_p^1 \\ \vdots & & & & \vdots \\ q_1^M & \dots & q_i^M & \dots & q_p^M \end{bmatrix}, \text{ and } B = \begin{bmatrix} \hat{q}_1^1 & \dots & \hat{q}_i^1 & \dots & \hat{q}_p^1 \\ \vdots & & & & \vdots \\ \hat{q}_1^M & \dots & \hat{q}_i^M & \dots & \hat{q}_p^M \end{bmatrix}.$$

   The entries q_i^j and $\hat{q}_i^j$ are quasi-random numbers drawn from the respective densities.

2. Create $A_B^{(i)}$

$$A_B^{(i)} = \begin{bmatrix} q_1^1 & \dots & \hat{q}_i^1 & \dots & q_p^1 \\ \vdots & & & & \vdots \\ q_1^M & \dots & \hat{q}_i^M & \dots & q_p^M \end{bmatrix}$$

   which is the matrix A except that i^{th} column is taken from B. Similarly, create $B_A^{(i)}$.

3. Create C which is the matrix B appended to matrix A such that

$$C = \begin{bmatrix} A \\ - \\ B \end{bmatrix}$$

   The rows of C are linearly independent, and this matrix C is used when estimating the total variance.

4. Compute column vectors $f(A)$, $f(B)$, $f(A_B^{(i)})$ and $f(B_A^{(i)})$ by evaluating the model at input values from the rows of matrices A, B, $A_B^{(i)}$ and $B_A^{(i)}$. Let $f(A)_j$ denote the output computed from the j^{th} row of A. The computation of $f(A)$ and $f(B)$ requires $2M$ model evaluations, whereas the evaluation of $f(A_B^{(i)})$ and $f(B_A^{(i)})$ for $i = 1, \dots, p$ requires $2Mp$ evaluations. The total number of model evaluations is $2M(1+p)$.

5. Estimate the Sobol indices. The first-order Sobol indices are approximated by

$$S_i = \frac{\frac{1}{M}\sum_{j=1}^{M}\left[f(A)_j f(B_A^{(i)})_j - f(A)_j f(B)_j\right]}{\frac{1}{2M}\sum_{j=1}^{2M} f(C)_j f(C)_j - \langle f(C)\rangle^2} \tag{9}$$

and the total Sobol indices are approximated by

$$S_{Ti} = \frac{\frac{1}{2M}\sum_{j=1}^{M}\left[f(A)_j - f(A_B^{(i)})_j\right]^2}{\frac{1}{2M}\sum_{j=1}^{2M} f(C)_j f(C)_j - \langle f(C)\rangle^2}. \tag{10}$$

In the last step, variances are approximated using Monte Carlo approximation. The denominator in (9) and (10) is the approximation for the total variance with $\mathbb{E}(Y^2) \approx \frac{1}{2M}\sum_{j=1}^{2M} f(C)_j f(C)_j$ and $(\mathbb{E}(Y))^2 = \langle f(C)\rangle^2$. In (9), the term $\frac{1}{M}\sum_{j=1}^{M} f(A)_j f(B_A^{(i)})_j$ approximates $\mathbb{E}(\mathbb{E}(Y|q_i))^2$. In essence, we are taking the mean of responses when all input parameters are varied except q_i. The effect of q_i is fixed since the i^{th} column is the same in both A and $B_A^{(i)}$.

The second term in (9),

$$\frac{1}{M}\sum_{j=1}^{M} f(A)_j f(B)_j,$$

represents the squared mean, f_0^2, using the identify

$$f_0^2 = \int_{\Gamma^2} f(x)f(x')dxdx'.$$

This approximation is shown in [22] to reduce the loss of accuracy when computing D, compared to

$$f_0^2 \approx \left(\frac{1}{M}\sum_{j=1}^{M} f(A)_j\right)\left(\frac{1}{M}\sum_{j=1}^{M} f(B)_j\right),$$

which is used in the previous versions of the algorithm.

The computation of S_{Ti} follows from the derivations in [12], which uses the approximation

$$\mathbb{E}[\mathrm{var}(Y|q_{\sim i})] \approx \frac{1}{2M}\sum_{j=1}^{M}\left[f(A)_j - f(A_B^{(i)})_j\right]^2$$

instead of the approximation

$$\mathrm{var}[\mathbb{E}(Y|q_{\sim i})] \approx \frac{1}{M}\sum_{j=1}^{M} f(A)_j f(A_B^{(i)})_j - f_0^2$$

in (8). The comparison of different versions of the algorithm can be found in [18].

3.2.4 Sobol Indices Results

The Sobol indices for the 15 parameters in (2) are plotted in Figure 7. It is clear that N_T has the largest S_{Ti} value, indicating that N_T affects the model output the most. We note that p_T is also almost as significant. On the other hand, $T_1^*(0)$ affects the output the least and a_E and $T_1(0)$ are also very insignificant.

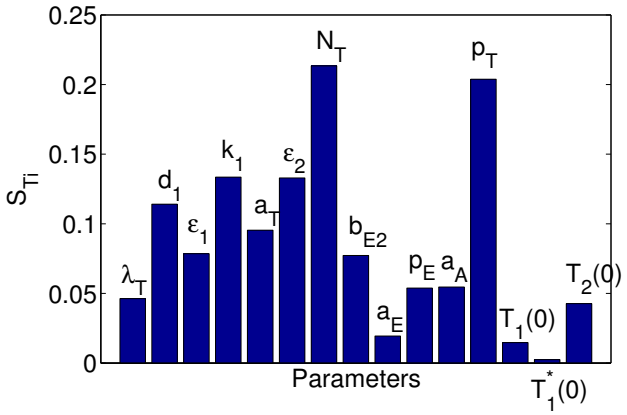


Figure 7: Sobol indices S_{Ti} for 15 parameters.

3.2.5 Verification of the Sobol Decomposition

Since the accuracy of the Sobol indices depends on the accuracy of the approximated second-order Sobol representation, we test whether the function is accurately approximated by the second-order Sobol decomposition.

To ensure that we can adequately approximate the integrals, we consider four parameters $q = [\lambda_T, d_1, \epsilon_1, k_1]$ with values in the 4-D hypercube $[3.1, 3.5] \times [0.11, 0.15] \times [0.43, 0.60] \times$ [4e-5, 5.5e-5]. We compute the model response using $n = 41$ equally-spaced quadrature points in each dimension to evaluate the integrals (6) and (7). The function is expanded with a zero-th, first, second, third and fourth order component functions so that

$$f = f_0 + \sum_i f_i(q_i) + \sum_{i<j} f_{ij}(q_i, q_j) + \sum_{i<j<k} f_{ijk}(q_i, q_j, q_k) + \sum_{i<j<k<h} f_{ijkh}(q_i, q_j, q_k, q_h).$$

In Figure 8, we plot the model response along with first- and second-order approximations, where the fixed parameter values are taken to be $\lambda_T = 3.19, \epsilon_1 = 0.119, d_1 = 0.46825, k_1 = 4.3375\text{e-}5$. The model response is represented by the blue solid line, while the first-order approximation and the second-order approximation are represented by dashed-dot black and by dashed red, respectively.

We note that both the first- and second-order approximations smooth out the jumps in the model

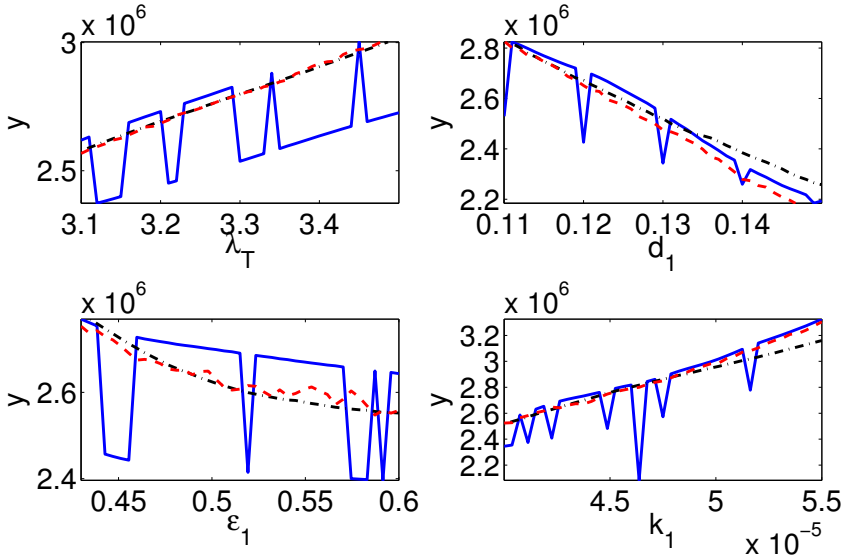


Figure 8: Model response (solid blue), 1st order (dash-dot black) and 2nd order approximation (dash red).

response, and they do not accurately represent the model response. There are little difference between the first-order and second-order approximations, which explains the similarity between the reported values of S_i and S_{Ti}. In the HIV model (1), the higher order interactions are non-negligible, and the second-order approximation is not sufficiently accurate to completely represent the model response. This may introduce some inaccuracy when determining the relative influence of parameters using the Sobol indices.

3.3 Morris Screening

The third method we consider is Morris screening [15, 17]. Screening methods rank the importance of parameters by averaging coarse difference relations termed elementary effects. The elementary effects are then used to compute sensitivity measures, based on the mean and variance, which represent the linear effect of parameters and the effect of interaction terms on the model response. Morris Screening employs neighbors to compute elementary effects, which reduces the total model evaluations by approximately a half. Whereas Morris Screening can only rank the parameter importance, and does not quantify the relative importance of each parameter, this method is significantly more efficient than computing Sobol indices. More details regarding the method can be found in [8, 20].

As with Sobol indices, we first map parameters to $[0, 1]$. We also assume no prior information about parameters and hence take them to be uniformly distributed. This latter assumption can be modified if prior parameter information is available. The elementary effect is given by

$$d_i(q) = \frac{f(q_1, \ldots, q_{i-1}, q_i + \Delta, q_{i+1}, \ldots, q_p) - f(q)}{\Delta} = \frac{f(q + e_i) - f(q)}{\Delta},$$

where Δ is the step size chosen from the set $\Delta \in \left\{ \frac{1}{\ell - 1}, \ldots, 1 - \frac{1}{\ell - 1} \right\}$. Constructed in this way, d_i quantifies the approximate, large scale, local sensitivity at q_i. We note that the step size is taken large to cover the entire parameter space. As detailed in [8, 15, 20], taking ℓ to be even and choosing $\Delta = \frac{\ell}{2(\ell-1)}$ has the advantage that it guarantees equal probability sampling from the distribution.

Let

$$d_i^k = \frac{f(q^k + \Delta e_i) - f(q^k)}{\Delta} \tag{11}$$

be the elementary effect associated with the i^{th} parameter and k^{th} sample. For r sample points, the Morris indices for the parameter q_i are

$$\mu^* = \frac{1}{r} \sum_{k=1}^{r} |d_s^k|$$

$$\sigma^2 = \frac{1}{r-1} \sum_{k=1}^{r} \left(d_s^r - \mu\right)^2, \text{ where } \mu = \frac{1}{r} \sum_{k=1}^{r} d_s^k.$$

The mean quantifies the individual effect of the input on output, whereas the variance incorporates the influence of parameter interactions. Since we must consider both the mean and the variance, we rank the parameter using the quantity $\sqrt{\mu^{*2} + \sigma^2}$ when ordering the importance of parameters. Computing (11) requires two model evaluations per parameter per sample. Hence, a total of $2pr$ model evaluations is required to compute the Morris indices, μ^* and σ^2. As detailed in Algorithm 3.3.1 below, taken from [8], one employs neighbors to reduce the number of total model evaluations to $(p + 1)r$.

3.3.1 Morris Screening Algorithm

1. Create a $(p + 1) \times p$ matrix A with ones in the lower triangle such that

$$A = \begin{bmatrix} 0 & 0 & \ldots & 0 \\ 1 & 0 & \ldots & 0 \\ \vdots & & \ddots & \\ 1 & 1 & \ldots & 1 \end{bmatrix}.$$

2. Choose the step size Δ. Unless specified by the user, take $\Delta = \dfrac{\ell}{2(\ell-1)}$.

3. Select a starting vector q^*.

4. Construct a diagonal matrix D^*, whose entries are randomly chosen from $\{-1, 1\}$.

5. Calculate the sampling matrix A_s as the following

$$A_s = J_{p+1,p}q^* + \frac{\Delta}{2}\left[(2A - J_{p+1,p})D^* + J_{p+1,p}\right]P^*,$$

where $J_{i,j}$ is a $i \times j$ matrix with all ones and P^* is a $p \times p$ permutation of the identity matrix.

6. If the parameters are not defined in the hypercube $[0,1]^p$ and instead $q \in [\ell b_i, ub_i]$ for $i = 1, \ldots, p$, take $\ell b = [\ell b_1, \ell b_2, \ldots ..., \ell b_p]$ and $ub = [ub_1, ub_2, \ldots, ub_p]$. The sampling matrix is then scaled to match the range of parameters

$$C = J_{p+1,1}\ell b + A_s(D(ub - \ell b)) \tag{12}$$

where $D(ub - \ell b)$ is a diagonal matrix with entries $ub - \ell b$.

7. Compute the elementary effect for $s = 1, \ldots, p$. We let C_k denote the k^{th} row of C. Then

$$d_s = \frac{f(C_i) - f(C_j)}{\Delta}, \tag{13}$$

where i and j denote the indices such that i^{th} row and j^{th} row differ in the s^{th} entry.

8. Repeat the steps $1 - 7$ for r samples. The Morris mean μ^* and σ^2 are computed by taking the average of the local elementary effect

$$\mu^* = \frac{1}{r}\sum_{k=1}^{r} |d_s^k|$$

$$\sigma^2 = \frac{1}{r-1}\sum_{k=1}^{r} \left(d_s^r - \mu\right)^2, \text{ where } \mu = \frac{1}{r}\sum_{k=1}^{r} d_s^k.$$

We note that the denominator of (13) in Step 7 is Δ for all $q_i, i = 1, \ldots, p$. The elementary effects must be computed using the scaled step size, even though model responses are computed at the parameter values, which are mapped using (12).

3.3.2 Morris Indices Results

We use $\ell = 20$, $r = 50$ and the default step size $\Delta = \ell/2(\ell - 1)$. We plot the elementary effects μ^* and σ^2 in Figure 9 to visualize those parameters that are more influential. The most influential parameter is again N_T followed by p_T and ϵ_2. The results also coincide with those from Partial Correlation and Sobol for the least influential parameters, which are $T_1^*(0)$ and $T_1(0)$. The parameter a_E, which is one of the least influential parameters in Partial Correlation and Sobol after $T_1^*(0)$ and $T_1(0)$, is still ranked low. One difference with Morris screening, however, is that all three initial conditions are identified as minimally influential.

3.4 Parameter Subset Selection

Finally, we discuss the parameter subset selection method presented in [3, 4, 6, 9]. This method can be used to determine a subset of n_p parameters, $n_p \leq p$, that are identifiable with the smallest uncertainty measure. The subset selection algorithm uses the optimal parameter estimates as well as standard errors associated with the parameters in the estimation process. We consider a ratio of standard errors and parameter estimates to rank the set of parameters that are most influential for a given n_p. The parameter subset selection can be used as a parameter selection technique since identifiable parameters are influential, and the n_p parameters isolated in this algorithm correspond to the n_p most influential parameters.

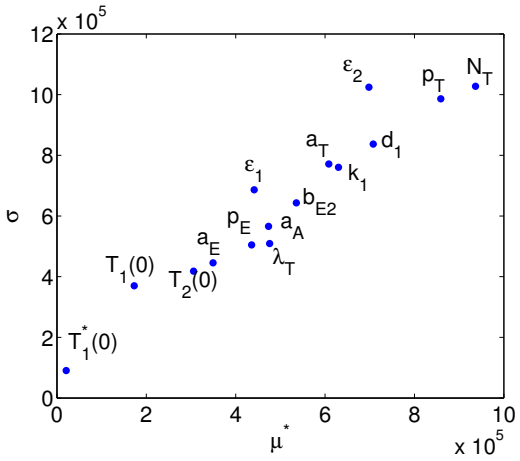


Figure 9: Morris μ^* and σ computed using the Morris screening algorithm.

For a vector of parameters $q = [q_1, \ldots, q_p]$, we first require the optimal parameter estimates of q, denoted by $\hat{q} = [\hat{q}_1, \ldots, \hat{q}_p]$, and the corresponding standard errors, $SE = [SE_1, \ldots, SE_p]$. Then, given the parameter vector q of size p and a number $n_p \leq p$, the subset selection algorithm returns a set of parameters of size n_p that minimizes the selection score,

$$\alpha(\hat{q}) = |\nu(\hat{q})|\,.$$

Here, $\nu(\hat{q}) = [\nu(\hat{q}_1), \ldots, \nu(\hat{q}_{n_p})]^T$, and $\nu(\hat{q}_i)$ is the coefficient of variation for $\hat{q}_i$ defined by

$$\nu(\hat{q}_i) = \frac{SE_i}{\hat{q}_i}, \qquad i = 1, \ldots, n_p.$$

The set of parameters with the smallest selection score gives n_p most influential parameters.

3.4.1 Optimal Parameter Estimates

This technique utilizes time-dependent responses. Following the strategy in [3], we employ the responses

$$\begin{aligned} z_1 &= T_1 + T_1^* + T_2 + T_2^* \\ z_2 &= V_I + V_{NI}, \end{aligned} \tag{14}$$

which are the total CD4+ T-cells and the total RNA copies, respectively. We assume a statistical model of the form

$$\begin{aligned} Y_1^i &= z_1(t_1^i; q_0) + e_1^i, \;\; i = 1, 2, , \ldots, N_1 \\ Y_2^j &= z_2(t_2^j; q_0) + z_2^{\gamma} e_2^j, \;\; j = 1, 2, \ldots, N_2, \end{aligned} \tag{15}$$

where y_1^i and y_2^j are realizations of the random variables Y_1^i and Y_2^j, respectively, and e_1^i and e_2^j are independently identically distributed such that $\mathbb{E}[e_1^i] = \mathbb{E}[e_2^j] = 0$ with $\mathrm{Var}(e_1^i) = \sigma_1^2$ and $\mathrm{Var}(e_2^j) = \sigma_2^2$ for $i = 1, \ldots, N_1$, $j = 1, \ldots, N_2$. Also, q_0 represents the hypothesized true parameter values.

The weighted least squares estimator is given by

$$\hat{q} = \underset{q \in Q}{\arg\min} \left(\frac{1}{N_1} \sum_{i=1}^{N_1} \frac{(y_1^i - z_1(t_1^i; q_0))^2}{\sigma_1^2} + \frac{1}{N_2} \sum_{j=1}^{N_2} \frac{(y_2^j - z_2(t_2^j; q_0))^2}{\sigma_2^2 z_2^{2\gamma}(t_2^j; q_0)} \right) \tag{16}$$

where the variance components are given by

$$\begin{aligned} \sigma_1^2(q_0) &= \frac{1}{N_1 - \dim(q_0)} \sum_{i=1}^{N_1} (y_1^i - z_1(t_1^i; q0))^2 \\ \sigma_2^2(q_0) &= \frac{1}{N_2 - \dim(q_0)} \sum_{j=1}^{N_2} \frac{(y_2^j - z_2(t_2^j; q0))^2}{z_2^{2\gamma}(t_2^j; q_0)}. \end{aligned} \tag{17}$$

The value of γ is determined based on the underlying assumption for the statistical models (15). More specifically, it was determined in [3, 7] that choosing $\gamma = 1.2$ results in the residuals being approximately iid, which is an assumption for the model (15). For this reason, the parameter estimation was performed with $\gamma = 1.2$.

Since the estimates in (16) and (17) involve an unknown, to-be-estimated parameter vector q_0, the optimal parameter is estimated iteratively with the initial variance $\sigma_k^2 = 1$ for $k = 1, 2$ and the weights $z_2^{2\gamma}(t_2^j; q_0) = 1$ for $j = 1, \ldots, N_2$. We summarize the parameter estimation algorithm from [3].

Parameter Estimation Procedure Algorithm

1. Obtain initial estimate $\hat{q}^{(0)}$ using (16) with $\sigma_k^2 = 1$ for $k = 1, 2$ and the weights $z_2^{2\gamma}(t_2^j; q_0) = 1$ for $j = 1, \ldots, N_2$.
2. Compute the variances σ_k^2 using (17), and the weights $z_2^{2\gamma}(t_2^j; q_0)$ with q_0 replaced by $\hat{q}^{(0)}$.
3. Initialize the iteration counter ℓ with the value 1.
4. Do each of the following:
   - Compute $\hat{q}^{(\ell)}$ using (16) with current variances σ_k^2 and weights $z_2^{2\gamma}(t_2^j; \hat{q}^{(\ell-1)})$.
   - Update the variances σ_k^2 using (17) and the weights $z_2^{2\gamma}(t_2^j; \hat{q}^{(\ell-1)})$ with q_0, $\hat{q}^{(\ell-1)}$ replaced by $\hat{q}^{(\ell)}$.
   - Compute $\Delta_\varepsilon = ||[\hat{q}^{(\ell)} - \hat{q}^{(\ell-1)}]./[\hat{q}^{(\ell-1)}]||$.
   - Increment ℓ by 1.
5. If $\Delta_\varepsilon > \varepsilon$, go back to Step 4. Otherwise, terminate the algorithm.

In this algorithm, ε is a user-defined threshold tolerance for a termination criterion, and ./ denotes element-by-element division.

3.4.2 Computing Standard Errors

The parameter subset selection algorithm also requires the computation of standard errors for the parameters. The standard errors are computed using standard asymptotic theory for generalized least squares (GLS) estimators q_{GLS}^n following the procedure discussed in [3]. The $p \times p$ Fisher Information Matrix (FIM) corresponding to z_1 and z_2 in (14) is approximated by

$$\Sigma_0^{N_1+N_2} \approx \left[\left(\sum_{i=1}^{N_1} \frac{1}{\sigma_1^2(\hat{q}^n)} \frac{\partial z_1(t_1^i; \hat{q}^n)}{\partial q_k} \frac{\partial z_1(t_1^i; \hat{q}^n)}{\partial q_\ell} + \sum_{j=1}^{N_2} \frac{1}{\sigma_2^2(\hat{q}^n) z_2^{2\gamma}(t_2^j; \hat{q}^n)} \frac{\partial z_2(t_2^j; \hat{q}^n)}{\partial q_k} \frac{\partial z_2(t_2^j; \hat{q}^n)}{\partial q_\ell} \right)_{k,\ell} \right] \quad (18)$$

where σ_1^2 and σ_2^2 are defined in (17) with q_0 approximated by $\hat{q}^n$.

To approximate q_0, we first let $z_1 = T_1 + T_1^* + T_2 + T_2^*$ and $z_2 = V_I + V_{NI}$. The sensitivities are computed by solving the system of equations

$$\frac{d}{dt}\left(\frac{\partial z_m}{\partial q}\right) = \frac{\partial g_m}{\partial x}\left(\frac{\partial x}{\partial q}\right) + \frac{dg_m}{dq}, \; m = 1, 2.$$

Here, x and q respectively denote the state variables and the parameters being estimated. Define the $2 \times p$ matrices

$$D_1^i(q_0) = \begin{bmatrix} \frac{\partial z_1}{\partial q_1}(t_1^i; q_0) & \cdots & \frac{\partial z_1}{\partial q_p}(t_1^i; q_0) \\ 0 & \cdots & 0 \end{bmatrix} \text{ for } i = 1, \ldots, N_1$$

$$D_2^i(q_0) = \begin{bmatrix} 0 & \cdots & 0 \\ \frac{\partial z_1}{\partial q_1}(t_1^i; q_0) & \cdots & \frac{\partial z_1}{\partial q_p}(t_1^i; q_0) \end{bmatrix} \text{ for } i = 1, \ldots, N_2.$$

and define the 2×2 matrix

$$V_0(t; q_0) = \begin{bmatrix} \sigma_1^2 & 0 \\ 0 & \sigma_2^2 z_2^{2\gamma}(t; q_0) \end{bmatrix}.$$

The matrices ${D_1^i}^T V_0^{-1}(t_1^i) D_1^i$ and ${D_2^j}^T V_0^{-1}(t_2^j) D_2^j$ respectively have entries

$$F_{k,\ell}^{1,i}(q_0) = \sigma_1^{-2} \frac{\partial z_1}{\partial q_k}(t_1^i; q_0) \frac{\partial z_1}{\partial q_\ell}(t_1^i; q_0), \ k, \ell = 1, \ldots, p, \ i = 1, \ldots, N_1$$
$$F_{k,\ell}^{2,j}(q_0) = \sigma_2^{-2} z_2^{-2\gamma}(t_2^j; q_0) \frac{\partial z_2}{\partial q_k}(t_2^j; q_0) \frac{\partial z_2}{\partial q_\ell}(t_2^j; q_0), \ k, \ell = 1, \ldots, p, \ i = 1, \ldots, N_2$$

Then, we define the $p \times p$ Fisher matrix $F(q_0) = F_{k,\ell}(q_0)$ with entries

$$F_{k,\ell}(q_0) = \sum_{i=1}^{N_1} F_{k,\ell}^{1,i}(q_0) + \sum_{j=1}^{N_2} F_{k,\ell}^{2,j}(q_0). \tag{19}$$

The approximate Fisher matrix (18) is obtained by evaluating (19) at $\hat{q}^n \approx q_0$. Using the Fisher matrix approximations, F, the standard errors for $\hat{q}_k^n, \ k = 1, \ldots, p$, are given by

$$SE_k = SE(\hat{q}_k^n) = \sqrt{(F^{-1}(\hat{q}^n))_{k,k}} \ .$$

It is illustrated in [20] that the standard errors are related to the variance of parameter estimates so they quantify the uncertainty of each parameter. Parameters with small standard errors are estimated with a high degree of certainty, so one can conclude that their impact on the response is influential. On the other hand, parameters that are noninfluential have minimal impact on responses, which yields more uncertainty and larger standard error when estimating optimal parameter values.

3.4.3 Parameter Subset Selection Results

As presented in [3], we compile the parameters that give the smallest selection score for a given number of parameters in the set, n_p, in Table 4. We note that these results are patient-dependent and N_T was not in the top three for the considered patient. For other patients, N_T is in the top 3.

For example, if we want a subset of three parameters that are most influential, we select λ_T, ϵ_2 and p_T. In this way, the parameter subset selection algorithm selects a set of parameters for a given number of n_p; however, it does not specify which parameter is more influential among the selected parameters. We see that the set for $n_p = k$ is a subset for $n_p = k+1$ for all k, except $k = 2$. Unlike Partial Correlation, Sobol indices and Morris indices, Parameter Subset Selection has a local sensitivity approach since the sensitivity matrices are computed around the mean values. Nevertheless, we can use the parameter subset selection result to provide a comparison regarding which parameters to include when we specify a number of parameters to choose from the entire set.

4 Comparison and Verification of Parameter Selection Techniques

In this section, we illustrate two techniques for verifying the accuracy of the parameter selection techniques. We first verify the results provided by the global sensitivity techniques, which rank the impact or influence of the inputs, and the parameter subset selection. We do this in Section 4.1 by comparing the input rankings provided by the four methods. In Section 4.2, we verify the noninfluential inputs by comparing responses obtained with various input combinations.

4.1 Verification of Input Rankings

Here, we provide comparisons of the four methods. First, we summarize in Table 5 sensitivity measures, a description and the computational cost of each method. The Sobol indices, Morris indices and Partial Correlation indices are summarized in Table 6 in order of importance. For Partial Correlation, we rank the importance by the absolute values of the partial correlation. For the Sobol indices, the parameters are ranked by the magnitude of S_{Ti}. For the Morris indices, we consider the quantity $\sqrt{\mu^{*2} + \sigma^2}$ to rank the parameters.

n_p	N_T	λ_T	ϵ_2	p_T	p_E	$T_2(0)$	$T_1(0)$	ϵ_1	d_1	b_{E2}	a_E	a_T	k_1	a_A	$T_1^*(0)$
1	x														
2	x	x													
3		x	x	x											
4	x	x	x	x											
5	x	x	x	x	x										
6	x	x	x	x	x	x									
7	x	x	x	x	x	x	x								
8	x	x	x	x	x	x	x	x							
9	x	x	x	x	x	x	x	x	x						
10	x	x	x	x	x	x	x	x	x	x					
11	x	x	x	x	x	x	x	x	x	x	x				
12	x	x	x	x	x	x	x	x	x	x	x	x			
13	x	x	x	x	x	x	x	x	x	x	x	x	x		
14	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
15	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 4: Parameter subset selection results from [3].

To provide a comparison among the four methods, we summarize in Table 7 and 8 the parameters to be selected for a given number of parameters. In Table 7 and 8, PCorr, S, M and PSS respectively denote Partial Correlation, Sobol indices via Saltelli algorithm, Morris indices and Parameter Subset Selection. For Partial Correlation, Sobol indices and Morris indices, n_p influential parameters correspond to the top n_p parameters from Table 6.

Overall, Partial Correlation is the cheapest method to measure linearity between parameters and response. This often corresponds to the first order Sobol indices. Computing Sobol indices is expensive and it becomes prohibitively slow as the number of input parameters increases. For a model with a moderate number of input parameters, we can apply Morris screening. This employs neighbors to compute statistically averaged local, very coarse approximations to derivatives. Morris indices are a good measure to isolate influential parameters from noninfluential parameters with much fewer evaluations than Sobol indices. Finally, the parameter subset selection algorithm provides sensitivity in terms of uncertainties involved in the estimation process. The noninfluential parameters determined by this method did not match the results from the other three.

In terms of accuracy, Sobol indices measure the first- and second-order interaction effects of parameters most accurately. However, we showed that second-order Sobol decomposition may not be sufficiently accurate depending on the model. Even though the Sobol indices are widely used for global sensitivity analysis, one must always consider the accuracy of Sobol decomposition as an approximation to the model before applying the results of Sobol indices.

When the parameter selection techniques are applied to the HIV model, we found that certain parameters are determined highly influential by all four methods. An example of highly influential parameters are N_T and p_T. These parameters respectively represent the number of RNA copies during the process of T_1^* lysis and net proliferation of T_1 and T_1 due to clonal expansion and programmed contraction. We also observed that both ϵ_1 and ϵ_2 were ranked above average in their importance. This is essential in designing the optimal control for drug therapy. We see from our global sensitivity analysis that the relative effectiveness of protease inhibitor, ϵ_2, has more affect on the model response than that of reverse transcriptase inhibitor, ϵ_1. On the other hand, for our specific response, it was shown that initial conditions $T_1(0), T_1^*(0)$ and $T_2(0)$ do not play a strong role in determining the response.

4.2 Verification of Noninfluential Inputs

To verify that the influential parameters are correctly identified, we compute the probability density functions of model responses by fixing noninfluential parameters.

Method	Sensitivity Measure	Description	Cost
Partial Correlation	Degree of linear correlation between parameters and response	Ranks the parameters in the order of strong linear correlation to response. Considers linearity only.	M model evaluations for M Monte Carlo samples.
Sobol by Saltelli	First order Sobol S_i and total sensitivity indices S_{Ti}	A type of variance-based method. Uses 2nd order Sobol decomposition. Ranks the parameters and quantifies relative importance. Measures the effects of individual parameters as well as interaction terms.	$2M(p+1)$ model evaluations for M Monte Carlo samples and p parameters.
Morris Screening	Mean μ_i^* and variance σ^2 of elementary effects	Averages coarse local derivative approximations. Only ranks parameters. Employs neighbors to reduce the cost.	$(p+1)r$ model evaluations for r sample points for averaging and p parameters.
Parameter Subset Selection	n_p parameters with minimum uncertainty	Provides identifiable subset of n_p parameters. Requires the optimal parameter estimate $\hat{q}$ and standard errors SE.	$C(p, n_p)$ subsets to check for minimum uncertainty for subset of n_p parameters among p parameters.

Table 5: Summary of parameter selection techniques.

	Partial Correlation		Sobol by Saltelli			Morris Indices	
Rank	Parameter	Corr(q, y)	Parameter	S_i	S_{Ti}	Parameter	$\sqrt{\mu^{*2} + \sigma^2}$
1	N_T	4.608e-1	N_T	1.455e-1	2.134e-1	N_T	1.390e+6
2	p_T	3.964e-1	p_T	1.046e-1	2.038e-1	p_T	1.308e+6
3	k_1	2.970e-1	k_1	1.066e-1	1.335e-1	ϵ_2	1.240e+6
4	d_1	-2.630e-1	ϵ_2	7.879e-3	1.329e-1	d_1	1.096e+6
5	b_{E2}	-2.526e-1	d_1	6.276e-2	1.141e-1	k_1	9.876e+5
6	a_T	2.178e-1	a_T	5.568e-2	9.541e-2	a_T	9.824e+5
7	ϵ_2	-2.167e-1	ϵ_1	5.426e-2	7.849e-2	b_{E2}	8.371e+5
8	a_A	2.111e-1	b_{E2}	8.948e-2	7.723e-2	ϵ_1	8.161e+5
9	p_E	-1.789e-1	a_A	3.727e-2	5.458e-2	a_A	7.378e+5
10	λ_T	1.774e-1	p_E	2.013e-2	5.384e-2	λ_T	6.971e+5
11	ϵ_1	-1.601e-1	λ_T	4.682e-2	4.626e-2	p_E	6.666e+5
12	$T_2(0)$	1.487e-1	$T_2(0)$	-1.032e-2	4.266e-2	a_E	5.662e+5
13	a_E	-9.089e-2	a_E	1.057e-2	1.943e-2	$T_2(0)$	5.180e+5
14	$T_1^*(0)$	-2.721e-2	$T_1(0)$	-3.974e-3	1.464e-2	$T_1(0)$	4.084e+5
15	$T_1(0)$	2.410e-2	$T_1^*(0)$	-8.715e-3	2.423e-3	$T_1^*(0)$	9.285e+4

Table 6: Sensitivity measures provided by Partial Correlation, Sobol by the Saltelli algorithm and Morris Screening.

	1				2				3				4			
	PCorr	S	M	PSS	PCorr	S	M	PSS	PCorr	S	M	PSS	PCorr	S	M	PSS
λ_T								x				x				x
d_1													x		x	
ϵ_1																
k_1									x	x			x	x		
a_T																
ϵ_2											x	x		x	x	x
N_T	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x
b_{E2}																
a_E																
p_E																
a_A																
p_T					x	x	x		x	x	x	x	x	x	x	x
$T_1(0)$																
$T_1^*(0)$																
$T_2(0)$																

	5				6				7				8			
	PCorr	S	M	PSS	PCorr	S	M	PSS	PCorr	S	M	PSS	PCorr	S	M	PSS
λ_T				x				x				x				x
d_1	x	x	x		x	x	x		x	x	x		x	x	x	
ϵ_1										x				x	x	x
k_1	x	x	x		x	x	x		x	x	x		x	x	x	
a_T					x	x	x		x	x	x		x	x	x	
ϵ_2		x	x	x		x	x	x	x	x	x	x	x	x	x	x
N_T	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
b_{E2}	x				x				x		x		x	x	x	
a_E																
p_E				x				x				x				x
a_A													x			
p_T	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
$T_1(0)$												x				x
$T_1^*(0)$																
$T_2(0)$								x				x				x

Table 7: Subsets of influential parameters for $n_p = 1, \ldots, 8$. Here, PCorr, S, M and PSS denote Partial Correlations, Sobol indices, Morris indices and Parameter Subset Selection.

	9				10				11				12			
	PCorr	S	M	PSS	PCorr	S	M	PSS	PCorr	S	M	PSS	PCorr	S	M	PSS
λ_T				x	x		x	x	x	x	x	x	x	x	x	x
d_1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ϵ_1		x	x	x		x	x	x	x	x	x	x	x	x	x	x
k_1	x	x	x		x	x	x		x	x	x		x	x	x	
a_T	x	x	x		x	x	x		x	x	x		x	x	x	x
ϵ_2	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
N_T	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
b_{E2}	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x
a_E												x			x	x
p_E	x			x	x	x		x	x	x	x	x	x	x	x	x
a_A	x	x	x		x	x	x		x	x	x		x	x	x	
p_T	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
$T_1(0)$				x				x				x				x
$T_1^*(0)$																
$T_2(0)$				x				x				x	x	x		x

	13				14			
	PCorr	S	M	PSS	PCorr	S	M	PSS
λ_T	x	x	x	x	x	x	x	x
d_1	x	x	x	x	x	x	x	x
ϵ_1	x	x	x	x	x	x	x	x
k_1	x	x	x	x	x	x	x	x
a_T	x	x	x	x	x	x	x	x
ϵ_2	x	x	x	x	x	x	x	x
N_T	x	x	x	x	x	x	x	x
b_{E2}	x	x	x	x	x	x	x	x
a_E	x	x	x	x	x	x	x	x
p_E	x	x	x	x	x	x	x	x
a_A	x	x	x		x	x	x	x
p_T	x	x	x	x	x	x	x	x
$T_1(0)$				x		x	x	x
$T_1^*(0)$					x			
$T_2(0)$	x	x	x	x	x	x	x	x

Table 8: Subsets of influential parameters for $n_p = 9, \ldots, 14$.

Verification Procedure

1. For a set of n_p influential parameters, sample $n = 1000$ parameter values from their respective distributions. For the results reported here, we took the distributions to be uniform with lower and upper bounds summarized in Table 3.

2. Fix $p - n_p$ noninfluential parameters at pre-specified values, which we take to be the lower bounds of the parameters.

3. Compute the model response with parameter values from Steps 1 and 2.

4. Construct probability density function using a kernel density estimation.

We then compare the densities for the model responses where all parameters are sampled randomly. We construct densities for $n_p = 8, 10, 12, 14$ influential parameters. That is, we examine four cases where the numbers of fixed parameters are 7, 5, 3 and 1, and plot the densities along with the density obtained by varying all the parameters. In Figure 10 (a) and (b), we see that we have fixed too many parameters. In Figure 10 (c), densities using Partial Correlation, Sobol and Morris match the sample density, whereas the density from parameter subset selection does not match the rest. This is reasonable since the influential parameters determined via Partial Correlation, Sobol and Morris indices are very similar as shown in Table 7. Finally in Figure 10 (d), we see that all four methods give comparable densities. The agreement of densities indicates that the parameter $T^*(0)$ was determined to be noninfluential and it did not affect the output significantly. Moreover, this is the only parameter that can be fixed without affecting this output.

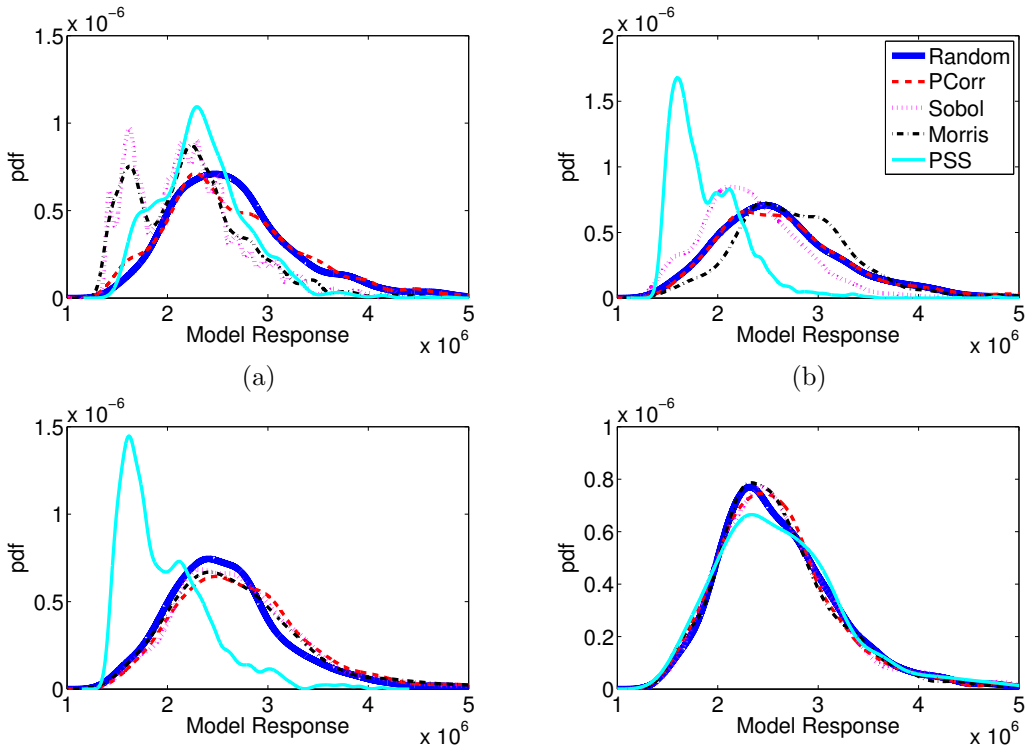


Figure 10: Densities obtained by fixing (a) 7, (b) 5, (c) 3 and (d) 1 least influential parameters. The density in solid is obtained by varying all the parameters.

In terms of parameter estimation to be followed after parameter selection, there are two inherent difficulties. First, the cut-off between influential and noninfluential parameters is not always clear. Depending on the model, one might observe a cluster of parameters with high sensitivity measures and another cluster with lower sensitivity measures. For the HIV example, it was only after we performed a verification test that we

Parameter	Partial Correlation	S	S_T	μ^*	σ^2
q_1	0.690	0.498	0.516	1	0.980
q_2	-0.700	0.481	0.498	1	1.020

Table 9: Sensitivity measures for $y = q_1 - q_2$.

learned that fixing one parameter resulted in insignificant variability of sample densities. This verification requires additional model evaluations and there is not a simple way to check which parameters are influential just by observing sensitivity measures.

Second, even if we are successful at isolating influential parameters, the parameter identifiability issues may still remain. Consider a simple example

$$y = q_1 - q_2$$

with $q_1, q_2 \sim U(0, 1)$. As we can see from the sensitivity measures summarized in Table 9, q_1 and q_2 are equally influential. Suppose that we have the observation $y = 0$. It is easy to see that parameter estimation using this observation will fail to estimate the densities of q_1 and q_2 correctly since there are several values of q_1 and q_2 that match the observation. Therefore, unless some prior knowledge is specified, q_1 and q_2 are unidentifiable.

This simple example illustrates that determining influential parameters may not eliminate parameter identifiability issues completely. In this regard, the parameter subset selection algorithm has the advantage that the selected subset is identifiable. Since Partial Correlation, Sobol and Morris methods only determine influential parameters, care must be exercised if these parameter selection techniques are used to isolate identifiable parameters for model calibration.

5 Conclusion

In this paper, we examined parameter selection techniques based on global sensitivity analysis and compared the results to a local sensitivity-based method originally performed on the model (1). Four parameter selection techniques were applied to the HIV model (1) to determine the set of influential parameters. This process enables us to fix the noninfluential parameters and hence reduce the parameter dimensions for subsequent uncertainty quantification. We also showed that the accuracy of Sobol indices depends greatly on the model. In our HIV model, the second-order decomposition was not sufficiently accurate to represent the response. If one is interested in determining parameter identifiability issues, then it is recommended that one uses the parameter subset selection algorithm since it returns a set of identifiable parameters with smallest uncertainty.

It is important to note that there are several alternate choices for the model response. Our choice of the model response was motivated by the types of data that are available to us. However, one must carefully examine the cases when different model responses are chosen. It is important to remember that the parameters were determined influential in our analysis for our specific choice of model response. One idea for future work is to examine global sensitivity analysis using solely the T-cell counts as a response. Since the treatment attempts to increase the T-cell counts in patients, it is reasonable to focus on the T-cell counts alone. Similarly, one could focus on the viral loads $V_I + V_{NI}$ in an attempt to keep the viral loads low. Another aspect of analysis that we did not cover in this paper is to consider model response as a function of time. Recall that in our analysis we integrated the response in time to take into consideration of response at several time steps. In reality, we see that the states $T_1, T_1^*, \ldots, E_2$ can be mostly flat except for some jumps. Considering time-dependent model response will enable us to incorporate jumps that occur at certain times.

Finally, there are other methods of parameter selection that eliminate parameter identifiability issues. In particular, Active Subspace Methods detailed in [2, 11] determine a subspace of input parameter space which affects the response the most. This method does not isolate influential parameters from noninfluential parameters and the interpretation of the results may be more complicated. However, finding a linear combination of parameters that affects the response will resolve the parameter unidentifiability issues. Moreover, responses can be approximated based on the reduced parameter space, which is useful in subsequent model calibration and uncertainty quantification. Examining active subspace methods more closely as a part of parameter selection techniques will likely add more complete analysis on parameter selection techniques.

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