XI CONGRESO LATINOAMERICANO DE BIOLOGÍA MATEMÁTICA SoLaBIMa 2019

Universidad Católica del Maule

22-25 de Octubre de 2019, Talca, Chile

Parameter estimation of a HIV-AIDS model using Bayesian inference

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Abstract

The research presented in this manuscript addresses the problem of fitting a mathematical model to epidemic data. We present a quantitative analysis of an epidemiological model of HIV-AIDS using Bayesian inference. The epidemic model considered consists of a suitable system of ordinary differential equations. We perform a local and global sensitivity analysis to determine which model parameters are the most relative important to disease transmission and prevalence. The data set is from the Mexican public health sector. We formulate an inverse problem associated to the fitting problem. We propose and implementation of Bayesian inference to solve the parameter estimation problem. We analyze the selection of the likelihood and a prior distribution of the parameters. We estimate the basic reproductive number $\mathcal{R}_0$ of this disease based on the estimation of the model parameters. Also, we perform an uncertainty quantification of the associated inverse problem.

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1 Introduction

About 38 million people worldwide are estimated to be living with human immunodeficiency virus (HIV) and around 8 hundred thousand people have died of acquired immunodeficiency syndrome

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(AIDS) in 2019 or 25 million have died from AIDS since the first cases were identified in 1981. About 2.5 million children under the age of 15 years are living with HIV and more than 12 million have been orphaned by AIDS by 2004. An increase number of individuals infected with HIV are now becoming ill and will die in the absence of intervention strategies in African countries. (people infected with Tuberculosis germ and HIV are thirty times more likely to become sick with Tuberculosis.) Progression from HIV infection to AIDS occurs approximately over a decade or two. In the regional analysis of UNAIDS shows that the main concentration of AIDS cases are in developing countries, 68% of persons living with HIV are in Subsaharian Africa in 2010. In second place is eastern and southeastern Asia, with an estimated number of 4 millions. Latin America, eastern Europe and central Asia are in the third place. The use of antiretroviral drug have decreased the number of deaths related to AIDS.

The HIV is a lentovirus of the Retroviridae family, the cause of AIDS. The main characteristic of the HIV is its large incubation period, several years in average. There exist two types of VIH, named VIH-1 and VIH-2, the former is more ineffective than the latter. The VIH-1 is the cause of most infections by HIV in the world. Figure 1 shows the cases of HIV and AIDS from 1983 to 2018 from CENSIDA. Figure 2 shows the cases of HIV and AIDS with respect to each quinquennial chronological group.

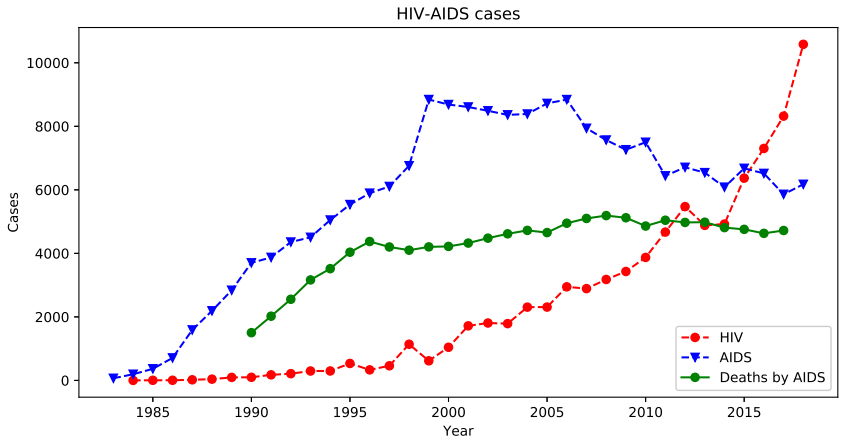

Figure 1: HIV-AIDS cases.

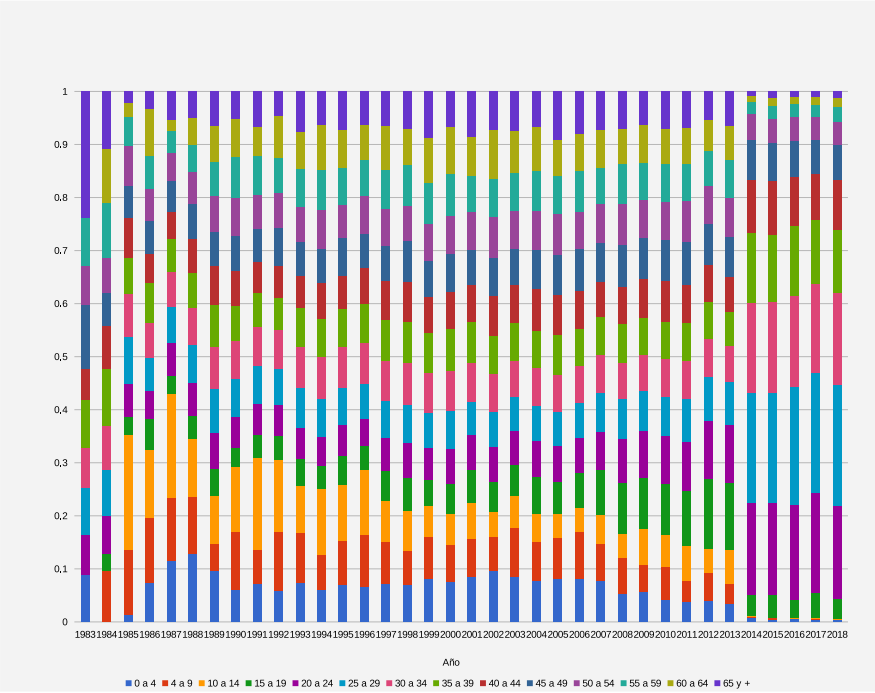

Figure 2: HIV-AIDS cases by chronological ages groups.

2 Model

We consider a simple age-structured epidemic model in which HIV/AIDS is spread in a population of ages in groups $[a_{i-1}, a_i]$ where $a_0 = 0$ and $a_n = \infty$. We divide the population into the compartments of susceptible individuals, infective individuals and AIDS, denoted by S, I and A, respectively. Assume a birth rate

We consider different infection stages during the course of HIV infection. According to data from WHO, HIV positive individuals pass through three main stages of infection before progressing to full-blown AIDS, as in figure . Also the population is divided into n age groups: $[a_0, a_1), [a_1, a_2), \cdots, [a_{n-1}, a_n)$. We have added vertical transmission, we assume that a fraction p of newborns from the infected population becomes infected at birth, and the remaining fraction $(1-p)$ are susceptible. Let $S = S(\alpha, t)$ denote the age-density of susceptible population at time t and chronological age α. Let α_M be the highest age attained by the individuals in the host population. Let $I = I(\alpha, \beta, t)$ be the density of individuals with HIV-positive virus at chronological age α, infection age β and time t. Let $A = A(\alpha, t)$ denote the age-density of individuals with AIDS at time t and chronological age α. For any given time $t \geq 0$, $I(\alpha, \beta, t)$ is defined on the following domain $\Omega_I = \{(\alpha, \beta) | 0 < \alpha < \alpha_M,\ 0 < \beta < \beta_M\}$. Let $\nu(\alpha)$, $\sigma(\alpha, \beta)$ and μ denote the age-specific mortality rate, the rate of transition from I-group to A-group and the birth rate of the population, respectively. According to the mechanism of infection, we introduce the following age-specific force of infection denoted by $\lambda(\alpha, t)$:

$$\lambda(\alpha, t) = r_1(\sigma) \int_{\alpha_0}^{\alpha_M} \int_0^{\beta_M} r_2(\alpha, \alpha', \beta') I(\alpha, \beta, t) d\beta' d\alpha' \tag{1}$$

where $r_1(\sigma)$ is the number of partners that an individual of age α has per unit time, $r_2(\alpha, \alpha', \beta')$ the transmission probability of a susceptible individual of age σ infected by an infected partner of age α' at infection age β'. The functions r_1 and r_2 satisfy the following assumption: $r_1(\alpha) \geq 0$ is

continuous on $[\alpha_0, \alpha_M]$ and $r_2(\alpha, \alpha', \beta') \geq 0$ is continuous on $\overline{\Omega}_I$ Under these definitions, and above assumptions, we formulate the following SIA type model

$$\begin{aligned} S_\alpha + S_t &= \mu - (\nu(\alpha) + \lambda(\alpha, t))S(\alpha, t) \\ S(\alpha_0, t) &= B \\ S(\alpha, 0) &= \Phi(\alpha) \end{aligned} \tag{2}$$

$$\begin{aligned} I_\alpha + I_\beta + I_t &= \lambda(\alpha, t)S(\alpha, t) - (\nu(\alpha) + \sigma(\alpha, \beta))I(\alpha, \beta, t) \\ I(\alpha_0, \sigma, t) &= 0 \\ I(\alpha_0, 0, t) &= \lambda(\alpha, t)S(\alpha, t) \\ I(\alpha_0, \sigma, 0) &= \Psi(\alpha, \sigma) \end{aligned} \tag{3}$$

$$\begin{aligned} A_\alpha + A_t &= \sigma(\alpha, \beta)A(\alpha, t) - (\nu(\alpha) + \kappa(\alpha, \sigma)A(\alpha, t) \\ A(\alpha_0, t) &= 0 \\ A(\alpha, 0) &= 0 \end{aligned} \tag{4}$$

where B is constant corresponding to the number of susceptible individuals of age α_0 and $\Psi(\alpha, \sigma)$ is the initial condition for the infected people at chronological age α_0 at time $t = 0$.

Under certain conditions, (the above) the chronological age and infection age PDE model can be reduced to a system of ODEs:

$$\begin{aligned} \dot{S}_1 &= \mu - \beta_{11}S_1 - (\nu_1 + \eta_1)S_1 - p\mu \sum\nolimits_{i=1,j=2}^{m,n} I_{ij} \\ \dot{S}_j &= \nu_{j-1}S_{j-1} - \beta_{11}S_j - (\nu_j + \eta_j)S_j, \quad i = 1, \ldots, m, j = 2, \ldots, n \\ \dot{I}_{11} &= S_1 \sum\nolimits_{i=1}^{3} \beta_{i1}I_{i1} - (\nu_1 + \sigma_1) \sum\nolimits_{i=1}^{3} I_{i1} + p\mu \sum\nolimits_{i=1,j=2}^{m,n} I_{ij} \\ \dot{I}_{ij} &= \sum\nolimits_{i=1,j=2}^{m,n} \beta_{ij}S_jI_{ij} - (\nu_j + \sigma_j)I_{ij}, \quad i = 1, \ldots, m, j = 2, \ldots, n \\ \dot{A}_1 &= \sigma_1 I_1 - (\nu_1 + \kappa_1)A_1 \\ \dot{A}_j &= \sigma_j I_j - (\nu_j + \kappa_j)A_j, \quad j = 2, \ldots, n \end{aligned} \tag{5}$$

The total number of newborns with is μ, $p\mu \sum_{i=1,j=2}^{m,n} I_{ij}$ is the number of newborns who are infected at birth. If we consider only one chronologica age group, we obtain the following diagram

The flow diagram of the infection is the following

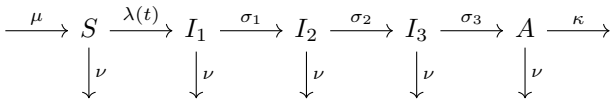

Figure 3: Transfer diagram for a SIA model.

where λ, the standard incidence function, can be approximated using three infection age stages, i.e., $\lambda(t) = \frac{c}{N}(\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_3)$. We highlight that we will use model (5) for future research. We have used the following model to illustrate preliminary results.

$$\begin{aligned} \frac{dS}{dt} &= \mu - \frac{S}{N}\beta I - \nu S \\ \frac{dI}{dt} &= \frac{S}{N}\beta I - (\sigma + \nu)I \\ \frac{dA}{dt} &= \sigma I - (\kappa + \nu)A. \end{aligned} \tag{6}$$

The feasible region of (5) is

$$\Omega = \left\{(i,a) \in \mathbb{R}^2_+ : 0 \leq i + a \leq 1\right\}, \tag{7}$$

where $\mathbb{R}^2_+$ denotes the positive quadrant of $\mathbb{R}^2$. The following lemma establish that the system is well-defined in the sense that solutions with initial conditions in Ω stay there for all $t > 0$. The basic reproductive number is

$$\mathcal{R}_0 = \frac{\beta}{(\sigma + \nu)}. \tag{8}$$

There exist two equilibrium points, P_0 and P_* for system (6), the disease-free point and endemic point, respectively

$$P_0 = \left(\frac{\mu}{\nu}, 0, 0\right), \tag{9}$$

$$P_* = \left(\frac{\mu(\kappa + \nu + \sigma)}{\beta(\kappa + \nu) - \kappa\sigma}, \frac{\mu(\kappa + \nu)}{\beta(\kappa + \nu) - \kappa\sigma}\left(\mathcal{R}_0 - 1\right), \frac{\mu\sigma}{\beta(\kappa + \nu) - \kappa\sigma}\left(\mathcal{R}_0 - 1\right)\right), \tag{10}$$

3 Sensitivity analysis

3.1 Local sensitivity

In determining how best to reduce the number of susceptible population due to the disease outbreak, it is necessary to know the relative importance of the different factors responsible for its transmission and prevalence. Initial disease transmission is directly related to $\mathcal{R}_0$, and disease prevalence is directly related to the endemic equilibrium point, $P_* = (S_*, I_*, A_*)$, specifically to the magnitude of I_*, since it represents the people who may be clinically ill. We calculate the sensitivity indices of the reproductive number, $\mathcal{R}_0$, and the infected population of the endemic equilibrium point, I_*, to the parameters in the model. These indices tell us how crucial each parameter is to disease transmission and prevalence. Sensitivity analysis is commonly used to determine the robustness of model predictions to parameter values since there are usually errors in data collection and presumed parameter values [8, 3]. Here we use it to discover parameters that have a high impact on $\mathcal{R}_0$ and I_*, and should be targeted by intervention strategies.

The prevalence of HIV, i.e., the accumulated cases of HIV incidence between two times of observation t_{i-1}, t_i is

$$\Phi_i = \int_{t_{i-1}}^{t_i} (\beta\frac{I}{N} + \xi)Sdt. \tag{11}$$

where ξ is a small parameter which corresponds the rate of infecting due to drug syringe exchange. Meanwhile the prevalence of AIDS, i.e., the accumulated cases of AIDS incidence between two times of observation t_{i-1}, t_i is The prevalence of the disease is

$$\Xi_i = \int_{t_{i-1}}^{t_i} \sigma ISdt. \tag{12}$$

Sensitivity indices allow us to measure the relative change in a state variable when a parameter changes. The normalized forward sensitivity index of a variable to a parameter is the ratio of the relative change in the variable to the relative change in the parameter. When the variable is a differentiable function of the parameter, the sensitivity index may be alternatively defined using partial derivatives [8, 3].

Definition 1 *The normalized forward sensitivity index of a variable, Q, that depends differentiably on a parameter, p, is defined as:*

$$\Upsilon^Q_p := \frac{\partial Q}{\partial p} \times \frac{p}{Q} \tag{13}$$

As we have an explicit formula for $\mathcal{R}_0$ (8) and P_* (10), we derive an analytical expression for the sensitivity of both $\mathcal{R}_0$ and P_0, to each of the seven different parameters described in table 1.

3.2 Global sensitivity

Global sensitivity analysis is to identify relevant and noninfluential parameters when parameter values are not specified but vary over the entire range of input values. One objective of global sensitivity analysis is to quantify how uncertainties in model outputs can be apportioned to uncertainties in model inputs that are considered in parameter space. Global sensitivity analysis techniques can be broadly categorized as regression, variance, or screening-based methods. Variance-based indices are advantageous over regression ans correlations-based indices since they do not require linearity or monotonicity. For this reason, they are sometimes referred to as model-free methods. We used variance-based indices, more specifically Sobol indices, in this manuscript. We briefly describe formulas for Sobol indices for uniform densities in this subsection and present their derivation in appendix

Consider the scalar-valued , nonlinear model $Y = f(Q)$, where $Q = [Q_1, \dots, Q_p] \in \Gamma \subset \mathbb{R}^p$. We initially assume that the random variables are independent and uniformly distributed on $[0, 1]$ so that

$$Q_i \sim \mathcal{U}(0, 1), \quad \Gamma = [0, 1]^p.$$

We consider the second-order High-dimensional model representation (HDMR) or Sobol expansion

$$f(q) = f_0 + \sum_{i=1}^{p} f_i(q_i) + \sum_{1 \le i \le j \le p} f_{ij}(q_i, q_j). \tag{14}$$

The first order Sobol sensitivity indices are defined by

$$S_i = \frac{\mathrm{var}[\mathbb{E}(Y|q_i)]}{\mathrm{var}(Y)}, \tag{15}$$

and total sensitivity index by

$$S_{T_i} = 1 - \frac{\mathrm{var}[\mathbb{E}(Y|q_{\sim i})]}{\mathrm{var}(Y)} = \frac{\mathbb{E}[\mathrm{var}(Y|q_{\sim i})]}{\mathrm{var}(Y)}. \tag{16}$$

4 Parameter estimation of the epidemic model

Even for the correct set of parameters, there is intrinsic discrepancy between the data and the model prediction because of noise measurements. The model may be incomplete, i.e., it may not consider all the relevant variables of the phenomena, or there could be a model error, where the model's assumptions may not be fulfilled. For the parameter estimation, we used Bayesian inference in this manuscript. First, we formulate the inverse problem associated to the parameter estimation. Denoting the state variable $x = (S, I, A)$, and the parameters $\theta = (\mu, N, \beta, \nu, \sigma, \kappa, \xi, S(0), I(0), A(0)) \in \mathbb{R}^{10}$, we can write the model (6) as the following Cauchy problem

$$\dot{x} = \varphi(x, \theta) \tag{17a}$$

$$x(0) = x_0. \tag{17b}$$

Problem (17), called the forward problem, defines a mapping $\Phi(\theta) = x$ from parameters θ to state variables x, where $\Phi : \mathbb{R}_+^m \to \left(L^2([0, T])\right)^n$, where $\mathbb{R}_+$ denotes the nonnegative real numbers and m is the dimension number of parameters to estimate and n is the number of state variables. We assume that Φ has a Fréchet derivative, denoted by Φ, and is injective, thus the forward problem (17) has a

unique solution x for a given θ. The Fréchet derivative of Φ is a mapping $\Phi'(\theta) : \mathbb{R}^m_+ \to \left(L^2([0,T]\right)^n$, resulting as the usual derivative since the domain and range of Φ' are finite dimensional spaces for the system (6).

Typically the data in epidemics consists of measurements of a subset of the sate variables at a discrete set of point $t_1, ..., t_k$. In case of HIV-AIDS, data consists of counting the number of infected with the HIV virus and people who have progressed to AIDS, and dead people caused by AIDS disease. This defines a linear observation mapping from state variables to data $\Psi : \left(L^2([0,T]\right)^n \to \mathbb{R}^{p\times k}$, where $p \leq n$ is the number of observed variables and k is the number of observation points. Considering infectious disease such as HIV-AIDS, $\Psi(x) = (I(t_1), \dots, I(t_k), A(t_1), \dots, A(t_k)) \in \mathbb{R}^{2\times k}$, i.e., in this case, the infected population with HIV, $I(t)$, and the people with AIDS, $A(t)$, are the measurable state variables. Let $F : \mathbb{R}^m \to \mathbb{R}^{s\times k}$ be defined by $F(\theta) = \Psi(\Phi(\theta))$, the inverse problem parameter estimation of ordinary differential equation systems is to find the parameter θ which minimize the cost functional J

$$\begin{gathered} \min_{\theta\in\mathbb{R}^m} J(\theta), \\ \text{subject to: } \dot{x} = \varphi(x,\theta), \quad x(0) = x_0; \end{gathered} \tag{18}$$

The cost functional ,J, is typically written as a Gaussian distribution or the following least-squares form

$$J(\theta) = \|\Psi(x) - x_\eta\|^2, \tag{19}$$

where $x_\eta \in \mathbb{R}^{p\times k}$ is the data which has error measurements of size η. Since the data in epidemics consists of counting the number people with HIV/AIDS, a Poisson distribution instead of a Gaussian distribution may be used to model the cost functional $J(\theta)$. Problem (17) may be solved using numerical tools to deal with a nonlinear least-squares problem or the Landweber method or the combination of both. The Landweber method has been used in [4]. We point out that faster methods as the Levenberg-Marquardt or Conjugate Gradient ones than Landweber method, may be used to obtain a faster convergence. The Landweber iteration is explained as follows [2]. We implement Bayesian inference to solve the inverse problem (18) in this manuscript. In this framework, we calculate the posterior distribution of the Bayes theorem θ is

$$\pi(\theta|x_\eta) \sim \pi(x_\eta|\theta)\pi(\theta) \tag{20}$$

Note that the right expression of (20) is not divided by the marginal density $\pi(x)$. For fit curve this is possible, not for comparison between models. The likelihood probability distribution is

$$x_i \sim \text{Poisson}(K\Phi_i(\theta))$$

where Φ_i the prevalence of HIV (11) and K is the rate of infected individuals' detection. Now, it is clear the reason for introducing the parameter ξ in (11), it is because in this way we can identify the parameters β and K, not only its product $K\beta$. Next, the likelihood density, $\pi(z|\theta)$, is calculated by the product of the individual probability densities of the observations

$$\pi(z|\theta) = \prod_{i=1}^{n} \pi(z_i|\theta) = \prod_{i=1}^{n} \frac{e^{-K\Phi_i(\theta)}(-K\Phi_i(\theta))^{z_i}}{z_i!} \tag{21}$$

We select Gamma distributions for the a priori distributions rates β, K.

$$\pi(\theta) = \prod_{i=1}^{n} \text{Gamma}(a_\beta, b_\beta) \times \text{Gamma}(a_K, b_K) \tag{22}$$

For the Markov Chain Monte Carlo Metropolis Hasting simulations we have used the following parameters values, corresponding to Mexican data, total population $N = 126577691$, $I_0 = 1, A_0 = 67$ (year 1984), $S_0 = N - (I_0 + A_0)$.

Parameter	Description	Baseline low	Baseline high
μ	natural birth rate (year^{-1})	1×10^{-5}	0.1
β	Probability of infecting per contact in I_1 (year^{-1})	1×10^{-5}	0.99
ν	natural death rate (year^{-1})	1×10^{-5}	0.1
σ	transmission rate from HIV to AIDS (year^{-1})	1×10^{-4}	0.9
κ	death rate caused by AIDS (year^{-1})	1×10^{-6}	1×10^{-4}
K	rate of infected individuals' detection (year^{-1})	1×10^{-2}	4

Table 1: Parameters values used for sensitivity analysis and problem (18).

Parameter	$\mathcal{R}_0$	I_*
μ	0.	1.0
β	1.	-11.1
ν	-0.09	-9.08
σ	-0.9	10.09
κ	0.	9.09

Parameter	$\mathcal{R}_0$	I_*
μ	0.	1.0
β	1.	-100.001
ν	-0.1	8.9
σ	-0.9	90.1
κ	0.	-0.00009

Table 2: Local sensitivity indices of $\mathcal{R}_0$ and P_* with respect to the parameter values, evaluated at the baseline low (left) and at the baseline high (right) given by 1.

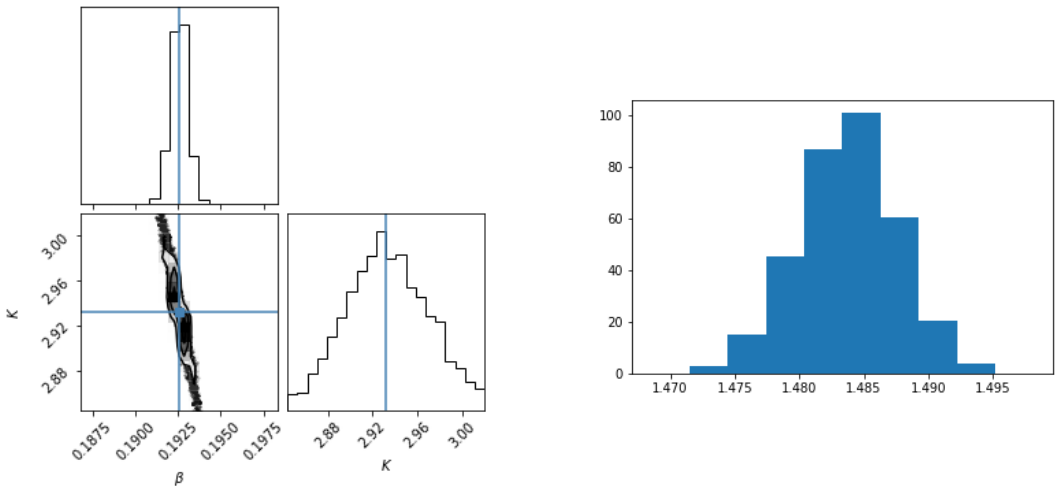

Figure 4: Parameter estimation of β and K (left), and the reproductive number $\mathcal{R}_0$ (right), using Bayesian inference.

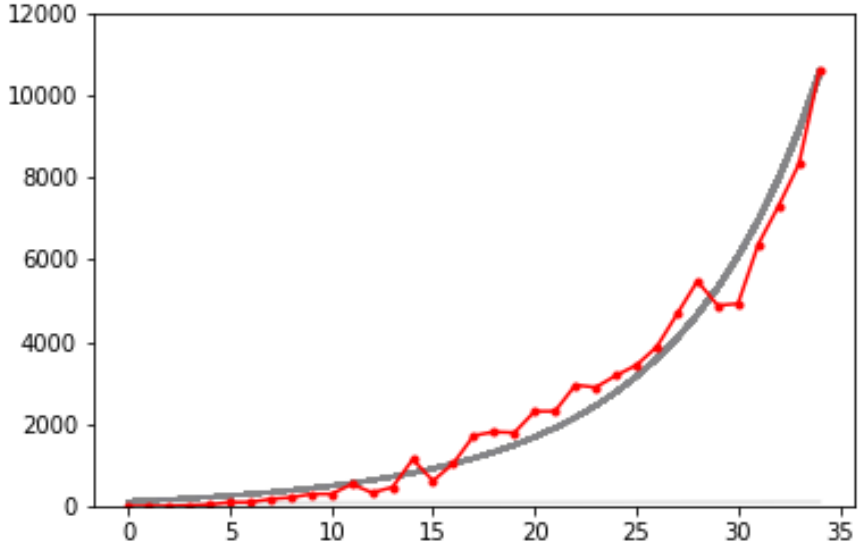

Figure 5: HIV curve fitting .

Appendix

In this appendix, we describe the Sobol indices derivation considering uniform densities and present and algorithm to calculate them. Sobol inidices for general densities are discussed in [6]. Consider the scalar-valued , nonlinear model $Y = f(Q)$, where $Q = [Q_1, \dots, Q_p] \in \Gamma \subset \mathbb{R}^p$. We initially assume that the random variables are independent and uniformly distributed on $[0, 1]$ so that

$$Q_i \sim \mathcal{U}(0, 1), \quad \Gamma = [0, 1]^p.$$

We consider the second-order High-dimensional model representation (HDMR) or Sobol expansion

$$f(q) = f_0 + \sum_{i=1}^{p} f_i(q_i) + \sum_{1 \le i \le j \le p} f_{ij}(q_i, q_j) \tag{23}$$

subject to the condition

$$\int_0^1 f_i(q_i) dq_i = \int_0^1 f_{ij}(q_i, q_j) dq_i = \int_0^1 f_{ij}(q_i, q_j) dq_j = 0, \tag{24}$$

which ensures that the functions are orthogonal in the sense that

$$\int_\Gamma f_i(q_i) f_j(q_j) dq_i dq_j = \int_\Gamma f_{ij}(q_i, q_j) dq_i dq_j = 0 \tag{25}$$

for $i, j = 1, \dots, p$.

Let

$$\mathbb{E}(Y|q_i) = \int_{\Gamma^{p-1}} f(q) dq_{\sim i}, \tag{26}$$

$$\mathbb{E}(Y|q_i, q_j) = \int_{\Gamma^{p-2}} f(q) dq_{\sim ij}, \tag{27}$$

denote the expected responses when the components q_i and q_i, q_j are fixed. Where $\Sigma^{p-1} = [0,1]^{p-1}$ and $\Sigma^{p-2} = [0,1]^{p-2}$ and $q_{\sim i}$ denotes the vector having all the components of q except those in the set i;

$$q_{\sim i} = [q_1, \dots, q_{i-1}, q_{i+1}, \dots q_p].$$

The expansion terms: zeroth-, first-, and second-order terms have variance interpretations as follows

$$f_0 = \int_0^1 \left[\int_{\Gamma^{p-1}} f(q) dq_{\sim i} \right] dq_i = \mathbb{E}[\mathbb{E}(Y|q_i)] = \mathbb{E}(Y), \tag{28a}$$

$$f_i(q_i) = \mathbb{E}(Y|q_i) - f_0, \tag{28b}$$

$$f_{ij}(q_i, q_j) = \mathbb{E}(Y|q_i dq_j) - f_i(q_i) - f_i(q_j) - f_0 \tag{28c}$$

The total variance D of the response Y is given by

$$D = \mathrm{var}(Y) = \int_\Gamma f^2(q) dq - f_0^2 \tag{29}$$

since $f_0 = \mathbb{E}(Y)$. By employing the expansion (14) and enforcing the orthonormality conditions (24) and (25), the total variance can be expressed as

$$D = \sum_{i=1}^{p} D_i + \sum_{1 \le i \le j \le p} D_{ij} \tag{30}$$

where the partial variances are

$$D_i = \int_0^1 f_i^2(q_i) dq_i,$$

$$D_{ij} = \int_0^1 \int_0^1 f_{ij}^2(q_i, q_j) dq_i dq_j.$$

The Sobol indices are defined to be

$$S_i = \frac{D_i}{D}, \quad S_{ij} = \frac{D_{ij}}{D}, \quad i, j = 1, \dots, p, \tag{31}$$

so, by the definition, they satisfy

$$\sum_{i=1}^{p} S_i + \sum_{1 \le i \le j \le p} S_{ij} = 1.$$

The terms S_i are often termed the *importance measures* or *first-order sensitivity indices*, and large values of S_i indicate parameters that strongly influence the response variance. Similarly, S_{ij} account for the influence of interaction terms. Because the number of first- and second-order Sobol indices is $p + \dfrac{p(p-1)}{2}$, their analysis quickly becomes untenable for large parameter dimensions. This motivates the consideration of *total sensitivity indices*

$$S_{T_i} = S_i + \sum_{j=1}^{p} S_{ij}, \tag{32}$$

which quantify the total effect of the parameter Q_i on the response Y.

Using the equation (28), it follows that

$$D_i = \mathrm{var}[\mathbb{E}(Y|q_i)] \tag{33}$$

and hence

$$S_i = \frac{\text{var}[\mathbb{E}(Y|q_i)]}{\text{var}(Y)}. \tag{34}$$

Similarly, one can show that

$$D_{ij} = \text{var}[\mathbb{E}(Y|q_i, q_j)] - \text{var}\mathbb{E}[(Y|q_i)] - \text{var}\mathbb{E}[(Y|q_j)], \tag{35}$$

which yields a variance interpretation for S_{ij}. Finally, the total sensitivity index has the interpretation

$$S_{T_i} = 1 - \frac{\text{var}[\mathbb{E}(Y|q_{\sim i})]}{\text{var}(Y)} = \frac{\mathbb{E}[\text{var}(Y|q_{\sim i})]}{\text{var}(Y)}. \tag{36}$$

The computation of S_i given by (34) requires the approximation of $\text{var}[\mathbb{E}(Y|q_i)]$. If one uses M Monte Carlo evaluations to approximate the conditional mean $\mathbb{E}(Y|q_i)$ for fixed q_i and repeats the procedure M times to approximate the variance, a total of M^2 evaluations will be required to evaluate a single sensitivity index. For large parameter dimensions p, this approach is prohibitive. The following algorithm of Saltelli, reduces the number of required function evaluations to $M(p+2)$.

Algorithm

1. Create two $M \times p$ sample matrices

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

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

2. Create $M \times p$ matrices

$$C_i = \begin{bmatrix} \hat{q}_1^1 & \cdots & \hat{q}_i^1 & \cdots & \hat{q}_p^1 \\ \vdots & & & & \vdots \\ \hat{q}_1^M & \cdots & \hat{q}_i^M & \cdots & \hat{q}_p^M \end{bmatrix} \tag{37}$$

which are identical to B with the exception that the i^{th} column is taken from A.

3. Compute $M \times 1$ vectors of model outputs

$$y_A = f(A), \quad y_B = f(B) \quad y_{C_i} = f(C_i) \tag{38}$$

by evaluating the model at the input values in A, B and C_i. The evaluation of y_A and y_B requires $2M$ model evaluations, wheras the evaluation of $y_{C_i}, i = 1, \ldots, p$, requires pM evaluations. Hence the total number of model evaluations is $M(p+2)$.

4. The estimates for the first-order sensitivity indices are

$$S_i = \frac{\text{var}[\mathbb{E}(Y|q_i)]}{\text{var}(Y)} = \frac{\frac{1}{M} y_A^T y_{C_i} - f_0^2}{y_A^T y_A - f_0^2} = \frac{\frac{1}{M}\sum_{j=1}^M y_A^j y_{C_i}^j - f_0^2}{\sum_{j=1}^M (y_A^j)^2 - f_0^2}, \tag{39}$$

where the mean is approximated by

$$f_0^2 = \left(\frac{1}{M}\sum_{j=1}^M y_A^j\right)\left(\frac{1}{M}\sum_{j=1}^M y_B^j\right). \tag{40}$$

The estimates for the total effects indices are

$$S_{T_i} = 1 - \frac{\text{var}[\mathbb{E}(Y|q_{\sim i})]}{\text{var}(Y)} = 1 - \frac{\frac{1}{M} y_B^T y_{C_i} - f_0^2}{y_A^T y_A - f_0^2} = \frac{\frac{1}{M}\sum_{j=1}^{M} y_B^j y_{C_i}^j - f_0^2}{\sum_{j=1}^{M} (y_A^j)^2 - f_0^2}. \tag{41}$$

The intuition for the algorithm is the following. In the scalar product $y_A^T y_{C_i}$, the response computed from values in A is multiplied by values for which all parameters except q_i have been resampled. If q_i is influential, then large (or small) values of y_A will be correspondingly multiplied by large (or small) values of y_{C_i}, yielding a large value of S_i. If q_i is not influential, large and small values of y_A and y_{C_i} will occur more randomly and S_i will be small.

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