

Hierarchical Bayesian Parameter Estimation for HIV Dynamic Models

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Abstract

Most studies on parameter estimation for HIV dynamic models have ignored pre-treatment viral load data hence utilizing only post-treatment viral load data. In this study we utilize pre-treatment viral load data to estimate parameters of the HIV dynamic model in the absence of therapy. By employing hierarchical Bayesian parameter estimation approach, we were able to get reasonably robust estimates of the model parameters. Using simulated data, the parameter estimation was done at both the individual and population levels with the implementation carried out via Markov Chain Monte Carlo methods.

Keywords: HIV dynamics; parameter estimation; MCMC; Bayesian Inference

1 Introduction

Human Immuno-deficiency Virus(HIV) dynamic studies are of paramount importance not only for understanding the pathogenesis of human HIV infection but also for helping with providing useful guidelines for the development of good treatment strategies and providing information for the evaluation of treatment efficacy. Particularly important in HIV dynamic data analysis are the statistical methods and the mathematical models involved. Therefore careful selection of such models and methods is critical to the success of the studies conducted.

We are made aware of the fact that "all models are wrong, but only some are useful", Box [4]. This statement is absolutely true, especially when referring to mathematical models. Since models are by their very nature approximations to unfathomably complicated reality, they are of course literally false. Indeed, some models are useful in the sense that models are pretty much the only instruments we have for understanding complex phenomena like HIV viral dynamics. A number of useful models have been developed to describe the immune system, its interaction with HIV and the decline of $CD4^+$ T cells. These models are usually a system of differential equations where the rates of flow between compartments are determined by parameters specific to the disease's natural history.

Because of their importance, estimation methods in viral dynamic studies have also been developed. These estimation methods and model fitting procedures have been used in viral dynamic studies focussing on post-treatment viral load longitudinal data. Amongst the methods used is the nonlinear least squares (NLS). The estimation approach is based on simulating the solutions to the model equations and identifying the parameters that minimize the sum of squared errors between observed and simulated cumulative number of cases. NLS requires that the viral load function be analytically tractable or its numerical solution be easily obtainable. This may not always be the case for more complicated models encountered in HIV dynamics, thus making the method less appealing. NLS methods also fail to capture the fact that viral dynamic processes for different patients share certain similar patterns while still having distinct individual characteristics. It is for these two reasons amongst others that the mixed effects models were considered by Wu and Ding [23] and Wu et al [24] as they offer more flexibility.

The Nonlinear Mixed-Effects (NLME) or hierarchical nonlinear model approach proposed by Wu and Ding [23] and Wu et al [24] can pool individual data together to estimate the population parameters first, and then estimate the individual parameters by the empirical Bayesian method, Davidian and Giltinian [5] and Vonesh and Chinchilli [20]. Although the individual NLS estimates can be pooled together to obtain the population estimates of parameters in the hierarchical model using the standard two-stage method or global two-stage method, linearization methods are more efficient. To efficiently make use of the NLME approach many methods have been used amongst them maximum likelihood method for parameter estimation proposed by Beal and Sheiner [2], while Vonesh and Carter [19] suggested iterative generalized least squares (GLS) (with and without basis) on conditional first order linearization. Detailed reviews of these methods can be found in Davidian and Giltinian [5]. Details on applications of NLME models to viral dynamic analysis can be found in Wu and Ding [23] and Wu et al [24]. The S-plus function `nmle()`, Pinheiro

and Bates [16], the procedure NLMIXED in SAS and other packages like NONMEM, Beal and Sheiner [3] and NLMEM can be used to fit the model. In practice, the difficulty of using these standard packages in fitting NLME models arises when the closed form of the nonlinear function is not available. For example, our viral dynamics nonlinear function is the solution of a system of nonlinear ordinary differential equations, which does not have a closed form. In this case the standard packages can not be used directly, and we must rely on the numerical solution to fit the mixed-effects models. Because of these issues that may arise from the methods discussed so far, the Bayesian approach seems to be able to provide solutions to such concerns.

Some of the proposed viral dynamic models are nonlinear differential equations, to which no closed-form solution is available. Some of these models can also have too many unknown parameters. This poses the challenge of how to identify all the parameters in such a system. Therefore some prior information is necessary to help with the parameter identification. To efficiently use prior information to identify many parameters, we need to resort to Bayesian methods which have been studied to estimate viral dynamic parameters by Han et al [9], Putter et al [17] and Wu [22]. In this study, we make use of simulated pre-treatment viral load data to estimate parameters of HIV dynamic model in absence as developed by Perelson and Nelson [14]. This is achieved by employing Markov Chain Monte Carlo (MCMC) methods within the Bayesian NLME (Hierarchical Bayesian Model) approach.

We present a review of HIV dynamic models (in the absence and presence of therapy) in Section 2. A note on 'Bayesian Inference for Pre-treatment HIV Data' is presented in Section 3. Then the implementation of parameter estimation employing the Hierarchical Bayesian approach methods and results are dealt with in Sections 4 and 5 respectively.

2 Models

HIV dynamics in the absence and presence of therapy have attracted the attention of many researchers, amongst them Ho et al [10], Perelson et al [13], and Perelson and Nelson [14]. Amongst the consequences of HIV infection is the selective depletion of CD4⁺ T cells. In fact the decline in the number of CD4⁺ T cells in peripheral blood and the peripheral blood ratio of CD4⁺ T/CD8⁺ T cells are both used in clinical settings as indicators of disease stage. To model the dynamics of CD4⁺ T cells (hereinafter referred to as T cells) in the absence of HIV (infection) the differential equation below has been proposed

by Perelson et al. [13];

$$\frac{dT}{dt} = s + pT\left(1 - \frac{T}{T_{max}}\right) - d_T T. \quad (1)$$

From the equation, T is the number of CD4⁺ T cells, as measured in the blood, s is the rate of supply of new T cells from sources within the body like the thymus, while the rate of T cells that can be produced from the proliferation of existing T cells is represented by p . The quantity T_{max} represents the T cell population density at which proliferation shuts off and d_T represents the death rate per T cell (assuming that T cells like all other cells have a natural lifespan).

2.1 HIV Dynamics in the Absence of Therapy

To model the dynamics of T cells in the presence of HIV it's worthy to consider T cells that are uninfected (i.e. targeted by HIV) T , and T cells that are productively infected, T^* . The dynamics of these populations can be captured by the following differential equations, Perelson and Nelson [14];

$$\frac{dT}{dt} = s + pT\left(1 - \frac{T}{T_{max}}\right) - d_T T - kVT, \quad (2)$$

$$\frac{dT^*}{dt} = kVT - \delta T^*, \quad (3)$$

$$\frac{dV}{dt} = N\delta T^* - cV. \quad (4)$$

where k , δ , N and c represent the infection rate, the death rate of infected cells, the average number of virions produced by a productively infected cell during its lifetime and the clearance rate of free virions, respectively. Equation (2) is a modification of equation (1) with the parameters s , p , T_{max} and d_T being the same as in equation (1).

A numerical solution of the equation (4) above, yields a viral load curve similar to the one in Figure 1(c), with time $t=0$ as the time of infection, with V_0 given. Such a solution was made possible by the use of the Matlab M-file `ode45.m`. Figure 1(a) and Figure 1(b) depict the healthy CD4⁺ T cells ($T(t)$) and infected CD4⁺ T cells ($T^*(t)$) dynamic curves after HIV infection.

2.2 HIV Dynamics in the Presence of Therapy

Without drug intervention the assumption is that starting from the time of infection (t_0) up to the time when plasma virus is in quasi-steady state, we have a viral load curve totally distinct from the one we would have after

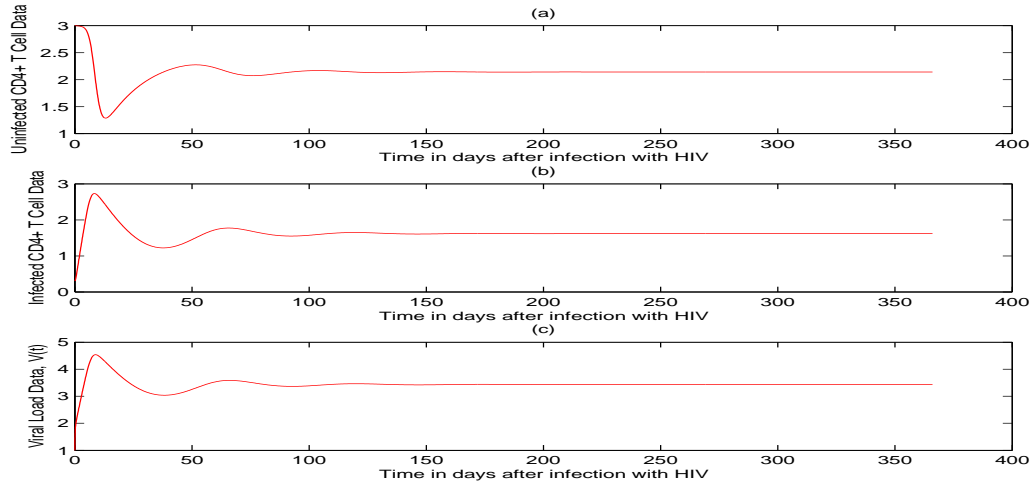


Figure 1: (a) Typical healthy($T(t)$) T cell decline, (b) infected($T^*(t)$) T cell curve and (c) Viral Load Curve $V(t)$, (all the curves are in \log_{10} scale for the first 366 days after infection.)

antiretroviral therapy is administered. The supposition is that both these viral load curves arise from the solutions (whether analytic or numerical) to the equation (4), with the differences being in the conditions imposed thereon. Such differences should of course include changes in parameters, of which given clinical trial data one can be able to estimate. Following the highly convincing examples of Perelson et al [13], Perelson and Nelson [14] and Perelson et al [15] we give a discussion of the dynamics of HIV in the presence of therapy.

By therapy in this study we mean treatment with protease inhibitors (PI) and reverse transcriptase inhibitors (RTI). An RT inhibitor blocks infection and hence reduces k , so that in the presence of a perfect RT inhibitor, $k = 0$ and the T cell dynamic equations become uncoupled from the viral dynamic equation hence getting the system;

$$\frac{dT}{dt} = s + pT \left(1 - \frac{T}{T_{max}}\right) - d_T T, \quad (5)$$

$$\frac{dT^*}{dt} = -\delta T^*, \quad (6)$$

$$\frac{dV_{NI}}{dt} = N\delta T^* - cV_{NI}. \quad (7)$$

Thus, the model predicts that if viral infection had not changed any of the parameters characterizing T cell dynamics, the T cell population should eventually recover and return to its preinfection steady state. Hence productively infected T cells are no longer generated and their number will decay exponentially; i.e., $T^*(t) = T_0^* e^{-\delta t}$. The amount of free virus will also decay but with

a more complicated exponential behavior, $V(t) = V_0 e^{-ct} + \frac{N\delta T_0^*}{c-\delta} (e^{-\delta t} - e^{-ct})$. Assuming quasi-steady state before treatment, $T_0^* = kV_0 T_0 / \delta$ and $NkT_0 = c$, yields;

$$V(t) = \frac{V_0}{c-\delta} [ce^{-\delta t} - \delta e^{-ct}] \quad (8)$$

It is a truism that RT inhibitors, like other drugs are not perfect. A more accurate model for the action of RT inhibitors and its analysis are availed in Perelson and Nelson [14].

In a nutshell, protease inhibitors cause infected cells to produce noninfectious virions. Virions that were created prior to treatment remain infectious. Thus, in the presence of protease inhibitors, we consider two types of virus particles: infectious virions at concentration V_I and noninfectious virions at concentration V_{NI} , with total virus concentration being $V = V_I + V_{NI}$. To be more precise, V_I denotes the population of virus particles that have not been influenced by a protease inhibitor and hence had their polyproteins cleaved, whereas V_{NI} denotes the population of virus particles with uncleaven proteins, since even in the absence of protease inhibitors not every virus particle is infectious. Hence after a 100% protease inhibitor is given, the model can be represented by the following system of equations;

$$\frac{dT}{dt} = s + pT \left(1 - \frac{T}{T_{max}}\right) - d_T T - kV_I T, \quad (9)$$

$$\frac{dT^*}{dt} = kVT - \delta T^*, \quad (10)$$

$$\frac{dV_I}{dt} = -cV, \quad (11)$$

$$\frac{dV_{NI}}{dt} = N\delta T^* - cV_{NI}. \quad (12)$$

The total concentration of the virus, an easily measured quantity, is then given as;

$$V(t) = V_I + V_{NI} = V_0 e^{-ct} + \frac{cV_0}{c-\delta} \left[\frac{c}{c-\delta} (e^{-\delta t} - e^{-ct}) - \delta t e^{-ct} \right]. \quad (13)$$

3 Bayesian Inference for Pre-treatment HIV Data

We let subject specific parameters be $\theta_i = (\log s_i, \log p_i, \log T_{max_i}, \log d_{T_i}, \log k_i, \log \delta_i, \log N_i, \log c_i)^T$. The log transformation of the parameters is used to guarantee their positivity. Also we denote $\Theta = \{\theta_1, \theta_2, \dots, \theta_n\}$ and $\Theta_{\{i\}} = \{\theta_l, l \neq i\}$. Then the Bayesian NLME can be written in the following three stages, Wakefield et al [21]:

◦ *Stage 1. Intra-individual variation in common logarithmic viral load measurements:*

$$\mathbf{y}_i = \mathbf{f}_i(\mathbf{t}_i, \theta_i) + \mathbf{e}_i, \quad [\mathbf{e}_i | \sigma^2, \theta_i] \sim N(0, \sigma^2 \mathbf{I}_{m_i}) \quad (14)$$

where $\mathbf{y}_i = (y_{i1}(t_1), \dots, y_{im_i}(t_{m_i}))^T$, are measurements of viral load data from the i th subject, $\mathbf{f}_i(\mathbf{t}_i, \theta_i) = (V_{i1}(\theta_i, t_1), \dots, V_{im_i}(\theta_i, t_{m_i}))^T$, are total virus concentration which can be numerical or closed-form solution, $\mathbf{e}_i = (e_i(t_1), \dots, e_i(t_{m_i}))^T$ are measurement errors and the bracket notation $[A|B]$ denotes the conditional distribution of A given B .

◦ *Stage 2. Inter-individual variation:*

$$\theta_i = \mu + b_i, \quad [b_i | \Sigma] \sim N(0, \Sigma) \quad (15)$$

◦ *Stage 3. Hyperprior distribution:*

$$\sigma^{-2} \sim Ga(a, b), \quad \mu \sim N(\eta, \Lambda), \quad \Sigma^{-1} \sim Wi(\Omega, \nu) \quad (16)$$

where the mutually independent Gamma (Ga), Normal (N) and Wishart (Wi) prior distributions are chosen to facilitate computations, Davidian and Giltinian [5], Gelfand et al [7]. The parametrization of Gamma and Wishart distributions is such that $Ga(a, b)$ has mean b and $Wi(\Omega, \nu)$ has mean matrix $\nu\Omega$. The parameters $a, b, \eta, \Lambda, \Omega$ and ν that characterize the hyperprior distributions are assumed to be known.

According to the studies by Davidian and Giltinian [5], Gelfand et al [7], and Wakefield et al [21] the full conditional distributions for the parameters σ^{-2}, μ and Σ^{-1} may be written explicitly as;

$$\begin{aligned} [\sigma^{-2} | \mu, \Sigma^{-1}, \Theta, \mathbf{Y}] &\sim Ga\left(a + \frac{\sum_{i=1}^n m_i}{2}, \left\{ \frac{1}{b} + \frac{1}{2} \sum_{i=1}^n \sum_{j=1}^{m_i} [y_{ij} - f_{ij}(\theta_i, t_j)]^2 \right\}^{-1}\right) \\ &= \pi(\sigma^{-2}, \Sigma^{-1}, \Theta, \mathbf{Y}) \\ [\mu | \sigma^{-2}, \Sigma^{-1}, \Theta, \mathbf{Y}] &\sim N\left(\left((n\Sigma^{-1} + \Lambda^{-1})^{-1}(\Sigma^{-1} \sum_{i=1}^n \theta_i + \Lambda^{-1}\eta)\right), \left(n\Sigma^{-1} + \Lambda^{-1}\right)^{-1}\right) \\ &= \pi(\mu | \sigma^{-2}, \Sigma^{-1}, \Theta, \mathbf{Y}) \\ [\Sigma^{-1} | \sigma^{-2}, \mu, \sigma^{-2}, \Theta, \mathbf{Y}] &\sim Wi\left(\left[\Omega^{-1} + \sum_{i=1}^n (\theta_i - \mu)(\theta_i - \mu)^T\right]^{-1}, n + \nu\right) \\ &= \pi(\Sigma^{-1} | \sigma^{-2}, \mu, \Theta, \mathbf{Y}) \end{aligned}$$

whereas the full conditional distribution of each θ_i , given the remaining parameters and the data, cannot be obtained explicitly. However, the distribution of $[\theta_i | \sigma^2, \mu, \Sigma, \Theta_{\{i\}}, Y]$ has a density function which is proportional to;

$$\exp\left\{-\frac{\sigma^{-2}}{2} \sum_{j=1}^{m_i} [y_{ij} - f_{ij}(\theta_i, t_j)]^2 - \frac{1}{2}(\theta_i - \mu)^T \Sigma^{-1}(\theta_i - \mu)\right\}. \quad (17)$$

$$= \pi(\theta_i | \sigma^{-2}, \mu, \Sigma^{-1}, \Theta, \mathbf{Y}) \quad (18)$$

Markov Chain Monte Carlo (MCMC) methods can then be used to obtain the estimates of the posterior distribution of the parameters. To implement a MCMC algorithm, Gibbs sampling steps are used to update σ^{-2} , μ and Σ^{-1} , whereas θ_i , $i = 1, \dots, n$, are updated using a Metropolis-Hastings step. Bayesian analysis for the investigation of a population HIV dynamic model with the studies focused on the dynamics of post-treatment HIV-RNA decline was used by Han et al [9] and Putter et al [17]. In these studies the function of viral load over time had a closed form solution, which is not the case in this study.

3.1 Estimation

In viral dynamic studies it is possible to, through quantitative polymerase chain reaction (PCR)-based methods, obtain data for the total viral load, $V(t)$. We let $V(\beta, t)$ to be the solution of viral load, for which in this case is the numerical solution to the system (2)-(4) obtained by the MATLAB solver `ode45.m`, with $\beta = (s, p, T_{max}, d_T, k, \delta, N, c)$ being the unknown parameter set. Thus we can simulate viral load measurements data $y_i(t) = V_i(\beta_i, t) + e(\beta_i)$ at time t after infection, where $e(\beta_i)$ is the noise term. In simulating data we followed the examples of Banks et al [1] and Huang and Wu [11]. Using the inter-individual variation model (15) we are able to generate true parameters $\theta_i = (\log s_i, \log p_i, \log T_{max_i}, \log d_{T_i}, \log k_i, \log \delta_i, \log N_i, \log c_i)^T$. A discussion of biologically realistic choices of θ_i are availed in Perelson et al [13]. It is assumed that θ_i is a linear function of the parameter vector μ whose value we set at $\mu = (1.0000, -1.5229, 3.1761, -1.6990, -4.6198, -0.6198, 3.0000, 0.3802)^T$. We also assumed random effects \mathbf{b}_i are normally distributed with mean 0 and standard deviation matrix Δ which has diagonal elements $diag(\Delta) = (0.1, 0.05, 0.05, 0.05, 0.08, 0.05, 0.05, 0.01)$. Thus we can obtain the corresponding values of the true parameter set $\beta_i = (s_i, p_i, T_{max_i}, d_{T_i}, k_i, \delta_i, N_i, c_i)$, ($i=1, \dots, 4$). Intra-individual variation model (14) is used to generate the viral load observations with measurement errors using the MATLAB multivariate random number generating function `mvrnd.m`. The baseline viral load V_{0i} for the i th patient, which is simply the amount of virus introduced into the body at time t_0 , is chosen as 44copies/ml, 29copies/ml, 38copies/ml and 45copies/ml for patient 1, patient 2, patient 3 and patient 4 respectively. The initial values T_0 and T_0^* , are chosen to be 1000 cells/mm³ and 0 cells/mm³ respectively for all four patients. We simulate data for the 4 'patients' with 30 data points; every day until the seventh day, then every two days until the third week and then every week until the nineteenth week. The data is then transformed to log₁₀ scale, with assumed variance of measurement error as $\sigma^2 = 1$. It is worth noting that the HIV-1 RNA assay has a limit of detection (50 copies/ml, below, Wu and Ding [23], and 750000 copies/ml, above, Banks et al [1], so for

such values below the limit of detection we simply impute 50 copies/ml(=1.7 in log₁₀ scale). We had no values above 750000 copies/ml. Figure 2 displays the viral load trajectories(in log₁₀ scale) for the 4 subjects.

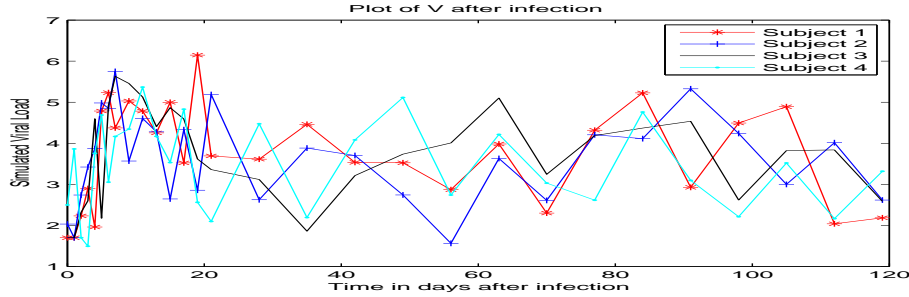


Figure 2: Viral Load Trajectories For 4 Patients

4 Implementation

Based on the discussion in Section 3, we established that when using Bayesian methods prior information can be used to help with parameter identification. Following the example of Huang and Wu [11], which was based on the idea of Han et al [9] for prior construction, we choose the values for the hyper-parameters as follows:

$a = 4.5, b = 9.0, \Lambda = \text{diag}(0.0025, 0.0025, 0.0025, 0.0025, 0.0010, 0.0025, 0.0025, 0.0025),$
 $\eta = (1.0000, -1.5229, 3.1761, -1.6990, -4.6198, -0.6198, 3.0000, 0.3802)^T,$
 $\Omega = \text{diag}(2.0, 2.0, 2.0, 2.0, 2.0, 2.5, 2.0, 2.5).$ where the notation $A = \text{diag}(\cdot)$ denotes the diagonal elements of matrix A . These values of the hyper-parameters were determined based on several published studies in Han et al [9], Ho et al [10], Huang and Wu [11], Perelson et al [13] and Putter et al [17]. The MCMC algorithm that we follow is as follows:

- Step 1.* Initialize the hyperprior parameters a, b, η, Λ, ν and Ω . Pick the candidate variance Δ for θ_i . Select the starting values for $\theta_1^0, \theta_2^0, \dots, \theta_n^0, \mu^0, \sigma^{-2(0)}, \Sigma^{-1(0)}$. Iteration counter is set at $\kappa = 1$.
- Step 2.* Calculate $f(t_{ij}, \theta_i^{\kappa-1}), j = 1, 2, \dots, m_i$ and $i = 1, \dots, n$.
- Step 3.* Generate sample $\sigma^{-2(\kappa)}$, from the distribution:

$$Ga\left(a + \frac{\sum_{i=1}^n m_i}{2}, \left\{ \frac{1}{b} + \frac{1}{2} \sum_{i=1}^n \sum_{j=1}^{m_i} [y_{ij} - f_{ij}(\theta_i^{\kappa-1}, t_j)]^2 \right\}^{-1}\right).$$

Step 4. Generate sample μ^κ from the distribution:

$$N((n\Sigma^{-1} + \Lambda^{-1})^{-1}(\Sigma^{-1} \sum_{i=1}^n \theta_i^{\kappa-1} + \Lambda^{-1}\eta), (n\Sigma^{-1} + \Lambda^{-1})^{-1}).$$

Step 5. Generate a sample $\Sigma^{-1(\kappa)}$ from distribution:

$$Wi([\Omega^{-1} + \sum_{i=1}^n (\theta_i^{\kappa-1} - \mu)(\theta_i^{\kappa-1} - \mu)^T]^{-1}, n + \nu).$$

Step 6. Generate a sample φ from $N(\theta_i^{\kappa-1}, \Delta)$. Define

$$\alpha(\varphi|\theta_i^{(\kappa-1)}) = \min\left\{1, \frac{\pi(\varphi|\sigma^{-2(\kappa)}, \mu^{(\kappa)}, \Sigma^{-1(\kappa)}, \Theta_{\{i\}}^{(\kappa-1)}, \mathbf{Y})}{\pi(\theta_i^{(\kappa-1)}|\sigma^{-2(\kappa)}, \mu^{(\kappa)}, \Sigma^{-1(\kappa)}, \Theta_{\{i\}}^{(\kappa-1)}, \mathbf{Y})}\right\}. \quad (19)$$

Then generate a sample u from a uniform distribution $U(0,1)$. Set $\theta_i^\kappa = \theta_i^{\kappa-1}$, if $\alpha < u$, otherwise we set $\theta_i^\kappa = \varphi$, if $\alpha \geq u$

Step 7. Set counter $\kappa = \kappa + 1$ and return to step 2 until convergence is reached.

The random number samples required in the algorithm drawn from the the gamma, normal and Wishart distributions, in steps 3,4 and 5 can be generated by the random generators `gamrnd.m`, `mvnrnd.m` and `wishrnd.m` in MATLAB, respectively using Gibbs sampling. In our implementation, the proposal distribution for φ is chosen to be a multivariate normal distribution centred at the current value of θ_i , as it can be easily sampled and is symmetric. We chose a random-walk Metropolis chain for updating θ_i . A critical issue is how to choose the value of the proposal variance. If the proposal variance is too large, an extremely large proportion of iterations will be rejected, and the algorithm will therefore be extremely inefficient. If the proposal variance is too small, the moves are generally accepted but will move around the parameter space slowly which leads to high autocorrelation and inefficiency. Therefore in order to stabilize the posterior distribution faster we kept on adjusting the value of the proposal variance. To examine the dependence of posterior mean on the prior distributions and initial values, we monitored several independent MCMC runs, starting from different initial values and they exhibited similar and stable behavior. Therefore we concluded that results are more sensitive to the priors than to the starting values. We ran a chain of length 200,000 and burn-in of length 100,000, then retaining every fifth sample from the samples after burn-in. Thus, we obtained 20,000 samples of targeted posterior distributions of the 8 unknown parameters. The results are availed in the next Section.

5 Results

In this Section we present the summary of the results of our study. We present the MCMC iterations and convergence diagnostics for the parameters with regard to varying initial values in Figure 3. Figure 3 shows that indeed the chains converge from different starting values and the autocorrelation function also verified convergence. The trace plots for the parameters are presented in Figure 4. The histograms plots are presented in Figure 5. We present in Table 1 a summary of the results of estimated population parameters and a summary of results of subject-specific estimated parameters is presented in Table 2. From Figure 3, Figure 4 and Figure 5, we are convinced that all the

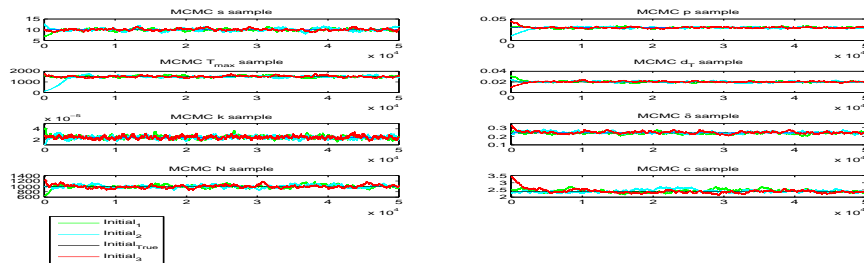


Figure 3: MCMC iterations and convergence diagnostics for the eight parameters with regard three different initial values on the simulated data set.

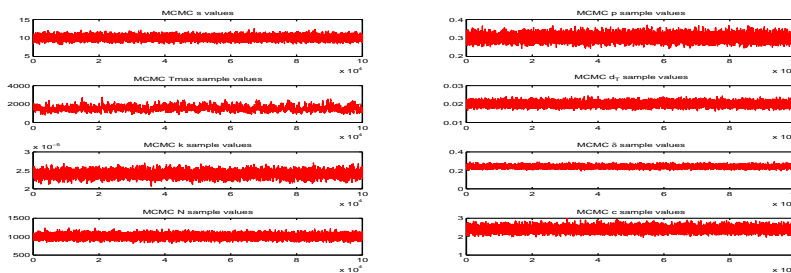


Figure 4: Trace plots for the eight parameters.

chains are stabilized and well mixed. We are also convinced that the results we obtained which are (i) population parameter estimates in Table 1 and (ii) parameter estimates for the 4 individuals/’patients’ in Table 2 are reasonably good.

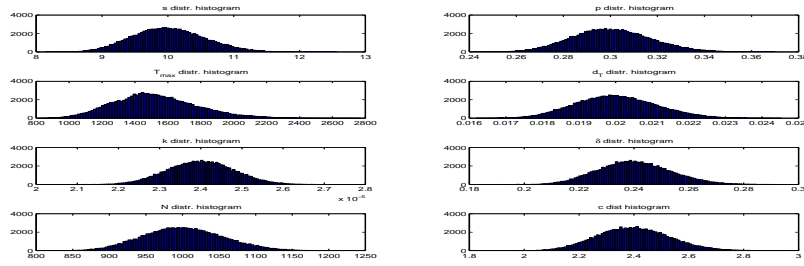


Figure 5: Histograms for the eight parameters.

Parameter	M	PM	STD	TV	95% CI
s	9.3541	9.3512	0.4662	10.2500	(8.4375, 10.2648)
p	0.0333	0.0334	0.0018	0.0294	(0.0299, 0.0369)
T_{max}	$1.2572 * 10^3$	$1.2584 * 10^3$	64.7615	1299	($1.1315 * 10^3$, $1.3854 * 10^3$)
d_T	0.0215	0.0215	0.0010	0.0231	(0.0195, 0.0235)
k	$2.5350 * 10^{-5}$	$2.5372 * 10^{-5}$	$7.0737 * 10^{-7}$	$2.4044 * 10^{-5}$	($2.3986 * 10^{-5}$, $2.6759 * 10^{-5}$)
δ	0.2427	0.2429	0.0100	0.2437	(0.2232, 0.2626)
N	954.7485	955.1604	38.3923	989.7500	($880.10304 * 10^3$)
c	2.3974	2.3994	0.0886	2.4892	(2.2257, 2.5731)

Table 1: The medians(M), posterior means (PM), true values (TV), standard deviation (STD) and 95% Credible Interval(95% CI) values of population parameters based on the simulated dataset.

5.1 Model Diagnostics

Data replicated from the model should resemble the data used to fit the model, therefore doing model checking and posterior predictive checks is always necessary, Sinharay and Stern [18]. Based on Gelman et al [8], from the data (for 'patient 4') that we simulated we chose the discrepancy measure as the difference between the maximum value and the minimum value at each iteration, i.e. $T(y_i, \theta) = y_{max} - y_{min}$. So at each iteration of the Markov chain we compute an outcome of $T(y, \theta)$. The posterior predictive distribution of $T(y, \theta)$ is plotted in Figure 6. It is known that if the data fits the model well then the observed discrepancy measure should not be in the tails of the distribution, Lekone and Finkenstädt [12]. In our case, a p -value of 0.5403 does not lead us to conclude that there's any lack of fit. Figure 7, also shows the fit of the model where most of the values of the observed viral load trajectory fall within the 95% credible interval predicted by the model.

6 Discussion

We have successfully implemented the hierarchical Bayesian approach to estimate HIV dynamic model parameters at both individual and population levels in the absence of therapy using simulated pre-treatment data. MCMC techniques were employed in this endeavor. The data we simulated was determin-

Patient	s	p	T_{max}	d_T	k	δ	N	c
PM 1	9.3840	0.0334	$1.2579 * 10^3$	0.0220	$2.5404 * 10^{-5}$	0.2441	953.8833	2.4071
TV	11	0.0280	1487	0.0233	$2.4000 * 10^{-5}$	0.2312	899	2.3929
Bias	-1.6160	0.0054	-229.1000	-0.0013	$0.1040 * 10^{-5}$	0.0129	54.8833	0.0142
PM 2	9.4114	0.0335	$1.2676 * 10^3$	0.0235	$2.5410 * 10^{-5}$	0.2434	958.4661	2.4054
TV	10	0.0310	1501	0.0235	$2.3176 * 10^{-5}$	0.2520	978	2.4112
Bias	-0.5886	0.0025	-233.4000	0.0000	$0.2234 * 10^{-5}$	-0.0086	-19.5339	-0058
PM 3	9.3308	0.0334	$1.2597 * 10^3$	0.0216	$2.5382 * 10^{-5}$	0.2429	957.2627	2.3991
TV	9	0.0329	1513	0.0253	$2.5036 * 10^{-5}$	0.2403	1090	2.6200
Bias	0.3308	0.0005	-253.3000	-0.0037	$0.0346 * 10^{-5}$	0.0026	-132.7373	-0.2209
PM 4	9.5420	0.0324	$1.2603 * 10^3$	0.0216	$2.5369 * 10^{-5}$	0.2428	956.7559	2.3982
TV	11	0.0257	1479	0.0246	$2.3964 * 10^{-5}$	0.2514	992	2.5327
Bias	-1.458	0.0067	-218.7000	-0.0030	$0.1405 * 10^{-5}$	-0.0086	-35.2441	-0.1345

Table 2: The posterior means (PM), true values (TV) and Bias of subject-specific individual parameters based on the simulated dataset.

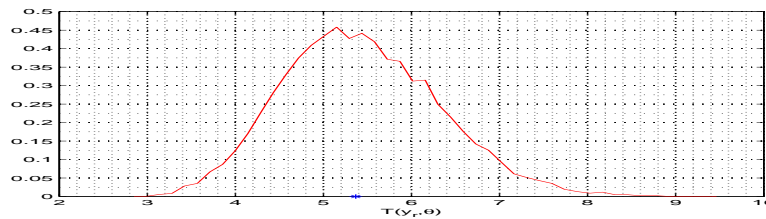


Figure 6: Posterior predictive distribution of the discrepancy measure, $T(y_i, \theta) = y_{max} - y_{min}$, with posterior predictive $p - value = 0.5403$. The \star represents the observed value $T(y_{i,obs}) = 5.3676$.

istic, using the numerical solution to the system (2)-(4), with the noise term added. This data may not be a true representation of real life data. One way to deal with this issue would be to generate data stochastically using the Gillespie algorithm. But, at the moment this is a computationally costly endeavor because the model solution is numerical. We believe that using real data the same process can be repeated. However, capturing all the pre-treatment real data at desired time intervals may be impossible in clinical trials. In these cases, methods that impute the unobserved processes (regularly spaced or otherwise) in between time points can be used, Durham and Gallant [6], and can substantially improve parameter estimation.

Indeed focusing not only on post-treatment data but also on pre-treatment data can help in addressing some important epidemiological questions such as, but not limited to, (i) when to start treatment, (ii) the best treatment to use. This would also be good way to increase the understanding of the pathogenesis of HIV infection and AIDS, because changes in HIV dynamic model parameters at any given time have important implications on the health of infected individuals.

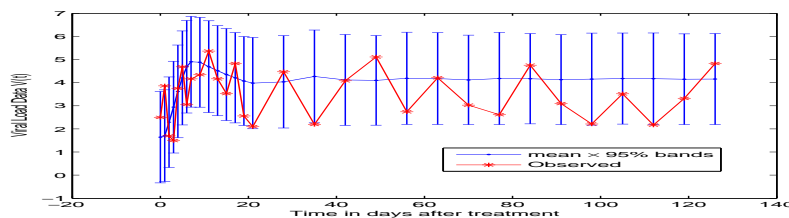


Figure 7: Observed viral load trajectory for patient 4 together with posterior predictive mean and 95% confidence bounds.

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