Published in final edited form as:

Biom J. 2010 August ; 52(4): 470–486. doi:10.1002/bimj.200900173.

Hierarchical Bayesian inference for HIV dynamic differential equation models incorporating multiple treatment factors

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Abstract

Studies of HIV dynamics in AIDS research are very important in understanding the pathogenesis of HIV-1 infection and also in assessing the effectiveness of antiretroviral (ARV) treatment. Viral dynamic models can be formulated through a system of nonlinear ordinary differential equations (ODE), but there has been only limited development of statistical methodologies for inference. This paper, motivated by an AIDS clinical study, discusses a hierarchical Bayesian nonlinear mixed-effects modeling approach to dynamic ODE models without a closed-form solution. In this model we fully integrate viral load, medication adherence, drug resistance, pharmacokinetics, baseline covariates and time-dependent drug efficacy into the data analysis for characterizing long-term virologic responses. Our method is implemented by a data set from an AIDS clinical study. The results suggest that modeling HIV dynamics and virologic responses with consideration of time-varying clinical factors as well as baseline characteristics may be important for HIV/AIDS studies in providing quantitative guidance to better understand the virologic responses to ARV treatment and to help evaluation of clinical trial design in response to existing therapies.

Keywords

Baseline characteristics; Bayesian nonlinear mixed-effects models; Long-term HIV dynamics; Longitudinal data; Time-varying drug efficacy; Treatment factors

1 Introduction

Studies of the HIV dynamics using biomathematical models have considerably improved the knowledge of the pathogenesis of HIV infection (Perelson *et al.*, 1996, 1997) and guided for the treatment of AIDS patients and evaluation of antiretroviral (ARV) therapies (Ding and Wu, 2001; Wu *et al.*, 2006). For instance, such studies have demonstrated the high turnover of infected cells and free virions (Perelson *et al.*, 1996, 1997). These pioneering works considered models based on a system of nonlinear ordinary differential equations (ODE), which were simplified and linearized. Nonlinear mixed-effects (NLME) models in conjunction with an ODE dynamic system have been popular in HIV dynamic studies (Ding and Wu, 1999, 2000, 2001; Han *et al.*, 2002; Wu *et al.*, 1998, 1999). However, as noted by Huang and Wu (2006), these ODE models are not able to describe the course of the infection

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for a long-term period. Although long-term treatment in HIV infected patients with highly active ARV therapies (HAART) results in a decrease of plasma HIV-1 RNA (viral load), the decay in viral load occurs in the first few weeks from beginning treatment (Perelson *et al.*, 1997). It may be sustained for a long period, but often is followed by resurgence of plasma viral load within months observed in clinical trial studies (Acosta *et al.*, 2004; Markowitz *et al.*, 2003; Notermans *et al.*, 1998). The resurgence of virus may be caused by multiple treatment factors such as drug resistance, poor patient adherence, pharmacokinetic (PK) variation during therapy and baseline characteristics (Bangsberg *et al.*, 2000). These general phenomena on viral load responses observed from real AIDS clinical trial studies are displayed in Figure 1 in Section 3 (indicated by circles) for the three representative patients; it motivates us to describe the effect of treatment associated with clinical factors and baseline characteristics (covariates) on viral load responses.

Following the study by Perelson *et al.* (1997), various HIV dynamic models with additional and/or alternative compartment formulations have been proposed (Ding and Wu, 2000; Guedj *et al.*, 2007; Huang *et al.*, 2003; Labbé and Vertoia, 2006; Nowak and May, 2000; Perelson and Nelson, 1999; Wu and Ding, 1999 and among others) to provide theoretical principles in guiding the development of treatment strategies for HIV-infected patients. However, some of these models are mostly developed to quantify short-term (< 60 days) dynamics without considering effects of both treatment factors and baseline covariates. In other words, these models do not include subject-specific treatment information, and thus do not help much to a better understanding of the mechanisms of the infection or an evaluation of treatment effect: this is why it is important to work with non-simplified models (i.e., based on nonlinear ODE systems) that are able to represent the complexity of the dynamics. Although some studies (Labbé and Vertoia, 2006; Verotta, 2005) explored long-term viral dynamic models incorporating clinical factors such as drug adherence to describe virologic responses with ARV therapies, they considered viral dynamic models incorporating only one factor without accounting for other potential confounding factors and covariates. Although Huang and Wu (2006) extended the work of these studies to investigate dynamic models with time-varying drug efficacy incorporating more than one clinical factor based on only a single drug agent, they did not consider effect of covariates in drug efficacy model. To the best of our knowledge, however, there have been only limited reports to investigate viral dynamic models in the integration of virologic, immunologic, drug exposures, drug resistance and baseline characteristics data into the analysis. There are needs to develop models including the confounding interactions of drug susceptibility, medication adherence, PK variation and baseline covariates on antiviral responses. Although the various statistical methods based on (stochastic) ODE models were investigated for making inference or assessing their agreement with observed data in the areas of engineering, econometrics and behavioral science (Elerian *et al.*, 2001; Singer 2002), there has been only limited development of statistical methodologies based on viral dynamic models formulated through a system of ODE. Thus, practical models and effective statistical modeling methods must address the following technical issues: (i) how to account for the confounding effects of both clinical treatment factors and baseline covariates on antiviral responses; (ii) how to investigate associated methodologies in conjunction with an ODE model with time-varying coefficient, but without a closed-form solution. Such extensive research efforts are warranted to study the intermediate to long-term drug effects on virologic responses in conjunction with a Bayesian nonlinear mixed-effects (BNLME) model.

The rest of this article is organized as follows. In Section 2, we introduce the HIV dynamic systems and propose a viral dynamic model with time-varying drug efficacy which incorporates the confounding interactions of drug resistance, medication adherence, PK variation and baseline covariates; we also briefly discuss a BNLME modeling approach implemented via Markov chain Monte Carlo (MCMC) procedures for statistical inference,

followed by introducing the deviance information criterion (DIC) for model comparison. In Section 3, we summarize the motivating data set from an AIDS clinical trial study which is applied to the proposed methodology and the results are presented. Finally, we conclude the paper with some discussions in Section 4.

2 Biological model and associated statistical approach

2.1 Mathematical models for HIV dynamics

HIV dynamic models can be formulated through a system of ODE which has been used to describe the interaction among target cells (T), infected cells (T^*) producing viruses, and circulating free virus (V). These three compartments (variables) are described as follows. Suppose, for simplicity, that the drug is 100% effective. The basic viral dynamic model falls into two unconnected parts, one describing the dynamics of uninfected cells and the other describing the decay of infected cell and free virus, as follows.

$$\begin{aligned}\frac{d}{dt}T &= \lambda - d_T T \\ \frac{d}{dt}T^* &= -\delta T^* \\ \frac{d}{dt}V &= N\delta T^* - cV\end{aligned}\quad (2.1)$$

where λ represents the rate at which new T cells are created from sources within the body, such as the thymus, d_T is the death rate of T cells, δ is the death rate of infected cells, N is the number of new virions produced from each of the infected cells during their life-time, and c is the clearance rate of free virions. Under the assumption of quasi-steady state before treatment, a closed-form solution to the above system of linear ODE can be obtained. The total free virions (V) can be written as $V(t) = \frac{V(0)}{c-\delta} \{ce^{-\delta t} - \delta e^{-ct}\}$ (Nowak and May, 2000). As indicated by Perelson *et al.* (1996), this model can only be used to very frequent HIV-1 RNA data during the first week of treatment.

However, the current drug therapies for HIV-infected patients are not perfect effective (Perelson *et al.*, 1997). HIV virions (V) will infect target cells (T) and turn them into infected cells (T^*) at a rate k . Due to the intervention of antiviral drugs, we assume that drugs reduce the infection rate in the infected cells (T^*) by $1 - \gamma_0$. Thus, the extended viral dynamic model with an imperfect constant drug treatment effect can be expressed in terms of the following system of ODE (Perelson and Nelson, 1999).

$$\begin{aligned}\frac{d}{dt}T &= \lambda - d_T T - [1 - \gamma_0]kTV \\ \frac{d}{dt}T^* &= [1 - \gamma_0]kTV - \delta T^* \\ \frac{d}{dt}V &= N\delta T^* - cV\end{aligned}\quad (2.2)$$

where the parameter γ_0 ($0 \leq \gamma_0 \leq 1$) denotes the constant antiviral drug efficacy. If the regimen is not 100% effective ($\gamma_0 < 1$), the system of ODE can not be solved analytically. The solution of (2.2) then has to be evaluated numerically. When $\gamma_0 = 0$ (the drug has no effect), the model (2.2) reduces to the model in the publications (Nowak *et al.*, 1997; Nowak and May, 2000; Stafford *et al.*, 2000); while $\gamma_0 = 1$ (the drug is 100% effective), the model (2.2) reverts to the model (2.1).

Since the model (2.2) assumes constant drug efficacy and does not consider the fact of variability in non-compliance (medication adherence), susceptibility (drug resistance) and PK variation (drug concentration) as well as baseline characteristics (covariate) in the presence of ARV therapy, this model is only used to quantify short-term dynamics (the early stage trajectories with viral load decline) and can not correctly describe the long-term

virologic responses with different shapes including viral rebound. In other words, the model is only used to fit the early segment data of the viral load trajectory. In this section we introduce a long-term HIV dynamic model incorporating drug resistance, medication adherence, drug concentration and baseline characteristics (covariates) as follows.

$$\begin{aligned}\frac{d}{dt}T &= \lambda - d_T T - [1 - \gamma(t)]kTV \\ \frac{d}{dt}T^* &= [1 - \gamma(t)]kTV - \delta T^* \\ \frac{d}{dt}V &= N\delta T^* - cV\end{aligned}\quad (2.3)$$

Although this model also includes the interaction of target uninfected cells, infected cells that actively produce viruses and free virus, it differs from the previous model (2.2) in that the model (2.3) includes a time-varying function $\gamma(t)$ (as defined below). $\gamma(t)$ quantifies the time-varying antiviral drug efficacy by fully integrating drug resistance, medication adherence, PK and baseline covariate data into the analysis. If we assume that the system of ODE (2.3) with time-varying coefficient, but without closed-form solutions is in a steady-state before initiating ARV treatment, then it is easy to show that the initial conditions for the system are $T_0 = \frac{c}{kN}$, $T_0^* = \frac{cV_0}{\delta N}$, $V_0 = \frac{\lambda N}{c} - \frac{d_T}{k}$.

It can be shown from the model (2.3) that there exists a drug efficacy threshold $e_c = 1 - cd_T/kN\lambda$ such that if $\gamma(t) > e_c$ for all t , virus will be eventually eradicated in theory. However, if $\gamma(t) < e_c$ (treatment is not potent enough) or if the potency falls below e_c before virus eradication (due to drug resistance, for example), viral load may rebound (see Huang *et al.* (2003) for a detailed discussion). We briefly discuss the drug efficacy model with two or more agents which includes the model described in Huang and Wu (2006) as a special case.

In clinical practice, genotypic or phenotypic tests can be performed to determine the sensitivity of HIV-1 to ARV agents before a treatment regimen is selected. Here we use the phenotypic marker, the median inhibitory concentration (IC_{50}) (Molla *et al.*, 1996) to quantify agent-specific drug susceptibility. Because experimental data tracking development of resistance suggest that the resistant fraction of the viral population grows exponentially, we propose a model of log-linear function to approximate the within-host changes over time in IC_{50} as follows.

$$IC_{50}(t) = \begin{cases} \log(S_0 + \frac{S_r - S_0}{t_r}t) & \text{for } 0 < t < t_r \\ \log(S_r) & \text{for } t \geq t_r \end{cases} \quad (2.4)$$

where S_0 and S_r are respective exponential values of IC_{50} at baseline and time point t_r at which the resistant mutations dominate. In our study, t_r is the observed time of virologic failure from clinical studies. Given that IC_{50} is only measured at baseline and at the time of treatment failure (Molla *et al.*, 1996), $IC_{50}(t)$ remains practical although more complex models for $IC_{50}(t)$ can be considered (Bonhoeffer *et al.*, 1997). For patients without a failure time IC_{50} , baseline IC_{50} was held constant overtime. In other words, if $S_r = S_0$, no new drug resistant mutation is developed during treatment.

Poor adherence to a treatment regimen is one of the major causes of treatment failure (Ickovics and Meisler, 1997). Patients may occasionally miss doses, may misunderstand prescription instructions or may miss multiple consecutive doses for various reasons. These deviations from prescribed dosing affect drug exposure in predictable ways. We use the following model to represent medication adherence,

$$A_d(t) = \begin{cases} 1 & \text{for } T_k < t \leq T_{k+1}, \text{ if all doses are taken in } [T_k, T_{k+1}] \\ R_d & \text{for } T_k < t \leq T_{k+1}, \text{ if } 100R_d\% \text{ doses are taken in } [T_k, T_{k+1}], \end{cases} \quad (2.5)$$

where $0 < R_d < 1$ ($d = 1, 2$), with R_d indicating the adherence rate for drug d (in our study, we focus on the two PI drugs to be discussed in Section 3). T_k denotes the adherence evaluation time at the k th clinical visit.

To model the relationship of multiple treatment factors with antiviral drug efficacy, we employ the following modified E_{max} model (Huang *et al.*, 2003; Sheiner, 1985) to represent the time-varying drug efficacy for two ARV agents within a class,

$$\gamma(t) = \frac{C_{min}^1 A_1(t)/IC_{50}^1(t) + C_{min}^2 A_2(t)/IC_{50}^2(t)}{\varphi + C_{min}^1 A_1(t)/IC_{50}^1(t) + C_{min}^2 A_2(t)/IC_{50}^2(t)} \quad (2.6)$$

where $\varphi = \exp(\beta_0 + \beta_1 w_1 + \beta_2 w_2)$; w_1 and w_2 are observed baseline viral load and CD4 cell counts, respectively; $\beta = (\beta_0, \beta_1, \beta_2)^T$ are unknown parameters to be estimated from clinical data; $A_d(t)$, C_{min}^d and $IC_{50}^d(t)$ ($d=1, 2$) are the adherence profile, the minimum drug concentration in plasma and the time-course of median inhibitory concentrations for the two agents, respectively. If $\beta_1 = \beta_2 = 0$ (without considering effect of covariates), $\varphi = \exp(\beta_0)$ can be used to quantify the conversion between in vitro and in vivo IC_{50} which is the case discussed by Huang *et al.* (2003, 2006). Note that C_{min} could be replaced by other PK parameters such as C_{max} and AUC (Wu *et al.*, 2006). $\gamma(t)$ ranges from 0 to 1. If $\gamma(t) = 1$, the drug is 100% effective, whereas if $\gamma(t) = 0$, the drug has no effect. Note that, if C_{min}^d , $A_d(t)$, $IC_{50}^d(t)$, w_1 and w_2 are measured or obtained from a clinical study and β can be estimated from clinical data, then the time-varying drug efficacy $\gamma(t)$ can be estimated for the whole period of ARV treatment.

2.2 Bayesian nonlinear mixed-effects modeling approach

A number of studies investigated various statistical methods, including Bayesian approach, to fit viral dynamic models and to predict virological responses (Han *et al.*, 2002; Huang and Wu 2006; Wu *et al.*, 1998; Wu and Ding, 1999). The Bayesian approach to viral dynamic modeling is particularly appealing from a biological perspective as it allows informative prior distributions to be incorporated. From statistical estimation point of view, a Bayesian approach is preferable because of the difficulties which are often encountered from a classical approach when models involve the large numbers of parameters, and complex nonlinearity of the subject-specific models. A BNLME model allows us to incorporate prior information at the population level into the estimates of dynamic parameters for individual patients. We briefly summarize the main concepts of BNLME modeling approach and the presentation is, of course, far from exhaustive (Davidian and Giltinan, 1995; Gelfand and Smith, 1990; Huang and Wu 2006; Wakefield, 1996).

Denote the number of patients by n and the number of measurements on the i th subject by m_i . For notational convenience, let $\theta_i = (\log c_i, \log \delta_i, \log \lambda_i, \log d_{Ti}, \log N_i, \log k_i, \log \varphi_i)^T$, $\mu = (\log c, \log \delta, \log \lambda, \log d_T, \log N, \log k, \beta_0, \beta_1, \beta_2)^T$, $\Theta = \{\theta_i, i = 1, \dots, n\}$, $\Theta_{\{i\}} = \{\theta_i, i = 1, \dots, n\}$ and $\mathbf{Y} = \{y_{ij}, i = 1, \dots, n; j = 1, \dots, m_i\}$. Let $f_{ij}(\theta_i, t_j) = \log_{10}(V_i(\theta_i, t_j))$, where $V_i(\theta_i, t_j)$ denotes the numerical solution of $V(t)$ in the system of ODE (2.3) with time-varying coefficient, but without closed-form solutions for the i th subject at time t_j . Let $y_{ij}(t)$ and $e_i(t_j)$ denote the repeated measurements of common logarithmic viral load and a measurement error with mean zero, respectively. Note that log-transformation of dynamic parameters and

viral load is used to make sure that estimates of dynamic parameters are positive, and to stabilize the variation of measurement errors and to speed up estimation algorithm, respectively. The BNLME model can be written in the following three stages (Gelfand and Smith, 1990; Davidian and Giltinan, 1995; Huang and Wu, 2006; Wakefield, 1996).

Stage 1 Within-individual variation:

$$\mathbf{y}_i = \mathbf{f}_i(\theta_i) + \mathbf{e}_i, \quad [\mathbf{e}_i | \sigma^2, \theta_i] \sim \mathcal{N}(\mathbf{0}, \sigma^2 \mathbf{I}_{m_i}) \quad (2.7)$$

where $\mathbf{y}_i = (y_{i1}(t_1), \dots, y_{im_i}(t_{m_i}))^T$, $\mathbf{f}_i(\theta_i) = (f_{i1}(\theta_i, t_1), \dots, f_{im_i}(\theta_i, t_{m_i}))^T$, $\mathbf{e}_i = (e_i(t_1), \dots, e_i(t_{m_i}))^T$ and the bracket notation $[A|B]$ denotes the conditional distribution of A given B .

Stage 2 Between-individual variation:

$$\theta_i = \mathbf{W}_i \boldsymbol{\mu} + \mathbf{b}_i, \quad [\mathbf{b}_i] \sim \mathcal{N}(\mathbf{0}, \boldsymbol{\Sigma}) \quad (2.8)$$

where $\boldsymbol{\mu} = (\log c, \log \delta, \log \lambda, \log d_T, \log N, \log k, \beta_0, \beta_1, \beta_2)^T$ is a vector of population parameters and $\mathbf{b}_i = (b_{i1}, \dots, b_{i7})^T$ are random effects with mean zero. It is noteworthy that for $\boldsymbol{\beta} = (\beta_0, \beta_1, \beta_2)^T$, no log-transformation is required as they are unnecessarily positive. $\mathbf{W}_i = (\mathbf{I}_7, \mathbf{J}_{1i}, \mathbf{J}_{2i})$, where $\mathbf{I}_7$ is an identity matrix and $\mathbf{J}_{si} = (0, 0, 0, 0, 0, 0, w_{si})^T$ ($s = 1, 2; i = 1, 2, \dots, n$) are 7×1 vector, with w_{1i} and w_{2i} being (standardized) individual baseline viral load (in $\log_{10}$ scale) and CD4 count, respectively. For $\boldsymbol{\beta} = (\beta_0, \beta_1, \beta_2)^T$, we are only interested in estimating them at population level. Thus, the individual parameter ϕ_i related to them is expressed as $\log \phi_i = \beta_0 + \beta_1 w_{1i} + \beta_2 w_{2i} + b_{i7}$ ($i = 1, 2, \dots, n$).

Stage 3 Hyperprior distributions:

$$\sigma^{-2} \sim Ga(a, b), \quad \boldsymbol{\mu} \sim \mathcal{N}(\boldsymbol{\eta}, \boldsymbol{\Lambda}), \quad \boldsymbol{\Sigma}^{-1} \sim Wi(\boldsymbol{\Omega}, \nu) \quad (2.9)$$

where the mutually independent Gamma (Ga), Normal ($\mathcal{N}$) and Wishart (Wi) prior distributions are chosen to facilitate computations (Davidian and Giltinan, 1995). The hyper-parameters $a, b, \boldsymbol{\eta}, \boldsymbol{\Lambda}, \boldsymbol{\Omega}$ and ν were determined from previous studies and literature (Han *et al.*, 2002; Perelson, *et al.*, 1996, 1997; Perelson and Nelson, 1999; Nowak and May, 2000; Wu *et al.*, 1998).

Following the studies by Gelfand and Smith (1990) and Davidian and Giltinan (1995), it is shown from (2.7)–(2.9) that the full conditional distributions for the parameters σ^{-2} , $\boldsymbol{\mu}$ and $\boldsymbol{\Sigma}^{-1}$ may be written explicitly as

$$[\sigma^{-2} | \boldsymbol{\mu}, \boldsymbol{\Sigma}^{-1}, \boldsymbol{\Theta}, \mathbf{Y}] \sim Ga\left(a + \frac{1}{2} \sum_{i=1}^n m_i, \mathbf{A}^{-1}\right) \quad (2.10)$$

$$[\boldsymbol{\mu} | \sigma^{-2}, \boldsymbol{\Sigma}^{-1}, \boldsymbol{\Theta}, \mathbf{Y}] \sim \mathcal{N}(\mathbf{B}^{-1} \mathbf{C}, \mathbf{B}^{-1}) \quad (2.11)$$

$$[\boldsymbol{\Sigma}^{-1} | \sigma^{-2}, \boldsymbol{\mu}, \boldsymbol{\Theta}, \mathbf{Y}] \sim Wi(\mathbf{D}^{-1}, n + \nu) \quad (2.12)$$

where

$A = b^{-1} + \frac{1}{2} \sum_{i=1}^n \sum_{j=1}^{m_i} [y_{ij} - f_{ij}(\theta_i, t_j)]^2$, $B = \sum_{i=1}^n \mathbf{W}_i^T \sum^{-1} \mathbf{W}_i + \Lambda^{-1}$, $C = \sum_{i=1}^n \mathbf{W}_i^T \sum^{-1} \theta_i + \Lambda^{-1} \eta$, and $D = \Omega^{-1} + \sum_{i=1}^n (\theta_i - \mathbf{W}_i \mu)(\theta_i - \mathbf{W}_i \mu)^T$. The full conditional distribution of each θ_i given the remaining parameters and the data, can not be written explicitly, but it can be seen that the density function of the conditional distribution of $[\theta_i | \sigma^{-2}, \mu, \Sigma^{-1}, \Theta_{\setminus i}, \mathbf{Y}]$ is proportional to

$$\exp \left\{ -\frac{\sigma^{-2}}{2} \sum_{j=1}^{m_i} [y_{ij} - f_{ij}(\theta_i, t_j)]^2 - \frac{1}{2} (\theta_i - \mathbf{W}_i \mu)^T \sum^{-1} (\theta_i - \mathbf{W}_i \mu) \right\} \quad (2.13)$$

The Bayesian approach incorporates the information through prior distribution into observed data to obtain its posterior distribution. While computation of the posterior distribution involves solving multidimensional integrals, the introduction of MCMC procedures such as the Gibbs sampler and Metropolis-Hastings algorithm opened the way to analysis of complex models through decomposition and sampling from full conditional distributions; see Gamerman (1997) for general theory and implementation details. The MCMC scheme for drawing samples from the posterior distributions of all parameters in the above three stage model is obtained by iterating between the following two steps: (i) sampling from one of the conditional distributions (2.10)–(2.12); (ii) sampling from the expression (2.13). To implement an MCMC algorithm, here Gibbs sampler is used to update σ^{-2} , μ and Σ^{-1} , while we update θ_i ($i = 1, 2, \dots, n$) using the Metropolis-Hastings (M-H) algorithm. After collecting the final MCMC samples, we are able to draw statistical inference for the unknown parameters. In particular, we are interested in the posterior means and quantiles. Some more specific discussion of the BNLME modeling approach, including the choice of the hyper-parameters, the iterative MCMC algorithm and the implementation of the MCMC procedures can be found in publications by Huang and Wu (2006) and Wakefield (1996).

The progress in Bayesian posterior computation due to MCMC procedures has made it possible to fit increasingly complex statistical models (Huang and Wu, 2006; Wakefield, 1996). Thus, it has become more and more important to develop efficient model selection criteria. A recent publication by Spiegelhalter *et al.* (2002) suggested a generalization of the Akaike information criterion (AIC) and also related to the Bayesian information criterion (BIC) that is deviance information criterion (DIC). Similar to AIC and BIC, DIC trades off a measure of model adequacy against a measure of complexity, and is easy to calculate and applicable to a wide range of statistical models. It is based on the posterior distribution of the log-likelihood or the deviance in the Bayesian framework. In this paper, we demonstrate its usefulness to compare BNLME models for longitudinal HIV dynamics discussed previously. For completeness, a brief summary of DIC follows. More detailed discussion of DIC and its properties can be found in publications by Spiegelhalter *et al.* (2002) and Zhu and Carlin (2000).

Assume that the distribution of the data, $\mathbf{Y}$, depends on the parameter vector Ψ . Spiegelhalter *et al.* (2002) suggested examining the posterior distribution of the deviance statistics defined by $D(\Psi) = -2 \log p(\mathbf{Y} | \Psi) + 2 \log g(\mathbf{Y})$ for Bayesian model comparison, where $p(\mathbf{Y} | \Psi)$ is the likelihood function and $g(\mathbf{Y})$ denotes a fully specified standardizing term that is a function of the data alone (which thus has no impact on model selection). Based on the posterior distribution of $D(\Psi)$, DIC consists of two components as follows.

$$DIC = \bar{D} + p_D = 2\bar{D} - D(\bar{\Psi}) \quad (2.14)$$

where $\bar{D} = E_{\Psi|Y}[D(\Psi)] = E_{\Psi|Y}[-2 \log p(Y|\Psi)]$ is the posterior expectation of the deviance and $p_D = \bar{D} - D(\bar{\Psi})$ is the effective number of parameters, defined as the difference between the posterior mean of the deviance and the deviance evaluated at the posterior mean $\bar{\Psi}$ of the parameters.

As with other model selection criteria, we caution that DIC is not intended for identification of the ‘correct’ model, but rather merely as a method of comparing a collection of alternative formulations. In our model with different baseline characteristics, DIC can be used to find out the most significant covariate in contribution to virologic responses whereby we may put more attention on the covariate for patient treatment. Under the model (2.7), in the absence of any standardizing function $g(Y)$, the deviance is

$$D(\sigma^{-2}, \Theta) = -2 \log p(Y|\sigma^{-2}, \Theta) = \sum_{i=1}^n \sigma^{-2} (\mathbf{y}_i - \mathbf{f}_i(\theta_i))^T (\mathbf{y}_i - \mathbf{f}_i(\theta_i)) - \log \sigma^{-2} \sum_{i=1}^n m_i \quad (2.15)$$

As discussed above, our MCMC approach to estimating DIC first draws $\{(\sigma^{-2}, \Theta)^{(k)}\}_{k=1}^g$ values from the posterior distribution, and then calculates corresponding $\{D^{(k)}\}_{k=1}^g$ values from (2.15), where g is the number of samples of posterior distribution. Finally, we estimate

DIC as $2\bar{D} - D(\bar{\sigma}^{-2}, \bar{\Theta})$, where $\bar{D} = \frac{1}{g} \sum_{k=1}^g D^{(k)}$, $\bar{\sigma}^{-2} = \frac{1}{g} \sum_{k=1}^g (\sigma^{-2})^{(k)}$, $\bar{\theta}_i = \frac{1}{g} \sum_{k=1}^g \theta_i^{(k)}$ and $\bar{\Theta} = \{\bar{\theta}_i, i = 1, \dots, n\}$.

3 Analysis of AIDS clinical data

3.1 Motivating application and observed data

AIDS Clinical Trials Group (ACTG) Protocol A5055 was a Phase I/II, randomized, open-label, 24-week comparative study of two regimens of indinavir (IDV) and zidovudine (ZDV), plus two nucleoside analogue reverse transcriptase inhibitors (NRTIs) on HIV-1-infected patients who failed protease inhibitor (PI)-containing ARV therapies (Acosta *et al.*, 2004). 44 patients were randomized to one of two IDV/ZDV regimens: IDV 800 mg twice daily (q12h) + ZDV 200 mg q12h (Arm A) and IDV 400 mg q12h + ZDV 400 mg q12h (Arm B). Out of the 44 patients, 42 patients are included in the analysis; for the remaining two patients, one was excluded from the analysis since the PK parameters were not obtained and the other was excluded since PhenoSense HIV could not be completed on this subject due to an atypical genetic sequence that causes the viral genome to be cut by an enzyme used in the assay. Patients were scheduled for follow-up visits at study day 0; at weeks 1, 2, and 4; and every 4 weeks thereafter through week 24. Since the main purpose of this study was to compare the PKs, safety and tolerability of IDV/ZDV at two arms, the data were only collected for IDV/ZDV drugs. More detailed descriptions of this study and data are given in publication by Acosta *et al.* (2004).

As indicated previously, the primary objective of this paper is to investigate the effect of confounding interaction of clinical factors with baseline covariates to prescribe ARV therapy on virologic responses. Along with this line, we have constructed a novel HIV dynamic model (2.3) with consideration of medication adherence (assessed by use of questionnaires), drug resistance (IC_{50}) and PK variation (evaluated by C_{min} which is the trough level of drug concentration in plasma) as well as covariates (baseline viral load and CD4 count) to the long-term changes in HIV-1 RNA observations. A summary of measurements of data from A5055 study to be used in our analysis is briefly described below.

RNA viral load—RNA viral load was measured in copies/mL at study days 0, 7, 14, 28, 56, 84, 112, 140 and 168 of follow-up. In this study, the HIV-1 RNA detectable limit is 50 copies/mL. The HIV-1 RNA measures below this limit are not considered reliable, therefore we simply imputed such values as 25 copies/mL (Acosta *et al.*, 2004; Davidian and Giltinan, 1995). The exact day of viral load measurement (not predefined study day) was used to compute study day in our analysis. The graph in Figure 1 shows the observed viral load measurements (in $\log_{10}$ scale) indicated by circles for the three representative patients.

Medication adherence—Medication adherence was measured by the use of questionnaires. It was completed by the study participant and/or by a face-to-face interview with study personnel. As an example, the adherence rates over time based on questionnaire data for IDV (dotted stairsteps) and RTV (dashed stairsteps) drugs are presented in Figure 1 for the three representative patients.

Phenotypic drug susceptibility—Phenotypic drug susceptibilities were retrospectively determined from baseline samples. Phenotypic determination of ARV drug resistance was performed at baseline and the time of virological failure. Some patients had virologic failure and phenotypic susceptibility testing done on samples at the time of failure. For analysis, we used the phenotype marker, IC_{50} (Molla *et al.*, 1996) to quantify agent-specific drug susceptibility. We refer to this marker as the median inhibitory concentration. The baseline ($\circ$) and failure time ($\times$) IC_{50} from 42 individuals for IDV/RTV drugs are displayed in Figure 2 (upper panel) which were used to construct $IC_{50}(t)$. Note that for patients without a failure time IC_{50} , baseline IC_{50} was held by a constant overtime.

Pharmacokinetic variation—An intensive PK evaluation was performed on day 14. Plasma for intensive PK analysis was obtained at pre-dose, and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours following an observed IDV/RTV dose. PK parameters of IDV and RTV were determined using noncompartmental methods. Calculated PK parameters included maximum (C_{max}), minimum (C_{min}) drug concentration, drug concentration measured after 12 hours from dose taken (C_{12h}) and area under the curve (AUC). Wu *et al.* (2006) compared the four PK parameters as predictors of virological responses and no significant differences were found. Thus, C_{min} displayed in Figure 2 (middle panel) was used in our analysis because it is easily obtained in clinical studies.

Baseline characteristics—The baseline viral load in $\log_{10}$ scale (VL) and CD4 count were chosen as covariates for data analysis. The baseline characteristics of 42 individuals is displayed in Figure 2 (lower panel). To avoid very small (large) estimates which may be unstable, we standardized these covariate values. For baseline $\log_{10}(\text{RNA})$, for instance, each $\log_{10}(\text{RNA})$ value is subtracted by mean (3.78) and divided by standard deviation (0.65).

3.2 Model fitting and parameter estimation results

In this section we apply the BNLME modeling approach to fit data described above. As discussed in Section 2, the prior distribution for μ was assumed to be $\mathcal{N}(\eta, \Lambda)$ with Λ being a diagonal matrix. The details of the prior construction for unknown parameters are discussed in Huang and Wu (2006). Thus, the values of the hyper-parameters are chosen as follows (Han *et al.*, 2002; Perelson *et al.*, 1996, 1997; Perelson and Nelson, 1999; Nowak and May, 2000; Wu *et al.*, 1998).

$$a = 4.5, b = 9.0, v = 10.0, \eta = (1.1, -1.0, 4.6, -2.3, 6.9, -9.0, 1.0, 0.5, 0.5)^T, \Lambda = \text{diag}(0.005, 0.005, 0.005, 0.005, 0.005, 1000.0, 1000.0, 1000.0), \Omega = \text{diag}(1.25, 2, 2, 2, 2, 2, 2).$$

One long chain was run which may be more efficient with the following considerations: (i) a number of initial “burn-in” simulations are discarded, since from an arbitrary starting point it would be unlikely that the initial simulations came from the stationary distribution targeted by the Markov chain; (ii) one may only save every k th (k being an integer) simulation samples to reduce the dependence among samples used for parameter estimation. We are going to adopt these strategies in our MCMC implementation using FORTRAN code that calls an ODE subroutine solver (DIVPRK) in IMSL library (1994), which uses the Runge-Kutta-Verner fifth-order method. The computer codes are available from the corresponding author upon request. An informal check of convergence is conducted based on graphical techniques according to the suggestion of Gelfand and Smith (1990). Based on the results, we propose that, after an initial number of 20,000 burn-in iterations, every 4th MCMC sample was retained from the next 80,000 samples. Thus, we obtained 20,000 samples of targeted posterior distributions of the unknown parameters. Along with this sampling procedure, we also check the k -lag serial correlation of the samples for each parameter to diagnose independence of MCMC samples. We graphically checked the last 500 samples drawn from MCMC sampling scheme for each parameter (plot not shown here) and found that the consecutive samples move randomly towards different directions, which indicates that MCMC is not “sticky” and MCMC samples are independent for each parameter, suggesting the convergence to the stationary distribution.

In order to assess how the three clinical factors interact with baseline covariates to contribute to virologic response, the BNLME modeling approach is used to fit the proposed models incorporating baseline covariates into $\chi(t)$ with the following four scenarios (i) Control model: $\varphi = \exp(\beta_0)$ in which no covariate is incorporated; (ii) VL model: $\varphi = \exp(\beta_0 + \beta_1 w_1)$ where baseline viral load is only included; (iii) CD4 model: $\varphi = \exp(\beta_0 + \beta_2 w_2)$ where baseline CD4 count is only included and (iv) Full model: $\varphi = \exp(\beta_0 + \beta_1 w_1 + \beta_2 w_2)$ where both baseline viral load and CD4 count are included.

From the model fitting results displayed in Figure 1 for three individual fitted (solid) curves using the full model, we have seen that, in general, all models provided a reasonably good fit to the observed data for most patients in our study, although the fitting for a few patients (<15%) was not completely satisfactory due to unusual viral load fluctuation patterns for these patients. To assess the goodness-of-fit for the proposed models, the diagnosis plots (the standardized residuals versus the fitted values) for each of the four models are provided in Figure 3. These plots indicate that no systematic patterns are found in the residual plots and the models fit the observed data reasonably well.

The population posterior means (PM) and corresponding 95% equal-tail credible intervals (CI) for nine parameters are presented in Table 1. The PM and CI for the six dynamic parameters (c , δ , λ , d_T , N , k) are quantitatively similar for the four models. As an example, we report results based on the full model. It is shown from Table 1 that the population estimates $c = 2.98$ (virus clearance rate) and $\delta = 0.38$ (death rate of infected cells) which are the most important parameters in understanding viral dynamics and the pathogenesis of HIV infection. In comparison with previous studies, Table 2 provides a summary of the estimated population parameters c and δ , and/or the corresponding CI along with those from previous studies and literature. It is seen that our estimated results are different from (i.e., less than most of those) those reported in the previous studies. These differences may be due to the following possible reasons as well as others which need to be explored further. The analysis in most of those studies assumed that viral replication was completely stopped by the treatment which leads to larger estimates of c and δ . This may be true for short term during the beginning of treatment. However, for long term treatment, viral load will resurgent due to drug resistance, pharmacokinetics, non-perfect adherence as well as baseline characteristics. Our model not only considers those clinical treatment factors by introducing

time-varying drug efficacy but also includes baseline characteristics which we believe affect drug efficacy. In addition, the first-phase decay rate, estimated from a biexponential viral dynamic model (Perelson *et al.*, 1996; Wu and Ding, 1999) under the assumption of a perfect treatment, is not the exact death rate of infected cells (δ) since the current ARV therapy can not completely block viral replication (Ding and Wu, 1999; Perelson *et al.*, 1996, 1997; Nowak and May, 2000). In this study, we estimated the death rate of infected cells directly by accounting for the time-varying drug efficacy (non-perfect treatment). Note that, as pointed out by one of the referees, the death rate estimate of infected cells may be low in this study due to the failure to model the long-lived cells separately. Also note that we are unable to validate our results of the other estimated parameters as no conclusive or comparable estimates have been published to date.

3.3 Treatment effect of baseline characteristics interacted with clinical factors

We applied the models based on the four scenarios to fit the viral load data, separately. As shown in Table 1, the baseline viral load ($\beta_1 = -0.131$) has positive effect on drug efficacy $\gamma(t)$ according to the model (2.6), while the baseline CD4 count ($\beta_2 = 0.142$) has negative effect on $\gamma(t)$. These findings are very interesting and clinically important. The higher baseline viral load requires more potent drug efficacy to suppress virus rebound. On the contrary, the higher baseline CD4 count would need a less potent drug efficacy to suppress the virus. The result from the full model indicates that the baseline viral load ($\beta_1 = -0.870$) and the baseline CD4 count ($\beta_2 = 0.819$) have opposite effect on drug efficacy $\gamma(t)$. This may lead to increase or decrease the effect on drug efficacy, compared with that based on the model incorporating only one baseline covariate. This result might be intuitively understandable due to a significantly negative correlation (with the correlation coefficient $r = -0.506$ and p -value $p = 0.001$) between baseline viral load and CD4 count. Here, we set up a connection between patient-specific baseline characteristics with interaction of multiple treatment factors and drug efficacy. Our results may be explained by the fact that for those patients with higher baseline viral load, the drug efficacy needs to be higher than that for those with lower baseline viral load. Therefore, a strong treatment is recommended for those patients with higher baseline viral load. On the other hand, patients with higher CD4 count may need a lower drug efficacy so that a strong treatment strategy is not necessary to avoid side-effect. The results may suggest the benefit of initiating ARV therapy with a lower baseline viral load and/or a higher baseline CD4 count.

3.4 Comparison of models with baseline characteristics

Table 3 presents estimated DIC values based on the four models. The CD4 model has the smallest DIC value (256.92), followed by the full model (302.01), VL model (316.26) and control model (429.37), respectively. As mentioned before, it is hard to tell which model is 'correct' but which one fits data better. Furthermore, the model which fits data better may be more accurate to describe mechanism of HIV infection, thus needs more attention for patient treatment. The CD4 model results in best fitting compared with the other two models as well as the control model (which performs worst) in terms of DIC criterion. This indicates that the model with considering baseline covariate provides more accurate prediction of virologic responses than that without covariate does. It is interestingly noticed that the estimated DIC based on the full model is smaller than that from the VL model, but greater than that from the CD4 model. This result may be explained as a compromise between those two covariates which displays a significantly negative correlation. In summary, these results may suggest that baseline CD4 count is more important than baseline viral load, when choosing a treatment strategy for HIV infected patients. This result is consistent with previous observations (Huang *et al.*, 2003, Notermans *et al.*, 1998, Wu *et al.*, 2004) that baseline CD4 count is more predictive of treatment outcomes (virologic responses) than baseline viral load.

4 Concluding discussion

In this paper, we demonstrate the use of the tractable model which can be used to characterize long-term HIV dynamics during therapy. The model is based on a well-known physiologically based HIV dynamic model, but can include treatment influences on HIV dynamics. This paper is, to the best of our knowledge, the first to consider a mechanism-based nonlinear time-varying ODE model for characterizing long-term dynamics that simultaneously describes both suppression and resurgence of virus, and establishes the relationship of virological response with drug susceptibility, medication adherence, PK variation and baseline covariates which quantifies the confounding effect of these clinically interested factors on virological response, (iii) directly incorporates observed data of multiple treatment factors into a function of drug efficacy and (iv) uses a BNLME modeling approach that can not only combine prior information with all possible clinical data for estimating dynamic parameters, but also characterize inter-patient variability. The Bayesian approach was developed and tailored as required by the unique features of the proposed HIV dynamic models. Although the basic principles of BNLME modeling approach were well established, their applications to our model, in conjunction with a system of nonlinear ODE with time-varying coefficient but without a closed-form solution, are nonetheless innovative. Thus, the results of estimated dynamic parameters based on this model should be more reliable and reasonable to interpret long-term HIV dynamics.

The following main findings are obtained from this study. (i) The interested dynamic parameters such as death rates of infected cells and free virions have been estimated with differences from the published studies, and possible reasons of those differences were discussed in Section 3.2. (ii) We investigated the relationships between drug efficacy and baseline covariates and some biologically meaningful and interesting associations were found (See Section 3.3). Thus we may be able to use the baseline characteristics to determine whether a treatment regimen is potent enough for a particular patient as drug efficacy can be an indicator of treatment potency. These relationships may be important for HIV/AIDS studies in providing quantitative guidance to better understand the virologic responses to ARV treatment. (iii) It was suggested from this study that the baseline CD4 count is more important clinically than the baseline viral load which might help clinicians evaluate AIDS progression.

As discussed in Wu *et al.*(2006), the analysis presented here used a model which appeared to perform well in capturing the observed patterns of viral load trajectories, and characterizing the biological mechanisms of HIV infection under relatively complex clinical situations. However, it is appropriate to mention at this point that some issues exist for the proposed models. First, our model is a simplified model and there are many possible variations (Perelson and Nelson, 1999; Nowak and May, 2000; Callaway and Perelson, 2002). As one referee pointed out, we did not separately consider the compartments of short-lived productively infected cells and long-lived and latently infected cells (Ding and Wu, 1999, 2000; Perelson *et al.*, 1997). Instead we pooled infected cell populations together because of the following possible reasons. (i) The proposed viral dynamic model in this paper is constructed fully based on data availability in A5055 study; (ii) only total CD4 cell counts were collected in this study; (iii) the more compartments are considered in the dynamic system, the more parameters are involved in viral dynamic models which need more data in order to overcome parameter identifiability problem. However, it is noticed that Ding and Wu (1999) investigated a viral dynamic model with considering short-lived (productively) infected cells and long-lived (latently) infected cells, separately, and showed theoretically that the death rate of long-lived infected cells is smaller than that of short-lived infected cells. This finding is also confirmed based on the study of an AIDS trial data by Ding and Wu (2000). Second, the virus compartment was not further decomposed into infectious

virions and non-infectious virions as in Perelson *et al.* (1996). Thus, different mechanisms of NRTI and PI drug effects were not modeled. In fact, we only considered PI drug effects in the drug efficacy model (2.6) since the information of NRTI drugs was not collected in A5055 study and the effect of NRTI drugs was considered less important compared to the PI drugs (Acosta *et al.*, 2004; Ding and Wu, 2001). Third, as questionnaire measurements of adherence may not reflect actual adherence profiles for individual patients, the data quality would affect our results of estimated parameters. More accurate measurements for adherence such as electronic monitoring devices may improve data quality. In addition, this paper combined new technologies in mathematical modeling and statistical inference to quantify complex HIV disease mechanisms. The complex nature of HIV/AIDS ARV therapy will naturally pose some challenges including missing data and measurement errors in clinical factors and covariates. These complicated problems, which are beyond the scope of this article, may be addressed using two-step methods (Higgins *et al.*, 1997) and the joint model method (Wu, 2002). We are actively investigating these issues. Nevertheless, these limitations would not offset the major findings from our modeling approach, although further improvement may be warranted. In summary, although this paper concentrated on HIV dynamics, the basic concept of longitudinal dynamic systems and the proposed methodologies in this paper are generally applicable to dynamic systems in other fields such as biology, medicine, engineering, or PK/PD studies as long as they meet the relevant technical specification (i.e., specified by a system of ODE).

Acknowledgments

The authors are extremely grateful to an Associate Editor, two referees and the Editor for their insightful comments and suggestions that led to a marked improvement of the article. We gratefully acknowledge A5055 study investigators for allowing us to use the clinical data from their study. This research was partially supported by NIAID/NIH grant AI080338 and MSP/NSA grant H98230-09-1-0053 to Y. Huang.

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Fig. 1.

The observed viral load measurements in $\log_{10}$ scale indicated by circles with the individual fitted curves (solid line) obtained by using the full model (see Section 3.2) and adherence rates (dotted and dashed stairs) over time based on questionnaire data for IDV and RTV drugs for the three representative patients.

Fig. 2.

The baseline ($\circ$) and failure time ($\times$) IC_{50} for IDV/RTV drugs (upper panel), the minimum (C_{min}) drug concentration for two drugs (middle panel) and the baseline viral load in $\log_{10}$ scale and CD4 count (lower panel) for the 42 individual patients from A5055 study. SD and CV denote the standard deviation and coefficient of variation, respectively.

Fig. 3. Scatter plots of standardized residuals versus the fitted values of log₁₀ (RNA)

Table 1

A summary of the estimated posterior means (PM) of population parameters and the corresponding 95% equal-tail credible intervals (CI) from the models incorporating one of four scenarios, respectively.

Covariate Parameter	Control model	VL model	CD4 model	Full model
	PM (CI)	PM (CI)	PM (CI)	PM (CI)
c	3.05 (2.78, 3.37)	3.09 (2.57, 4.33)	3.01 (2.15, 3.51)	2.98 (1.49, 4.01)
δ	0.36 (0.33, 0.40)	0.35 (0.29, 0.41)	0.37 (0.32, 0.57)	0.38 (0.32, 0.60)
λ	97.7 (88.8, 107.6)	92.0 (89.8, 107.9)	91.6 (89.2, 107.8)	92.3 (85.9, 111.0)
d_T	0.10 (0.09, 0.11)	0.10 (0.04, 0.11)	0.11 (0.09, 0.27)	0.11 (0.09, 0.40)
N	971.9 (181.4, 1071.4)	837.6 (103.0, 1063.5)	876.7 (191.3, 1066.2)	855.5 (154.3, 1071.5)
k	0.0001 (0.0001, 0.0012)	0.0001 (0.0001, 0.0007)	0.0001 (0.0001, 0.0002)	0.0001 (0.0001, 0.0007)
β_0	-0.46 (-1.96, 1.05)	-1.96 (-4.87, 0.78)	-1.87 (-6.68, 2.88)	-2.62 (-10.92, 4.41)
β_1	NA NA	-0.13 (-0.80, 0.37)	NA NA	-0.87 (-3.26, 0.69)
β_2	NA NA	NA NA	0.14 (0.05, 0.50)	0.82 (0.37, 1.66)

Estimates of variance components (model with each of 4 scenarios) are

$$\widehat{\sigma}_{Control}^{-2}=4.29, \widehat{\sigma}_{VL}^{-2}=4.22, \widehat{\sigma}_{CD4}^{-2}=4.06, \widehat{\sigma}_{Full}^{-2}=4.25.$$

Table 2

A summary of the estimated population parameters c and d , and/or the corresponding 95% equal-tail credible intervals (CI), compared with those from literature.

	c (CI)	d (CI)
This paper	2.98 (1.49, 4.01)	0.38 (0.32, 0.60)
Perelson <i>et al.</i> (1996)	<3.07	<0.49
Perelson and Nelson (1999)	<3.10	<0.50
Putter <i>et al.</i> (2002)	<12.01 (7.46, 19.30)	>0.18 (0.05, 0.41)
Huang and Wu (2006)	<3.09 (2.80, 3.40)	>0.37 (0.35, 0.41)
Labbé and Verotta (2006)	>2.12 (1.84, 2.40)	–
Han <i>et al.</i> (2002)	>2.83 (1.73, 4.51)	<0.39 (0.32, 0.46)
Stafford <i>et al.</i> (2000)	3 (constant)	<0.39
Klenerman <i>et al.</i> (1996)	–	>0.37
Notermans <i>et al.</i> ,(1998)	3 (constant)	<0.54
Perelson <i>et al.</i> (1997)	3 (constant)	<1.00
Markowitz <i>et al.</i> (2003)	23 (constant)	<0.70
Guedj <i>et al.</i> (2007)	30 (constant)	<0.67

Table 3

The DIC, posterior mean of the deviance and effective number of parameters for the four models based on BNLME modeling approach.

Model	Control	VL	CD4	Full
DIC	429.37	316.26	256.92	302.01
$\bar{D}$	254.98	180.84	105.30	193.27
p_D	174.39	135.42	151.62	108.74