Use of dynamical models for treatment optimization in HIV infected patients : a sequential Bayesian analysis approach.

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Use of dynamical models for treatment optimization in HIV infected patients : a sequential Bayesian analysis approach.

Title: Utilisation de modèles dynamiques pour l'optimisation des traitements des patients infectés par le VIH: une approche par analyse bayésienne séquentielle.

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Abstract: The use of dynamic mechanistic models based on ordinary differential equations (ODE) has greatly improved the knowledge of the dynamics of HIV and of the immune system. Their flexibility for fitting data and prediction abilities make them a good tool for optimization of the design delivery and efficacy of new intervention in the HIV field. We present the problem of inference in ODE models with mixed effects on parameters. We introduce a Bayesian estimation procedure based on the maximization of the penalized likelihood and a normal approximation of posteriors, which is implemented in the NIMROD software. We investigate the impact of pooling different data by using a sequential Bayesian analysis (SBA), which uses posteriors of a previous study as new priors. We show that the normal approximation of the posteriors, which constrains the shape of new priors, leads to gains in accuracy of estimation while reducing computation times. The illustration is from two clinical trials of combination of antiretroviral therapies (cART): ALBI ANRS 070 and PUZZLE ANRS 104. This paper reproduces some unpublished work from my PhD thesis. It is an extension of my oral presentation on the same topic at the 47th Journées de Statistique organized by the French Statistical Society (SFdS) in Lille, France, May 2015, when being awarded the Marie-Jeanne Laurent-Duhamel prize.

Résumé : L'utilisation des modèles mécanistes dynamiques basés sur des équations différentielles ordinaires (ODE) a considérablement amélioré les connaissances de la dynamique HIV-système immunitaire. Leur flexibilité à ajuster des données et leur capacité de prédictions en font un bon outil pour l'optimisation du plan d'expérience et de l'analyse d'efficacité d'interventions nouvelle dans le domaine du VIH. Nous traitons des méthodes d'estimation pour les ODEs dont les paramètres sont représentés par des modèles à effet mixtes. Nous proposons une estimation bayésienne par maximisation de la vraisemblance pénalisée et basée sur l'approximation normale des *a posteriori*, implémentée dans le logiciel NIMROD. Nous discutons l'impact d'une analyse séquentielle bayésienne (SBA) permettant d'analyser plusieurs jeux de données en utilisant comme nouvel loi *a priori* la loi *a posteriori* des analyses précédentes. Nous illustrons que l'approximation normale de la loi *a posteriori*, qui contraint la forme des nouvelles lois *a priori*, permet un gain en précision de l'estimation et diminue les temps de calculs. Nous illustrons la méthode avec des données issues de deux essais cliniques testant des combinaisons d'antirétroviraux (cART) : ALBI ANRS 070 et PUZZLE ANRS 104. Cet article reproduit des résultats non publiés de mon manuscrit de thèse. C'est une extension de la conférence sur le même sujet que j'ai eu l'honneur de donner lors de la réception du prix Marie-Jeanne Laurent-Duhamel, dans le cadre des 47èmes Journées de Statistique organisées par la Société Française de Statistique à Lille, France, en mai 2015.

Keywords: AIDS, antiretroviral drugs, Bayesian approach, causal models, dynamical models, HIV, *in vitro*, *in vivo*, mixed effects models, model choice, normal approximation of the *a posteriori*, mutations, numerical optimization, ordinary differential equation (ODE), personalized medicine, pharmacology, prediction

Mots-clés : antirétroviraux, approximation normale de l'*a posteriori*, approche bayésienne, choix de modèle, équation différentielles ordinaire (ODE), *in vitro*, *in vivo*, médecine personnalisée, mutations, modèles causaux, modèles dynamiques, modèles à effets mixtes, optimisation numérique, pharmacologie, prédiction, SIDA, VIH

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1. Introduction

1.1. The epidemiology of HIV: a variety of biological question

The Human Immunodeficiency Virus (HIV) had been discovered in the beginning of the 80s (Barré-Sinoussi et al., 1983; Gallo et al., 1983), almost two years after the first cases of AIDS (Stahl et al., 1982). This was classified as a pandemic disease in 1987 and is still a main public health issue. In 2014, the UNAIDS reported a prevalence of 35.3 millions [32.2-38.8 millions] with an annual incidence of 2.3 millions [1.9 - 2.7 millions]. Over the last 10 years, improvement of treatment and intensification of their use reduced by 42% the risk of dying from AIDS. An European study (Lewden et al., 2011) showed that mortality patterns in HIV-infected individuals with high CD4 counts on treatment are similar to those in general population. Thus, treatment management and its optimization is a main concern but requires a deep understanding, possibly through mathematical and statistical modeling, of the infection dynamics.

Although new HIV cures are being investigated, virus eradication cannot be reached with actual treatments. This is mainly due to the presence of latent reservoirs of infected cells (Chun and Fauci, 1999), perpetual replication of the virus and failure of the immune system to recognize infected cells (Deeks et al., 2012). Consequently the main interest of cART is to decrease mortality, increase life expectancy and improve life quality by slowing the natural course of the infection. This is possible by preserving the immunologic function and suppressing the viral load in blood. Most clinical trial demonstrated the need to prescribe three or more antiretroviral (ARV) in combination therapies called cART (Bierman et al., 2009). Adherence to treatment, which is the respect of the dosage and timing of drug intakes prescribed by the clinician, is a major factor of success (Parienti et al., 2013). For example, a decrease in adherence of 10% may lead to a 90% increase of the risk of virological failure (Gardner et al., 2009), partially driven by the occurrence of resistance mutation of the virus. Altogether, understanding the infection trajectory and treatment action including pharmacometrics is a highly non-linear multifactorial problem.

Although adverse effects are present in more than 10% of the subjects, the associated cost is generally inferior to the cost associated with non-treating HIV infected patients (Lichtenstein et al., 2008). However, they may impact the treatment adherence. Hence, optimization of treatment in HIV infected-patients, which ranges from population level to individual level personalized medicine, is important for efficacy but also for quality of life and good compliance. The concept of 'personalized medicine' is nothing but a protocol that identify which patient with which treatment will present the best therapeutic response in term of safety and efficacy (Woodcock, 2007). It consists in integrating as much information as possible about the patient. The goal is to propose biomathematical and statistical tools that are built on as many available data and knowledge as possible. Thus, it will be possible to understand the infection mechanism, by data adjustment, and to project the effect of multiple scenarios to investigate the optimal strategies, by data prediction.

1.2. Challenges in modeling HIV dynamics: the viral load and CD4 counts biomarkers

Generally, a biomarker is the quantitative measure of a type or subtype of population of cells or viruses that is correlated with an outcome of interest, such as a clinical status. One of the big challenges is to find relevant biomarkers for a disease, but this is not the question of interest in

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this article. In HIV, opportunistic infections and AIDS are more and more infrequent in patients under treatment. Thus, patients' follow-up is essentially done by analyzing the viral load and the CD4 count trajectories (Vajpayee and Mohan, 2011),called biomarkers of interest. For example, it has been demonstrated that a low or undetectable viral load is correlated with a good clinical prognostic (Murray et al., 1999). Likewise, a high number of CD4 is a good predictor of the infection progression and survival (Egger et al., 2002). In pioneering works, dynamics of viral load and CD4 count were considered separately (Ho et al., 1995; Boscardin et al., 1998). Then, extension to joint modeling improved comprehension of the prey-predator dynamics (Volterra, 1928) between the virus and the immune system. Depending on the clinical questions and the treatment to optimize, one may extend the methods developed in this article to models including different or larger number of biomarkers (Bains et al., 2009; Thiebaut et al., 2014).

The biomarkers are supposed to be collected longitudinally for various patients with possibly intermittent missing data and lost of follow up, thus they can be time-censored. We assume that the missingness is Missing at Random (MAR), which means that it only depends on observed outcome and covariates. Some biomarkers may be value-left-censored, such as the viral load. This latter can be detected only if its level is above a detection threshold usually 50 copies/mm^3.

1.3. Statistical approaches to model biomarkers trajectories

Trajectories of biomarkers had been extensively described by linear and non-linear mixed effect models, see Boscardin et al. (1998) for a review. These model had been extended to take into account value-left-censored biomarkers (Jacqmin-Gadda et al., 2000), informative missing data (Lyles et al., 2000), stochastic randomness (Taylor et al., 1994), joint modeling of all biomarkers (Thiébaut et al., 2003, 2005) and joint modeling with clinical progression (De Gruttola and Tu, 1994; Guedj et al., 2011). These types of models are very useful to analyze data from clinical trials where all the possible confounders are controlled for. When trying to characterize the mechanism of an infection, we want to account for observational data where there is interdependency between biomarkers trajectories and treatments trajectories. For example, the treatment may be initiated because of low CD4 count (Hernán et al., 2000). This causal problem can be resolved using marginal nested models (Robins, 2004) or marginal structural models (Robins et al., 2000). The latter is particularly valid in presence of time-dependent treatment and confounders (Robins, 2000). The parameters of a marginal structural model can be consistently estimated using a class of inverse-probability-of-treatment weighted estimators according to the probability of being under treatment (Cole et al., 2003, 2010). These models rely on a counterfactual approach that assumes that there are potential trajectories with and without treatment associated to each patient, while only one trajectory can be actually observed. All the approaches described above are rather deterministic and descriptive. They have been compared with the dynamic approach to causality (Gégout-Petit and Commenges, 2010; Aalen et al., 2012) and demonstrated as less efficient. Finally, dynamical models have a steady state and give more reliable long-term prediction of biomarkers Prague et al. (2015). Thus, in this article, we focus on dynamical models to model biomarkers trajectories.

We propose to consider mechanistic models because they rely on the physio-pathological mechanism of the infection. Most common types of mechanistic models are based on ordinary, partial or stochastic differential equations (ODE, PDE or SDE). They all describe the relations

between continuous quantities, which are the biomarkers values, and rates of changes over time. PDE allow accounting for multidimensional dynamics and SDE for randomness in the process. PDE had particularly been used for spacial problem or when different paces of dynamics have to be defined, for example to distinguish the intra and extra cellular dynamics of action of treatments for hepatitis C virus (Rong et al., 2013). SDE are particularly used to model the virus dynamics in particular the viral strains and mutations that appear randomly Wang et al. (2013). While they account for different scale and non-deterministic changes, they are computationally demanding and are mostly used for simulations (Tan and Wu, 1998; Conway and Coombs, 2011) rather than for estimations. They are also relevant for models with a very small number of compartments (Donnet and Samson, 2013). In this article, we focus on dynamical mechanistic models based on ODE.

1.4. Outline of this article

The article is organized as follow. Section 2 describes the general formulation of a mechanistic model based on ODE, which includes the definition of a biological model, a statistical model and an observation model. Section 3 discusses methods for inference and focuses on a Bayesian approach based on maximization of the penalized likelihood and normal approximation of the posterior. Then, it introduces the idea of sequential Bayesian analysis (SBA) to pool information from different datasets. Section 4 illustrates these methods to fit and predict real data from the ALBI and PUZZLE clinical trials. Because observed prediction abilities are good, Section 5 illustrates mechanistic models use for treatment optimization by describing selected already published work and concludes.

2. Mechanistic Dynamical models based on ODE

2.1. The bio-mathematical model

For a patient i, for each time $t \in \mathbb{R}^+$, the space of states includes K components $X_i(t) = \left(X_i^1(t), \ldots, X_i^K(t)\right)$, which are the different types of population of cells considered. The trajectories of these components depend on parameters of the model representing rates of production or death for the population of cells dynamics for each individual $\xi_i(t) = \left(\xi_i^1(t), \ldots, \xi_i^{n_p}(t)\right)$; f and h are twice-differentiable one-to-one functions, and the biological model is defined as:

$$\begin{cases} \frac{dX_i(t)}{dt} &= f(X_i(t), \xi_i(t)) \\ X_i(0) &= h(\xi_i(0)) \end{cases} . \tag{1}$$

The models for HIV dynamics have first been modeled considering only the viral load (V) using the simple ODE $\frac{dV(t)}{dt} = \pi - \mu_V V(t)$, where π is the production rate of viruses and μ_V is the viral clearance (Ho et al., 1995). Wei et al. (1995) proposed a similar model for the CD4 count dynamics. In this simple example, the first advantage of mechanistic models is obvious: it clearly identifies parameters with a biological interpretation. Similarly to a prey-predator model, Perelson et al. (1996) combined the dynamics of the viral load and the CD4 count in a three compartments ODE model (see Figure 1a). The observed biological rule is the following: CD4 (T)

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cells are created at a rate λ and get infected at a rate $\gamma V(t)$ depending on the number of circulating viruses and die at rate μ_T. The number of new infected cells (T^*) is given by a mass action law $\gamma V(t)T(t)$. Each infected cell produces π viruses per time-unit. Infected cells die at rate μ_{T^*} and viral clearance is μ_V. Exhaustive lists of mechanistic models had been reviewed in Xiao et al. (2013). It is important to notice that the evolution of mechanistic models is driven by the increase of medical knowledge and the need to test new hypotheses. For example, adding information such as listed below can lead to a model as complex as the one defined in Figure 1c, see Adams et al. (2005) for another example:

- In order to model latent reservoirs, new compartments of infected and non-infected latent cells (Q and Q^*) can be added. These cells get activated in T or T^* cells at rate α and α^* and return to latent state at rate ρ and ρ^* (Selinger and Katze, 2013);
- CD4 are not the only population of cells that are likely to be infected by the virus V. For example macrophage (M and M^*) are also likely to get infected and have smaller death rates (μ_M and μ_{M^*}) (Perelson and Nelson, 1999);
- The infected cells (denoted by *) disappear by natural death but also by being destroyed by killer effector cells (E) (Bonhoeffer et al., 2000; Banks et al., 2008);
- Virus exists as a quasi species in host, which can explain the mechanism of mutations by a process of resistance selection. Different types of virus with different genotypes can be modeled ($V^1,\dots,V^R$) (Nowak et al., 1990). In presence of protease inhibitor as treatment, virus can also be unable to infect new T cells. Thus, infectious (V_I) and non-infectious (V_{NI}) viruses can be distinguished.

Such complex models are very computationally demanding and often over-parameterized in particular when only sparse information is collected. Although they can easily be used for simulations when holding parameters fixed or varying them as in a sensitivity analysis (Smith and Wahl, 2005), they are not very useful when the interest is to quantify biological aspects. Actually, too complex models are often source of problems of practical or theoretical identifiability of parameters (Petersen et al., 2001; Guedj et al., 2007b). While practical identifiability can be investigate by computing the Fisher information (Nyberg et al., 2015), simulations of trajectories (Wu et al., 2008) or likelihood profile (Raue et al., 2009), keeping the biological model as simple as possible regarding the question of interest is a good goal. We propose to use the target cells model displayed in Figure 1b, parameters are described in Table 1. The ODE-based mathematical model is given by:

$$\begin{cases} \frac{\mathrm{d}Q(t)}{\mathrm{d}t} &= \lambda + \rho T(t) - \alpha Q(t) - \mu_Q Q(t), \\ \frac{\mathrm{d}T(t)}{\mathrm{d}t} &= \alpha Q(t) - \gamma T(t)V(t) - \rho T(t) - \mu_T T(t), \\ \frac{\mathrm{d}T^*(t)}{\mathrm{d}t} &= \gamma T(t)V(t) - \mu_{T^*} T^*(t), \\ \frac{\mathrm{d}V(t)}{\mathrm{d}t} &= \pi T^*(t) - \mu_V V(t). \end{cases} \tag{2}$$

2.2. *The statistical model*

Each individual may have different biomarker trajectories and dynamics, this is possible because $\xi_i(t)$ is individual- and time-specific. However, a patient-by-patient fit may be suboptimal (Dixit

and Perelson, 2005) and we propose a non-linear mixed effect model approach (NLME). The inter-individual variability will be captured by the presence of random effects (Lindstrom and Bates, 1988). Because these parameters have a biological interpretation, they need to be positive. We use a log transformation, which is denoted by a tilde. Other link functions, such as logistic transformation could be used to constrain some parameters to be in $[0,1]$. Finally, n_e explanatory covariates for individual i at time t ($z_i(t)$) may have an effect on the value of some parameters. We define the NLME for $\xi_i(t)$ by:

$$\widetilde{\xi_i(t)} = log(\xi_i(t)) = \phi + f(\beta^T, z_i(t)) + u_i, \tag{3}$$

where ϕ is a vector of size n_p and represents the fixed effect, which can be interpreted as the mean value in population. The coefficient β^T is a matrix of size $n_p \times n_e$ and can be interpreted as the mean effect of covariates on the biological parameters. In natural scale, for a linear function f, the parameter $\xi_i(t)$ is the value of the fixed effect in population multiplied by $exp(\beta^T z_i(t))$. Finally, we assume that we have $n_q \leq n_p$ random effects and $u_i \sim \mathcal{N}(0,\Sigma)$ with $\Sigma = [\omega_j^2 I_{i=j}]_{i,j=1,\ldots,n_p}$ and $\omega_j^2 = 0$ if parameter j has no random effect.

The pharmacometrics, particularly the effect of treatment, is often modeled in the function $f(.)$ on $\widetilde{\xi_i(t)}$. For cART composed of S ARVs, the dose of each ARV $d_i^s(t)$, with $s = 1,\ldots,S$, impacts the infectivity parameter (γ) in the target cells model. The function $\psi(.)$ includes both pharmacokinetics and pharmacodynamics aspects. It links the dose with the effect. This function can range from a step function $\psi(d_i^1(t),\ldots,d_i^S(t)) = \sum_{s=1}^S I_{d_i^s(t)>0}$, which is what we use in this article, to more complex shapes such as sigmoidal functions including *in vitro* information (Shen et al., 2008; Rosenbloom et al., 2012). The score test approach developed by (Drylewicz et al., 2010a) can be used to test the effect of explanatory variable and random effects.

2.3. *The observation model*

Such dynamical systems are rarely observed in continuous time. Moreover, the K components of the system may not be observed and information may be collected for $n_C \leq K$ combinations of the K ODE components. Thus, collected data are often longitudinal repeated measurements in every patient $i = 1,\ldots,N$ with n_{im} observations at times t_{ijm} with $j = 1,\ldots,n_i$ for each observed biomarker $m = 1,\ldots,n_C$. The observed biomarker can be written $(g_1^1[X_i(t_{ijm})],\ldots,g_{n_C}^1[X_i(t_{ijm})])$, which is a function g^1 of all the component X for the ODE. Then, we assume a one-to-one function $g^2(.) = [g_1^2(.),\ldots,g_{n_C}^2(.)]$ ensuring normality and homoscedasticity of the measured biomarkers (Box and Cox, 1964). We denote by $g = g^1 o g^2$ the link function between the observations of biomarkers $Y_{ij}(t_{ijm}) = [Y_i^1(t_{ij1}),\ldots,Y_i^{n_C}(t_{ijn_C})]$ and the ODE component values $X_i(t_{ijm})$. The observation model is:

$$\left\{\begin{array}{ccc} Y_{ij}^m(t_{ijm}) & = & g_m[X_i(t_{ijm})] + \varepsilon_{ijm}, \\ \varepsilon_{ijm} & \sim & \mathcal{N}(0,W) \\ W & = & [\sigma_j^2 I_{i=j}]_{i,j=1,\ldots n_C} \end{array}\right. . \tag{4}$$

The ε_{ijm} are the normally distributed measurement errors. In the particular example of the target cells model, we assume that only the CD4 count $Y_{ij}^1(t_{ij1}) = \sqrt[4]{Q_i(t_{ij1}) + T_i(t_{ij1}) + T_i^*(t_{ij1})}$ and the viral load $Y_{ij}^2(t_{ij2}) = log_{10}(V_i(t_{ij2}))$ are observed.

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3. Estimation in NLME-ODE and sequential Bayesian analysis (SBA)

3.1. *Algorithms for Estimation: a Bayesian estimation to improve identifiability*

The mechanistic models are NLME-ODE models composed of a bio-mathematical model (Equation 1), a statistical model (Equation 3) and an observation model (Equation 4). Statistical inference consists of estimating the parameter $\theta = [(\phi_k)_{k=1,\ldots,n_p}, (\beta_k)_{k=1,\ldots,n_p \times n_e}, (\omega_k)_{k=1,\ldots,n_q}, (\sigma_k)_{k=1,\ldots,n_C}]$.

Non-parametric approaches using functional analysis exist but they are limited to a small number of observed biomarkers and no implementation is publicly available (Wang et al., 2012). When we assume normality of observations, a likelihood-based approach can be used with a numerical solver of ODE (Radhakrishnan and Hindmarsh, 1993). The likelihood can be computed for a multistep model where the conditional likelihood is first computed conditionally on the random effects then integrated to get the marginal likelihood. This integration step is difficult since it does not exist any analytic close form. Pinheiro and Bates (1995) proposed a Laplace approximation and Lee and Nelder (1996) proposed hierarchical likelihood, but both can be biased when the approximation is too far from the likelihood structure (Ding and Wu, 2001; Commenges et al., 2011). Alternatively, the Stochastic Approximation Expectation Maximization (SAEM) algorithm (Kuhn and Lavielle, 2005) will most of the time converge toward local maximums for large ODE. Numerical approximation of the integral using an adaptive Gaussian quadrature has been proven accurate (Plan et al., 2012). It has been used for estimation in mechanistic models by Guedj et al. (2007a) and this is what we propose to do in this paper. Moreover, this type of model is also often subject to identifiability issues (Miao et al., 2011). While full-Bayesian MCMC approaches (Huang et al., 2006) may be used, Drylewicz et al. (2010b); Prague et al. (2013a) showed that they are very time consuming and sometimes intractable for large ODE. We propose to use a penalized log-likelihood approach (LL^p) where priors ($\pi(\theta)$) on parameters improve identifiability (Drylewicz et al., 2012):

$$LL^P(\theta) = log[P(\theta|D)] = L(\theta) + log[\pi(\theta)] + C,$$

where D are the data , C is a normalization constant and $L(\theta)$ is the log-likelihood. Details on the computation of $L(\theta)$ as described above can be found in Guedj et al. (2007a) and Prague et al. (2013a). The posteriors of θ are obtained by a normal approximation where the mean is given by the values of θ leading to a maximized $LL^P(\theta)$, and the variance-covariance matrix is given by the Hessian computed at the maximum.

Many softwares are available to fit NLME-ODE with various advantages and drawbacks. WinBUGS (Lunn et al., 2000) implements full-Bayesian approach. We propose to use NIMROD (Prague et al., 2013a), which we proved in simulation to be more stable for large ODE. However, MONOLIX (Chan et al., 2011), which is based on the Bayesian SAEM algorithm, is probably more user friendly and is a good alternative.

3.2. *Sequential Bayesian Analysis (SBA): Improving the fit qualities and prediction abilities*

As mentioned above, these models suffer from identifiability issues: having a large number of individuals from multiple studies or incorporating information from different sources of information improves practical identifiability (Guedj et al., 2007b). In both cases, computation

times may make the estimation intractable; an alternative approach is to use a Sequential Bayesian Analysis (SBA). We consider data arriving sequentially $\{D_1,\dots,D_n\}$ and wish to update inference on the unknown parameter θ defined in Section 3.1; the different batches of data are not necessarily independent. In a Bayesian setting, we have a prior $\pi(\theta)$ and we have a density for all these data conditionally on θ defined by:

$$f(\overline{D_N}|\theta) = f(D_1|\theta)f(D_2|D_1,\theta)\dots f(D_n|\overline{D_{n-1}},\theta),$$

where $\overline{D_i} = (D_1,\dots,D_i)$. For the k first datasets, we may have updated our prior distribution of θ ($\pi(\theta)$) into its posterior:

$$\pi_k(\theta) = f(\theta|\overline{D_k}) \propto \pi(\theta)f(\overline{D_k}|\theta).$$

If we obtain a new observed individual, or a new dataset D_{k+1} we may either start afresh and write:

$$\pi_{k+1}(\theta) = f(\theta|\overline{D_{k+1}}) \propto \pi(\theta)f(\overline{D_{k+1}}|\theta).$$

The estimation of $\pi_{k+1}(\theta)$ is then obtained by running again the estimation procedure onto the entire dataset $\overline{D_{k+1}}$ as proposed in Section 3.1 and using the priors ($\pi(\theta)$). Or we could claim that just before time $k+1$, our knowledge of θ is summarized in the posterior distribution $\pi_k(\theta)$ so we just use this as a new prior distribution for the update:

$$\tilde{\pi}_{k+1}(\theta) \propto \pi_k(\theta)f(D_{k+1}|\overline{D_k},\theta).$$

The estimation of $\tilde{\pi}_{k+1}(\theta)$ is then obtained by running the estimation procedure onto the new dataset D_{k+1} as proposed in Section 3.1 and using as priors $\tilde{\pi}_k(\theta)$. Indeed, these updates are identical in pure theory since:

$$\begin{aligned}
\tilde{\pi}_{k+1}(\theta) &\propto \pi_k(\theta)f(D_{k+1}|\overline{D_k},\theta)\\
&\propto \pi(\theta)f(\overline{D_k}|\theta)f(D_{k+1}|\overline{D_k},\theta)\\
&= \pi(\theta)f(\overline{D_{k+1}}|\theta)\\
&= \pi_{k+1}(\theta).
\end{aligned}$$

Because the estimation approach we propose is not full-Bayesian and that the posteriors cannot be specified entirely, this sequential updating and the demonstration above do not hold exactly. Actually, for the normal approximation of the posteriors we take $\tilde{\pi}_n^*(\theta) \sim \mathcal{N}(\text{mode}[\tilde{\pi}_n(\theta)], \text{sd}[\tilde{\pi}_n(\theta)])$.

Asymptotically if D_{k+1} is large enough, no bias should appear in inference whether we are using $\tilde{\pi}_k^*(\theta)$, $\tilde{\pi}_k(\theta)$ or $\pi(\theta)$ as priors. However, in applications the number of individuals in D_{k+1} is likely to be small. Thus, the priors are likely to leverage the values of the posteriors. Assuming that information is present in data $\overline{D_k}$, then $\tilde{\pi}_k(\theta)$ is an informative prior. Ghosal (1997) showed that in most generalized linear and non-linear equations, the posteriors are consistent and admits a normal approximation. When analytically solvable, the NLME-ODE can be represented as a set of generalized linear and non-linear equations, thus this result also applies to the NLME-ODE class of models. Furthermore, Prague et al. (2013a) verified in simulation the validity of this assumption. Thus $\tilde{\pi}_k^*(\theta)$ is a reasonable approximation for $\tilde{\pi}_k(\theta)$ and analyzing D_{k+1} with priors $\tilde{\pi}_k^*(\theta)$ will give similar results as analyzing $\overline{D_{k+1}}$ with priors $\pi(\theta)$. By adopting this SBA, we expect that the mean of $\tilde{\pi}_k^*(\theta)$ will converge to the true value of parameters denoted θ^* and will have a standard deviation that will shrink around this value.

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4. Simulation and illustration

Mechanistic models are particularly designed to perform individual predictions of the response to an intervention and could therefore be useful tools for optimization of an intervention. The key for such models to be useful is to have good fitting and prediction abilities. Using two clinical trials (ALBI ANRS 070 and PUZZLE ANRS 104), we propose to illustrate 1) the good properties of SBA; 2) how pooling different datasets with SBA actually improves the quality of fit; and 3) the accurate quality of prediction that can be achieved by mechanistic models;.

4.1. Data description

The ALBI ANRS 070 trial is a three-arm randomized trial of 148 antiretroviral-naive patients who received cART: 50 patients received stavudine+didanosine (d4T+ddI) and 49 patients received zidovudine and lamivudine (AZT+3TC) over 24 weeks. The third arm of 49 patients received d4T+ddI for 12 weeks and switched to AZT+3TC. Results of this trial are described elsewhere (Molina et al., 1999) but conclusion of this trial was that d4T+ddI is more effective compared to AZT+3TC. The PUZZLE ANRS 104 is a trial of 37 patients for a salvage therapy combining lopinavir (LPV), amprenavir (APV), ritonavir (/r) with nucleoside reverse transcriptase inhibitors (NRTI), over a 26-week period in HIV-infected patients in whom multiple anti-retroviral regimens had failed. Results of this trial are described elsewhere (Raguin et al., 2004). In both study, CD4 count and viral load with a lower detection limit of 50 copies/mL were collected longitudinally one or twice a month. Adherence was self reported or declared by the clinician.

We propose to model the trajectories of biomarkers with a mechanistic model as it had been done in (Prague et al., 2012). We use the bio-mathematical model described in Section 2.1. Regarding the statistical model, the pharmacological link between the dose of treatment and the effect is modeled such as in Section 2.2. The infectivity parameter is supposed to be a function of the dose of treatment for each regimen:

$$\tilde{\gamma}_i(t) = \gamma_0 + \sum_{k=1}^{3} \beta_k I_{d_i^k(t)>0},$$

where $k=1$ indexes AZT+3TC, $k=2$ indexes d4T+ddI and $k=3$ indexes LPV+APV/r. Random effects are put on $\lambda = \lambda_0 + u_i^{\lambda}$ and $\mu_{T^*} = \mu_{T^*0} + u_i^{\mu_{T^*}}$ with $u_i^{\lambda} \sim \mathcal{N}(0, \omega_{\lambda})$ and $u_i^{\mu_{T^*}} \sim \mathcal{N}(0, \omega_{\mu_{T^*}})$. The observation model is the same as the one described in Section 2.3.

4.2. Validation of the SBA

In this section we want to compare two approaches: analyzing $\overline{D_{n+1}}$ with priors $\pi(\theta)$ and analyzing D_{n+1} with priors $\tilde{\pi}_n^*(\theta)$. We split the ALBI dataset in three sub-studies (D_1, D_2 and D_3) of different sizes ($n_1 = 50$, $n_2 = 25$ and $n_3 = 73$). We first analyzed $\overline{D_3} = \{D_1, D_2, D_3\}$ with the priors from the literature $\pi(\theta)$ given in the Table 2. This posteriors is denoted $\pi_3^*(\theta)$. Then we sequentially analyzed: 1) D_1 with priors $\pi(\theta)$, we denote the posteriors $\tilde{\pi}_1^*(\theta)$; 2) D_2 with SBA using priors $\tilde{\pi}_1^*(\theta)$, we denote the posteriors $\tilde{\pi}_2^*(\theta)$; and finally 3) D_3 with SBA using priors $\tilde{\pi}_2^*(\theta)$, we denote the posteriors $\tilde{\pi}_3^*(\theta)$. Finally, we also analyzed D_2 and D_3 with priors $\pi(\theta)$

giving posteriors $\pi^*_{D_2}(\theta)$ and $\pi^*_{D_3}(\theta)$. The results are available in Table 2. We are interested in comparing $\pi^*_3(\theta)$ and $\tilde{\pi}^*_3(\theta)$. While both analysis provide the same conclusion regarding the superiority of d4T+ddI compared to AZT+3TC ($|\beta_{AZT+3TC}| \leq |\beta_{d4T+ddI}|$), values of elements of θ are quite different. First, we notice that there is no contradiction between the two posteriors: mean values of each one is included in the normal 95 % confidence interval of the other. Second, Figure 2 shows that when looking at the mean biomarker trajectories (averaged over all the individuals in the ALBI dataset), there is actually no difference in the two curves. Thus, the difference in posteriors for θ may be attributed to identifiability problems. Regarding estimation times, because of volume and complexity of the surface to optimize, the SBA is way faster than the analysis of $\overline{D_3}$. Because the code had been parallelized on a different number of cores for each setting it is difficult to compare elapsed times for computation. However, the analysis of $\overline{D_3}$ took 403 iterations, thus the time is proportional to 148×403=59644 computations of the likelihood. On the contrary, for the SBA, this time is proportional to $57\times50+27\times25+45\times73$=6810 computations of the likelihood. Both analysis lead to the same accuracy of the maximization of the likelihood, the analysis of $\overline{D_3}$ leads to a non-penalized log-likelihood of -1066.5 and the SBA leads to -1067.3. Whereas these two approaches seem similar, they are superior to analyzing separately the data D_1, D_2 and D_3 using $\pi(\theta)$, which leads to a non-penalized log-likelihood of -1123.1. Finally, using accurate priors estimated on existing data can greatly improve the inference when the sample size is small. For example, $\pi^*_{D_2}(\theta)$ and $\tilde{\pi}^*_2(\theta)$ are significantly different with log-likelihood of -230.1 versus -171.7. This phenomenon will also be illustrated on real data in Section 4.3. Thus, even if the SBA is an approximation, it brings information and allows more accurate estimations. Overall, we conclude that the SBA approach, which is often used in practice, gives valid results, even with normal approximation of the priors. However, we acknowledge that it is inferior to using the true posteriors without normal approximation or pooling all the data together.

4.3. Analyzing PUZZLE using Bayesian sequential update from ALBI

In this section, we want to confirm that analyzing the PUZLLE dataset with priors $\tilde{\pi}^*_{ALBI}(\theta)$ ($= \tilde{\pi}^*_3(\theta)$ in Table 2) instead of $\pi(\theta)$ from the literature leads to better estimation and also improves the quality of fit. Table 3 provides the posteriors estimates for θ. The values of the non-penalized log-likelihood at maximum is significantly better when pooling the PUZZLE data with the ALBI data by using a SBA than when using the priors from literature ($\pi(\theta)$), respectively -430.1 and -453.8. Figure 3 displays for 4 patients the different biomarker trajectories. Pooling data from PUZZLE and ALBI tend to improve the quality of fit.

4.4. Quality of prediction

Good quality of fit is not enough to envisage optimization of treatment. The model must also have good abilities for prediction. In this section, we selected at random 10 patients in the ALBI study, this is our validation dataset. We ran the analysis on the estimation dataset composed of the remaining 138 patients from ALBI study using priors $\pi(\theta)$. We used the first two measurements of each individual from the validation dataset to update the individual random effect for parameters λ and μ_{T^*} using parametric empirical Bayes, see details in Prague et al. (2013b); Kass and Steffey (1989). Then, we predicted the trajectories of their biomarkers for subsequent times. We compared

the observed with the predicted values. Figure 4A and 4B confirm a good adjustment. Figure 4C and 4D display that both for viral load and CD4, there is no time-trend and the difference between observed and predicted values is not increasing with time. Because we are able to predict the biomarker trajectories of patients, these NMLE-ODE models can be considered for optimization of treatment.

5. Conclusion

We have reviewed methods to estimate and predict the biomarker trajectory of HIV infected patient under cART. Despite the normal approximation of the posterior, we showed that the SBA consisting of pooling data by using posteriors from previous analysis as new priors, can improve accuracy of estimation in practice. We did not provide mathematical proof of the validity of the normal approximation of the posterior. Thus this results could be extended using Van der Vaart (2000) to investigate for which sample size (n), number of observations (n_i) and number of parameters ($n_p + n_e + n_q + n_C$) estimated simultaneously these approximations are valid. The quality of fit of NLME-ODE models is clearly depicted in Section 4.3, the qualities of prediction are also discussed in Section 4.4 and elsewhere (Prague et al., 2013b). Thus, one of the new challenge with these models is the optimization of interventions efficacy or design delivery.

Prague et al. (2012) have demonstrated that these models can be used to adaptively update the dose of treatment to find an individual optimal dose in HIV infected patients on cART. Similarly, NMLE-ODE models have been used to investigate the efficacy of an immune restoration agent, the Interleukine-7 (IL-7). Thiebaut et al. (2014) demonstrated that such a strategy may allow maintaining CD4+ T cell counts above 500 cells/μL with 4 cycles or fewer over a period of two years. This consists in a proof of concept showing that IL-7 can sustain CD4+ T cell restoration with limited IL-7 exposure in HIV-1 infected patients with immune failure despite antiretroviral therapy. However, these model need to be made more complex either by allowing a larger number of compartments or by including other types of information such as transcriptomic data or phylogenetic data (host and virus genomic). For example, recent mathematical modeling approaches have been used to identify molecular signatures that can be used to predict vaccine immunity in humans (Querec et al., 2009). Current directions for research mainly focus on how to integrate system biology in mechanistic modeling with the particular concern of dealing with high-dimensional ODE.

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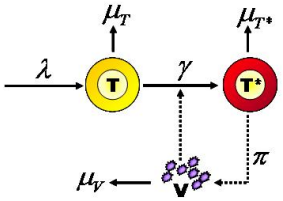
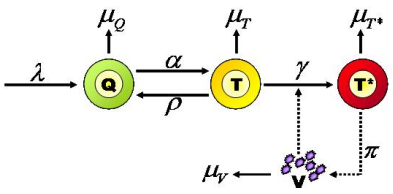
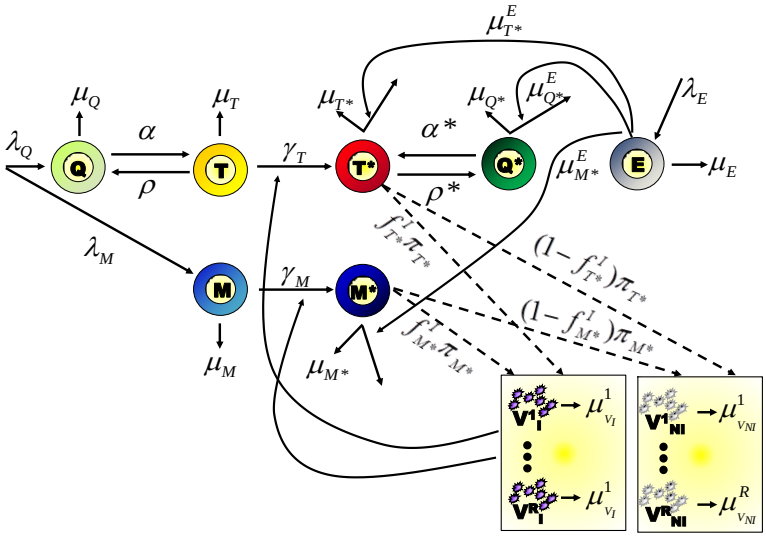
Figure 1: Example of mechanistic model based on ODE. They can be defined as complex as needed to describe the biological mechanism of interest (from (a) to (c) and more, the target cells model (b) has good prediction abilities). CD4 cells can be quiescent (Q) or activated (T). They are labeled with a $*$ when they are infected by the virus (V). Virus may have different genotypes and be infectious ($V_I^1, \ldots, V_I^R$) or non-infectious ($V_{NI}^1, \ldots, V_{NI}^R$). Other types of cells are effector cells E and macrophages M. Creation, Death and transition rates describe the dynamics of these cells.



(a) Perelson et al. (1996) Model



(b) Target cells model



(c) Complex dynamical model of interaction between immune system and HIV

TABLE 1. *Meaning of parameters in the dynamical models presented in Figure 1b and Equation 2. Prior means and standard deviations for normal a priori distributions can be found in Prague et al. (2012).*

			Normal priors used for analysis on the log value of the parameter	
Name	Description	Unity	Mean	sd.
λ	Natural production rate	$\frac{cells}{\mu L.day}$	12.80	24.3
μ_{T^*}	Natural death rate of T^* cells	$\frac{1}{day}$	0.95	0.65
μ_Q	Natural death rate of Q cells	$\frac{1}{day}$	0.0001	0.0001
α	Transition rates between Q and T cells	$\frac{1}{day}$	0.018	0.037
ρ	Transition rates between T and Q cells	$\frac{1}{day}$	0.013	0.018
μ_T	Virions natural death rate	$\frac{1}{day}$	0.075	0.026
γ	Infectivity parameter	$\frac{\mu L}{day}$	0.003	0.013
π	Rate of production of virions by infected cells	$\frac{1}{day}$	56.82	151.2
μ_V	Natural death rate of T^* cells	$\frac{1}{day}$	16.95	11.52

Figure 2: Mean biomarkers trajectories of viral load an CD4 count in the 148 patients of the ALBI trial. Dashed line uses the values of $\pi_3^*(\theta)$ on the full dataset. Plain line uses the values of $\tilde{\pi}_3^*(\theta)$ from the SBA.

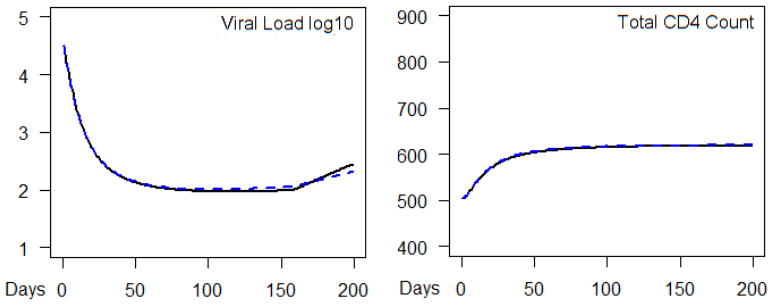


TABLE 2. *SBA of three subsets of the ALBI study. The posteriors $\pi_3^*(\theta)$ is given by the analysis of $\overline{D_3} = \{D_1, D_2, D_3\}$ using $\pi(\theta)$ as priors. The posteriors $\pi_{D_1}^*(\theta)$, $\pi_{D_2}^*(\theta)$ and $\pi_{D_3}^*(\theta)$ given by the analysis of D_1, D_2 and D_3 respectively using $\pi(\theta)$ as priors. The posteriors $\tilde{\pi}_2^*(\theta)$ is given by the SBA of D_2 using $\tilde{\pi}_1^*(\theta) = \pi_{D_1}^*(\theta)$ as priors. The posteriors $\tilde{\pi}_3^*(\theta)$ is given by the SBA of D_2 using $\tilde{\pi}_2^*(\theta)$ as priors.*

	Priors			*Posteriors*			
	$\pi(\theta)$	$\pi_3^*(\theta)$	$\tilde{\pi}_1^*(\theta) = \pi_{D_1}^*(\theta)$	$\pi_{D_2}^*(\theta)$	$\pi_{D_3}^*(\theta)$	$\tilde{\pi}_2^*(\theta)$	$\tilde{\pi}_3^*(\theta)$
Data used	Literature	$\overline{D_3}$	D_1	D_2	D_3	D_2	D_3
Priors	-	$\pi(\theta)$	$\pi(\theta)$	$\pi(\theta)$	$\pi(\theta)$	$\pi_1^*(\theta)$	$\tilde{\pi}_2^*(\theta)$
$L(\theta, y)$	-	-1066.5	-418.0	-230.1	-475.0	-171.7	-477.6
$L^P(\theta, y)$	-	-1070.8	-414.5	-225.7	-475.2	-166.3	-480.1
Iterations	-	403	57	415	238	27	45
Biological parameters :							
Parameters	Mean (sd.)	Mean (sd.)	Mean (sd.)	Mean (sd.)	Mean (sd.)	Mean (sd.)	Mean (sd.)
$\tilde{\lambda}$	2.55 (1.90)	1.70 (0.10)	2.02 (0.27)	2.13 (0.12)	1.96 (0.17)	2.01 (0.17)	1.94 (0.11)
$\tilde{\mu}_{T^*}$	-0.05 (0.68)	-1.61 (0.05)	-1.04 (0.16)	-0.78 (0.07)	-1.30 (0.11)	-0.95 (0.12)	-1.23 (0.07)
$\tilde{\mu}_Q$	-9.00 (1.00)	-9.34 (0.99)	-8.98 (0.99)	-9.00 (0.99)	-9.31 (0.99)	-8.98 (0.99)	-9.21 (0.99)
$\tilde{\alpha}$	-4.00 (2.00)	-4.07 (0.13)	-3.80 (0.36)	-3.34 (0.24)	-3.70 (0.22)	-3.54 (0.24)	-3.74 (0.13)
$\tilde{\rho}$	-4.34 (1.38)	-7.88 (1.34)	-5.74 (1.08)	-4.63 (1.15)	-5.96 (1.08)	-4.99 (0.88)	-5.22 (0.56)
$\tilde{\mu}_T$	-2.59 (0.34)	-3.53 (0.03)	-3.07 (0.17)	-3.07 (0.05)	-3.43 (0.13)	-3.11 (0.12)	-3.33 (0.08)
$\tilde{\gamma}_0$	-5.76 (4.02)	-5.14 (0.12)	-6.05 (0.19)	-6.27 (0.04)	-5.76 (0.09)	-6.06 (0.13)	-5.73 (0.07)
$\tilde{\pi}$	4.04 (2.66)	2.75 (0.67)	3.94 (0.72)	3.96 (0.59)	3.41 (0.68)	3.84 (0.51)	3.46 (0.37)
$\tilde{\mu}_V$	2.90 (0.68)	3.16 (0.66)	3.0 (0.66)	2.91 (0.43)	3.40 (0.66)	3.05 (0.50)	3.29 (0.37)
Treatment effects							
Parameters	Mean (sd.)	Mean (sd.)	Mean (sd.)	Mean (sd.)	Mean (sd.)	Mean (sd.)	Mean (sd.)
$\beta_{AZT+3TC}$	-1.10 (0.37)	-1.13 (0.10)	-0.96 (0.15)	-0.73 (0.03)	-0.78 (0.06)	-0.81 (0.10)	-0.78 (0.05)
$\beta_{d4T+ddI}$	-1.10 (0.37)	-1.45 (0.13)	-1.02 (0.16)	-0.80 (0.03)	-1.05 (0.07)	-0.91 (0.10)	-1.04 (0.06)
Standard errors for random effects :							
Parameters	Median	Mean (sd.)	Mean (sd.)	Mean (sd.)	Mean (sd.)	Mean (sd.)	Mean (sd.)
ω_λ	0.10	0.26 (0.02)	0.25 (0.06)	0.22 (0.01)	0.24 (0.04)	0.23 (0.09)	0.24 (0.04)
$\omega_{\mu_{T^*}}$	0.37	0.25 (0.02)	0.24 (0.06)	0.21 (0.01)	0.25 (0.03)	0.21 (0.06)	0.23 (0.03)
Standard errors for measurement errors :							
Parameters	-	Mean (sd.)	Mean (sd.)	Mean (sd.)	Mean (sd.)	Mean (sd.)	Mean (sd.)
σ_{CV}	-	0.58 (0.01)	0.61 (0.02)	0.46 (0.01)	0.51 (0.02)	0.47 (0.06)	0.50 (0.02)
σ_{CD4}	-	0.20 (0.01)	0.20 (0.01)	0.21 (0.01)	0.20 (0.01)	0.21 (0.01)	0.20 (0.01)

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TABLE 3. *Analysis of the PUZZLE data using priors from the literature $\pi(\theta)$ and from the normal approximation of the posteriors of the analysis of the ALBI data $\tilde{\pi}^*_{ALBI}(\theta)$.*

	Posteriors			
	PUZZLE		POOLED	
Priors	$\pi(\theta)$		$\tilde{\pi}^*_{ALBI}(\theta)$	
$L(\theta, y)$	-453.8		-430.1	
Iterations	108		87	
	Mean	sd.	Mean	sd.
λ	1.48	0.49	2.31	0.10
μ_{T^*}	-1.33	0.46	-0.33	0.12
μ_Q	-9.01	0.99	-11.2	0.99
α	-3.07	0.30	-2.86	0.11
ρ	-4.85	1.07	-4.60	0.46
μ_T	-3.33	0.19	-2.79	0.08
γ_0	-6.60	0.19	-5.38	0.03
π	4.21	0.72	1.29	0.24
μ_V	2.73	0.66	-0.75	0.13
$\beta_{LPV+APV/r}$	-0.76	0.12	-0.88	0.08
σ_λ	1.0	0.23	0.96	0.23
$\sigma_{\mu_{T^*}}$	0.98	0.11	0.81	0.12
σ_{CV}	0.62	0.04	0.57	0.04
σ_{CD4}	0.24	0.01	0.22	0.01

Figure 3: Individual biomarkers trajectories of viral load an CD4 count for 4patients of the PUZZLE trial. Dashed line represents the fit when only knowledge from literature is used ($\pi(\theta)$ as priors). Plain line represents the fit after pooling with ALBI data using a SBA ($\tilde{\pi}^*_{ALBI}(\theta)$ as priors).

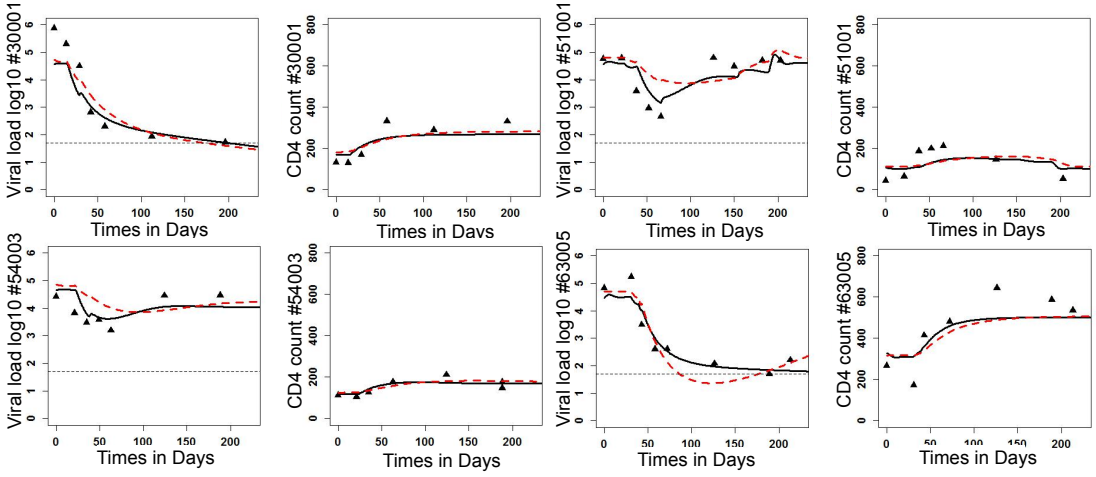

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Figure 4: Residuals plots for assessing the quality of prediction on ALBI validation dataset constituted of 10 patients chosen at random: (A,B) displays the scatterplot of observed against predicted values for viral load and CD4 count. (C,D) displays the time-trend for residuals, which is the difference between observed and predicted values. Dashed lines represent the confidence interval given by the standard deviation of the errors measurement.