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Résumé. Différentes méthodes ont été utilisées dans le domaine de la statistique pour estimer les paramètres dans les modèles mécanistes. En particulier, l'approche basée sur la vraissemblance pénalisée pour l'estimation des paramètres dans les équations différentielles ordinaires avec des modèles non linéaires à effets mixtes sur les paramètres (ODE-NLME) est souvent employée. Nous utilisons ici le programme NIMROD [Prague2013] comme référence pour l'estimation dans ces modèles. Cependant, une telle approche prend beaucoup de temps de calcul. Nous proposons d 'envisager l'assimilation de données, historiquement utilisée dans le contexte de la géophysique. Nous proposons un observateur d'état de Luenberger couplé à un observateur de Kalman (filtre RoUKF, également appelé filtre SEIK) pour effectuer une estimation conjointe des états et des paramètres sur un ensemble de données composé d'observations longitudinales de biomarqueurs pour de multiples patients. Nous comparons ces méthodes en termes de performances et de temps de calcul. Nous discutons comment le concept d'effets aléatoires peut être modélisé en utilisant les filtres de Kalman et ses limites. Nous illustrons les deux méthodes en simulation et sur deux ensembles de données (l'essai clinique randomisé ALBI ANRS 070 et les données d'observation de la cohorte d'Aquitaine ANRS CO3) en utilisant un modèle mécaniste du VIH.

Mots-clés. Bayésien; Equation Différentielle ordinaire; Kalman and Luenberger filters; Modèles m/'ecanistes; Modèles non linéaire à effets mixtes; VIH; Vraissemblance pénalisée.

Abstract. Various methods have been used in the statistical field to estimate parameters in mechanistic models. In particular, approach based on penalised likelihood for estimation of parameters in ordinary differential equations with non linear models on parameters (ODE-NLME) has proven successful. We will consider the NIMROD program [Prague2013] as a benchmark for estimation in these models. However, such approach is time consuming. We propose to consider data assimilation which historically arose in the context of geophysics. We propose a Luenberger (also called nudging) state observer coupled with a parameter Kalman-based observer (RoUKF filter, also called SEIK filter) to perform a joint state and parameter estimation on a dataset composed of longitudinal observations of biomarkers for multiples patients. We compare these methods in term of performances and computation time. We discuss how the concept of random effect can be modelled using Kalman-based filter and its limitations. We illustrate both methods in simulation and on two datasets

(the ALBI ANRS 070 trial and the Aquitaine cohort observational data) using an HIV mechanistic model.

Keywords. Ordinary Differential Equations; Bayesian; HIV; Kalman and Luenberger filters; Mechanistic models; Non-Linear Mixed Effect Models; Penalized-likelihood.

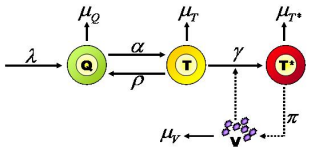
1 Estimation in Mechanistic models

When interactions between many variables are dynamical, mechanistic models based on ordinary differential equations (ODE) are particularly useful. In these models, we account for longitudinal data in which parameters are made individual-specific using a mixed effect model. Classical methods consist in computing the log-likelihood using an ODE solver and to maximise it. However, the large number of parameters to jointly estimate can imply problems of identifiability that are often difficult to detect. Many algorithm and softwares have been developed, among others we can cite NONMEM [Pinheiro1995], MONOLIX [Kuhn2005] implementing a SAEM algorithm, full-MCMC technics implemented in Winbugs [Wu2005]. An alternative approach based on penalized log-likelihood maximisation is so far preferred because Bayesian framework improve identifiability. It is implemented in NIMROD [Prague2013] and will serve as benchmark on this work.
On the other hand, data assimilation methods have been extensively developed in the engineering field and historically arose in the context of geophysics – e.g. in oceanographics and weather forecasting [Navon2009]. Nowadays, there is an increased focus on new application fields. It consists in reducing the uncertainties and also estimating uncertain quantities – as for example the model parameters – for dynamical models by exploiting the available data. To reach this goal, we choose to rely on a sequential approach where the original dynamic is corrected at each time by a feedback control involving a discrepancy computed between the actual data and synthetic data reconstructed from the simulated trajectory. This family of methods comprises both the classical Kalman-based filtering approaches in which the feedback is computed from some kind of Riccati equation solution, and a Luenberger filtering approach [Luenberger1971] – popularized in data assimilation under the nudging terminology. We use the method developed by Moireau et al. [Moireau2008] to formulate a joint state and parameter observer, where a Luenberger observer corrects the state, and an reduced-order optimal Kalman-based filter is restricted to the parametric space. It allows to perform the estimation with reasonable computing times in particular for large-size ODE. This is particularly what motivated this work of comparison with NIMROD.

2 The HIV target cell model

We recall that the "target cells model" – where Q represents the quiescent cells, T the target cells, T^* the infected target cells and V the HIV viruses – reads

$$\begin{cases} Q' &= \lambda + \rho T - \alpha Q - \mu_Q Q, \\ T' &= \alpha Q - \gamma T V - \rho T - \mu_T T, \\ (T^*)' &= \gamma T V - \mu_{T^*} T^*, \\ V' &= \pi T^* - \mu_V V, \end{cases}, \quad (1)$$



where, λ is the immune system cells input, α and ρ are activation and deactivation rates for target cells, $\gamma = \gamma_0 + \beta \mathbb{1}_{t>0}$ is infectivity rate, π is the production of viruses rate, and finally μ's are death rates for each type of cells and viruses. In the NLME-ODE approach with NIMROD, we use a mixed effect model, with the structure proposed by [Guedj2007], on the ODE parameters in log-transformation to ensure their positivity. Normally distributed random effects are put on immune system cells input (λ) and death rate of infected cells (μ_{T^*}). In HIV studies, longitudinal data collected in routine are the total CD4 count in cells/μL and viral load in copies RNA/μL. To model measurement error, we use transformations to achieve normality and homoscedasticity of noises. Thus, we assume that combinations of compartments are observed, to say $(Q + T + T^*)^{0.25}$ and $log_{10}(V)$. The standard deviation of measurement errors are respectively σ_{CD4} and σ_{VL}. More information can also be found in [Prague2012, Prague2016].

3 Sequential methods in data assimilation

3.1 Introduction

We consider a system of ordinary (or partial) differential equations, find x,

$$\begin{cases} \dot{\mathrm{x}}(t) &= \mathrm{A}(\mathrm{x}, \theta, t), \\ \mathrm{x}(0) &= \mathrm{x}_\diamond + \zeta_{\mathrm{X}}, \\ \theta(0) &= \theta_\diamond + \zeta_\theta. \end{cases} \quad (2)$$

The dynamical operator A can be non-linear. Here, θ represents the set of unknown model parameters. In practice, we just have an a priori on the initial condition and on the values of the parameters represented. That is why we decompose them into two parts: $\mathrm{x}_\diamond$ and $\theta_\diamond$ are the known parts (or *a priori*) and ζ_{X} and ζ_θ, the uncertainties. We assume that we have at our disposal some observations of a real trajectory denoted by z. In many cases, an observation operator denoted by H represents the data generation procedure. Sequential methods consist in constructing an estimator by coupling the model and the observations z. This implies that the dynamics of the system is modified. This new system is named the observer and reads

$$\begin{cases} \dot{\hat{\mathrm{x}}}(t) &= \mathrm{A}(\hat{\mathrm{x}}, \hat{\theta}, t) + \mathrm{G}_{\mathrm{X}}\big(\mathrm{z} - \mathrm{H}(\hat{\mathrm{x}}(t))\big), \\ \dot{\hat{\theta}}(t) &= \mathrm{G}_\theta\big(\mathrm{z} - \mathrm{H}(\hat{\mathrm{x}}(t))\big), \\ \mathrm{x}(0) &= \mathrm{x}_\diamond, \\ \theta(0) &= \theta_\diamond, \end{cases} \quad (3)$$

where $\mathrm{G_X}$ and G_θ are the state and parameter gain operators respectively, also called the state and parameter filters. The goal of a sequential method is thus to find an observation operator and gains such that $\lim_{t\to+\infty} \hat{\mathrm{x}} = \mathrm{x}$ and $\lim_{t\to+\infty} \hat{\theta} = \theta$, where x is the solution of (2).

Using the joint state and parameter strategy introduced in [Moireau2008], we can use two different gains – one for the state space and one for the parameters space. In Section 3.2, we will present the state observer – which is a Luenberger (or nudging) observer – and in Section 3.3, we will present the parameter observer – which is a Kalman-based filter.

3.2 State observer

The objective of this section is to present the state observer then we will consider uncertainties only on the initial conditions. We extend the system defined in System 1 by allowing the following initial conditions,

$$Q(0) = Q_\diamond + \zeta_Q,\ T(0) = T_\diamond + \zeta_T,\ T^*(0) = T^*_\diamond + \zeta^*_T,\ V(0) = V_\diamond + \zeta_V.$$

As we observe $\Sigma = Q + T + T^*$ and V, System 1 is rewritten, find Q, T, Σ, V such that

$$\left\{\begin{array}{rcl} Q' &=& \lambda - (\mu_Q + \alpha)Q + \rho T, \\ T' &=& \alpha Q - (\rho + \mu_T)T - \gamma V T, \\ \Sigma' &=& \lambda + (\mu_{T^*} - \mu_Q)Q + (\mu_{T^*} - \mu_T)T - \mu_{T^*}\Sigma, \\ V' &=& \pi(\Sigma - Q - T) - \mu_V V. \end{array}\right. \tag{4}$$

We propose the following Luenberger observer, find $\hat{Q}$, $\hat{T}$, $\hat{\Sigma}$, $\hat{V}$,

$$\left\{\begin{array}{rcl} \hat{Q}' &=& \lambda - (\mu_Q + \alpha)\hat{Q} + \rho\hat{T}, \\ \hat{T}' &=& \alpha\hat{Q} - (\rho + \mu_T)\hat{T} - \gamma\hat{V}\hat{T}, \\ \hat{\Sigma}' &=& (\mu_{T^*} - \mu_Q)\hat{Q} + (\mu_{T^*} - \mu_T)\hat{T} - \mu_{T^*}\hat{\Sigma} - \delta_1(\hat{\Sigma} - \Sigma), \\ \hat{V}' &=& \pi(\hat{\Sigma} - \hat{Q} - \hat{T}) - \mu_V\hat{V} - \delta_2(\hat{V} - V), \end{array}\right. \tag{5}$$

and where δ_1 and δ_2 correspond to the state gain parameters and with the initial conditions,

$$Q(0) = Q_\diamond,\ T(0) = T_\diamond,\ T^*(0) = T^*_\diamond,\ V(0) = V_\diamond.$$

It is very easy to see that the observer effect is energy-decreasing in the error defined by $\tilde{M} = M - \hat{M}$, for $M = Q, T, \Sigma, V$.
The time-sampling of the data is imposed and is different from the time-step used in the model. In order to handle the data time-sampling, two strategies are conceivable, namely, we can either use the data only when they are available, or we can rely on some time-interpolation. In this work, we interpolate linearly the corrections.

3.3 Parameter observer

We can now focus on the parameter identification identification compatible with our state estimator. We will follow the strategy proposed in [Moireau2008,Moireau2011]. This assumes

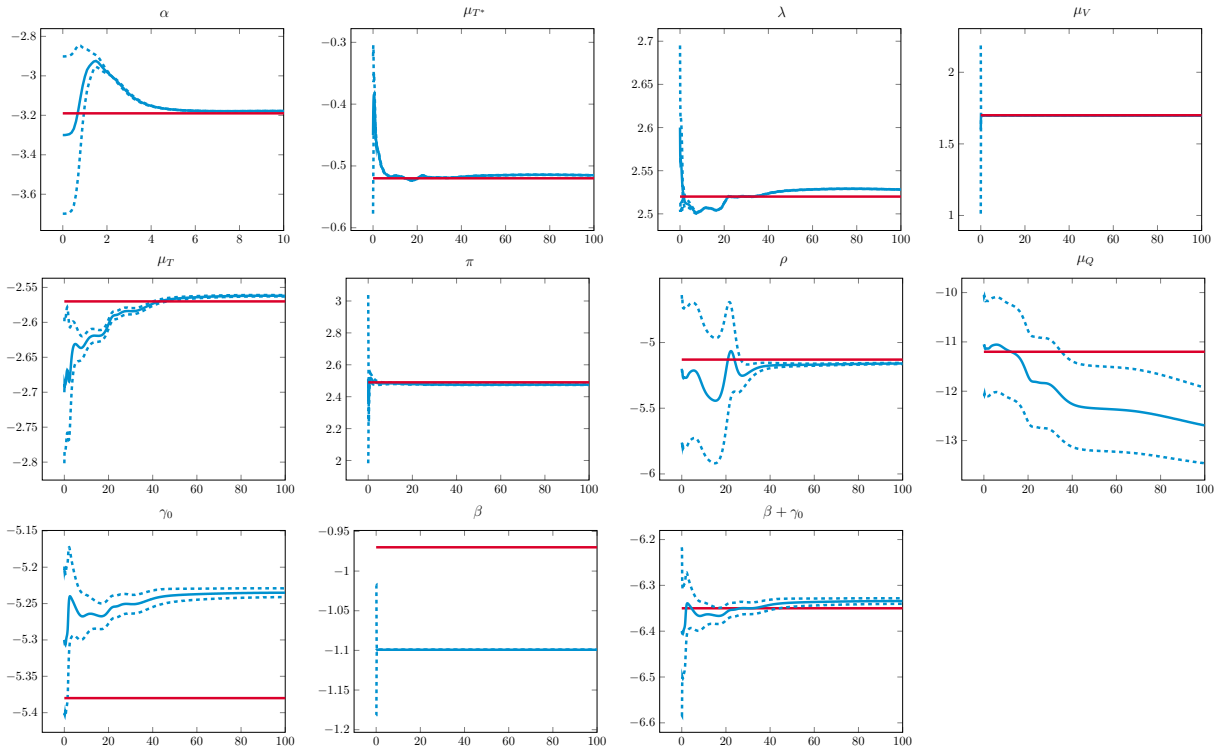


Figure 1: Estimated parameters with estimated standard deviation bands (where red represents references values). Identifiability of parameters in the Target cell model.

that an effective state observer is already available, as in our case, indeed. The uncertainties on the system trajectory are thus controlled by the state observer, hence, the overall uncertainties can then be considered to be reduced to the parameter space, where a Kalman-based filter is designed. Here, we will use a Ro-UKF (Reduced order-Unscented Kalman Filter) also called SEIK filter [Pham2001].

4 Assessment of identifiability

Structural non-identifiability is related to the model structure independent of experimental. In contrast, practical non-identifiability also takes into account the amount and quality of measured data, that was used for parameter calibration. The first advantage of data assimilation methods is that it provides a good tool for assessing identifiability of parameters. For example, Figure 4 shows a structural identifiability for γ_0 and β, while $\gamma_0 + \beta$ is identifiable. On the contrary μ_Q is practically non identifiable and could be estimated if all compartment Q, T and T^* were observed instead of their sum. We show that using the data assimilation strategy (Luenberger state observer and Kalman-based filter) for assessing identifiability is very similar to the profile likelihood methods [Raue2009].

5 Simulations and Illustrations on clinical data

We perform simulations to compare the performance the data assimilation method with NIMROD. We will discuss to what extend the Kalman-based approach is similar to a NLME-ODE approach and how we can reconstruct the concept of "random effect" in an approach which is not based on mixed effect model. Then, we perform Kalman-based and NLME-ODE estimation of parameters on two sets of data. The data of the ALBI ANRS 070 trial [Molina1999] is a three arms controlled trial, where 151 antiretroviral naive patients (with viral loads between 10,000 and 100,000 copies/ml and CD4 counts greater than 200 cells/mm3) received 24 weeks of treatment, both AZT+3TC and D4T+DDI and a combination of both were tested. The Aquitaine ANRS CO3 data [Thiebaut2000] are from an observational cohort with 3870 patients in which we investigate the effect of 35 antiretroviral treatments (AZT, DDI, 3TC, D4T, FTC, ABA, TEN, TAF, DDC, ADE, NEV, EFA, TMC, DEL, RIL, LOV, SAQ, RIT, RITB, IND, NEL, AMP, ABT, ATA, TIP, FOS, DAR, T20, MAR, RAL, ELV, DOL, FOSC, HYD, COB, FOST). We will describe the advantages and drawbacks of each method in term of 1) performances for estimation, 2) interpretation of parameters and 3) computation time.

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