MAP Estimation in Models with Random effects based on ODE :

applied to Treatment Monitoring in HIV.

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Biological background

- **HAART :** Antiretroviral are highly active in developed countries but many adverse effects exist
- **Life expectancy improved :** for HIV infected patients $\sim$ 35 years
- **Individualized monitoring of treatment is of interest :**
  - to improve quality of life,
  - to improve patient adherence to treatment.

Brief state of the art and objectives

- **ODE modeling for HIV :** understand the interaction between the virus and the immune system [Perelson96]
- **Non-Identifiability :** potentially due to insufficient experimental data [Guedj07, Raue12]
- **Bayesian Estimation :** MCMC (Gibbs Sampler and Metropolis-Hasting algorithm) takes a lot of time[Wu05, Huang06]

  → We propose a MAP estimation in ODE systems with random effects.

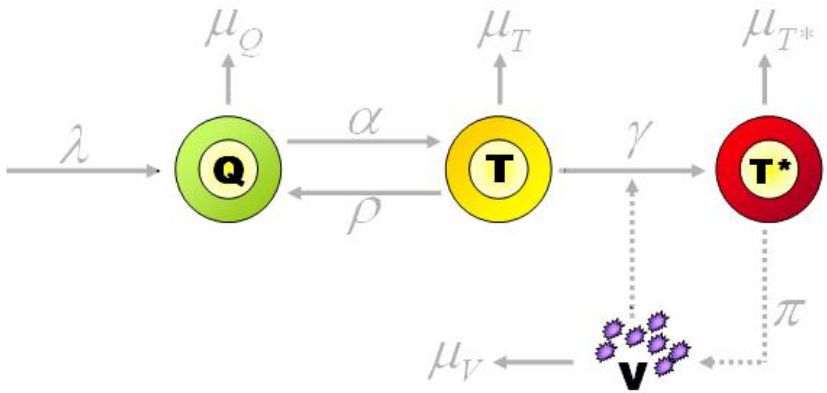
- **Optimal control :** link dose and effect to control a medical outcome [Kirschner97]

  → We propose a dose individualization strategy without specifying a cost function

Modelling

Biological Model : Dynamical System (1)

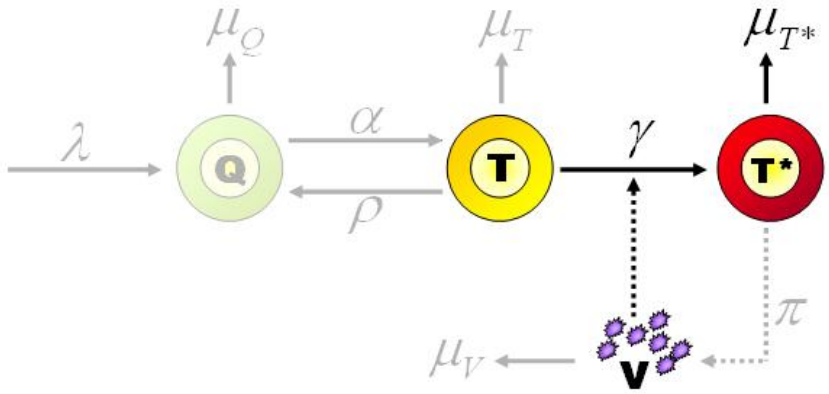
Biological Compartments



Compartment	Meaning
Q	Quiescents CD4
T	Activated CD4
T^*	Activated Infected CD4
V	Virus

Biological Model : Dynamical System (2)

T^* cells (infected CD4) dynamics

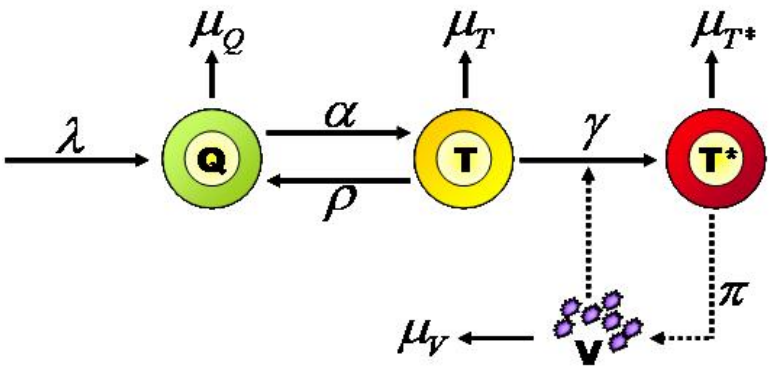


$$\frac{dT^*}{dt} = \gamma V T - \mu_{T^*} T^*$$

Parameter	Meaning
μ_{T^*}	Death rate of T^* cells
γ	Infectivity : Infection rate of T cells by virus

Biological Model : Dynamical System (3)

Activated T cells model



$$\begin{cases} \frac{dQ}{dt} &= \lambda - \mu_Q Q - \alpha Q + \rho T \\ \frac{dT}{dt} &= \alpha Q - \rho T - \mu_T T - \gamma V T \\ \frac{dT^*}{dt} &= \gamma V T - \mu_{T^*} T^* \\ \frac{dV}{dt} &= \pi T^* - \mu_V V \end{cases}$$

Statistical and observational model

Statistical Model : Mixed Effects Model
Individual variability and Pharmacodynamics

$$
\begin{aligned}
\tilde{\xi}^i &= \left(\tilde{\alpha}^i, \tilde{\lambda}^i, ..., \tilde{\gamma_0}^i, \tilde{\mu}_V^i\right) \\
\tilde{\xi}_l^i &= \underbrace{\phi_l + d_l^i(t)\beta_l}_{\text{Fixed effects}} + \underbrace{\omega_l^i(t)u_l^i}_{\text{Random effects}} \\
u^i &\sim \mathcal{N}(0, I_q)
\end{aligned}
$$

Observational Model

$$
\begin{aligned}
\text{Viral Load :} \quad & Y_{ij1} = \log_{10}(V) + \epsilon_{ij1} \\
\text{Total CD4 count :} \quad & Y_{ij2} = (Q + T + T^*)^{0.25} + \epsilon_{ij2} \\
& \epsilon_{ijm} \sim \mathcal{N}(0, \sigma_m^2)
\end{aligned}
$$

→ At least 16 parameters to estimate.

Penalization

Priors specification

- Fixed effects and treatment effects (ϕ and β) :
  $\longrightarrow$ Informative Normal law $\sim \mathcal{N}(\mathbb{E}, \mathbb{V})$

- Random effects (I_q) :
  $\longrightarrow$ Semi-Informative Half-Cauchy [Gelman06]

$$\pi(x) = \frac{1}{(x^2 + \text{median}^2)}$$

- Measurement errors (σ_{VL} and σ_{CD4}) :
  $\longrightarrow$ Non-informative Jeffreys-like priors ($\pi(\sigma) = 1/\sigma$)

Penalization $J(\theta)$ **:** sum of the log of these priors.

Algorithm

Estimation Algorithm : Newton-Raphson like

→ Log-Likelihood Computation

$$L^P_{\mathcal{O}}(\theta_k) = \sum_{i \leq n} L_{\mathcal{O}_i}(\theta_k) - J(\theta_k)$$

→ RVS : Robust Variance Scoring [Commenges06, Guedj08]

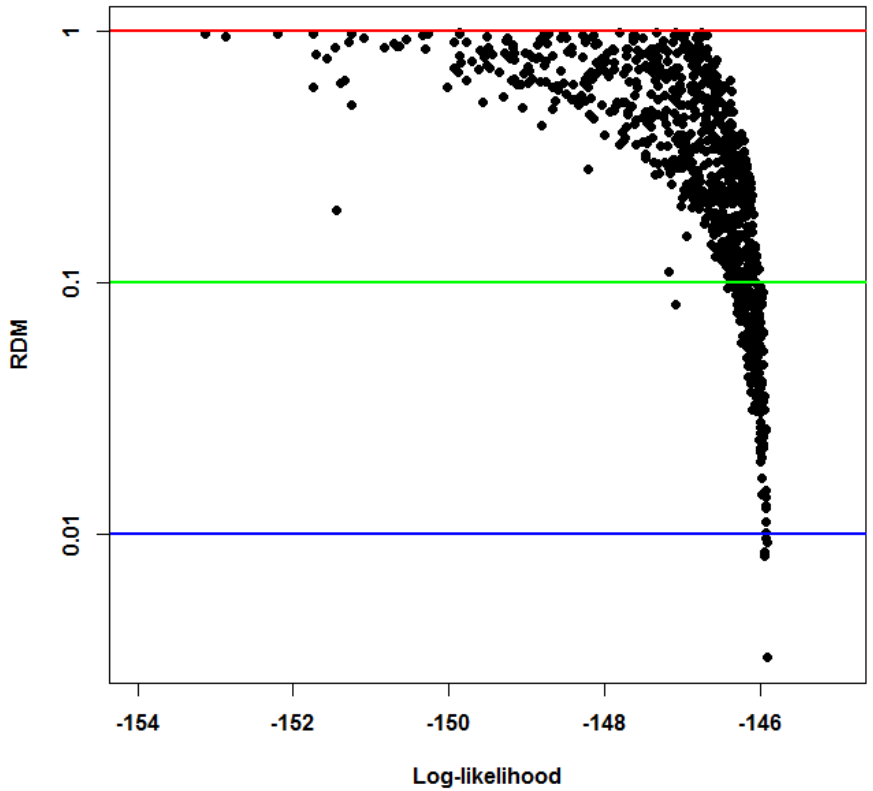
$$U_{\mathcal{O}_i}(\theta_k) = \frac{\partial L^P_{\mathcal{O}_i}}{\partial \theta}|_{\theta_k} - \frac{\partial J(\theta)}{\partial \theta}|_{\theta_k}$$

$$H(\theta_k) \approx G(\theta_k) = \sum_{i \leq n} \left(U_{\mathcal{O}_i}(\theta_k) U'_{\mathcal{O}_i}(\theta_k) \right) + \frac{\nu}{n} U(\theta_k) U'(\theta_k) - \frac{\partial^2 J(\theta)}{\partial \theta^2}|_{\theta_k}$$

Estimation Algorithm : Convergence criteria

→ RDM : Relative distance to Maximum [Commenges06]

$$rdm_k = \frac{U(\theta_k)G^{-1}(\theta_k)U'(\theta_k)}{m} << 1$$



EMRODE : Estimation in Models with Random effects based on Ordinary Differential Equations

→ MPI parallelization [1] to optimize computation time.

- 149 pat. 20 parameters - lasted ~ 21 days → ~ 7 hours.
- 27 pat. 17 parameters - lasted ~ 5 hours → 15 minute.
- 39 pat. 8 parameters - lasted ~ 30 minutes → < 1 minute.

→ **Fortran program EMRODE :**

- **Version 1.0 available from 1^{st} July 2012 on request. (melanie.prague@isped.u-bordeaux2.fr)**

1. Mésocentre de Calcul Intensif Aquitain

Dose individualisation

ODE equilibrium $\longrightarrow$ critical dose $\longrightarrow$ optimal dose

$\longrightarrow$ **Equilibrium in ODE :**

- $(\bar{Q}, \bar{T}, \bar{T^*}, \bar{V}) \quad | \quad \frac{dQ}{dt} = 0; \frac{dT}{dt} = 0; \frac{dT^*}{dt} = 0; \frac{dV}{dt} = 0$
- **Reproductive number :** $R_0 = \frac{\pi\alpha\lambda\gamma_0 \exp^{\beta\psi(d(t))}}{\mu_V \mu_{T^*}(\alpha\mu_T + \rho\mu_Q + \mu_T\mu_Q)}$
- $R_0 > 1$: non trivial equilibrium ($\bar{V} \neq 0$ and $\bar{T^*} \neq 0$)
- $R_0 <= 1$: trivial equilibrium ($\bar{V} \longrightarrow 0$ and $\bar{T^*} \longrightarrow 0$)

$\longrightarrow$ **Critical dose :**

- Find $R_0(\tilde{\xi}^i, d^i_{crit}) = 1$

$\longrightarrow$ **Optimal dose knowing $\mathcal{H}^i_{t_k}$:**

- MCMC Metropolis-Hasting update of $\tilde{\xi}^i$.
- Control the probability that $R_0 <= 1$.

$$(d_{opt})_{t_k} | \quad \mathbb{P}\left(R0(\tilde{\xi}^i, (d_{opt})_{t_k}) < 1 \middle| \mathcal{H}^i_{t_k} \right) = \omega$$

ODE equilibrium $\longrightarrow$ critical dose $\longrightarrow$ optimal dose

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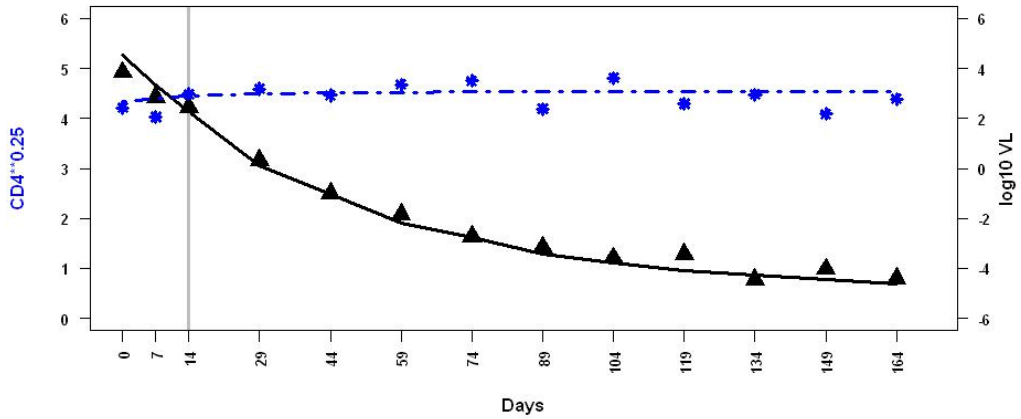
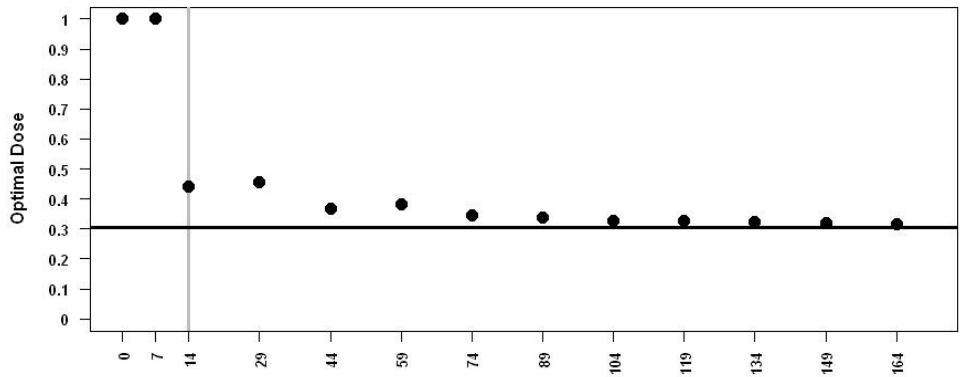
Mathematical hypothesis of convergence and simulations

- **Asymptotically :**
  - If t_k and t_{k+1} enough spaced so that $(\bar{Q}, \bar{T}, \bar{T}^*, \bar{V})$ are reached.
  - If information increases $\mathcal{H}^i_{t_0} \subset \mathcal{H}^i_{t_1} \subset ... \subset \mathcal{H}^i_{t_\infty}$

$$(d_{opt})_{t_k} \rightarrow d_{crit}$$

- **In simulation : This is a Proof of concept**





Conclusion

- **Future Prospects :**
  - EMRODE - Make a User-friendly application or a R package ;
  - Increase the number of random effects estimated ;
  - Information synthesis of many clinical trials ;
- **If you were interested :**
  - M. Prague, D. Commenges, J. Drylewicz, R. Thiébaut, *Treatment monitoring of HIV infected patients based on mechanistic models*. (Biometrics to appear 2012)

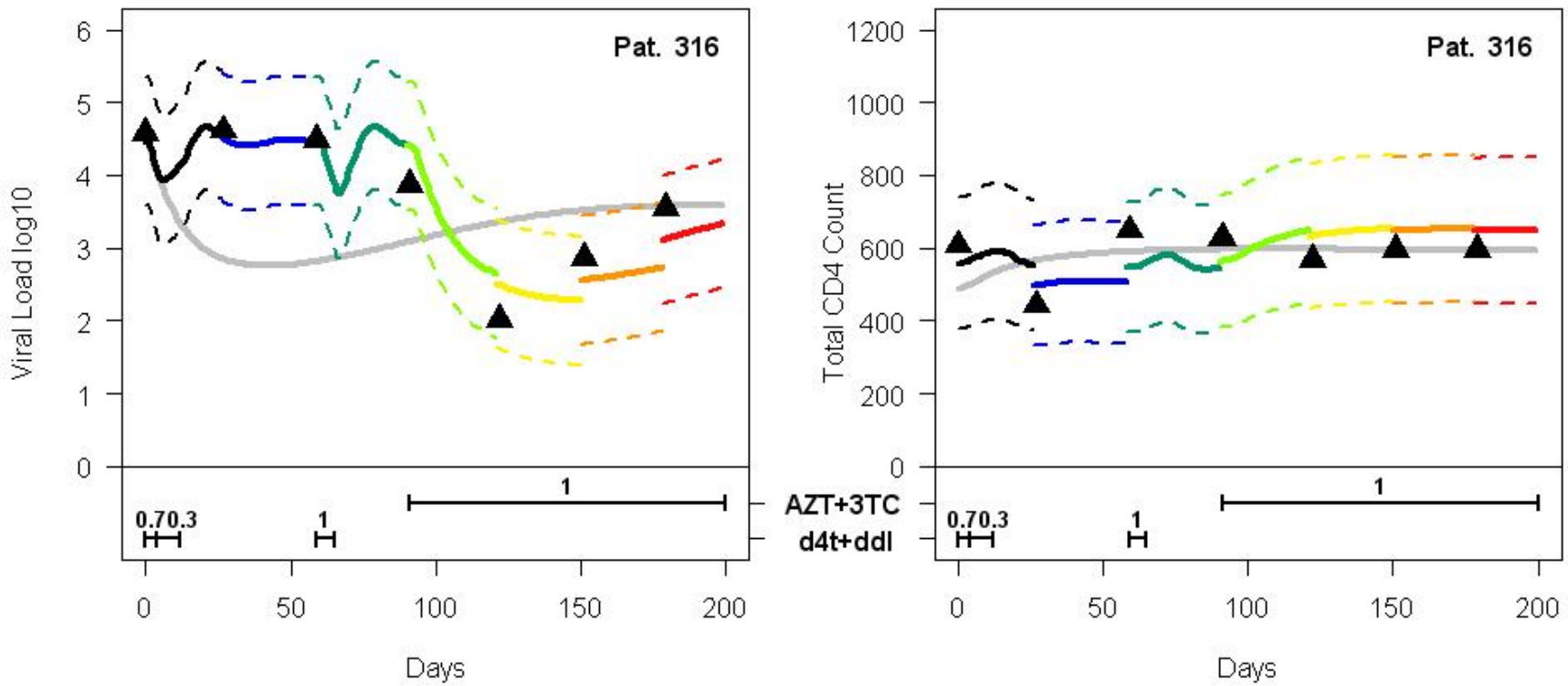
Reference

- **[Perelson96]**, HIV-1 dynamics in vivo : virion clearance rate, infected cell life-span, and viral generation time. (Science)
- **[Guedj10]**, Practical identifiability of HIV dynamics models. (Bull. of math. biol.)
- **[Raue12]**, Joining Forces of Bayesian and Frequentist Methodology : A Study for Inference in the Presence of Non-Identifiability. (arXiv)
- **[Wu05]**, Statistical methods for HIV dynamic studies in AIDS clinical trials. (Stat. Meth. in Med. research)
- **[Huang06]**, Hierarchical Bayesian methods for estimation of parametersin a longitudinal HIV dynamic system. (Biometrics)
- **[Kirschner97]**, Optimal control of the chemotherapy of HIV. (J. of math. biol.)
- **[Commenges06]**, A newton-like algorithm for likelihood maximization : The robust-variance scoring algorithm. (ArXiv)
- **[Marquardt63]**, An algorithm for least-squares estimation of nonlinear parameters. (J. of the soc. for Industrial and Applied Math.)
- **[Guedj08]**, Maximum likelihood estimation in dynamical models of HIV. (Biometrics)
- **[Gelman06]**, Prior distributions for variance parameters in hierarchical models. (Bayesian Analysis)

Discussion

Thank you ! Questions ?

Prediction abilities on ALBI clinical trial



We are able to predict the Viral load and CD4 count trajectories for patients who change treatment dose and molecule.