GDR MaMoVi 2017

Parameter estimation in Models with Random effects based on Ordinary Differential Equations: A bayesian maximum a posteriori approach.

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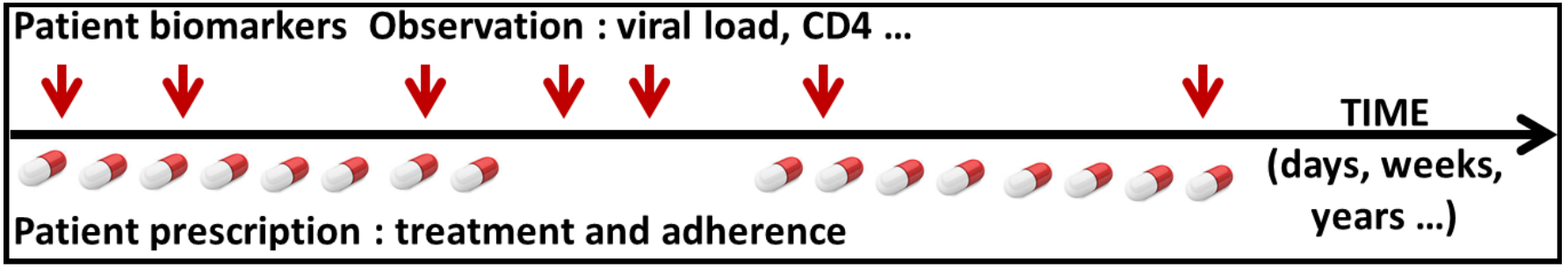
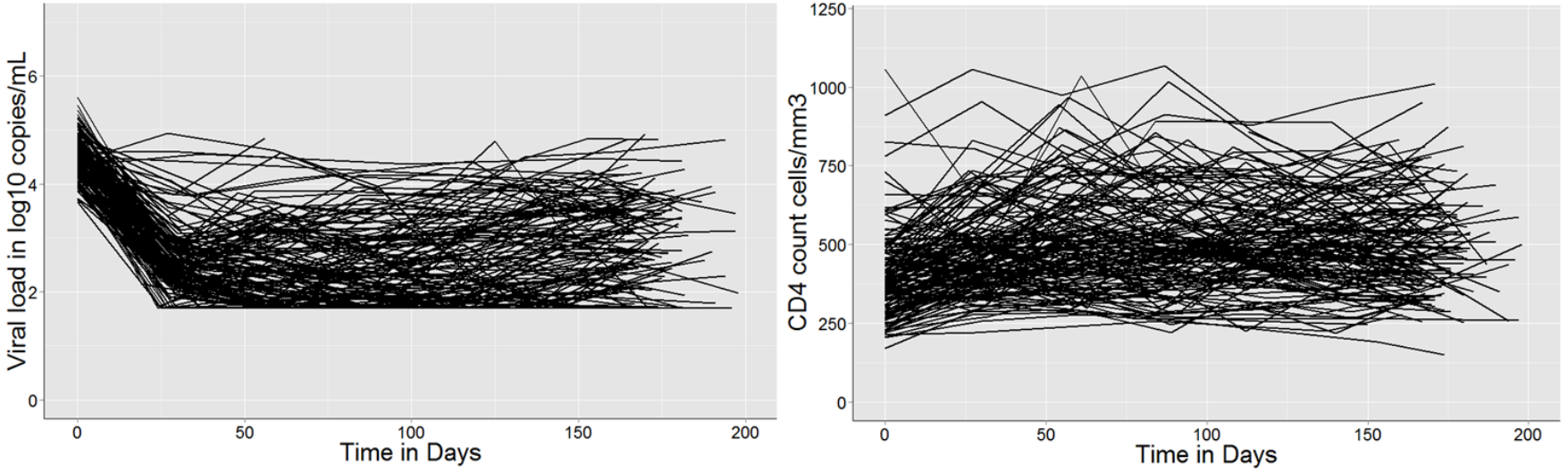
Non Linear mixed effects ordinary differential equations models

Available

→ Data come from clinical trials and observational studies

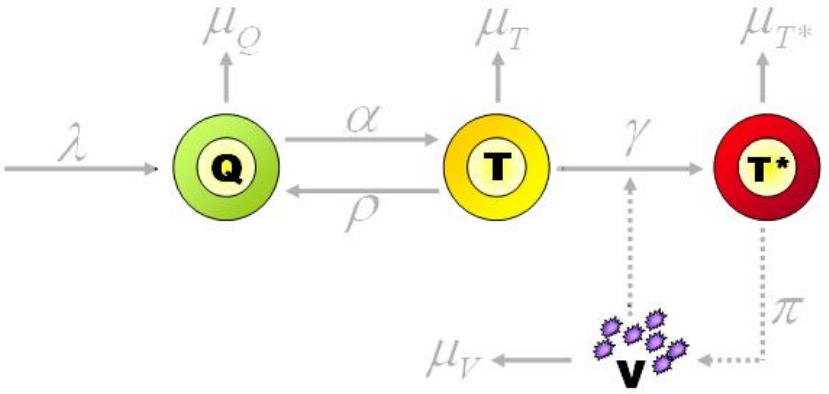


→ Longitudinal data Y_{iik} : patient i, time j and biomarker k



Mathematical Model for mechanistic models

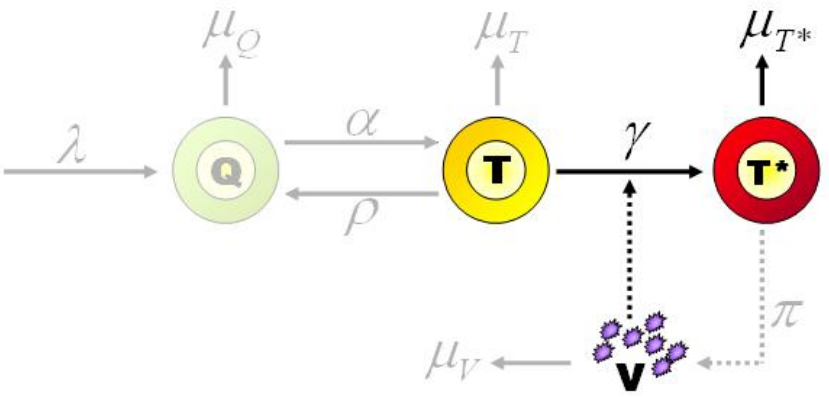
Compartiments Biologiques



Compartiment	Signification
Q	CD4 Quiescents
T	CD4 Activés
T^*	CD4 Activés Infectés
V	Virions

Mathematical Model for mechanistic models

Dynamique des cellules T^* (CD4 infectés)

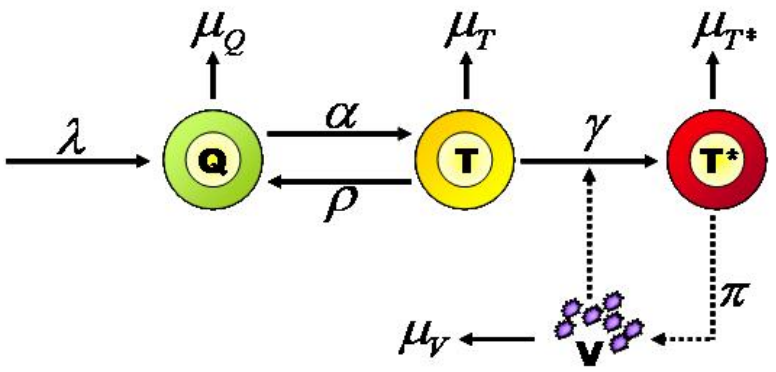


$$\frac{dT^*}{dt} = \gamma VT - \mu_{T^*} T^*$$

Paramètre	Signification
μ_{T^*}	Taux de décès des cellules T^*
γ	Infectivité : Taux d'infection des cellules T par les virions

Mathematical Model for mechanistic models

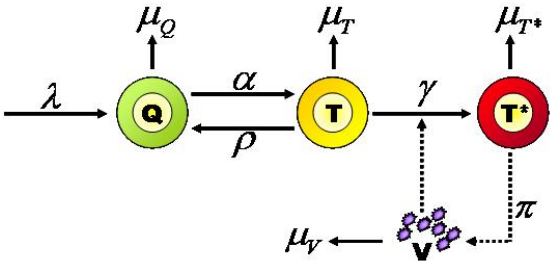
Target cells model



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

Statistical Model for mechanistic models

Target cells model



Mixte effects models on parameters

$$\tilde{\xi}^i = \left(\tilde{\alpha}^i, \tilde{\lambda}^i, ..., \tilde{\gamma_0}^i, \tilde{\mu}_V^i\right)$$

$$\tilde{\xi}_l^i = \underbrace{\phi_l + z_l^i(t)\beta_l}_{\text{Effets fixes}} + \underbrace{\omega_l^i(t)u_l^i}_{\text{Effets aléatoires}}$$

$$u^i \sim \mathcal{N}(0, I_q)$$

Observational Model for mechanistic models

Among,

$$X(t_{ij}, \tilde{\xi}^i) = (Q(t_{ij}, \tilde{\xi}^i), T(t_{ij}, \tilde{\xi}^i), T^*(t_{ij}, \tilde{\xi}^i), V(t_{ij}, \tilde{\xi}^i))$$

We only observe (with measurement errors):

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

Donc,

$$\begin{aligned} g_1(.) &= \log_{10}(.) \\ g_2(.) &= (.)^{0.25} \end{aligned}$$

Parameters of interest

We want to estimate more than 15 parameters:

$$\theta = \{\underbrace{\lambda, \mu_Q, \alpha, \rho, \mu_T, \gamma\pi, \mu_{T^*}, \mu_V}_{\text{Effet fixes}}, \underbrace{\beta_1, \ldots, \beta_r}_{\text{Covariates effects}} , \underbrace{\sigma_1, \ldots, \sigma_s}_{\text{Random effects}} , \underbrace{\Sigma_1, \ldots, \Sigma_k}_{\text{Measurement errors}} \}$$

→ There are sometimes problems of identifiability [1]

→ This approach is unbiased more efficient than marginal structural models in presence of dynamic treatment regimens [2]

[1] [1] Guedj et al. (2010), Bull. Math. Biol.
[2] [2] Prague et al. (2016), Biometrics.

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Bayesian penalised likelihood estimation

Existing methods

Method	Ref.	Software
Non parametric Functional analysis	[Ramsay et al. 2012]	-
Non Bayesian parametric FOCE	[Pinheiro et Bates 1995]	R
Bayesian SAEM	[Kuhn et al. 2005 Lavielle et al. 2007]	MONOLIX
Bayesian MCMC	[Lunn et al 2000 Huang et al. 2011]	WinBUGS
Bayesian penalized likelihood	[Guedj et al 2007; Prague et al. 2013]	NIMROD[3]

[3] [3] Prague et al. (2013), Comp. Meth. and Prog. in Biomed.

Penalization for the log-likelihood

It is possible to have an approximate idea of the value of biological parameters and treatment effects, for example from previous in vitro experiment or analysis of studies.

Normal approximation of the posterior of previous analysis can be used as new prior for analysis as in a sequential bayesian meta-analysis[4]:

$$
\begin{aligned}
J(\theta) \quad = \quad & \sum_{j=1}^{9} \frac{\left\{\phi_j - \mathrm{E}^0(\phi_j)\right\}^2}{\sqrt{\mathrm{var}^0(\phi_j)}} \\
& + \sum_{j=1}^{n_{TRT}} \frac{\left\{\beta_j - \mathrm{E}^0(\beta_j)\right\}^2}{\sqrt{\mathrm{var}^0(\beta_j)}}
\end{aligned}
$$

[4] [4] Prague et al. (2016) Journal de la statistique francaise

Penalized likelihood computation (1)

→ Individual likelihood (censorship $\delta_{ij} = I_{Y_{ij1}<\zeta}$)

$$
\begin{aligned}
L_{\mathcal{F}_i|u^i} \quad = \quad & \prod_{j,1} \left\{ \frac{1}{\sigma_1\sqrt{(2\pi)}} \exp\left[-\frac{1}{2} \left(\frac{Y_{ij1} - g_1(X(t_{ij}, \tilde{\xi}^i))}{\sigma_1} \right)^2 \right] \right\}^{1-\delta_{ij}} \\
& * \left\{ \Phi\left(\frac{\zeta - g_1(X(t_{ij}, \tilde{\xi}^i)}{\sigma_1} \right) \right\}^{\delta_{ij}} \\
& \prod_{j,2} \frac{1}{\sigma_2\sqrt{(2\pi)}} \exp\left[-\frac{1}{2} \left(\frac{Y_{ij2} - g_2(X(t_{ij}, \tilde{\xi}^i))}{\sigma_2} \right)^2 \right]
\end{aligned}
$$

→ Φ Repartition function of a Normal law.

→ ODE Solver (dlsode Fortran) - [Radhakrishnan et Hindmarsh (1993)]

Penalized likelihood computation (2)

- Observed individual likelihood

$$L_{\mathcal{O}_i} = \int_{\mathbb{R}^q} L_{\mathcal{F}_i|u^i}(u)\phi(u)du,$$

with $\phi \sim \mathcal{N}(0, I_q)$

→ Numerical integration: Adaptive Gaussian Quadrature [Genz et Keister (1996)]

- Penalized log-Likelihood

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

→ Parallel computing: Each computation $L_{\mathcal{O}_i}$ are independent.

Robust-Variance Scoring (RVS)

We use a Newton-Raphson-like algorithm to maximize the penalized likelihood.

Score computation (Gradients approximation)

$$U_{\mathcal{O}}(\theta_k) \quad = \quad \sum_{i=1}^{n} \left(\frac{\partial L^{P}_{\mathcal{O}_i}}{\partial \theta} |_{\theta_k} \right)$$

- $\rightarrow$ ODE solver (dlsode Fortran)
- $\rightarrow$ Sensitivity Equation of ODE systems
- $\rightarrow$ Adaptive Gaussian Quadrature
- $\rightarrow$ Parallel computing

Robust-Variance Scoring (RVS)

Computation of G (Approximation of the Hessian H)

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

$\rightarrow$ Switch to a Marquardt-Levenberg algorithm [Marquardt, JSIAM, 1963] when the RVS algorithm does not provide maximization for multiple iterations.

Convergence criteria

Stabilization of parameters estimates :

$$|\theta_{(k+1)} - \theta_k| < \eta_1$$

Stabilization of log-likelihood :

$$|L^P_{\mathcal{O}}(\theta_{(k+1)}) - L^P_{\mathcal{O}}(\theta_k)| < \eta_2$$

Relative Distance to Maximum (main) :

$$RDM(\theta_k) = \frac{U(\theta_k)G^{-1}(\theta_k)U'(\theta_k)}{m} < \eta_3$$

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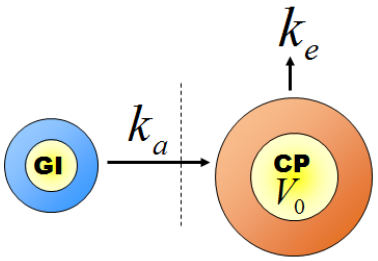
Some Illustration

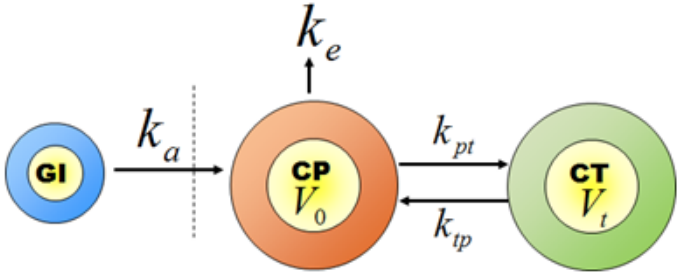
Example in pharmacokinetics

Pharmacokinetics model 1 compartment:



$$\begin{cases} \frac{dA_{GI}}{dt} &= -k_a A_{GI}, \\ \frac{dA_P}{dt} &= k_a A_{GI} - k_e A_P. \end{cases}$$

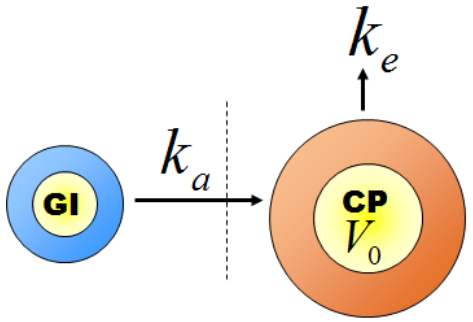
Pharmacokinetics model 2 compartments:



$$\begin{cases} \frac{dA_{GI}}{dt} &= -k_a A_{GI}, \\ \frac{dC_P}{dt} &= \frac{k_a}{V_0} A_{GI} - k_e C_P - k_{PT} C_P + \frac{k_{TP}}{V_0} C_T, \\ \frac{dC_T}{dt} &= \frac{k_{PT}}{V_T} C_P - k_{TP} C_T. \end{cases}$$

Label	Name
GI	Gastro-intestinal tract
CP	Plasma compartment
GT	Tissue compartment

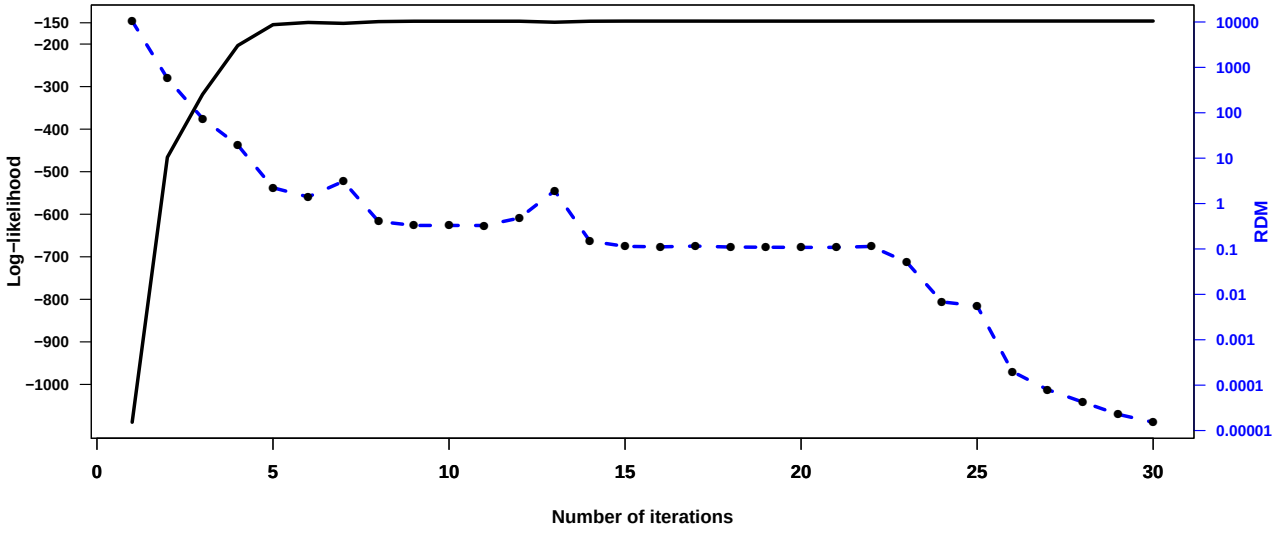
Simulations

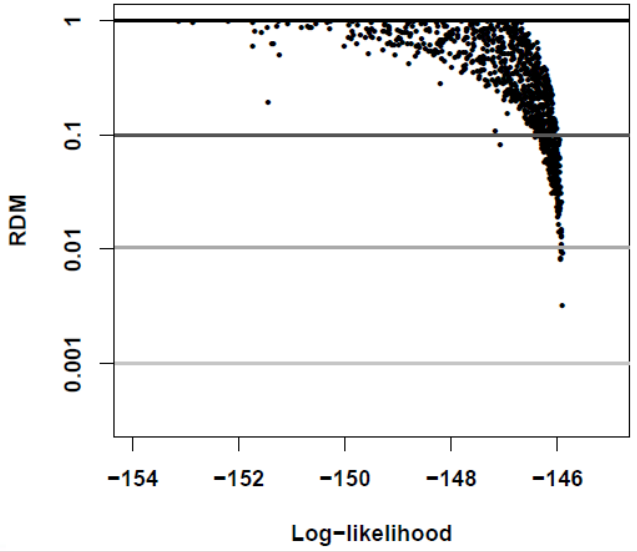


- FOCE is not stable and less accurate (Laplace integration)
- MCMC is more computationally demanding than NIMROD
- NIMROD gives more efficient results than MCMC
- NIMROD sometimes achieve estimation where MCMC fails

	Failure (%)	Time (s)	Empirical SE	Overall Abs. Bias	Overall RMSE
FOCE	52	0.5	0.183	0.202	0.281
MCMC	0	233	0.174	0.060	0.195
NIMROD	0	109	0.060	0.060	0.092

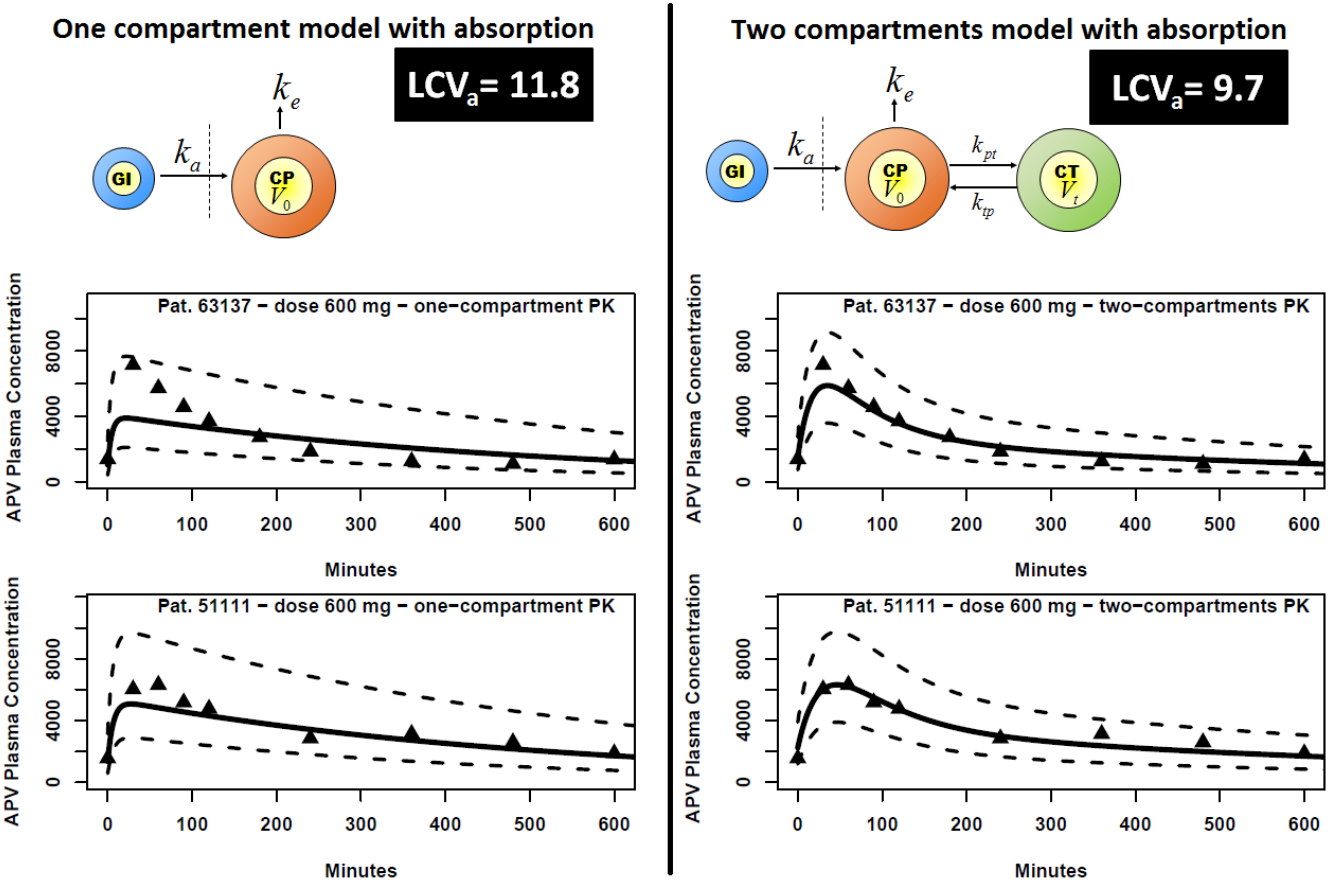
Properties of RDM





Real Data: The PUZZLE study [Raguin et al. 2004]

- Explain the 600 mg Amprenavir (APV) concentrations in blood (A_{C_P}) in 39 HIV infected patients
- Longitudinal data $\{0, 1/2, 1\ 1/2, 2, 3, 4, 6, 8, 10\}$ hours



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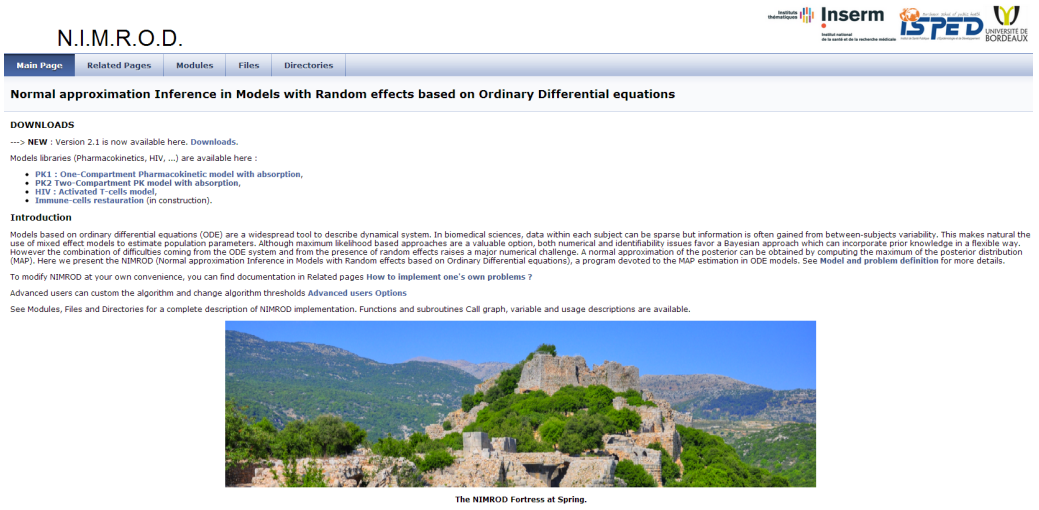
Conclusion

Existing and perspectives

- **www.isped.u-bordeaux2.fr/NIMROD/documentation.aspx**



- **Increase the dimension of the mechanistic models:** Limited number of inter-individual variability (random effects).
- **Investigate alternative algorithms:** Explore Kalman filters.

References

1. Guedj, J., Thiébaut, R., and Commenges, D. (2010). Practical identifiability of HIV dynamics models. Bulletin of mathematical biology, 69(8), 2493-2513.
2. Prague, M., Commenges, D., Gran, J. M., Ledergerber, B., Young, J., Furrer, H., and Thiébaut, R. (2016). Dynamic models for estimating the effect of HAART on CD4 in observational studies: Application to the Aquitaine Cohort and the Swiss HIV Cohort Study. Biometrics, 73(1), 294-304.
3. Prague M., Commenges D., Guedj J., Drylewicz J., Thiébaut R. (2013) NIMROD: A Program for Inference via Normal Approximation of the Posterior in Models with Random effects based on Ordinary Differential Equations. Computer methods and Programs in Biomedecine 111(2) 447-458
4. Prague M. (2016) Dynamical modeling for Optimization of treatment in HIV infected patients. Invited paper in Statistical French Society journal. 157(2), 19-38

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