Toward information synthesis with mechanistic models of HIV dynamics.

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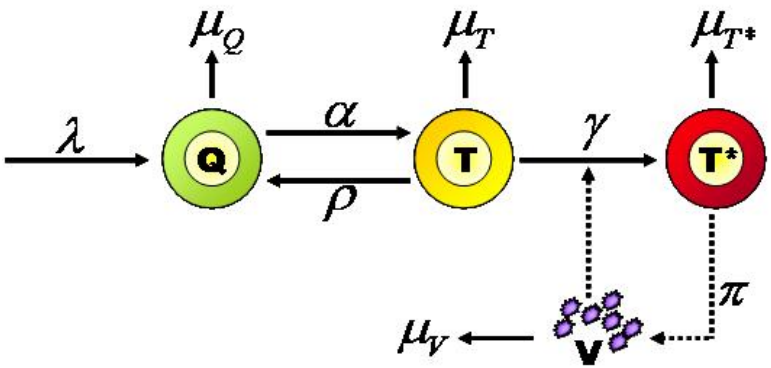
Brief state of the art

- **ODE modeling for HIV :** understanding the interaction between the virus and the immune system [Perelson96].

Biological Model : Dynamical System

Activated T cells model



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

Brief state of the art

- **ODE modeling for HIV :** understanding the interaction between the virus and the immune system [Perelson96].
- **Random effects :** accounting for inter individual variability in parameters [Wu05] and allowing the use of longitudinal data.

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.

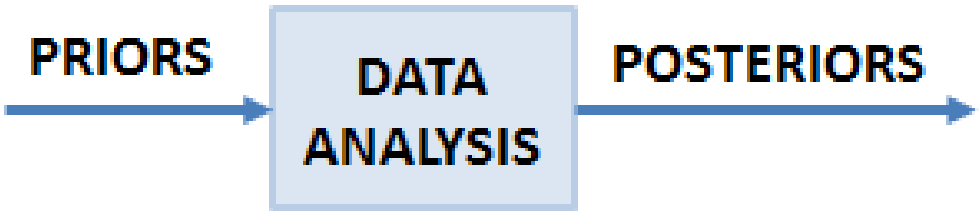
Brief state of the art

- **ODE modeling for HIV :** understand the interaction between the virus and the immune system [Perelson96].
- **Random effects :** account for inter individual variability in parameters [Wu05] and allow use of longitudinal data.
- **Non-Identifiability :** potentially due to insufficient experimental data [Guedj10, Raue12].
- **Bayesian Estimation :** MCMC (Gibbs Sampler and Metropolis-Hasting algorithm) takes a lot of time [Huang06].

NIMROD (Normal approximation Inference in Models with Random effects based on Ordinary Differential equations)

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

→ **Fortran program NIMROD** : Version 1.0 is available on request (melanie.prague@isped.u-bordeaux2.fr).



Objectives

Questions raised

- How realistic is it to assume that parameters have an intrinsic meaning over studies ?
- Does the normal approximation of the posterior give consistent results when sequentially pooling the data ?
- Does information synthesis increase the model fit and prediction abilities ?

Intrinsic meaning of the Parameters

Two available studies : ALBI and PUZZLE

ALBI : 150 patients

- Untreated patients starting dual nucleosides therapy
- 3 groups of treatment (AZT+3TC ; d4T+ddI ; switch)

PUZZLE : 40 patients

- Heavily pre-treated patients starting salvage therapy
- APV + LPV + RTV + peripheral treatments

Data available & used :

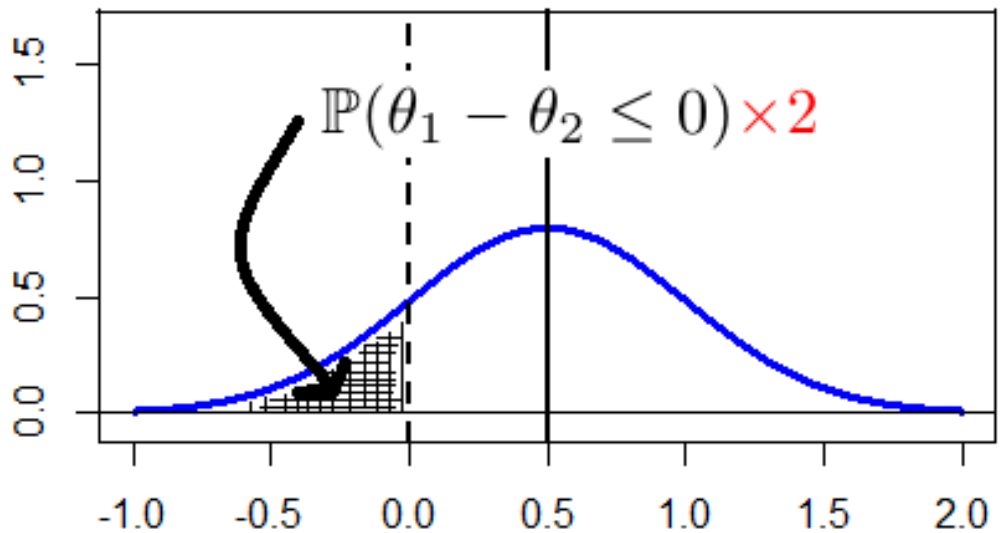
Viral load, CD4 count, Treatment (stated and self-reported).

"Bayesian" p-value

For each parameter, we assess the difference of the posterior in term of "Bayesian" p-value.

Let $\theta_1 \geq \theta_2$ and $(\theta_1 \perp \theta_2)$

$$\begin{aligned} \theta_1 &\sim \mathcal{N}(\mu_1; \sigma_1^2) \\ \theta_2 &\sim \mathcal{N}(\mu_2; \sigma_2^2) \\ \theta_1 - \theta_2 &\sim \mathcal{N}(\mu_1 - \mu_2; \sigma_1^2 + \sigma_2^2) \end{aligned}$$



Posterior of $\theta_1 - \theta_2$.

Separate analysis of ALBI and PUZZLE

	PRIOR		POSTERIORS				
	BIBLIOGRAPHY		ALBI		PUZZLE		Bp-value
	Mean	sd.	Mean	sd.	Mean	sd.	
α	-4.00	2.00	-4.90	0.34	-4.73	0.63	0.82
μ_{T*}	-0.05	0.68	-3.13	0.19	-3.08	0.38	0.91
λ	**2.55**	**1.90**	**0.32**	**0.38**	**-2.22**	**0.64**	**0.01**
μ_T	-2.59	0.34	-2.82	0.33	-2.96	0.34	0.78
π	**4.04**	**2.66**	**0.716**	**0.79**	**5.00**	**1.21**	**0.00**
ρ	-4.34	1.38	-1.43	0.65	1.88	1.26	0.02
γ_0	-5.76	4.02	-2.51	0.60	-4.13	1.38	0.28
μ_Q	-9.00	1.00	-8.92	0.99	-10.4	0.99	0.30
μ_V	2.90	0.68	3.31	0.66	2.55	0.66	0.41
$\sigma_{\mu_{T*}}$	0.37	-	0.33	0.04	1.04	0.42	0.00
σ_λ	0.10	-	0.40	0.06	1.42	0.56	0.09
σ_{CV}	-	-	0.85	0.03	0.90	0.05	0.33
σ_{CD4}	-	-	0.22	0.04	0.29	0.03	0.13

Differences of parameters between ALBI and PUZZLE patients in mechanistic model of HIV in log-transformation.

Bayesian pooling methodology

Information synthesis

Global Pooling :

Sequential Pooling :

Do these approaches have the same result ?

Information synthesis

We cut ALBI study into 3 sub-studies of different sizes :

→ A (50 pat.), B (25 pat.) et C (74 pat.)

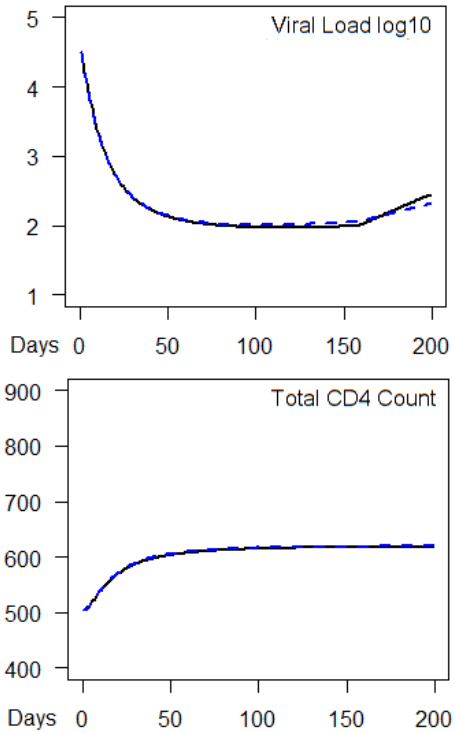
- **Log-likelihood at parameters posterior mode comparison :**

	Global Pooling	Sequential Pooling		
	Study A+B+C	Study A	Study B	Study C
Prior	Bibliography	Bibliography	Prior A	Prior B (Prior A)
LL	-1066.5	-418.0	-171.7	-477.6
			= -1067.3	

Information synthesis

- **Comparison of the modes of the posteriors :**

	POSTERIORS MODE	
	Global Pooling	Sequential pooling
	Mean	Mean
α	-3.80	-3.54
μ_{T^*}	-1.04	-0.95
λ	2.02	2.01
μ_T	-3.07	-3.11
π	3.94	3.84
ρ	-5.74	-4.99
γ_0	-6.05	-6.06
μ_Q	-8.98	-8.92
μ_V	3.00	3.05
$\sigma_{\mu_{T^*}}$	0.26	0.24
σ_λ	0.25	0.23
σ_{CV}	0.58	0.50
σ_{CD4}	0.20	0.20



Application

Pooled estimation : ALBI then PUZZLE

No pooling, we analysed roughly PUZZLE :

- Log-Likelihood PUZZLE with Priors from bibliography : -453.8

Sequential pooling, we analysed ALBI then PUZZLE :

- Log-Likelihood PUZZLE with ALBI posteriors as Priors : -430.1

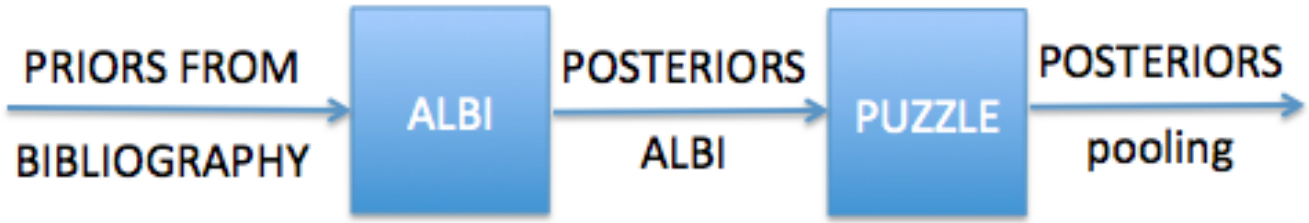
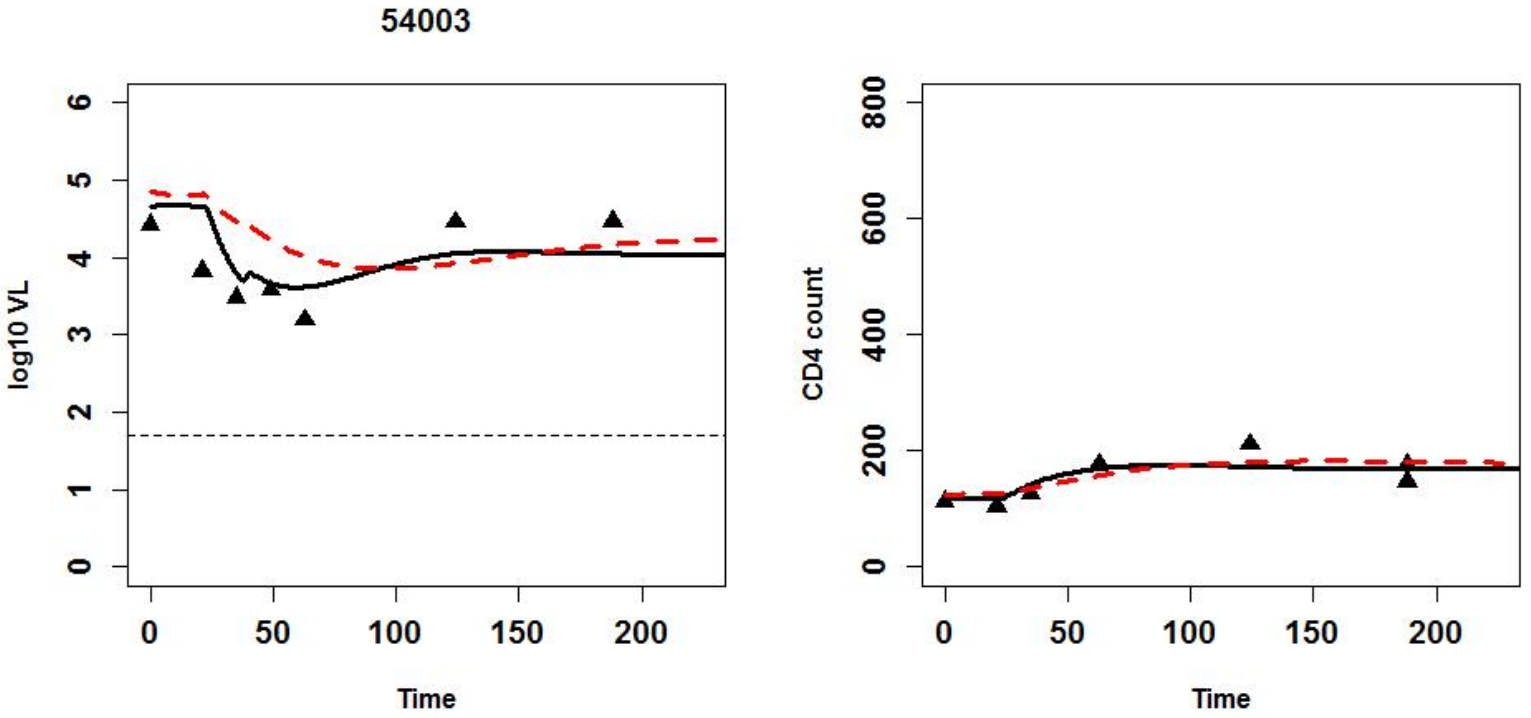


Illustration of information increase on a patient



Fits on PUZZLE for a random patient.

Red dashed line : No pooling - Priors from bibliography ;
Black plain line : Sequential pooling - ALBI posteriors as Priors.

Conclusion

- **Proposed methodology**
  - Analyze various studies to identify parameters with inter-study variability.
  - Sequentially pool only for parameters which do not differ among studies.

- **Further concerns**
  - Find a proper penalization to account for different parameters values among studies.
  - The Pharmacodynamic function must be carefully defined.

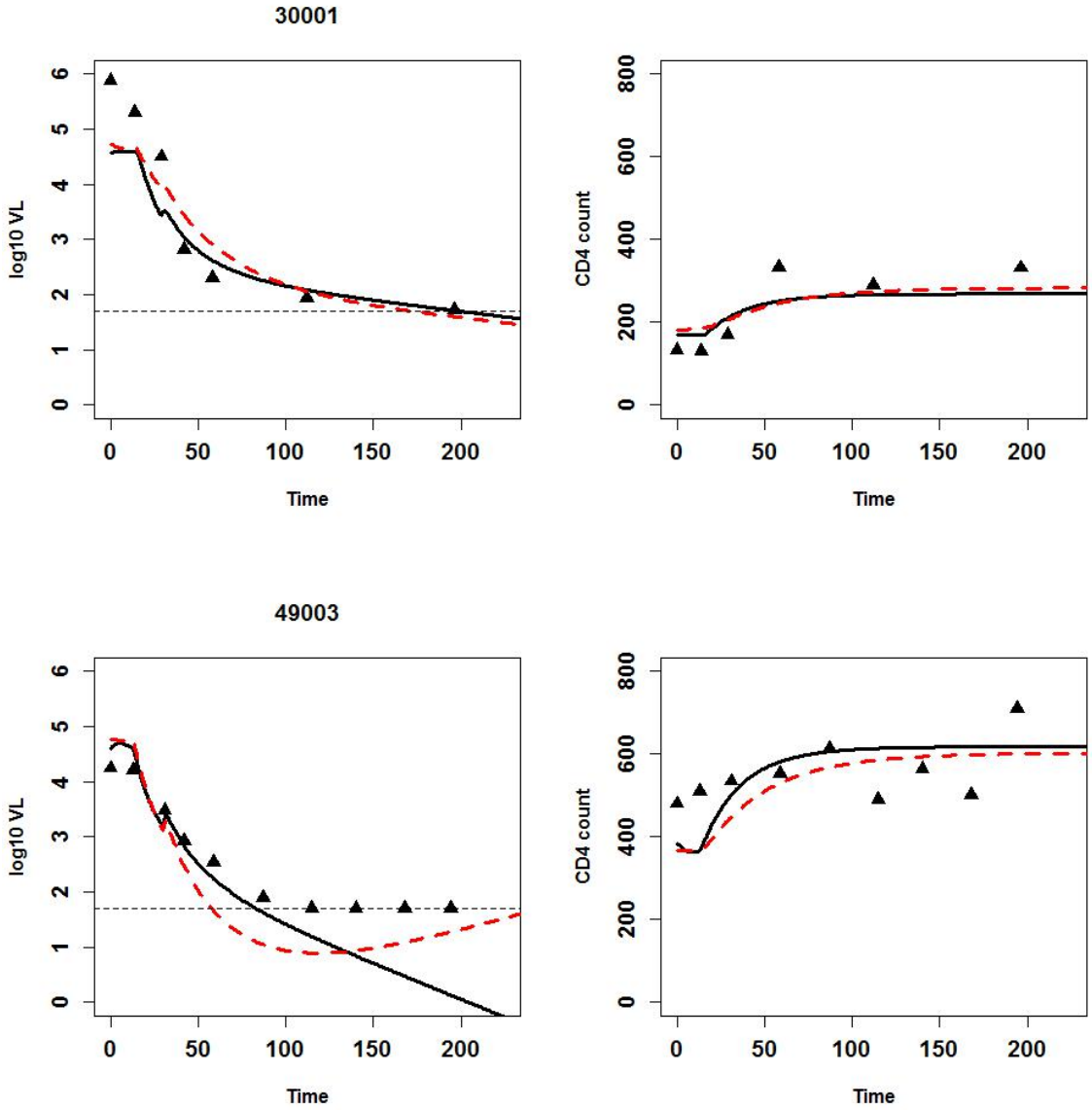
Reference

- **[Perelson96]**, HIV-1 dynamics in vivo : virion clearance rate, infected cell life-span, and viral generation time. (Science)
- **[Wu05]**, Statistical methods for HIV dynamic studies in AIDS clinical trials. (Stat. Meth. in Med. research)
- **[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)
- **[Huang06]**, Hierarchical Bayesian methods for estimation of parametersin a longitudinal HIV dynamic system. (Biometrics)
- **[Molina99]**,The ALBI trial : a randomized controlled trial comparing stavudine plus didanosine with zidovudine plus lamivudine and a regimen alternating both combinations in previously untreated patients infected with human immunodeficiency virus. (J. of Inf. Dis.)
- **[Raguin04]**, Salvage therapy with amprenavir, lopinavir and ritonavir 200 mg/d or 400 mg/d in HIV-infected patients in virological failure. (Antiviral therapy)

Discussion

Thank you ! Questions ?

Graphical adjustment



Graphical adjustment