

Toward information synthesis with mechanistic models of HIV dynamics.

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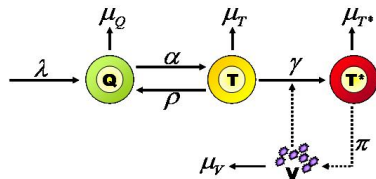
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Brief state of the art

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

Biological Model : Dynamical System

Activated T cells model



$$\left\{ \begin{array}{l} \frac{dQ}{dt} = \lambda - \mu_Q Q - \alpha Q + \rho T \\ \frac{dT}{dt} = \alpha Q - \rho T - \mu_T T - \gamma VT \\ \frac{dT^*}{dt} = \gamma VT - \mu_{T^*} T^* \\ \frac{dV}{dt} = \pi T^* - \mu_V V \end{array} \right.$$

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

$$\tilde{\xi}^i = \left(\tilde{\alpha}^i, \tilde{\lambda}^i, \dots, \tilde{\gamma}_0^i, \tilde{\mu}_V^i \right)$$

$$\tilde{\xi}_l^i = \underbrace{\phi_l + d_l^i(t)\beta_l}_{\text{Fixed effects}} + \underbrace{\omega_l^i(t)u_l^i}_{\text{Random effects}}$$

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

Observational Model

$$\text{Viral Load : } Y_{ij1} = \log_{10}(V) + \epsilon_{ij1}$$

$$\text{Total CD4 count : } Y_{ij2} = (Q + T + T^*)^{0.25} + \epsilon_{ij2}$$

$$\epsilon_{ijm} \sim \mathcal{N}(0, \sigma_m^2)$$

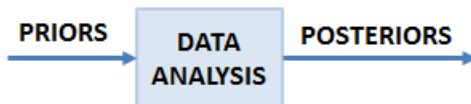
→ At least 16 parameters to estimate.

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+ddl ; 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

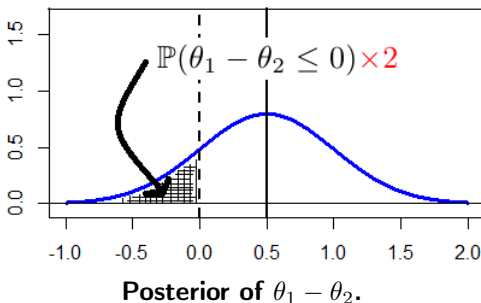
For each parameter, we assess the difference of the posterior in term of “Bayesian” p-value.

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

$$\theta_1 \sim \mathcal{N}(\mu_1; \sigma_1^2)$$

$$\theta_2 \sim \mathcal{N}(\mu_2; \sigma_2^2)$$

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



Separate analysis of ALBI and PUZZLE

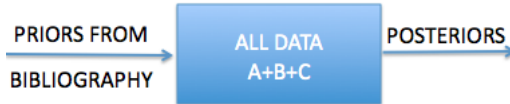
| | PRIOR | | POSTERIORES | | | | Bp-value |
|----------------------|--------------|-------------|--------------|-------------|--------------|-------------|-------------|
| | BIBLIOGRAPHY | | ALBI | | PUZZLE | | |
| | Mean | sd. | Mean | sd. | Mean | sd. | |
| α | -4.00 | 2.00 | -4.90 | 0.34 | -4.73 | 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.

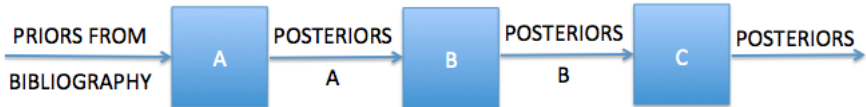
Bayesian pooling methodology

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.)

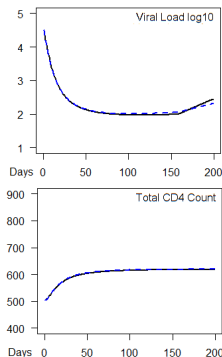
- **Log-likelihood at parameters posterior mode comparison :**

| | 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

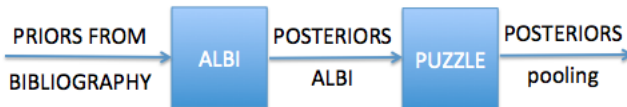
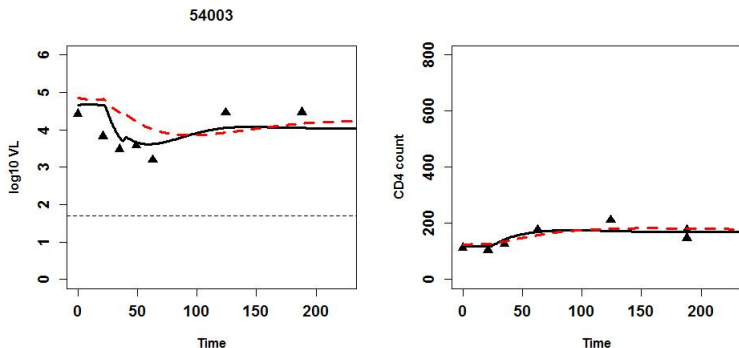


Illustration of information increase on a patient



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 parameters in 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)

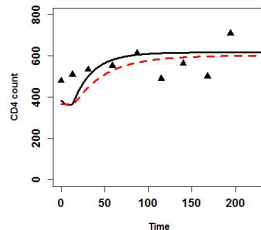
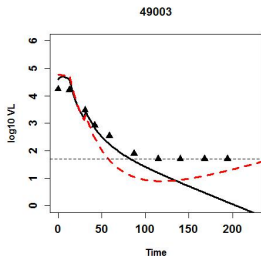
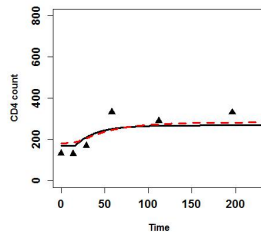
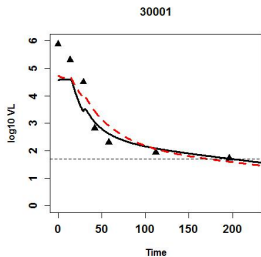
Discussion

Thank you ! Questions ?

Pooled estimation : ALBI then PUZZLE

| | A PRIORI BIBLIO | | A PRIORI ALBI | | PUZZLE -453.8 | | POOLED -430.1 | |
|----------------------|--------------------|------|------------------|------|------------------|------|------------------|------|
| | Moy. | e-t. | Moy. | e-t. | Moy. | e-t. | Moy. | e-t. |
| α | -4.00 | 2.00 | -3.19 | 0.14 | -3.07 | 0.30 | -2.86 | 0.11 |
| μ_{T^*} | -0.05 | 0.68 | -0.52 | 0.12 | -1.33 | 0.46 | -0.33 | 0.12 |
| λ | 2.55 | 1.90 | 2.52 | 0.10 | 1.48 | 0.49 | 2.31 | 0.10 |
| μ_T | -2.59 | 0.34 | -2.57 | 0.10 | -3.33 | 0.19 | -2.79 | 0.08 |
| π | 4.04 | 2.66 | 2.49 | 0.54 | 4.21 | 0.72 | 1.29 | 0.24 |
| ρ | -4.34 | 1.38 | -5.13 | 0.54 | -4.85 | 1.07 | -4.60 | 0.46 |
| γ_0 | -5.76 | 4.02 | -5.38 | 0.10 | -6.60 | 0.19 | -5.38 | 0.03 |
| μ_Q | -9.00 | 1.00 | -11.2 | 0.99 | -9.01 | 0.99 | -11.2 | 0.99 |
| μ_V | 2.90 | 0.68 | 1.70 | 0.59 | 2.73 | 0.66 | -0.75 | 0.13 |
| σ_α | 0.53 | - | 0.38 | 0.03 | 0.40 | 0.12 | 0.43 | 0.13 |
| $\sigma_{\mu_{T^*}}$ | 0.37 | - | 0.03 | 0.01 | 0.98 | 0.11 | 0.81 | 0.12 |
| σ_λ | 0.10 | - | 0.03 | 0.01 | 1.0 | 0.23 | 0.96 | 0.23 |
| σ_{CV} | - | - | 0.45 | 0.03 | 0.62 | 0.04 | 0.57 | 0.04 |
| σ_{CD4} | - | - | 0.20 | 0.02 | 0.24 | 0.01 | 0.22 | 0.01 |

Graphical adjustment



Graphical adjustment

