Use of mathematical modeling for optimizing and adapting immunotherapy protocols in HIV-infected patients

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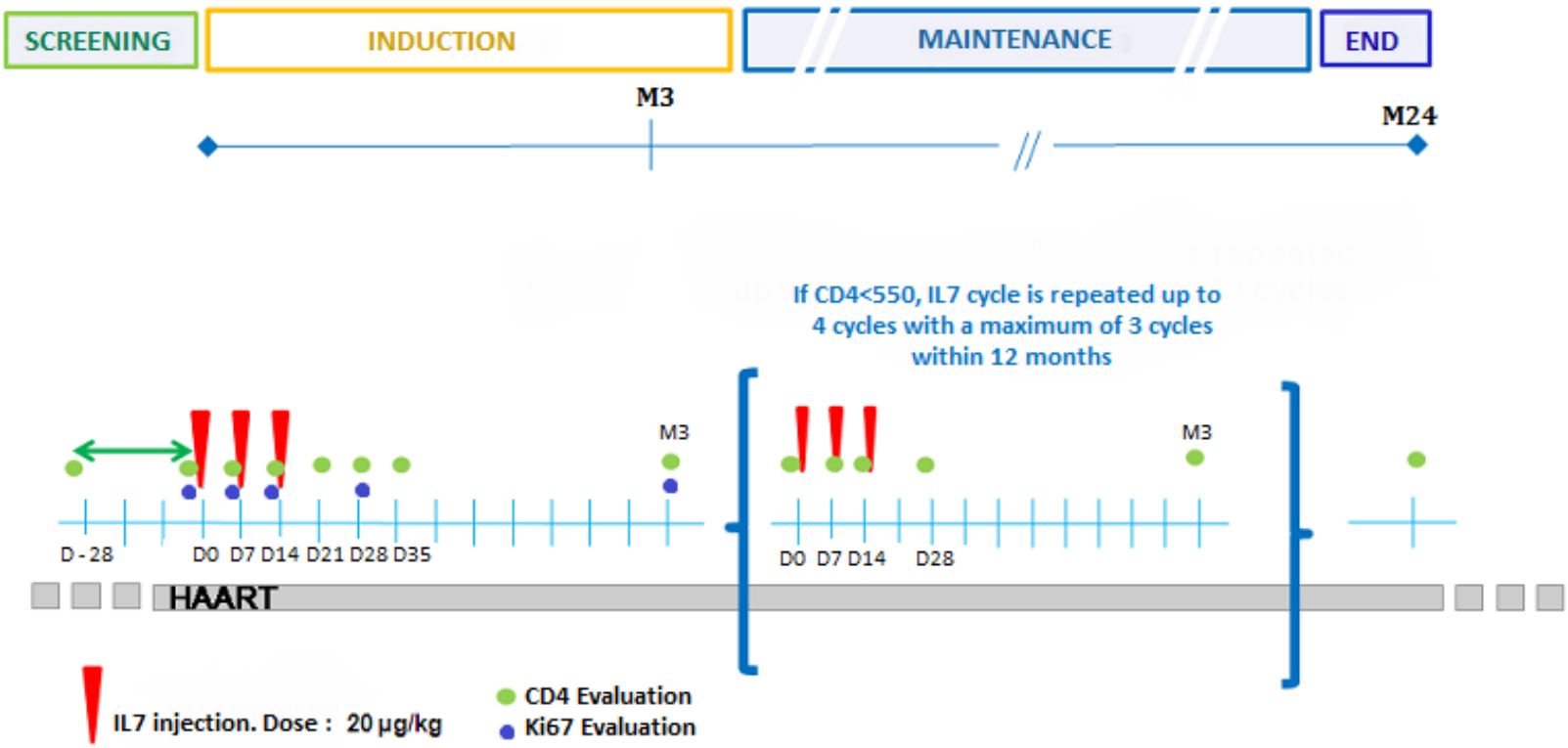
Context

- Infection by the Human Immunodeficiency Virus (HIV) compromises the immune system: depletion of $CD4^+$ T lymphocytes
- Combination antiretroviral therapies (cART) $\Longrightarrow$ improvment of patient's survival
- Some HIV-infected patients under cART are unable to recover normal $CD4^+$ T cell levels
- Immune therapy using interleukine 7 (IL7) complements cART:
  - Phase I trials and observational studies $\Longrightarrow$ safety and beneficial effect of IL7 injections
  - Phase I/II human clinical trials (INSPIRE 1, 2 and 3 studies) $\Longrightarrow$ repeated cycles of 3 weekly IL7 injections help maintaining $CD4^+$ T cells levels above 500 cells/μL [Levy et al. (2012), Thiébaut et al. 2016]

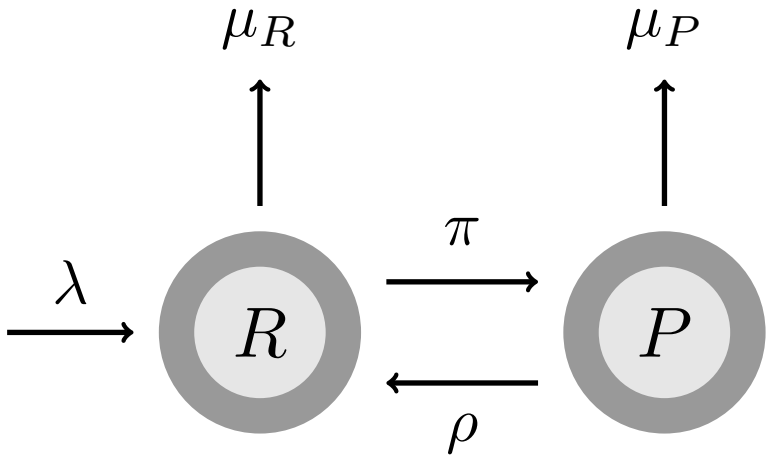
INSPIRE studies



- Total of 128 HIV-infected patients under cART with CD4 levels between 100-400 cells/μL and undetectable viral load for at least 6 months
- Cycles of 3 weekly IL7 injections of dose 20μg/kg (21 received dose 10 or 30)
- Regular measurements of $CD4^+$ levels and proliferation marker Ki67
- Visits every three months. $CD4^+$ levels < 550 cells/μL $\Longrightarrow$ new cycle
- Total duration of the studies: between 12 and 24 months

Mechanistic model

Dynamics of CD4$^+$ T lymphocytes, resting (R) or proliferating (P) [Thiébaut et al. (2014)]



$$\begin{cases} \dfrac{dR}{dt} = \lambda - \mu_R R - \pi R + 2\rho P \\ \dfrac{dP}{dt} = -\mu_P P - \rho P + \pi R \end{cases}$$

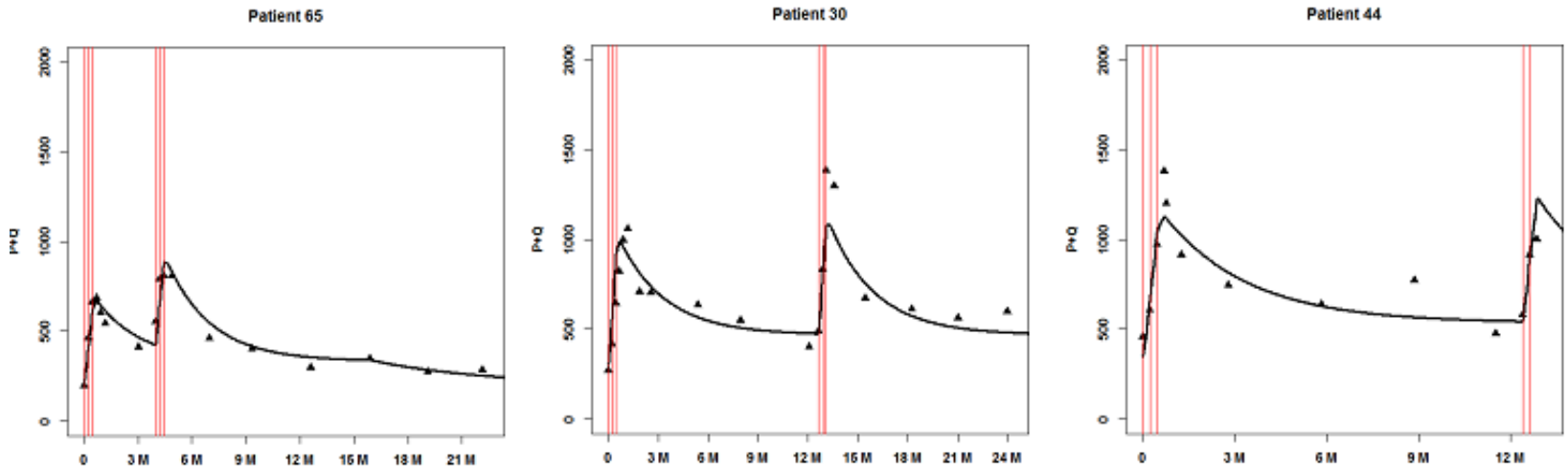
initial condition = equilibrium

- Parameters estimation with a population approach [Prague et al. (2013)]
- Identification of random effects on parameters λ and ρ
- IL-7 injection: effect on the proliferation rate π (differs for each injection within a cycle) [Jarne et al. (2017)]

$$\tilde{\pi}^i = \tilde{\pi}_0 + \beta_\pi^{(n)} d_i^{0.25} \mathbb{1}_{\{t \in [t_{inj}^i, t_{inj}^i + \tau^i]\}}$$

d : injected dose, $n \in \{1, 2, 3\}$: injection of the cycle, τ : time of effect of the injection

Predictive ability of the model



- Main issue: criterion in the original protocol (decision to begin a new cycle when CD4 levels < 550 cells/μ) inadequate for some patients
- Next step: optimizing and adapting protocols of injections
- Aim: maintaining the CD4 levels > 500 cells/μL without using too many injections

Pipeline

Parameters estimation

Estimation of the ODE parameters θ using INSPIRE data

$\Longrightarrow$ determination of a posterior distribution.

Inclusion of a new patient

Estimation of its individual parameters using the first observations.

Optimal control approach

- Use of optimal control theory to determine an optimal strategy of injections from a cost function.
- Stochasticity attributed to the biological process.

Bayesian approach

- Treatment decision is adapted at each new observation, by updating individual parameters estimation with MCMC algorithm.
- Stochasticity attributed to the uncertainty on the parameters estimation.

Assessment of the methods

Parameters estimation

Estimation of the ODE parameters θ using INSPIRE data

$\Longrightarrow$ determination of a posterior distribution.

Pseudo-patients parameters generation

Sample N parameter sets from the posterior distribution of θ.

Optimal control approach

- Use of optimal control theory to determine an optimal strategy of injections from a cost function.
- Stochasticity attributed to the biological process.
- N=50, horizon = 1 year

Bayesian approach

- Treatment decision is adapted at each new observation, by updating individual parameters estimation with MCMC algorithm.
- Stochasticity attributed to the uncertainty on the parameters estimation.
- N=150, horizon = 2 years

Optimal control: proof-of-concept

- Objective: to determine actions (injection of not and choice of dose) at given time points over an horizon of time
  $\Longrightarrow$ impulse control problem in the optimal control theory

- Two-steps method:
  - Developing an adapted mathematical model for the process: Piecewise Deterministic Markov model [Davis (1984)]
  - Using the theory of optimal control from [Costa et al. (2016)] to solve the impulse control problem by iteration of an integro-differential operator
    - computation of the optimal cost
    - determination of an optimal strategy of injections
    - comparison of the obtained optimal strategy to other clinical protocols

C. Pasin, F. Dufour, L. Villain, H. Zhang, R. Thiébaut. Controlling IL-7 injections in HIV-infected patients. To appear in *Bulletin of Mathematical Biology*

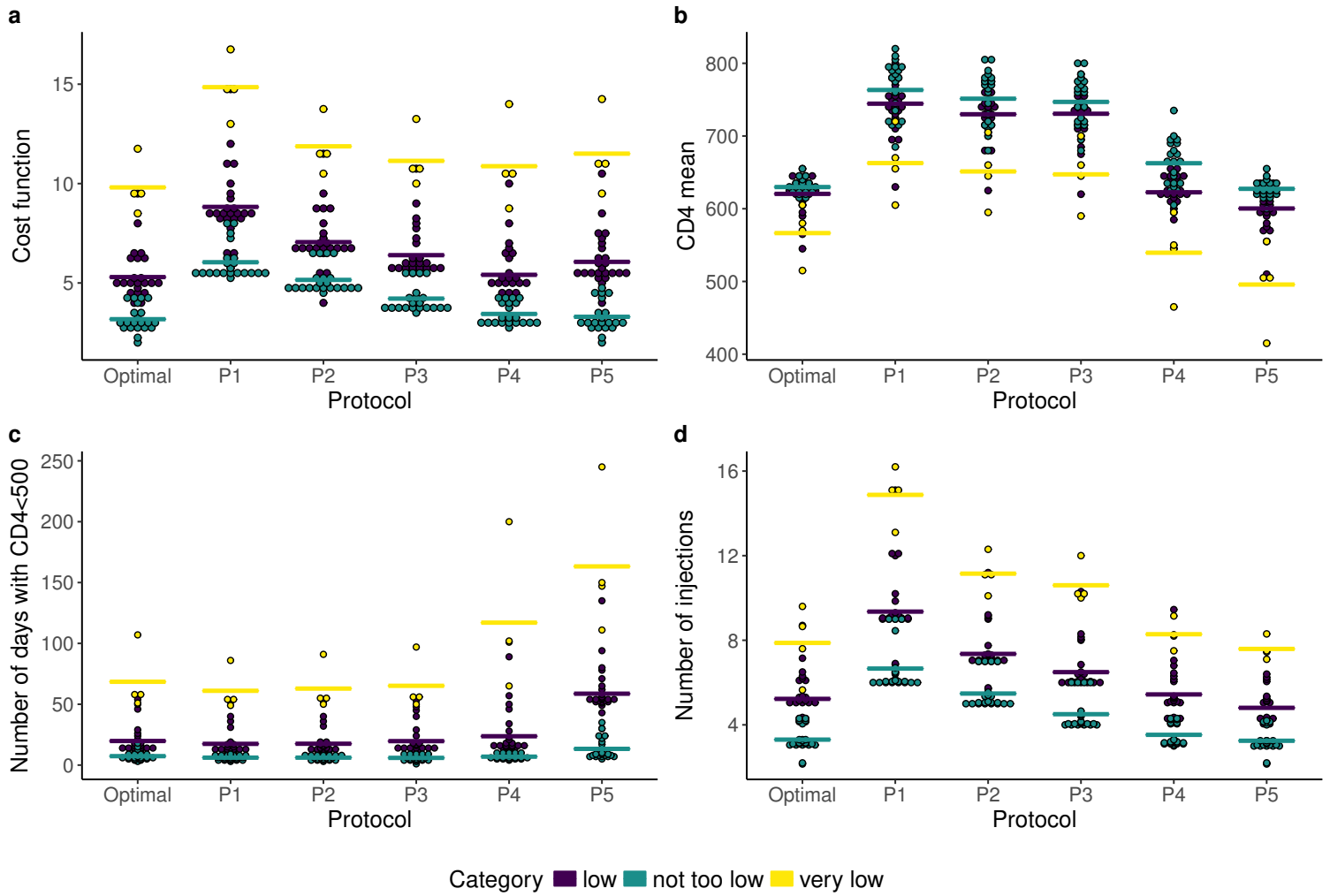
Optimal control: method

- Jump in the process : modification of parameter π
  - Deterministic: CD4 levels < 500 cells/μL $\implies$ IL7 injection
  - Random: stochastic time τ of effect of an IL7 injection

$$\tilde{\pi} = \tilde{\pi}_0 + \beta_\pi^{(n)} d^{0.25} \mathbb{1}_{\{t \in [t_{inj}, t_{inj}+\tau]\}}$$

- Cost function: combination of two criteria
  - Time spent with CD4 levels < 500 cells/μL
  - Number of injections realized
- Application of the method to determine the optimal strategy of 50 pseudo-patients on a reduced model:
  - 2 possible doses (10,20)
  - horizon of 1 year

Optimal control: results on 50 pseudo-patients

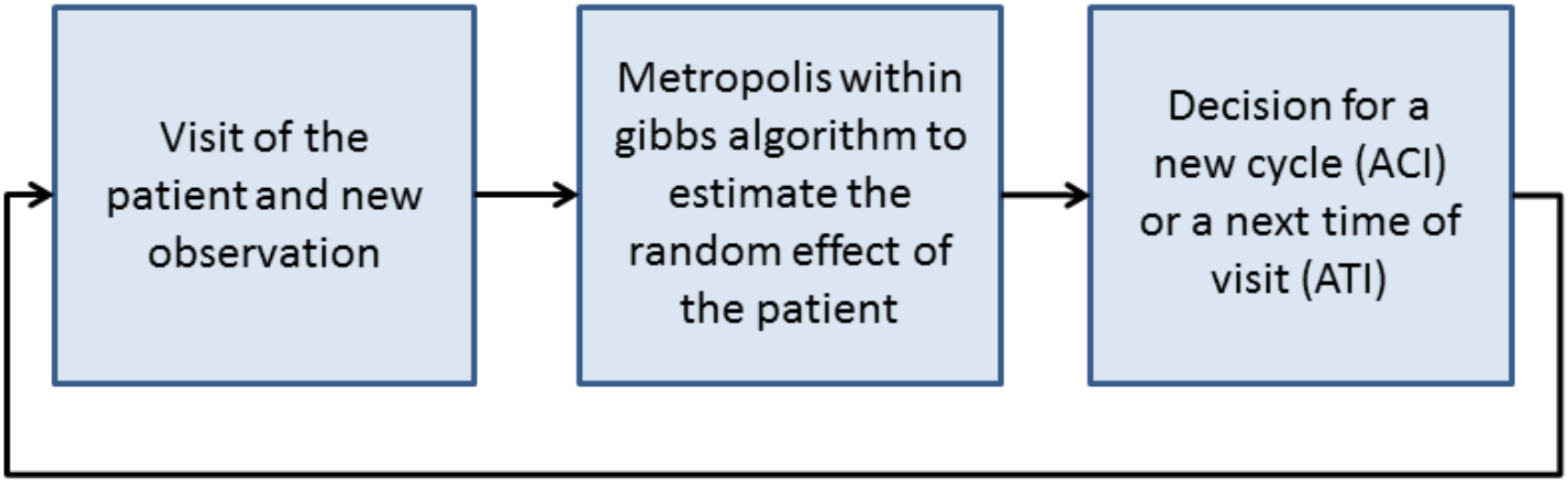


Protocols. P1: 3-injections cycles. P2: 3-injections cycle then 2-injections cycles. P3: 2-injections cycles. P4: 2-injections cycle then 1-injection cycles. P5: 1-injection cycles.

Optimal control: conclusion

- Development of a dynamic programming method to apply the theory of optimal control in a biological framework
- Intuitive optimal strategy: first cycles of 2 injections to increase the number of $CD4^+$ then cycles of 1 injection to maintain the CD4 levels
- Limitations:
  - One year horizon only due to computational time
  - Main hypothesis: known individual parameters

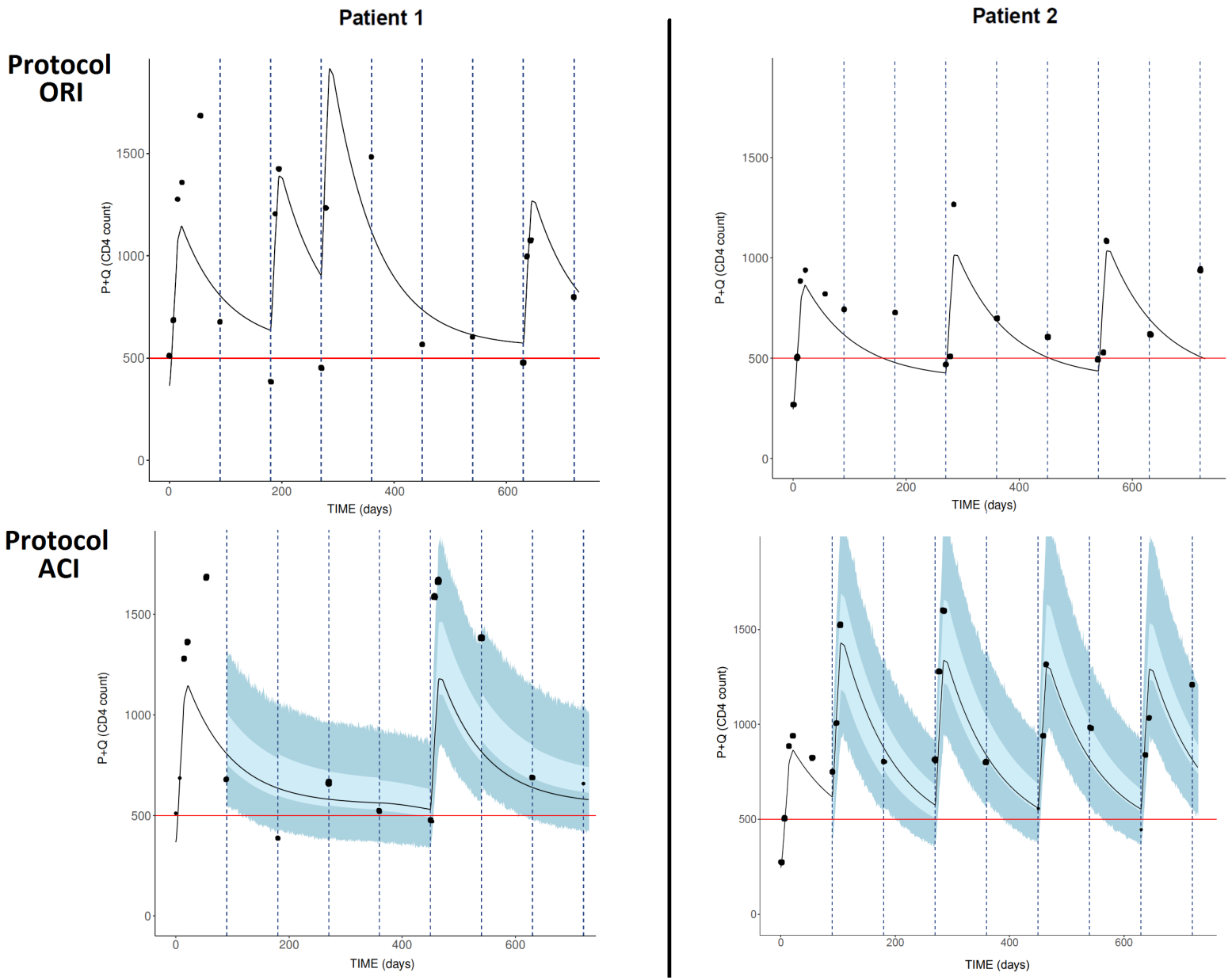
Bayesian approach: pipeline



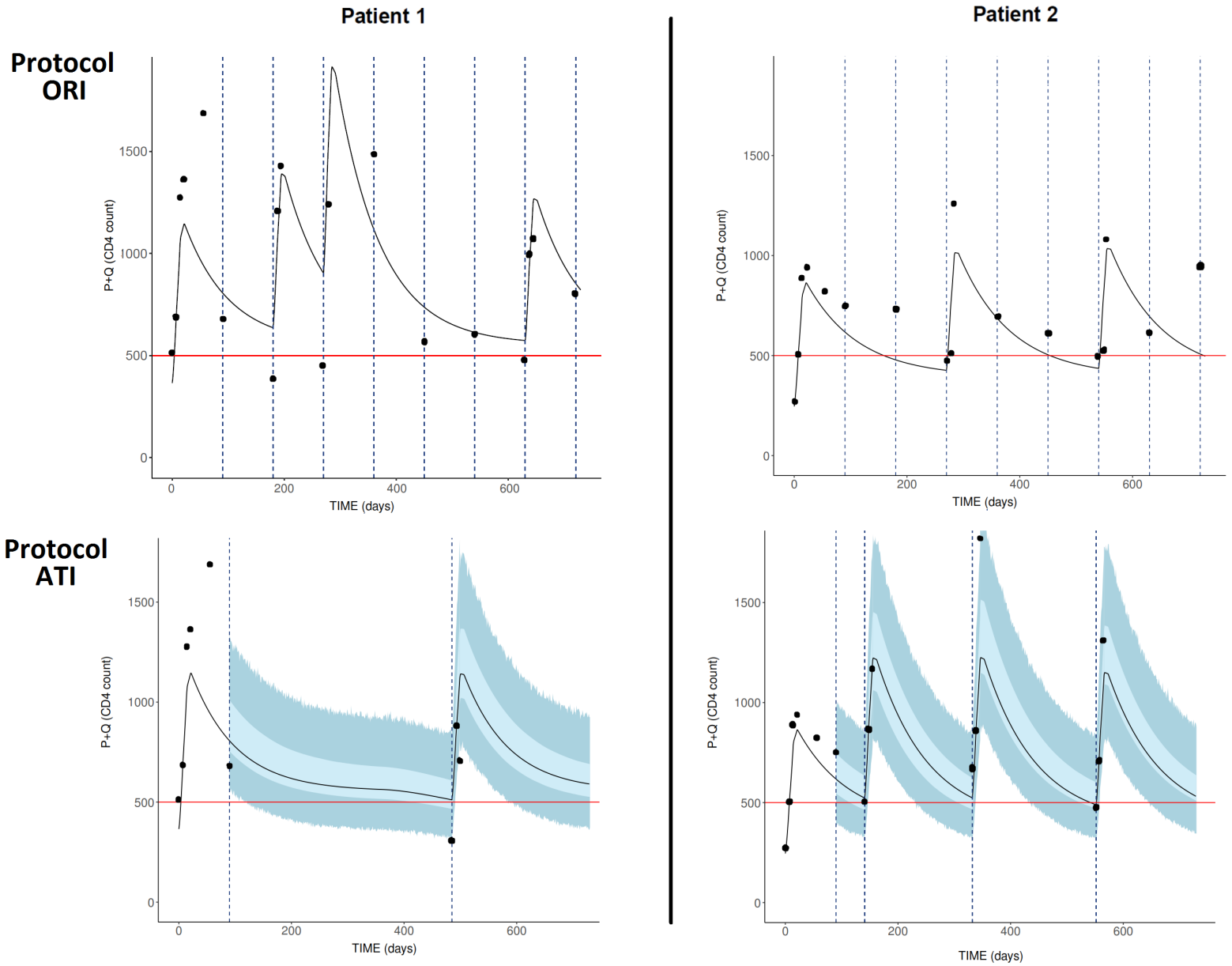
- ACI: Adaptive Criterion of Injection. Based on the predicted risk to have CD4 levels < 500 before the next visit (at 3 months)
- ATI: Adaptive Time of Injection. Based on the predicted time at which CD4 levels will reach 500.
- Both criteria: computed from estimated individual parameters, obtained thanks to observations

L. Villain, D. Commenges, C. Pasin, M. Prague, R. Thiébaut. Adaptive protocols based on predictions from a mechanistic model of the effect of IL7 on CD4 counts. *Statistics in Medicine* (under revision).

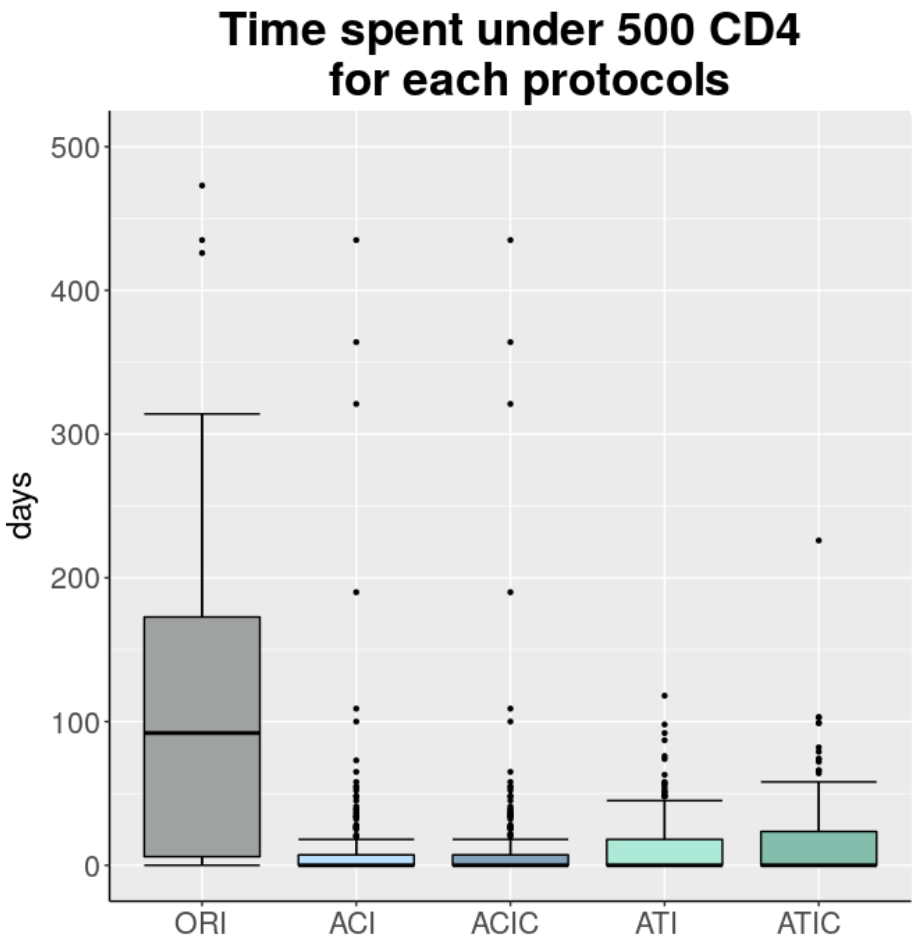
Bayesian approach: protocols comparison

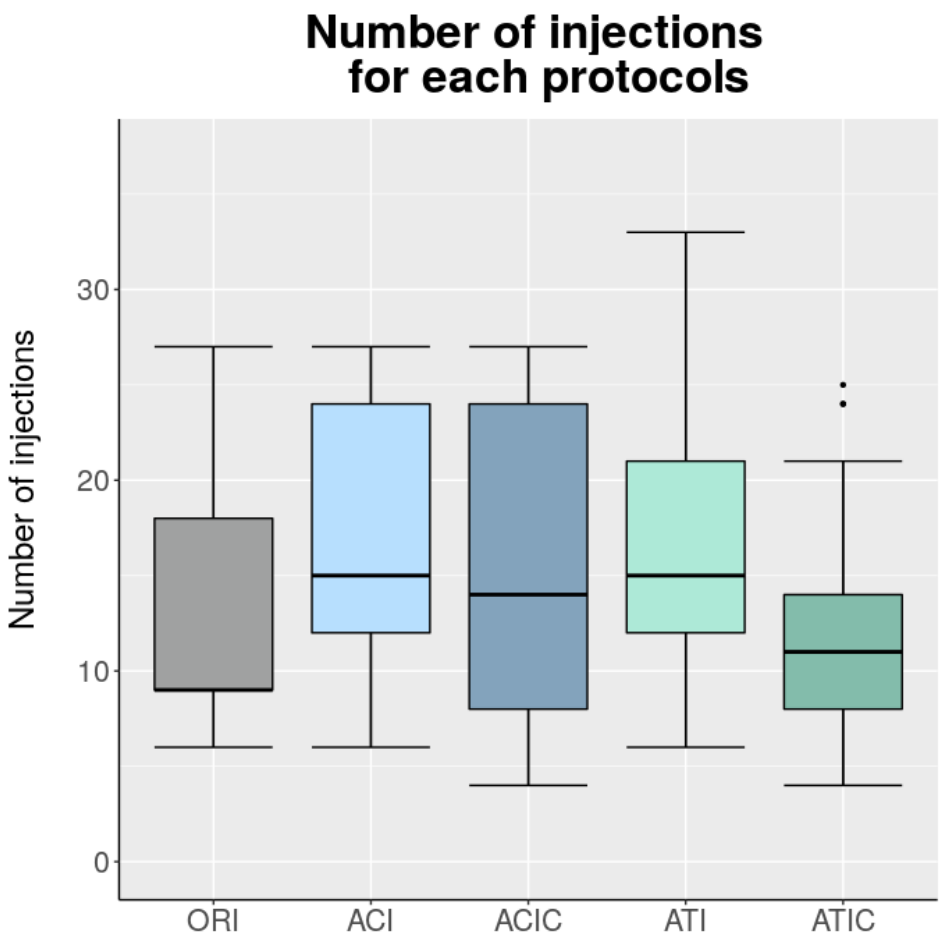


Bayesian approach: protocols comparison



Bayesian approach: results on 150 pseudo-patients





Discussion

- Possibility to adapt the schedules of injections with both approaches
- Specific context: very good predictive ability of the model
  - Deterministic model
  - Only 2 markers needed
  - Short phase of learning
- Limitations of the optimal control approach:
  - Does not consider uncertainty on parameters
  - Requests large computing time
- But could be more adapted in a case where deterministic model fails at describing the biological process and stochastic model is needed
- Statistical approach: very powerful in this context
- Prospects:
  - Other biological applications
  - Evaluation of the adaptive strategy on clinical outcomes in future trials

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