



**HAL**  
open science

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

Chloé Pasin, Laura Villain, François Dufour, Daniel Commenges, Mélanie Prague, Rodolphe Thiébaud

► **To cite this version:**

Chloé Pasin, Laura Villain, François Dufour, Daniel Commenges, Mélanie Prague, et al.. Use of mathematical modeling for optimizing and adapting immunotherapy protocols in HIV-infected patients. Population Approach Group Europe, May 2018, Montreux, Switzerland. hal-01934340

**HAL Id: hal-01934340**

**<https://inria.hal.science/hal-01934340v1>**

Submitted on 26 Nov 2018

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

C. Pasin<sup>1,2,3\*</sup>, L. Villain<sup>1,2,3\*</sup>, F. Dufour<sup>4,5</sup>, D. Commenges<sup>1,2,3</sup>, M. Prague<sup>1,2,3</sup>, R. Thiébaud<sup>1,2,3</sup>

<sup>1</sup>INRIA Bordeaux Sud-Ouest, SISTM team, Talence, France

<sup>2</sup>Univ. Bordeaux, centre INSERM U1219 BPH, Bordeaux, France

<sup>3</sup>Vaccine Research Institute, Créteil, France

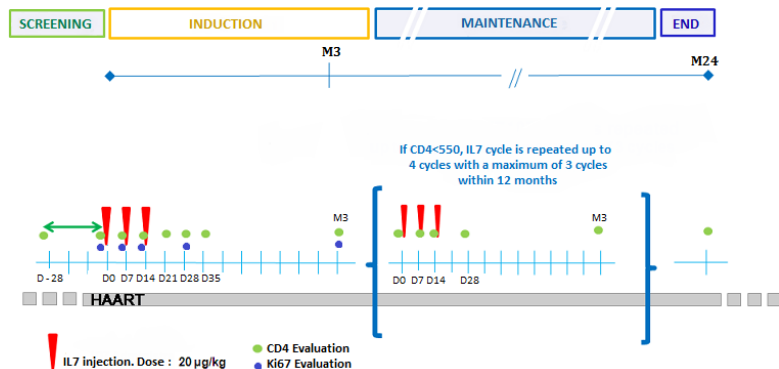
<sup>4</sup>INRIA Bordeaux Sud-Ouest, CQFD team, Talence, France

<sup>5</sup>INP, IMB, Bordeaux, France

PAGE meeting, Montreux, May 29 2018

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

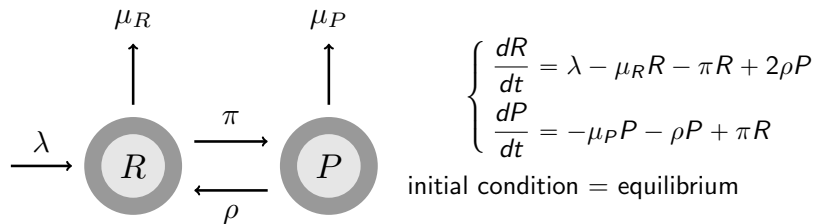
# INSPIRE studies



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

# Mechanistic model

Dynamics of CD4<sup>+</sup> T lymphocytes, resting (R) or proliferating (P) [Thiébaud et al. (2014)]

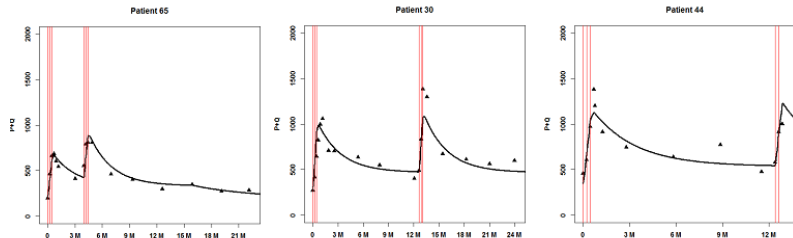


- Parameters estimation with a population approach [Prague et al. (2013)]
- Identification of random effects on parameters  $\lambda$  and  $\rho$
- IL-7 injection: effect on the proliferation rate  $\pi$  (differs for each injection within a cycle) [Jarne et al. (2017)]

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

$d$  : injected dose,  $n \in \{1, 2, 3\}$  : injection of the cycle,  $\tau$  : 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/ $\mu$ ) inadequate for some patients
- Next step: optimizing and adapting protocols of injections
- Aim: maintaining the  $CD4$  levels  $> 500$  cells/ $\mu$ L without using too many injections

# Pipeline

## Parameters estimation

Estimation of the ODE parameters  $\theta$  using INSPIRE data  
 $\implies$  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  $\theta$  using INSPIRE data  
⇒ determination of a posterior distribution.

## Pseudo-patients parameters generation

Sample  $N$  parameter sets from the posterior distribution of  $\theta$ .

## 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  
⇒ 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. Thiébaud. Controlling IL-7 injections in HIV-infected patients. To appear in *Bulletin of Mathematical Biology*

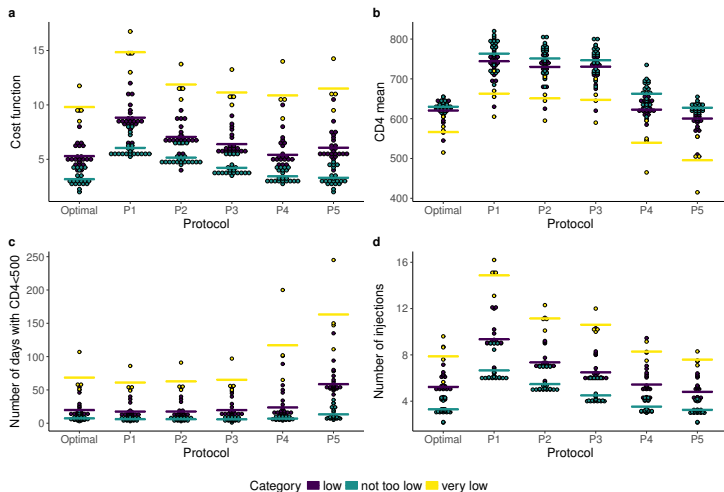
# Optimal control: method

- Jump in the process : modification of parameter  $\pi$ 
  - ▶ Deterministic: CD4 levels  $< 500$  cells/ $\mu\text{L}$   $\implies$  IL7 injection
  - ▶ Random: stochastic time  $\tau$  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/ $\mu\text{L}$
  - ▶ 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

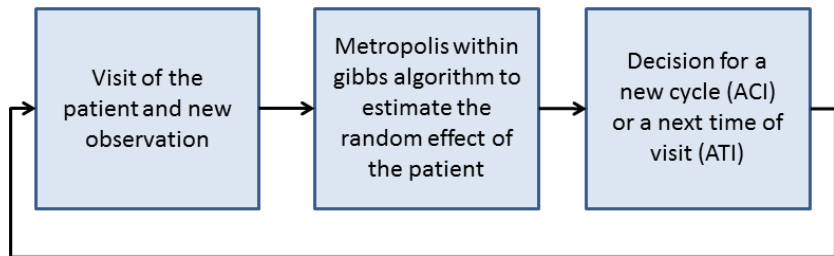


Protocols. P1: 3-injections cycles. P2: 3-injections cycle then 2-injections cycles. P3: 2-injections cycles. P4: 2-injections cycle then 1-injection cycles. P5: 1-injection cycles.

# 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<sup>+</sup> then cycles of 1 injection to maintain the CD4 levels
- Limitations:
  - ▶ One year horizon only due to computational time
  - ▶ Main hypothesis: known individual parameters

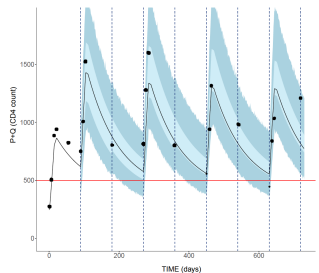
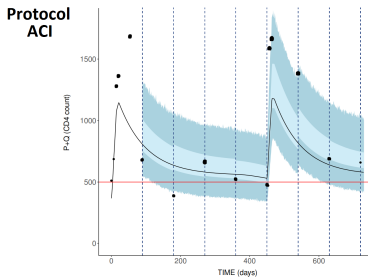
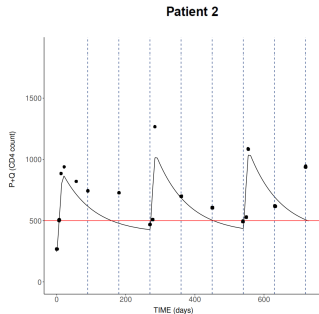
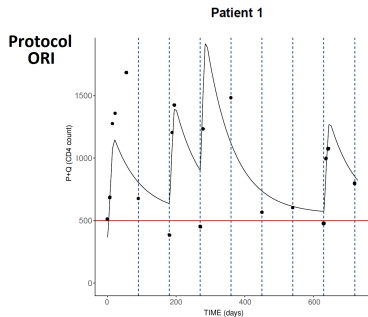
# Bayesian approach: pipeline



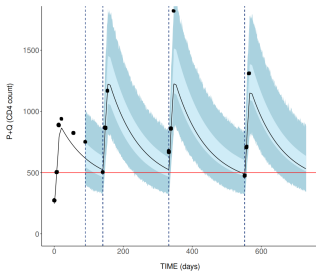
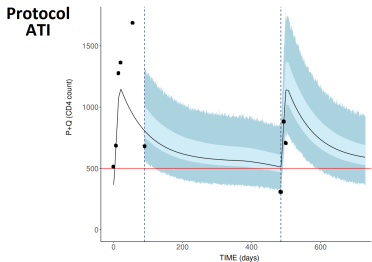
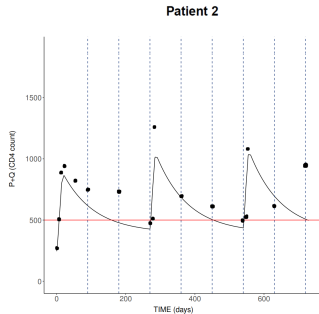
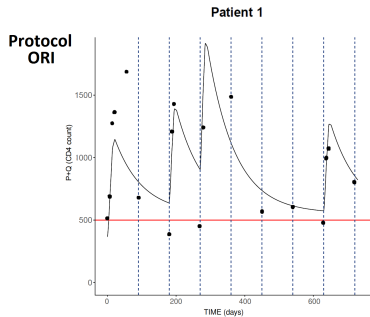
- ACI: Adaptive Criterion of Injection. Based on the predicted risk to have CD4 levels  $< 500$  before the next visit (at 3 months)
- ATI: Adaptive Time of Injection. Based on the predicted time at which CD4 levels will reach 500.
- Both criteria: computed from estimated individual parameters, obtained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

L. Villain, D. Commenges, C. Pasin, M. Prague, R. Thiébaud. 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

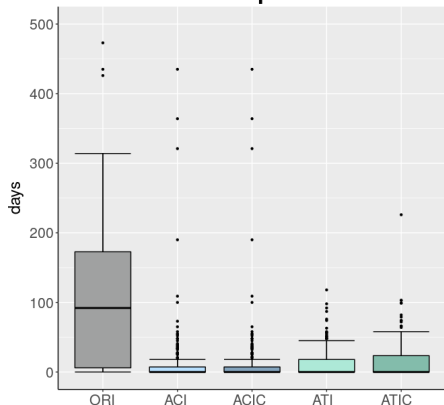


# Bayesian approach: protocols comparison

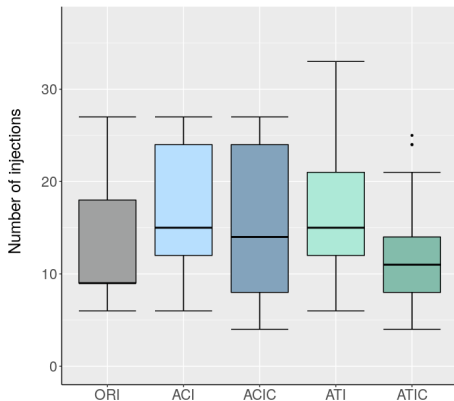


# Bayesian approach: results on 150 pseudo-patients

## Time spent under 500 CD4 for each protocols



## Number of injections for each protocols





# 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

# Acknowledgments

- INRIA SISTM / CQFD teams and other collaborators
- Vaccine Research Institute (Y Levy, JD Lelievre)
- INSPIRE Study group (JP Routy, I Sereti, M Fischl, P Ive, RF Speck, G D'offizi, S Casari, S Foulkes, V Natarajan, T Croughs, Jean-F Delfraissy, G Tambussi, MM Lederman)

école  
normale  
supérieure  
paris-saclay

