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

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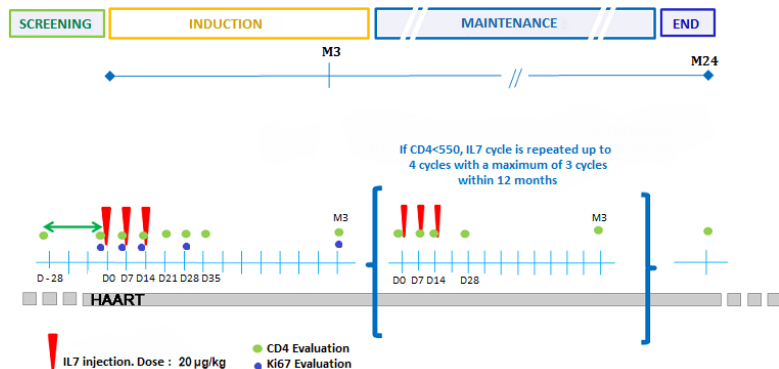
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PAGE meeting, Montreux, May 29 2018

- Infection by the Human Immunodeficiency Virus (HIV) compromises the immune system: depletion of CD4⁺ T lymphocytes
- Combination antiretroviral therapies (cART) \implies improvement 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 \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⁺ T cells levels above 500 cells/ μ L [Levy et al. (2012), Thiébaud et al. 2016]

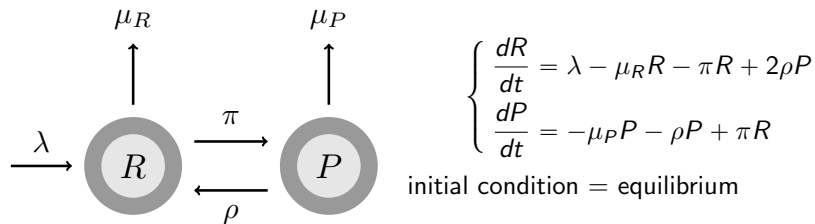
INSPIRE studies



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

Mechanistic model

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

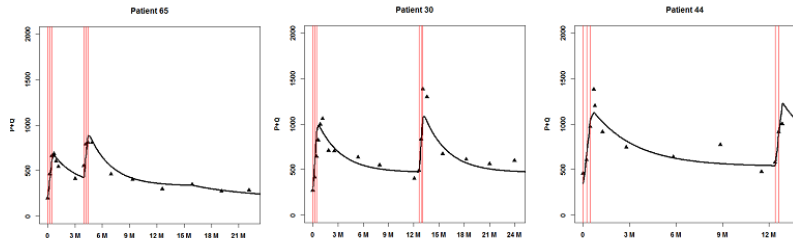


- Parameters estimation with a population approach [Prague et al. (2013)]
- Identification of random effects on parameters λ and ρ
- IL-7 injection: effect on the proliferation rate π (differs for each injection within a cycle) [Jarne et al. (2017)]

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

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/ μ L without using too many injections

Pipeline

Parameters estimation

Estimation of the ODE parameters θ 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 θ using INSPIRE data
⇒ 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
⇒ 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*

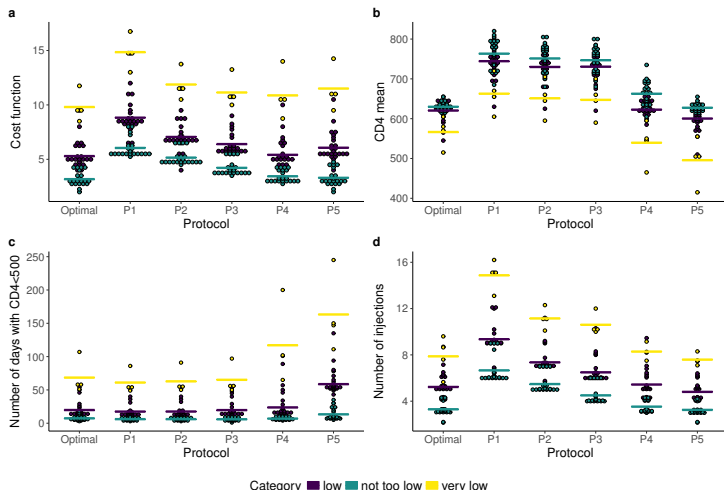
Optimal control: method

- Jump in the process : modification of parameter 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

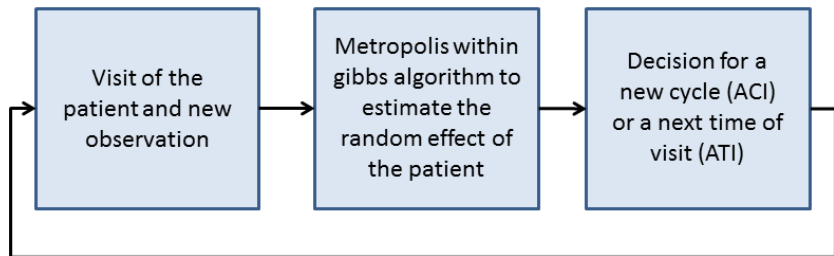


Protocols. P1: 3-injections cycles. P2: 3-injections cycle then 2-injections cycles. P3: 2-injections cycles. P4: 2-injections cycle then 1-injection cycles. P5: 1-injection cycles.

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

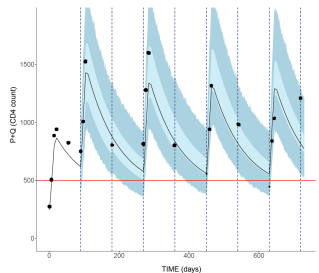
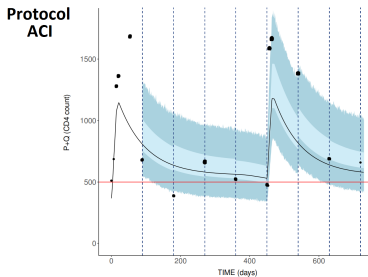
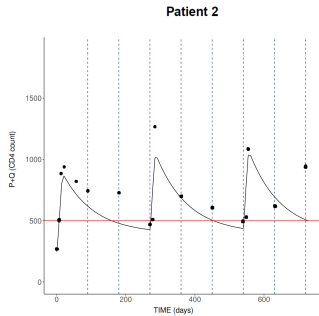
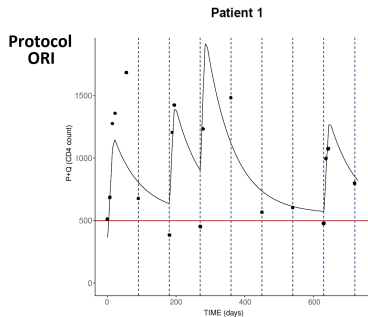
Bayesian approach: pipeline



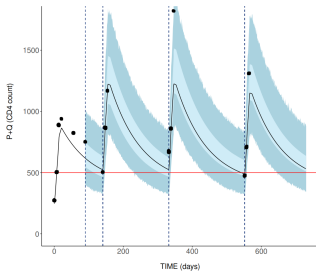
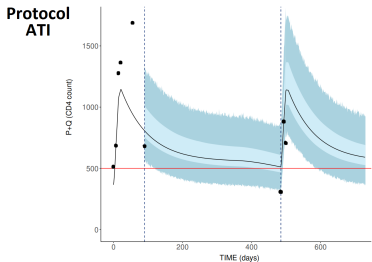
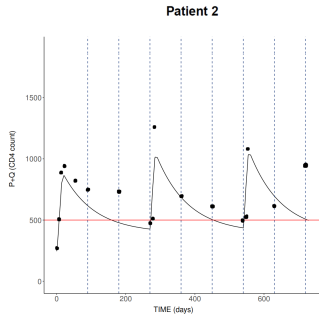
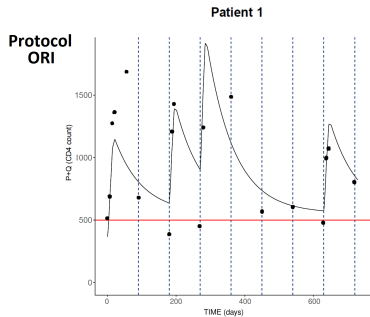
- ACI: Adaptive Criterion of Injection. Based on the predicted risk to have CD4 levels < 500 before the next visit (at 3 months)
- ATI: Adaptive Time of Injection. Based on the predicted time at which CD4 levels will reach 500.
- Both criteria: computed from estimated individual parameters, obtained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

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

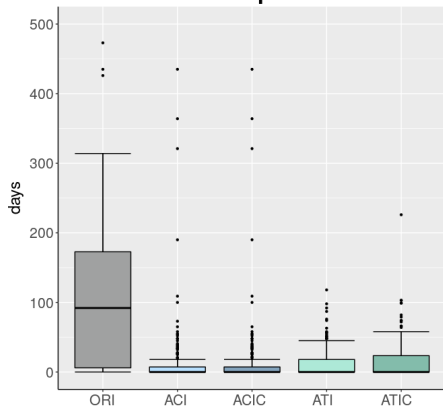


Bayesian approach: protocols comparison

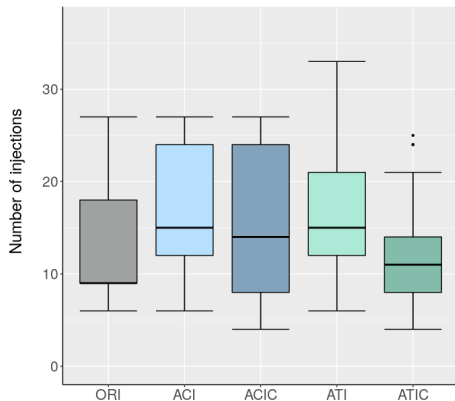


Bayesian approach: results on 150 pseudo-patients

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

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