Modeling the effect of Interleukin 7 on CD4+ T cells

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Background

- ART allows for only a partial immune reconstitution in HIV-infected patients: normal CD4+ T cell counts ($\geq 500/\mu l$) is not always restored
- **r-hIL-7** (recombinant human Interleukin-7) **increases T cell counts** in chronic HIV-infected patients (Levy et al., JCI 2009)
- **Biological mechanisms** involved in this increase have not been clarified

Data

- Inspire HIV study (Cytheris) with 27 ART-treated HIV-infected patients: 100-400 CD4 cells/μl and plasma HIV RNA $<$ 50 copies/ml
- 7, 8 and 6 patients are included in the first (10 $\mu g/kg$), second (20 $\mu g/kg$) and third (30 $\mu g/kg$) dose level arm, respectively
- Patients received 3 injections of r-hIL-7 at days 0, 7 and 14 and had a 3 months follow-up with 10 visits in average
- Biomarkers of interest here are: total CD4, Ki67+, CD45RA/O

Aim

We present an **APPROACH BASED ON MECHANISTIC MODELING** in order to

- **Explain** the action of IL-7 therapy on CD4+ T cells dynamics
- **Elucidate** biological mechanisms of in vivo effects of IL-7, (i.e. increase of peripheral proliferation, production and/or cells survival)
- **Predict** the effect during repeated administrations of IL-7

Methodology

- These mechanistic models are based on **ordinary differential equations** distinguishing different compartments in CD4+ T pool
- Between-subjects variability makes natural the use of **mixed effect models** to estimate population parameters
- Numerical and identifiability issues favor a **Bayesian approach**

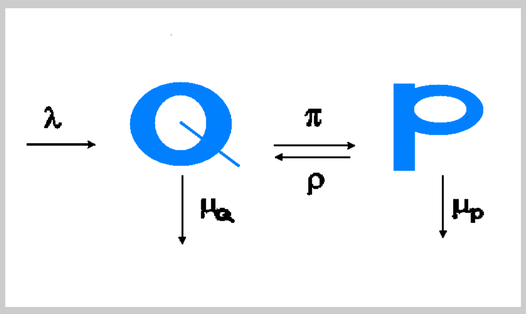
Computation

All parameters were estimated using the **NIMROD program** (**N**ormal approximation **I**nference in **M**odels with **R**andom effects based on **O**rdinary **D**ifferential equations), that maximize the likelihood taking into account priors through the computation of maximum of the posterior distribution (MAP)

www.isped.u-bordeaux2.fr/NIMROD/documentation.aspx
(Prague et al., Comp. Methods Programs Biomed. 2013)

TWO COMPARTMENTS MODEL : $\mathcal{M}^{\theta}$

A possible model ($\mathcal{M}^{\theta}$) distinguishes quiescent CD4 (Q) and proliferating CD4 (P)



$$\begin{cases} \frac{dQ}{dt} = \lambda + 2\rho P - \mu_Q Q - \pi Q \\ \frac{dP}{dt} = \pi Q - \rho P - \mu_P P \end{cases}$$

For subject i, $\tilde{\xi}_i = ln(\xi_i)$, with
$\xi_i = (\lambda_i, \rho_i, \pi_i, \mu_{Qi}, \mu_P)$ vector of 5 biological parameters

An effect of IL-7 on proliferation rate (π) and mortality rate of Q cells (μ_Q) has been supposed

$\tilde{\pi}_i = \tilde{\pi}_0 + \beta_\pi dose_i^{0.25}$ during the treatment, $\tilde{\pi}_i = \tilde{\pi}_0$ else
$\tilde{\mu}_{Q_i} = \tilde{\mu}_{Q_0} + \beta_{\mu_Q} dose_i^{0.25}$ after the treatment, $\tilde{\mu}_{Q_i} = \tilde{\mu}_{Q_0}$ else

$\tilde{\lambda}_i = \tilde{\lambda}_0 + u_{1i}$ with $u_{1i} \sim \mathcal{N}(0, \sigma^2_{u_1})$
$\tilde{\rho}_i = \tilde{\rho}_0 + u_{2i}$ with $u_{2i} \sim \mathcal{N}(0, \sigma^2_{u_2})$

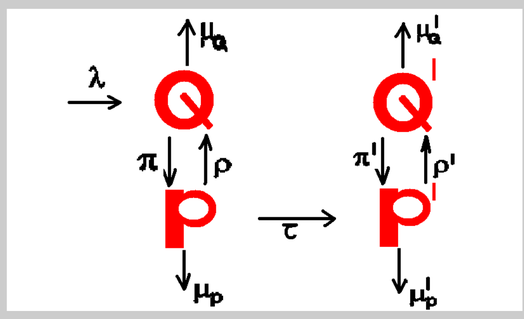
In practice, we do not observe $(P^i(t), Q^i(t))$ directly, but we have discrete-time observations $Y^i(t_{ij})$

- $Y_1^i(t_{ij}) = (P^i(t_{ij}) + Q^i(t_{ij}))^{0.25} + e_{ij1}$
- $Y_2^i(t_{ij}) = (P^i(t_{ij}))^{0.25} + e_{ij2}$

$e_{ijk} \sim \mathcal{N}(0, \sigma^2_k)$

FOUR COMPARTMENTS MODEL : $\mathcal{M}^{\theta'}$

Another possible model ($\mathcal{M}^{\theta'}$) distinguishes quiescent naive CD4 (Q), proliferating naive CD4 (P), quiescent memory CD4 (Q') and proliferating memory CD4 (P').



$$\begin{cases} \frac{dQ}{dt} = \lambda + 2\rho P - \mu_Q Q - \pi Q \\ \frac{dP}{dt} = \pi Q - \rho P - \mu_P P - \tau P \\ \frac{dQ'}{dt} = 2\rho' P' - \mu'_Q Q' - \pi' Q' \\ \frac{dP}{dt} = \pi' Q' - \rho' P' - \mu'_P P' + \tau P \end{cases}$$

$\xi_i = (\lambda_i, \tau_i, \rho, \rho', \pi_i, \pi'_i, \mu_Q, \mu'_Q, \mu_P, \mu'_P)$ biological parameters

An effect of IL-7 on proliferation rate of naive and memory cells (π and π') has been supposed

$\tilde{\pi}_i = \tilde{\pi}_0 + \beta_\pi dose_i^{0.25}$ during the treatment, $\tilde{\pi}_i = \tilde{\pi}_0$ else
$\tilde{\pi}'_i = \tilde{\pi}'_0 + \beta_{\pi'} dose_i^{0.25}$ during the treatment, $\tilde{\pi}'_i = \tilde{\pi}'_0$ else

$\tilde{\lambda}_i = \tilde{\lambda}_0 + u_{1i}$ with $u_{1i} \sim \mathcal{N}(0, \sigma^2_{u_1})$
$\tilde{\tau}_i = \tilde{\tau}_0 + u_{2i}$ with $u_{2i} \sim \mathcal{N}(0, \sigma^2_{u_2})$

- $Y_1^i(t_{ij}) = (P^i(t_{ij}) + Q^i(t_{ij}) + P'^i(t_{ij}) + Q'^i(t_{ij}))^{0.25} + e_{ij1}$
- $Y_2^i(t_{ij}) = (P^i(t_{ij}) + P'^i(t_{ij}))^{0.25} + e_{ij2}$
- $Y_3^i(t_{ij}) = (P^i(t_{ij}) + Q^i(t_{ij}))^{0.25} + e_{ij3}$
- $Y_4^i(t_{ij}) = (P^i(t_{ij}))^{0.25} + e_{ij4}$

$e_{ijk} \sim \mathcal{N}(0, \sigma^2_k)$

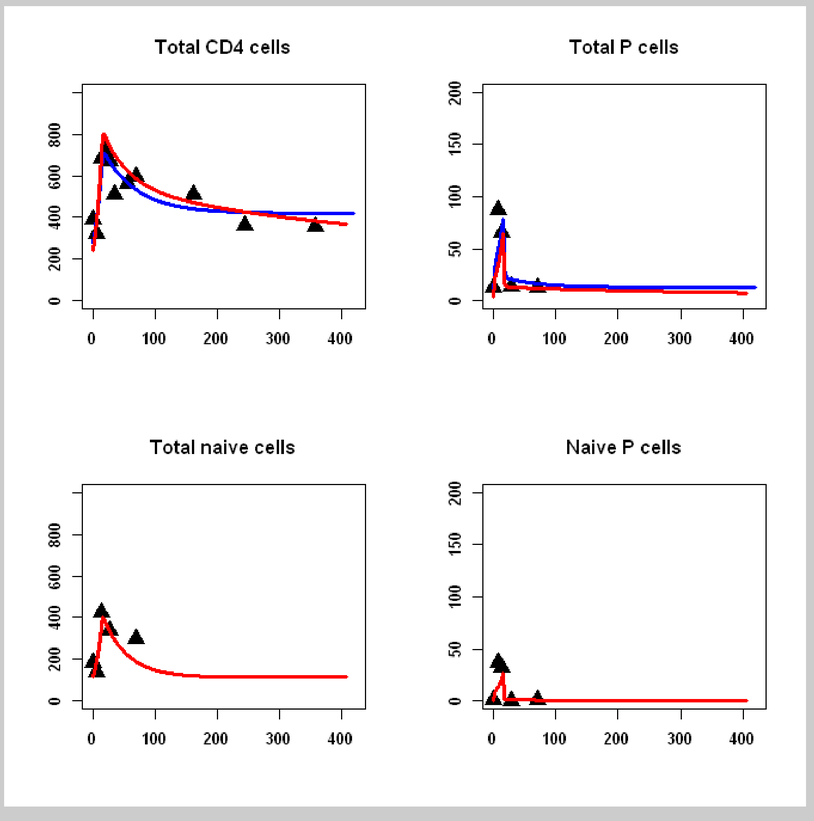
Results

	$\mathcal{M}^{\theta}$ 2 compartments		$\mathcal{M}^{\theta'}$ 4 compartments *	
	Mean	**IC 95%**	**Mean**	**IC 95%**
λ_0	**7.70**	[5.35;10.05]	**2.55**	[0.67;4.42]
τ_0			**0.65**	[0.02;1.27]
μ_{P_0}	**0.07**	[0.01;0.13]	**0.10**	[-0.09;0.29]
$\mu_{P'_0}$			**0.10**	[-0.10;0.30]
ρ_0	**1.29**	[0.95;1.62]	**1.89**	[1.25;2.54]
ρ'_0			**0.77**	[0.29;1.24]
π_0	**0.029**	[0.023;0.035]	**0.010**	[0.006;0.014]
π'_0			**0.024**	[0.004;0.044]
μ_{Q_0}	**0.055**	[0.041;0.069]	**0.032**	[0.012;0.052]
$\mu_{Q'_0}$			**0.021**	[0.005;0.037]
β_π	**1.23**	[1.15;1.31]	**2.37**	[1.97;2.76]
β_{μ_Q}	**-0.18**	[-0.25;-0.10]		
$\beta_{\pi'}$			**1.00**	[0.09;1.91]

* Preliminary work : To consider an effect on π, μ_Q, λ ...

Fits

For patient 16_572_273 in second dose level arm



2 compartments model
4 compartments model

Conclusions

- The increase of proliferation rate is confirmed as being the main biological mechanism in the increase of CD4 count insight in vivo effect of IL-7
- An additional mechanism could be an improvement of CD4 cells survival

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