INDIVIDUAL PREDICTIONS USING MECHANISTIC MODELS

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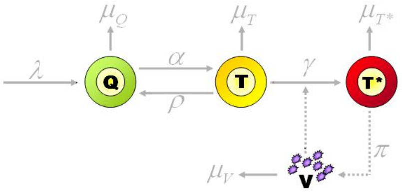
Examples of mechanistic model

Biological Model : Dynamical System (1)

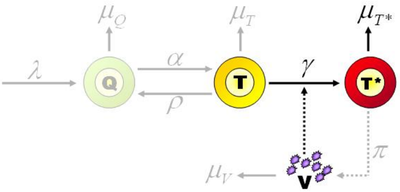
Biological Compartments :
In HIV, cells of interest are viruses and imune cells.



Compartment	Meaning
Q	Quiescents CD4
T	Activated CD4
T^*	Activated Infected CD4
V	Virus

Biological Model : Dynamical System (2)

T^* cells (infected CD4) dynamics :
Exhibit the relation between a quantity and its changing rates over time.

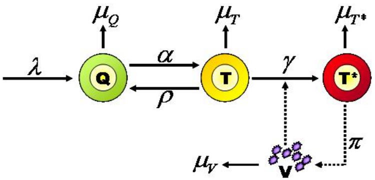


$$\frac{dT^*}{dt} = \gamma V T - \mu_{T^*} T^*$$

Parameter	Meaning
μ_{T^*}	Death rate of T^* cells
γ	Infectivity : Infection rate of T cells by V

Biological Model : Dynamical System (3)

Target cells model



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

Mechanistic models rely on the transcription of physiopathologic knowledge of a disease.

Statistical model

Mixed Effects Model :

- Fixed effects : Pharmacokinetics/Pharmacodynamics/Covariates. . .
- Random effects : Inter-individual variability

$$\begin{aligned}
\tilde{\xi}^i &= \left(\tilde{\alpha}^i, \tilde{\lambda}^i, ..., \tilde{\gamma_0}^i, \tilde{\mu}_V^i\right) \\
\tilde{\xi}_l^i &= \underbrace{\phi_l + d_l^i(t)\beta_l}_{\text{Fixed effects}} + \underbrace{\omega_l^i(t)u_l^i}_{\text{Random effects}} \\
u^i &\sim \mathcal{N}(0, I_q)
\end{aligned}$$

Observation model & Estimations

Observational Model :

$$\begin{aligned} \text{Viral Load :} \quad & Y_{ij1} = \log_{10}(V) + \epsilon_{ij1} \\ \text{Total CD4 count :} \quad & Y_{ij2} = (Q + T + T^*)^{0.25} + \epsilon_{ij2} \\ & \epsilon_{ijm} \sim \mathcal{N}(0, \sigma_m^2) \end{aligned}$$

Estimation :

$$\theta = \left[(\phi_l)_{l=1\ldots n_b}, (\beta_l)_{l=1\ldots n_e}, (\omega_l)_{l=1\ldots q}, (\sigma_l)_{l=1\ldots M} \right]$$

Inference methods in mechanistic model

State of the art

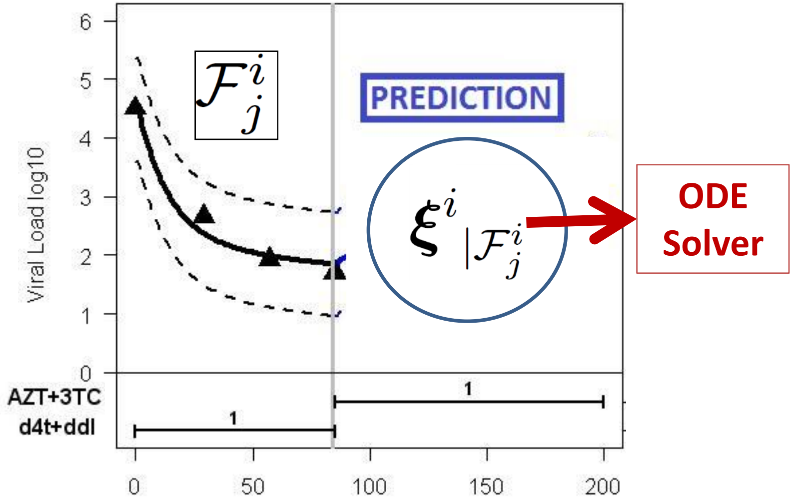
→ **Build a learning dataset** excluding pat. / obs. to predict.

→ **Estimation** of model parameters $\hat{\theta}$.

Method	Ref.	Software
Non parametric Functional analysis	Ramsay et al. 2012	-
Non Bayesian parametric FOCE	Pinheiro et Bates 1995	R
Bayesian SAEM	Kuhn et al. 2005	MONOLIX
	Lavielle et al. 2007	
Bayesian MCMC	Lunn et al 2000	WinBUGS
	Huang et al. 2011	
Bayesian penalized likelihood	Prague et al. 2013	NIMROD

Predictions in mechanistic model

What do we need for predictions ?



Parametric Empirical Bayes for predictions

Parametric Empirical Bayes (Kass, JASA, 1989)

$$\hat{\xi}^i_{|\mathcal{F}^i_j} = \underbrace{\hat{\phi} + \hat{\beta}^T \mathbf{z}(t)^i}_{\text{KNOWN IN POPULATION}} + \underbrace{\hat{\mathbf{u}}^i_{|\mathcal{F}^i_j}}_{\text{UPDATED}}$$

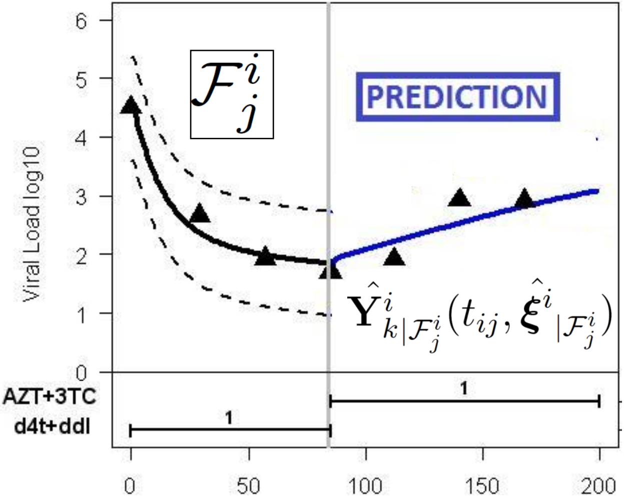
with,

- $\hat{\phi}, \hat{\beta}$: Estimates of fixed effects
- $\mathbf{z}(t)$: Explicative covariates
- $\hat{\mathbf{u}}^i_{|\mathcal{F}^i_j}$: Posterior mode for random effects for individual i with observations to time j

Computationally,

$$\hat{\mathbf{u}}^i_{|\mathcal{F}^i_j} = argmax \left[p(y_{i1}, ..., y_{ij} | \hat{\theta}) \right]$$

Predictives trajectories



Predictions confidence intervals

Credibility interval

Sample L times : Classical MCMC is long, we propose to use a Normal approximation.

- Fixed effects

$$\left(\phi^l, {\beta^T}^l\right) \sim \mathcal{N}\left(\hat{\boldsymbol{\theta}}, H^{-1}(\hat{\boldsymbol{\theta}})\right)$$

- Random effects

$$\mathbf{u}^{i\,l}{}_{|\mathcal{F}_j^i} \sim \mathcal{N}\left(\hat{\mathbf{u}}^i{}_{|\mathcal{F}_j^i}, \frac{\mathcal{I}^{-1}_{\hat{\mathbf{u}}^i{}_{|\mathcal{F}_j^i}}}{j}\right)$$

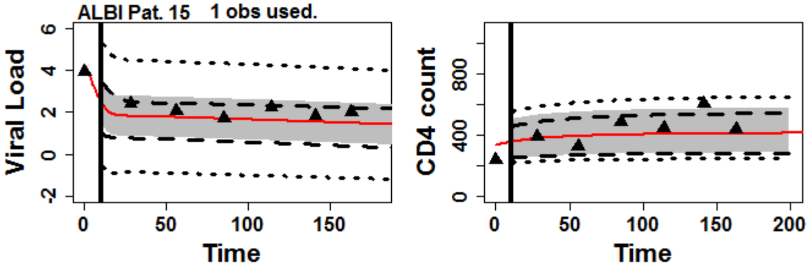
Compute L times :

$$\xi^{i\,l}{}_{|\mathcal{F}_j^i} = \phi^l + {\beta^T}^l \mathbf{z}(t)^i + \mathbf{u}^{i\,l}{}_{|\mathcal{F}_j^i} \quad (1)$$

Credibility interval

$$Y_k^i(t) \quad \in \quad \left[q_{5\%}\left(\left\{ \hat{\mathbf{Y}}_k^i(t_{ij}, {\xi^i}'^{l}_{|\mathcal{F}_j^i}) \right\}_{l=1\ldots L} \right) ; q_{95\%}\left(\left\{ \hat{\mathbf{Y}}_k^i(t_{ij}, {\xi^i}'^{l}_{|\mathcal{F}_j^i}) \right\}_{l=1\ldots L} \right) \right].$$

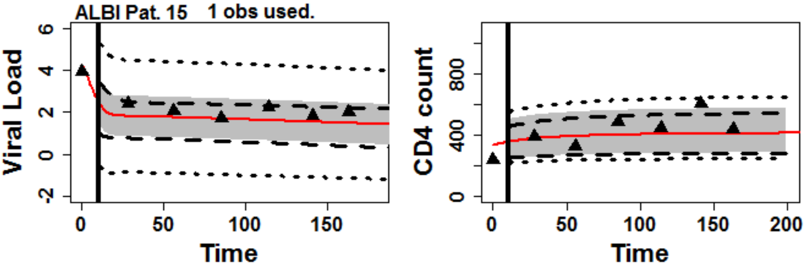
- **DASHED LINES : 95% Credibility interval.**



Error measurement interval

$$Y_k^i(t) \in \left[\hat{\mathbf{Y}}^i_{k|\mathcal{F}^i_j}(t_{ij}, \hat{\xi}^i{}_{|\mathcal{F}^i_j}) \pm 1.96\hat{\sigma}_k \right].$$

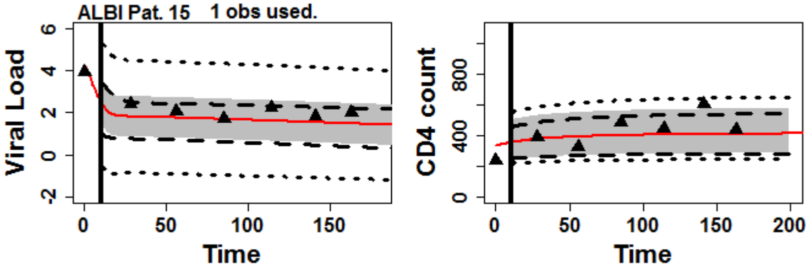
- **SHADED ZONE : 95% Error measurement interval.**



Predictibility interval

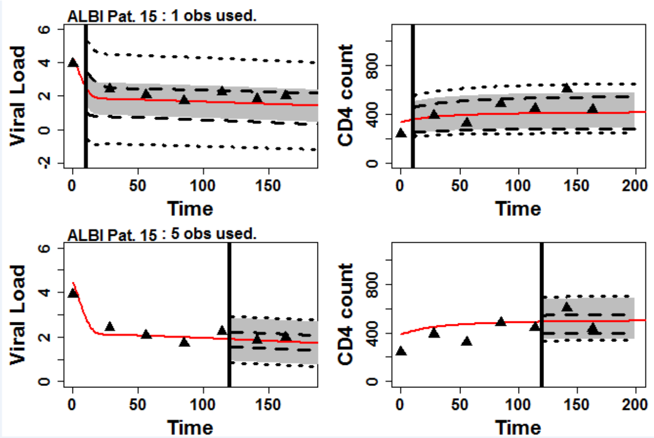
$$Y_k^i(t) \in \left[\hat{\mathbf{Y}}^i_{k|\mathcal{F}_j^i}(t_{ij}, \hat{\xi}^i_{|\mathcal{F}_j^i}) \pm 1.96 \sqrt{\hat{\sigma_k}^2 + \hat{Var}\left(\hat{\mathbf{Y}}^i_k(t_{ij}, {\xi^i}^l_{|\mathcal{F}_j^i})\right)} \right].$$

- **DOTTED LINES : 95% Predictibility interval.**



Intervals comparison

- **SHADED ZONE : 95% Error measurement interval,**
- **DASHED LINES : 95% Credibility interval,**
- **DOTTED LINES : 95% Predictibility interval.**



Conclusion and perspectives

Parametric empirical Bayes are a useful tool for predictions in ODE if :

-> The model is mechanistic enough,

-> Measurement error uncertainty is accounted,

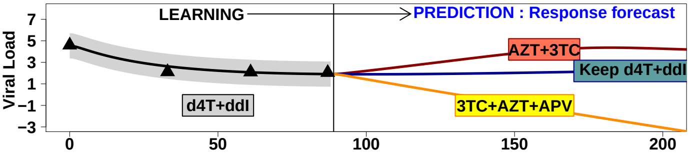
-> Estimation uncertainty is accounted

As a **proof of concept** we shown that :

-> It could help in **personalize medecine**,

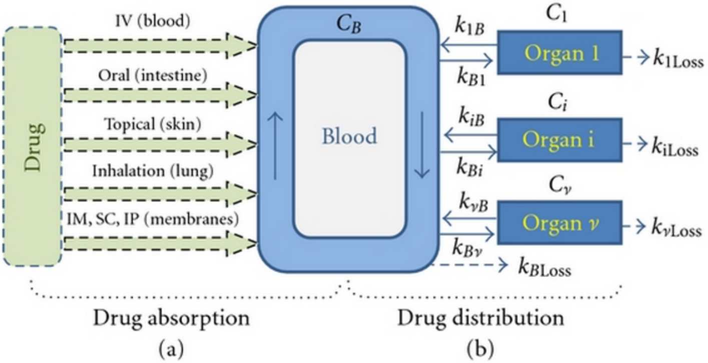
-> Optimize the treatment dose (Prague et al. 2013),

-> Choose the best treatment



Exemple in cancer

Tang et al. 2012 An Integrated Multiscale Mechanistic Model for Cancer Drug Therapy (Biomathematics)



Acknowedgements

Thanks to :

Personnal publications :

- **Concerning parameters estimation methods :**
  Prague et al. (2013) *Comp. Methods Programs Biomed.*
  http ://www.isped.u-bordeaux2.fr/NIMROD/documentation.aspx
- **Concerning HIV dynamical models in personalized medecine :**
  Prague et al. (2013) *Adv Drug Deliv Rev*
  Prague et al. (2012) *Biometrics*

Properties of PEB predictions

Bernstein Von Mises Theorem :

$$\left\| p(\mathbf{u}^i|\mathcal{F}_j^i) - \mathcal{N}\left(\hat{\mathbf{u}^i}_{|\mathcal{F}_j^i}, \frac{\mathcal{I}^{-1}_{\hat{\mathbf{u}^i}_{|\mathcal{F}_j^i}}}{j}\right)\right\| \underset{j\to+\infty}{\longrightarrow} 0$$

When n is fixed, $\hat{\phi}$ and $\hat{\beta}$ hold :

$$\left\| p(\xi^i|\mathcal{F}_j^i) - \mathcal{N}\left(\hat{\xi^i}_{|\mathcal{F}_j^i}, \frac{\mathcal{I}^{-1}_{\hat{\mathbf{u}^i}_{|\mathcal{F}_j^i}}}{j}\right)\right\| \underset{j\to+\infty}{\longrightarrow} 0$$

Let n becomes greater, the Doob consistency gives :

$$p(\boldsymbol{\theta}|\mathbf{Y}_1, \ldots, \mathbf{Y}_n) \underset{n\to+\infty}{\overset{\mathcal{L}}{\longrightarrow}} \delta_{\boldsymbol{\theta}^*}.$$

Let denote ξ^{i^*} the true parameters for patient i :

$$p(\xi^i|\mathcal{F}_j^i) \underset{j\to+\infty}{\overset{n\to+\infty}{\longrightarrow}} \delta_{\xi^{i^*}}$$