



LABORATOIRE
JEAN KUNTZMANN
MATHÉMATIQUES APPLIQUÉES - INFORMATIQUE



Parameter estimation in a stochastic model for immunotherapy of cancer

Modibo DIABATE

PhD Student in Applied Mathematics
Laboratoire Jean Kuntzmann - University Grenoble Alpes

Supervised by
Loren COQUILLE: UGA - IF
Adeline LECLERCQ SAMSON: UGA - LJK

Septièmes rencontres des Jeunes Statisticien-ne-s

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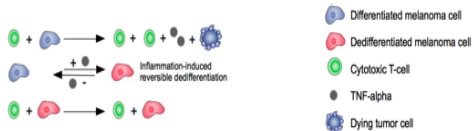
Outline

- 1 Context
- 2 Modeling of tumor evolution
- 3 Parameter estimation
- 4 Results

Context: Immunotherapy/ACT therapy

■ Previous works:

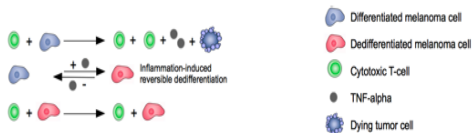
- stochastic model for skin cancer **immunotherapy** (Baar et al., 2015)
- Adoptive Cell Transfer (ACT) therapy (Landsberg et al., 2012)



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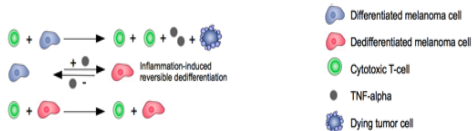
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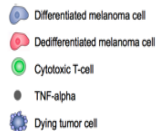
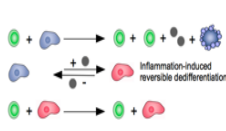


Objective: understanding the resistance of tumors

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Objective: understanding the resistance of tumors

- Modeling the mechanism
- Estimating parameters using real data



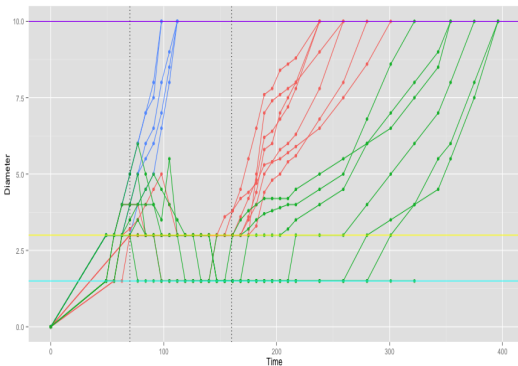
Experimental data

Therapy and groups of mice

- CTRL mice (5): no therapy
- ACT mice (7): ACT therapy (70th day)
- ACT+Re mice (7): ACT therapy (70th, 160th day)

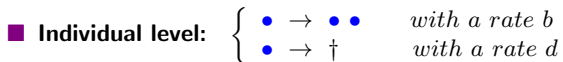
Tumor evolution measurement

$$y_{ij}^{obs} = \begin{cases} y_{ij} & \text{if } y_{ij} \in]3 \text{ mm}, 10 \text{ mm}[\\ 1.9 \text{ mm} & \text{if } y_{ij} \in [0 \text{ mm}, 1.9 \text{ m} \\ 3 \text{ mm} & \text{if } y_{ij} \in [2 \text{ mm}, 3 \text{ mm}] \\ 10 \text{ mm} & \text{if } y_{ij} \geq 10 \text{ mm} \end{cases}$$



Modeling of tumor evolution: Birth and death process (BDP)

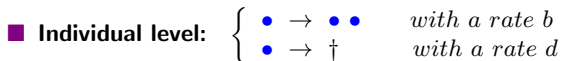
Cell populations involved in the dynamic are modeled by BDP (continuous time Markov process).



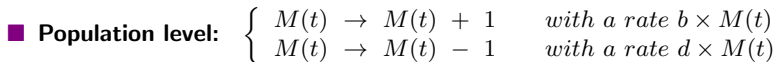
waiting time before an event modeled by an exponential distribution

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Modeling of tumor evolution: Birth and death process (BDP)

Cell populations involved in the dynamic are modeled by BDP (continuous time Markov process).

■ **Individual level:**
$$\begin{cases} \bullet \rightarrow \bullet \bullet & \text{with a rate } b \\ \bullet \rightarrow \dagger & \text{with a rate } d \end{cases}$$

waiting time before an event modeled by an exponential distribution

■ **Population level:**
$$\begin{cases} M(t) \rightarrow M(t) + 1 & \text{with a rate } b \times M(t) \\ M(t) \rightarrow M(t) - 1 & \text{with a rate } d \times M(t) \end{cases}$$

■ **Large population approximation:** $M^K(t) = \frac{M(t)}{K}$

$$\begin{cases} M^K(t) \rightarrow M^K(t) + \frac{1}{K} & \text{with a rate } b \times M^K(t) \times K \\ M^K(t) \rightarrow M^K(t) - \frac{1}{K} & \text{with a rate } d \times M^K(t) \times K \end{cases}$$

Modeling of tumor evolution: BDP - Large population approximation

Let $M^K(t) = \frac{M(t)}{K}$,

$$\lim_{K \rightarrow \infty} M^K(t) \text{ (in law)} = n^*$$

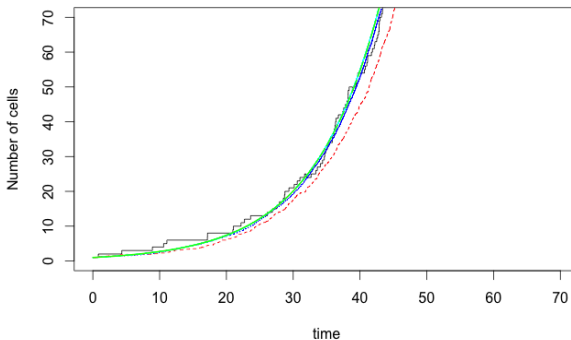
where n^* is the solution of $\dot{n}_M = (b - d)n_M$ with initial condition n_0 .
(Ethier and Kurtz, 2009)

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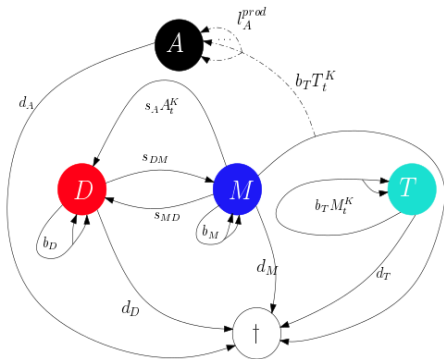
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Modeling of tumor evolution: Stochastic model

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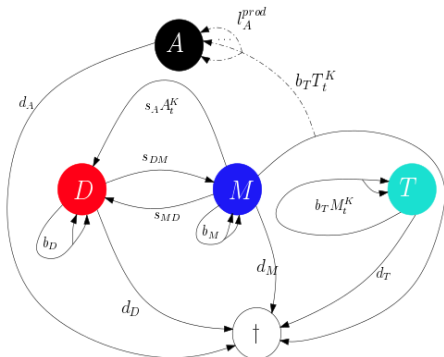
- ●: T cell, $T(t)$: population of therapy cells
- ●: differentiated cell, $M(t)$: population of differentiated cells at time t
- ●: dedifferentiated cell, $D(t)$: population of dedifferentiated cells
- ●: cytokine TNF_α , $A(t)$: population of cytokines TNF_α



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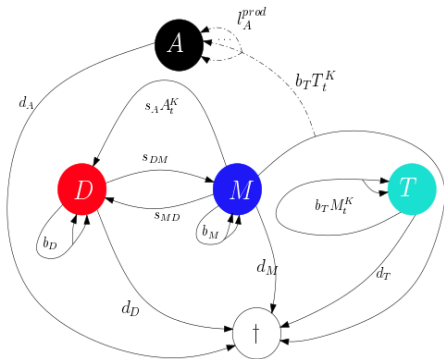
Stochastic model = BDP + switch + predator-prey (Baar et al., 2015)

$$Z(t) = (M(t), D(t), T(t), A(t))$$

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$$Z(t) = (M(t), D(t), T(t), A(t))$$

$$\mu = (b_M, b_D, b_T, l_A^{prod}, d_M, d_D, t_T, d_T, d_A, s_A, s_{MD}, s_{DM})$$

Modeling of tumor evolution: Deterministic model

Large population approximation: **Stochastic model** → **Deterministic model**

Let $M^K(t) = \frac{M(t)}{K}$, $D^K(t) = \frac{D(t)}{K}$, $T^K(t) = \frac{T(t)}{K}$, $A^K(t) = \frac{A(t)}{K}$

$$\lim_{K \rightarrow \infty} (M^K(t), D^K(t), T^K(t), A^K(t)) \text{ (in law)} = (n_M^*, n_D^*, n_T^*, n_A^*)$$

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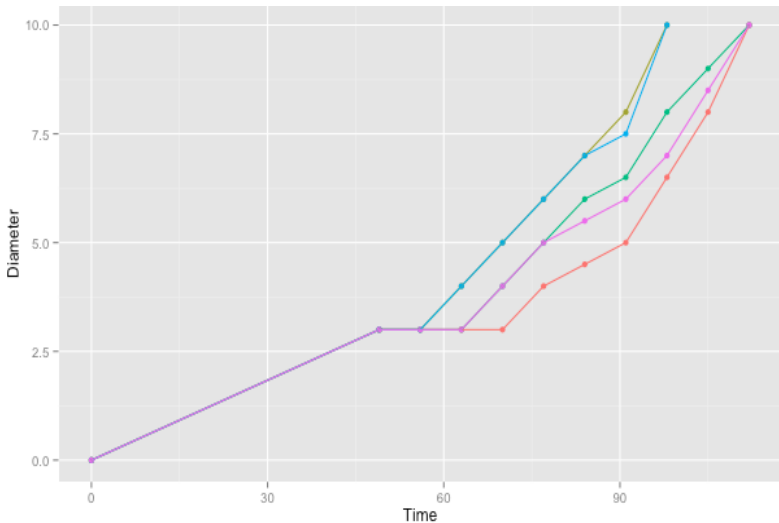
with $(n_M^*, n_D^*, n_T^*, n_A^*)$ the solution of the deterministic system:

$$\begin{cases} \dot{\mathbf{n}}_M = (b_M - d_M)\mathbf{n}_M - t_T \mathbf{n}_T \mathbf{n}_M - s_{MD} \mathbf{n}_M + s_{DM} \mathbf{n}_D - s_A \mathbf{n}_A \mathbf{n}_M \\ \dot{\mathbf{n}}_D = (b_D - d_D)\mathbf{n}_D + s_{MD} \mathbf{n}_M - s_{DM} \mathbf{n}_D + s_A \mathbf{n}_A \mathbf{n}_M \\ \dot{\mathbf{n}}_T = -d_T \mathbf{n}_T + b_T \mathbf{n}_M \mathbf{n}_T \\ \dot{\mathbf{n}}_A = -d_A \mathbf{n}_A + l_A^{prod} b_T \mathbf{n}_M \mathbf{n}_T \end{cases}$$

with initial condition $(n_{M_0}, n_{D_0}, n_{T_0}, n_{A_0})$ (Baar et al., 2015).

$$\mu = (b_M, b_D, b_T, l_A^{prod}, d_M, d_D, t_T, d_T, d_A, s_A, s_{MD}, s_{DM}) \text{ (to be estimated)}$$

Parameter estimation: Mixed Effects Models



Parameter estimation: Mixed Effects Model - Likelihood function

- NonLinear Mixed Effects Model (NLMEM):

$$y_{ij} = f(\psi_i, t_{ij}) + \epsilon_{ij}, \quad \epsilon_i \sim \mathcal{N}(0, \sigma^2 I_{n_i}), \quad \psi_i = \mu + r_i, \quad \text{with } r_i \sim \mathcal{N}(0, \Omega),$$

$$f(\psi_i, t) = (n_M^*(\psi_i, t) + n_D^*(\psi_i, t))^{\frac{1}{3}}, \quad n_M^*, n_D^*: \text{deterministic system solution}$$

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$r_i = (b_{M_i}, b_{D_i}, b_{T_i}, \dots, s_{A_i}, s_{MD_i}, s_{DM_i})$: vector of random effects,

Ω : variance matrix of the random effects

$$\Theta = \{\mu, \sigma, \Omega\}$$

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- Likelihood function:

$$L(y^{obs}, \delta; \theta) = \prod_{i=1}^N \int L(y_i^{obs}, \delta_i, y_i^{cens}, \psi_i; \theta) d\psi_i dy_i^{cens}$$

ψ_i : individual parameters; y_i^{cens} : censored data ($\delta_{ij} = 0$); y_i^{obs} : observed data ($\delta_{ij} = 1$),

$$L(y_i^{obs}, \delta_i, y_i^{cens}, \psi_i; \theta) = \prod_{(i,j)|\delta_{ij}=1} p(y_{ij}^{obs} | \psi_i; \theta) p(\psi_i; \theta) \prod_{(i,j)|\delta_{ij}=0} p(y_{ij}^{cens} | \psi_i; \theta) p(\psi_i; \theta)$$

$p(y_{ij}^{obs} | \psi_i; \theta)$ and $p(y_{ij}^{cens} | \psi_i; \theta)$ are gaussian (Samson et al., 2006)

Parameter estimation: SAEM (Stochastic Approximation EM)

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Iteration k of the algorithm:

■ step E:

- Simulation step: draw $(y^{cens(k)}, \psi^{(k)})$ with the conditional distribution $p(y^{cens}, \psi | y, \hat{\theta}_{k-1})$

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- Stochastic approximation step:

$$Q_k(\theta) = Q_{k-1}(\theta) + \gamma_k \left[\log p(y^{obs}, \delta, y^{cens(k)}, \psi^{(k)}; \theta) - Q_{k-1}(\theta) \right]$$

(γ_k) is a decreasing sequence: $\sum_{k=1}^{\infty} \gamma_k = \infty$, $\sum_{k=1}^{\infty} \gamma_k^2 < \infty$

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■ step M:

- Maximization step: update $\hat{\theta}_{k-1}$ according to

$$\hat{\theta}_k = \arg \max_{\theta \in \Theta} Q_k(\theta)$$

Parameter estimation: SAEM - MCMC

SAEM-MCMC for regular exponential families:

$$p(y^{obs}, y^{cens}, \psi; \theta) = \exp\{-\xi(\theta) + \langle \tilde{S}(y^{obs}, y^{cens}, \psi), \Psi(\theta) \rangle\}$$

Iteration k of the algorithm:

- **Simulation step:** simulation of $(y^{cens(k)}, \psi^{(k)})$ through the simulation of a Markov Chain having $p(y^{cens}, \psi | y, \hat{\theta}_{k-1})$ as stationary distribution

- **Stochastic approximation:** update s_k according to

$$s_k = s_{k-1} + \gamma_k (\tilde{S}(y^{obs}, y^{cens(k)}, \psi^{(k)}) - s_{k-1})$$

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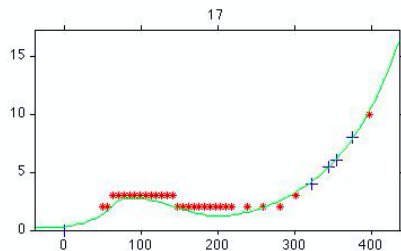
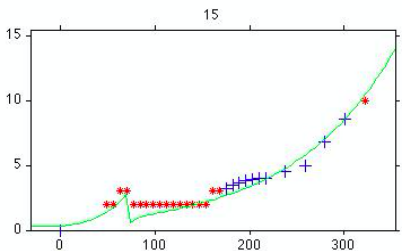
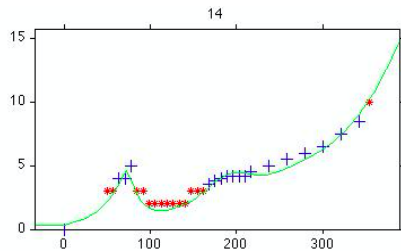
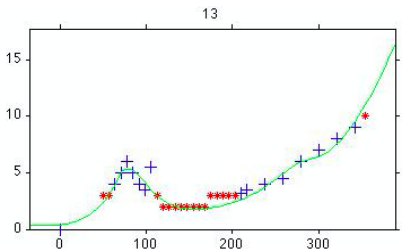
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SAEM is considered to estimate correctly population parameters as well as having good theoretical properties

Convergence of the estimate sequence of the SAEM-MCMC to a local maximum of the likelihood proved by (Delyon et al., 1999) using:

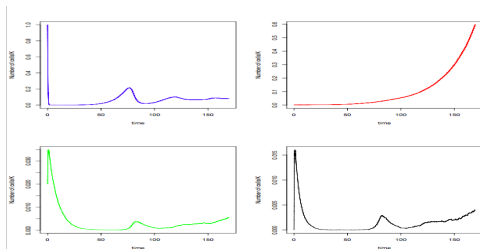
- the assumption that $p(y, \psi, \theta)$ belongs to a regular exponential families,
- some continuity and differentiability assumptions on the likelihood and $\tilde{S}(y, \psi)$,
- the uniform ergodicity assumption on Markov Chains in the MCMC algorithm.

Estimated parameters: Individuals fits (group ACT+Re)

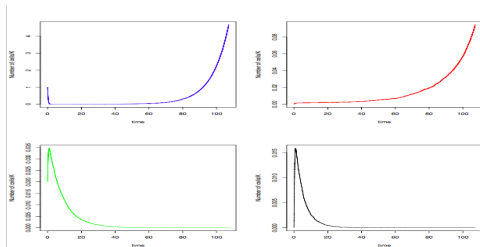


T-cells extinction & Relapse: Simulation of extinction with the stochastic model using estimated parameters

Scenario (a): T cells survive



Scenario (b): Extinction of T cells



T-cells extinction & Relapse : Rare events probability estimation

■ Monte Carlo, Importance Sampling

T-cells extinction & Relapse : Rare events probability estimation

■ Monte Carlo, Importance Sampling

■ Importance Splitting (Jacquemart-Tomi et al., 2013)

- T_t : stochastic process
- S : threshold
- $t_S = \inf\{t \geq 0, T_t \leq S\}$
- The rare event :
 $\{t_S \leq t_F\} = \{T_t \leq S, \text{ for } t \leq t_F\}$

T-cells extinction & Relapse : Rare events probability estimation

■ Monte Carlo, Importance Sampling

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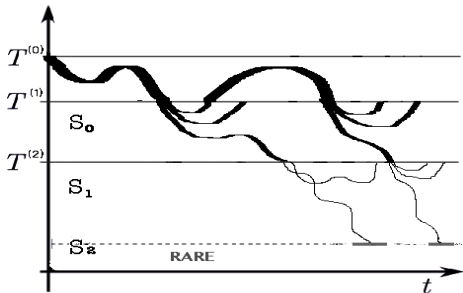
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Extinction probability $\mathbb{P}(t_S \leq t_F)$

$$\mathbb{P}(t_S \leq t_F) = \prod_{k=1}^m p_k$$

$$p_1 = \mathbb{P}(t_1 \leq t_F) = \mathbb{P}\{T_t \leq S_1, \text{ for } t \leq t_F\}$$

$$p_k = \mathbb{P}(t_k \leq t_F \mid t_{k-1} \leq t_F) \text{ for } k = 2, \dots, m$$



Conclusion & Future Works

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- Simplification/adaptation of the model for parameter estimation
- Parameter estimation using real biological data (censored data)
- Estimation of the probability of T cell population extinction (relapse)

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■ Future Works

- Optimal selection of parameters for the relapse probability estimation
- Parameter estimation (with an Expectation Propagation algorithm) from a diffusion approximation of the stochastic model (Barthelmé and Chopin, 2014), (Cseke et al., 2016)
- Development (and parameter estimation) of a probabilistic model for lung cancer using MRI images

Thank you for your attention !

References

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