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Analysis of *in vivo* Responses by Mixed-Effect Models

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Objectives. In *in vivo* experimentation, the large intra-group variability between animals is a major obstacle that prevents to **detect significant therapeutic effects** of treatment factors. Our objective is to assess a new statistical method able to better estimate and characterize the additive effects of the combination of an **oncolytic virus** (TG6002) and the **prodrug flucytosine** (5-FC) associated in an anti-cancer treatment. The experimental data are kinetics of tumor growth collected during *in vivo* assays carried out on mice.

Method

$$y_{ij} = x(t_{ij}, \theta_i) + \epsilon_{ij}, \quad \forall i = 1, \dots, r, \forall j = 1, \dots, n_i,$$

$$x(t_{ij}, \theta_i) = k_{1,i}(t_{ij} + t_0) + x_{0,i} + k_{2,i}(t_{ij} + t_0 - \tau_i)$$

$$\theta_i = \lambda + c_i \beta + \theta_i, \quad \theta_i \sim \mathcal{N}(\mathbf{0}, \mathbf{\Omega}), \quad \forall i = 1, \dots, r,$$

$$\theta_i = (x_{0,i} \quad k_{1,i} \quad k_{2,i} \quad \tau_i)^T$$

$$\epsilon_{ij} = \sigma e_{ij}, \quad e_{ij} \stackrel{i.i.d.}{\sim} \mathcal{N}(0, 1), \quad \forall i = 1, \dots, r, \forall j = 1, \dots, n_i,$$

$$c_i = (c_{c,i} \quad c_{d,i} \quad c_{0,i})$$

$x_{0,i}$ Initial diameter

$k_{1,i}$ First growth rate

$k_{2,i}$ Second growth rate

τ_i Time delay between effects

c_c TG6002 concentration factor

c_d 5-FC presence factor

c_0 Initial diameter variation

The experimental set up is decomposed into 4 main steps:

1. a **full factorial design of experiments** is proposed. TG6002 was tested at four concentrations in combination or not with 5-FC. Eight groups of 13 mice are randomly affected to each experimental condition.
2. we propose a **mixed-effect model** to describe the kinetic growth of the mean tumor diameter.
3. the model parameters are determined with a **maximum likelihood estimator** based on an expectation-maximization algorithm.
4. effects of the two examined components are assessed with a **Wald test**.

Group. No.	TG6002	5-FC
1	0	With
2	0	Without
3	Dose 1	With
4	Dose 1	Without
5	Dose 2	With
6	Dose 2	Without
7	Dose 3	With
8	Dose 3	Without

Tab.1: Full Factorial Design of Experiments with 2 factors

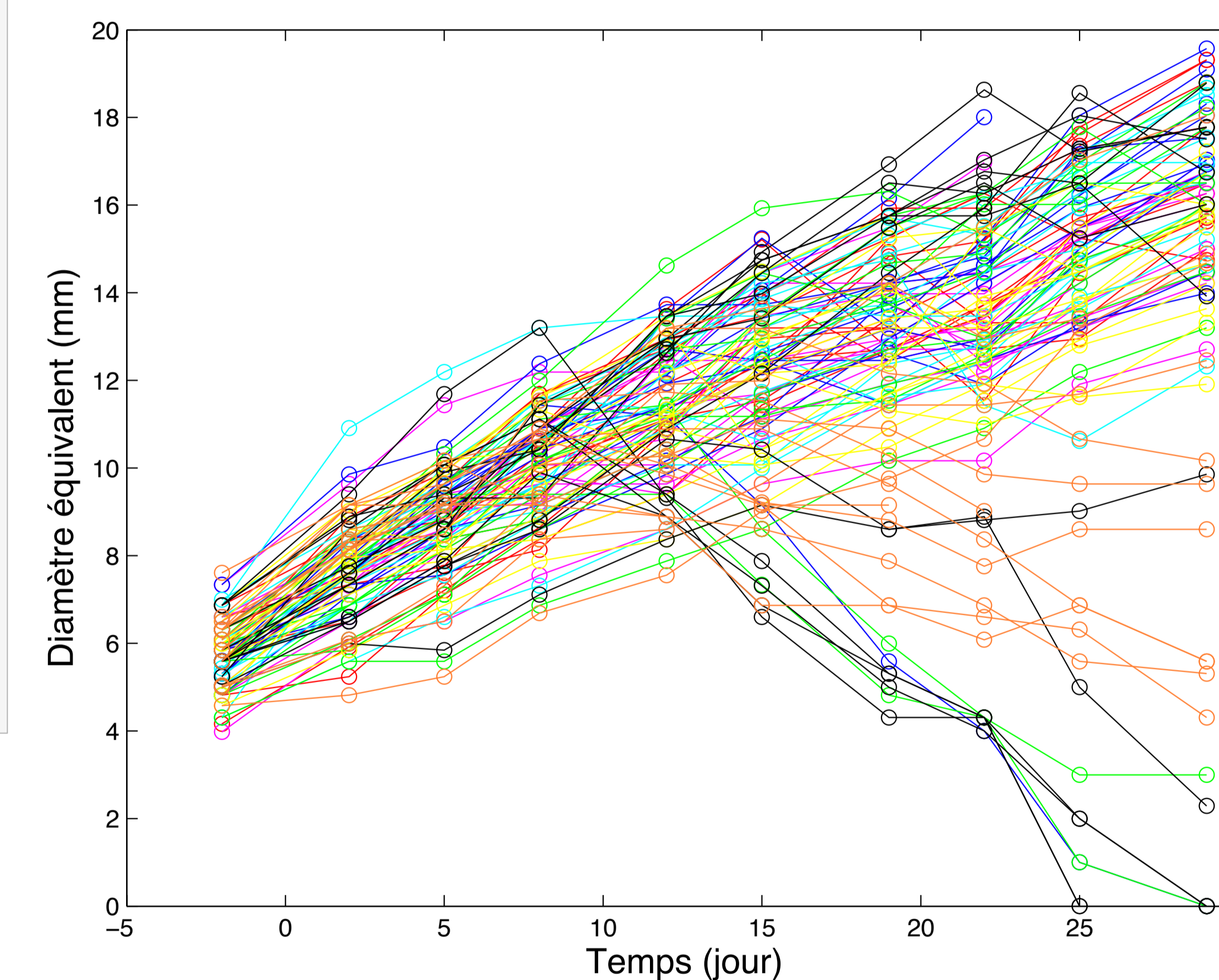


Fig.1: Longitudinal Data: growth kinetics of the tumor equivalent diameter (mm) for 104 mice distributed between 8 groups of treatment: group 1 (magenta), group 2 (red), group 3 (cyan), group 4 (blue), group 5 (yellow), group 6 (green), group 7 (orange), group 8 (black)

Results

Our model structure fits correctly all the 104 observed growth responses. The confidence on the estimation results is such that we can detect two treatment effects. Indeed, we show a 3% reduction of the therapeutic response time due to 5-FC and a division by five of the growth delay with TG6002.

Conclusion

Results confirm the relevance of mixed-effect kinetic models to increase the power of statistical tests applied to *in vivo* studies and efficacy of the combination TG6002 with 5-FC.

Reference

T. Bastogne, A. Samson, P. Vallois, S. Wantz-Mézières, S. Pinel, D. Bechet, and M. Barberi-Heyob. Phenomenological modeling of tumor diameter growth based on a mixed effects model. Journal of Theoretical Biology, 262:544–552, 2010.

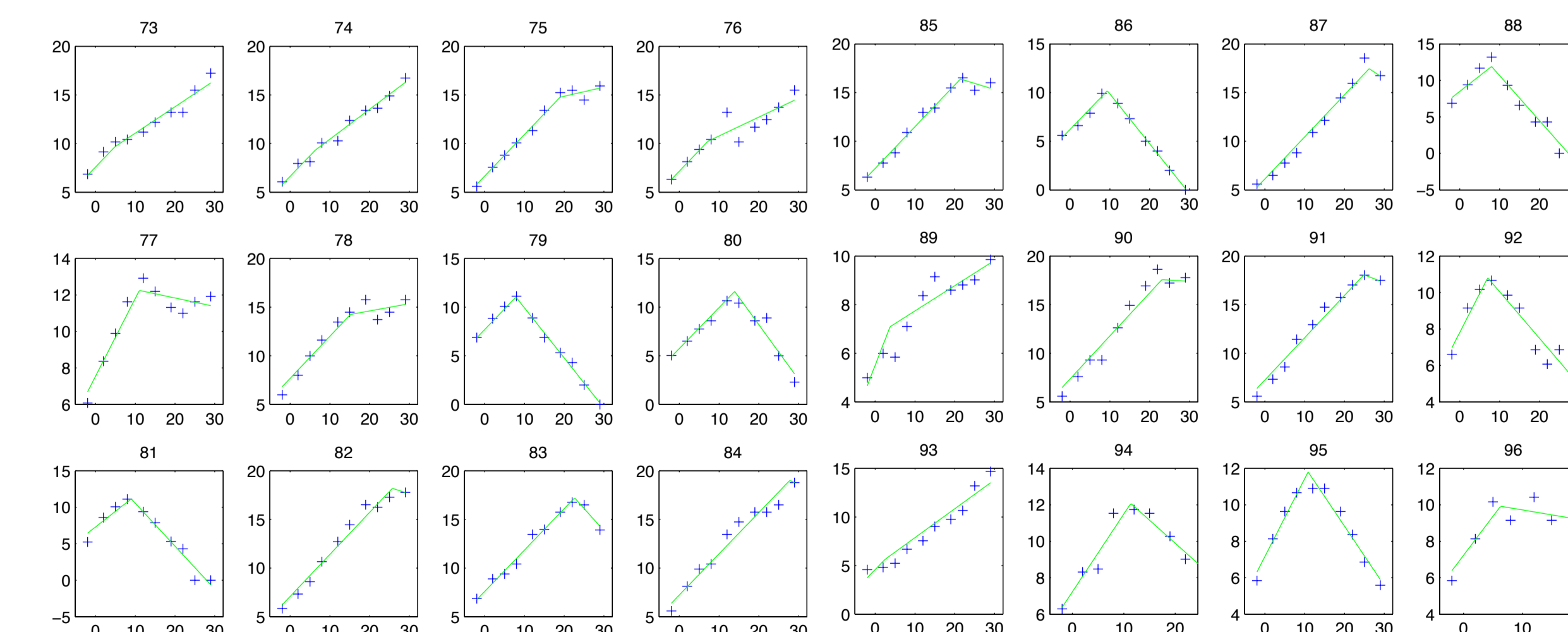


Fig.2: Mixed-effect modeling of the time responses for 24 mice. Measured responses (blue) & Model responses (green)

Effect	Value	P-value
$\beta_{k_2}(D_{TG} = 3)$	-0.42	$1.4 \cdot 10^{-10}$
$\beta_{\tau}(5FC)$	-0.45	$1.7 \cdot 10^{-4}$

Tab.2: Estimated effects of the therapeutic factors on the post-treatment growth rate (k_2) and response delay (τ). Only the 2 most significant effects are indicated here.