



HAL
open science

Analysis of in vivo responses by mixed-effect models reference

Levy Batista, Bérangère Bastien, Thierry Bastogne, Johann Foloppe, Philippe Erbs

► **To cite this version:**

Levy Batista, Bérangère Bastien, Thierry Bastogne, Johann Foloppe, Philippe Erbs. Analysis of in vivo responses by mixed-effect models reference. 8th International Meeting on Statistical Methods in Biopharmacy, SMB 2017, Sep 2017, Paris, France. hal-01670100

HAL Id: hal-01670100

<https://hal.science/hal-01670100v1>

Submitted on 21 Dec 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

L. BATISTA^{1,3,4}, B. BASTIEN², T. BASTOGNE^{1,3,4}, J. FOLOPPE², P. ERBS²

¹CRAN, ²TRANSGENE, ³INRIA BIGS, ⁴CYBERnano

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

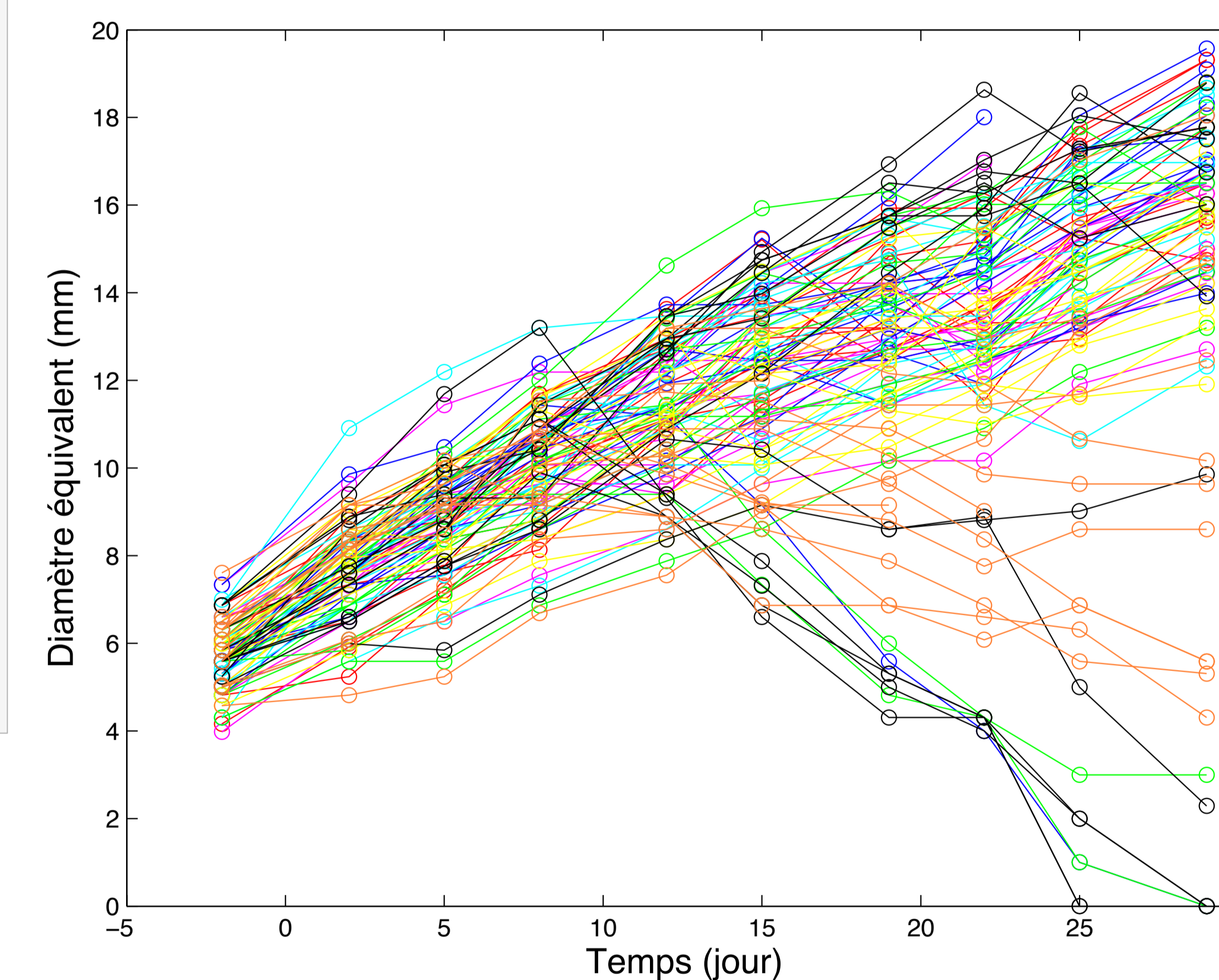


Fig.1: Longitudinal Data: growth kinetics of the tumor equivalent diameter (mm) for 104 mice distributed between 8 groups of treatment: group 1 (magenta), group 2 (red), group 3 (cyan), group 4 (blue), group 5 (yellow), group 6 (green), group 7 (orange), group 8 (black)

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.

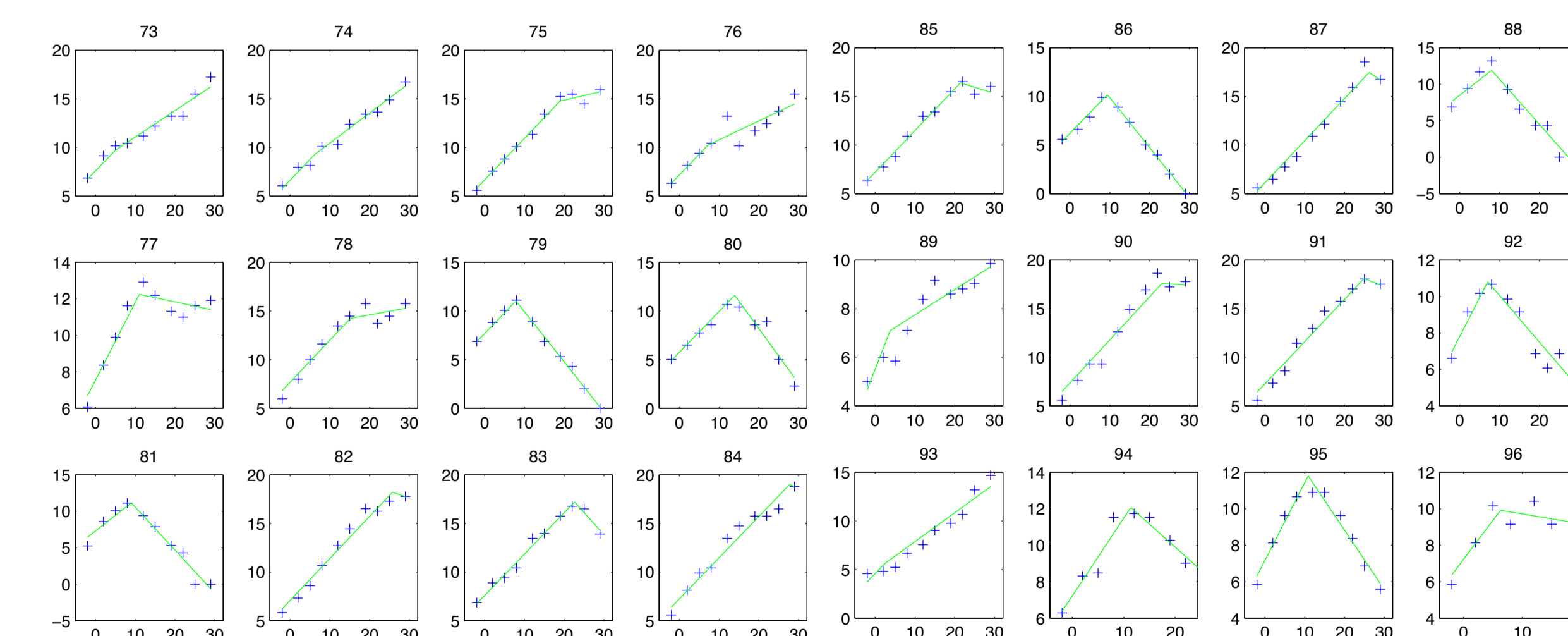


Fig.2: Mixed-effect modeling of the time responses for 24 mice. Measured responses (blue) & Model responses (green)

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.