Analysis of in vivo responses by mixed-effect models reference
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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

\[ y_{ij} = x(t_{ij}, \theta_i) + e_{ij}, \quad \forall i = 1, \ldots, n, \forall j = 1, \ldots, n_i \]

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

\[ \theta_i = \lambda + c_{i,\lambda} + \theta_i, \quad \theta_i \sim N(0, \Omega), \quad \forall i = 1, \ldots, n, \]

\[ c_{i} = (c_{c,i}, c_{d,i}, c_{0,i}) \]

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. The experimental set up is decomposed into 4 main steps:

### 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 treatments 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