The use of tumor dynamics and new lesions to predict survival with multivariate joint frailty models

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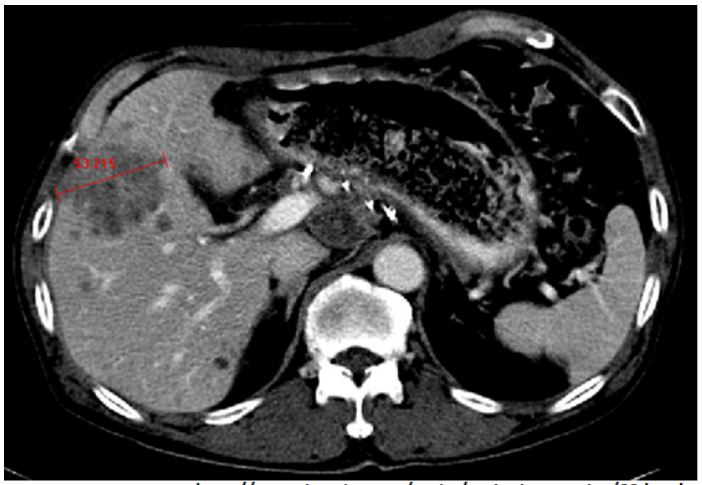
Context

- Continuously increasing number of cancer clinical trials for treatment evaluation $\rightarrow$ necessity of a "common language"
- Some history
  - 1979 - WHO criteria
  - 2000, 2009 (v1.1) - RECIST(Response Evaluation Criteria in Solid Tumors)
  - 2009 - irRC (Immune Related Response Criteria)
- Critics of RECIST (J. Bogaerts, TAT, 2015) :
  - not adapted to certain tumor types, based on anatomical burden, does not include functional imaging or 3D, not relevant with novel agents, ...
  - progressive disease developed for use with primary endpoint of best objective response (phase II) but used for phase III endpoint $\rightarrow$ **surrogate discussion**

RECIST criteria



http://www.irrecist.com/recist/recist-in-practice/02.html

- Target lesions
  - Unidimensional size, max 2 lesions per organ and up to 5 total
  - Progression : >20% increase over smallest sum observed ($>$ 5 mm absolute increase)
- Appearance of new lesions $\rightarrow$ global progression
- Unequivocal progression of non-target lesions $\rightarrow$ global progression

4 categories (Complete Response, Partial Response, Progressive Disease, Stable Disease)

$\Rightarrow$ dichotomization : response or no response / progression or no progression

Trivariate joint model (Król et al., *Biometrics* 2016)

- **Objective** : Evaluation of predictive accuracy - longitudinal tumor size and recurrent appearance of new lesions vs. progression based on categorical criteria
- Joint model for longitudinal data, recurrent events and a terminal event :

$$\begin{cases} Y_i(t_{ik}) = \boldsymbol{X}_{i,l}(t_{ik})^\top \beta_l + \boldsymbol{Z}_i(t_{ik})^\top \boldsymbol{b}_i + \epsilon_i(t_{ik}) & \text{(Biomarker)} \\ r_{ij}(t|v_i, \boldsymbol{b}_i) = r_0(t) \exp\left(v_i + \boldsymbol{X}_{ij,r}^\top \beta_r + g(\boldsymbol{b}_i, t)^\top \eta_r\right) & \text{(Recurrences)} \\ \lambda_i(t|v_i, \boldsymbol{b}_i) = \lambda_0(t) \exp\left(\alpha v_i + \boldsymbol{X}_{i,t}^\top \beta_t + h(\boldsymbol{b}_i, t)^\top \eta_t\right) & \text{(Death)} \end{cases}$$

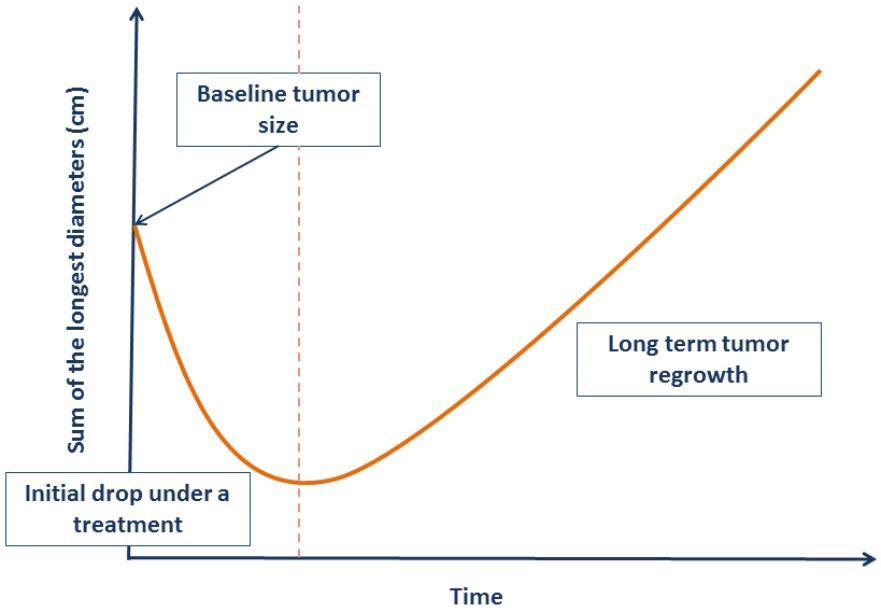
  - $u_i = (\boldsymbol{b}_i^T, v_i)^T \sim \mathcal{N}(\mathbf{0}, \mathbf{B})$ with $\mathbf{B} = \begin{pmatrix} \mathbf{B_1} & \mathbf{0} \\ \mathbf{0} & \sigma_v^2 \end{pmatrix}$
  - measurement errors *iid*, $\epsilon_i(t_{ik}) \sim \mathcal{N}(0, \sigma_\epsilon^2)$
  - $g(\boldsymbol{b}_i, t)$ and $h(\boldsymbol{b}_i, t)$ - link functions
  - $r_0(t)$, $\lambda_0(t)$ - baseline hazard functions

Trivariate joint model (Król et al., *Biometrics* 2016)

- Application : randomized phase III clinical trial of metastatic colorectal cancer (FFCD 2000-05 trial), 410 patients
  - Better predictive accuracy of the joint model with tumor size and appearance of new lesions
- Implementation of the proposed model into the R package `frailtypack` Krol et al., *JSS (In Press)*

Objective

- Incorporation of information on progression of non-target disease
- Application to other clinical trials, in particular to a meta-analysis
- More flexible modeling of the biomarker
  - Tumor dynamics modeled using a mechanistic model (Claret et al., *JCO* 2009)
  - Comparison with : approach with two slopes of time, approximation by B-splines



Review of Tumor Growth Models Ribba et al., *CPT* 2014

1. Models expressed as algebraic equations, ex. $y(t) = \underbrace{y_0 \cdot e^{-d \cdot t}}_{\text{Exponential decay}} + \underbrace{g \cdot t}_{\text{Linear growth}}$

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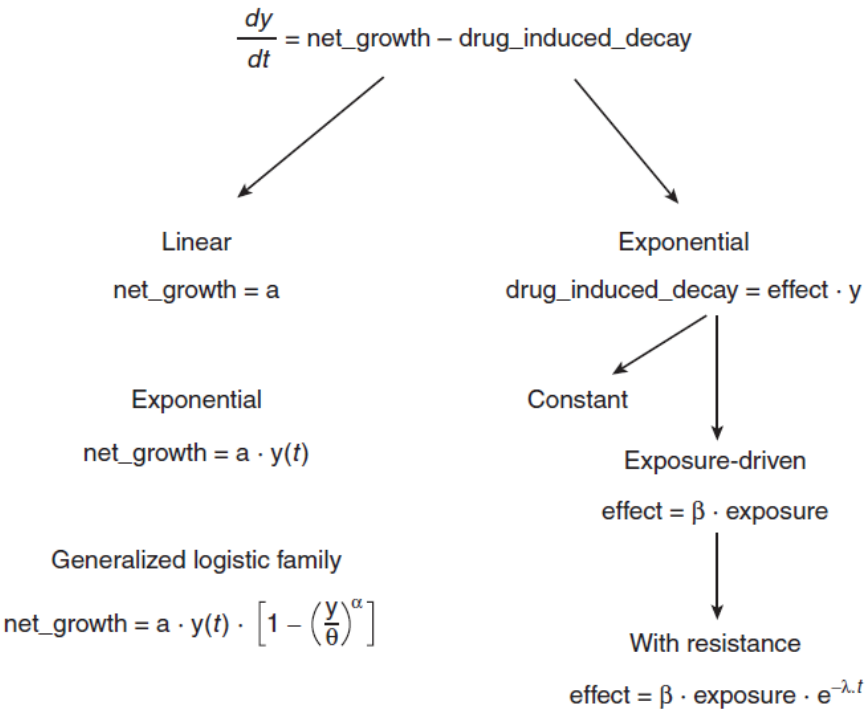
2. Models expressed as ordinary differential equations (ODE)



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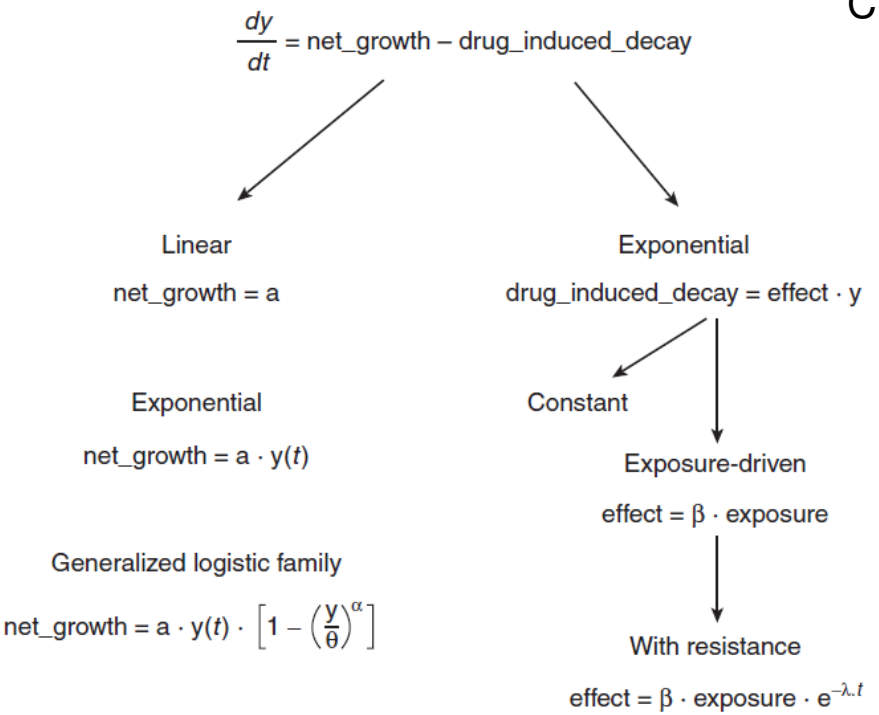


Tumor growth inhibition (TGI) model

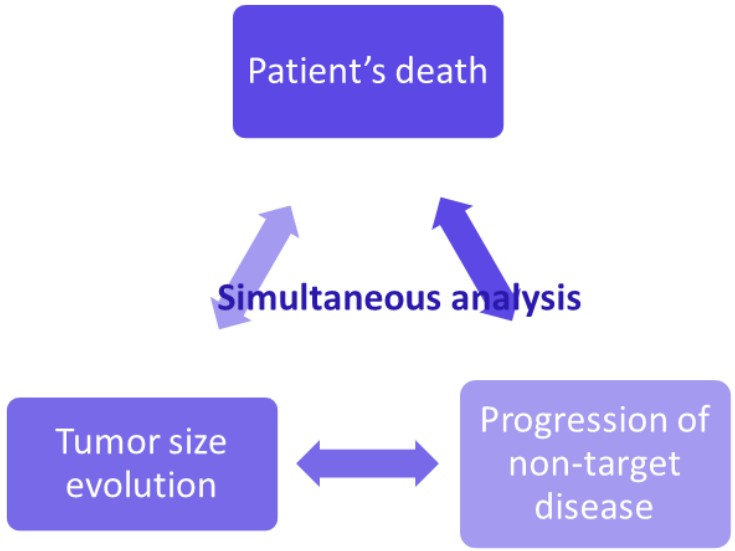
Claret et al., *JCO* 2009

- Accounts for dynamics of tumor growth, antitumor drug effect, resistance to drug effect
- $\frac{dy(t)}{dt} = K_L \cdot y(t) - K_D(t) \cdot \text{Exposure}(t) \cdot y(t)$
  $y(0) = y_0$
- Interpatient variability via lognormal random effects
- Two-stage model : tumor-size metrics estimates to predict OS (Claret et al., *JCO* 2013)

Notation

For individual i ($i = 1, \ldots, N$) we observe :

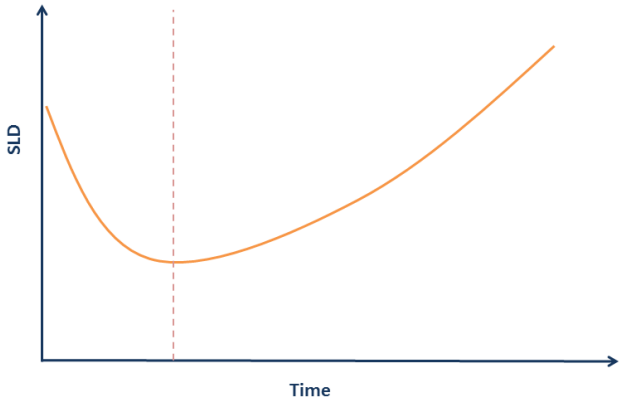
- n_i measurements of **longitudinal biomarker** (sum of the longest diameters, SLD) : $y_i(t_{ik})$
- r_i **recurrent events** (appearance of new lesions or progression of non-target lesions, NT) : $R_{ij} = \min(R_{ij}^*, C_i, T_i^*)$ and $\delta_{ij}^R = \mathbb{1}_{\{R_{ij}^* = R_{ij}\}}$
- **Time to terminal event** (death) : $T_i = \min(C_i, T_i^*)$ and $\delta_i^T = \mathbb{1}_{\{T_i^* = T_i\}}$



Model for the biomarker

- Dynamics of tumor size defined by an **ordinary differential equation**

$$\begin{cases} \frac{dy_i(t)}{dt} = K_{G,i} y_i(t) - d_i(t) K_{D,i}(t) e^{-\lambda t} y_i(t) \\ \log(y_i(0)) = y_{i,0} + b_{y_0,i} \\ \log(K_{G,i}) = K_{G,0} + b_{G,i} + \boldsymbol{x}_{G,i}^\top \beta_G \\ \log(K_{D,i}(t)) = K_{D,0} + b_{D,i} + \boldsymbol{x}_{D,i}^\top \beta_D \\ \log(\lambda) = \lambda_0 + b_{\lambda,i} + \boldsymbol{x}_{\lambda,i}^\top \beta_\lambda \end{cases}$$



  - $e^{K_G,0}$ - rate of tumor growth
  - $d_i(t)$ - drug concentration at t (eg. dose) ($\forall_{t>0}$, $d_i(t) > 0$)
  - $e^{K_{D,0}}$ - constant drug induced tumor decline rate
  - e^{λ} - rate of exponential tumor decay change with time (eg. caused by development of resistance to drug)
  - $\boldsymbol{b}_i^\top = (b_{y_0,i}, b_{G,i}, b_{D,i}, b_{\lambda,i})^\top \sim \mathcal{N}(0, \boldsymbol{B_1})$ ($\boldsymbol{B}_1$ - diagonal matrix, elements σ_j^2, $j \in \{1,2,3,4\}$)
  - $\boldsymbol{x}_{G,i}, \boldsymbol{x}_{D,i}, \boldsymbol{x}_{\lambda,i}$ - covariates

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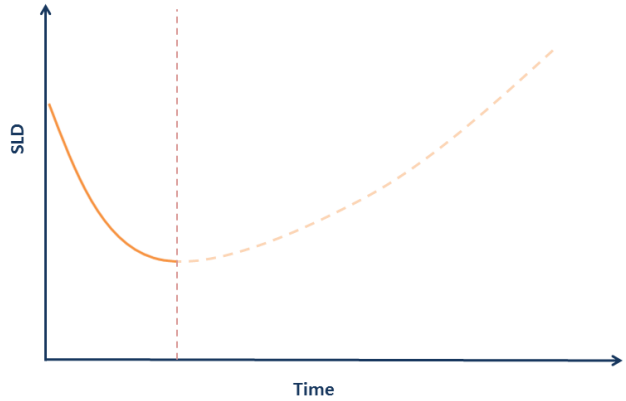

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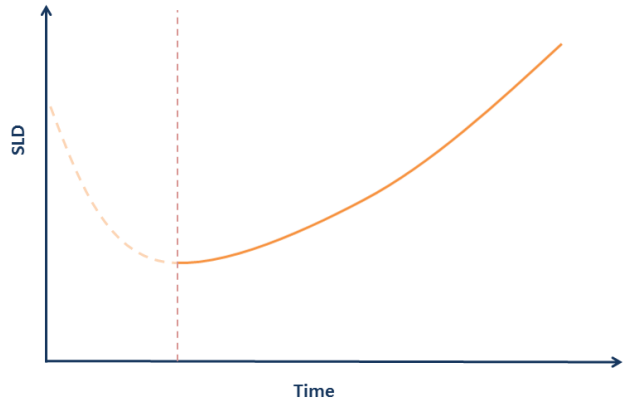

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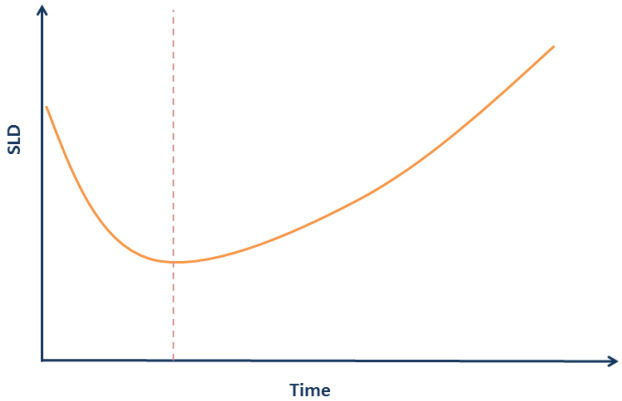

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Model for the biomarker

- Model for transformed observations $y_i^*(t_{ik})$:

$$y_i^*(t_{ik}) = f(y_i(t_{ik})) + \epsilon_i(t_{ik})$$

  - $f(\cdot)$ - transformation function
  - measurement errors *iid*, $\epsilon_i(t_{ik}) \sim \mathcal{N}(0, \sigma_\epsilon^2)$
- Left-censored biomarker due to a detectability threshold s :
  - n_i^o-vector of observed measurements $\boldsymbol{y}_i^o$
  - n_i^c-vector of censored measurements $\boldsymbol{y}_i^c$

Proposed joint model

System of a non-linear mixed model and two proportional hazards models :

$$\begin{cases} y_i^*(t_{ik}) & = f(y_i(t_{ik})) + \epsilon_i(t_{ik}) & \text{(SLD)} \\ r_{ij}(t|\boldsymbol{u}_i) & = r_0(t)\exp(v_i + \boldsymbol{x}_{R,i}^\top \boldsymbol{\beta}_R + h(y_i(t))^\top \boldsymbol{\eta}_R) & \text{(non-target progression)} \\ \lambda_i(t|\boldsymbol{u}_i) & = \lambda_0(t)\exp(\alpha v_i + \boldsymbol{x}_{T,i}^\top \boldsymbol{\beta}_T + g(y_i(t))^\top \boldsymbol{\eta}_T) & \text{(death)} \end{cases}$$

- random effects $\boldsymbol{u}_i = \begin{pmatrix} b_{y_0,i} \\ b_{G,i} \\ b_{D,i} \\ b_{\lambda,i} \\ v_i \end{pmatrix} \sim \mathcal{N}\left(\boldsymbol{0}, \boldsymbol{B} = \begin{bmatrix} \boldsymbol{B}_1 & \boldsymbol{0} \\ \boldsymbol{0} & \sigma_v^2 \end{bmatrix}\right)$
- $\boldsymbol{x}_{R,i}$ - prognostic factors for NL-NTL events
- $\boldsymbol{x}_{T,i}$ - prognostic factors for death
- $h(y_i(t))$, $g(y_i(t))$ - link functions (eg., random effects $\boldsymbol{b}_i$ or current level of the biomarker $f(y_i(t_{ik}))$

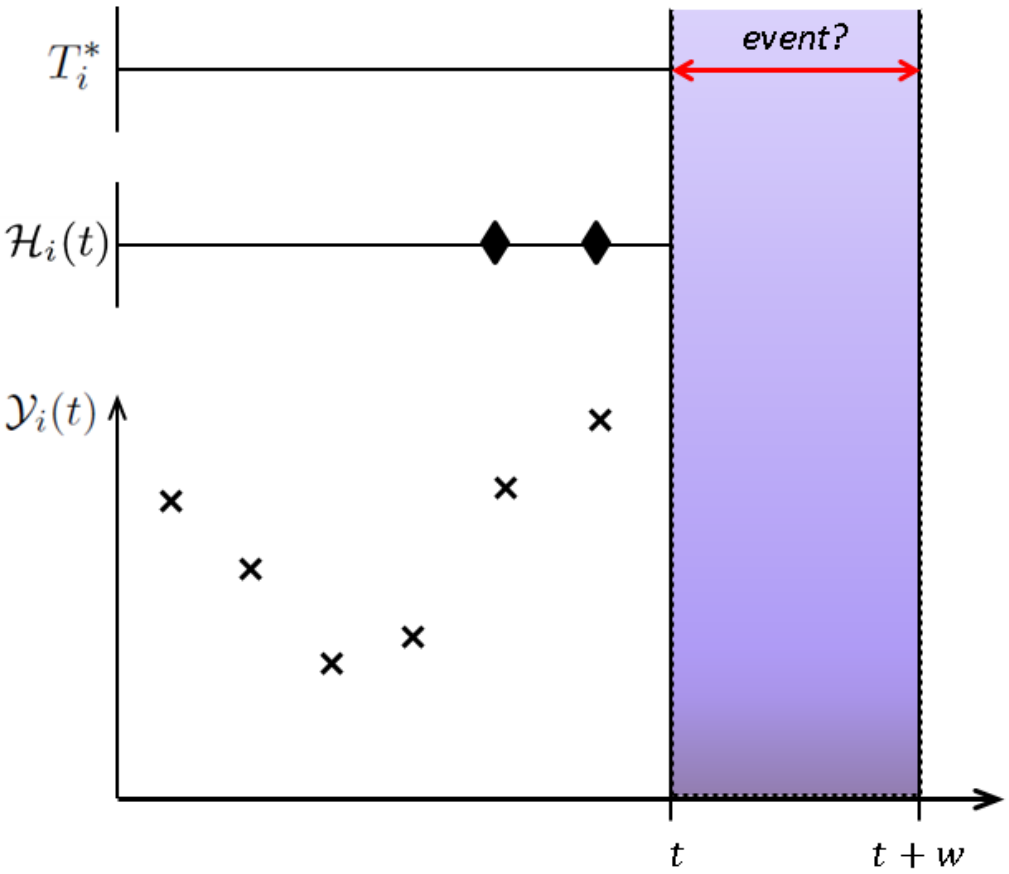
Estimation

- Given $\boldsymbol{u}_i$ $\boldsymbol{y}_i$, $\boldsymbol{R}_i$ and T_i are independent. The marginal likelihood is

$$L(\boldsymbol{\Theta}_i;\boldsymbol{\xi}) = \int_{\boldsymbol{u}_i} L(\boldsymbol{y}_i^*|\boldsymbol{u}_i;\boldsymbol{\xi}) L(\boldsymbol{R}_i,\boldsymbol{\delta}_i^R|\boldsymbol{u}_i;\boldsymbol{\xi}) L(T_i,\delta_i^T|\boldsymbol{u}_i;\boldsymbol{\xi}) f_{\boldsymbol{u}_i}(\boldsymbol{u}_i;\boldsymbol{\xi}) \mathrm{d}\boldsymbol{u}_i,$$

  - $\boldsymbol{\Theta}_i = \{\boldsymbol{y}_i^*, \boldsymbol{R}_i, T_i, \boldsymbol{\delta}_i^R, \delta_i^T\}$, $\boldsymbol{R}_i = \{R_{ij}, j = 1,\ldots,r_i\}$, $\boldsymbol{\delta}_i^R = \{\delta_{ij}, j = 1,\ldots,r_i\}$
  - Parameters $\boldsymbol{\xi} = \{y_{i,0}, K_{L,0}, K_{D,0}, \lambda, \boldsymbol{\beta}_G, \boldsymbol{\beta}_D, \boldsymbol{\beta}_\lambda, \boldsymbol{B}, \sigma_\epsilon^2, r_0(\cdot), \lambda_0(\cdot), \boldsymbol{\beta}_E, \boldsymbol{\beta}_T, \alpha\}$
- Baseline hazard functions approximation using splines
- Integrals approximated using pseudo-adaptive Gauss-Hermite quadrature
- Penalized maximum likelihood estimation using Marquardt algorithm

Dynamic predictions



- $\mathcal{H}_i(t)$ - history of the NT progressions
- $\mathcal{Y}_i(t)$ - history of the biomarker of individual *i* until *t*
- Predicted probability of the terminal event T_i^* in a horizon $[t, t+w]$

$$\mathbb{P}(T_i^* \leq t+w | T_i^* > t, \mathcal{H}_i(t), \mathcal{Y}_i(t), \boldsymbol{x}_i; \boldsymbol{\xi})$$

$\boldsymbol{x}_i$ - covariates included in the model

Measures of predictive accuracy

- EPOCE (Expected Prognostic Observed Cross-Entropy) *Commenges et al.*, 2012
  - Evaluation of conditional density of the event given the individual history
  - Internal validation : approximate cross-validated estimator CVPOL_a
- Brier score
  - The inverse probability of censoring weighted error estimator (data-based Brier score) *Gerds and Schumacher*, 2006
  - Comparison of predictions and actual observed events
  - Internal validation : *k*-fold cross-validation

Simulation study

We consider a trivariate model for $N = 400$ subjects

$$\begin{cases} y_{ik} = \exp\left\{ y_{i,0} + b_{y_0,i} + e^{K_{G,0}+b_{G,i}+\beta_1 X_{1,i}} \cdot t_{ik} + Dose_i \cdot e^{K_{D,0}+b_{D,i}-\lambda+\beta_2 X_{1,i}} \cdot (e^{-e^{\lambda}\cdot t_{ik}} - 1) \right\} + \epsilon_{ik} \\ r_i(t|\boldsymbol{u}_i) = r_0(t) \exp\{ v_i + \beta_3 X_{1i} + \eta_{r1} b_{y_0,i} + \eta_{r2} b_{G,i} + \eta_{r3} b_{D,i} \} \\ \lambda_i(t|\boldsymbol{u}_i) = \lambda_0(t) \exp\{ \alpha v_i + \beta_4 X_{2i} + \eta_{t1} b_{y_0,i} + \eta_{t2} b_{G,i} + \eta_{t3} b_{D,i} \} \end{cases}$$

- $X_1 \sim B(1, 0.5)$, $X_2 \sim B(1, 0.5)$
- fixed right-censoring $C = 3.5$
- exponential death time T_i^* with $\lambda_0(t) = 0.7 \rightarrow T_i = \min(T_i^*, C)$
- recurrent exponential gap times S_{ij} with $r_0(t) = 1.5 \rightarrow$ calendar times $T_{ij} = \min(T_i^*, C, \sum_{l_1}^{j} S_{il})$
- maximum 6 recurrent events
- biomarker times t_{ik} every 0.15 ; maximum 15 repeated measurements
- $Dose_i \sim \mathcal{N}(1, 0.02)$

Results

Parameter	Mean (SE)	ESE	CP	Parameter	Mean (SE)	ESE	CP
Fixed regression coefficients				**Matrix B_1 parameters**			
$\beta_1 = 0.2$	0.195 (0.03)	0.05	97.0%	$\sigma_{b_{y_0}} = 0.8$	0.783 (0.03)	0.03	93.1%
$\beta_2 = 0.1$	0.096 (0.05)	0.06	96.3%	$\sigma_{b_G} = 0.7$	0.627 (0.07)	0.06	75.2%
$\beta_3 = 0.5$	0.515 (0.10)	0.10	94.3%	$\sigma_{b_D} = 0.7$	0.672 (0.04)	0.04	86.8%
$\beta_4 = 0.5$	0.553 (0.20)	0.18	95.9%	$\sigma_v = 0.8$	0.768 (0.09)	0.08	92.3%
Biomarker parameters				**Link parameters with biomarker**			
$K_{G,0} = -1.0$	-0.952 (0.05)	0.05	83.9%	$\eta_{r_1} = 0.2$	0.217 (0.09)	0.08	92.3%
$K_{D,0} = 1.0$	1.019 (0.06)	0.07	93.9%	$\eta_{r_2} = 0.2$	0.279 (0.20)	0.18	89.4%
$\lambda = 0.8$	0.789 (0.06)	0.05	92.9%	$\eta_{r_3} = 0.2$	0.189 (0.14)	0.13	93.9%
$y_0 = 1.0$	0.993 (0.03)	0.03	96.1%	$\eta_{t_1} = 0.4$	0.462 (0.15)	0.15	96.3%
				$\eta_{t_2} = 0.4$	0.613 (0.36)	0.34	91.9%
				$\eta_{t_3} = 0.4$	0.384 (0.27)	0.27	96.1%
Measurement error				**Alpha parameter**			
$\sigma_\epsilon = 0.5$	0.499 (0.01)	0.01	95.1%	$\alpha = 1.6$	1.823 (0.64)	0.45	91.1%

TABLE: Results of the simulation study, 500 simulations (99% convergence rate).

SE - empirical standard error, ESE - estimated standard error, CP - coverage probability
Baseline hazard functions approximated by splines, $Q = 7$, $\kappa_1 = 1.32$ for $r_0(t)$, $\kappa_2 = 0.01$ for $\lambda_0(t)$

Pseudo-adaptive Gauss-Hermite quadrature with 7 points for the r.e. related to the biomarker and 20 points for the frailty

GERCOR study Tournigand et al., *JCO* 2004

- Phase III randomized clinical trial
- 220 patients with metastatic colorectal cancer in two treatment strategies
  - Arm A (LVFU2 + FOLFIRI $\rightarrow$ LVFU2 + FOLFOX)
  - Arm B (LVFU2 + FOLFOX $\rightarrow$ LVFU2 + FOLFIRI)
- Result of the study :
  - both sequences performed similar efficacy
  - toxicity was more frequent with FOLFOX6 in first-line therapy (arm B)

Data description

N=212 patients analyzed. Observed :

- 217 NL-NTL events (1.02 per patient, range 0-7)
- 170 deaths ; median survival 21.5 months in arm A and 20.6 in arm B
- 7.12 tumor size measurements per patient (range 1-15)

Data Analysis

- Estimation of the mechanistic joint model (Model 1) with random effects $\boldsymbol{b}_i$ as the link function and time-independent dose
- Dynamic predictions for example patients
- Evaluation of the model fit and predictive accuracy with the alternative models
  - Parametric model (Model 2) : two functions of time for the biomarker : $f_1(t) = \exp(-3t)$ and $f_2(t) = t^{1.1}/(t+1)^{0.1}$
  - Spline model (Model 3) quadratic B-splines with no interior knots for the biomarker

Results

TABLE: Results of the mechanistic joint frailty model for the GERCOR data.

Covariate	NT Progression HR (95% CI)	Death HR (95% CI)	Parameter	Tumor Size[1] Est. (SE)
Treatment(B/A)	1.16 (0.83 - 1.62)	1.56 (0.92 - 2.63)	Treatment (B/A)[2]	0.86 (0.19)***
Age (60-70/<60)	1.02 (0.70 - 1.47)	1.44 (0.82 - 2.55)	$K_{G,0}$	−2.05 (0.28)***
Age (≥70/<60)	1.14 (0.73 - 1.76)	1.36 (0.68 - 2.73)	$K_{D,0}$	0.01 (0.22)
Sex (Female/Male)	0.85 (0.60 - 1.21)	1.14 (0.68 - 1.92)	λ	1.28 (0.31)***
WHO PS (1/0)	1.19 (0.84 - 1.69)	2.05 (1.09 - 3.83)*	y_0	4.46 (0.05)***
WHO PS (2/0)	1.12 (0.58 - 2.15)	5.76 (2.02 - 16.41)***		
Prev. chemotherapy	1.70 (1.18 - 2.45)**	-		
Metachron. metast.	-	2.53 (1.41 - 4.53)**		

Model Parameters	Est. (SE)		Est. (SE)		Est. (SE)
$\sigma_{b_{y_0}}$	0.63 (0.05)***	α	1.78 (0.82)*	η_{t_4}	1.69 (0.04)***
σ_{b_G}	1.55 (0.18)***	σ_ϵ	1.69 (0.04)***	η_{r_1}	0.19 (0.10)
σ_{b_D}	1.43 (0.16)***	η_{t_1}	0.35 (0.20)	η_{r_2}	−0.19 (0.11)
σ_{b_λ}	2.34 (0.34)***	η_{t_2}	−0.58 (0.24)*	η_{r_3}	0.21 (0.06)***
σ_v	0.44 (0.06)***	η_{t_3}	0.58 (0.16)***	η_{r_4}	0.15 (0.32)

[1] SLD transformed using Box-Cox transformation (0.2), [2] Variable related to the tumor decline $K_{D,0}$

* p-value $\leq$ 0.05, ** p-value $\leq$ 0.01, *** p-value $\leq$ 0.001

HR - hazard ratio, CI - confidence interval, SE - standard error

Dynamic predictions

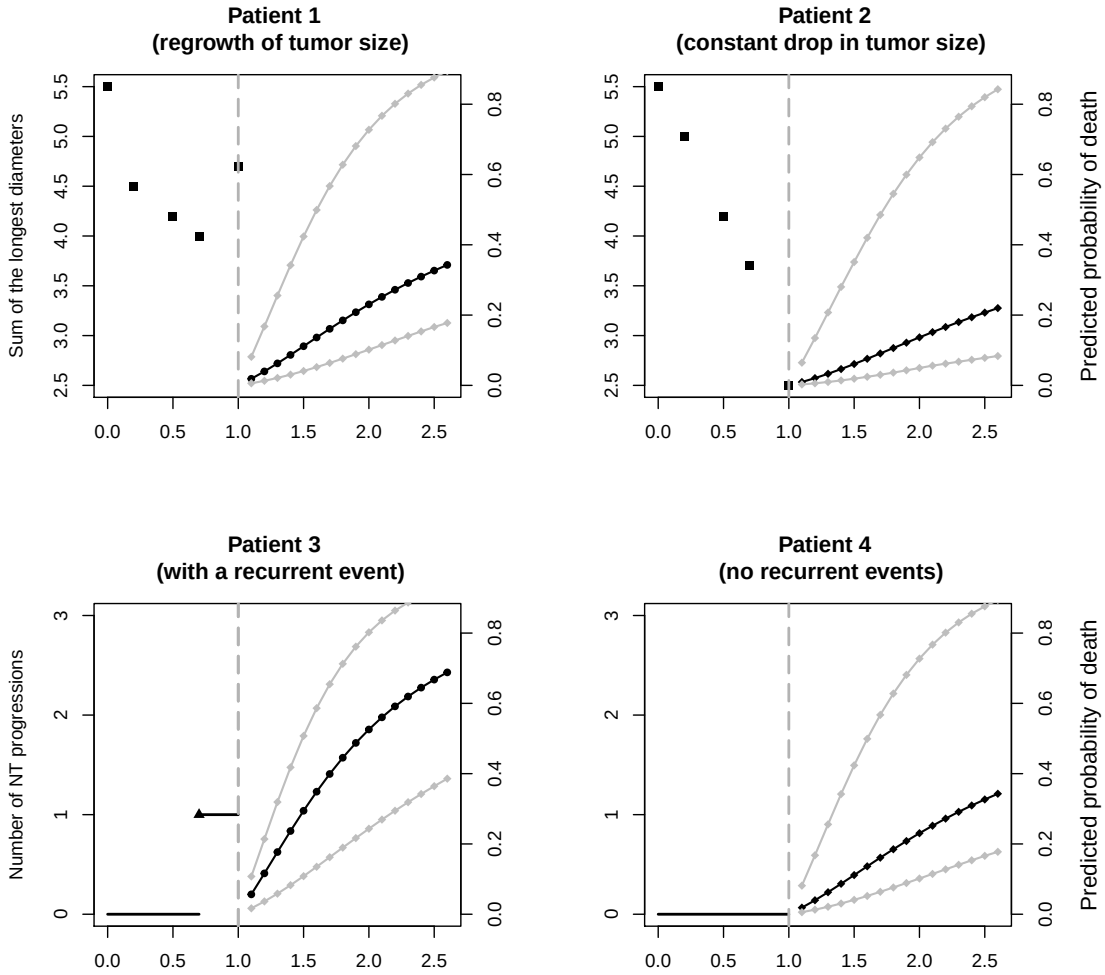


FIGURE: Predicted probabilities of death with time of prediction $t = 1$ and moving window from 0.1 to 1.5 (years) for example patients. Top graphs represent predictions for patients that were different from each other by the measurements of SLD (black squares), bottom graphs for patients with a recurrent event (black triangle) was observed for only one of them. The vertical line represents the time of predictions and the grey lines, the confidence intervals.

Comparison with the alternative models

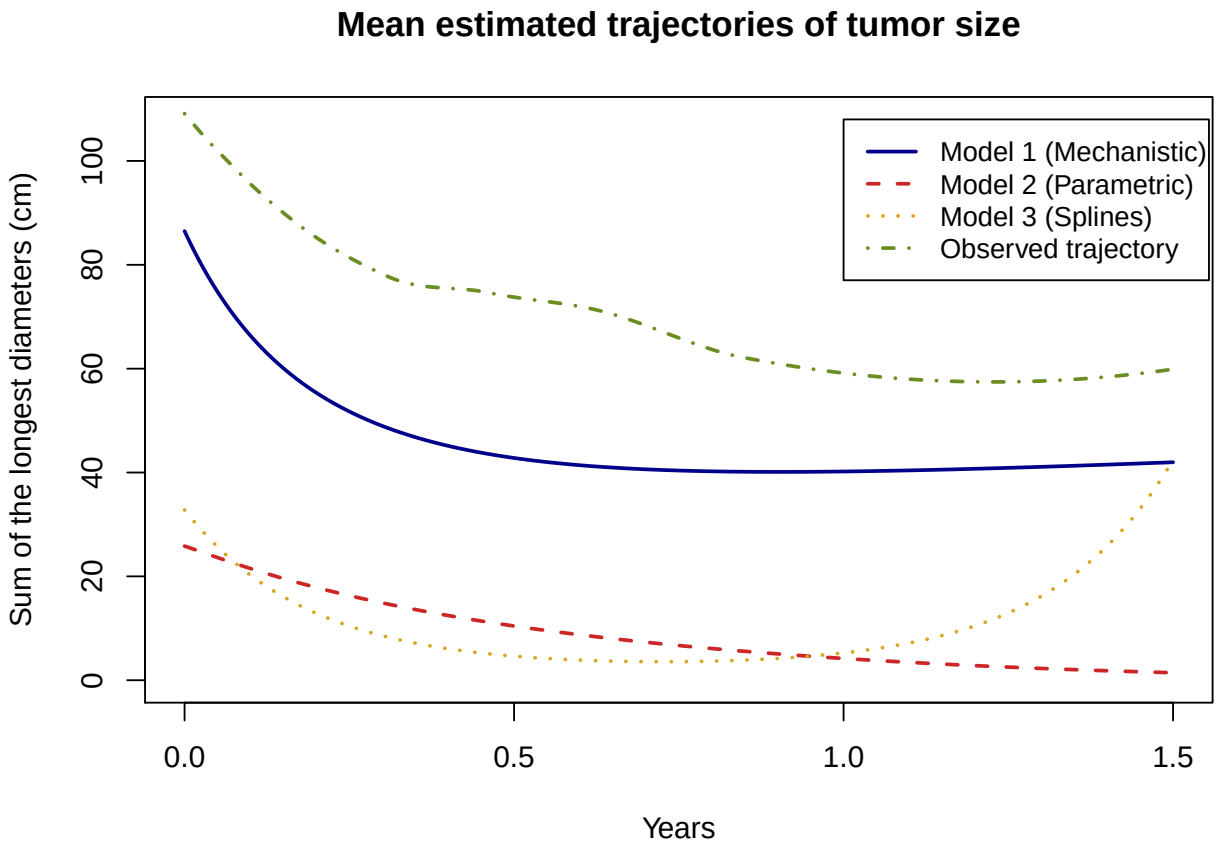


FIGURE: Population-averaged tumor size (SLD) trajectories for the trivariate joint models : mechanistic (Model 1, LCV = 1.93), parametric (two parametric functions of time, Model 2, LCV = 2.31) and splines (quadratic B-splines for the biomarker's time, Model 3, LCV = 2.17) and the observed mean trajectory (obtained with the `loees` function of the `R` software).

Predictive accuracy

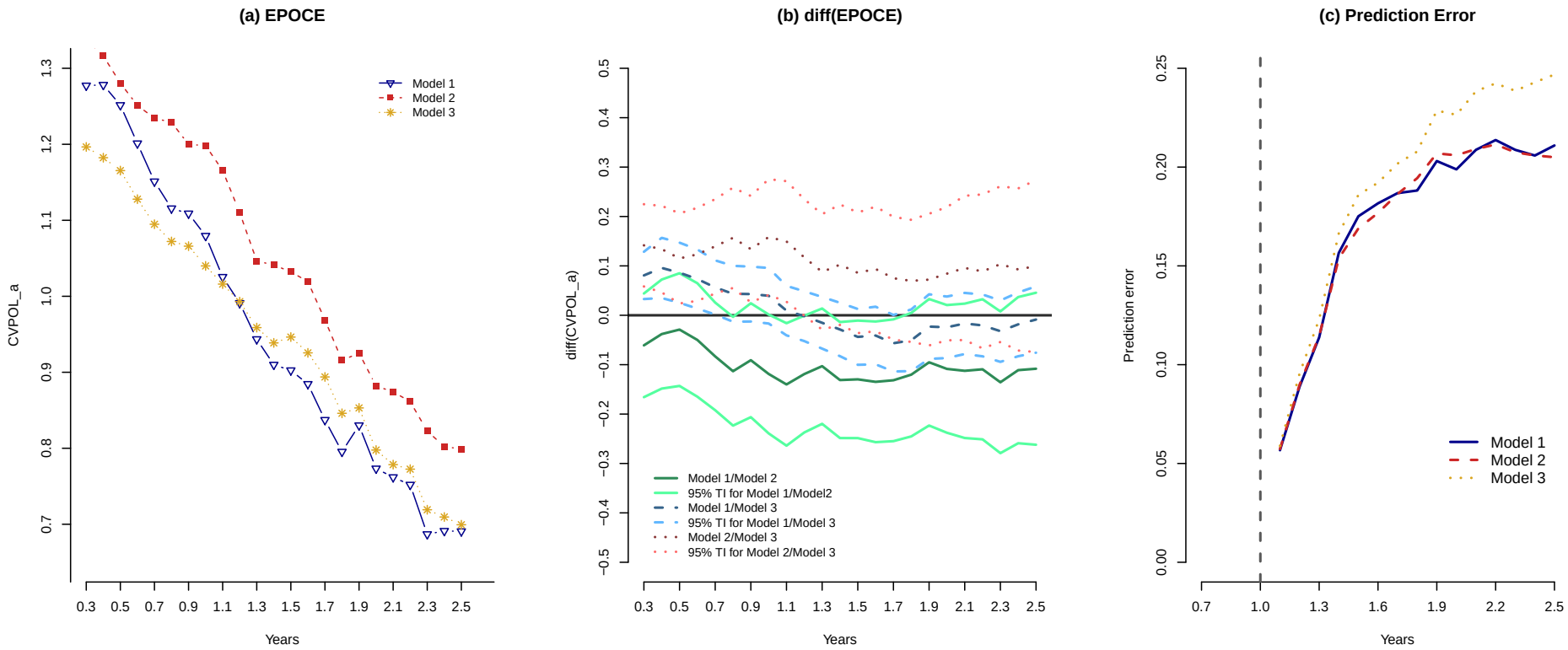


FIGURE: (a) Estimator $CVPOL_a$ of the EPOCE in the time window 0.3 - 2.5 years for the models applied to the GERCOR study. (b) Differences in the $CVPOL_a$ with the 95% tracking intervals between the analyzed models. Model 1 - the mechanistic model, Model 2 - the parametric model, Model 3 - the spline model. (c) Error of prediction using 10-fold cross-validation with time of prediction t = 1 year and varying window *w* from 0.1 to 1.5.

Conclusions

- Proposition of a multivariate mechanistic joint model for longitudinal data, recurrent events and a terminal event
  - Useful approach for assessment of cancer treatment effects
- Statistical tools for dynamic predictions and predictive accuracy evaluation
- GERCOR study :
  - significant difference between treatment lines on tumor size decrease
  - better fit to the data of the model with ODE than the linear mixed-effects models for the biomarker
  - generally similar or better predictive accuracy of the mechanistic model

Perspectives

- Consideration of a time-dependent dose
- Extension to a meta-analysis : trial random effect
- Consideration of multiple lines of treatment in the modeling
- Implementation to `frailtypack` package

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Thank you for your attention !