Joint modeling and dynamic predictions with applications to cancer research

Agnieszka Król

Postdoctoral Research Fellow

Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto

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PhD Supervisor: Prof. Virginie Rondeau (Biostatistics Team, INSERM U1219, Bordeaux)

PhD Co-Supervisor: Dr. Stefan Michiels (INSERM U1018 CESP, Gustave Roussy, U. Paris-Sud, Villejuif)
Context

- Continuously increasing number of cancer clinical trials for treatment evaluation → 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, e.g.:
  - not adapted to certain tumor types
  - based on anatomical burden
  - does not include functional imaging or 3D
  - neglect the longitudinal character of data
**RECIST criteria** (Eisenhauer et al., 2009)

- **Target lesions**
  - Unidimensional size, max 2 lesions per organ and up to 5 total
  - **Progression**: > 20% increase over smallest sum observed
- **Appearance of new lesions** → global progression
- **Unequivocal progression of non-target lesions** → global progression
Do the continuous measurements of tumor size and appearance of new lesions enable better prediction of overall survival (OS) than times of progression?
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 (Król et al., JSS 2017)
Objectives

- Incorporation of information on progression of non-target disease
- 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
Notation

For individual $i, i = 1, ..., N$, 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): $T_{ij} = \min(T_{ij}^*, C_i, T_i)$ and $\delta_{ij} = \mathbb{I}_{T_{ij}^* = T_{ij}}$

- **Time to terminal event** (death): $T_i = \min(T_i^*, C_i)$ and $\delta_i = \mathbb{I}_{T_i^* = T_i}$
Dynamics of tumor size defined by an **ordinary differential equation**

\[
\begin{align*}
\frac{dy_i(t)}{dt} &= K_{G,i} y_i(t) - d_i(t) K_{D,i}(t) e^{-\lambda t} y_i(t) \\
\log(y_i(0)) &= y_{i,0} + b_{y_0,i} \\
\log(K_{G,i}) &= K_{G,0} + b_{G,i} + \mathbf{x}_{G,i}^T \beta_G \\
\log(K_{D,i}(t)) &= K_{D,0} + b_{D,i} + \mathbf{x}_{D,i}^T \beta_D \\
\log(\lambda) &= \lambda_0 + b_{\lambda,i} + \mathbf{x}_{\lambda,i}^T \beta_{\lambda}
\end{align*}
\]

- $e^{K_{G,0}}$ - rate of tumor growth
- $d_i(t)$ - drug concentration at $t$ (e.g. dose) ($\forall t > 0, d_i(t) > 0$)
- $e^{K_{D,0}}$ - constant drug induced tumor decline rate
- $e^{\lambda}$ - rate of exponential tumor decay change with time (e.g. caused by development of resistance to drug)
- $\mathbf{b}_i^T = (b_{y_0,i}, b_{G,i}, b_{D,i}, b_{\lambda,i})^T \sim \mathcal{N}(0, \mathbf{B}_1)$ ($\mathbf{B}_1$ - diagonal matrix, elements $\sigma_j^2$)
- $j \in \{1, 2, 3, 4\}$
- $\mathbf{x}_{G,i}, \mathbf{x}_{D,i}, \mathbf{x}_{\lambda,i}$ - covariates
Proposed joint model

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

\[
\begin{align*}
\left\{
\begin{array}{ll}
y^*_i(t_{ik}) &= f(y_i(t_{ik}))+\epsilon_i(t_{ik}) \\
r_{ij}(t|u_i) &= r_0(t)\exp(v_i + x_{R,i}^T\beta_R + h(y_i(t))^T\eta_R) \\
\lambda_i(t|u_i) &= \lambda_0(t)\exp(\alpha v_i + x_{T,i}^T\beta_T + g(y_i(t))^T\eta_T)
\end{array}
\right.
\end{align*}
\]

\[\text{(SLD)}\]
\[\text{(non-target progression)}\]
\[\text{(death)}\]

- random effects \( u_i = \begin{pmatrix} b_{y_{0,i}} \\ b_{G,i} \\ b_{D,i} \\ b_{\lambda,i} \\ v_i \end{pmatrix} \sim \mathcal{N}\left(0, B = \begin{bmatrix} B_1 & 0 \\ 0 & \sigma_v^2 \end{bmatrix}\right)\)

- \( x_{R,i} \) - prognostic factors for NL-NTL events
- \( x_{T,i} \) - prognostic factors for death
- \( h(y_i(t)), g(y_i(t)) \) - link functions (e.g., random effects \( b_i \) or current level of the biomarker \( f(y_i(t_{ik})) \))
Estimation

• Marginal joint likelihood is

\[ L(\Theta_i; \xi) = \int_{u_i} L(y^*_i|u_i; \xi)L(R_i, \delta_i^R|u_i; \xi)L(T_i, \delta_i^T|u_i; \xi)f_{u_i}(u_i; \xi)du_i, \]

• 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 $[t; t + w]$

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

$X_i$ - 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 CVPOLa

- **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: 10-fold cross-validation
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 → LVFU2 + FOLFOX)
  - Arm B (LVFU2 + FOLFOX → LVFU2 + FOLFIRI)
- Result of the study:
  - both sequences performed similar efficacy
  - toxicity was more frequent with FOLFOX 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 $b_i$ 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 $f_1(t) = e^{-3t}$ 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

- Significant difference between treatment lines on tumor size decrease: The drug induced greater tumor decline in arm B than in arm A (0.86, SE = 0.19)
- Significant associations between the processes via the shared random effects

→ Indirect effect of treatment on OS via the evolution of tumor size
Dynamic predictions

- Predicted probabilities of death with time of prediction $t = 1$ and moving window from 0.1 to 1.5 (years) for example patients

- Patients 1 and 2: the same history of recurrent non-target progressions (no progressions until $t$) and different tumor size trajectories
  - Patient 1: regrowth of target lesions
  - Patient 2: constant drop in target lesions size

- Patients 3 and 4: the same tumor size trajectories (constant drop in size) and different history of recurrent non-target progressions
  - Patient 3: non-target progression at 10 months of treatment
  - Patient 4: no progressions until $t$
Dynamic predictions

Patient 1
(regrowth of tumor size)

Patient 2
(constant drop in tumor size)

Patient 3
(with a recurrent event)

Patient 4
(no recurrent events)
Comparison with alternative models

• Model with ODE better fit the biomarker data than the models with linear mixed-effects sub-models
  • Using the approximated LCV criterion (1.93 for the mechanistic model, 2.31 for the model with two parametric functions and 2.17 for the spline model)

• Generally similar or better predictive accuracy of the mechanistic model (using EPOCE and Brier score)
  • The best performance of the mechanistic model at longer prediction time
  • The worst predictive accuracy of the model with the parametric functions
Conclusions

- Development of a multivariate mechanistic joint model for longitudinal data, recurrent events and a terminal event
- Useful approach for complex assessment of treatment effects in cancer research
- More appropriate approach for modeling tumor kinetics than linear mixed model
- Towards personalized treatment of cancer patients
References


