Mechanistic joint models characterizing the relationship between nonlinear prostate specific antigen kinetics and survival in prostate cancer patients

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BIOSTATISTICAL MODELLING AND PHARMACOMETRICS

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Outline

Introduction

1. Clinical Trial Simulation to Compare two-stage and joint modelling
2. Development of a mechanistic joint model for PSA and survival in metastatic patients
3. Individual dynamic prediction using joint model

Conclusion
INTRODUCTION

- Hormono-resistant metastatic prostate cancer
  - Monitoring via Prostate Specific Antigen (PSA)
  - Reference treatment: docetaxel + prednisone

- All results presented based on the control arm of a phase III trial (Tannock et al, Lancet Oncol, 2013)
  - Training set: 400 patients randomly selected
  - Development of mechanistic joint model

- Validation set: 196 patients
  - Model evaluation and individual predictions
Joint modeling of longitudinal and time to event data

**Longitudinal data**
- $y_i$: vector of longitudinal measurements
- can be described by a nonlinear model

**Time-to-event data**
- $T_i$: observed event time
- $\delta_i$: event indicator
  - $\delta_i = \begin{cases} 1 & \text{if event observed} \\ 0 & \text{if event not observed} \end{cases}$

**Two objectives**
1. To characterize the (non-linear) kinetics of a biomarker in presence of a time-to-event
2. To characterize the impact of this kinetics on a time-to-event
Joint modeling of longitudinal and time to event data

mainly in clinical epidemiology with linear models
Informative censoring: Not a new issue

- Informative censoring: probability to not observe the biomarker depends on current unobserved value
  - Poor responders: more likely of early events and less longitudinal data
  - Good responders: more likely of late events and more data

  - Sample of longitudinal data is not representative
  - Some kinetic parameters identified only in survivors
  - High shrinkage in poor responders

- When longitudinal and survival data analyzed separately
  - (Some) bias in longitudinal parameters
  - Problems in VPC and simulations of longitudinal data


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- When longitudinal and survival data analyzed separately
  - (Some) Bias in longitudinal parameters
  - Problems in VPC and simulations of longitudinal data
  - Bias in estimated survival parameters
  - Induced or hidden correlation between marker evolution and survival (inflated Type I error)

1. CTS to compare two-stage and joint modelling approaches

Nonlinear Mixed-Effect Models for Prostate-Specific Antigen Kinetics and Link with Survival in the Context of Metastatic Prostate Cancer: a Comparison by Simulation of Two-Stage and Joint Approaches

Solène Desmée, France Mentré, Christine Veyrat-Follet, and Jérémie Guedj

\[
\begin{align*}
\frac{dC}{dt} &= r(1 - e(t))C - dC \\
\frac{dPSA}{dt} &= pC - \delta PSA \\
\psi &= \{r, PSA_0, \varepsilon, T_{esc}\}
\end{align*}
\]

\[
h_i(t|\psi_i) = h_0(t) \exp(\beta PSA(t, \psi_i))
\]

Weibull \( h_0(t) = \frac{k}{\lambda} (\frac{t}{\lambda})^{k-1} \)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>No link</th>
<th>Low link</th>
<th>High link</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \beta )</td>
<td>0</td>
<td>0.005</td>
<td>0.02</td>
</tr>
<tr>
<td>( \lambda ) (day)</td>
<td>580</td>
<td>765</td>
<td>2150</td>
</tr>
<tr>
<td>( k )</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>
**Results** (100 replicates, 500 patients)

- Small bias in biomarker parameters when ignoring censoring for fitting (two-stage or sequential approaches)
- Strong bias in survival parameters when using two-stage approach (i.e. no link, two-stage: type I error = 14%)
2. Development of a mechanistic joint model for PSA and survival in metastatic patients

Using the SAEM Algorithm for Mechanistic Joint Models Characterizing the Relationship between Nonlinear PSA Kinetics and Survival in Prostate Cancer Patients

Solène Desmée, France Mentré, Christine Veyrat-Follet, Bernard Sébastien, Jérémie Guedj

\[ h_i(t | PSA(t, \psi_i)) = h_0(t) \exp(f(t, \psi_i)) \]

Weibull \[ h_0(t) = \frac{k}{\lambda} \left( \frac{t}{\lambda} \right)^{k-1} \]

- Link function \( f \)
  - No link
  - Initial PSA
  - Current PSA
  - PSA slope
  - Area under PSA
  - S and R

Monolix
Results: model selection
(training set, 400 patients)

BIC and parameters estimates (r.s.e.%) of PSA kinetics and survival in the 400 patients of the training dataset

<table>
<thead>
<tr>
<th></th>
<th>No link</th>
<th>Initial PSA</th>
<th>PSA</th>
<th>PSA slope</th>
<th>Area under PSA</th>
<th>S+R</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIC</td>
<td>14598</td>
<td>14582</td>
<td>14446</td>
<td>14581</td>
<td>14575</td>
<td>14421</td>
</tr>
<tr>
<td>$\alpha_S$</td>
<td>0.066 (3)</td>
<td>0.060 (3)</td>
<td>0.078 (3)</td>
<td>0.078 (3)</td>
<td>0.061 (3)</td>
<td>0.067 (3)</td>
</tr>
<tr>
<td>$RF$</td>
<td>0.9997 (0)</td>
<td>0.9996 (0)</td>
<td>0.9998 (0)</td>
<td>0.9998 (0)</td>
<td>0.9997 (0)</td>
<td>0.9998 (0)</td>
</tr>
<tr>
<td>$RE$</td>
<td>0.81 (1)</td>
<td>0.79 (1)</td>
<td>0.84 (1)</td>
<td>0.84 (0)</td>
<td>0.79 (1)</td>
<td>0.82 (1)</td>
</tr>
<tr>
<td>$\varepsilon$</td>
<td>0.42 (4)</td>
<td>0.46 (4)</td>
<td>0.35 (4)</td>
<td>0.35 (5)</td>
<td>0.47 (4)</td>
<td>0.43 (3)</td>
</tr>
<tr>
<td>$PSA_b$</td>
<td>22.2 (8)</td>
<td>22.2 (8)</td>
<td>22.0 (8)</td>
<td>22.5 (8)</td>
<td>22.2 (8)</td>
<td>21.9 (8)</td>
</tr>
<tr>
<td>$N_{\text{max}}$</td>
<td>56 (4)</td>
<td>57 (4)</td>
<td>81 (4)</td>
<td>77 (4)</td>
<td>57 (4)</td>
<td>120 (4)</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>885 (4)</td>
<td>1615 (8)</td>
<td>4259 (15)</td>
<td>920 (4)</td>
<td>1435 (7)</td>
<td>906 (7)</td>
</tr>
<tr>
<td>$k$</td>
<td>1.52 (5)</td>
<td>1.53 (3)</td>
<td>1.28 (2)</td>
<td>1.48 (2)</td>
<td>1.19 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>$\beta_i$</td>
<td>-</td>
<td>0.21 (12)</td>
<td>0.40 (7)</td>
<td>17 (17)</td>
<td>0.00023 (8)</td>
<td>0.00032 (21)</td>
</tr>
<tr>
<td>$\beta'$</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.39 (7)</td>
</tr>
</tbody>
</table>

**S+R model:** $f(t, \psi_i) = \beta \log(S(t, \psi_i)) + \beta' \log(R(t, \psi_i))$ with a constant baseline hazard function ($k = 1$) provided the smaller BIC

- Delta -2LL PSA vs no link = 158 ($p<10^{-35}$)
- Delta BIC S & R vs PSA = 25
Results (training set, 400 patients)

Individual fits of PSA and hazard functions
**Results** (validation set, 196 patients)

**Prediction in the validation sample**

Assumption: *true* joint model is known

- *Population parameters $\theta$ used as priors*
- *Individual EBEs $\hat{\psi}_i$ estimated using only the PSA measurements*
- *Mean survival function* $= \frac{1}{N} \sum_{i=1}^{N} S_i(t|\hat{\psi}_i, \hat{\theta})$

![Graph showing survival over time since treatment initiation](image)
3. Individual dynamic prediction using joint model

- Learning sample: prior estimates
- New patient from validation sample
  - Observed PSA data until landmark $s$
  - Prediction of PSA and survival after $s$ with uncertainty
  - Using Hamiltonian Monte Carlo in STAN
Dynamic predictions for 2 patients

Patient 1 died at 24 months - Patient 2 was censored at 24 months
**TIME-DEPENDENT AUC**

**Discrimination**: ability of the model to distinguish patients of low and high risk of death

- **Area under the ROC curve (AUC)**

- Poor discrimination at time 0 beyond 6 months
- Good discrimination (AUC > 0.75) after 6, 12 or 18 months
CONCLUSION

• New mechanistic model of PSA during metastatic cancer
  • Use of joint modelling (here with SAEM)
  • Model building and parameter estimates in learning data set

• Use Bayesian method (here with STAN) in validation set
  • Predict PSA and survival with uncertainty
  • Various landmark times
  → Can be used for individual patient monitoring
  • Need to assess overall predictability (Time-dependent AUC)

• **Be careful** of two-stage approaches and of using model-derived metrics in survival analysis
  • Time-dependent bias
  • ‘To good to be true’
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LETTERS TO THE EDITOR

Time-Dependent Bias of Tumor Growth Rate and Time to Tumor Regrowth

To the Editor:

In a recent study by Han et al.¹ the authors highlight that a tumor growth inhibition metric termed time-to-tumor-growth (TTG) derived from imaging time-series data is a strong predictor of survival. The authors demonstrate the strength of TTG’s correlation to survival using Kaplan-Meier curves in Figure 2 of their article. Indeed, the relationship seems incredibly strong, maybe too good to be true. Perhaps it could well be as we now explain. One of the key forms of bias when using covariates that are time-dependent, which TTG and, in fact, any model-derived metrics are, is time-dependent (immortal time) bias.² In basic terms, this form of bias relates to the failure to account for the time taken to estimate a time-dependent covariate when performing a survival analysis. The Kaplan-Meier’s plotted in Figure 2 of Han et al.¹ assume that TTG is known at the beginning of the study; which is clearly not true. TTG can only be calculated once a certain amount of time-series data has been collected. Therefore, the Kaplan-Meier curves in Figure 2 are incredibly misleading and biased. The article by Suissa²

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Figure 2: Survival distribution by quartiles of time to tumor growth (each group represents 25% of the patients), TTG, time to tumor growth; OS, overall survival.
The Use of Model-Based Tumor-Size Metrics to Predict Survival

B Ribba¹, N Holford² and F Mentré³

Figure 1 Relationship of the type I error of the Wald test with mean survival times for tumor-size reduction (TSR6, blue continuous line) and time-to-tumor-growth (Ttg, red continuous line) metrics. The type I error of falsely concluding an association between each tumor metric and hazard was estimated from the frequency of rejecting the null hypothesis using a Wald test of size 5%. A total of 1,000 data sets were created for each of the nine survival-simulation scenarios. By design, the survival distribution was independent of tumor size, so the empirical type I error rates are all expected to fall within the 95% prediction interval. The gray band represents the 95% prediction interval around 5% type I error (for 1,000 replicates: 3.65 to 6.35%). The dashed lines represent the values of the metrics calculated using the reference “true” individual parameter values. Inset: Shrinkage of TSR6 and Ttg with mean survival time.
Joint model = 2 submodels

**Longitudinal part:** Nonlinear mixed-effect models (NLMEM)

\[ y_i(t) = \log(X(t, \psi_i) + 1) + e_i(t) \]

- **X:** process of interest (PSA) **possibly non-linear**
- **\( \psi_i \):** individual longitudinal parameters
- **\( e_i(t) \):** residual error

**Survival part:** Hazard function for patient \( i \):

\[ h_i(t|\psi_i) = h_0(t) \exp(\beta \times f(t, \psi_i)) \quad \text{for } t \geq 0 \]

\[ S_i(t|\psi_i) = P(T_i \geq t) = \exp \left[ -\int_0^t h_i(u|\psi_i) du \right] \]

- Link function \( f \) depends on \( \psi_i \) and longitudinal model (e.g., \( \log[PSA(t, \psi_i)] \))

Joint log-likelihood for a patient \( i \):

\[ LL_i(\theta) = \log \int p(y_i|\eta_i; \theta) \{ h_i(T_i|\eta_i; \theta)^{\delta_i} S_i(T_i|\eta_i; \theta) \} p(\eta_i; \theta) d\eta_i \]