Real-time individual predictions of prostate cancer recurrence using joint models: Online supplementary material

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1. Online Supplementary Material

1.1 MCMC algorithm for the training data

- The form of the longitudinal model is:
  \[ Y_i(t) = EY_i(t) + \epsilon_{it} = U(t)^T \beta_i + \epsilon_{it} = \beta_0 + \beta_{1i}\{(1 + t)^{-1.5} - 1\} + \beta_{2i}t + \epsilon_{it}, \]  
  \[ (1) \]
  where \( \epsilon_{it} \sim T(0, \sigma^2, 5) \), \( U(t)^T = (1, (1 + t)^{-1.5} - 1, t) \) and \( \beta_i^T \sim N_3(x_i^T \alpha, \Sigma_{3 \times 3}) \).

- The longitudinal model covariates matrix \( x_i = (x_{0i}, x_{1i}, x_{2i})^T \) is composed of:
  1. \( x_{0i} = (1, \text{PSA}_i, 0, \ldots, 0)^T \), corresponding to parameters \((\alpha_1, \alpha_2)\);
  2. \( x_{1i} = (0, 0, 1, T_{2i}, T_{34i}, \text{PSA}_i, 0, \ldots)^T \), corresponding to parameters \((\alpha_3, \alpha_4, \alpha_5, \alpha_6)\)
  3. \( x_{2i} = (0, \ldots, 0, 1, T_{2i}, T_{34i}, G_7i, G8U_i, \text{PSA}_i)^T \), corresponding to parameters \((\alpha_7, \ldots, \alpha_{12})\);
  4. Where the notation for the baseline variables is:
     - \( T_{2i} = I(\text{T-stage}_i = 2) \),
     - \( T_{34i} = I(\text{T-stage}_i \geq 3) \),
     - \( G_7i = I(\text{Gleason}_i = 7) \),
     - \( G8U_i = I(\text{Gleason}_i \geq 8) \),
     - \( \text{PSA}_i = \log(\text{basePSA}_i + 0.1) \),

- The fixed effect parameters in the longitudinal model are:
  1. \( \alpha = (\alpha_1, \cdots, \alpha_{12}) \): 12 parameters;
  2. \( \sigma^2 \): 1 parameter;
  3. \( \Sigma \): \(3 \times 3\) covariance matrix with 6 parameters.

- The form of the survival model is:
  \[ \lambda_i(t) = \lambda_0(t) \exp\{Z_i(t)^T \theta\}, \]
  \[ (2) \]
  where
  \[ Z_i(t)^T \theta = [W_i^T \theta_0 + \theta_6 \log(\exp(EY_i(t) - 0.7)/0.45 + \theta_7 EY_i(t) + \theta_8 I(t \geq H_i))], \]
\( \theta_0 = \{\theta_1, \ldots, \theta_8\}^T \), \( W_i = \{T2_i, T34_i, PSA_i, G7_i, G8U_i\}^T \), \( H_i \) is salvage hormone therapy time, and the baseline hazard is given by

- \( \lambda_0(t) = \sum_{j=1}^5 \lambda_{0j} I(B_j < t \leq B_{j+1}) \), where \( B = (0.95, 2, 3, 5, 7, 30) \),
- \( \lambda_0(t) = 0 \) for \( t \leq 0.95 \).

- The 13 parameters in the survival model are:
  - \( \theta = (\theta_1, \ldots, \theta_8) \), 8 parameters
  - \( \lambda_0 = (\lambda_{01}, \ldots, \lambda_{05}) \), 5 parameters
  - The joint likelihood of the observations conditional on the fixed and random effects is given by:
    \[
    L \propto \prod_i^n \lambda_i(R_i)^{\delta_i} \exp \left\{ - \sum_i \int_0^{R_i} \lambda_i(t) dt \right\} \times \sigma^{-m} \exp \left[ - \sum_i \sum_j \frac{(Y_{ij} - U_{ij}^T \beta_i)^2 s_{ij}}{2\sigma^2} \right] \times |\Sigma|^{-n/2} \exp \left\{ - \sum_i (\beta_i - x_i^T \alpha)^T \Sigma^{-1} (\beta_i - x_i^T \alpha) \right\},
    \]
    where \( Y_{ij} = Y_i(t_{ij}), U_{ij} = U(t_{ij}); R_i \) is the observed time of clinical recurrence or censoring and \( \delta_i \) is event indicator for subject \( i \); \( t_{ij} \) is PSA longitudinal data measurement time for subject \( i \); \( s_{ij} \) is the scaling factor for the T distribution; \( m \) is the total observed number of longitudinal PSA measurements; and \( n \) is the total number of subjects.
  - The prior distributions are:
    \[
    \lambda_{0j} \sim \text{gamma}(0.01, 0.01), j = 1, \ldots, 5;
    \]
    \[
    \sigma^{-2} \propto 1;
    \]
    \[
    \Sigma^{-1} \sim \text{Wishart} (\Sigma_p, 13), \text{where } \Sigma_p^{-1} = 0.5I_{3 \times 3};
    \]
    \[
    \alpha \sim \mathcal{N}_{12} (\alpha_p, \Sigma_\alpha), \text{where } \alpha_p = (0.01, \ldots, 0.01)^T, \Sigma_\alpha^{-1} = 0.2I_{12 \times 12};
    \]
    \[
    s_{ij} \sim \text{gamma} (\nu/2, \nu/2), \text{ where } \nu = 5;
    \]
Conditional distributions used in the MCMC algorithm:

\[
\lambda_{0j} \sim \text{gamma}(0.01 + \sum_{i=1}^{n} I(B_j < R_i \leq B_{j+1}) \delta_i, \\
0.01 + \sum_{i} \int_{B_j}^{\min(B_{j+1}, R_i)} I(R_i > B_j) \exp[Z_i(t)^T \theta] dt ; j = 1, \ldots, 5 ;
\]

\[
\sigma^{-2} \sim \text{gamma} \left( \frac{m}{2}, \frac{1}{2} \sum_{i} \sum_{j} (Y_{ij} - W_{ij}^T \beta_i)^2 s_{ij} \right);
\]

\[
s_{ij} \sim \text{gamma} \left( \frac{\nu + 1}{2}, \frac{\nu}{2} + \frac{(Y_{ij} - W_{ij}^T \beta_i)^2}{2\sigma^2} \right);
\]

\[
\Sigma^{-1} \sim \text{Wishart} \left( \frac{1}{2} \sum_{i} ((\beta_i - x_i^T \alpha)(\beta_i - x_i^T \alpha)^T + \Sigma_p^{-1}) , n + 13 \right);
\]

\[
\alpha \sim N_{12} \left( \alpha_p + \sum_{i} (x_i^T \Sigma^{-1} \beta_i), \{\Sigma^{-1}_{\alpha} + \sum_{i} (x_i^T \Sigma^{-1} x_i)\}^{-1} \right);
\]

\[
\alpha_p = (0.01, \ldots, 0.01)^T, \Sigma_{\alpha}^{-1} = 0.2I_{12 \times 12};
\]

MCMC algorithm to draw \( \beta_i \) using the Metropolis-Hastings method: draw \( \beta_i^{\text{new}} \) from the conditional distribution:

\[
\beta_i \sim N_3(\mu, V);
\]

\[
\mu = V \left( \Sigma^{-1} x_i^T \alpha + \sum_{j=1}^{Y_{ij}} W_{ij} s_{ij} \sigma^{-2} \right);
\]

\[
V = \left( \Sigma^{-1} + \sum_{j=1}^{Y_{ij}} W_{ij} W_{ij}^T s_{ij} \sigma^{-2} \right)^{-1}.
\]

Let

\[
r = \exp \left\{ \sum_{i} \int_{0}^{R_i} \lambda_i(t \mid \theta, \beta_i) dt - \int_{0}^{R_i} \lambda_i(t \mid \theta, \beta_i^{\text{new}}) dt \right\}.
\]

If \( r \geq 1 \), set \( \beta_i = \beta_i^{\text{new}} \). Otherwise set \( \beta_i = \beta_i^{\text{new}} \) with probability \( r \).

MCMC algorithm to draw \( \theta \) using Metropolis-Hastings method: draw \( \theta^{\text{new}} \) from pre-defined \( N_8(\mu_8, \Sigma_\theta) \). The specific values for \( \mu_8 \) and \( \Sigma_\theta \) were based on a preliminary Cox model analyses of the University of Michigan data with imputed values of PSA and slope.
of PSA.

\[ \mu_8 = (1.08, 1.33, -0.41, -1.35, 1.03, 1.49, 4.65, 0.42)^T \]

\[
\Sigma_\theta = \begin{pmatrix}
0.0981 & 0.0887 & -0.0017 & 0.0027 & -0.0073 & 0.0006 & -0.0022 & -0.0041 \\
0.1175 & -0.0056 & 0.0049 & -0.0092 & -0.0086 & -0.0099 & -0.0032 \\
0.0113 & 0.0009 & -0.0020 & -0.0042 & -0.0116 & 0.0016 \\
0.0631 & -0.0042 & -0.0141 & -0.0109 & -0.0092 \\
0.0362 & 0.0246 & 0.0083 & -0.0047 \\
0.0793 & 0.0177 & -0.0079 \\
0.1597 & -0.0374 \\
0.0283
\end{pmatrix}
\]

Let

\[
r = \exp \left[ \sum_i \int_0^{R_i} \lambda_i(t|\theta, \beta_i) dt - \int_0^{R_i} \lambda_i(t|\theta^{(\text{new})}, \beta_i) dt \right] + (\theta - \mu_8)^T \Sigma_\theta^{-1} (\theta - \mu_8) - (\theta^{(\text{new})} - \mu_8)^T \Sigma_\theta^{-1} (\theta^{(\text{new})} - \mu_8) \right].
\]

If \( r \geq 1 \), set \( \theta = \theta^{(\text{new})} \). Otherwise set \( \theta = \theta^{(\text{new})} \) with probability \( r \).

- The MCMC algorithm was run for 500,000 iterations after a 100,000 iteration burn-in period. The proposal densities for the Metropolis-Hastings draws gave approximately a 2.33% acceptance rate for survival model parameters and 97.5% for random effects (\( \beta_i \)). The convergence was assessed graphically. 1,000 draws from the converged algorithm were saved, consisting of every five hundredth draw from the final 500,000 draws.

1.2 Estimates of fixed effects from training data

[Table 1 about here.]

1.3 Quick MCMC algorithm for the testing data

1.3.1 Notation and description of the necessary elements.

- \( Y = (Y_1, \cdots, Y_m)^T \): longitudinal PSA data of new patient at times \( t_1, \ldots, t_m \);
• \( \mathbf{U} = (U_1, \ldots, U_m) \), where \( U_i = (1, (1 + t_i)^{-1.5} - 1, t_i) \);
• \( \mathbf{W} \): baseline covariates of new patient;
• \( \mathbf{x} \): 12 by 3 matrix of intercepts and baseline covariates, derived from \( \mathbf{W} \);
• \( c \): truncation time from which the prediction will be made (usually today);
• \( R \): random variable of time to recurrence for the new patient;
• \( \alpha, \theta \): fixed effect estimates obtained from the training data;
• \( \beta_N \): random effect of new patient to be estimated;
• \( (s_1, \ldots, s_m) \): scaling factors to give \( T \) distribution for measurement error;
• \( Z(t) \): time-dependent covariate vector in hazard model, derived from \( \mathbf{W} \) and \( \beta_N \).

Assumed distributions:

1. \((\alpha, \theta, \Sigma, \sigma^2, \lambda_0 | \text{Training Data})\): posterior draws of parameters based on analysis of the training data, which is independent of the new patient;
2. \( \beta_N \sim N(\mathbf{x}^T \alpha, \Sigma) \): distribution of random effects (multivariate normal).
3. \( Y_j \sim T(U_j \beta_N, \sigma^2, 5) \): distribution of longitudinal data (\( T_5 \) distribution);
4. \( R | \mathbf{W}, \beta_N, \theta, \lambda_0, R > c \): residual time to recurrence distribution;

The quantities to be estimated

• \( P(R > c + t | \mathbf{W}, \mathbf{Y}, R > c, \text{Training data}) \);
• \( \mathbb{E}Y(t | \mathbf{x}, \mathbf{Y}, R > c, \text{Training data}) \).

The likelihood for the new patient

\[
f(\beta_N, s_1, \ldots, s_m) \propto \prod_{j=1}^{m} \left[ s_j^{1/2} \exp \left\{ -\frac{(Y_j - U_j \beta_N)^2 s_j}{2\sigma^2} \right\} \right] s_j^{\nu/2 - 1} \exp \left\{ -\frac{\nu s_j}{2} \right\} \exp \left\{ -\frac{1}{2} (\beta_N - \mathbf{x}^T \alpha)^T \Sigma^{-1} (\beta_N - \mathbf{x}^T \alpha) \right\} \exp \left[ -\int_0^c \lambda_0(t) \exp \{ Z(t)^T \theta \} dt \right],
\]

where \( \nu = 5 \).

Conditional distributions in the MCMC algorithm:

\[
s_j \sim \text{gamma} \left( \frac{\nu + 1}{2}, \frac{(Y_j - U_j \beta_N)^2}{2\sigma^2} + \frac{\nu}{2} \right)
\]
Metropolis-Hastings draw for $\beta_N$: The proposal distribution for $\beta_N$ is trivariate normal as described below.

1.3.2 Algorithm.

1. Draw $(\alpha, \theta, \sigma^2, \Sigma, \lambda_0)$ from posterior distribution derived from training data set;
2. Set initial values. Let $s_j = 1, j = 1, \cdots, m$ and $\beta_N = x^T \alpha$;
3. Draw $\beta_N^{(\text{new})}$ from multivariate normal $N_3(\mu, V)$ proposal distribution, where
   \[
   \mu = V \left( \Sigma^{-1} x^T \alpha + \sum_{j=1}^m Y_j U_j s_j \sigma^{-2} \right)
   \]
   \[
   V = \left( \Sigma^{-1} + \sum_{j=1}^m U_j^T U_j s_j \sigma^{-2} \right)^{-1}
   \]
4. Let $r = \exp \left[ \int_0^c \lambda_0(t) \exp \{ Z(t|\beta_N)^T \theta \} dt - \int_0^c \lambda_0(t) \exp \{ Z(t|\beta_N^{(\text{new})})^T \theta \} dt \right]$;
5. If $r \geq 1$, let $\beta_N = \beta_N^{(\text{new})}$.
   Otherwise let $\beta_N = \beta_N^{(\text{new})}$ with probability $r$.
6. Draw $T$ distribution scale $s_j$ from gamma $\left\{\frac{\nu + 1}{2}, \frac{(Y_j - U_j \beta_N)^2}{2\sigma^2} + \frac{\nu}{2}\right\}$, $j = 1, \cdots, m$;
7. Repeat steps 3 - 6 $M$ times and save the draw of $\beta_N$ ($M = 50$);
8. Calculate $P(R < t|W, \beta_N, \theta, \lambda_0, R > c)$ for $c < t < c + 3$;
9. Repeat 1,000 times steps 1 - 8.
10. Average the values of $P(R < t|W, \beta_N, \theta, \lambda_0, R > c)$.

1.4 Percentiles of summary statistics for warning messages

[Table 2 about here.]

1.5 Use of the internet calculator

The website psacalc.sph.umich.edu contains a number of other programs as well as the one described in this paper. The specific one in this paper can be found by following the link to "Predicting future disease progression using baseline characteristics and post-treatment
PSA values, when Androgen deprivation treatment was not given.” The user enters his pre-treatment PSA, Gleason and T-stage values and the date radiation therapy treatment ended. He then enters the post treatment PSA values together with their dates. Pressing “Calculate” starts the quick MCMC, and the predictions of future PSA and probability of recurrence are displayed together with any warning messages.

Table 1: Summary statistics of posterior distributions of the population parameters.

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>Median</th>
<th>Mean</th>
<th>SD</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$ :</td>
<td>0.281</td>
<td>0.282</td>
<td>0.0404</td>
<td>-0.362</td>
<td>-0.202</td>
</tr>
<tr>
<td>$\alpha_2$ :</td>
<td>0.842</td>
<td>0.842</td>
<td>0.0179</td>
<td>0.807</td>
<td>0.878</td>
</tr>
<tr>
<td>$\alpha_3$ :</td>
<td>0.688</td>
<td>0.688</td>
<td>0.0912</td>
<td>0.51</td>
<td>0.865</td>
</tr>
<tr>
<td>$\alpha_4$ :</td>
<td>0.360</td>
<td>0.360</td>
<td>0.0531</td>
<td>0.256</td>
<td>0.465</td>
</tr>
<tr>
<td>$\alpha_5$ :</td>
<td>0.268</td>
<td>0.267</td>
<td>0.139</td>
<td>-0.00961</td>
<td>0.542</td>
</tr>
<tr>
<td>$\alpha_6$ :</td>
<td>0.75</td>
<td>0.75</td>
<td>0.0393</td>
<td>0.673</td>
<td>0.826</td>
</tr>
<tr>
<td>$\alpha_7$ :</td>
<td>-0.231</td>
<td>-0.231</td>
<td>0.0299</td>
<td>-0.289</td>
<td>-0.172</td>
</tr>
<tr>
<td>$\alpha_8$ :</td>
<td>0.193</td>
<td>0.192</td>
<td>0.0201</td>
<td>0.154</td>
<td>0.232</td>
</tr>
<tr>
<td>$\alpha_9$ :</td>
<td>0.447</td>
<td>0.447</td>
<td>0.0541</td>
<td>0.338</td>
<td>0.553</td>
</tr>
<tr>
<td>$\alpha_{10}$ :</td>
<td>0.0234</td>
<td>0.0236</td>
<td>0.0177</td>
<td>-0.00961</td>
<td>0.542</td>
</tr>
<tr>
<td>$\alpha_{11}$ :</td>
<td>0.135</td>
<td>0.135</td>
<td>0.0294</td>
<td>0.078</td>
<td>0.193</td>
</tr>
<tr>
<td>$\alpha_{12}$ :</td>
<td>0.178</td>
<td>0.178</td>
<td>0.0127</td>
<td>0.153</td>
<td>0.203</td>
</tr>
<tr>
<td>$\sigma^2$ :</td>
<td>0.0392</td>
<td>0.0392</td>
<td>0.000565</td>
<td>0.0382</td>
<td>0.0404</td>
</tr>
<tr>
<td>$\Sigma_{11}$ :</td>
<td>0.356</td>
<td>0.356</td>
<td>0.0146</td>
<td>0.328</td>
<td>0.385</td>
</tr>
<tr>
<td>$\Sigma_{12}$ :</td>
<td>0.267</td>
<td>0.267</td>
<td>0.0237</td>
<td>0.221</td>
<td>0.314</td>
</tr>
<tr>
<td>$\Sigma_{13}$ :</td>
<td>0.00927</td>
<td>0.00946</td>
<td>0.00684</td>
<td>-0.00380</td>
<td>0.0230</td>
</tr>
<tr>
<td>$\Sigma_{22}$ :</td>
<td>1.41</td>
<td>1.41</td>
<td>0.0635</td>
<td>1.29</td>
<td>1.54</td>
</tr>
<tr>
<td>$\Sigma_{23}$ :</td>
<td>0.275</td>
<td>0.276</td>
<td>0.0183</td>
<td>0.242</td>
<td>0.314</td>
</tr>
<tr>
<td>$\Sigma_{33}$ :</td>
<td>0.172</td>
<td>0.172</td>
<td>0.00793</td>
<td>0.157</td>
<td>0.188</td>
</tr>
<tr>
<td>$\theta_1$ :</td>
<td>0.73</td>
<td>0.724</td>
<td>0.219</td>
<td>0.29</td>
<td>1.16</td>
</tr>
<tr>
<td>$\theta_2$ :</td>
<td>0.951</td>
<td>0.951</td>
<td>0.256</td>
<td>0.444</td>
<td>1.46</td>
</tr>
<tr>
<td>$\theta_3$ :</td>
<td>-0.269</td>
<td>-0.27</td>
<td>0.077</td>
<td>-0.416</td>
<td>-0.116</td>
</tr>
<tr>
<td>$\theta_4$ :</td>
<td>0.554</td>
<td>0.553</td>
<td>0.145</td>
<td>0.28</td>
<td>0.838</td>
</tr>
<tr>
<td>$\theta_5$ :</td>
<td>0.401</td>
<td>0.399</td>
<td>0.195</td>
<td>0.00887</td>
<td>0.768</td>
</tr>
<tr>
<td>$\theta_6$ :</td>
<td>4.26</td>
<td>4.26</td>
<td>0.318</td>
<td>3.65</td>
<td>4.88</td>
</tr>
<tr>
<td>$\theta_7$ :</td>
<td>0.953</td>
<td>0.952</td>
<td>0.148</td>
<td>0.669</td>
<td>1.25</td>
</tr>
<tr>
<td>$\theta_8$ :</td>
<td>-1.25</td>
<td>-1.25</td>
<td>0.183</td>
<td>-1.61</td>
<td>-0.912</td>
</tr>
<tr>
<td>$\lambda_{01} \times 10^{-3}$ :</td>
<td>1.84</td>
<td>1.93</td>
<td>0.614</td>
<td>0.993</td>
<td>3.35</td>
</tr>
<tr>
<td>$\lambda_{02} \times 10^{-3}$ :</td>
<td>1.60</td>
<td>1.68</td>
<td>0.531</td>
<td>0.872</td>
<td>2.95</td>
</tr>
<tr>
<td>$\lambda_{03} \times 10^{-3}$ :</td>
<td>1.28</td>
<td>1.33</td>
<td>0.407</td>
<td>0.709</td>
<td>2.32</td>
</tr>
<tr>
<td>$\lambda_{04} \times 10^{-3}$ :</td>
<td>1.09</td>
<td>1.15</td>
<td>0.376</td>
<td>0.580</td>
<td>2.05</td>
</tr>
<tr>
<td>$\lambda_{05} \times 10^{-3}$ :</td>
<td>1.39</td>
<td>1.46</td>
<td>0.479</td>
<td>0.725</td>
<td>2.59</td>
</tr>
</tbody>
</table>
Table 2: Percentiles of the statistics estimated from training data.

<table>
<thead>
<tr>
<th>Statistics</th>
<th>95% Percentiles</th>
<th>99% Percentiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\frac{1}{m} \sum_{j=1}^{m} (Y_j - \hat{Y}_j)^2$</td>
<td>0.234</td>
<td>2.293</td>
</tr>
<tr>
<td>$m \leq 4$</td>
<td>0.204</td>
<td>0.534</td>
</tr>
<tr>
<td>$m &gt; 4$</td>
<td>0.204</td>
<td>0.534</td>
</tr>
<tr>
<td>$(Y_m - \hat{Y}_m)^2$</td>
<td>0.359</td>
<td>2.562</td>
</tr>
<tr>
<td>$\max_j (Y_j - \hat{Y}_j)^2$</td>
<td>1.201</td>
<td>4.007</td>
</tr>
<tr>
<td>$\hat{\beta}_0 - \mathbf{x}_0^T \hat{\alpha}$</td>
<td>Upper 0.972, Lower -1.093</td>
<td>Upper 1.310, Lower -1.730</td>
</tr>
<tr>
<td>$\hat{\beta}_1 - \mathbf{x}_1^T \hat{\alpha}$</td>
<td>Upper 2.023, Lower -1.873</td>
<td>Upper 2.890, Lower -2.801</td>
</tr>
<tr>
<td>$\hat{\beta}_2 - \mathbf{x}_2^T \hat{\alpha}$</td>
<td>Upper 0.925, Lower -0.588</td>
<td>Upper 1.396, Lower -0.853</td>
</tr>
<tr>
<td>$(\hat{\beta} - \mathbf{x}^T \hat{\alpha})^T \Sigma^{-1} (\hat{\beta} - \mathbf{x}^T \hat{\alpha})$</td>
<td>8.360</td>
<td>16.810</td>
</tr>
<tr>
<td>$\text{var}{\hat{E}\hat{Y}(c + 3)}$</td>
<td>1.762</td>
<td>2.801</td>
</tr>
</tbody>
</table>