Dynamic prediction using joint models for recurrent and terminal events:
Evolution after a breast cancer

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Introduction

- **After a breast cancer diagnosis**
  → single or multiple events
  (recurrences, metastases, death)
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- **Prediction of death**
  - clinical therapeutic decisions, and patient monitoring
  - patient information
  - trials: defining patient subpopulations
Introduction

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- **Prediction of death**
  → clinical therapeutic decisions, and patient monitoring
  → patient information
  → trials : defining patient subpopulations

- **Account for**
  → individual characteristics
  → tumour characteristics
  → previous treatments
  → evolution of longitudinal markers (*Rizopoulos, 2011*; *Proust-Lima 2009*)
Introduction: Motivating example

- Cohort of patients with *operable breast cancer*
- Treated in a *comprehensive cancer centre* and followed 13.9 years (median)
- **Recurrent events** observed: loco-regional relapses, distant metastases; until 3 events per patient
- Hypothesis: individual covariates but also **recurrent event process** may improve prediction of death risk
Objective

To predict the risk of death between time $t$ and $t + h$ given the recurrent event process before time $t$ in the context of joint modelling.
Joint Models

- Recurrent events and death processes are potentially correlated
- Standard (naive) approach of Cox with time-dependent covariate only for external covariates!

Interest:
- investigating the strength of association between recurrent events and death
- allows to study impact of covariates both on recurrent events and death
- treat informative censoring by death
Joint models: some notations

- $t$ time of prediction and $h$ window of prediction
- $D_i$ time of death for subject $i$, $i = 1, \ldots, n$
- $X_{ij}$ time of the $j$th recurrence for subject $i$
- $Z^R_{ij}$ and $Z^D_i$ covariates vectors for recurrence and death
- $\lambda^R_{ij}$ and $\lambda^D_i$ baseline hazards for risk of recurrence or death
Joint models

Joint modelling for the risk of recurrent event (disease relapses) and terminal event (death)

\[
\begin{align*}
\lambda_{ij}^R(t|u_i) &= u_i \lambda_0^R(t) \exp(\beta_1' Z_{ij}^R) \\
\lambda_i^D(t|u_i) &= u_i^\alpha \lambda_0^D(t) \exp(\beta_2' Z_i^D)
\end{align*}
\]

- calendar timescale (time from origin)
- \(u_i \sim \Gamma(1/\theta; 1/\theta)\), i.e. \(E(u_i) = 1\) and \(\text{var}(u_i) = \theta\)
- \(\theta\) dependency between recurrent events and death
- \(\alpha\) sense and strength of the association (more flexibility)

Inference in the joint model

Penalized log-likelihood:
- smooth baseline hazard functions
- approximated by cubic M-splines

\[ pl(\xi) = l(\xi) - \kappa_1 \int_0^\infty (\lambda_0^R(t))''^2 dt - \kappa_2 \int_0^\infty (\lambda_0^D(t))''^2 dt \]

With the vector of parameters: \( \zeta = (\lambda_0^D(\cdot), \lambda_0^R(\cdot), \beta, \alpha, \theta) \) and \( \kappa_1 \) and \( \kappa_2 \) two smoothing parameters for the baseline hazard functions
Dynamic prediction

- Consider a new subject $i$ free of death at time $t$ (i.e. $D > t$), for whom we observe $j$ recurrences before $t$ and for whom the vector of covariates $Z_{ij}^R$ and $Z_{ij}^D$ are available at time of prediction.

- The history of recurrences for patient $i$ until time $t$ is:

$$\mathcal{H}_i^j(t) = \{N_{ij}^R(t) = J, X_{i1} < \ldots < X_{ij} \leq t\}$$
Dynamic prediction
Distinguish **two settings** for the probability of death

**Setting 1**
Exactly 3 recurrent events before $t$

**Setting 2**
Whatever the history of recurrent events before $t$

- Recurrent event
- Period where we consider what happens
- Window of prediction of death
- Period where we do not consider what happens
Dynamic prediction

Setting 1 : with exactly $j$ recurrences before $t$

$$P^1(t, t + h; \xi) = P(D_i \leq t + h | D_i > t, \mathcal{H}_i^{J,1}(t), Z_{ij}^R, Z_i^D, \xi)$$

$$= \frac{\int_0^\infty [S_i^D(t|Z_i^D, u_i, \xi) - S_i^D(t + h|Z_i^D, u_i, \xi)](u_i)^J S_{i(J+1)}(t|Z_{ij}^R, u_i, \xi) g(u_i)du_i}{\int_0^\infty S_i^D(t|Z_i^D, u_i, \xi)(u_i)^J S_{i(J+1)}(t|Z_{ij}^R, u_i, \xi) g(u_i)du_i}$$

and $\mathcal{H}_i^{J,1}(t) = \{N_i^R(t) = J, X_{i1} < \ldots < X_{iJ} \leq t\}$, with $X_{i0} = 0$ and $X_{i(J+1)} > t$
Dynamic prediction

Setting 1: with exactly \( j \) recurrences before \( t \)

\[
P^1(t, t + h; \xi) = P(D_i \leq t + h | D_i > t, \mathcal{H}_{i}^{J,1}(t), Z_{ij}^R, Z_i^D, \xi)
\]

\[
= \frac{\int_{0}^{\infty} [S_i^D(t|Z_i^D, u_i, \xi) - S_i^D(t + h|Z_i^D, u_i, \xi)](u_i)^JS_{i(J+1)}^R(t|Z_{ij}^R, u_i, \xi)g(u_i)du_i}{\int_{0}^{\infty} S_i^D(t|Z_i^D, u_i, \xi)(u_i)^JS_{i(J+1)}^R(t|Z_{ij}^R, u_i, \xi)g(u_i)du_i}
\]

and \( \mathcal{H}_{i}^{J,1}(t) = \{N_i^R(t) = J, X_{i1} < \ldots < X_{iJ} \leq t\} \), with \( X_{i0} = 0 \) and \( X_{i(J+1)} > t \)

Example:
"Up to now Mrs Martin has developed 3 recurrences of her initial cancer, her probability of dying in the next 5 years is \( x\% \)"
Dynamic prediction

Setting 2: considering the recurrence history only in the parameters estimation

\[ P^2(t, t + h; \xi) \]

\[ = P(D_i \leq t + h | D_i > t, Z_i^D, \xi) \]

\[ = \int_0^\infty \left[ S_i^D(t|Z_i^D, u_i, \xi) - S_i^D(t + h|Z_i^D, u_i, \xi) \right] g(u_i) du_i \]

\[ \int_0^\infty S_i^D(t|Z_i^D, \xi, u_i) g(u_i) du_i \]
Dynamic prediction

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\[ = \int_0^\infty \left[ S_i^D(t|Z_i^D, u_i, \xi) - S_i^D(t + h|Z_i^D, u_i, \xi) \right] g(u_i) du_i \]

\[ = \frac{\int_0^\infty S_i^D(t|Z_i^D, \xi, u_i) g(u_i) du_i}{\int_0^\infty S_i^D(t|Z_i^D, \xi) g(u_i) du_i} \]

Example:
“her probability of dying in the next 5 years is x%”
“if still alive in 5 years, her probability of dying over the next 5 years will be x%”
Dynamic prediction: variability of the probability estimators

by Monte Carlo:

- at each $b$ step ($b=1,...,B=1000$): 
  \[ \hat{\xi} = (\hat{\lambda}_0^R(.), \hat{\lambda}_0^D(.), \hat{\beta}, \hat{\alpha}, \hat{\theta}) \text{ from } \mathcal{MN}(\hat{\xi}, \hat{\Sigma}_\xi). \]
  estimate $P^b(t, t+h; \hat{\xi})$

- Percentile confidence interval: using the 2.5$^{th}$ and the 97.5$^{th}$ percentiles
Dynamic prediction: Error of prediction
Based on a weighted estimator of a time-dependent Brier Score (IPCW error)

\[ Err_{t+h} = \frac{1}{N_t} \sum_{i=1}^{N_t} \left[ I(T_i^D > t + h) - (1 - \hat{P}(t, t + h; \hat{\xi})) \right]^2 \hat{w}_i(t + h, \hat{G}_N(\cdot)) \]

with

\[ \hat{w}_i(t + h, \hat{G}_N(\cdot)) = \frac{I(T_i^D \leq t + h)\delta_i^D}{\hat{G}_N(T_i^D)/\hat{G}_N(t)} + \frac{I(T_i^D > t + h)}{\hat{G}_N(t + h)/\hat{G}_N(t)} \]

\( T_i^D = \) observed survival time; \( \delta_i = \) event indicator

\( N_t = \) patients alive and uncensored at \( t \)

\( \hat{G}_N(t) = \) KM estimate or adjusted Cox estimate of the censoring distribution

Validated by a 10-fold cross-validation

Dynamic prediction: Error of prediction

To be able to compare different populations: residual error $R^2$

$$ R^2 = 1 - \frac{Err_{t+h}}{Err^0_{t+h}} $$

with $Err_{t+h}$ as previously defined, $Err^0_{t+h}$ the prediction error from a Kaplan-Meier model (average survival predicted for each patient)

1. On the French cohort
Development cohort

- Model development
  - Variable selection
  - Parameters estimation
- Internal validation of the prediction
  - Apparent error
  - Cross-validated error
French cohort

- 1067 patients
- median follow-up: 13.8 years (min=5 months)
- 427 recurrent events (locoregional relapses and distant metastases) in 362 patients (mean 0.40)

<table>
<thead>
<tr>
<th>N events</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>600</td>
<td>114</td>
<td>20</td>
<td>3</td>
<td>737</td>
</tr>
<tr>
<td>Died</td>
<td>105</td>
<td>187</td>
<td>37</td>
<td>1</td>
<td>330</td>
</tr>
<tr>
<td>All</td>
<td>705</td>
<td>301</td>
<td>57</td>
<td>4</td>
<td>1067</td>
</tr>
</tbody>
</table>

with the R package `frailtypack`

http://cran.r-project.org/web/packages/frailtypack/
Prognostic joint model

\[ \theta = 1.03 \text{ (se=0.06)} \text{ and } \alpha = 4.66 \text{ (se=0.28)} \]
Prediction values between 5 and 10 years

<table>
<thead>
<tr>
<th>Recurrence history</th>
<th>$P_{\text{Recurrence}}(5, 10; \hat{\xi})$</th>
<th>$P_{\text{Ignoring}}(5, 10; \hat{\xi})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No recurrence</td>
<td>10.8 (4.2)</td>
<td>12.7 (4.5)</td>
</tr>
<tr>
<td>One recurrence</td>
<td>30.3 (8.9)</td>
<td>12.7 (4.5)</td>
</tr>
<tr>
<td>Two recurrences</td>
<td>50.6 (11.4)</td>
<td>12.7 (4.5)</td>
</tr>
<tr>
<td>Three recurrences</td>
<td>67.4 (11.9)</td>
<td>12.7 (4.5)</td>
</tr>
</tbody>
</table>

For a given patient: age > 55y, no PVI, size ≤ 20mm, HER2 negative, HR positive, no lymph node involvement, grade II.
### Prediction values between 5 and 15 years

<table>
<thead>
<tr>
<th>Recurrence history</th>
<th>$P_{\text{Recurrence}}^{(5, 15; \hat{\xi})}$</th>
<th>$P_{\text{Ignoring}}^{(5, 15; \hat{\xi})}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No recurrence</td>
<td>22.7 (4.8)</td>
<td>25.6 (4.7)</td>
</tr>
<tr>
<td>One recurrence</td>
<td>53.0 (6.9)</td>
<td>25.6 (4.7)</td>
</tr>
<tr>
<td>Two recurrences</td>
<td>75.6 (6.0)</td>
<td>25.6 (4.7)</td>
</tr>
<tr>
<td>Three recurrences</td>
<td>88.4 (4.1)</td>
<td>25.6 (4.7)</td>
</tr>
</tbody>
</table>

For a given patient: age > 55y, no PVI, size ≤ 20mm, HER2 negative, HR positive, no lymph node involvement, grade II.
Death prediction for 2 particular cases

Baseline prediction
between 40 and 55 y, no peritum. vasc. invasion, tumour size $\leq$ 20 mm, HER2 -, HR +, no lymph node involv., grade II

**Patient 1**
With recurrences

**Patient 2**
Without recurrence
Death prediction for 2 particular cases

Prediction time $t=2$ years

Patient 1
With recurrences

Patient 2
Without recurrence
Death prediction for 2 particular cases

Prediction time $t=5$ years

**Patient 1**
With recurrences

**Patient 2**
Without recurrence
Death prediction for 2 particular cases

Prediction time $t=10$ years

Patient 1
With recurrences

Patient 2
Without recurrence

Death probability with prediction time $t=10$
Death prediction error
Prediction at 5 years (949 patients alive)
Prediction error

Prediction at 5 years (949 patients alive), with 10-fold cross-validation
Prediction error
Prediction at 5 years (267 patients alive with recurrence), with 10-fold cross-validation
At this step

- Found the prognostic factors of interest

- Estimated parameters (factor effects, correlation between the two endpoints)

- Were able to account for relapses in the prediction of the risk of death

- Not clear whether accounting for relapses has an interest for prediction
2. External validation
External validation - why?

- Model designed to perform well on development data
  - problem with the design or methods
  - absence of an important predictor
- To check the **reproducibility** of the model and predictions
  - overfitting
    - correct for optimism
  - difference case-mix
- To update the proposed prognostic model
Models to be compared

- **Joint frailty model**
  + One model $\rightarrow$ dynamic prediction
  + Correlation between the two processes fully accounted for
    - more parameters $\rightarrow$ less stability

- **Landmark Cox model**
  + Robust and simple model
  + Time-dependent effects
    - One model for each prediction time $t$
    - Information about recurrent events: number of recurrent events
Populations - description

West Midlands
- 1196 subjects
- Diagnosed in 1996
- Follow-up: 16 years
- 376 relapses in 301 patients (mean=0.31)
- 613 deaths (51%)

Dutch registry
- 31,075 subjects
- Diagnosed in 2003-2006
- Median follow-up: 7.7 y
- 3854 relapses in 3844 patients (mean=0.12)
- 7162 deaths (23%)
Populations - missing data

- Missing data problem not much discussed in the literature in that context
- Not an effect estimation problem
- Clinical point of view
  → complete case analysis

West Midlands
- 1196 subjects
- from 3168 cases (38%)
- HER2 and hormonal receptor unavailable

Dutch registry
- 31,075 subjects
- from 41,676 cases (75%)
- HER2 and hormonal receptor unavailable
- Perivascular invasion unavailable
Populations - Relapses definitions

West Midlands
- Recurrence defined from treatment
- 376 relapses
  - 22% <2 years
  - 59% <5 years

Dutch registry
- Recurrences recorded (only the 1\textsuperscript{st} one of each type)
- 3854 relapses
  - 41% <2 years
  - 93% <5 years
Populations - recurrent event

![Bar chart showing populations distribution in French, Dutch registry, and West Midlands.](chart.png)
Populations - prognostic factors
Populations - overall survival
West Midlands population

$t=2$ years

$t=5$ years
West Midlands population

Fixed window of prediction h=5 y

![Graph showing prediction times and R² values for various models (P-Recurrence, P-Ignoring, P-Cox LM).]
West Midlands population - Calibration at 10 years ($t=5$ years)

P–Recurrence

10–y predicted probability of death

10–y observed probability of death
West Midlands population

Calibration at 10 years (t=5 years)
West Midlands population

Calibration at 15 years ($t=5$ years)
Subgroup analysis

West Midlands population - operated patients
Dutch population

$t=2$ years

$t=3$ years

R2

P−Recurrence
P−Ignoring
P−Cox LM

Prediction horizon

R2

P−Recurrence
P−Ignoring
P−Cox LM

Prediction horizon
Dutch population

Calibration at 7 years ($t=2$ years)
At the end

- Relapses information is **useful to predict** the death of patients with breast cancer

- The **more information**, the better
  relapses information prior to 2-3 years not enough

- Two approaches (joint and landmark) give similar performance
  → Do not be afraid to use complex model (with more parameters) in prediction **if needed**
At the end

- The model estimated on a selected cohort of patients can be useful in more general populations
  - Good performance in West Midlands population despite
    - a different survival in the population
    - a different period of inclusion
    - a different case-mix
  - Prediction not good in Dutch registry patients
    - Short follow-up
    - Patient recently diagnosed
    - impact of change in the clinical practice?
And then?

- Considering the **type of recurrence**
  Different effect of loco-regional relapse and metastasis on the risk of death

- Predict the **risk of recurrence**
  For example, risk of metastasis considering the previous loco-regional relapses
References

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http://cran.r-project.org/web/packages/pec/

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