Parametric Estimation of The Mean Number of Events in The Presence of Competing Risks

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Background

- Recurrent events are common in time-to-event data, e.g., cardiovascular events, hospital admissions, childbirths, etc.
- The mean number of events is one useful summary measure in these situations.
- Estimation of the mean number of events in the presence of competing events is more challenging

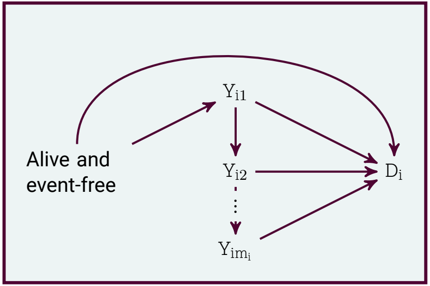

Figure 1. Illustration of the event process where the nodes symbolise different states of the event process.

Estimating The Mean Number of Events

Mean Number of Events Function

$$\mathbb{E}[N(t)] = \int_0^t S(u)\lambda(u)du \qquad (1)$$

where $S(t)$ is the survival function of the competing event and $\lambda(t)$ the intensity function of the recurrent event process.

- Cook and Lawless suggested using the Kaplan-Meier and Aalen-Johansen estimate for estimating $S(t)$, and $\lambda(t)$ respectively.
- We instead suggest using a flexible parametric model (FPM) to jointly model the recurrent and competing event process.

The Joint Flexible Parametric Model

We define one model for the log cumulative hazard function of the j^{th} recurrent event (Λ_{ij}) and the competing event (H_i):

$$\begin{aligned} \log \Lambda_{ij}(t|x_{1ij}) &= s[\log(t)|\boldsymbol{\gamma}_1, l_1] + x_{1ij}^T \boldsymbol{\beta}_1, \\ \log H_i(t|x_{2i}) &= s[\log(t)|\boldsymbol{\gamma}_2, l_2] + x_{2i}^T \boldsymbol{\beta}_2. \end{aligned} \tag{2}$$

Both models are jointly estimated using a combined likelihood L_i, where L_{1i} and L_{2i} are the contributions of the i^{th} individual to the likelihood of the recurrent and competing event process, respectively.

$$\begin{aligned} \log L_i(\boldsymbol{\theta}|x_i, t_{ij}, t_i) &= \log L_{1i}(\boldsymbol{\theta}_1|x_{1ij}, t_{ij}) + \log L_{2i}(\boldsymbol{\theta}_2|x_{2i}, t_i) \\ &= \sum_{j=1}^{m_i} \left\{ \delta_{ij} \log[\lambda(t_{ij}|x_{1ij})] - \Lambda(t_{ij}|x_{1ij}) + \Lambda(t_{ij-1}|x_{1ij}) \right\} \\ &\qquad + \delta_i \log[h(t_i|x_{2i})] - H(t_i|x_{2i}) \end{aligned} \tag{3}$$

Implementation

The model is implemented in the R package `JointFPM`

- Available on CRAN
- Based on the `rstpm2` package for estimating FPMs
- Currently supports predictions of $\mathbb{E}[\mathrm{N}(\mathrm{t})]$ and differences thereof, as well as standardised estimates

Link to `JointFPM` package

Example: Readmission After Colon Cancer Surgery

- Aim: Investigate hospital readmission patterns in patients that underwent colon cancer surgery by chemotherapy status.

- Data: Based on the `readmission` dataset included in the `frailtypack` package for R

- Follow-up: Followed for hospital readmission from the date of surgery until the date of censoring, death, or a maximum follow-up of 1 500 days.

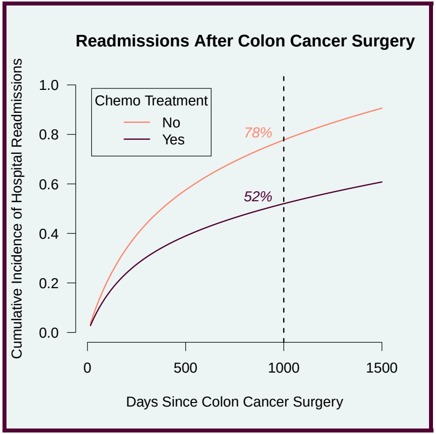

Figure 2. CIF of hospitalisation after colon cancer surgery.

JointFPM Data Set-Up

Table 1. Data setup for the joint likelihood. *t.start*: time at the start of follow-up; *t.stop* is time at the end of follow-up; *re*: indicator for rows contributing to L_1; *ce*: indicator for rows contributing to L_2; x: a vector of covariates for modelling the intensity function of the recurrent (x_1) and the competing event (x_2).

id	t.start	t.stop	δ	ce	re	x
i	0	t_{i1}	δ_{i1}	0	1	x_{1i1}
i	t_{i1}	t_{i2}	δ_{i2}	0	1	x_{1i2}
i	t_{ij-1}	t_{ij}	δ_{ij}	0	1	x_{1ij}
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
i	t_{im_i-1}	t_{im_i}	δ_{im_i}	0	1	x_{1im_i}
i	0	t_i	δ_i	1	0	x_{2i}

JointFPM Data Set-Up (Cont'd)

Table 2. Example of a dataset in stacked long format for the first 3 individuals in the readmission dataset included in the *frailtypack* package for R. *chemo*: chemotherapy treatment indicator

id	t.start	t.stop	event	ce	re	chemo
1	0	24	1	0	1	1
1	24	457	1	0	1	1
1	457	1037	0	0	1	1
1	0	1037	0	1	0	1
2	0	489	1	0	1	0
2	489	1182	0	0	1	0
2	0	1182	0	1	0	0
3	0	15	1	0	1	0
3	15	783	0	0	1	0
3	0	783	1	1	0	0

Model Specification in JointFPM

```
> JointFPM(surv = Surv(t.start, t.stop, event,
+                      type = "counting") ~ 1,
+          re_model = ~ chemo,
+          ce_model = ~ chemo,
+          re_indicator = "re",
+          ce_indicator = "ce",
+          df_ce = 2,
+          df_re = 3,
+          tvc_re_terms = list(chemo = 1),
+          tvc_ce_terms = list(chemo = 2),
+          cluster = "id",
+          data = data)
```

Mean Number of Events

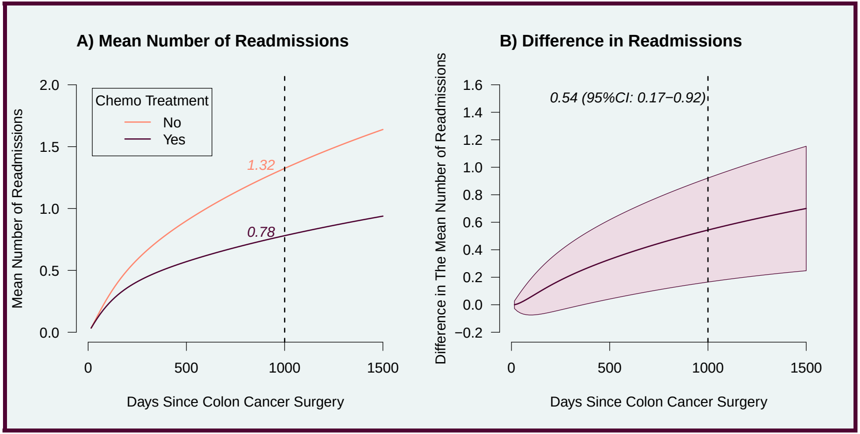

Figure 3. Mean number of hospital readmission after surgery for colon cancer, by chemotherapy treatment (A) and differences thereof (B).

Standardised Mean Number of Events

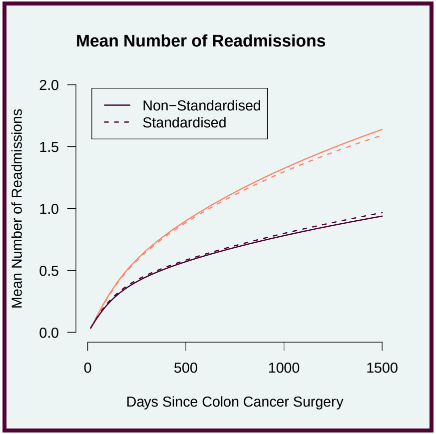

Figure 4. Comparison of non-standardised and standardised estimates of the mean number of events after colon cancer surgery in patient treated and not treated with neoadjuvant chemotherapy.

Comparison of CIF and Mean Number of Events

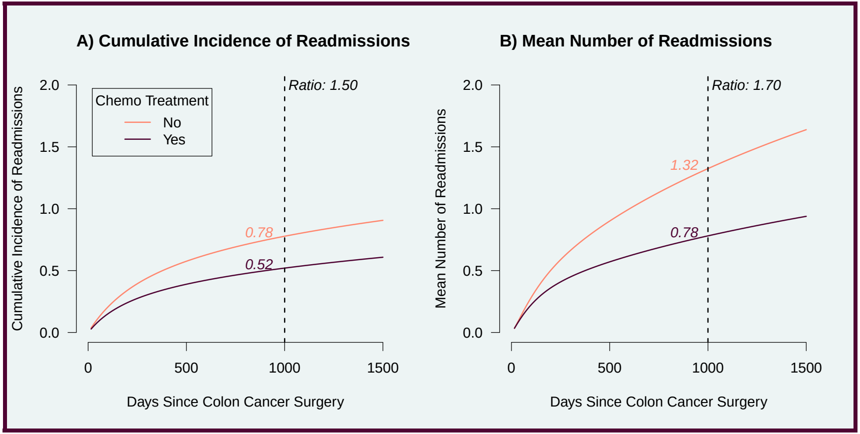

Figure 5. Comparison of the CIF of hospitalisation (A) with the mean number of hospitalisation (B).

Discussion

Strengths:

- Easy estimation of functions of $\mathbb{E}[N(t)]$
- Use of delta method for obtaining confidence intervals
- Possibility obtaining standardised estimates

Limitations

- Summary measure of the recurrent event process
- So far limited to one competing event
- Computationally intensive

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Link to the presentation slides