Modeling the cumulative incidence function of clustered competing risk data: a multinomial GLMM approach

Henrique Laureano | Wagner Bonat

http://leg.ufpr.br/~henrique | http://leg.ufpr.br/~wagner

Cause-specific **cumulative incidence function** (CIF), $F(\cdot)$

for a type k failure,
$$F_k(t \mid \{X, R\}) = \mathbb{P}[T \le t, K = k \mid \{X, R\}]$$
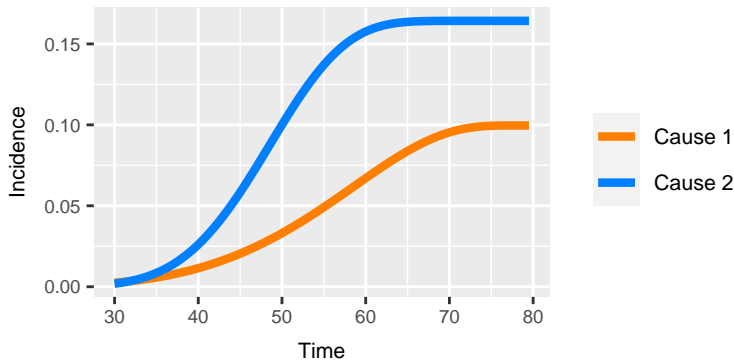$$= \underbrace{\pi_k(\{X, R\})}_{\text{risk level}} \times \underbrace{\Phi[t \mid \{X, R_k\}]}_{\substack{\text{failure time} \\ \text{trajectory}}}.$$

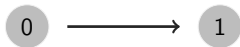As proposed by Cederkvist et al., 2019.

for a type k failure, $\quad F_k(t \mid \{X, R\}) = \mathbb{P}[T \le t, K = k \mid \{X, R\}]$
$$= \underbrace{\pi_k(\{X, R\})}_{\text{risk level}} \times \underbrace{\Phi[t \mid \{X, R_k\}]}_{\substack{\text{failure time} \\ \text{trajectory}}}.$$
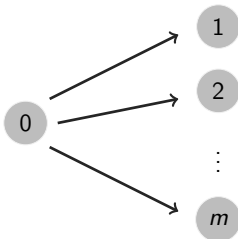
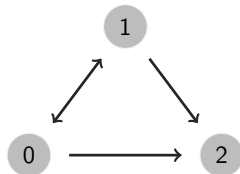As proposed by Cederkvist et al., 2019.

Survival data designs

Failure time process

Competing risks process

Multistate process
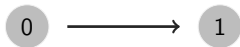
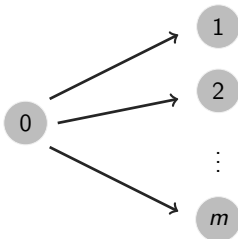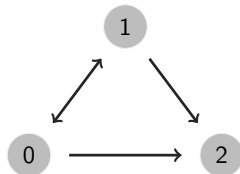Failure time process

Competing risks process

Multistate process

for a type k failure, $\quad F_k(t \mid \{X, R\}) = \mathbb{P}[T \leq t, K = k \mid \{X, R\}]$
$$= \underbrace{\pi_k(\{X, R\})}_{\text{risk level}} \times \underbrace{\Phi[t \mid \{X, R_k\}]}_{\substack{\text{failure time} \\ \text{trajectory}}}.$$

» We work on the probability scale, modeling the

> **Cause-specific cumulative incidence function (CIF)**
>
> for a type k failure, $\quad F_k(t \mid X) = \mathbb{P}[T \leq t, K = k \mid X]$
> $$= \int_0^t f_k(a \mid X)da, \quad t > 0,$$
>
> where $f_k(t \mid X) = \lambda_k(t \mid X) \times S(t \mid X)$ is the (sub)density for the time to a type k failure

» We go beyond the independence supposition, having clusters of subjects with a possible correlation

» Our latent structure to capture this possible correlation has audacity, allowing for within-cluster dependence of both risk and timing

Considering a competing risks setup of three competing causes. . .

Considering a competing risks setup of three competing causes. . .

. . . we want to model the CIF in the following specific manner

$$F_k(t \mid X, U) = \mathbb{P}[T \leq t, K = k \mid X, U]$$
$$= \underbrace{\pi_k(X, u_1, u_2)}_{\substack{\text{cluster-specific} \\ \text{risk level}}} \times \underbrace{\Phi[w_k g(t) - X^\top \gamma_k - \eta_k]}_{\substack{\text{cluster-specific} \\ \text{failure time trajectory}}}, \quad k = 1, 2.$$

i.e., a product of two functions

  » the first models the absolute risk of a competing cause in the presence of another
  » the second models the failure time distribution,

both varying between clusters

Considering a competing risks setup of three competing causes. . .

. . . we want to model the CIF in the following specific manner

$$F_k(t \mid X, U) = \mathbb{P}[T \leq t, K = k \mid X, U]$$
$$= \underbrace{\pi_k(X, u_1, u_2)}_{\substack{\text{cluster-specific} \\ \text{risk level}}} \times \underbrace{\Phi[w_k g(t) - X^\top \gamma_k - \eta_k]}_{\substack{\text{cluster-specific} \\ \text{failure time trajectory}}}, \quad k = 1, 2.$$

i.e., a product of two functions

  » the first models the absolute risk of a competing cause in the presence of another
  » the second models the failure time distribution,

both varying between clusters

  » The third competing cause is left to accommodate the censorship
  » Which probability distribution fits this setup? Multinomial

Scheike works out this idea via a pairwise composite likelihood approach,

```
@article{Scheike,
  author  = {L. Cederkvist and K. K. Holst and K. K. Andersen and
             T. H. Scheike},
  title   = {Modeling the cumulative incidence function of
             multivariate competing risks data allowing for
             within-cluster dependence of risk and timing},
  year    = {2019},
  journal = {Biostatistics},
  volume  = {20},
  number  = {2},
  pages   = {199--217},
}
```

And we? We try a hierarchical approach via a GLMM

Our approach: what we do

For an observed response y_{ijt} of a subject i, with cluster j, in the time t, we have

$$y_{ijt} \mid \{u_{1j}, u_{2j}, \eta_{1j}, \eta_{2j}\} \sim \text{Multinomial}(p_{1ijt}, p_{2ijt}, p_{3ijt}),$$

$$\begin{bmatrix} u_{1j} \\ u_{2j} \\ \eta_{1j} \\ \eta_{2j} \end{bmatrix} \sim \mathcal{N} \left(\begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_{u_1}^2 & \varrho_{u_1,u_2} & \varrho_{u_1,\eta_1} & \varrho_{u_1,\eta_2} \\ & \sigma_{u_2}^2 & \varrho_{u_2,\eta_1} & \varrho_{u_2,\eta_2} \\ & & \sigma_{\eta_1}^2 & \varrho_{\eta_1,\eta_2} \\ & & & \sigma_{\eta_2}^2 \end{bmatrix} \right).$$

For an observed response y_{ijt} of a subject i, with cluster j, in the time t, we have

$$y_{ijt} \mid \{u_{1j}, u_{2j}, \eta_{1j}, \eta_{2j}\} \sim \text{Multinomial}(p_{1ijt}, p_{2ijt}, p_{3ijt}),$$

$$\begin{bmatrix} u_{1j} \\ u_{2j} \\ \eta_{1j} \\ \eta_{2j} \end{bmatrix} \sim \mathcal{N} \left(\begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_{u_1}^2 & \varrho_{u_1,u_2} & \varrho_{u_1,\eta_1} & \varrho_{u_1,\eta_2} \\ & \sigma_{u_2}^2 & \varrho_{u_2,\eta_1} & \varrho_{u_2,\eta_2} \\ & & \sigma_{\eta_1}^2 & \varrho_{\eta_1,\eta_2} \\ & & & \sigma_{\eta_2}^2 \end{bmatrix} \right).$$

This model structure is connected via a link function, i.e., a functional form for the multinomial probabilities.

Here we use the CIF derivative w.r.t. time t,

$$p_{kijt} = \frac{\exp\{\boldsymbol{x}_{kij}\boldsymbol{\beta}_{ki} + u_{kj}\}}{1 + \sum_{m=1}^{K-1} \exp\{\boldsymbol{x}_{mij}\boldsymbol{\beta}_{mi} + u_{mj}\}} \qquad \{k = 1, 2\}$$
$$\times w_k \frac{\delta}{2\delta t - 2t^2} \phi[w_k \text{arctanh}\left(\frac{t - \delta/2}{\delta/2}\right) - \boldsymbol{x}_{kij}\boldsymbol{\gamma}_{ki} - \eta_{kj}].$$

Our approach: how we do

TMB: Template Model Builder

Quickly implement complex random effect models through simple C++ templates. The R package combines

» `CppAD`: C++ automatic differentiation
» `Eigen`: templated matrix-vector library
» `CHOLMOD`: sparse matrix routines available from R

to obtain an efficient implementation of the applied Laplace approximation with exact derivatives.

Also, key features are

» automatic sparseness detection
» parallelism through `BLAS`
» parallel user templates.

Clustered competing risks data
↳ Clusters? Families
↳Family studies
↳ Twins data

within-cluster dependence ⇒ within-family dependence

within-family dependence may reflect both disease **heritability** and
the impact of shared **environmental effects**

References

» [Cederkvist et al., 2019]
L. Cederkvist, K. K. Holst, K. K. Andersen and T. H. Scheike (2019).
Modeling the cumulative incidence function of multivariate competing
risks data allowing for within-cluster dependence of risk and timing.
Biostatistics, v. 20, n. 2, p. 199-217