

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

master thesis defense



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Clustered competing risk data



Key terms:

- 1 **Clustered**: groups with a dependence structure (e.g. families);
- 2 Causes **competing** by *something*.

Something?

- **Failure** of an industrial or electronic component;
- **Occurrence** or **cure** of a disease or some biological process;
- **Progress** of a patient clinic state.

Independent of the application, always the same framework

Cluster	ID	Cause 1	Cause 2	Censorship	Time	Feature
1	1	Yes	No	No	10	A
1	2	No	No	Yes	8	A
2	1	No	No	Yes	7	B
2	2	No	Yes	No	5	A

Big picture: Failure time data

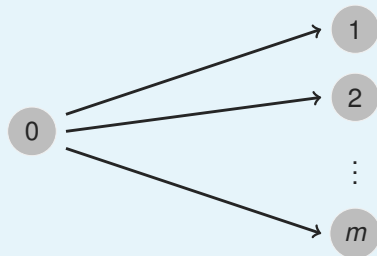


Failure time process



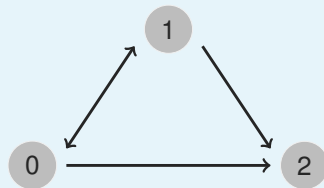
*Same methodologies,
different names.*

Competing risk process



Survival analysis Biomedical studies;
Reliability analysis Industrial life testing.

Multistate process



A comprehensive reference is Kalbfleisch and Prentice (2002)'s book.

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Modeling clustered competing risks data



What?



Why?



How?

Failure time data → Survival models



First of all, we have to choose which **scale** we model the **survival experience**.

① Usually, is in the

$$\text{hazard (failure rate) scale : } \lambda(t | \text{features}) = \lambda_0(t) \times c(\text{features}). \quad (1)$$

We have a Equation 1 for each competing cause.

The cluster dependence is something actually not measured...

Not measured dependence → **random/latent effects** → Frailty models.

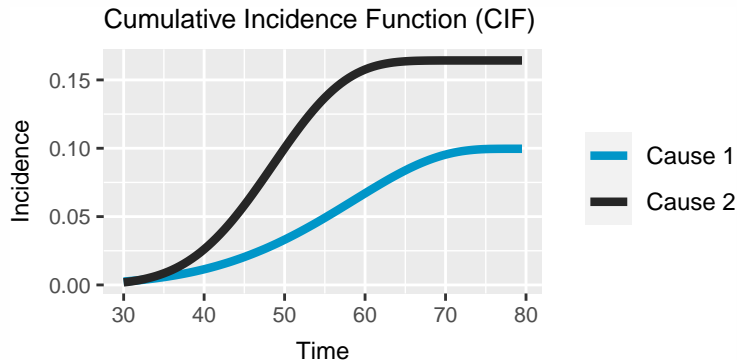
Full likelihood analysis with frailty models for competing risks data is generally complicated, when not impracticable.

② *Not* usually, the **probability scale**.

Probability scale → Cause-specific CIF



Besides the within-cluster dependence, there is an often interest in describing the time at event onset, directly described by the cause-specific



i.e., $\text{CIF} = \mathbb{P}[\text{failure time} \leq t, \text{ a given cause} \mid \text{features \& latent effects}]$.

for a cause-specific of failure k ,
the cumulative incidence function (CIF) is defined as

$$\begin{aligned} F_k(t | \mathbf{x}) &= \mathbb{P}[T \leq t, K = k | \mathbf{x}] \\ &= \int_0^t f_k(z | \mathbf{x}) \, dz \quad (f_k(t | \mathbf{x}) \text{ is the (sub)density for the time to a type } k \text{ failure}) \\ &= \int_0^t \underbrace{\lambda_k(z | \mathbf{x})}_{\text{cause-specific hazard function}} \underbrace{S(z | \mathbf{x})}_{\text{overall survival function}} \, dz, \quad t > 0, \quad k = 1, \dots, K. \end{aligned}$$



Again, a comprehensive reference is Kalbfleisch and Prentice (2002)'s book.



Here, we use the same CIF specification of Cederkvist et al. (2019).

Cederkvist et al. (2019)'s CIF specification



For two competing causes of failure,
the cause-specific CIFs are specified in the following manner

$$F_k(t \mid \mathbf{x}, u_1, u_2, \eta_k) = \underbrace{\pi_k(\mathbf{x}, u_1, u_2)}_{\text{cluster-specific risk level}} \times \underbrace{\Phi[w_k g(t) - \mathbf{x}\gamma_k - \eta_k]}_{\text{cluster-specific failure time trajectory}}, \quad t > 0, \quad k = 1, 2, \quad (2)$$

with

- ❶ $\pi_k(\mathbf{x}, \mathbf{u}) = \exp\{\mathbf{x}\beta_k + u_k\} / \left(1 + \sum_{m=1}^{K-1} \exp\{\mathbf{x}\beta_m + u_m\}\right), \quad k = 1, 2, \quad K = 3;$
- ❷ $\Phi(\cdot)$ is the cumulative distribution function of a standard Gaussian distribution;
- ❸ $g(t) = \text{arctanh}(2t/\delta - 1), \quad t \in (0, \delta), \quad g(t) \in (-\infty, \infty).$



In Cederkvist et al. (2019), this CIF specification is modeled under a *complicated* pairwise composite likelihood approach (Lindsay 1988; Varin, Reid, and Firth 2011).

Our contribution: a full likelihood analysis



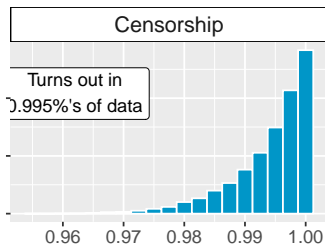
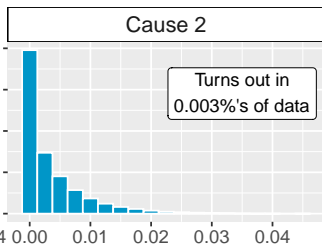
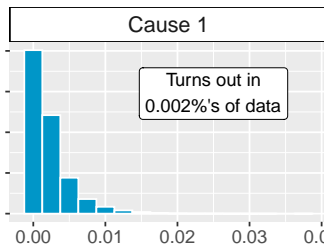
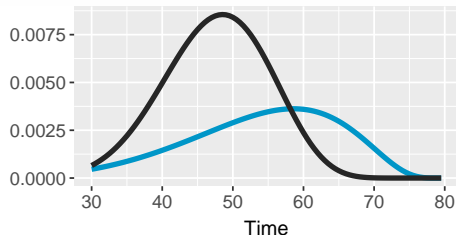
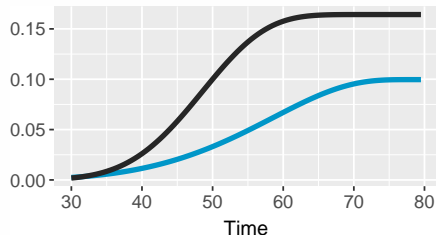
For two competing causes of failure, a subject i , in the cluster j , in time t , we have

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

$$\begin{bmatrix} u_1 \\ u_2 \\ \eta_1 \\ \eta_2 \end{bmatrix} \sim \text{Multivariate Normal} \left(\begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_{u_1}^2 & \text{cov}(u_1, u_2) & \text{cov}(u_1, \eta_1) & \text{cov}(u_1, \eta_2) \\ & \sigma_{u_2}^2 & \text{cov}(u_2, \eta_1) & \text{cov}(u_2, \eta_2) \\ & & \sigma_{\eta_1}^2 & \text{cov}(\eta_1, \eta_2) \\ & & & \sigma_{\eta_2}^2 \end{bmatrix} \right)$$

$$\begin{aligned} p_{kijt} &= \frac{\partial}{\partial t} F_k(t \mid \mathbf{x}, \mathbf{u}, \eta_k) \\ &= \frac{\exp\{\mathbf{x}_{kij}\beta_k + u_{kj}\}}{1 + \sum_{m=1}^{K-1} \exp\{\mathbf{x}_{mij}\beta_m + u_{mj}\}} \\ &\quad \times w_k \frac{\delta}{2\delta t - 2t^2} \phi \left(w_k \text{arctanh} \left(\frac{t - \delta/2}{\delta/2} \right) - \mathbf{x}_{kij}\gamma_k - \eta_{kj} \right), \quad k = 1, 2. \end{aligned} \quad (3)$$

Simulating from the model



Probability

bandwidth=0.0025

Marginal likelihood function for two competing causes



$$\begin{aligned}
 L(\theta; \mathbf{y}) &= \prod_{j=1}^J \int_{\Re^4} \pi(\mathbf{y}_j | \mathbf{r}_j) \times \pi(\mathbf{r}_j) d\mathbf{r}_j \\
 &= \prod_{j=1}^J \int_{\Re^4} \underbrace{\left\{ \prod_{i=1}^{n_j} \prod_{t=1}^{n_{ij}} \left(\frac{(\sum_{k=1}^K y_{kijt})!}{y_{1ijt}! y_{2ijt}! y_{3ijt}!} \prod_{k=1}^K p_{kijt}^{y_{kijt}} \right) \right\}}_{\text{fixed effect component}} \times \\
 &\quad \underbrace{(2\pi)^{-2} |\Sigma|^{-1/2} \exp \left\{ -\frac{1}{2} \mathbf{r}_j^\top \Sigma^{-1} \mathbf{r}_j \right\}}_{\text{latent effect component}} d\mathbf{r}_j \\
 &= \prod_{j=1}^J \int_{\Re^4} \underbrace{\left\{ \prod_{i=1}^{n_j} \prod_{t=1}^{n_{ij}} \prod_{k=1}^K p_{kijt}^{y_{kijt}} \right\}}_{\text{fixed effect}} \underbrace{(2\pi)^{-2} |\Sigma|^{-1/2} \exp \left\{ -\frac{1}{2} \mathbf{r}_j^\top \Sigma^{-1} \mathbf{r}_j \right\}}_{\text{latent effect component}} d\mathbf{r}_j, \quad (4)
 \end{aligned}$$

with p_{kijt} from Equation 3 and where $\theta = [\beta \ \gamma \ \mathbf{w} \ \sigma^2 \ \rho]^\top$ is the parameters vector.

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Kristensen et al. (2016).

An R (R Core Team 2021) package for the quickly implementation of complex random effect models through simple C++ templates.

Workflow

- 1 Write your objective function in a .cpp through a `#include <TMB.hpp>`;
- 2 Compile and load it in R via `TMB::compile()` and `base::dyn.load(TMB::dynlib())`;
- 3 Compute your objective function derivatives with `obj <- TMB::MakeADFun()`;
- 4 Perform the model fitting, `opt <- base::nlminb(objpar, objfn, obj$gr)`;
- 5 Compute the parameters standard deviations, `TMB::sdreport(obj)`.



For details about TMB, AD, and Laplace approximation: Laureano (2021).

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Risk model

Latent effects only on the risk level
i.e.,

$$\Sigma = \begin{bmatrix} \sigma_{u_1}^2 & \text{COV}_{u_1, u_2} \\ & \sigma_{u_2}^2 \end{bmatrix}.$$

Time model

Latent effects only on the failure
time trajectory level i.e.,

$$\Sigma = \begin{bmatrix} \sigma_{\eta_1}^2 & \text{COV}_{\eta_1, \eta_2} \\ & \sigma_{\eta_2}^2 \end{bmatrix}.$$

Block-diag model

Latent effects on the risk and time levels
without cross-correlations i.e.,

$$\Sigma = \begin{bmatrix} \sigma_{u_1}^2 & \text{COV}_{u_1, u_2} & 0 & 0 \\ & \sigma_{u_2}^2 & 0 & 0 \\ & & \sigma_{\eta_1}^2 & \text{COV}_{\eta_1, \eta_2} \\ & & & \sigma_{\eta_2}^2 \end{bmatrix}.$$

Complete model

A *complete* latent effects structure
i.e.,

$$\Sigma = \begin{bmatrix} \sigma_{u_1}^2 & \text{COV}_{u_1, u_2} & \text{COV}_{u_1, \eta_1} & \text{COV}_{u_1, \eta_2} \\ & \sigma_{u_2}^2 & \text{COV}_{u_2, \eta_1} & \text{COV}_{u_2, \eta_2} \\ & & \sigma_{\eta_1}^2 & \text{COV}_{\eta_1, \eta_2} \\ & & & \sigma_{\eta_2}^2 \end{bmatrix}.$$

Simulation study setup



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Thanks for watching and have a great day



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Wagner H. Bonat

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