

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

master thesis defense



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April 8, 2021

- 1 Data
- 2 Model
- 3 Template Model Builder
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Clustered competing risk data



Key terms:

- **Clustered**: groups with a dependence structure (e.g. families);
- 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

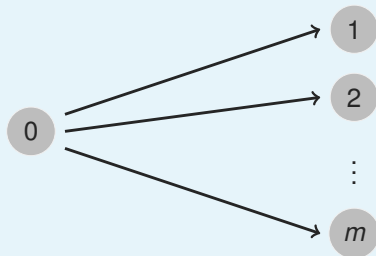


Failure time process



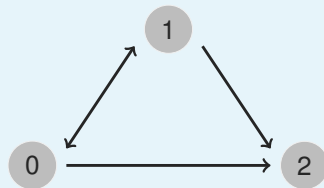
*Same methodologies,
different names.*

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

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

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.

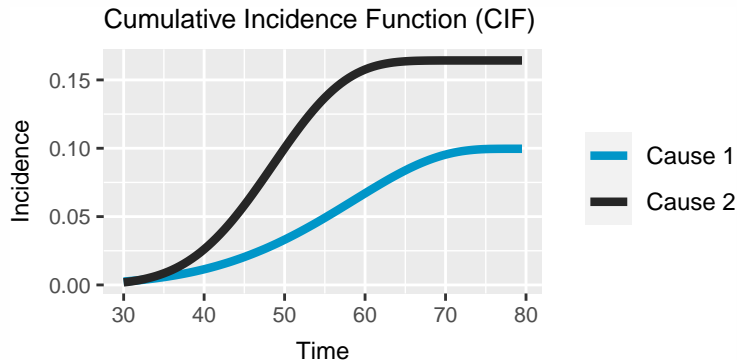
Full likelihood analysis with frailty models for competing risks data is generally complicated, when not impracticable.

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

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



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



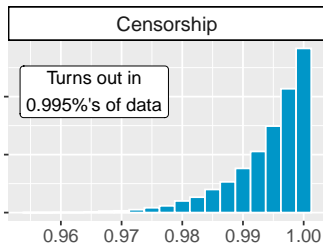
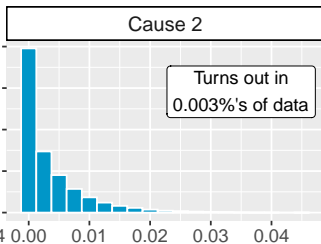
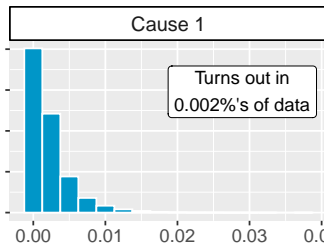
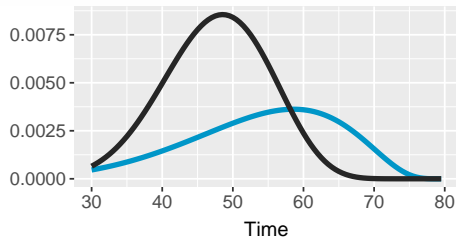
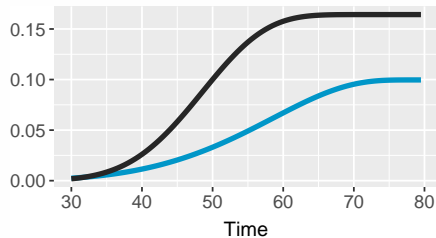
For two competing causes of failure, a subject i , in the cluster j , in time t , we have

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

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

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

Simulating from the model



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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.

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Thanks for watching and have a great day



Special thanks to



PPGMNE

Programa de Pós-Graduação em
Métodos Numéricos em Engenharia



Joint work with

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Cederkvist, L., 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* 20 (2): 199–217.

Kalbfleisch, J. D., and R. L. Prentice. 2002. *The Statistical Analysis of Failure Time Data*. Second Edition. Hoboken, New Jersey: John Wiley & Sons, Inc.

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Varin, C., N. Reid, and D. Firth. 2011. “An Overview of Composite Likelihood Methods.” *Statistica Sinica* 21 (1): 5–42.