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

master thesis defense

Henrique Laureano (.github.io)
LEG @ UFPR

April 12, 2021

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;
- **Occurence** or **cure** of a disease or some biological process;
- **Progress** of a patient clinic state.

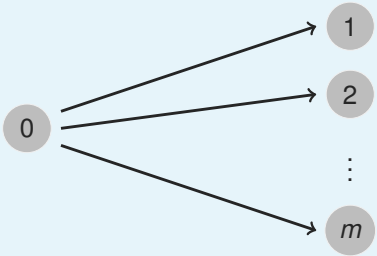
Independent of the application, always the same framework

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

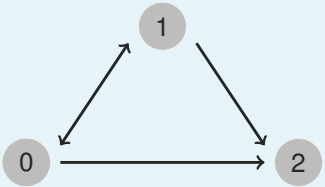
Big picture: Failure time data

Failure time process

Competing risk process



Multistate process

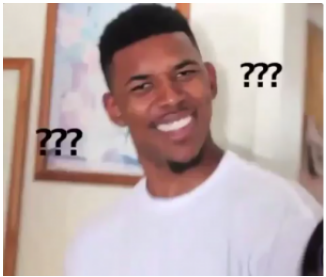


Same methodologies, different names.

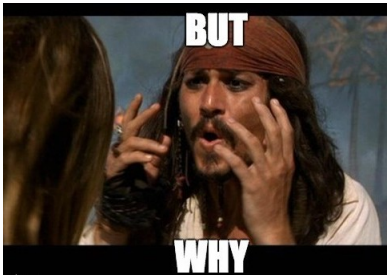
Survival analysis Biomedical studies;
Reliability analysis Industrial life testing.

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

Modeling clustered competing risks data



What?



Why?

How?

Failure time data $\rightarrow$ Survival models

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

1. Usually, is in the

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

We have a Equation 1 for each competing cause.

The cluster dependence is something actually not measured...

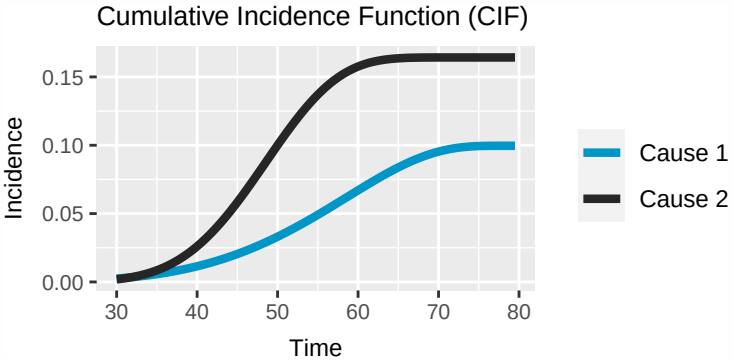
Not measured dependence $\rightarrow$ **random/latent effects** $\rightarrow$ Frailty models.

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

2. *Not* usually, the probability scale.

Probability scale $\rightarrow$ 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., CIF $= \mathbb{P}[$ failure time $\leqslant t,$ a given cause $|$ features & latent effects $]$.

Formally,

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

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


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

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

with

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

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

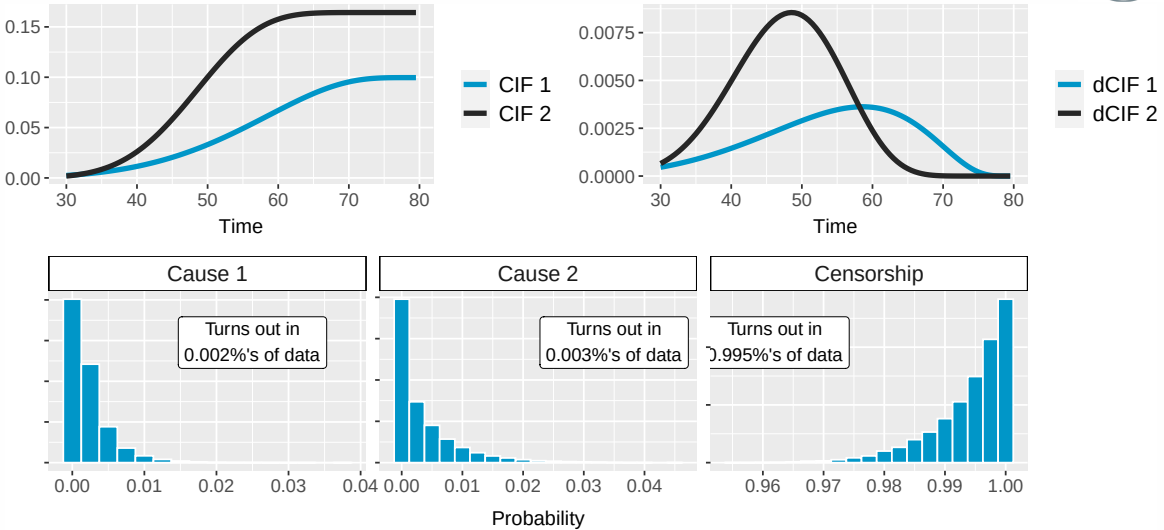
For two competing causes of failure, a subject i, in the cluster j, in time t, we have

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

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

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

Simulating from the model



bindwidth=0.0025

Marginal likelihood function for two competing causes

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

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

TMB: Automatic Differentiation and Laplace Approximation

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(obj$par, obj$fn, obj$gr)`;
5. Compute the parameters standard deviations, `TMB::sdreport(obj)`.

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

Simulation study model designs

Risk model

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

$$\Sigma = \begin{bmatrix} \sigma^2_{u_1} & \mathrm{cov}_{u_1,u_2} \\ & \sigma^2_{u_2} \end{bmatrix}.$$

Time model

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

$$\Sigma = \begin{bmatrix} \sigma^2_{\eta_1} & \mathrm{cov}_{\eta_1,\eta_2} \\ & \sigma^2_{\eta_2} \end{bmatrix}.$$

Block-diag model

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

$$\Sigma = \begin{bmatrix} \sigma^2_{u_1} & \mathrm{cov}_{u_1,u_2} & 0 & 0 \\ & \sigma^2_{u_2} & 0 & 0 \\ & & \sigma^2_{\eta_1} & \mathrm{cov}_{\eta_1,\eta_2} \\ & & & \sigma^2_{\eta_2} \end{bmatrix}.$$

Complete model

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

$$\Sigma = \begin{bmatrix} \sigma^2_{u_1} & \mathrm{cov}_{u_1,u_2} & \mathrm{cov}_{u_1,\eta_1} & \mathrm{cov}_{u_1,\eta_2} \\ & \sigma^2_{u_2} & \mathrm{cov}_{u_2,\eta_1} & \mathrm{cov}_{u_2,\eta_2} \\ & & \sigma^2_{\eta_1} & \mathrm{cov}_{\eta_1,\eta_2} \\ & & & \sigma^2_{\eta_2} \end{bmatrix}.$$

Simulation study setup

Four latent effects structures:

1. Risk model;
2. Time model;
3. Block-diag model;
4. Complete model.

Two CIF configurations:

Low max incidence ≈ 0.15; **High** max incidence ≈ 0.60.

For each of those $4 \times 2 = 8$ scenarios, we vary the sample and cluster sizes:

5000 data points	*30000 data points*	*60000 data points*
• 2500 clusters of **size 2**;	• 15000 clusters of **size 2**;	• 30000 clusters of **size 2**;
• 1000 clusters of **size 5**;	• 6000 clusters of **size 5**;	• 12000 clusters of **size 5**;
• 500 clusters of **size 10**.	• 3000 clusters of **size 10**.	• 6000 clusters of **size 10**.

Totalizing, $8 \times 3 \times 3 = 72$ scenarios.
For each scenario, we simulate **400** samples, totalizing $72 \times 400 = 28800$ model fittings.

Simulation study results

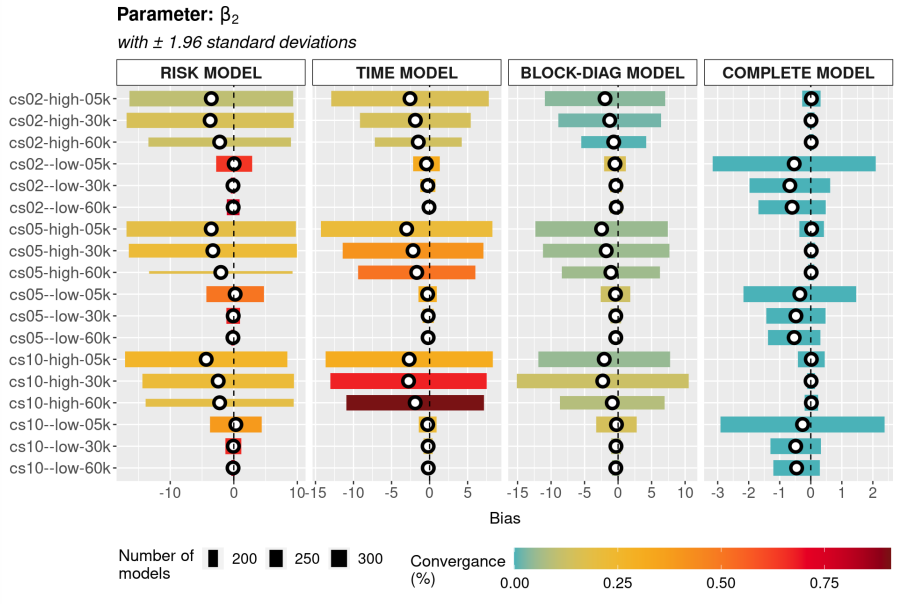
First of all, the **time**.

- The *non-complete* models (2D Laplace aprox.) are kind of fast, taking always **less than 5 min**.
- In the most expensive scenarios (30K 4D Laplaces), **the complete model takes 30 min**.
  In a **full R** implementation with 10K 4D Laplaces, it **took 30hrs**. **TMB is fast**.
- We also did a Bayesian analysis via Stan/NUTS-HMC (Stan Development Team 2020).
  - **1 week of parallelized processing** for a 2500 size 2 clusters scenario with tuned NUTS. This just reinforces the MCMC impracticability for some complex models.

Model **identifiability**.

- The *non-complete* models fail to learn the data.
  They appear to be *not structured enough* to capture the data characteristics.

Some simulation study results



Final remarks

The complete model works. It's not magnificent, but it works.

1. It works better in the high CIF scenarios;
2. As expected, as the sample size increases the results get better;
3. Given the low data representativity,
   the model needs a considerable amount of data to perform well;
4. In standard multinomial GLMMs, as bigger the clusters better the results.
   In our CIF-based formulation, this characteristic is not so clear.

What else can we do?

1. Instead of a conditional approach (latent effects model),
   we can try a marginal approach e.g., an McGLM (Bonat and Jørgensen 2016);
2. We can also try a copula (Embrechts 2009), on maybe two fronts:
   1) for a full specification; 2) to accommodate the within-cluster dependence.

For more read Laureano (2021) master thesis.

Thanks for watching and have a great day

Special thanks to

PPGMNE
Programa de Pós-Graduação em
Métodos Numéricos em Engenharia

Joint work with

Wagner H. Bonat
http://leg.ufpr.br/~wagner

Paulo Justiniano Ribeiro Jr.
http://leg.ufpr.br/~paulojus

henriquelaureano.github.io

References

Bonat, W. H., and B. Jørgensen. 2016. “Multivariate Covariance Generalized Linear Models.” *Journal of the Royal Statistical Society, Series C (Applied Statistics)* 65 (5): 649–75.

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.

Embrechts, P. 2009. “Copulas: A Personal View.” *The Journal of Risk and Insurance* 76 (3): 639–50.

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

Kristensen, K., A. Nielsen, C. W. Berg, H. J. Skaug, and B. M. Bell. 2016. “TMB: Automatic Differentiation and Laplace Approximation.” *Journal of Statistical Software* 70 (5): 1–21.

Laureano, H. A. 2021. “Modeling the Cumulative Incidence Function of Clustered Competing Risks Data: A Multinomial Glmm Approach.” Master’s thesis, Federal University of Paraná (UFPR).

Lindsay, B. G. 1988. “Composite Likelihood Methods.” *Comtemporary Mathematics* 80 (1): 221–39.

R Core Team. 2021. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing. Vienna, Austria.

Stan Development Team. 2020. “RStan: The R Interface to Stan.” https://mc-stan.org/.

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