

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

master thesis defense



Henrique Laureano ([.github.io](https://github.io))
LEG @ UFPR

April 12, 2021

- 1 Data
- 2 Model
- 3 TMB: Template Model Builder
- 4 Simulation study
- 5 Conclusion
- 6 References

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

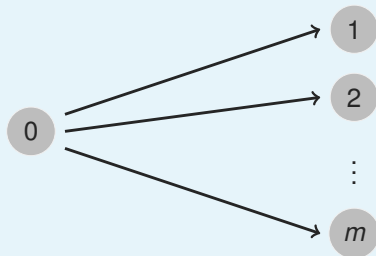


Failure time process



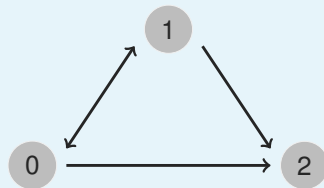
*Same methodologies,
different names.*

Competing risk process



Survival analysis Biomedical studies;
Reliability analysis Industrial life testing.

Multistate process



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

- 1 Data
- 2 Model
- 3 TMB: Template Model Builder
- 4 Simulation study
- 5 Conclusion
- 6 References

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.

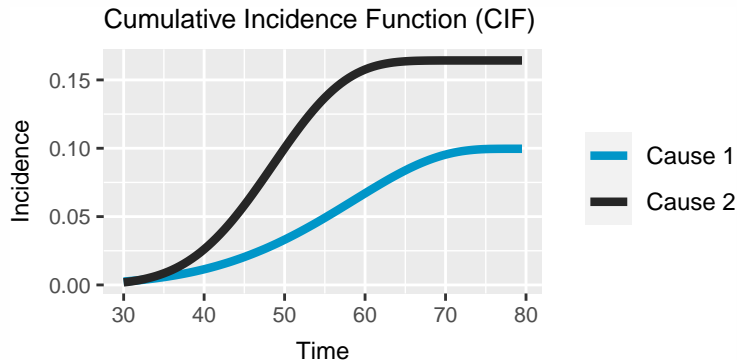
Full likelihood analysis with frailty models for competing risks data is generally complicated, when not impracticable.

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



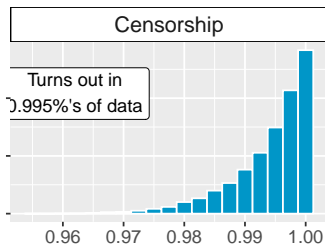
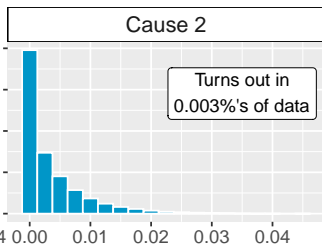
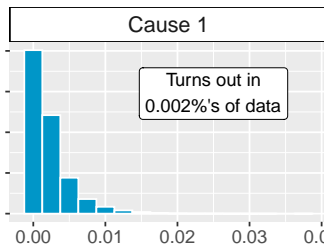
For two competing causes of failure, a subject i , in the cluster j , in time t , we have

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

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

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

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.

- 1 Data
- 2 Model
- 3 TMB: Template Model Builder**
- 4 Simulation study
- 5 Conclusion
- 6 References



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).

- 1 Data
- 2 Model
- 3 TMB: Template Model Builder
- 4 Simulation study**
- 5 Conclusion
- 6 References

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



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

- 2500 clusters of **size 2**;
- 1000 clusters of **size 5**;
- 500 clusters of **size 10**.

30000 data points

- 15000 clusters of **size 2**;
- 6000 clusters of **size 5**;
- 3000 clusters of **size 10**.

60000 data points

- 30000 clusters of **size 2**;
- 12000 clusters of **size 5**;
- 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.

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.

- 1 Data
- 2 Model
- 3 TMB: Template Model Builder
- 4 Simulation study
- 5 Conclusion**
- 6 References

Final remarks



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

What else we can do?

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

- 1 Data
- 2 Model
- 3 TMB: Template Model Builder
- 4 Simulation study
- 5 Conclusion
- 6 References**

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.

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.” *Contemporary 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.