

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

master thesis defense



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- 1 Data
- 2 Model
- 3 TMB: Template Model Builder
- 4 Simulation study
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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/time-to-event outcomes

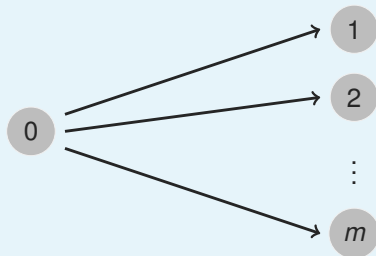


Failure time process



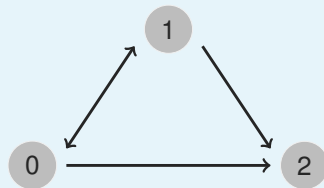
*Same methodologies,
different names.*

Competing risks 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?

Modeling failure time data



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.

Frailty-based models for (**multiple**) survival experiences turn out in challengeable likelihood functions with inference routines mostly done via

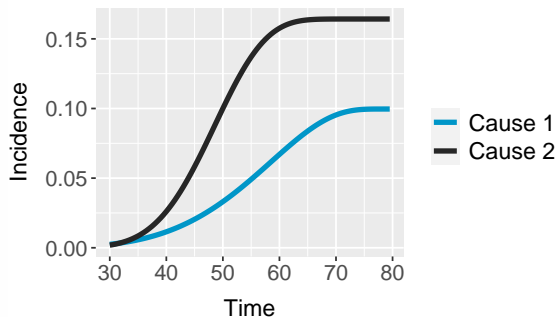
- Elaborated and slow expectation–maximization (EM) algorithms;
- Inefficient Markov chain Monte Carlo (MCMC) schemes.

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

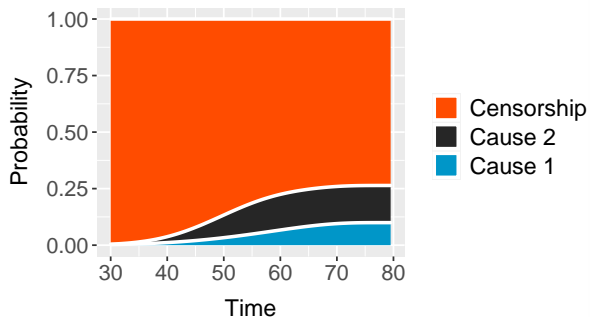
Probability scale → Cause-specific CIF



Cumulative Incidence Function (CIF)



All CIFs sum up to 1



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

Common applications: *family studies*.

↳ Keywords: *within-family/cluster dependence; age at disease onset; populations*.

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 *challengeable* pairwise composite likelihood approach (Lindsay 1988; Varin, Reid, and Firth 2011).

Our contribution: a full likelihood analysis



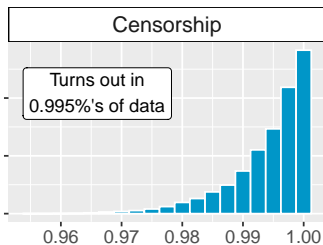
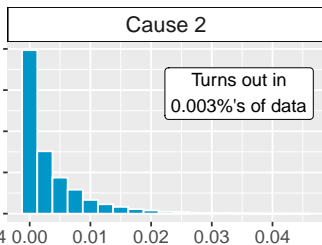
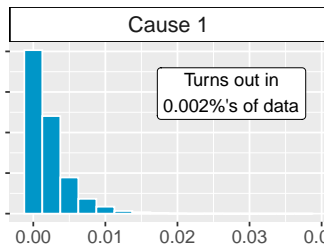
For two competing causes of failure, a subject i , in the cluster j , in time t , we have

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

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

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

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



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 **500** samples, totalizing $72 \times 500 = 36000$ 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**.

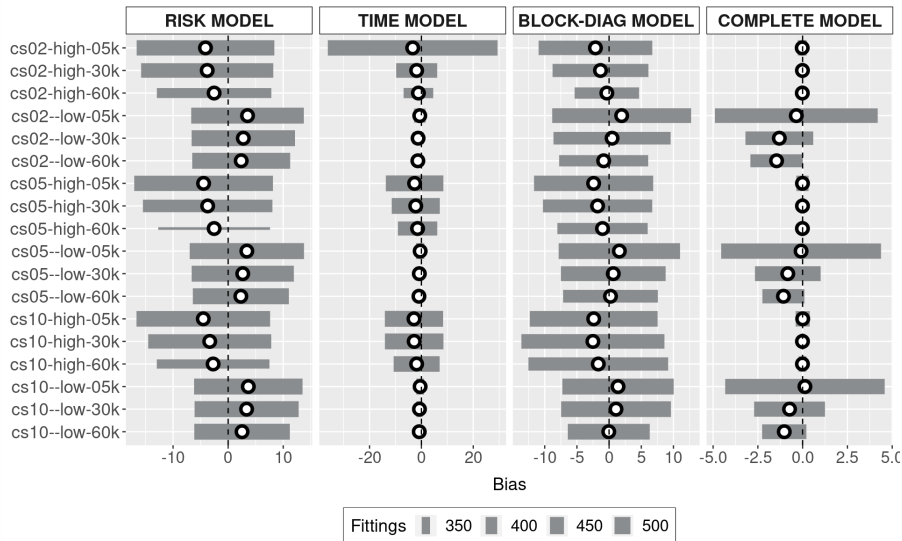
- The *non-complete* models fail to learn the data.
They appear to be *not structured enough* to capture the data characteristics.

Some simulation study results



Parameter: β_1

with ± 1.96 standard deviations

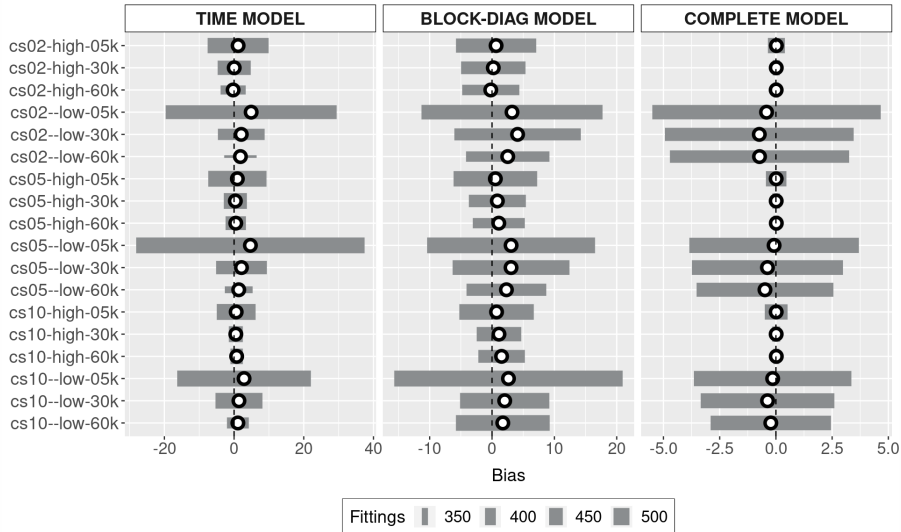


Some simulation study results



Parameter: $\log(\sigma_4^2)$

with ± 1.96 standard deviations

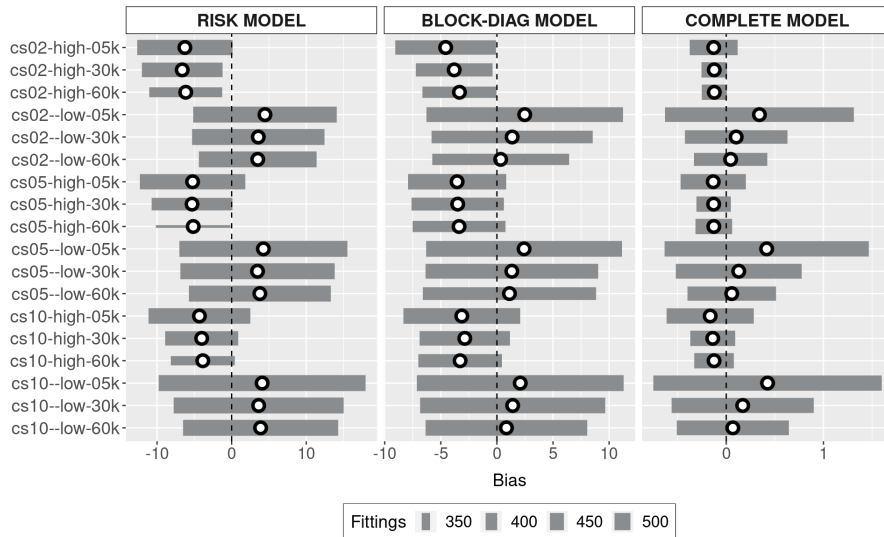


Some simulation study results



Parameter: $z(\rho_{12})$

with ± 1.96 standard deviations

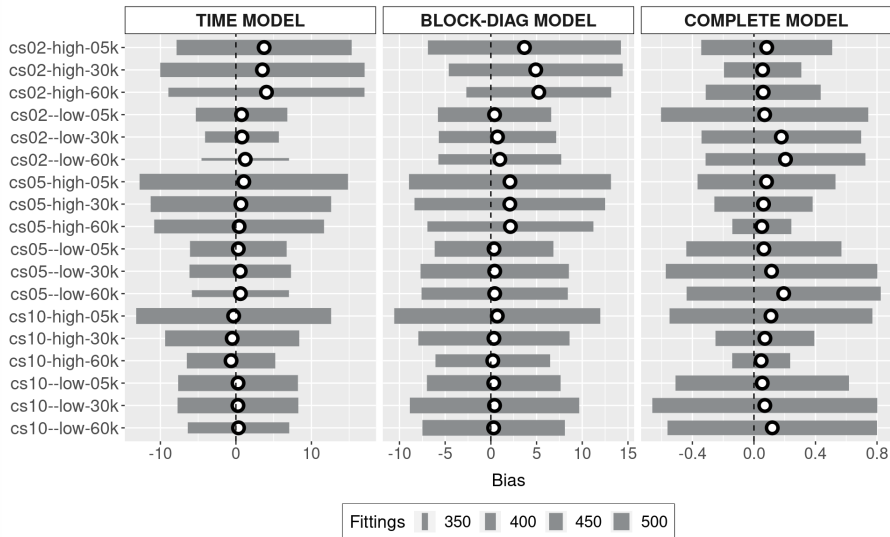


Some simulation study results



Parameter: $z(\rho_{34})$

with ± 1.96 standard deviations

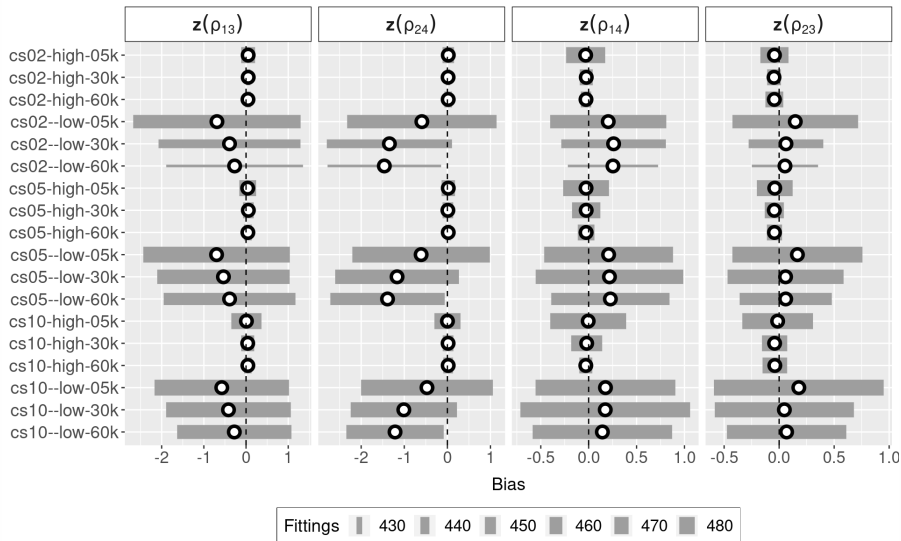


Some simulation study results



Complete model's cross-correlations

with ± 1.96 standard deviations

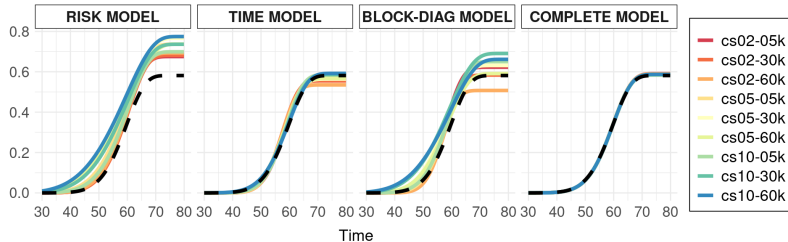


Simulation study results: High CIF scenario



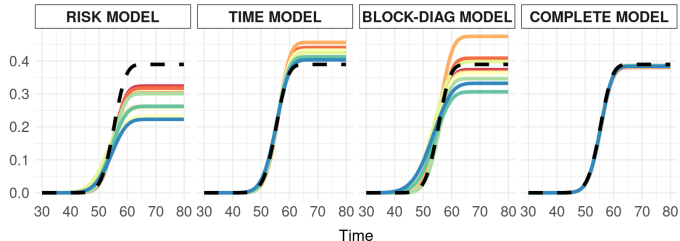
CIF of failure cause 1

True curve in dashed black



CIF of failure cause 2

True curve in dashed black

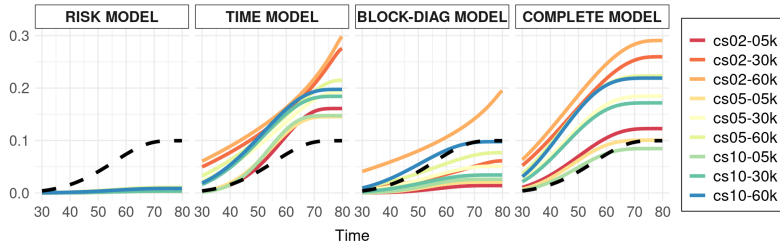


Simulation study results: Low CIF scenario



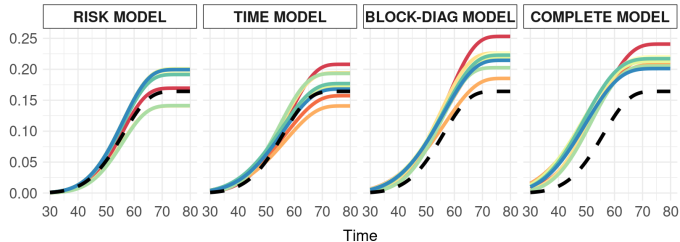
CIF of failure cause 1

True curve in dashed black



CIF of failure cause 2

True curve in dashed black



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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



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Joint work with

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<http://leg.ufpr.br/~wagner>

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