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;
- **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/time-to-event outcomes

Failure time process

$0 \longrightarrow 1$

Competing risks process

$0 \longrightarrow 1$
$0 \longrightarrow 2$
$\vdots$
$0 \longrightarrow m$

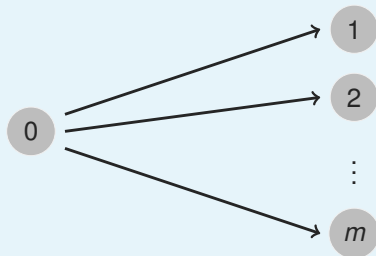Multistate process
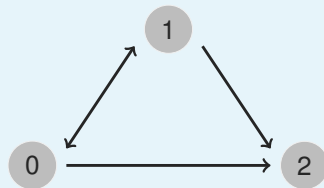
Same methodologies, different names.

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?

Modeling failure time data

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

1 Usually, is in the

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

We have a Equation 1 for each competing cause.

The cluster dependence is something actually not measured. . .

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

Frailty-based models for (multiple) survival experiences turn out in challengeable likelihood functions with inference routines mostly done via
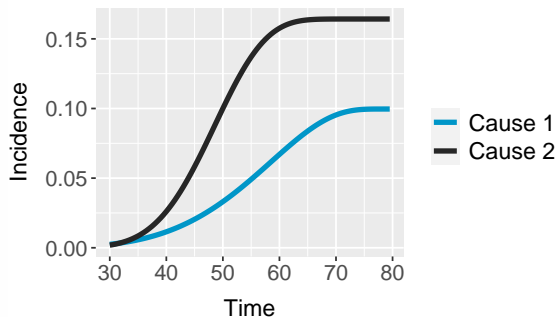
- Elaborated and slow expectation–maximization (EM) algorithms;

- Inefficient Markov chain Monte Carlo (MCMC) schemes.

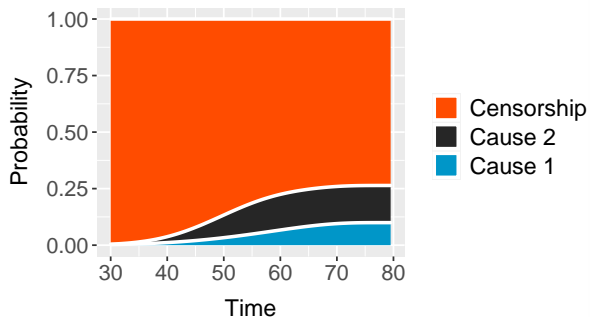**2** *Not* usually, the probability scale.

Probability scale → Cause-specific CIF

Cumulative Incidence Function (CIF)

All CIFs sum up to 1

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

Common applications: *family studies*.

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

Formally,

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

$$F_k(t \mid \boldsymbol{x}) = \mathbb{P}[T \leqslant t,\ K = k \mid \boldsymbol{x}]$$

$$= \int_0^t f_k(z \mid \boldsymbol{x})\, \mathrm{d}z \quad (f_k(t \mid \boldsymbol{x}) \text{ is the (sub)density for the time to a type } k \text{ failure})$$

$$= \int_0^t \underbrace{\lambda_k(z \mid \boldsymbol{x})}_{\substack{\text{cause-specific} \\ \text{hazard function}}}\ \underbrace{S(z \mid \boldsymbol{x})}_{\substack{\text{overall} \\ \text{survival} \\ \text{function}}}\, \mathrm{d}z, \quad t > 0, \quad k = 1,\ \ldots,\ K.$$

📖 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

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

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. $g(t) = \arctanh(2t/\delta - 1), \quad t \in (0,\, \delta), \quad g(t) \in (-\infty,\, \infty).$

📚 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

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

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

$$p_{kijt} = \frac{\partial}{\partial t} F_k(t \mid \boldsymbol{x}, \boldsymbol{u}, \eta_k)$$

$$= \frac{\exp\{\boldsymbol{x}_{kij}\beta_k + u_{kj}\}}{1 + \sum_{m=1}^{K-1} \exp\{\boldsymbol{x}_{mij}\beta_m + u_{mj}\}}$$

$$\times \ w_k \frac{\delta}{2\delta t - 2t^2} \ \phi\left(w_k \text{arctanh}\left(\frac{t - \delta/2}{\delta/2}\right) - \boldsymbol{x}_{kij}\gamma_k - \eta_{kj} \right), \quad k = 1, 2.$$

(3)

Simulating from the model
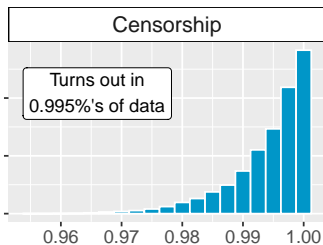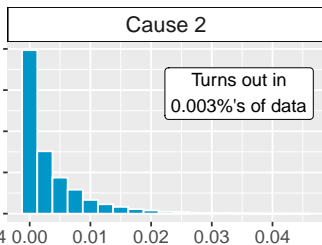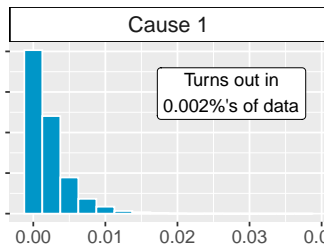
Marginal likelihood function for two competing causes

$$L(\boldsymbol{\theta}; y) = \prod_{j=1}^{J} \int_{\mathfrak{R}^4} \pi(\boldsymbol{y}_j \mid \boldsymbol{r}_j) \times \pi(\boldsymbol{r}_j) \, d\boldsymbol{r}_j$$

$$= \prod_{j=1}^{J} \int_{\mathfrak{R}^4} \underbrace{\left\{ \prod_{i=1}^{n_j} \prod_{t=1}^{n_{ij}} \left(\frac{(\sum_{k=1}^{K} y_{kijt})!}{y_{1ijt}! \, y_{2ijt}! \, y_{3ijt}!} \prod_{k=1}^{K} p_{kijt}^{y_{kijt}} \right) \right\}}_{\text{fixed effect component}} \times$$

$$\underbrace{(2\pi)^{-2} |\Sigma|^{-1/2} \exp\left\{ -\frac{1}{2} \boldsymbol{r}_j^\top \Sigma^{-1} \boldsymbol{r}_j \right\} d\boldsymbol{r}_j}_{\text{latent effect component}}$$

$$= \prod_{j=1}^{J} \int_{\mathfrak{R}^4} \underbrace{\left\{ \prod_{i=1}^{n_j} \prod_{t=1}^{n_{ij}} \prod_{k=1}^{K} p_{kijt}^{y_{kijt}} \right\}}_{\text{fixed effect}} \underbrace{(2\pi)^{-2} |\Sigma|^{-1/2} \exp\left\{ -\frac{1}{2} \boldsymbol{r}_j^\top \Sigma^{-1} \boldsymbol{r}_j \right\} d\boldsymbol{r}_j}_{\text{latent effect component}}, \quad (4)$$

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

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

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.

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

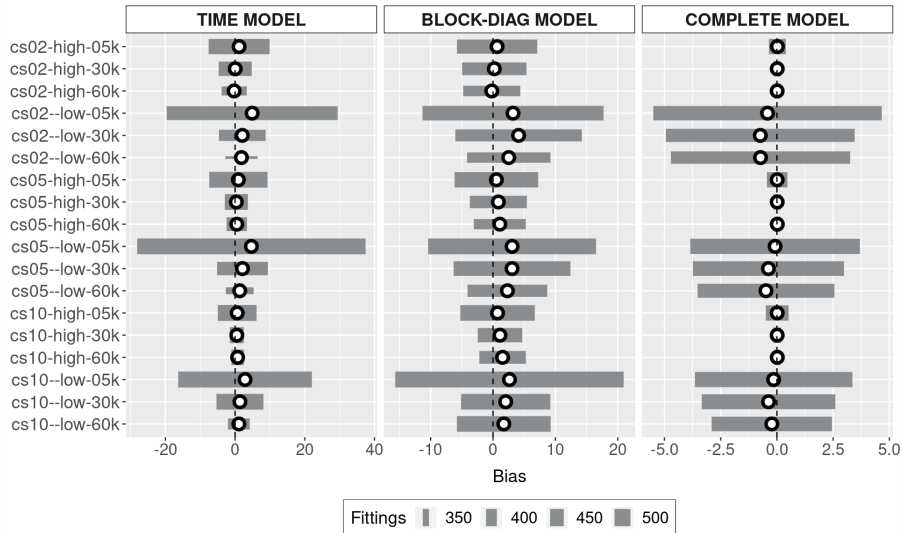**Parameter:** β_1

with ± 1.96 standard deviations
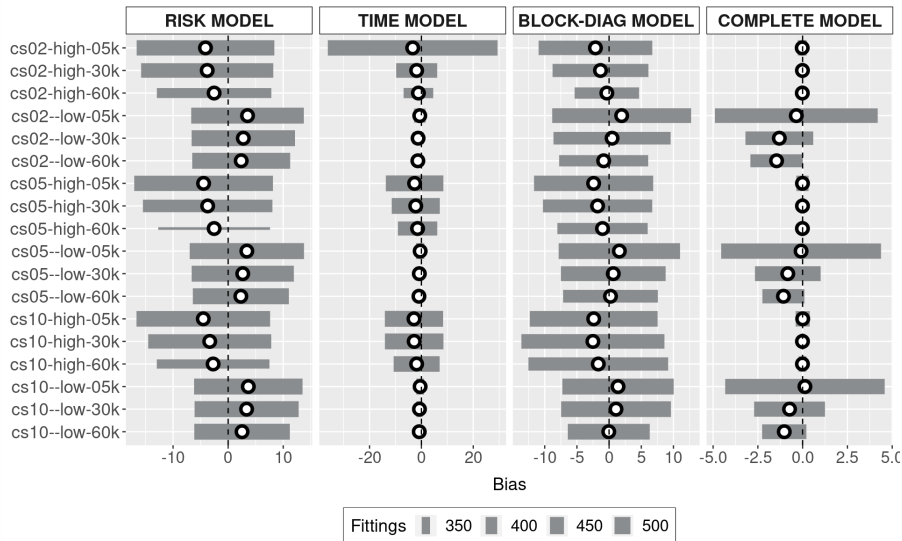
Some simulation study results

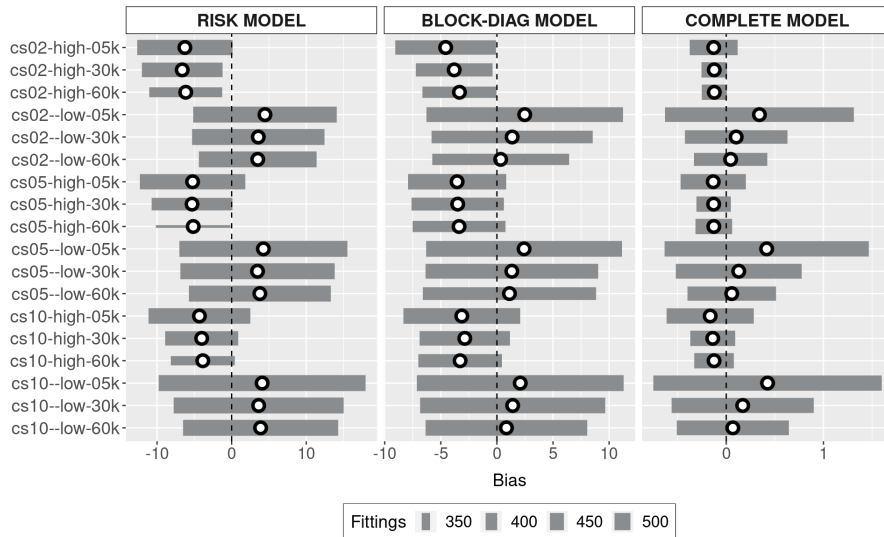**Parameter: $\log(\sigma_4^2)$**

with ± 1.96 standard deviations
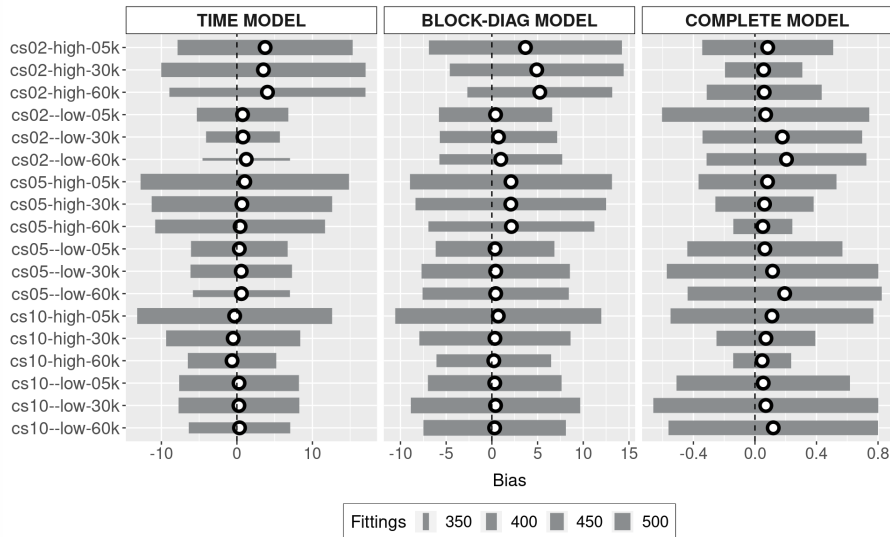
Some simulation study results

Some simulation study results

Parameter: $z(\rho_{34})$
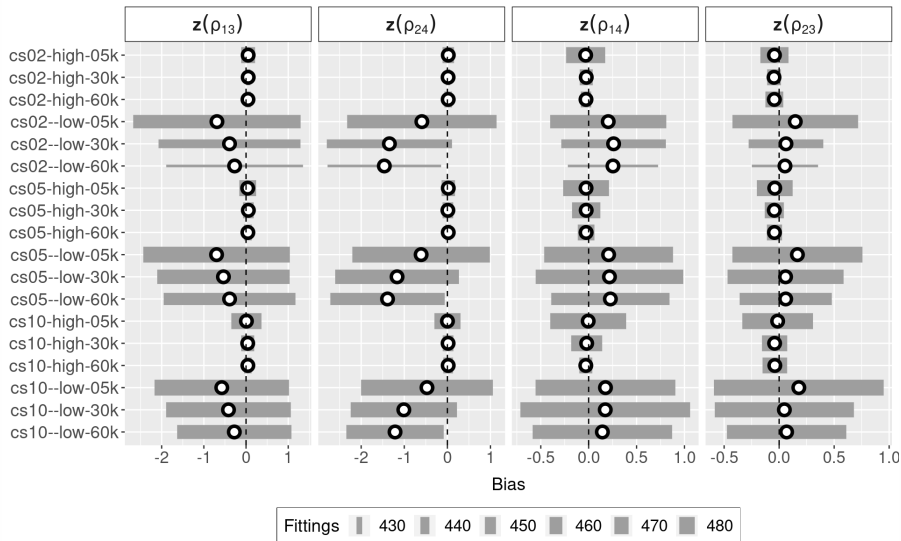
with ± 1.96 standard deviations

Some simulation study results

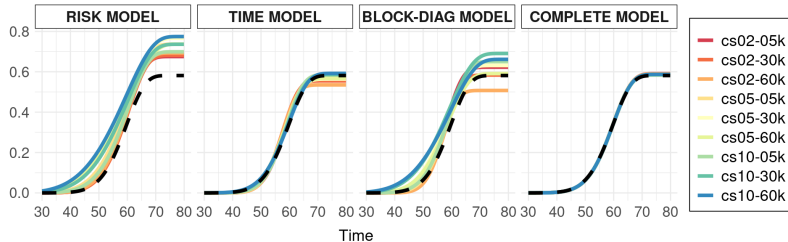Complete model's cross-correlations
with ± 1.96 standard deviations
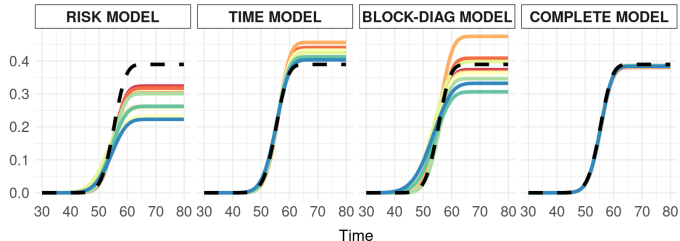
Simulation study results: High CIF scenario

CIF of failure cause 1
True curve in dashed black

RISK MODEL | TIME MODEL | BLOCK-DIAG MODEL | COMPLETE MODEL

cs02-05k
cs02-30k
cs02-60k
cs05-05k
cs05-30k
cs05-60k
cs10-05k
cs10-30k
cs10-60k

Time

CIF of failure cause 2
True curve in dashed black

RISK MODEL | TIME MODEL | BLOCK-DIAG MODEL | COMPLETE MODEL
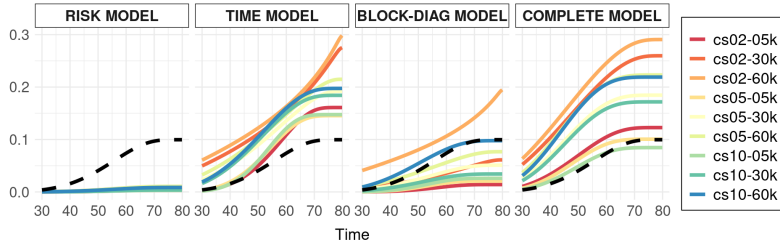
Time

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
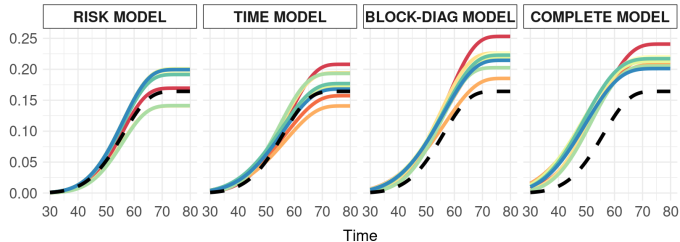
Take-home message

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

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

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