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

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Giving context: defining where we are and what we did

Object

- Handle clustered competing risks data (a kind of failure time data) through the cumulative incidence function (CIF).

Goal

- Perform maximum likelihood estimation in terms of a full likelihood formulation based on Cederkvist et al. (2019)'s CIF specification (**Scheike's**).

Contribution

- The full likelihood formulation is in terms of a generalized linear mixed model (GLMM) - a conditional approach (with fixed and random/latent effects);
- The optimization and inference are tacked down via an efficient model implementation with the use of *state-of-art* computational libraries (Kristensen et al. (2016)'s TMB).

Outline

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

Clustered competing risk data

Key ideas:

1. Clustered: groups with a dependence structure (e.g. families);
2. Causes competing by *something*;
3. Occurrence time of this *something*.

Something?

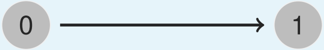
- **Failure** of an industrial or electronic component;
- **Occurrence** or **cure** of a disease or some biological process;
- **Progress** of a patient clinic state.

Independent of the application, always the same framework

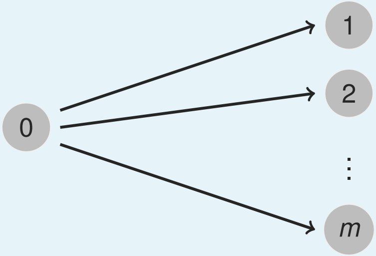
Cluster	ID	Cause 1	Cause 2	Censorship	Time	Feature
1	1	Yes	No	No	10	A
1	2	No	No	Yes	8	A
2	1	No	No	Yes	7	B
2	2	No	Yes	No	5	A

Big picture: Failure time data/time-to-event outcomes

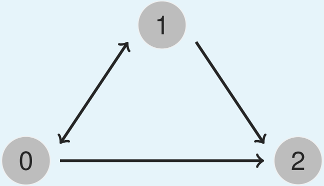
Failure time process



Competing risks process



Multistate process

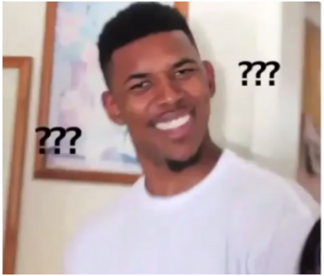


Same methodologies, different names.

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?

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...

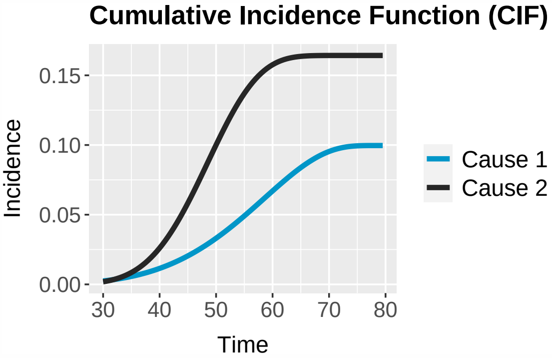
Not measured dependence → **random/latent effects** → Frailty models.

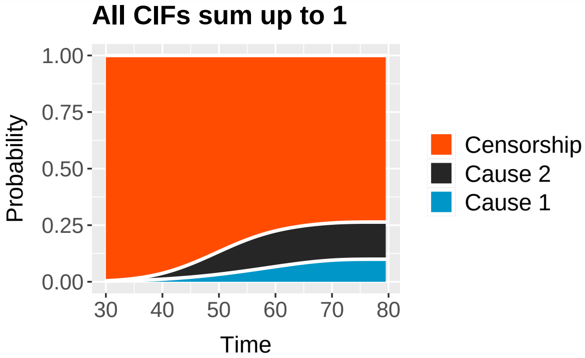
Frailty-based models for (multiple) survival experiences turn out in challengeable likelihood functions with inference routines mostly done via

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

2. *Not* usually, the probability scale.

Probability scale $\to$ Cause-specific CIF





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

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

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

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

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

with

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

In Cederkvist et al. (2019), this CIF specification is modeled under a pairwise composite likelihood approach (Lindsay 1988; Varin, Reid, and Firth 2011).

Our contribution: a full likelihood analysis

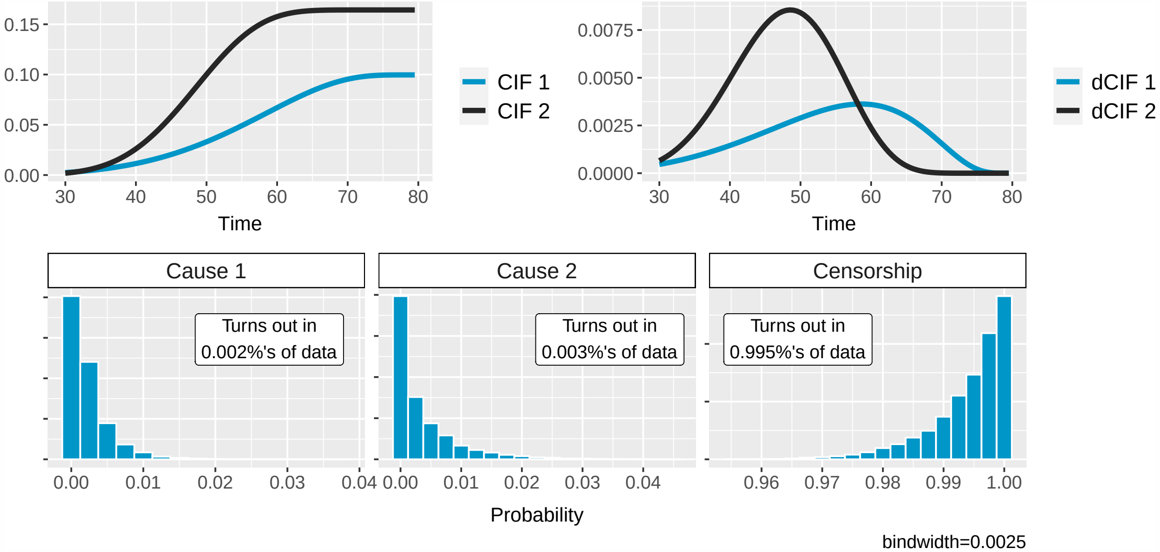
For two competing causes of failure, a subject i, in the cluster j, in time t, we have

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

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

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

Simulating from the model



Marginal likelihood function for two competing causes

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

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

TMB: Template Model Builder

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)`.

TMB: Template Model Builder

Key features:

1. Automatic differentiation;
   The state-of-art in derivatives computation

2. Laplace approximation.
   An efficient fashion to approximate the latent effect integrals

A code example:

emacs@laureano

```
// PARALLEL LOGISTIC MIXED MODEL
#include <TMB.hpp>
template<class Type>
Type objective_function<Type>::operator() ()
{
  DATA_VECTOR(y); DATA_SPARSE_MATRIX(Z); DATA_SCALAR(n);
  PARAMETER(beta);
  PARAMETER(logsd);             Type sd = exp(logsd);
  PARAMETER_VECTOR(u); vector<Type> Zu = Z*u;
  vector<Type>  risk = exp(beta+Zu);
  vector<Type> level = 1+risk;
  vector<Type>  prob = risk/level;
  parallel_accumulator<Type> nll(this);
  nll -= dnorm(u, Type(0), sd, true).sum();
  nll -= dbinom(y, n, prob, true).sum();
  ADREPORT(sd);
  return nll;
}
```

-:--- mixedlogistic_parallel.cpp   All (19,0)   (TMB//l WS)

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.,

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

Time model

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

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

Block-diag model

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

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

Complete model

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

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

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 $\mathbf{4} \times \mathbf{2} = \mathbf{8}$ 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**.

$\mathbf{8} \times \mathbf{3} \times \mathbf{3} = \mathbf{72}$ scenarios.
For each scenario, we simulate **500** samples. $\mathbf{72} \times \mathbf{500} = \mathbf{36000}$ model fittings.

Simulation study results

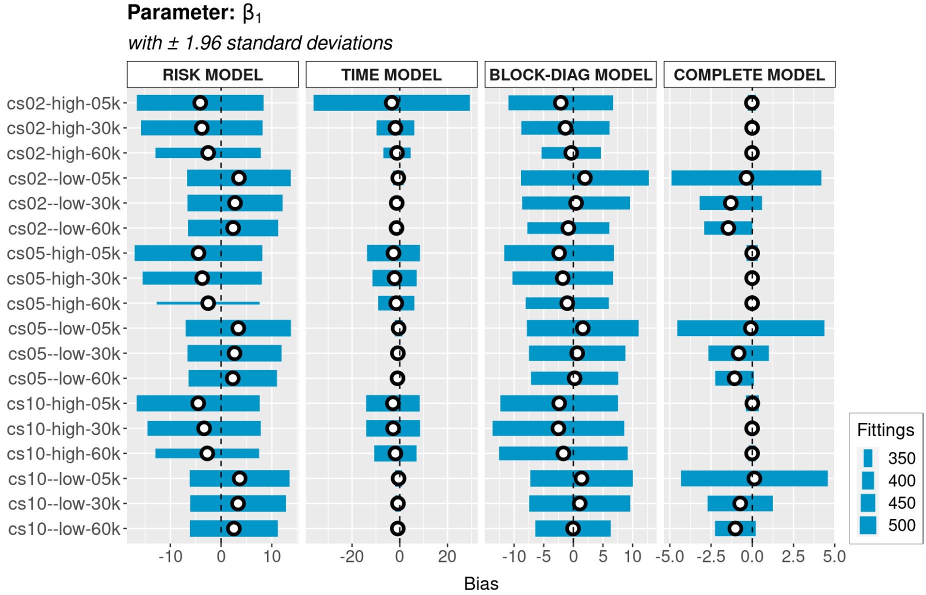
First of all, the **time**.

- 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.

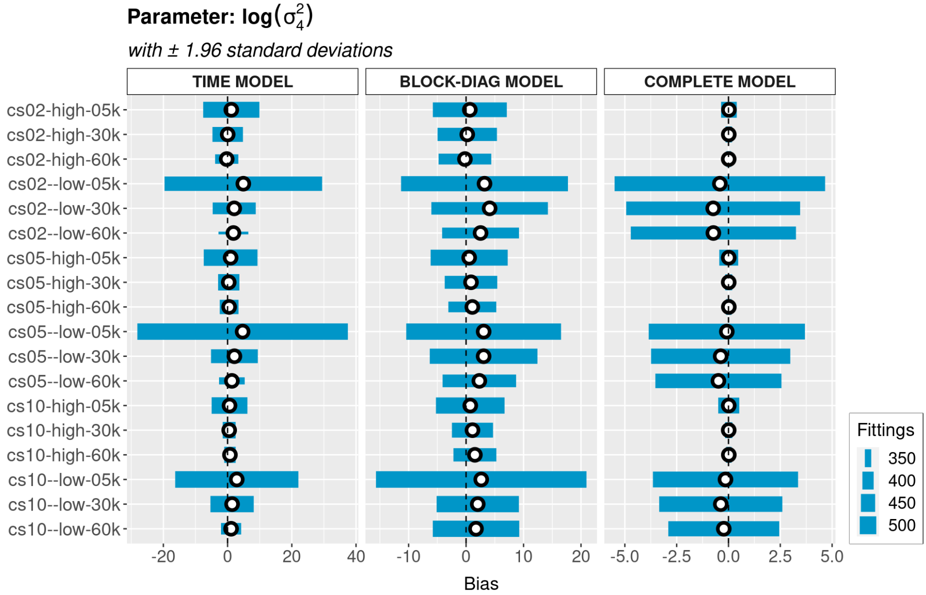
Parameters estimation.

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

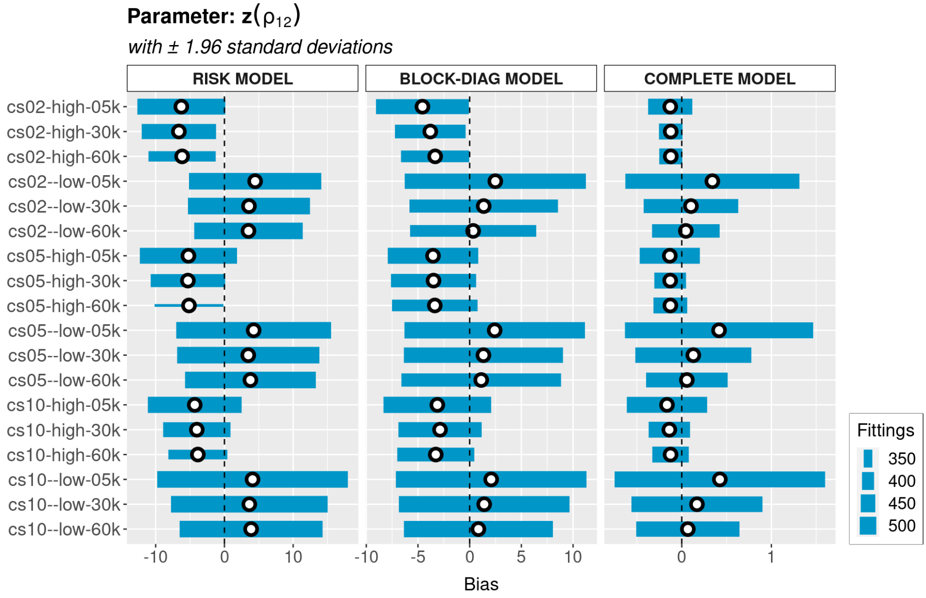
Some simulation study results



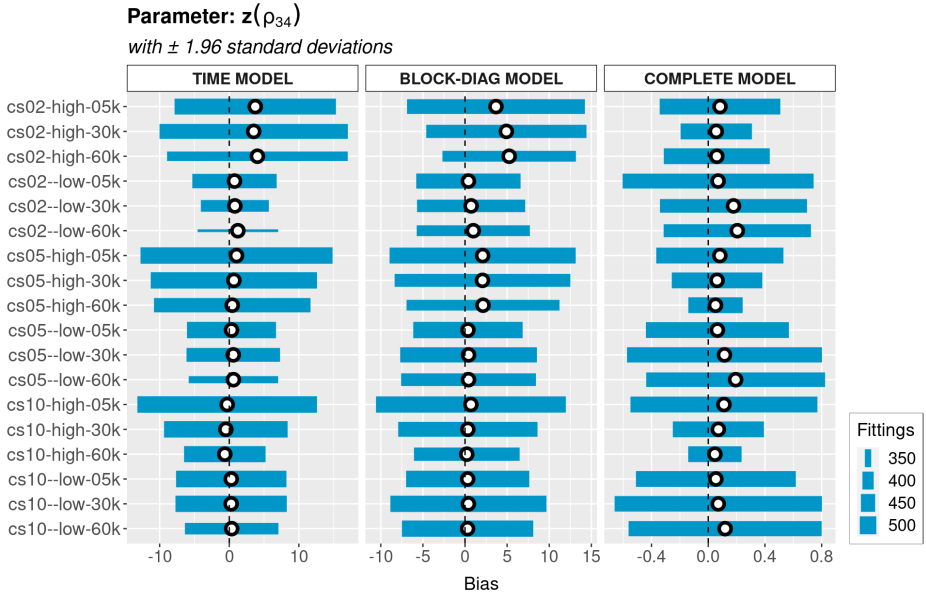
Some simulation study results



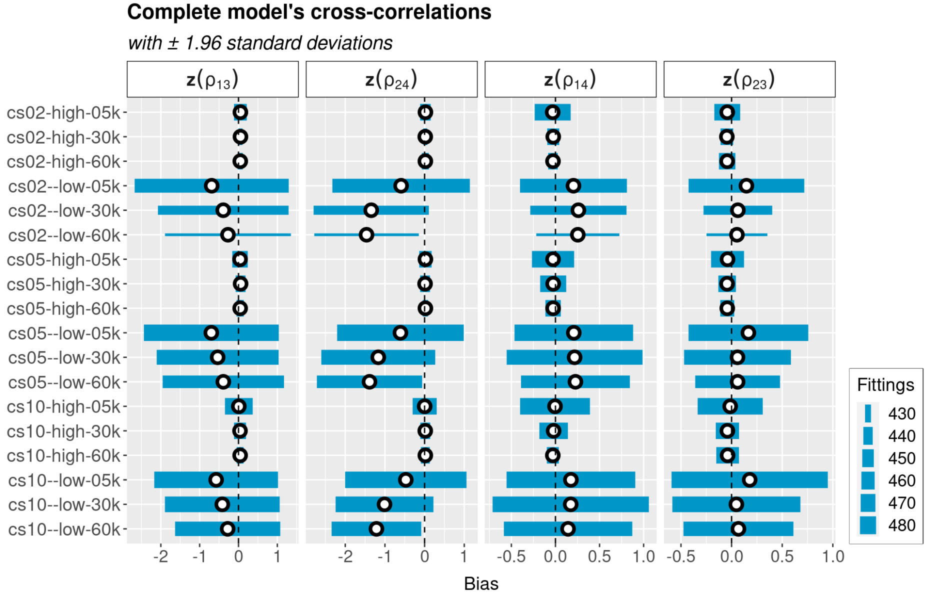
Some simulation study results



Some simulation study results



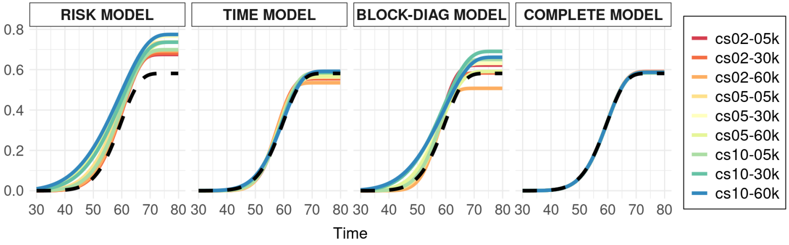
Some simulation study results



Simulation study results: High CIF scenario

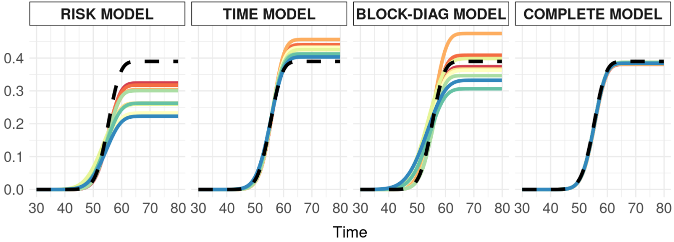
CIF of failure cause 1

True curve in dashed black

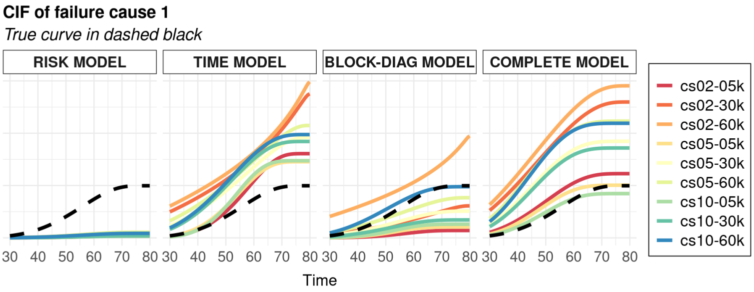


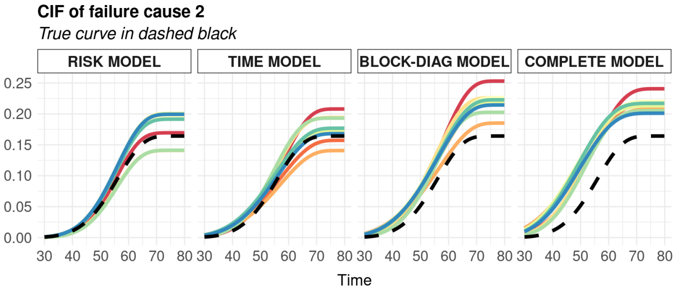
CIF of failure cause 2

True curve in dashed black



Simulation study results: Low CIF scenario





Take-home message

The complete model works.

1. It works better in the high CIF scenarios;
2. As expected, as the sample size increases the results get better;
3. We do not see any considerable performance difference between cluster/family sizes;
4. Satisfactory full likelihood analysis under the maximum likelihood estimation framework.

What else can we do?

1. 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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