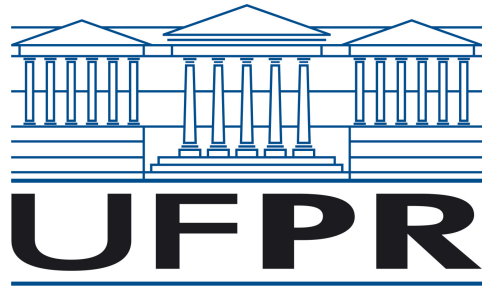
Modeling the cumulative incidence function of multivariate competing risks data allowing for within-cluster dependence of risk and timing

paper presentation



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"Modeling the **cumulative incidence function** of **multivariate competing risks data** allowing for **within-cluster dependence** of risk and timing"

what?

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» cause-specific **cumulative incidence function** (CIF).

$$\text{for a type } j \text{ failure,} \quad F_j(t \mid X) = \mathbb{P}[T \leq t, J = j \mid X]$$
$$= \int_0^t f_j(u \mid X) du, \quad t > 0,$$

where $f_j(t \mid X) = \lambda_j(t \mid X) \times S(t \mid X)$ is the (sub)density for the time to a type j failure.

» ...

"Modeling the **cumulative incidence function** of **multivariate competing risks data** allowing for **within-cluster dependence** of risk and timing"

what?

- ...
- **multivariate competing risks**,

  *we have more than one, that is why it is **multivariate**, cause of interest **competing** to be responsible by the failure (if not censor).*

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- **multivariate competing risks**,

  *we have more than one, that is why it is **multivariate**, cause of interest **competing** to be responsible by the failure (if not censor).*

- multivariate competing risks **data**, i.e.,

  we'll not do a multivariate competing risks model,
  we'll do a model for multivariate competing risks data!

"Modeling the **cumulative incidence function** of **multivariate competing risks data** allowing for **within-cluster dependence** of risk and timing"

what?

- ...
- **within-cluster dependence**, i.e., a random/latent effect structure for
  - risk: how a failure occurrence relates to other;
  - timing: some failures aren't likely to happen equally all time and the failure time distribution may vary between clusters.

paper structure

- **intro**: ideas, motivation and 'selling the fish';
- **model**: model specification, likelihood, estimation and extras;
- simulation results;
- application: **Danish register-based family data on breast cancer**;
- final remarks.

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focus: **family studies** and why a random effects approach

- the within-cluster dependence, which is here a **within-family dependence**, is often the key point of interest or at least as important as determining the role of different risk factors;

ideas, motivation and 'selling the fish'

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focus: **family studies** and why a random effects approach

- the within-cluster dependence, which is here a **within-family dependence**, is often the key point of interest or at least as important as determining the role of different risk factors;

- the within-family dependence can be viewed as an expression of familial aggregation and may reflect both disease **heritability** and the impact of shared **environmental effects**.

About the **model approach**: *what we could do?*

- a frailty-based two-stage approach, where the marginal CIFs are estimated in the 1st stage and a dependence parameter is estimated in the 2nd stage using an Archimedean **copula**.

And why we don't do that?

- The necessary to **adjust for right-censoring**. This is done through modeling of the censoring distribution and employment of inverse probability of censoring weights (IPCWs);
- If the **censoring distribution is misspecified**, the weighting may introduce bias.

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For two competing causes of failure we write

$$F_i(t \mid X, \eta_i, u_1, u_2) = \underbrace{\pi_i(X, u_1, u_2)}_{\substack{\text{cluster-specific} \\ \text{risk level}}} \times \underbrace{\Phi[\alpha_i\{g(t)\} - X^\top \gamma_i - \eta_i]}_{\substack{\text{cluster-specific} \\ \text{failure time trajectory}}}, \quad i = 1, 2,$$

where

$$\begin{pmatrix} \eta_1 \\ \eta_2 \\ u_1 \\ u_2 \end{pmatrix} \sim \mathcal{N}\left[\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma^2_{\eta_1} & \varrho_{\eta_1,\eta_2} & \varrho_{\eta_1,u_1} & \varrho_{\eta_1,u_2} \\ & \sigma^2_{\eta_2} & \varrho_{\eta_2,u_1} & \varrho_{\eta_2,u_2} \\ & & \sigma^2_{u_1} & \varrho_{u_1,u_2} \\ & & & \sigma^2_{u_2} \end{pmatrix} \right].$$

- The cluster-specific survivor function is given as $S(t \mid X, \boldsymbol{\eta}, \boldsymbol{u}) = 1 - F_i(t \mid X, \eta_i, \boldsymbol{u})$, $i = 1, 2$.

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Why modeling the CIF?

Proposing a model for the CIF provides a framework for exploring and making inference about the distribution of age at disease onset.

cluster-specific CIF

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This separation of the CIF is possible via the transformation of the time variable t, given as

$$g(t) = \text{arctanh}\left(\frac{t - \delta/2}{\delta/2}\right) \quad \text{for} \quad t \in]0, \delta[.$$

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- With this transformation the value of the cluster-specific **failure time trajectory** will equal 1 at time δ, a fixed time point at which all individuals still at risk are censored.
- $\alpha_i(x)$, $i = 1, 2$, are monotonically increasing functions of x and known up to a parameter vector, w_i, $i = 1, 2$. e.g., monotonically increasing B-spline or piecewise linear functions.

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The cluster-specific **risk levels** are modeled using a **multinomial logistic regression model with random effects**, i.e.

$$\pi_i(X, \boldsymbol{u}) = \frac{\exp\{X^\top \beta_i + u_i\}}{1 + \sum_{j=1}^{2} \exp\{X^\top \beta_j + u_j\}}, \quad i = 1, 2.$$

- We employ that **multinomial model** to ensure that the sum of the predicted CIFs do not exceed 1.

nice aspects or consequences

» at time δ, where $F_i(\delta \mid X, \eta_i, \boldsymbol{u}) = \pi_i(X, \boldsymbol{u})$, the cluster-specific **survival function** is given by

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- the regression coefficients $\boldsymbol{\gamma}$s reflect how covariates affect the **failure time trajectories**, i.e., the shape of the CIFs;

- ...

Likelihood

I'm already telling you, this paper has a bad and not very explained, notation

---

To accommodate the censorship and the cluster structures, the chosen approach is the **pairwise composite likelihood** given as

$$L(\theta; \boldsymbol{T}, \boldsymbol{\epsilon}, \boldsymbol{X}, \boldsymbol{\eta}, \boldsymbol{u}) = \prod_{i=1}^{n} \prod_{j=1}^{n_i - 1} \prod_{k=j+1}^{n_i} L(\theta; T_{ij}, \epsilon_{ij}, X_{ij}, T_{ik}, \epsilon_{ik}, X_{ik}, \boldsymbol{\eta}_i, \boldsymbol{u}_i),$$

where $\theta = \{\beta_1, \beta_2, \gamma_1, \gamma_2, w_1, w_2, \Sigma_{\boldsymbol{\eta u}}\}^\top$. i.e., still considering just two competing causes.

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1st step? The same as always.
Integrating out in the random effects **to get the marginal** and using the Bayes'rule to reduce the dimensionality of the integral, we have

$$L_M(\theta; \boldsymbol{T}, \boldsymbol{\epsilon}, \boldsymbol{X}) = \int \pi(\boldsymbol{T}, \boldsymbol{\epsilon} \mid \boldsymbol{X}, \boldsymbol{u}) \pi(\boldsymbol{u}) d\boldsymbol{u}.$$

pairwise composite likelihood

Ignoring the cluster subscript i, the likelihood contribution of the pair j, k to the *pairwise composite likelihood* is given as

$$
\begin{aligned}
L_{jk}(\theta; T_j, \epsilon_j, X_j, T_k, \epsilon_k, X_k, \boldsymbol{\eta}, \boldsymbol{u}) = & \left\{ \prod_{h=1}^{2} \prod_{l=1}^{2} f_h(T_j \mid X_j, \eta_h, \boldsymbol{u}) f_l(T_k \mid X_k, \eta_l, \boldsymbol{u}) \right\} \\
& \times \left\{ \prod_{h=1}^{2} f_h(T_j \mid X_j, \eta_h, \boldsymbol{u}) S(T_k \mid X_k, \boldsymbol{\eta}, \boldsymbol{u}) \right\} \\
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& \times \left\{ S(T_j \mid X_j, \boldsymbol{\eta}, \boldsymbol{u}) S(T_k \mid X_k, \boldsymbol{\eta}, \boldsymbol{u}) \right\}.
\end{aligned}
$$

The indicator functions were omitted,
but the equation is still 'clear' and readable.

pairwise composite likelihood

In that likelihood, we have four contributions:

- the one when **both** individuals experience failure (either cause);
- two for the case when **only one** individual experiences failure;
- and one for the case when **both** individuals don't experience failure.

We have basically two quantities: $f(\cdot)$ and $S(\cdot)$, i.e, the CIFs derivative wrt t and the survival function.

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Writing down each of the four components (the 2nd and 3rd are symmetric) and, again, integrating out in the random effects based in a Bayes'rule, we obtain the contributions to the conditional densities necessary in the marginal.

- The resulting contributions are basically products of the **multinomial logistic regression model** with **univariate** or **bivariate normals**.

pairwise composite likelihood
↳ ESTIMATION

As expected, the marginal likelihood doesn't have a closed-form. The numerical approach chosen for parameter estimation is the **adaptive Gaussian quadrature** (AGQ) with Gauss-Hermite rules.

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- the likelihood contributions to the **composite likelihood** from pairs within the same cluster are not independent, as consequence:
  - the Fisher information needs to be substituted by the so-called **sandwich estimator** when estimating the variance of the parameter estimates.

Danish register-based family data on breast cancer

The cohort study is too big (1 292 051 families) and the model is also too complicated (plus the extra computational cost of the **AGQ** approximation).

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Consequences? We need an estimator of the pairwise composite log-likelihood - a **weighted log-likelihood**; the score function changes and we need a new sandwich estimator for the variance of the parameter estimates.

1000 populations of 50 000 clusters of size three and two competing causes

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- AGQ approximation with five quadrature points and Gauss-Hermite rules.

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- approximately 50% censoring;
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Overall, the model performed well, the parameter estimates were unbiased and the coverage rates were good.

irregularities: caused by the numerical derivative of the AGQ approximation *or* the number of quadrature points.

Danish register-based family data on breast cancer
↳ more details

*family data on **breast cancer** among women - the most common malignancy in women.*

The cohort consisted of 1 292 051 families and 3 029 653 individuals:

- 908 002 (70.3%) families with a mother and a single daughter;
- 322 547 (25.0%) families with a mother and two daughters;
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failure causes: 1) breast cancer; 2) death; and 3) other cancers, which were grouped together.

Danish register-based family data on breast cancer
↳ general results

- AGQ approximation with five quadrature points and Gauss-Hermite rules;
- *found*: within-cluster dependence of breast cancer with regard to both risk and timing;
- The model provides a framework for exploring and making inference about the distribution of age at disease onset and to investigate how absolute risk of disease is related to age at onset.

```
@article{PAPER_PRESENTED,
   title = "Modeling the cumulative incidence function of
            multivariate competing risks data allowing for
            within-cluster dependence of risk and timing",
   author = "Luise Cederkvist and Holst, {Klaus K.} and
             Andersen, {Klaus K.} and Scheike, {Thomas H.}",
   year = "2019",
   volume = "20",
   pages = "199--217",
   journal = "Biostatistics",
   publisher = "Oxford University Press",
   number = "2",
}
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