A flexible class of generalized joint frailty models for the analysis of survival endpoints

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1. Motivations
2. Generalized Joint Frailty Models
3. Real-world applications

General context: When an event occurs many times for a subject (e.g., appearance of new cancerous lesions, hospital readmissions, repeated epileptic seizures)

Models developed to tackle this kind of data:

- Andersen-Gill's model
- Shared frailty models
- ...

Main assumptions: Independent and noninformative censoring

⚠ Assumptions may be violated by the existence of a terminal event that permanently stops the recurrent process (e.g., death)

⚠ Ignoring terminal events in the analysis may lead to biased results

Solution: Considering joint models that analyze simultaneously the recurrent and terminal events as well as their dependence (both event types may have an impact on the other)

Joint Frailty Models for the simultaneous analysis of:

- **Recurrent events** (e.g., appearance of new cancerous lesions)
- **a Terminal event** (typically, death)

For patient i:

- $\lambda_{\mathrm{R}ij}$ the hazard function of recurrent event j
- $\lambda_{\mathrm{D}i}$ the hazard function of terminal event

$$\begin{cases} \lambda_{\mathrm{R}ij}(t|u_i) = u_i \, \lambda_{\mathrm{R}0}(t) \exp(\boldsymbol{\beta}_{\mathrm{R}}^{\mathsf{T}} \boldsymbol{x}_{\mathrm{R}ij}) \\ \lambda_{\mathrm{D}i}(t|u_i) = u_i^{\alpha} \, \lambda_{\mathrm{D}0}(t) \exp(\boldsymbol{\beta}_{\mathrm{D}}^{\mathsf{T}} \boldsymbol{x}_{\mathrm{D}i}) \end{cases}$$

$\lambda_{\mathrm{R}0}$, $\lambda_{\mathrm{D}0}$: baseline hazard functions
$\boldsymbol{x}_{\mathrm{R}ij}$, $\boldsymbol{\beta}_{\mathrm{R}}$, $\boldsymbol{x}_{\mathrm{D}i}$, $\boldsymbol{\beta}_{\mathrm{D}}$: covariates and associated fixed effects
u_i: random frailty term of patient i
α: modulates the association between recurrent and terminal events

Problem: What if a covariate does not satisfy the PH assumption?

Most common strategies:

- Considering time-varying coefficient
- Stratified analysis

Our proposal: switch to *Generalised Survival Models* (GSMs) !

Generalized version of the usual survival models

$$S(t) = g^{-1}\left[\eta(t, \boldsymbol{x})\right]$$

Proportional hazards — $g(x) = \log(-\log(x))$

$$\lambda(t) = \lambda_0(t)\exp(\boldsymbol{\beta}'\boldsymbol{x})$$

Additive hazards — $g(x) = -\log(x)$

$$\lambda(t) = \lambda_0(t) + \boldsymbol{\beta}'\boldsymbol{x}$$

Proportional odds — $g(x) = -\operatorname{logit}(x)$

$$\frac{S(t)}{1-S(t)} = \frac{S_0(t)}{1-S_0(t)}\exp(\boldsymbol{\beta}'\boldsymbol{x})$$

Probit model — $g(x) = -\Phi(x)$

$$S(t) = 1 - \Phi(k_0(t) + \boldsymbol{\beta}'\boldsymbol{x})$$

For patient i, we define:

Terminal event

- $t_i^\star$: true terminal event time
- c_i: censoring time

Recurrent events $(j \in \{1, \ldots, n_i\})$

- $t_{ij}^\star$: true recurrent event time

For patient i, we observe:

- $t_i = \min\left(t_i^\star, c_i\right)$
- $\delta_i = \mathbb{1}_{\{t_i^\star \leqslant c_i\}}$
- $\boldsymbol{x}_{\mathsf{D}i}$

- $t_{ij} = \min\left(t_{ij}^\star, t_i^\star, c_i\right)$
- $\delta_{ij} = \mathbb{1}_{\{t_{ij}^\star = t_{ij}\}}$
- $\left\{\boldsymbol{x}_{\mathsf{R}ij} \mid j = 1, \ldots, n_i\right\}$

System of Generalized Survival Frailty Models:

$$\begin{cases} S_{\mathsf{R}ij}\left(t|u_i\,;\boldsymbol{\xi}_{\mathsf{R}}\right) = \left[g_{\mathsf{R}}^{-1}\left(\eta_{\mathsf{R}ij}\left(t,\boldsymbol{x}_{\mathsf{R}ij}\,;\boldsymbol{\xi}_{\mathsf{R}}\right)\right)\right]^{u_i} & \text{(Recurrent events)} \\ S_{\mathsf{D}i}\left(t|u_i\,;\boldsymbol{\xi}_{\mathsf{D}}\right) = \left[g_{\mathsf{D}}^{-1}\left(\eta_{\mathsf{D}i}\left(t,\boldsymbol{x}_{\mathsf{D}i}\,;\boldsymbol{\xi}_{\mathsf{D}}\right)\right)\right]^{u_i^{\alpha}} & \text{(Terminal event)} \end{cases}$$

where

- $u_i \sim \Gamma\left(\frac{1}{\theta}, \frac{1}{\theta}\right)$
- $\boldsymbol{\xi}_{\mathsf{R}}$, $\boldsymbol{\xi}_{\mathsf{D}}$: vector of parameters for recurrent and terminal events
- $g_{\mathsf{R}}^{-1}(\cdot)$, $g_{\mathsf{D}}^{-1}(\cdot)$: inverse link functions
- $\eta_{\mathsf{R}ij}$, $\eta_{\mathsf{D}i}$: linear predictors for recurrent and terminal events

Nota bene: If $g_{\mathsf{R}}^{-1}(x) = g_{\mathsf{D}}^{-1}(x) = \exp(-\exp(x))$, our Generalized Joint Frailty Models goes back to the usual Joint Frailty Model.

Marginal contribution to the likelihood for patient i:

$$\mathcal{L}_i(\boldsymbol{\xi}, \theta) = \int_0^{+\infty} \mathcal{L}_i(\boldsymbol{\xi}|u_i)\, p(u_i\,;\theta)\, \mathrm{d}u_i$$

where $\mathcal{L}_i(\boldsymbol{\xi}|u_i) =$

$$\left[\prod_{j=1}^{n_i} \left[\lambda_{\mathsf{R}ij}(t_{ij}|u_i\,;\boldsymbol{\xi}_\mathsf{R})\right]^{\delta_{ij}} \exp\left(-u_i \int_{t_{i(j-1)}}^{t_{ij}} \lambda_{\mathsf{R}ij}(t\,;\boldsymbol{\xi}_\mathsf{R})\mathrm{d}t\right)\right]^{1-\delta_i}$$

$$\times \left[\lambda_{\mathsf{D}i}(t_i|u_i\,;\boldsymbol{\xi}_\mathsf{D})\right]^{\delta_i} \exp\left(-u_i^\alpha \int_0^{t_i} \lambda_{\mathsf{D}i}(t\,;\boldsymbol{\xi}_\mathsf{D})\mathrm{d}t\right)$$

- Parameters to estimate: $\boldsymbol{\xi} = \left(\boldsymbol{\xi}_\mathsf{R}^\mathsf{T}, \boldsymbol{\xi}_\mathsf{D}^\mathsf{T}, \theta, \alpha\right)^\mathsf{T}$
- Maximum likelihood estimation using the Levenberg-Marquardt algorithm
- Integrals approximated using Gauss-Hermite quadrature

Only the writing of the hazard functions differs:

$$\lambda_{\mathsf{R}ij}\left(t\,;\boldsymbol{\xi}_{\mathsf{R}}\right) = -\frac{g_{\mathsf{R}}^{-1'}\left(\eta_{\mathsf{R}ij}\left(t,\boldsymbol{x}_{\mathsf{R}ij}\,;\boldsymbol{\xi}_{\mathsf{R}}\right)\right)}{g_{\mathsf{R}}^{-1}\left(\eta_{\mathsf{R}ij}\left(t,\boldsymbol{x}_{\mathsf{R}ij}\,;\boldsymbol{\xi}_{\mathsf{R}}\right)\right)}\,\frac{\partial\eta_{\mathsf{R}ij}\left(t,\boldsymbol{x}_{\mathsf{R}ij}\,;\boldsymbol{\xi}_{\mathsf{R}}\right)}{\partial t}$$

$$\lambda_{\mathsf{D}ij}\left(t_i\,;\boldsymbol{\xi}_{\mathsf{D}}\right) = -\frac{g_{\mathsf{D}}^{-1'}\left(\eta_{\mathsf{D}i}\left(t,\boldsymbol{x}_{\mathsf{D}i}\,;\boldsymbol{\xi}_{\mathsf{D}}\right)\right)}{g_{\mathsf{D}}^{-1}\left(\eta_{\mathsf{D}i}\left(t,\boldsymbol{x}_{\mathsf{D}i}\,;\boldsymbol{\xi}_{\mathsf{D}}\right)\right)}\,\frac{\partial\eta_{\mathsf{D}i}\left(t,\boldsymbol{x}_{\mathsf{D}i}\,;\boldsymbol{\xi}_{\mathsf{D}}\right)}{\partial t}$$

For PH and AH submodels:

- Baseline hazard functions computed using **parametric distributions** or **M-splines** (smooth estimation by likelihood penalization)

$$\ell(\boldsymbol{\xi},\theta) - \kappa_{\mathsf{R}}\int_0^{+\infty}\left[\lambda''_{\mathsf{R}0}(t)\right]^2\mathrm{d}t - \kappa_{\mathsf{D}}\int_0^{+\infty}\left[\lambda''_{\mathsf{D}0}(t)\right]^2\mathrm{d}t$$

- Time-varying coefficients are allowed (using B-splines)

Special case of additive models:

All estimated hazards have to be non-negative!

Constrained optimization problem:

$$\max_{\boldsymbol{\xi},\theta} \ \ell(\boldsymbol{\xi},\theta) \ \text{ such that } \begin{cases} \lambda_{\mathsf{R}ij}\left(t_{ij}\,;\boldsymbol{\xi}_{\mathsf{R}}\right) > 0, & i=1,\dots,N,\ j=1,\dots,n_i \\ \lambda_{\mathsf{D}i}\left(t_i\,;\boldsymbol{\xi}_{\mathsf{D}}\right) > 0, & i=1,\dots,N \end{cases}$$

To solve it: Iterative maximization of

$$\ell(\boldsymbol{\xi},\theta) - \frac{\nu_{\mathsf{R}}}{2}\sum_{i=1}^{N}\sum_{j=1}^{n_i}\lambda_{\mathsf{R}ij}^2\left(t_{ij}\,;\boldsymbol{\xi}_{\mathsf{R}}\right)\,\mathbb{1}_{\{\lambda_{\mathbf{R}ij}(t_{ij};\boldsymbol{\xi}_{\mathbf{R}})<0\}}$$

$$- \frac{\nu_{\mathsf{D}}}{2}\sum_{i=1}^{N}\lambda_{\mathsf{D}i}^2\left(t_i\,;\boldsymbol{\xi}_{\mathsf{D}}\right)\,\mathbb{1}_{\{\lambda_{\mathbf{D}i}(t_i;\boldsymbol{\xi}_{\mathbf{D}})<0\}}$$

The *diabetic retinopathy* study:

- Each patient had diabetic retinopathy on both eyes, which can lead to blindness
- Objective: assess whether laser treatment was effective in delaying blindness
- Treatment administered to one randomly-selected eye in each patient, leaving the other untreated

Focus on patients with adult diabetes:

- 83 patients
- Observed follow-up time: time between the initiation of treatment until the time when visual acuity dropped to below 5/200
- Possible censorship due to study dropout or end of the study

Treatment as covariate: $\text{treated}_{ij} = \begin{cases} 1 & \text{if eye } j \text{ of patient } i \text{ is treated} \\ 0 & \text{for not treated} \end{cases}$

Results:

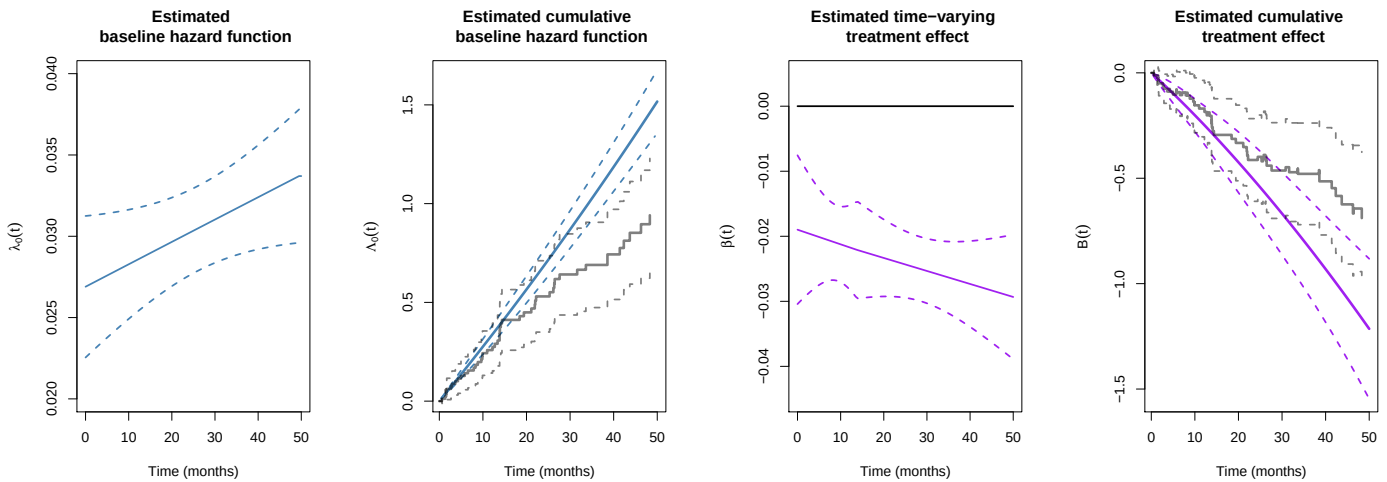
	Treatment effect			Frailty variance			
Model	$\widehat{\beta}$	**(SE)**	**Significance**	$\widehat{\theta}$	**(SE)**	**Significance**	**AIC**
shared frailty PHM	-1.59	(0.32)	$\star\star\star$	1.13	(0.55)	$\star$	2.059
shared frailty AHM	-0.02	(0.01)	$\star\star\star$	0.96	(0.45)	$\star$	2.060
shared frailty POM	-1.83	(0.38)	$\star\star\star$	0.76	(0.43)	$\star$	2.064
shared frailty probit	-0.99	(0.21)	$\star\star\star$	0.59	(0.40)	$\bullet$	2.067

Instead of fitting a single model (based on unverifiable assumptions), we have four consistent models (based on different assumptions)

Focus on the additive hazards model:

$$\lambda_{ij}\left(t|\,\text{treated}_{ij}, u_i\,;\boldsymbol{\xi}\right) = u_i \times \left[\lambda_0(t) + \beta(t)\cdot \text{treated}_{ij}\right]$$

Comparison with nonparametric estimation of Martinussen *et al*:



Advantages of our flexible semi-parametric approach:

- The hazard rates we estimate are forced to be positive
- Our method provides a direct estimate of the regression coefficients $\boldsymbol{\beta}$ or $\boldsymbol{\beta}(t)$ and is not restricted to estimating cumulative effects.
- The baseline hazard function and the time-varying coefficients we obtain are smooth functions — as is reasonable to expect.

The *Readmission* data:

- 403 patients with colorectal cancer who had a surgery
- Contains calendar time of their successive rehospitalizations
- 112 patients died during follow-up (the others were censored because of migration or end of the study)

Covariates of interest for both recurrent event and death:

- sex ("Male" and "Female")
- Dukes' tumor stage ("A-B", "C" or "D")
- chemotherapy ("Non treated" and "Treated")

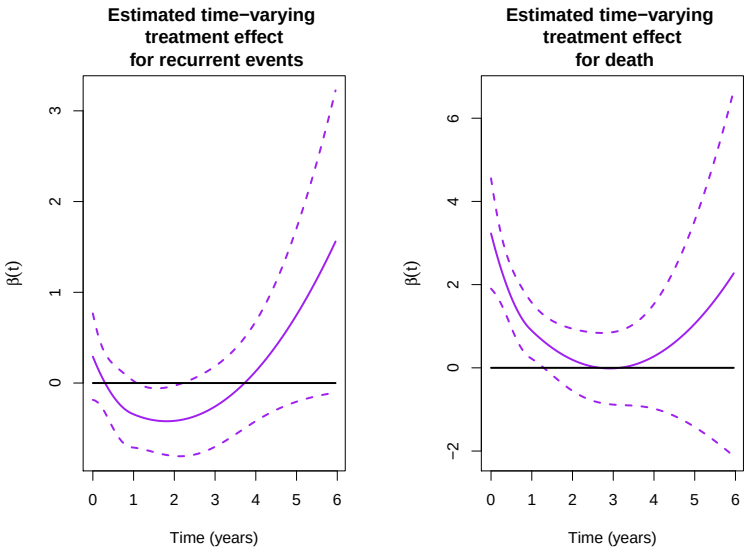
Best models:

- Dual-PHM and dual-AHM
- Fixed effects for sex and Dukes's tumor stage, time-varying effect for chemotherapy

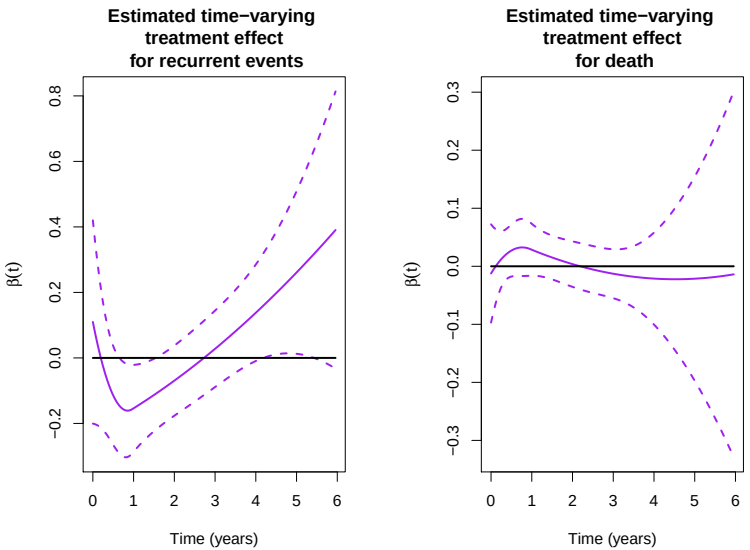
Results for fixed-effect and association parameters:

		PHM/PHM	AHM/AHM
		Estimate (SE)	Estimate (SE)
Recurrent events	Female	-0.60 (0.15) ⋆⋆⋆	-0.20 (0.07) ⋆⋆
	Dukes' stage C	0.47 (0.16) ⋆⋆	0.13 (0.06) ⋆⋆
	Dukes' stage D	1.80 (0.20) ⋆⋆⋆	1.87 (0.39) ⋆⋆⋆
Death event	Female	-0.31 (0.24)	-0.05 (0.02) ⋆⋆
	Dukes' stage C	1.50 (0.36) ⋆⋆⋆	0.06 (0.02) ⋆⋆⋆
	Dukes' stage D	3.87 (0.39) ⋆⋆⋆	1.00 (0.19) ⋆⋆⋆
θ & α	Frailty variance (θ)	0.98 (0.11) ⋆⋆⋆	0.99 (0.11) ⋆⋆⋆
	Association parameter (α)	0.96 (0.20) ⋆⋆⋆	0.88 (0.16) ⋆⋆⋆
	LCV	1.03	1.05

Dual-PHM plots



Dual-AHM plots



- For both dual-PHM and -AHM, the treatment initially tends to reduce the risk of readmission but increases this risk after a certain period of time.
- For the dual-PHM: Treatment = prognostic factor for death during the first year
- For the dual-AHM: Treatment has no effect on the risk of death

CONCLUSION

- New flexible class of GSMs adapted to shared and joint frailty models
  - ↪ 4 available models (PHM, AHM, POM and probit)
  - ↪ Parametric or flexible baseline hazard functions
  - ↪ Time-varying effect
- Our additive models have a higher interpretability than classical Aalen-type approaches

PERSPECTIVES

- Make the POM and the probit model as flexible as PHM and AHM.
- Adapt our strategy to joint models for recurrent events and a longitudinal biomarker.

Thank you very much for your attention !

Chauvet, J., and Rondeau, V (2021). *A flexible class of generalized joint frailty models for the analysis of survival endpoints.* Under review.

+ Package R : frailtypack
https://CRAN.R-project.org/package=frailtypack

Liu L, Wolfe RA, and Huang X (2004). *Shared frailty models for recurrent events and a terminal event.* Biometrics, **60**(3), 747–756.

Rondeau V, Mathoulin-Pélissier S, Jacqmin-Gadda H, Brouste V, and Soubeyran P (2007). *Joint frailty models for recurring events and death using maximum penalized likelihood estimation: application on cancer events.* Biostatistics, **8**(4), 708–721.

Liu XR, Pawitan Y, and Clements MS (2017). *Generalized survival models for correlated time-to-event data.* Statistics in Medicine, **36**(29), 4743–4762.

Liu XR, Pawitan Y, and Clements MS (2018). *Parametric and penalized generalized survival models.* Statistical Methods in Medical Research, **27**(5), 1531–1546.