Simulating Recurrent Event Data with a Calendar Time Scale

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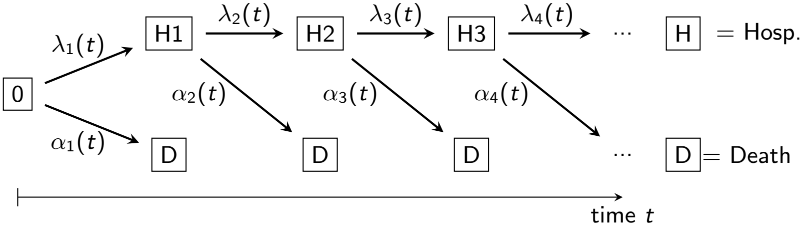
Outline

- Motivation: Clinical trials in heart failure disease
- Simulation: Recurrent event data with a dependent terminal event
- Application: Estimates in misspecified models

Motivation

- Clinical trials in heart failure disease
- Effect on both morbidity (heart failure hospitalizations) and mortality (CV death)



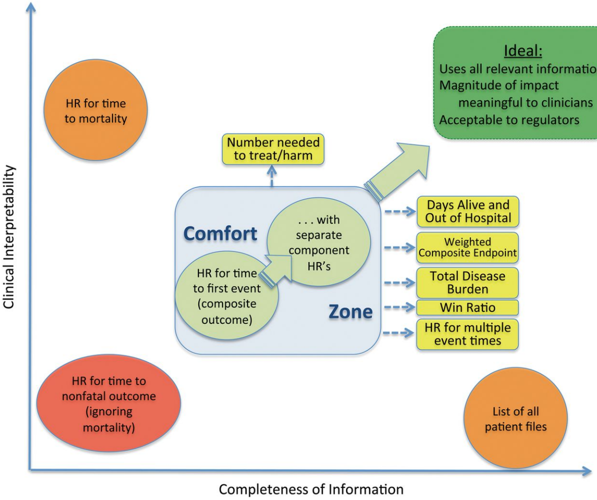
- Standard approach: Time to first composite endpoint

Time to First Composite Endpoint: Loss of Information

trial	endpoint	# events	**not** in 1st comp. endpoint
Val-HeFT	death	846	385 (45.5%)
	hosp.	2111	962 (45.6%)
CHARM-Added	death	649	333 (51.3%)
	hosp.	1443	738 (51.1%)
CHARM-Alternative	death	471	234 (49.7%)
	hosp.	1053	550 (52.2%)
EMPHASIS-HF	death	332	144 (43.4%)
	hosp.	702	285 (40.6%)
SHIFT	death	940	396 (42.1%)
	hosp.	2113	927 (43.9%)
I-PRESERVE	death	613	221 (36.1%)
	hosp.	1176	515 (43.8%)
CHARM-Preserved	death	340	150 (44.1%)
	hosp.	968	459 (47.4%)

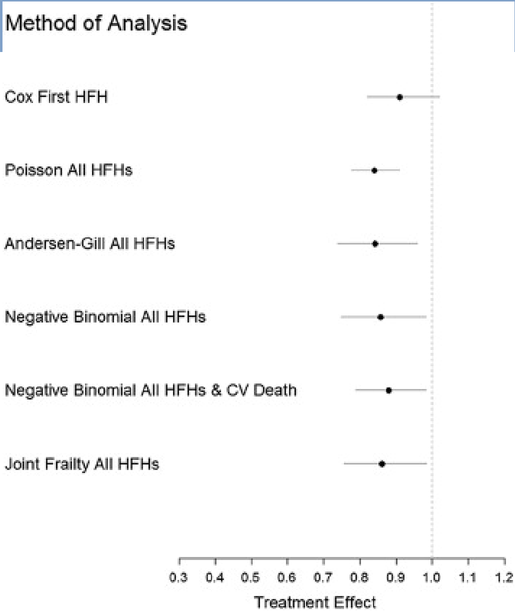
Anker, S.D. (2012): Time to move on from 'time-to-first': should all events be included in the analysis of clinical trials? Eur Heart J 33 (22): 2764-2765.

Time to First Composite Endpoint: Loss of Information



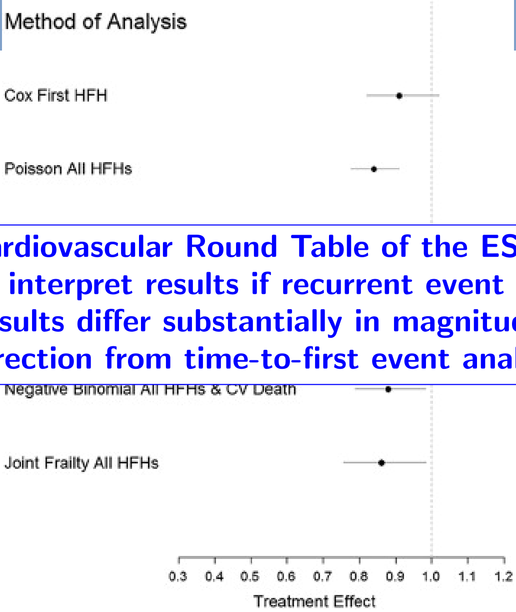
Claggett B. *et al.* (2013): Moving beyond our comfort zone. Eur Heart J 34: 869-871.

Example



Rogers, J. *et al.* (2014): Effect of rosuvastatin on repeat heart failure hospitalizations: the CORONA Trial. JACC Heart Fail 2:289-97.

Example



Cardiovascular Round Table of the ESC:
How to interpret results if recurrent event analysis results differ substantially in magnitude or direction from time-to-first event analysis?

The Cardiovascular Round Table of the European Society of Cardiology (2016): Traditional and new composite endpoints in heart failure clinical trials. Eur J Heart Fail 18: 482-9.

Need for simulations

Simulation studies to investigate the effects of model misspecification, thereby

- allowing for a calendar time scale
- allowing for dependent terminal events

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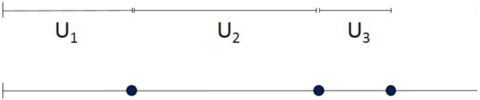
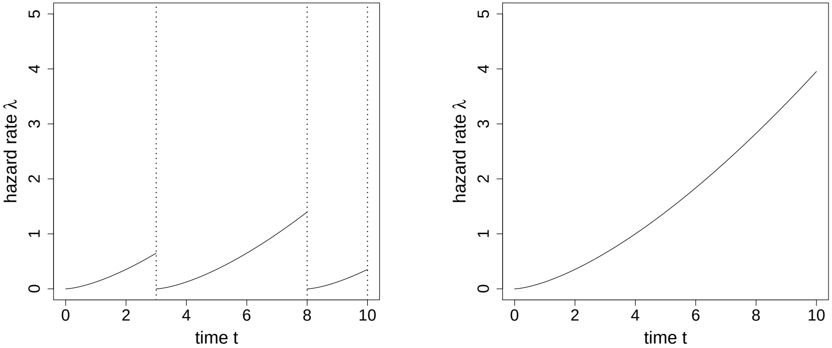
Simulation of the recurrent process





Simulation of the recurrent process

1. Define a calendar time model by specifying λ

2. Distribution of the inter-event times conditional on the calendar time of last event $U_i | T_{i-1} = t$:
   - hazard $\tilde{\lambda}_t(u) = \lambda(u + t)$
   - cumulative hazard $\tilde{\Lambda}_t(u) = \Lambda(u + t) - \Lambda(t)$

3. Use $\left(U_i | T_{i-1} = t\right) \sim \tilde{\Lambda}_t^{-1}(-\log(A))$ with $A \sim U[0,1]$

4. Simulate (a_i) from iid $U[0,1]$-distributions and recursively apply

$$
\begin{aligned}
i = 0: \qquad & t_0 := 0 \\
i - 1 \to i: \qquad & u_i := \tilde{\Lambda}_{t_{i-1}}^{-1}(-\log(a_i)) \\
& t_i := \sum_{j=1}^{i} u_i
\end{aligned}
$$

Closed form solutions

- Weibull-shaped hazard $\Lambda(t) = \lambda t^{\nu}$:

$$\tilde{\Lambda}_t^{-1}(u) = \sqrt[\nu]{\left(\frac{u + \lambda \cdot t^{\nu}}{\lambda}\right)} - t$$

- Exponential-shaped hazard $\Lambda(t) = \lambda t$:

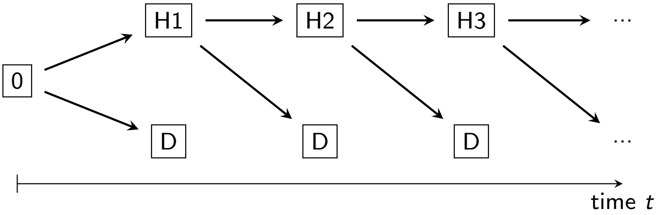
$$\tilde{\Lambda}_t^{-1}(u) = \frac{u}{\lambda}$$

- Lognormal-shaped hazard $\Lambda(t) = -\log\left(1 - \Phi\left(\frac{log(x)}{\sigma}\right)\right)$

$$\tilde{\Lambda}_t^{-1}(u) = \exp\left(-\Phi^{-1}\left(\frac{1 - \Phi\left(\frac{\log(t)}{\sigma}\right)}{\exp(u)}\right) \cdot \sigma\right) - t$$

Simulation of the competing terminal event

Nested competing risk models:

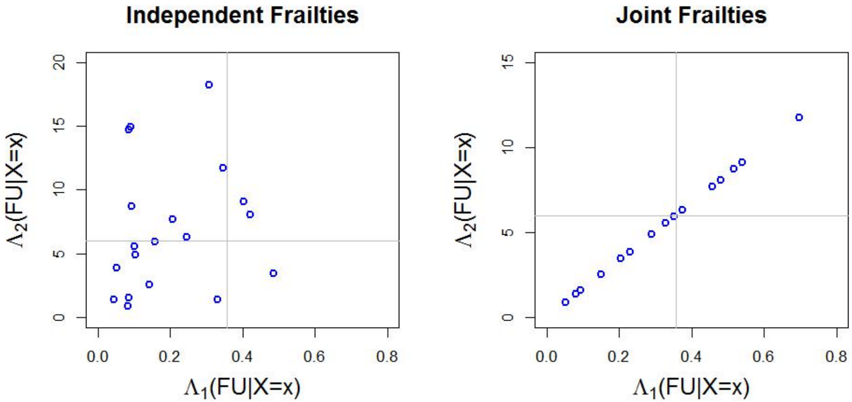


1. Simulate failure time T with all-cause-hazard $\tilde{\lambda}_t(u) + \tilde{\alpha}_t(u)$
2. Decide with probability $\frac{\tilde{\lambda}_t(u)}{\tilde{\lambda}_t(u)+\tilde{\alpha}_t(u)}$ for H
3. Continue until decision for D

Simulation of the competing terminal event

$$\text{hosp. rate:} \quad \lambda(t|Z=z,x) = z\lambda_0(t)\exp(\beta_1 x)$$

$$\text{mort. rate:} \quad \alpha(t|Z=z,x) = z\alpha_0(t)\exp(\beta_2 x)$$



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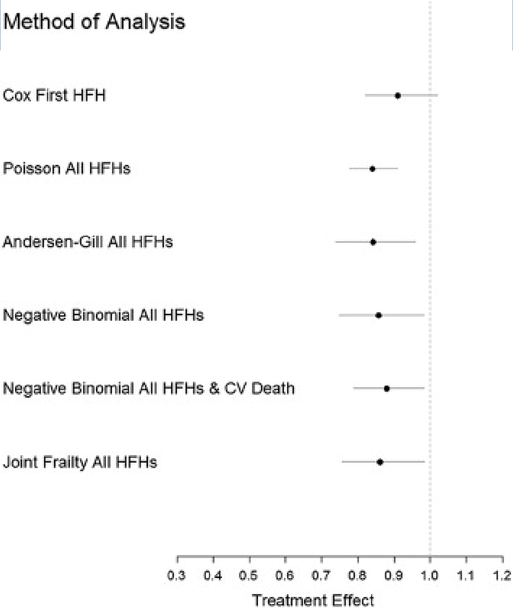
- **Application: Estimates in misspecified models**

Example



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Misspecification of conditionally independent risk processes

Simulation model: Joint Frailty Model

$$\text{hosp. rate:} \quad \lambda(t|Z=z,x) = z\lambda_0(t)\exp(\beta_1 x)$$
$$\text{mort. rate:} \quad \alpha(t|Z=z,x) = z\alpha_0(t)\exp(\beta_2 x)$$

- proportional hazards conditional on Z
- poisson property
- Gamma-distributed frailty term Z with $E(Z)=1$, $Var(Z)=\theta$
- binary covariate (intervention)

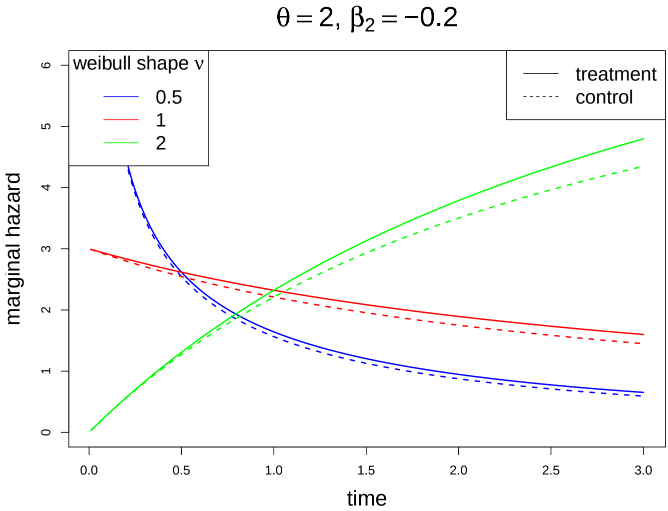
Analysis model: Indep. risk processes (cond. on covariates)

$$\text{hosp. rate:} \quad \lambda(t|x) = \lambda_0(t)\exp(\beta_1 x)$$
$$\text{mort. rate:} \quad \alpha(t|x) = \alpha_0(t)\exp(\beta_2 x)$$

Considered situation

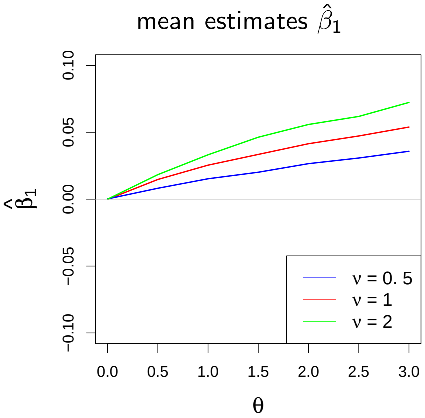
- 2 years follow-up
- Cumulative hospitalization rate at end of follow-up $\Lambda(2) = 6$ applying different Weibull shapes
- No intervention effect on hospitalization rate ($\beta_1 = 0$)
- Baseline survival rate $\alpha_0 = 0.18$ ($S(2) = 70\%$)
- Positive / no intervention effect on survival ($\beta_2 \in \{-0.2, 0\}$)
- Gamma-frailty variance $\theta \in [0, 3]$

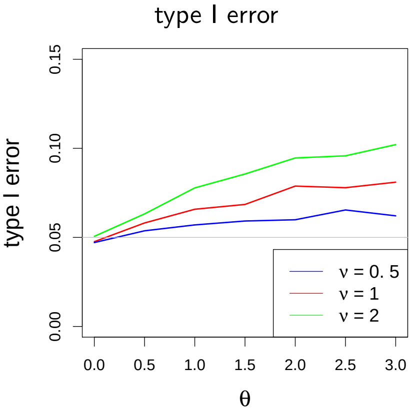
Misspecification of conditionally independent risk processes



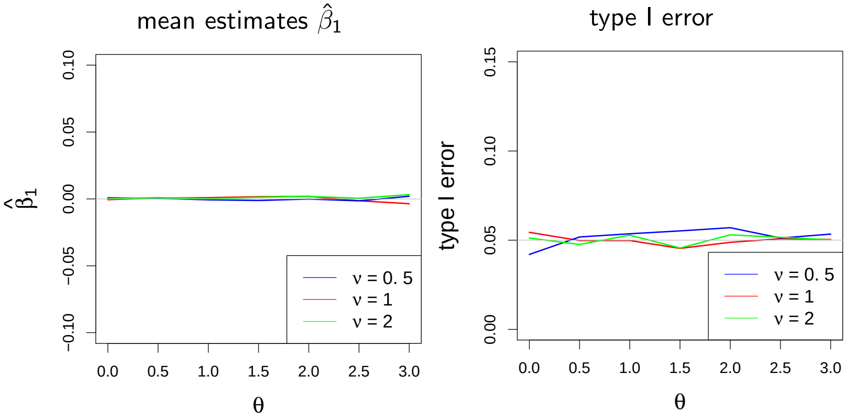
$$\lambda(t|X, D \geq t) = \lambda_0(t)exp(\beta X)E(Z|X, D \geq t)$$

Protective interventional effect on mortality ($\beta_2 = -0.2$)

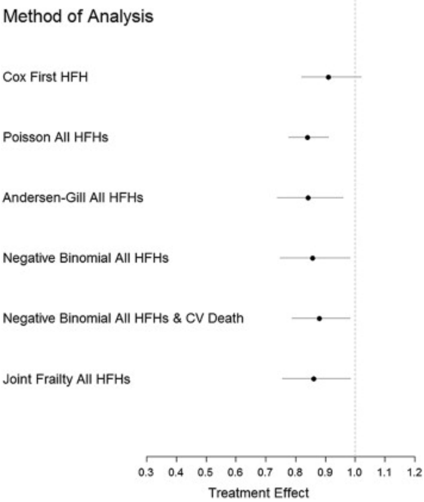




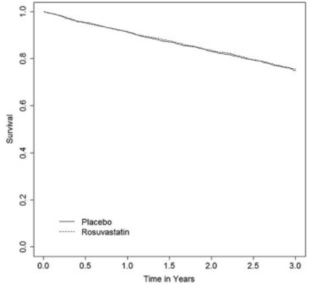
No intervention effect on survival ($\beta_2 = 0$)



Simulation results



CV death



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- Can explain the similar results between JF- and AG-analysis
- Can not explain the differences between Cox and recurrent event analyses (violation of the Poisson assumption?)

Summary

- All models are wrong but some are useful
- Simulation studies are a useful tool only if they approximate the complexity of risk processes
- Bootstrapping could complement simulation results

- Further applications: Sample size calculation where closed form solutions are not available (e.g. Joint Frailty Model)

- Code available on GitHub (katharinaingel)

Thanks to...

- Katharina Ingel, Ann-Kathrin Ozga, Stella Preussler
- Gerrit Toenges
- Harald Binder

- Contact: jahna@uni-mainz.de