Multiplicity issues in multistate models for recurrent event data subject to a competing terminal event with an application to cardiovascular disease

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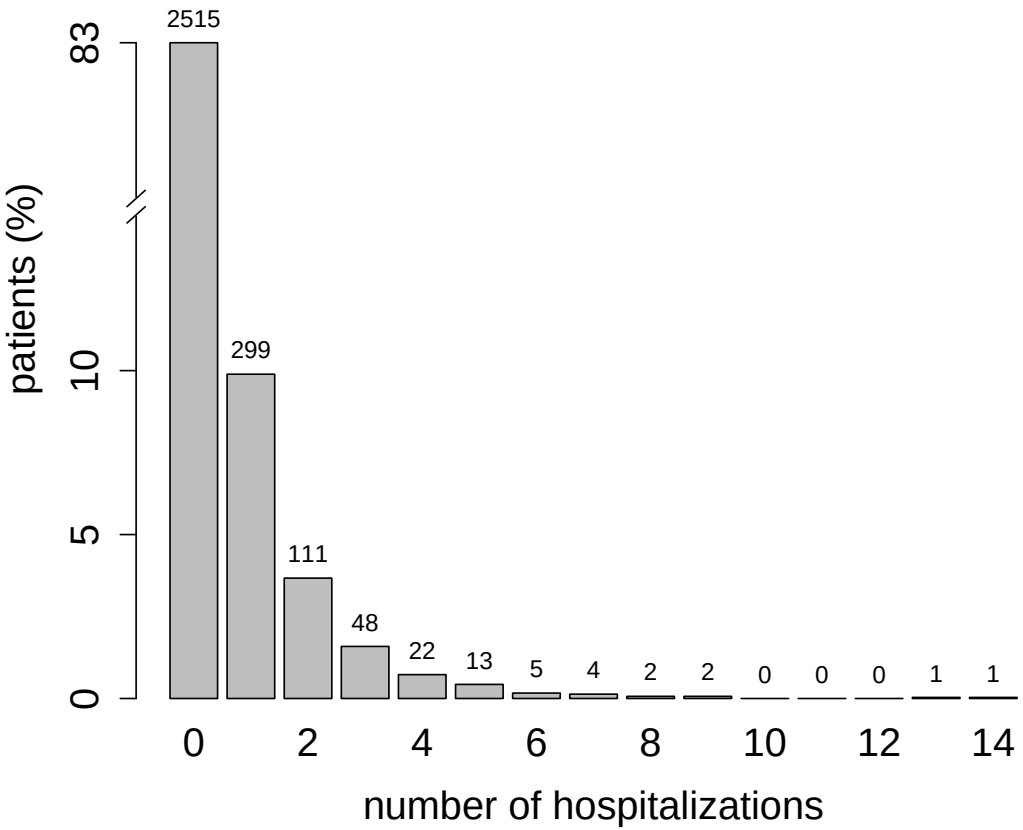
MAINZ

Heart failure hospitalizations in CHARM-Preserved trial



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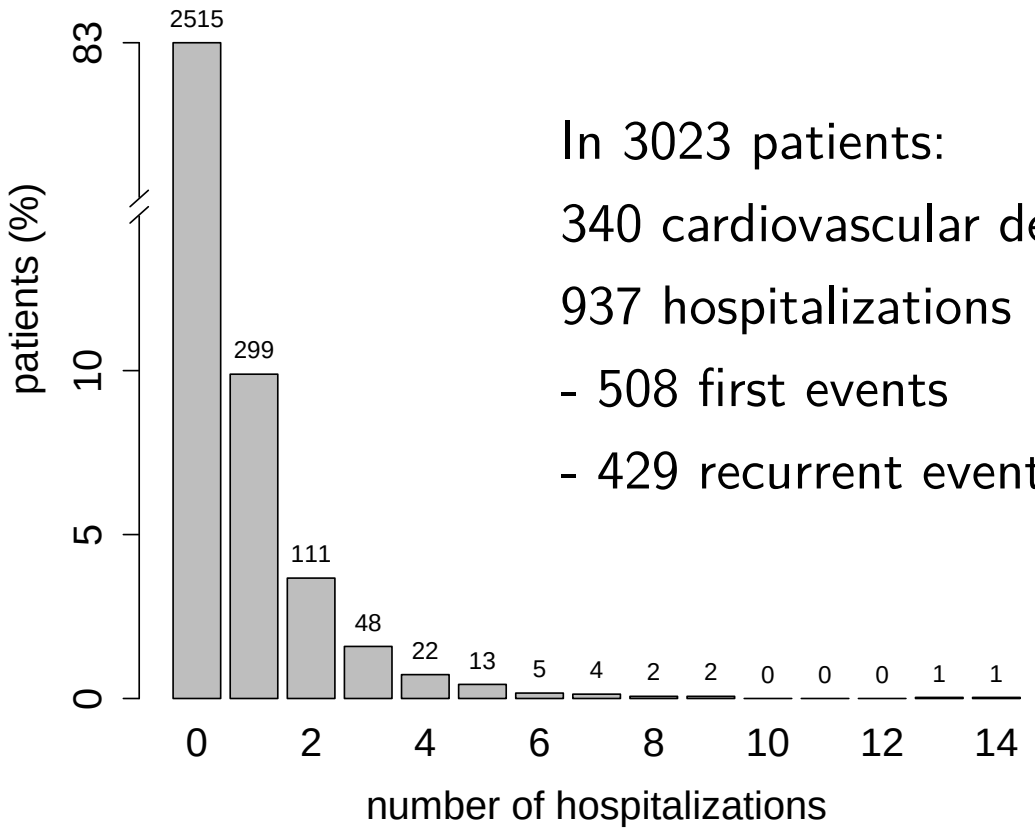

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340 cardiovascular deaths

937 hospitalizations

- 508 first events
- 429 recurrent events

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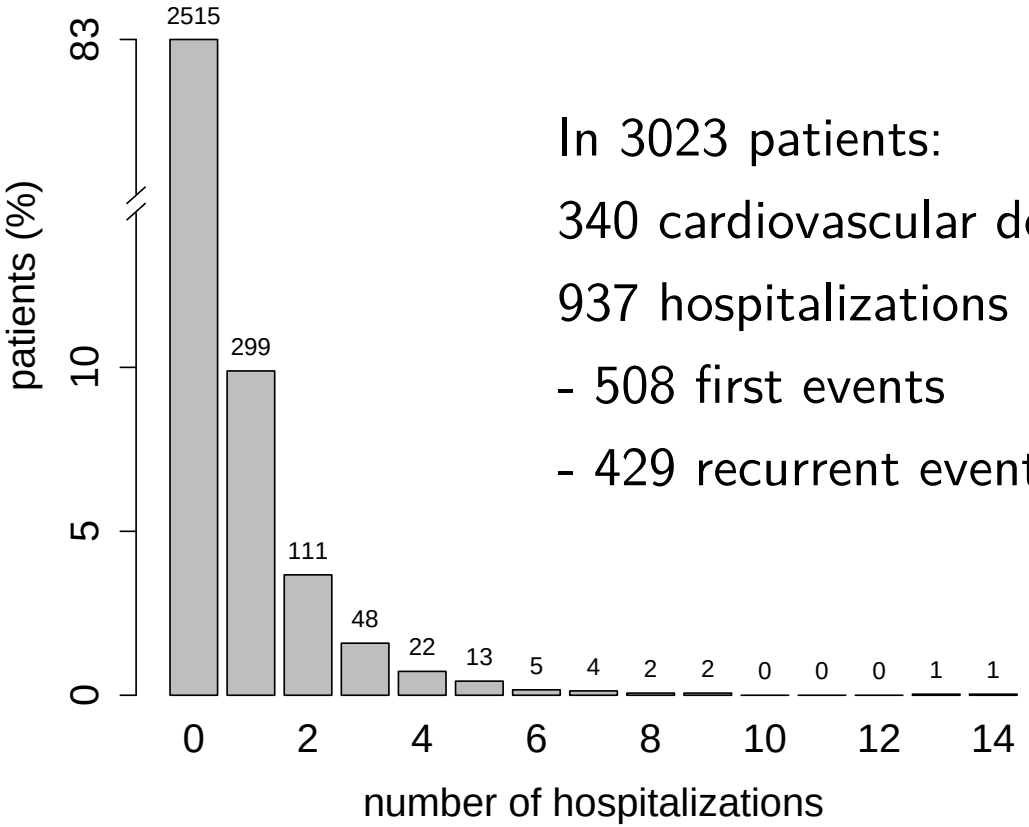

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- Inclusion of recurrent events in analysis

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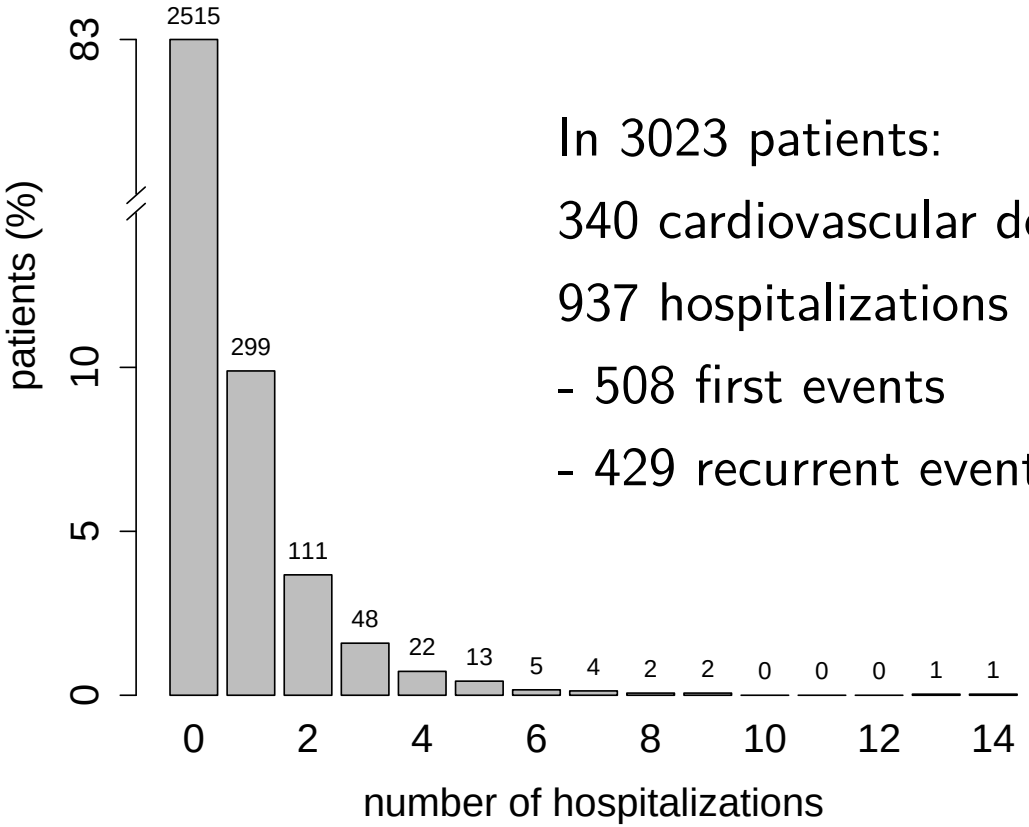

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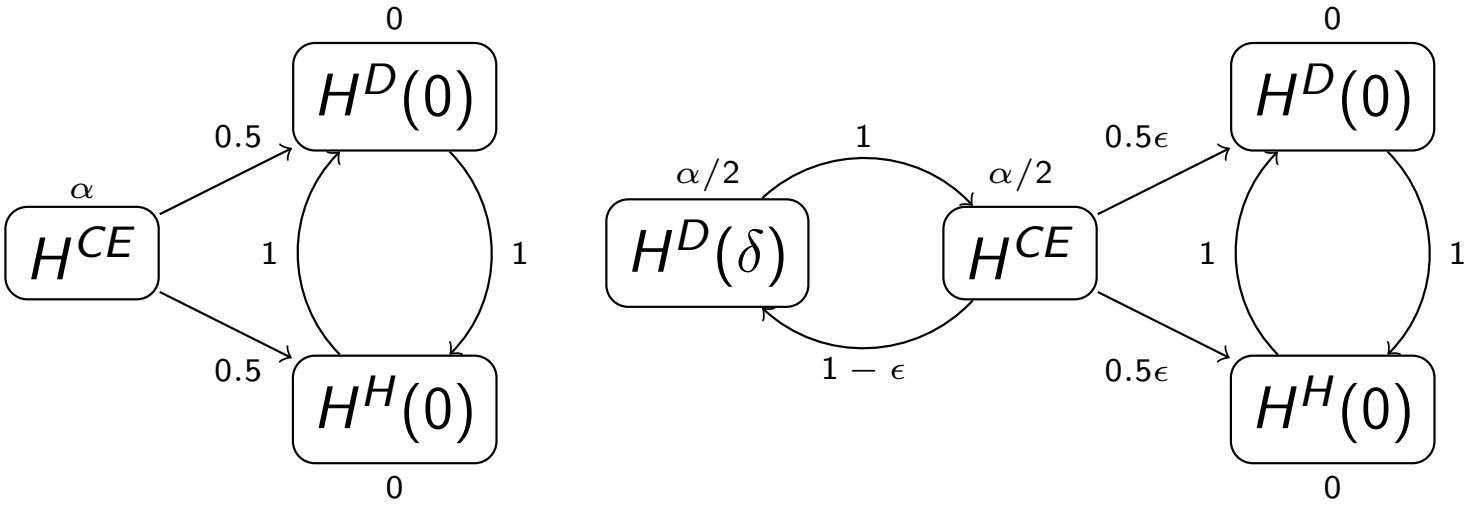
Potential sequentially rejective multiple test procedures



- H^{CE}: hypothesis on composite endpoint
- H^D: hypothesis on death rate
- H^H: hypothesis on hospitalization rate

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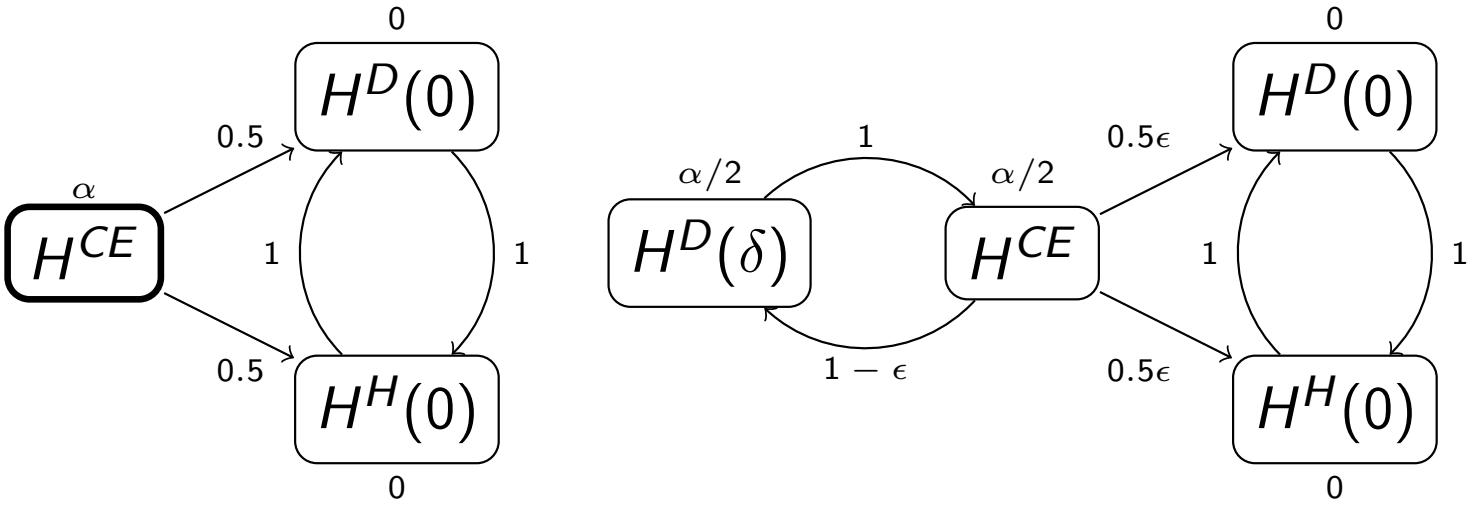

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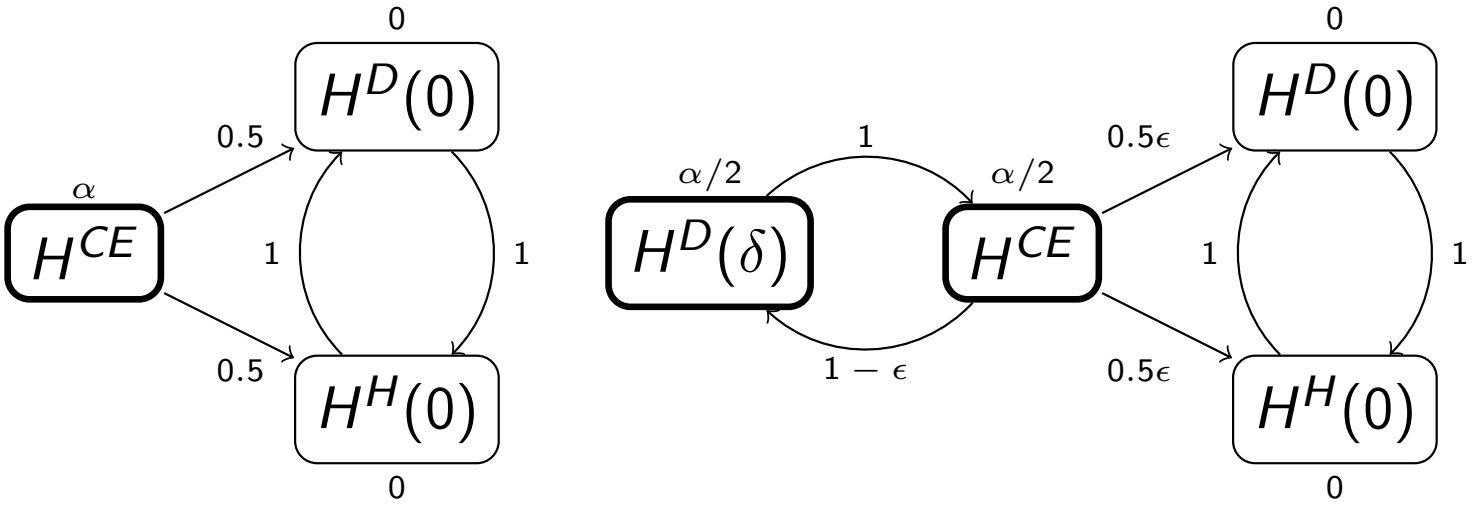

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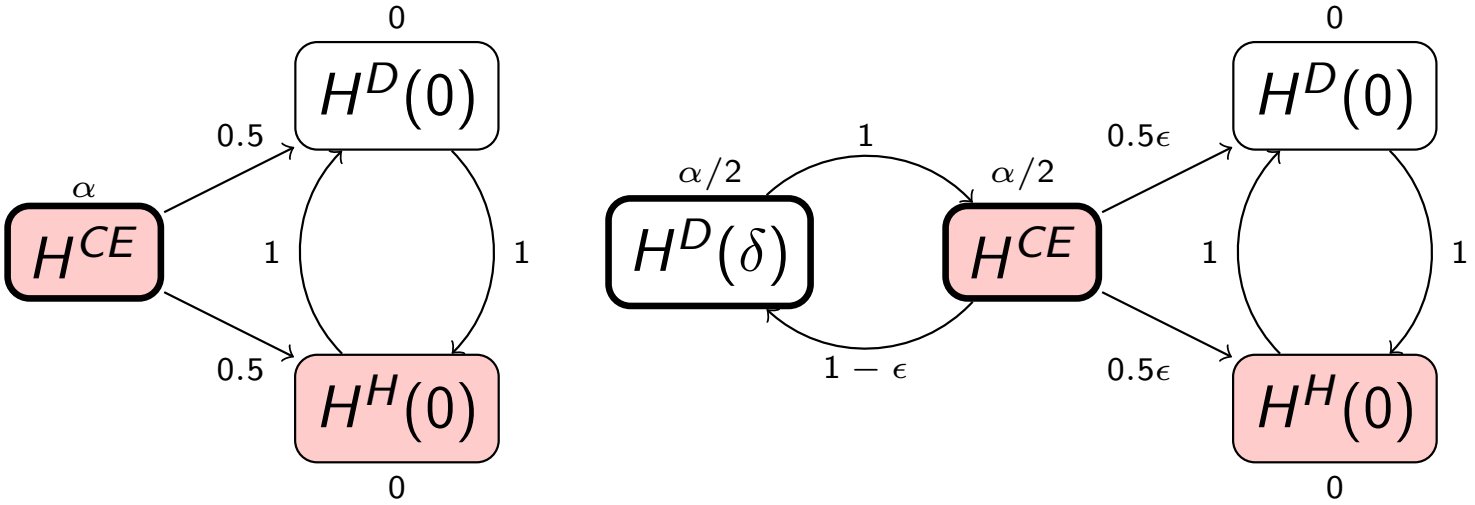

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Objective: Contrasting composite endpoint hypotheses versus global hypotheses within a multistate model

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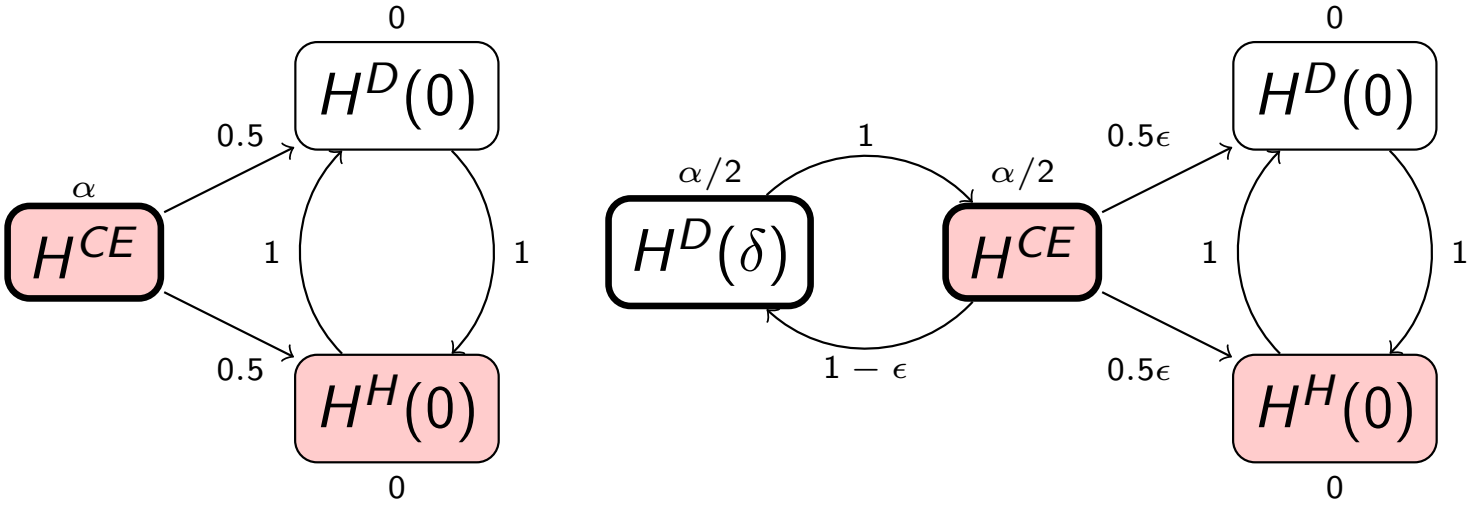

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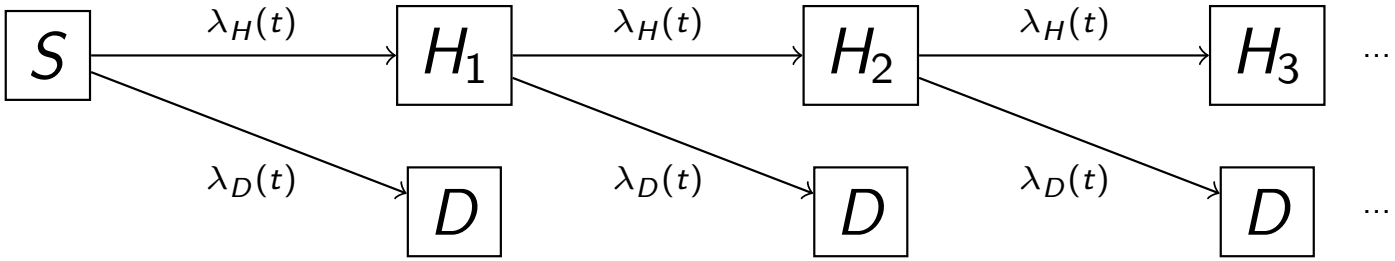

where

$$\begin{aligned} \lambda_H(t) &= \lambda_{0H}(t)\exp(\beta_H x) \\ \lambda_D(t) &= \lambda_{0D}(t)\exp(\beta_D x) \end{aligned}$$

corresponding partial likelihood

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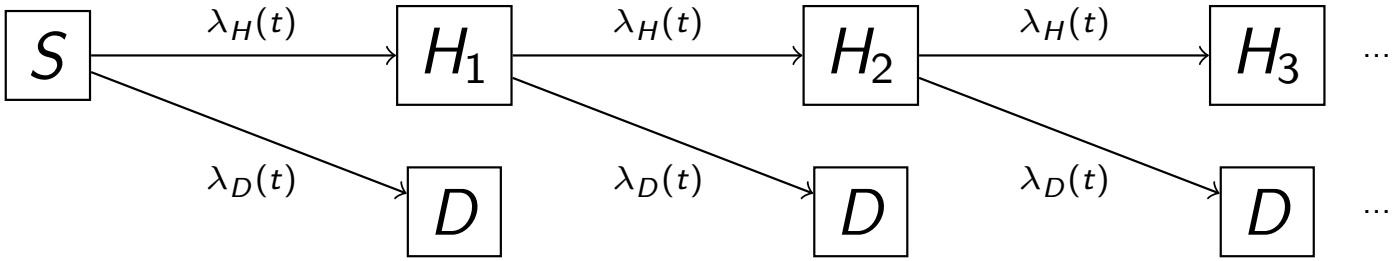

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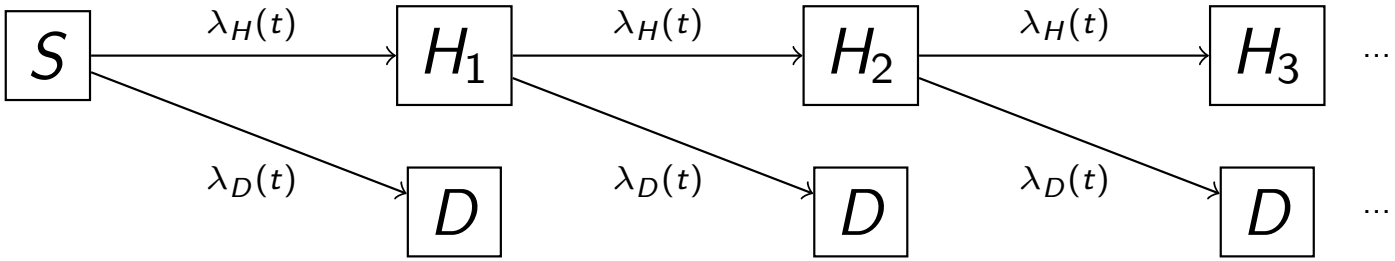
Investigation of single endpoints



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$\Rightarrow$ Investigation of H^D (β_D) and H^H (β_H) within the multistate model

Investigation of composite endpoint

- Andersen-Gill model:

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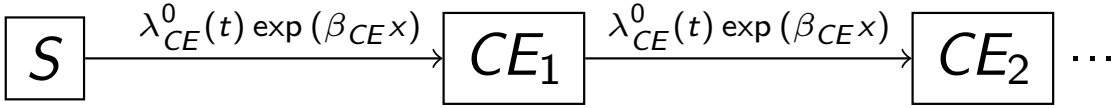

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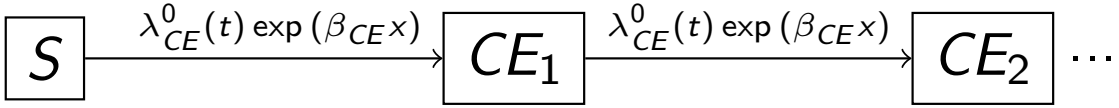

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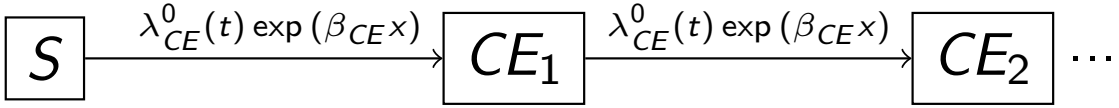

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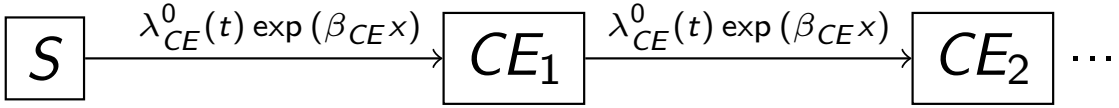

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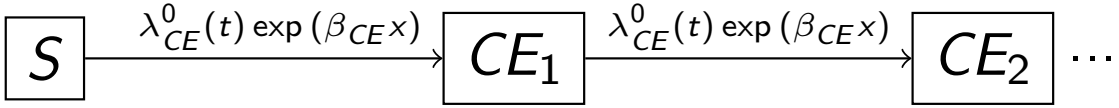

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What is gained or lost in terms of power?

$$H^D = \{\beta_D = 0\}$$
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$$H^{CE} = \{\beta_{CE} = 0 | \beta_H = \beta_D\}$$
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$\Rightarrow$ Investigate by simulation

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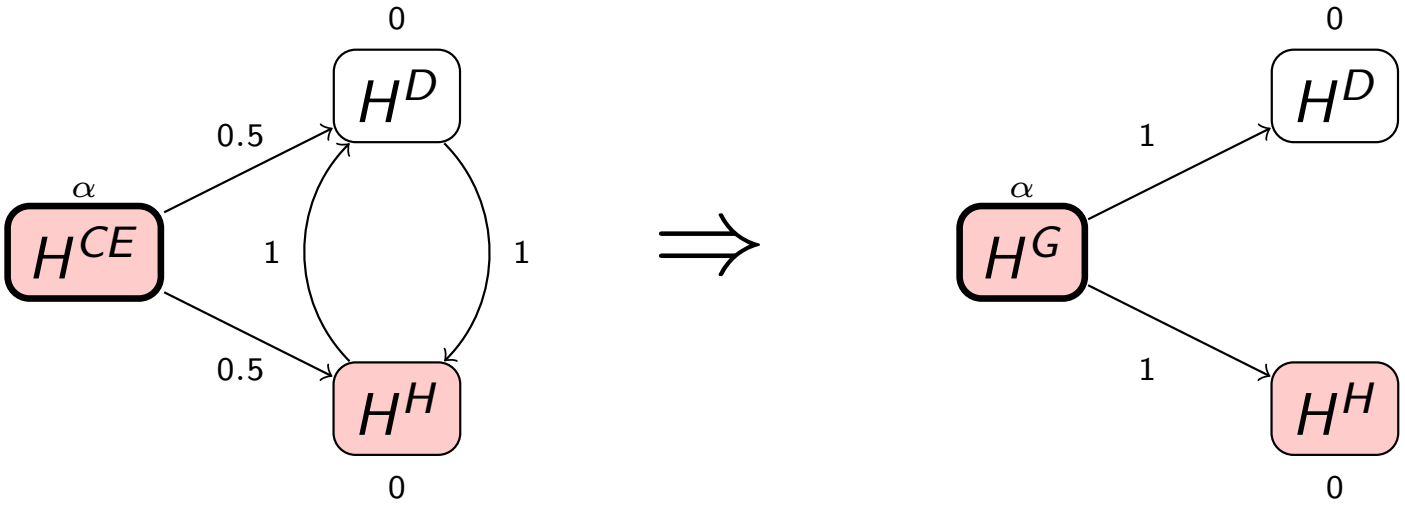

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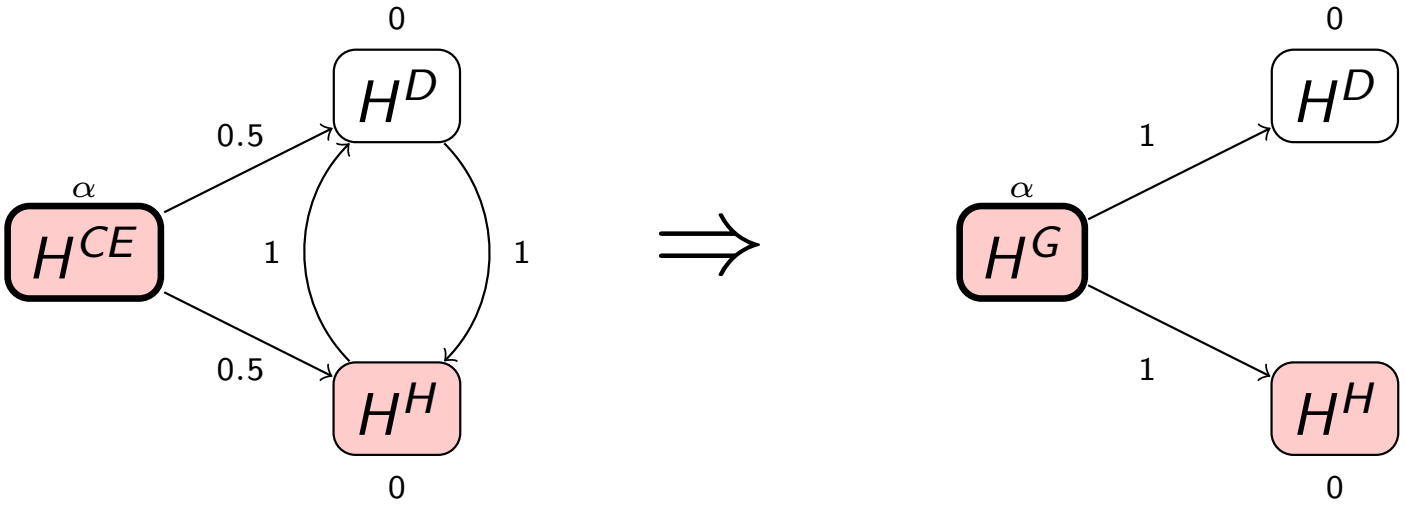

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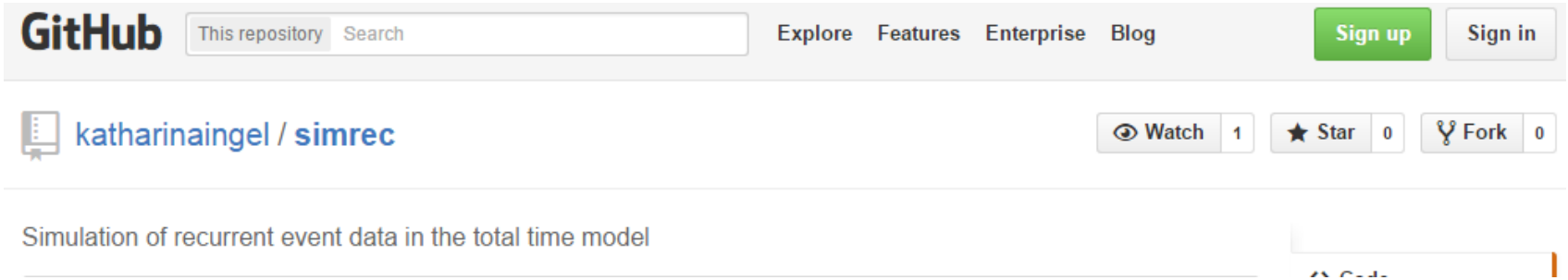

- Subjects followed for 3 years with 10% censoring
- X fixed $B(1, 0.5)$-distributed covariate coding treatment
- Transition hazards

$$\begin{aligned} \lambda_H(t|z,x) &= \lambda_H \cdot \nu \cdot t^{\nu-1} \cdot z \cdot \exp(\beta_H x) \\ \lambda_D(t|z,x) &= \lambda_D \cdot \nu \cdot t^{\nu-1} \cdot z \cdot \exp(\beta_D x) \end{aligned}$$

- 2 Simulation settings
  - $\beta_H = \log(0.7) = \beta_D$ („CE-friendly setting“)
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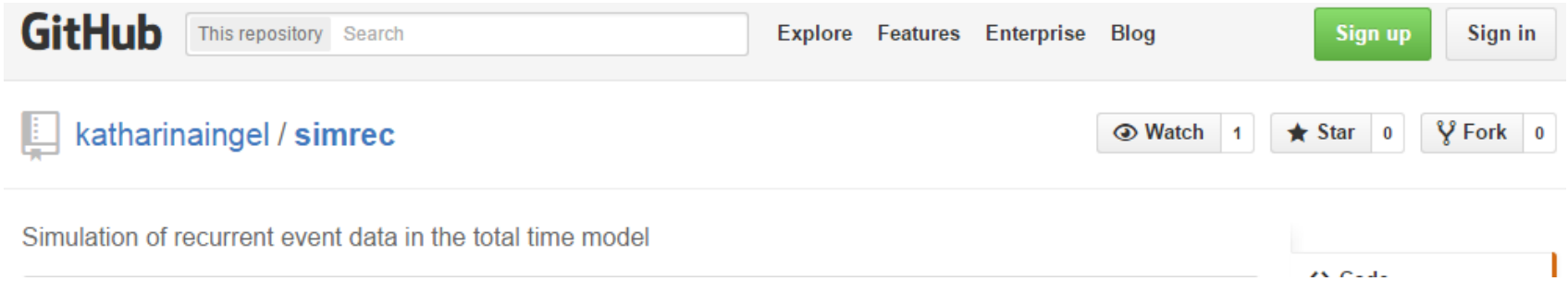

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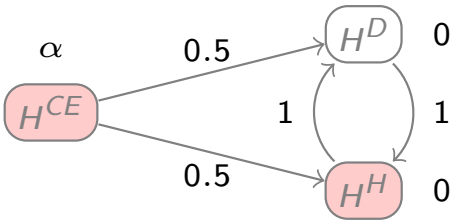
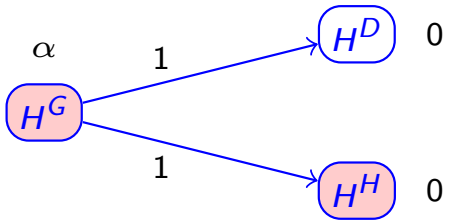
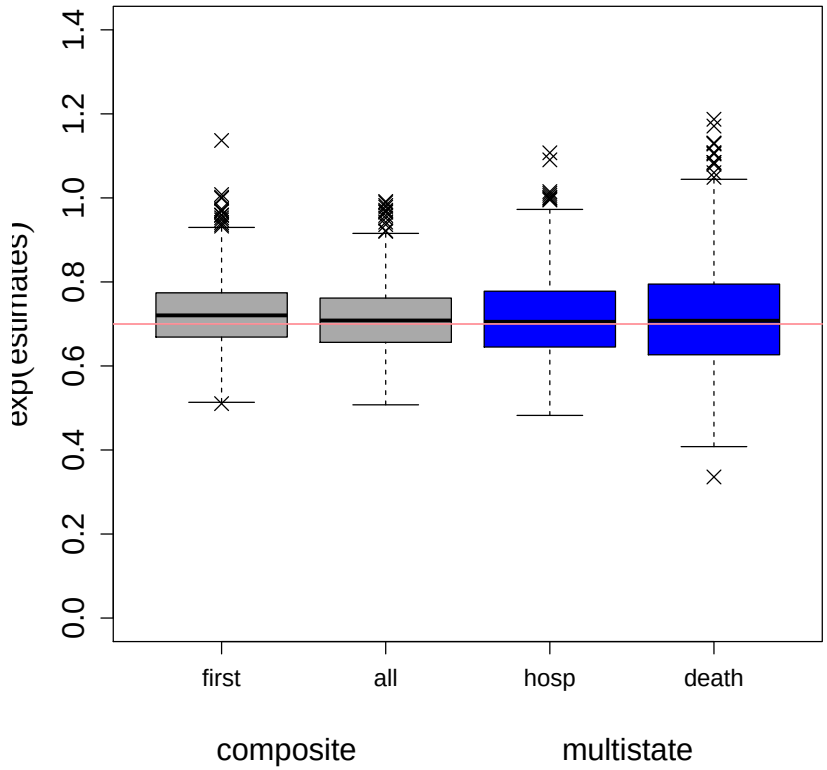
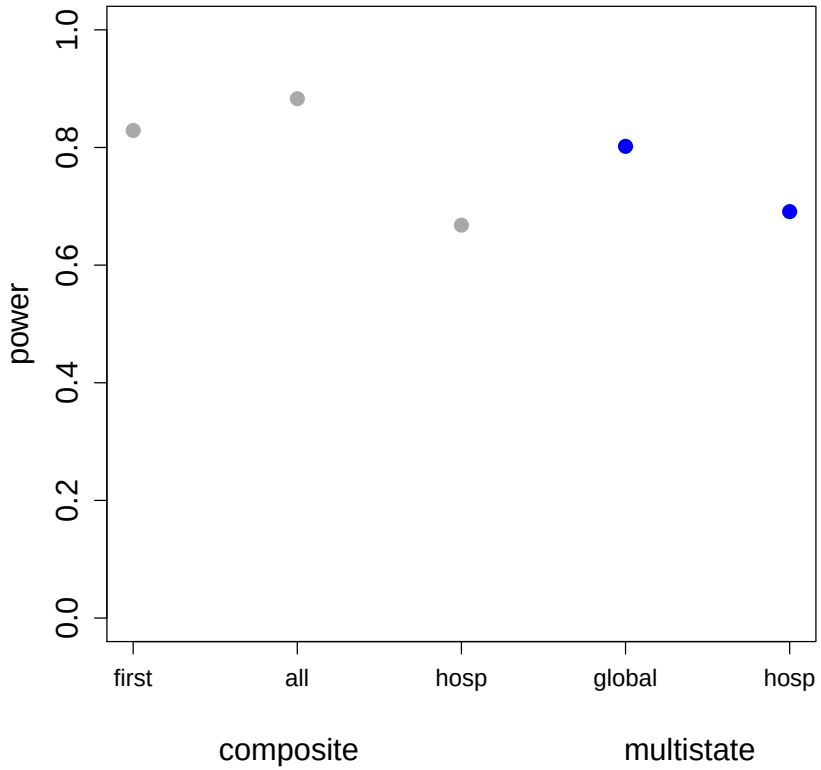
Results: $\beta_H = \log(0.7) = \beta_D$ („CE-friendly“)

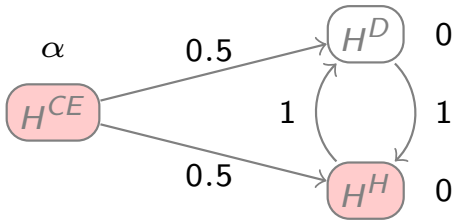


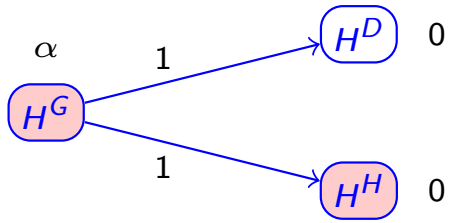


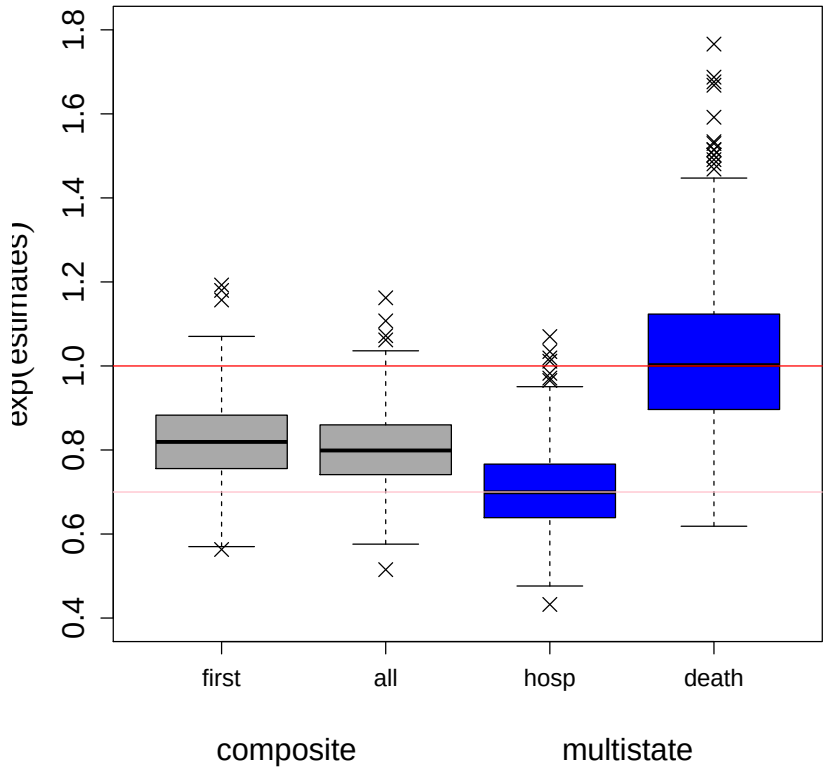


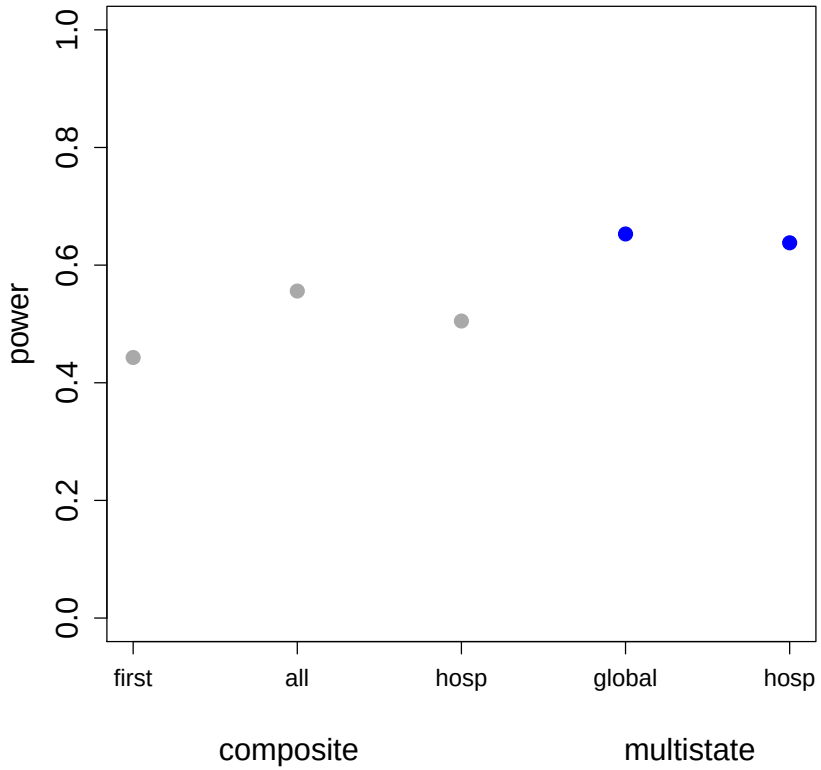


Results for $\beta_H = \log(0.7), \beta_D = 0$ (CHARM-Preserved)









Summary

- Multiple testing procedures can be improved by the use of multistate models
- Try it yourself: Download from GitHub

```
devtools::install_github("katharinaingel/simrec")
simres <- simreccomp(N,fu.min,fu.max,cens.prob=0,...)
```

- Contact: spreussl@students.uni-mainz.de

Settings of simulation data

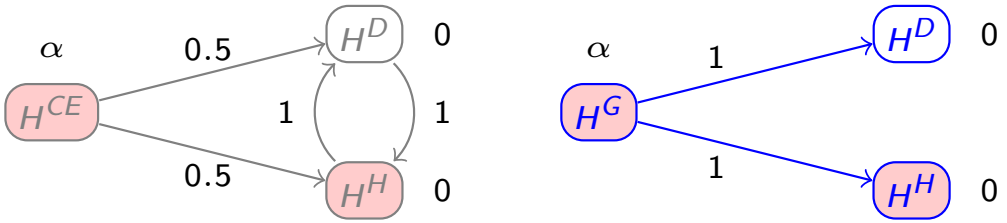
- $\nu = 0.5$ shape parameter for weibull hazard for hosp. and death
- scale parameter for weibull hazard
  - $\lambda_H = 3^{0.5} * \frac{\#events}{\#patients} = 3^{0.5} * \frac{547}{1509} = 0.2092847$
  - $\lambda_D = 0.1$
- frailty term: $z \sim \Gamma(\theta = 0.5)$
- nsim $= 1000$
- N $= 1000$
- $P(death \leq 3) = 1 - exp(-0.1 * 3^{0.5}) = 0.1590349$

The CHARM-Preserved Trial

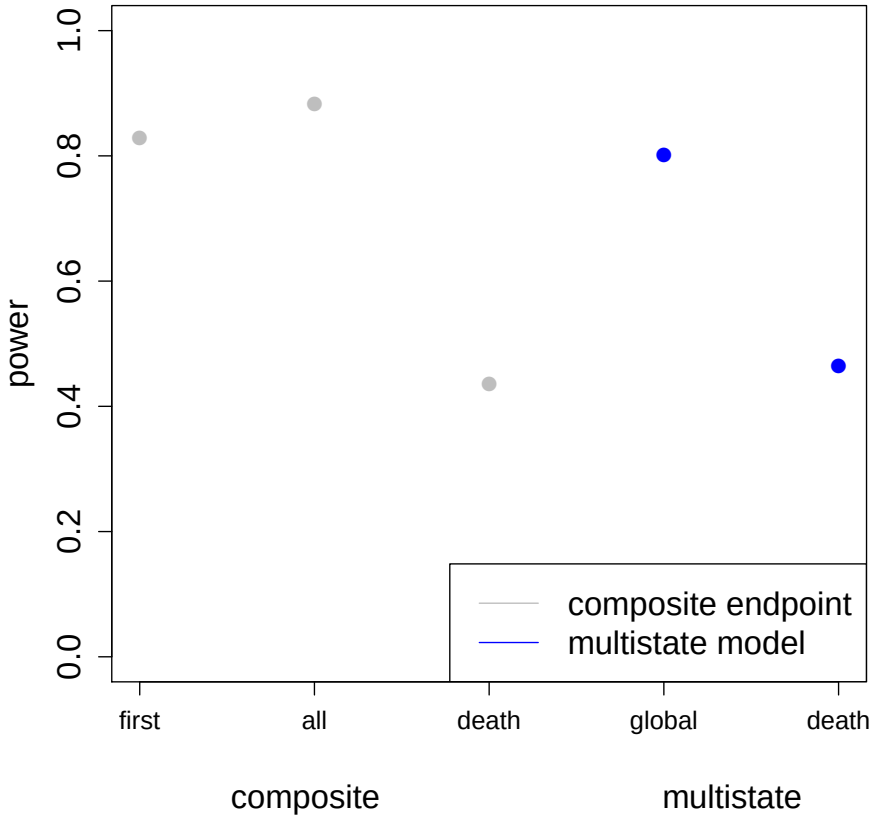
- „Between March, 1999, and July, 2000, we randomly assigned 3023 patients candesartan ($n = 1514$, target dose 32 mg once daily) or matching placebo ($n = 1509$) [double-blind]. Patients had New York Heart Association functional class II-IV CHF and LVEF higher than 40%.“
- „...we tested the hypothesis that another inhibitor of the renin-angiotensin system, an angiotensin-receptor blocker, candesartan, would be of benefit in patients with CHF and preserved LVEF. The primary goal was to assess the effects of candesartan on the composite outcome of cardiovascular mortality or admission to hospital for worsening CHF.“
- „Candesartan has a moderate impact in preventing admissions for CHF among patients who have heart failure and LVEF higher than 40%.“

Yusuf S et al. (2003): Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777-781.

Results: Power of H^D in simulation

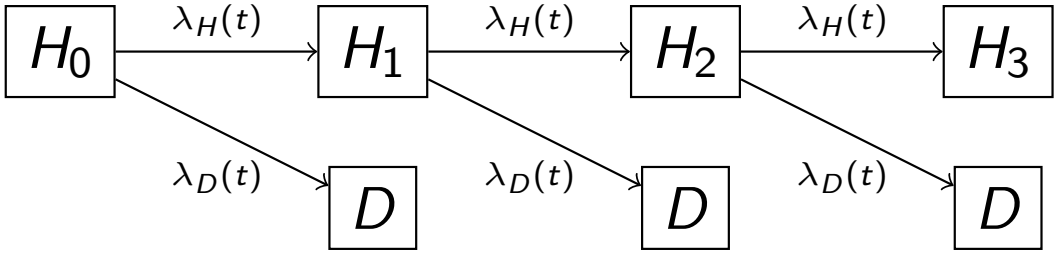


$\beta^H = \log(0.7) = \beta^D$



CE model = MS model with constraint

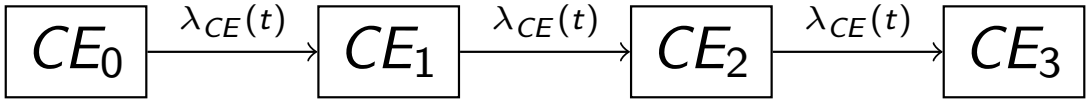
- Multistate model



$$\cdots \quad \lambda_H(t) = \lambda_{0H}(t)\exp(\beta_H x)$$

$$\cdots \quad \lambda_D(t) = \lambda_{0D}(t)\exp(\beta_D x)$$

- Composite endpoint model



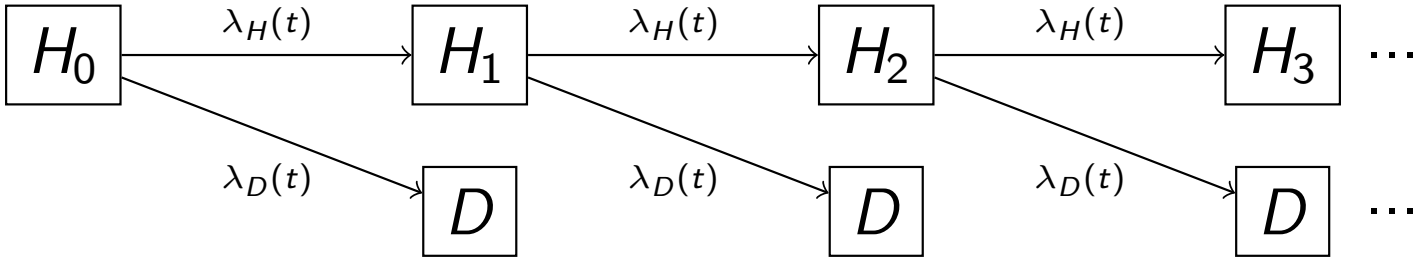
$$\cdots \quad \lambda_C E(t) = \lambda_{0CE}(t)\exp(\beta_{CE} x)$$

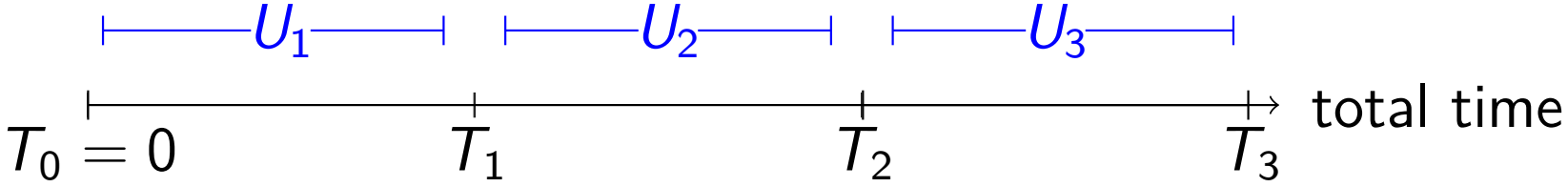
- Comparison of MS and CE model:

$$\begin{aligned}
\lambda_{0CE}(t)\exp(\beta_{CE}x) &= \lambda_{CE}(t) \stackrel{!}{=} \lambda_H(t) + \lambda_D(t) \\
&= \lambda_{0H}(t)\exp(\beta_H x) + \lambda_{0D}(t)\exp(\beta_D x) \\
&= \stackrel{\beta_H=\beta_D=\beta_{CE}}{} [\lambda_{0H}(t) + \lambda_{0D}(t)]\exp(\beta_{CE}x)
\end{aligned}$$

$\Rightarrow$ MS model = CE model with constraint $\beta_H = \beta_D = \beta_{CE}$

Simulation algorithm





1. Simulate inter-event time U_{H_1}
2. Recursive step: Simulate inter-event time $U_{H_{i+1}}$ conditional on T_i

$$U_{H_i,H_{i+1}} | T_i = t_i \quad \sim \quad \Lambda^{-1}_{H,t_i}(-log(A)), \quad A \sim U[0,1]$$

3. Analogue:

$$U_{D_i,D_{i+1}} | T_i = t_i \quad \sim \quad \Lambda^{-1}_{D,t_i}(-log(A)), \quad A \sim U[0,1]$$

Closed form solutions

Model	$\Lambda_H(t)$	$\Lambda^{-1}_{H,t_i}(u)$
Exponential	λt	$\frac{u}{\lambda}$
Weibull	λt^ν	$\sqrt[\nu]{\left(\frac{u+\lambda \cdot t_i^\nu}{\lambda}\right)} - t_i$
Gompertz	$\frac{\lambda}{\alpha}(\exp(\alpha t) - 1)$	$\frac{1}{\alpha}\log\left(\frac{\alpha}{\lambda}u + \exp(\alpha t_i)\right) - t_i$