Simulating competing risks data in survival analysis.

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- Survival & competing risks analyses are hazard-based.

- Literature review: What is the problem with *simulating* competing risks data?

- Cause-specific hazards-based simulation design

- Application: Numerical approximation of time-averaged effect on the cumulative event probability.

  Connected to the usual interpretational difficulties that come with competing risks.

Survival analysis is hazard-based.

- Process $(X_t)_{t \geq 0}$, $X_t \in \{0, 1\}$, $P(X_0 = 0) = 1$

- Survival time $T = \inf\{t \,|\, X_t \neq 0\}$, censoring time C: $T \wedge C$, $\mathbf{1}(T \leq C)$

- Modeling and inference is based on the hazard

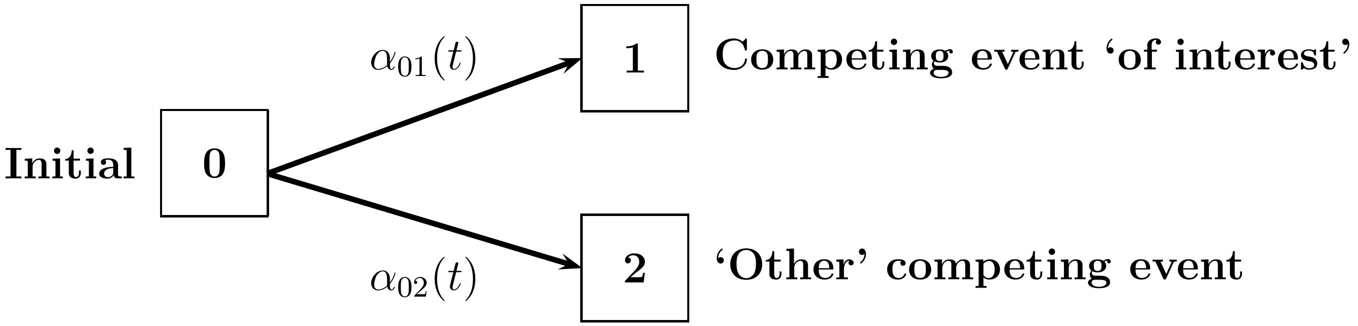
$$\alpha(t)\mathrm{d}t = P(T \in \mathrm{d}t \,|\, T \geq t)$$

  because it remains 'undisturbed' by censoring.

- E.g. Kaplan-Meier is a product over 1 minus empirical hazards.

- Simulation:
  - Specify $\alpha(t)$.
  - Simulate event times T with $P(T > t) = \exp(-\int_0^t \alpha(u)\mathrm{d}u)$.
  - Simulate censoring times.

Competing risks: Cause-specific hazards (CSHs).



- $X_t \in \{0, 1, 2\}, \ P(X_0 = 0) = 1$
- Survival time $T = \inf\{t \,|\, X_t \neq 0\}$, failure cause $X_T \in \{1, 2\}$
- The CSHs $\alpha_{0i}(t)$ completely determine the stochastic behaviour of the competing risks process,

$$\alpha_{0i}(t)\mathrm{d}t = P(T \in \mathrm{d}t, X_T = i \,|\, T \geq t), \ i = 1, 2.$$

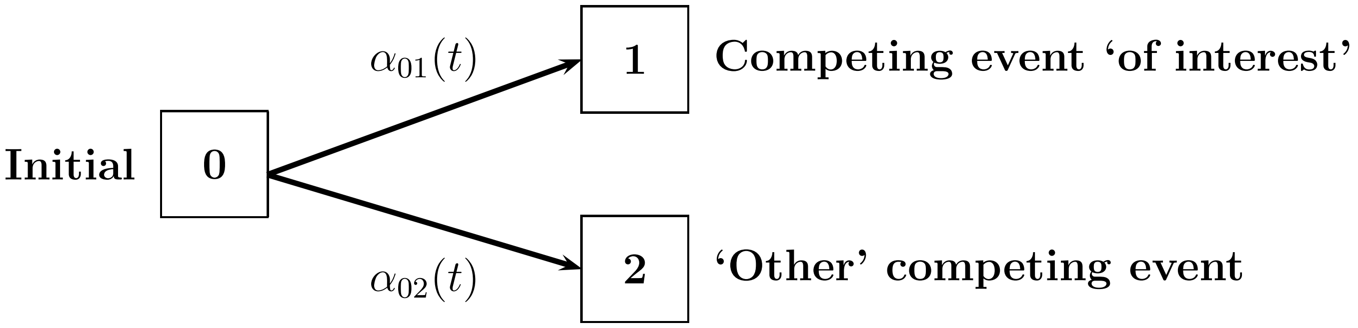
- Survival function $P(T > t) = \exp(-\int_0^t \alpha_{01}(u) + \alpha_{02}(u)\mathrm{d}u)$.
- Cumulative incidence functions $P(T \leq t, X_T = i) = \int_0^t P(T > u-)\, \alpha_{0i}(u)\, \mathrm{d}u$, $i = 1, 2$.
- Competing risks simulations: CSHs only rarely used.

Competing risks simulations since 2000.

Journal	# Articles	Constant CSHs	Latent failure	Conditional on cause	Other
B'trics	19	1 (5.3%)	14 (73.7%)	2 (10.5%)	3 (15.8%)
B'trika	9	2 (22.2%)	3 (33.3%)	4 (44.4%)	1 (11.1%)
CSDA	4	0 (0%)	3 (75%)	1 (25%)	0 (0%)
LiDA	9	1 (11.1%)	7 (77.8%)	1 (11.1%)	0 (0%)
SiM	25	3 (12%)	15 (60%)	3 (12%)	4 (16%)

- 56%–90% of all competing risks papers with simulations.
- CSHs: rarely used, only constant CSHs used.
- Constant hazards often a too simple model.
- Latent failure times mostly used:
  - **Hypothetical** latent cause-specific times
  - Dependency structure **not empirically identifiable**

Simulation: the way CSHs generate competing risks data.



1. Specify the CSHs $\alpha_{01}(t)$ and $\alpha_{02}(t)$.

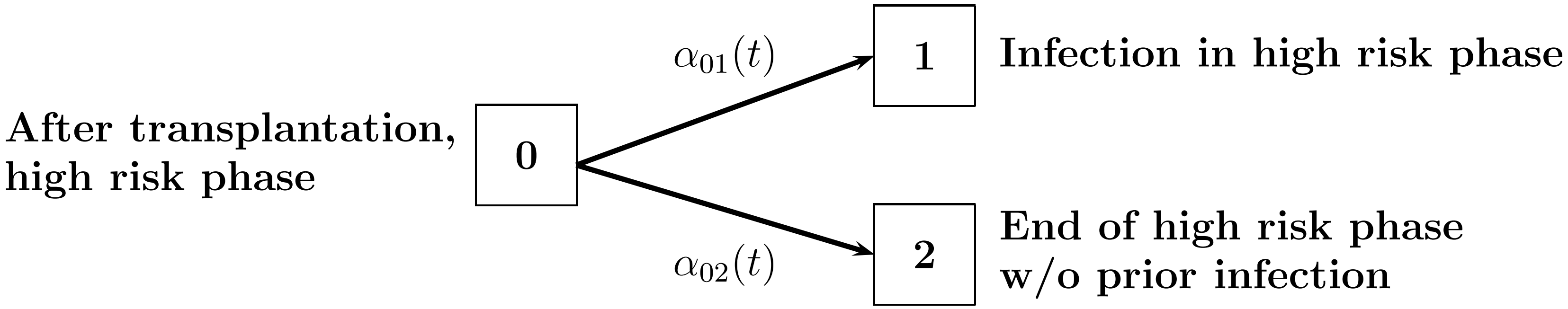
2. Simulate survival time T with all-cause hazard $\alpha_{0\cdot}(t) = \alpha_{01}(t) + \alpha_{02}(t)$.

3. Decide on cause $X_T = 1$ with binomial probability $\alpha_{01}(T)/\alpha_{0\cdot}(T)$.

4. Generate censoring times C.

- As easy as any other simulation design.

Motivating example for simulation study: infectious complications in stem-cell transplantated patients.



After transplantation, high risk phase

0

$\alpha_{01}(t)$

1 **Infection in high risk phase**

$\alpha_{02}(t)$

2 **End of high risk phase w/o prior infection**

- Physicians know: Allogeneic transplants ($Z = 1$) lead to more infections than autologous transplants ($Z = 0$).

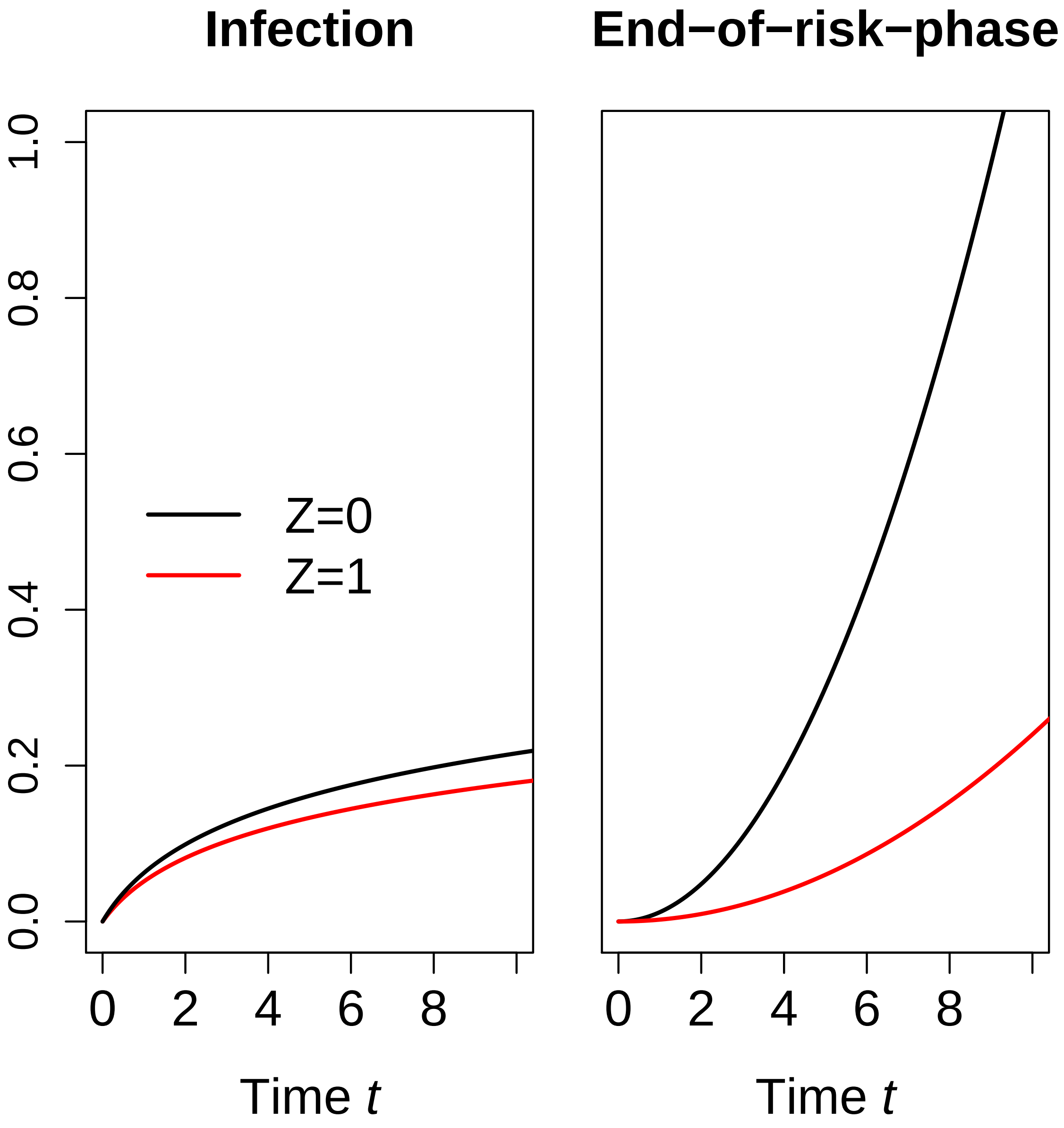
- Proportional CSHs specification, motivated by ONKO-KISS data, but with emphasis on simple functional form, $P(Z = 1) = 0.565$:

$$\text{Autologous: } \alpha_{01;Z=0}(t) = \frac{0.09}{t+1} \quad \& \quad \alpha_{02;Z=0}(t) = 0.024 \cdot t$$

$$\text{Allogeneic: } \alpha_{01;Z=1}(t) = 0.825 \cdot \alpha_{01;Z=0}(t) \quad \& \quad \alpha_{02;Z=1}(t) = 0.2 \cdot \alpha_{02;Z=0}(t).$$

- Allogeneic transplants ($Z = 1$) reduce the infection-CSH, but lead to more infections.

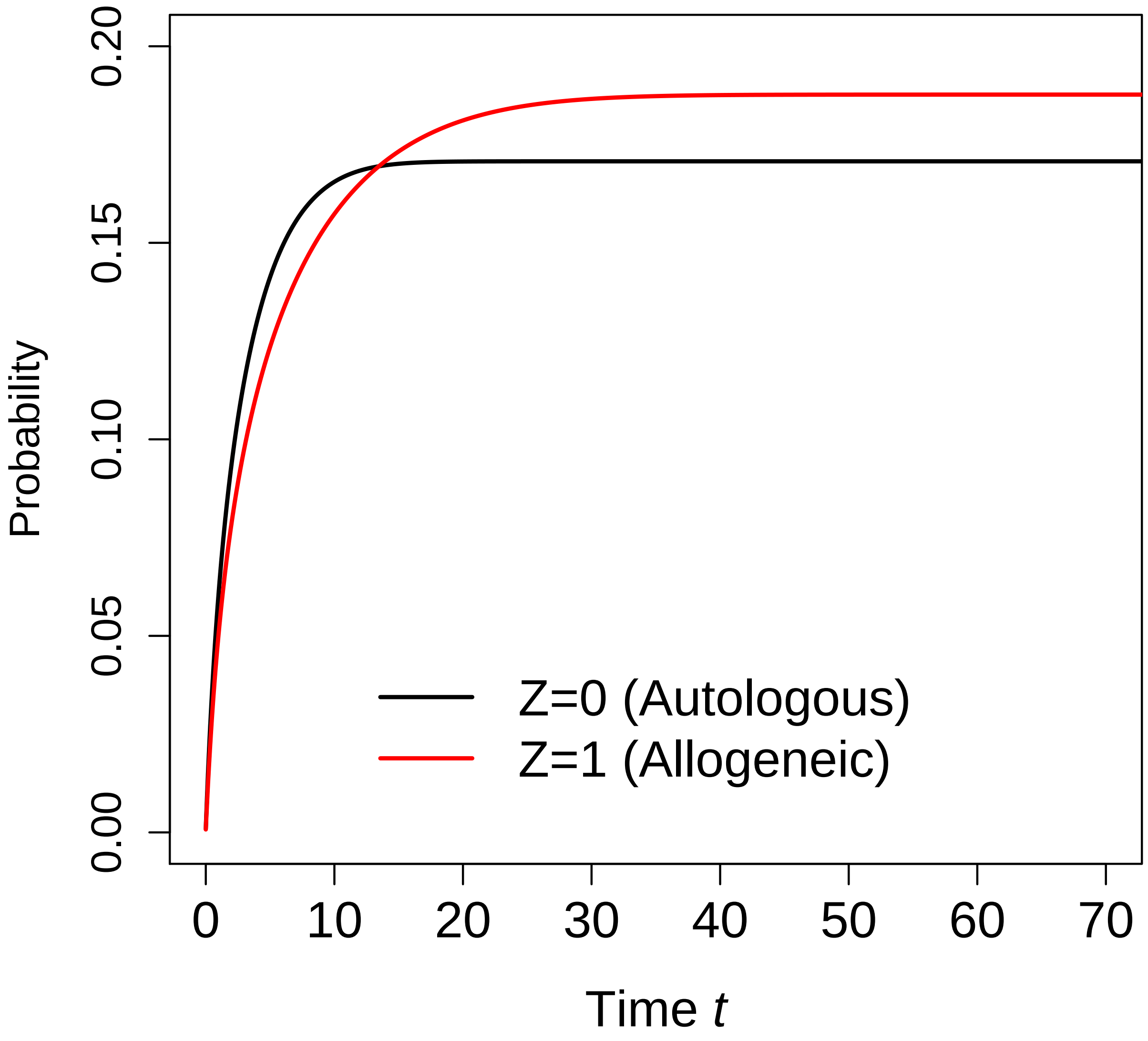
Cumulative cause-specific hazards for . . .



$Z = 1$ (allogeneic transplant): longer at risk, exposed to an only slightly reduced infection CSH.

Cumulative incidence functions (CIF)

$P(T \le t, X_T = 1 \,|\; Z = 1\;)$ **for infection eventually higher.**



Infections occur early: binomial simulation experiment argument.

Interpretational obstacles led to <u>direct</u> CIF modelling.

- Popular approach: subdistribution hazard (SH) $\lambda(t)$ such that

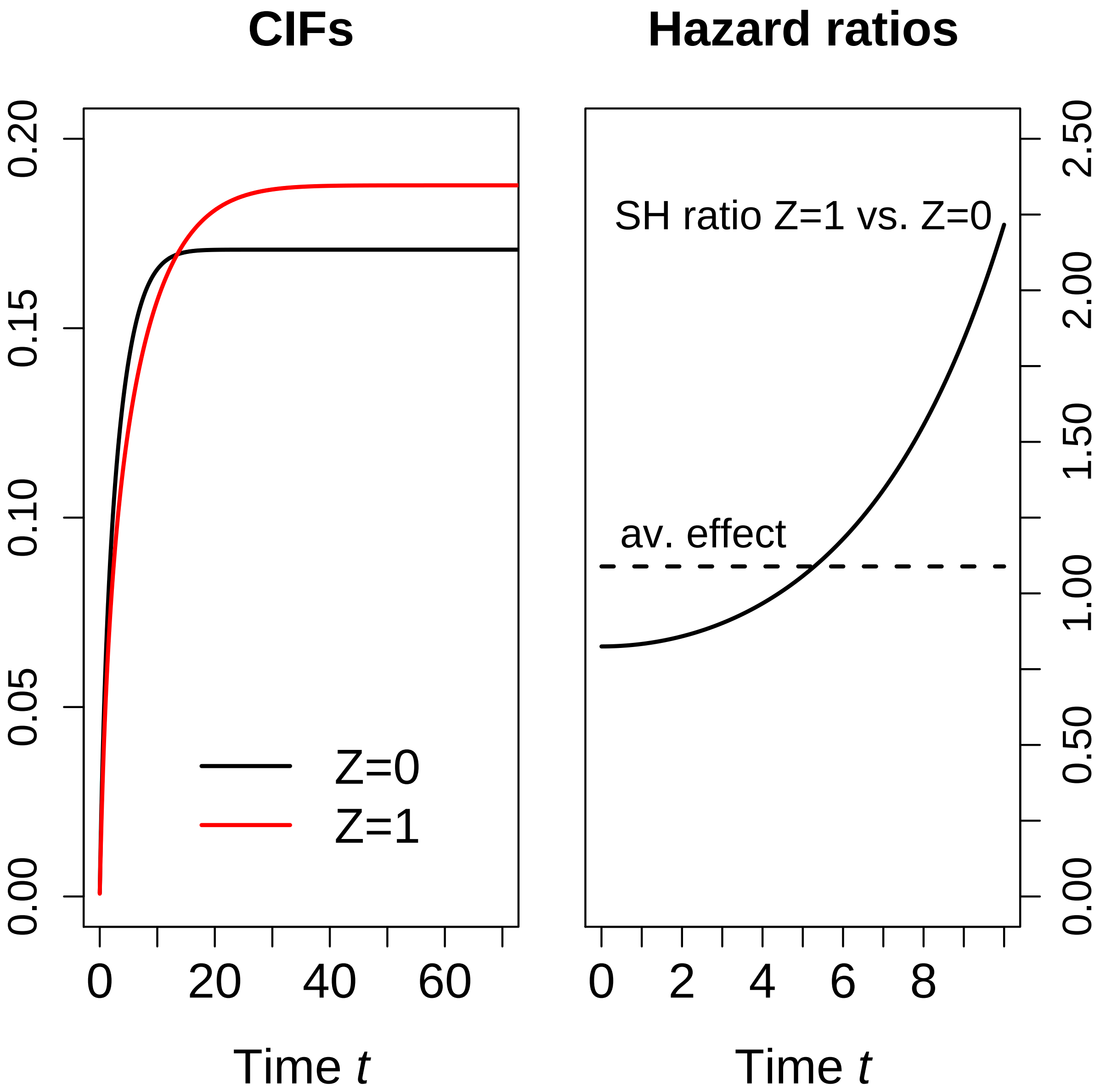
$$P(T \leq t, X_T = 1) \overset{!}{=} 1 - \exp(-\int_0^t \lambda(u) \mathrm{d}u)$$

- Fine & Gray (JASA 1999): proportional SH model.

- Misspecified under the usual proportional CSHs assumption.

- But a proportional SH analysis yields consistent estimate of a **time-averaged effect: least false parameter (LFP)**. (Hjort, Int Stat Rev 1992)

Time-dependent and average effect of $Z = 1$ on CIF.



Time-averaged effect LFP only implicitly given.

Approximate via simulation.

Numerical approximation of LFP: simulate until close enough to the truth.

- Aim of a numerical approximation: each simulation with 10000 individuals.

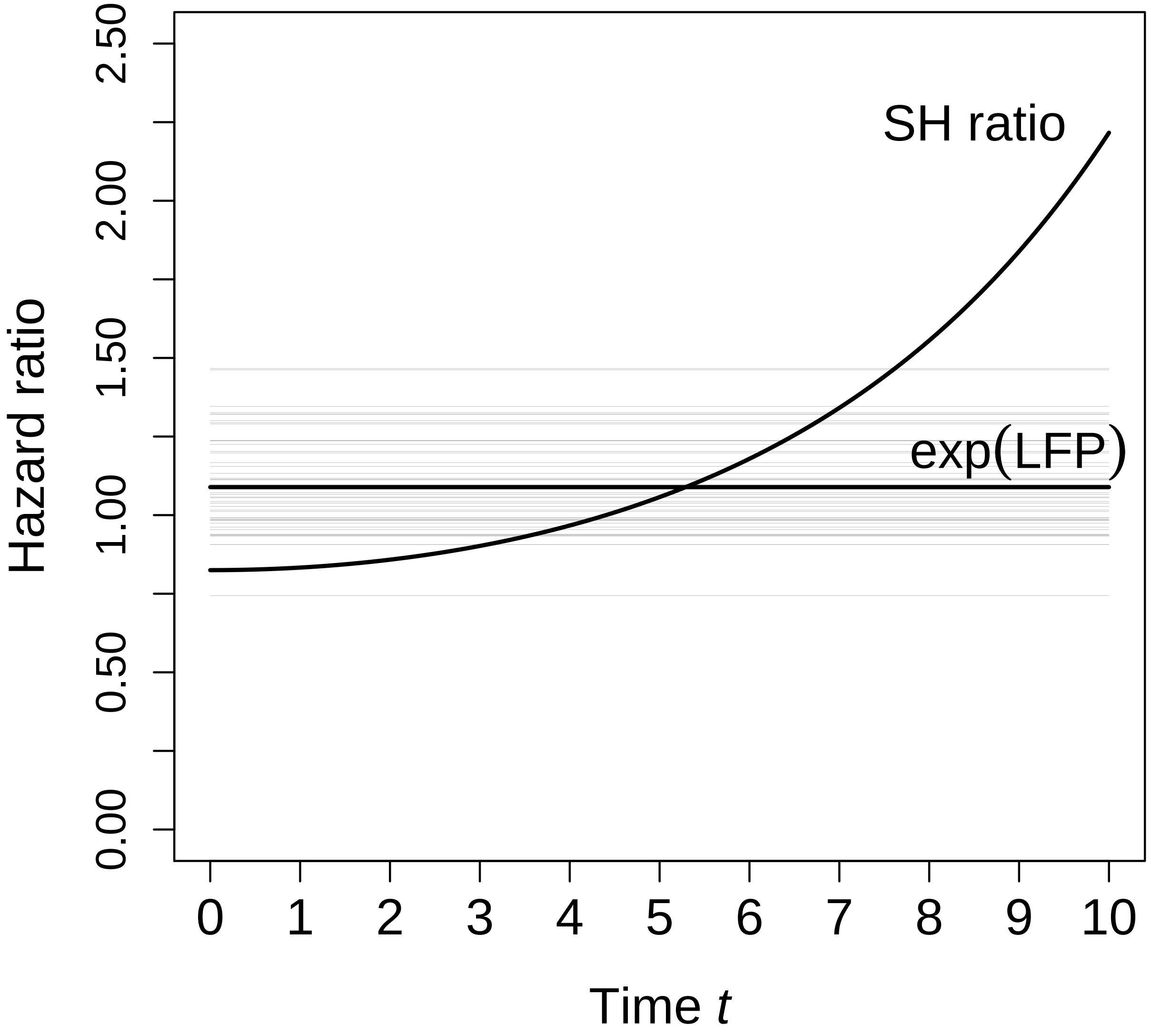
- Number of simulations: stop criterion for numerical approximation. Checked every 100 simulations.

- Stopped after 500 simulations.

- Time-averaged SH ratio exp(LFP) $\approx$ 1.09 indicates slight increase of the infection-CIF for allogeneic patients ($Z = 1$).

- Asymptotic 95%-confidence interval for exp(LFP) based on normal approximation and 500 simulations: $[1.07, 1.10]$.

Subdistribution hazard ratio: time-dependent and averaged.



Also shown (grey): Estimate from every 10th simulation.

Discussion of the recommended simulation design

- CSH-driven: This is the way CSHs generate competing risks data.

- Generalizes to more complex multistate models: series of competing risks experiments.

- E.g. useful for generating time-dependent covariates, say, in a proportional hazards model.

- Complies with Occam's razor: 'It is vain to do with more what can be done with fewer.'

- Also in Beyersmann et al. (StatMed 2009):
  - More standard simulation example.
  - Simulate proportional SH data.

Some references.

- Beyersmann J, Latouche A, Buchholz A, Schumacher M. Simulating competing risks data in survival analysis. *Statistics in Medicine* 2009; **28**:956–971.

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- Fine J, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association* 1999; **94**(446):496–509.

- Hjort NL. On inference in parametric survival data models. *International Statistical Review* 1992; **60**:355–387.

Simulation: numerical approximation of LFP

- R; times T via inversion method, `uniroot()` for numerical inversion; each simulation with 10000 individuals.

- Stop criterion for numerical approximation:
  - Start with 100 simulations and compute mean estimate from proportional SH model.
  - Add 100 new simulations, until updated mean estimate differs by less than 0.1% from the previous mean estimate.

- Stopped after 500 simulations, LFP ≈ 0.085.

- Time-averaged SH ratio exp(LFP) ≈ 1.09 indicates slight increase of the infection-CIF for allogeneic patients ($Z = 1$).

- Asymptotic 95%-confidence interval for exp(LFP) based on normal approximation and 500 simulations: $[1.07, 1.10]$.