# Resampling complex time-to-event data without individual patient data, with a view toward recurrent events

PSI One Day Meeting: Time-to-Event and Recurrent Event Endpoints in Clinical Trials

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# Why Multistate Models in Recurrent Event Trials?

Typical primary efficacy analysis (here: heart failure): Time-to-**first** (composite) event including, e.g.,

- first heart failure hospitalization (HFH)
- first major adverse cardiovascular event (MACE)
- cardiovascular death (CVD)
- non-cardiovascular death (NCVD)
- ...

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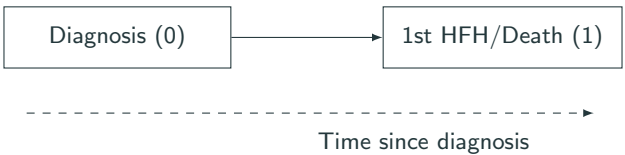
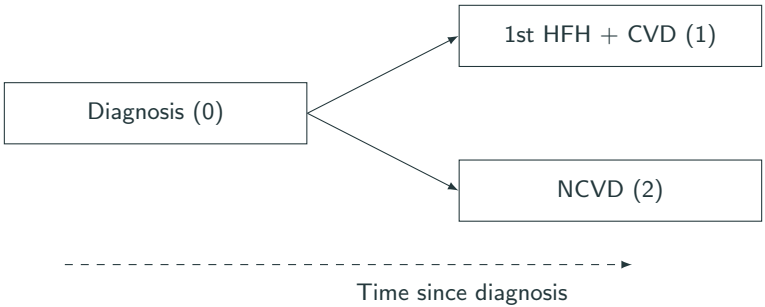
$\Rightarrow$ **Standard survival setting** (Cox, Kaplan-Meier, log-rank, etc.)




- Box $\hat{=}$ 'state', Arrow $\hat{=}$ 'Transition'

# Why Multistate Models in Recurrent Event Trials?

- Interest in the event **type**: Decomposition of composite endpoint into its single components
- **Competing risks model**: Time until first event + type of first event (cause-specific Cox, cumulative incidence function, Fine & Gray, etc.)



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- Time-to-first analysis: All subsequent events are 'ignored' $\Rightarrow$ **Intermediate events** informative?
  - May influence outcome (clinical events, treatments)
  - May give important information on the
    - Effect of treatment/covariates on the endpoint before and after intermediate event
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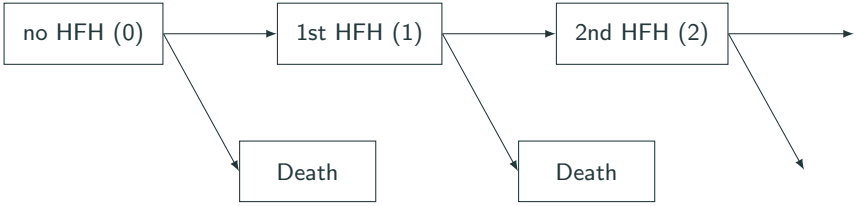
  - Decreasing event rates potentially lead to infeasible samples sizes
- **Multistate methodology** can help us to ...
  - appropriately describe the course of disease
  - account for, e.g., a positive association between HFHs and (CV) death
  - quantify/assess treatment effects

# Examples: Recurrent events (without duration)



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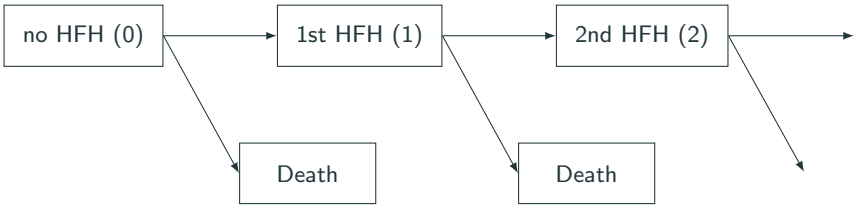


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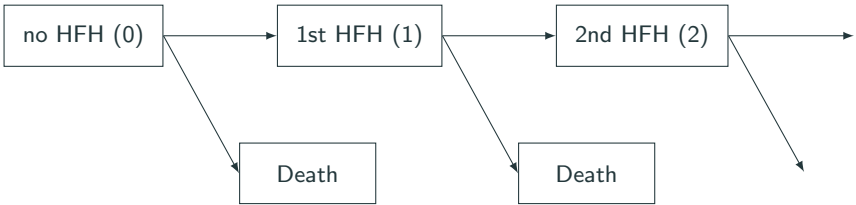
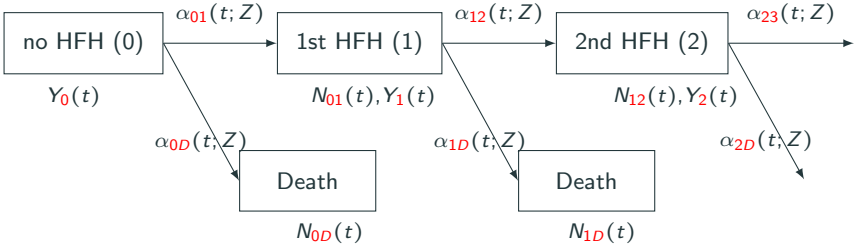



- **Multistate Model**: Concept to connect 'clinical states' and potential transition between these states
- Number of states usually finite
- Transient states vs. absorbing states
- Notation:
  - $N_{\ell m}(t)$ = number $\ell \to m$ transitions up to time $t$
  - $Y_\ell(t)$ = at risk indicator for transition out of state $\ell$ (accounts for periods not at risk, here, censoring or death)
  - $Z$ covariate(s) (may be time-dependent, $Z(t)$)

# A hazard-based perspective




The key-quantities are the **intensities**, which can be seen as the **instantaneous 'risk'** of a transition (event) given the past information:

$$\begin{aligned}\lambda_{\ell m}(t)\mathrm{d}t &= \mathbb{P}(\ell \to m \text{ transition between } t \text{ and } t+\mathrm{d}t | \text{Past}) \\ &\overset{!}{=} \alpha_{\ell m}(t;Z)\mathrm{d}t \cdot Y_\ell(t),\end{aligned}$$

where $\alpha_{\ell m}$ is a non-negative deterministic function (**transition-specific hazard**)

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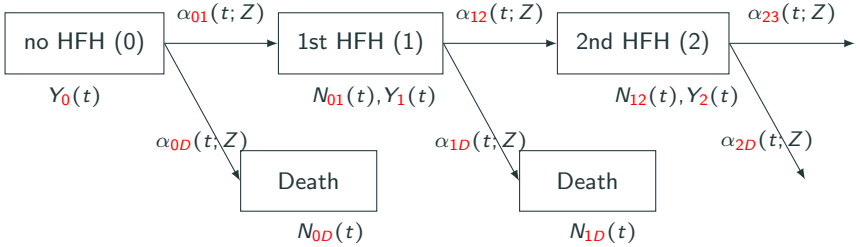
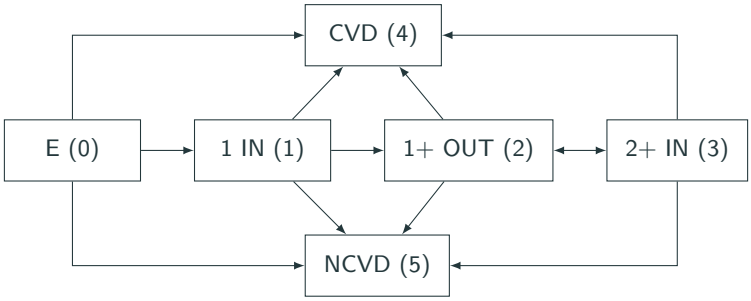



- Poisson Regression (parametric): $\alpha_{01}(t;Z) = \alpha_{02}(t;Z) \ldots \equiv \alpha \cdot \exp(\beta Z)$
- Andersen-Gill Model (semi-parametric): $\alpha_{01}(t;Z) = \alpha_{02}(t;Z) \ldots \equiv \alpha(t) \cdot \exp(\beta Z)$, with $\alpha(t)$ unspecified
- Prentice-Williams Peterson Model (semi-parametric): $\alpha_{(k-1)k}(t;Z) = \alpha_k(t) \cdot \exp(\beta Z)$, with $\alpha_k(t)$ unspecified

# Another Example: Recurrent Events (with duration)




E: 'event-free'; 1st HF admission to hospital: '1 IN'; recurrent HF admission to hospital: '2+ IN'; discharge alive from hospital: '1+ OUT'

- See e.g, Bakal et al. (2014); Ieva et al. (2017)
- Competing events 'CV death' & 'non-CV death' + recurrent heart failure hospitalizations admissions
- Hospital durations

# Alternative Estimands (related to transition probabilities)

- **Nelson-Aalen estimator** $\widehat{A}_{\ell m}(t) = \sum_{u \leq t} \frac{\mathrm{d}N_{\ell m}(u)}{Y_\ell(t)}$ non-parametrically estimates $A_{\ell m}(t) = \int_0^t \alpha_{\ell m}(u)\mathrm{d}u$
- **Aalen-Johansen estimator** $\widehat{P}_{\ell j}(s,t)$ generalizes the Kaplan-Meier estimator to multiple states and estimates the **transition probability** $P_{\ell j}(s,t) = \mathbb{P}(\text{state } j \text{ at time } t | \text{ state } \ell \text{ at time } s)$
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- Previous slide: (Expected Excess) Hospital-free survival
- Eefting et al. (2016), Bluhmki et al. (2018): Relapse-free survival free of immunosuppressive therapy
- James et al. (2019): Graft-versus-host-disease- and relapse-free survival
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**Next slides:** How can such complex time-to-event data be **simulated?**
⇒ time-dependent covariate(s) + terminal event(s)

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RESEARCH ARTICLE

WILEY Statistics in Medicine

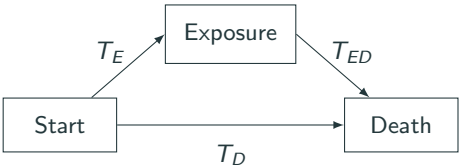
# Bootstrapping complex time-to-event data without individual patient data, with a view toward time-dependent exposures

Tobias Bluhmki[1] | Hein Putter[2] | Arthur Allignol[3] | Jan Beyersmann[1], on behalf of the COMBACTE-MAGNET consortium

- Important for the development of novel estimation procedures, sample size calculations, etc.
- Simulation studies (often) aim to mimic **real-world** settings

# Simulation of complex time-to-event data

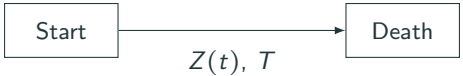
- Recent developments in **simulation** of time-to-event data with **longitudinal** covariate patterns (simple example)




**Latent failure time approach I**

Simulate $T_D$, $T_E$, and $T_{ED}$ **separately** (possibly assuming some dependence structure, Fleischer et al., 2009)

# Simulation of complex time-to-event data




**Latent failure time approach II:**

- Leemis et al. (1990); Shih and Leemis (1993); Austin (2012); Mi et al. (2016); Crowther and Lambert (2013), ...
- **Exposure status** $Z(t) = \mathbf{1}\left(t > T_E\right) \in \{0, 1\} \Rightarrow$ **time-dependent** covariate
- Cox-type survival hazard $\tilde{\alpha}(t|\text{Past}) = \mathbf{1}(t \leq T_E) \cdot \alpha_0(t) + \mathbf{1}(t > T_E) \cdot \alpha_0(t) \cdot \exp(\beta)$

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- Generate $T_E$ **a priori** and the **survival time** $T$ (by e.g., inversion method) from

$$\mathbb{P}\left(T > t | T_E = t_E\right) = \begin{cases} \exp\left(-\int_0^{t_0} \alpha_0(u)du\right), & \text{if } t \leq t_E, \\ \exp\left(-\left(\int_0^{t_0} \alpha_0(u)du + \int_{t_0}^{t} \alpha_0(u) \cdot \exp(\beta)du\right)\right), & \text{if } t > t_E \end{cases}$$

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- **Conceptual challenge (not highlighted so far):** Reasonable for **exogenous** exposures such as environmental factors, because the occurrence of a failure in $[u, u + du)$ does not dependent on the future exposure status at a later time $t$ (Kalbfleisch and Prentice, 2002)

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- Violates the fundamental principle to **not condition on the future** (Breslow, 2014; Andersen and Keiding, 2012)

- Latent failure time approaches impose **impossible** sampling spaces in real life + latent failure time structure with **unclear** interpretation
  - **each** individual is supposed to be exposed at **some** time (possibly after death)
  - death may be observed **prior** to exposure
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- Note: Problem is **not** the Cox model

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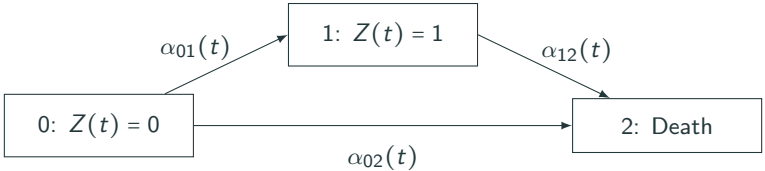
- Dito: multistate simulation approach used in e.g., Crowther and Lambert (2017) or James et al. (2019)

# Hazard-based multistate algorithm going back to Gill and Johansen (1990)

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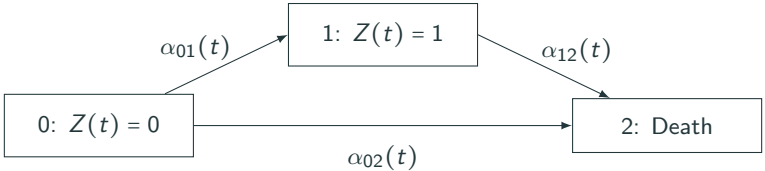


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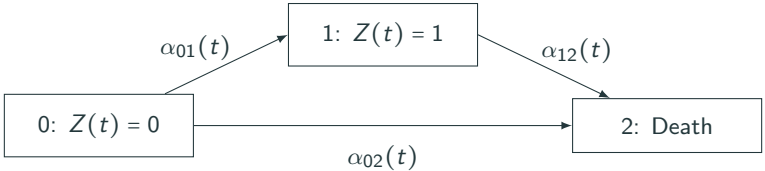


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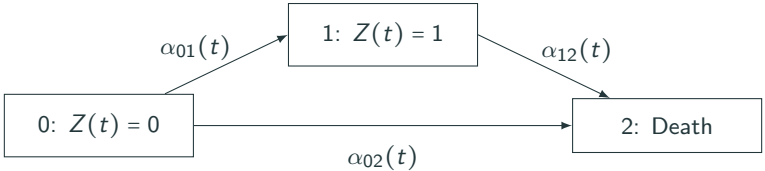
- Benefit: $T_E$ has **not** to be generated a priori but is **part of the model** via $\alpha_{01}$!
  - **Natural** interpretation: Real-world and no hypothetical times
    $\Rightarrow$ **Occam's razor**: *'More things should not be used than are necessary.'*
  - Natural order of events and **population**-level quantities are guaranteed
  - Still allows for flexible parametrizations as in, e.g., Crowther and Lambert (2017)

# Empirical simulation




**Challenge to simulate 'biologically plausible' time-to-event data**

- **Adequately** specify transition hazards $\alpha_{\ell m}(t)$!
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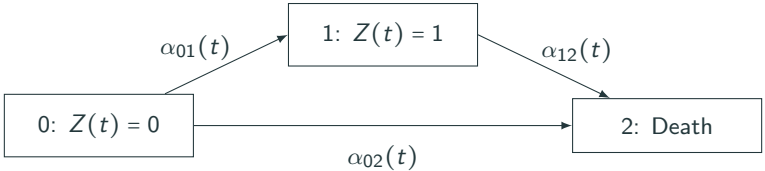


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- Requires (involved) **pre-processing** procedures (parametric assumptions, smoothing, etc.)
- Convenient alternative: **Empirical** analogue of Gill and Johansen framework (Bluhmki et al., 2019)
  - **Published** information
  - In principle: **No** individual patient data needed!

# Empirical simulation

Derive $\Delta\widehat{A}_{\ell m}$ from **published** information. Repeat the following steps, starting in state $\ell$ at time $t^* = 0$:

1. Compute (increment of) the **all-cause hazard** out of state $\ell$ given by $\Delta\widehat{A}_{\ell\bullet}(t) = \sum_{m, m\neq\ell} \Delta\widehat{A}_{\ell m}(t)$.

2. If $\Delta\widehat{A}_{\ell\bullet}(t) \equiv 0 \ \forall t$, stop. Else, compute the **distribution function** of the transition time out of state $\ell$
$$\widehat{F}_\ell(t) = 1 - \prod_{t^* < u \leq t} \left(1 - \Delta\widehat{A}_{\ell\bullet}(u)du\right)$$

3. Event time $t > t^*$ is sampled from a multinomial distribution with probabilities $\Delta\widehat{F}_\ell(t)$ to each time $t$ with $\Delta\widehat{F}_\ell(t) > 0 \Rightarrow t \in \{\textbf{original times}\}$

4. The new state $m$ is sampled with probability $\Delta\widehat{A}_{\ell m}(t)/\Delta\widehat{A}_{\ell\bullet}(t), \ \ell \neq m$.

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**Remark**

- $\widehat{F}_\ell$ degenerated in right-censored data $\Rightarrow$ Put missing point mass to $2 \cdot t_{max}$ and individual is censored
- Empirical analogue of Gill and Johansen (1990) $\Rightarrow$ **Bootstrap/Resampling**

# Empirical simulation – Remarks

- Requires (at least) ...
  1. ... the (increments of the) Nelson-Aalen estimators
  2. ... the initial distribution
  3. ... information on right-censoring mechanism (Kaplan-Meier plot, risk sets, etc.)
- Ready-to-use: `mssample` in the `R`-package `mstate`
- Bluhmki et al. (2019):
  - Mimicking real-world time-to-event data without pre-processing procedures
  - Novel **bootstrap** procedure in order to assess statistical uncertainty $\Rightarrow$ beyond Efron's bootstrap

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  1. ... the (increments of the) Nelson-Aalen estimators
  2. ... the initial distribution
  3. ... information on right-censoring mechanism (Kaplan-Meier plot, risk sets, etc.)
- Ready-to-use: `mssample` in the `R`-package `mstate`
- Bluhmki et al. (2019):
  - Mimicking real-world time-to-event data without pre-processing procedures
  - Novel **bootstrap** procedure in order to assess statistical uncertainty $\Rightarrow$ beyond Efron's bootstrap
- Other field of applications (work in progress):
  - Can be used to overcome **copyright restrictions** in order to make patient data publicly available
  - **Sample size calculations**, when historical data should be incorporated

## Discussion – Multistate perspective

- Multistate methodology allows for the estimation of **alternative estimands**
- Treatment effects may be evaluated by the application of the **wild bootstrap** (Bluhmki et al., 2018)

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- Plausibility:
  - **Natural** interpretation (real-world, population level, etc.)
  - Parsimony in terms of **Occam's razor**
  - In-line with fundamental **principles** of time-to-event methodology and statistical analysis
  - Important for **study planning** (sample size calculations/trial protocol)

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- Multistate methodology allows for the estimation of **alternative estimands**
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  - **Natural** interpretation (real-world, population level, etc.)
  - Parsimony in terms of **Occam's razor**
  - In-line with fundamental **principles** of time-to-event methodology and statistical analysis
  - Important for **study planning** (sample size calculations/trial protocol)
- Flexibility:
  - Qualitative and reversible exposures & more complex disease histories
    $\Rightarrow$ **Continuous covariates** need to be categorized into a finite number of categories
  - Independent **right-censoring** and **left-truncation** + **degenerated initial distributions**
  - Modeling assumptions: **Non-Markov** situations, Aalen's additive model, ...
  - Covers Poisson-Regression, AG model, and PWP model as special cases
- **Note:** Competing approaches lead on average to the **same** (and correct) data structure, but simulation designs have no real-world interpretation

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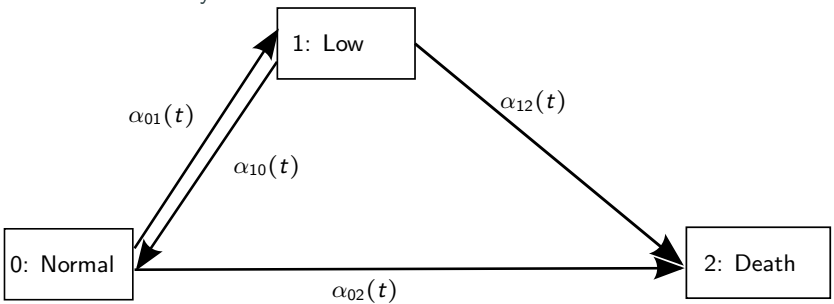
# Backup

# Proof of concept

## Simulation Study

- **Published** CSL 1 trial (Example 1.3.12 in Andersen et al., 1993)
- 251 hormone-treated liver cirrhosis patients
- Study aim: Effect of **prothrombin index** (low vs. normal) on overall survival
- Illness-death model **with** recovery



# Proof of concept

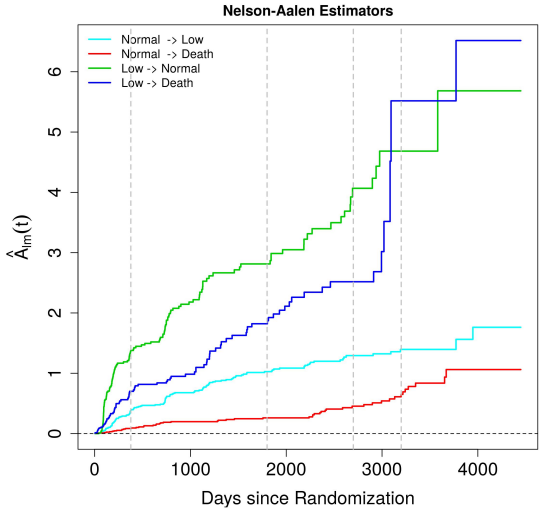
## Simulation Study

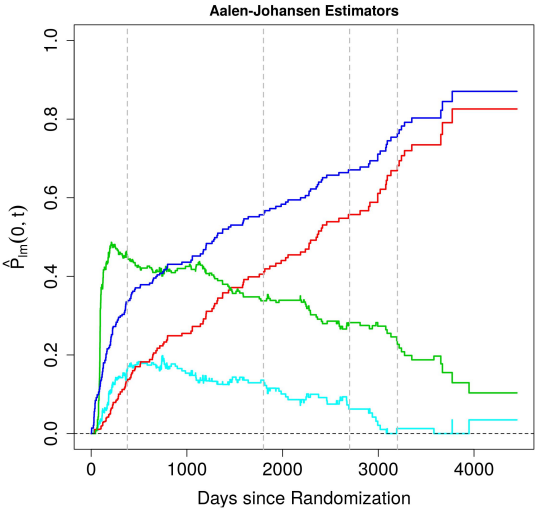
- **Published** CSL 1 trial (Example 1.3.12 in Andersen et al., 1993)
- 251 hormone-treated liver cirrhosis patients
- Study aim: Effect of **prothrombin index** (low vs. normal) on overall survival
- Illness-death model **with** recovery
- Initial distribution: 43% normal and 57% abnormal indices at randomization
- Random right-censoring according to the censoring Kaplan-Meier estimator
- **Aim:** Recover the (study-based) Aalen-Johansen estimator of the matrix of **transition probabilities**

$$\widehat{\mathbf{P}}(0,t) = \left(\widehat{\mathrm{P}}_{\ell m}(0,t)\right)_{\ell,m} = \left(\widehat{\mathbb{P}}(X_t = m | X_0 = \ell)\right)_{\ell,m} = \prod_{u \le t} \left(\mathbf{I} + \Delta\widehat{\mathbf{A}}(u)\right)$$

- Sample sizes $n \in \{50, 100, \mathbf{251}, 1000\}$, $t \in \{378, 1800, 2700, 3200\}$, 2000 datasets for each study
- For each dataset and transition: Check whether the 95% log-log CI for $\widehat{\mathrm{P}}^*_{\ell m}(0,t)$ covers $\widehat{\mathrm{P}}_{\ell m}(0,t)$

# Proof of concept



# Proof of concept

| $n$ | $t$ | Coverage Probability (%) $\widehat{P}_{01}(0,t)$ | $\widehat{P}_{02}(0,t)$ | $\widehat{P}_{10}(0,t)$ | $\widehat{P}_{12}(0,t)$ |
|---|---|---|---|---|---|
| 50 | 378 | 94.9 | 92.5 | 93.8 | 94.0 |
| | 1800 | 92.6 | 92.6 | 93.6 | 92.8 |
| | 2700 | 71.5 | 90.7 | 92.7 | 91.5 |
| | 3200 | 14.8 | 90.0 | 92.0 | 90.5 |
| 100 | 378 | 94.6 | 94.8 | 95.1 | 94.3 |
| | 1800 | 93.3 | 94.2 | 93.7 | 93.0 |
| | 2700 | 87.6 | 94.2 | 94.3 | 93.8 |
| | 3200 | 28.5 | 93.0 | 94.0 | 93.1 |
| 251 | 378 | 95.3 | 95.2 | 94.7 | 95.0 |
| | 1800 | 94.0 | 94.4 | 94.6 | 94.2 |
| | 2700 | 92.5 | 94.4 | 94.3 | 94.6 |
| | 3200 | 59.0 | 93.3 | 94.9 | 93.4 |
| 1000 | 378 | 95.2 | 94.6 | 94.5 | 94.7 |
| | 1800 | 95.5 | 94.9 | 94.5 | 93.9 |
| | 2700 | 94.2 | 94.2 | 95.2 | 95.2 |
| | 3200 | 94.1 | 94.4 | 94.7 | 94.6 |

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|---|---|---|---|---|---|
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| | 3200 | 14.8 | 90.0 | 92.0 | 90.5 |
| 100 | 378 | 94.6 | 94.8 | 95.1 | 94.3 |
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| | 2700 | 87.6 | 94.2 | 94.3 | 93.8 |
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| 251 | 378 | 95.3 | 95.2 | 94.7 | 95.0 |
| | 1800 | 94.0 | 94.4 | 94.6 | 94.2 |
| | 2700 | 92.5 | 94.4 | 94.3 | 94.6 |
| | 3200 | 59.0 | 93.3 | 94.9 | 93.4 |
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| | 1800 | 95.5 | 94.9 | 94.5 | 93.9 |
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| 251 | 378 | 95.3 | 95.2 | 94.7 | 95.0 |
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| | 2700 | 92.5 | 94.4 | 94.3 | 94.6 |
| | 3200 | 59.0 | 93.3 | 94.9 | 93.4 |
| 1000 | 378 | 95.2 | 94.6 | 94.5 | 94.7 |
| | 1800 | 95.5 | 94.9 | 94.5 | 93.9 |
| | 2700 | 94.2 | 94.2 | 95.2 | 95.2 |
| | 3200 | 94.1 | 94.4 | 94.7 | 94.6 |

# Proof of concept

| $n$ | $t$ | Coverage Probability (%) | | | |
|---|---|---|---|---|---|
| | | $\widehat{P}_{01}(0,t)$ | $\widehat{P}_{02}(0,t)$ | $\widehat{P}_{10}(0,t)$ | $\widehat{P}_{12}(0,t)$ |
| 50 | 378 | 94.9 | 92.5 | 93.8 | 94.0 |
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| | 3200 | 14.8 | 90.0 | 92.0 | 90.5 |
| 100 | 378 | 94.6 | 94.8 | 95.1 | 94.3 |
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| | 3200 | 28.5 | 93.0 | 94.0 | 93.1 |
| 251 | 378 | 95.3 | 95.2 | 94.7 | 95.0 |
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| | 2700 | 94.2 | 94.2 | 95.2 | 95.2 |
| | 3200 | 94.1 | 94.4 | 94.7 | 94.6 |

# Proper Survival Hazard

$$\begin{aligned}
\alpha(t)dt = \mathbb{P}(T \in dt | T \geq t) &= \frac{\mathbb{P}(T \in dt, Z(t) = 0) + \mathbb{P}(T \in dt, Z(t) = 1)}{\mathbb{P}(T \geq t)} \\
&= \frac{\mathbb{P}(T \in dt | Z(t) = 0, T \geq t) \cdot \mathbb{P}(Z(t) = 0, T \geq t) + \mathbb{P}(T \in dt | Z(t) = 1, T \geq t) \cdot \mathbb{P}(Z(t) = 1, T \geq t)}{\mathbb{P}(T \geq t)} \\
&= \frac{\mathbb{P}(Z(t) = 0, T \geq t)}{\mathbb{P}(T \geq t)} \cdot \underbrace{\mathbb{P}(T \in dt | Z(t) = 0, T \geq t)}_{=:\alpha_{02}(t)dt} + \frac{\mathbb{P}(Z(t) = 0, T \geq t)}{\mathbb{P}(T \geq t)} \cdot \underbrace{\mathbb{P}(T \in dt | Z(t) = 1, T \geq t)}_{=:\alpha_{12}(t)dt}.
\end{aligned}$$

Note that if $Z(t)$ is external, $\alpha(t)$ equals the expectation of the right-hand side for $\alpha_{02}(t) = \alpha_0(t)$ and $\alpha_{12}(t) = \alpha_0(t) \cdot \exp(\beta)$,

# Proof equal data structure

Let $T_0 > 0$ be the random time to exposure with abs. cont. $F_{T_0}(t)$ and density function $f_{T_0}(t)$
$\Rightarrow \alpha_{01}(t) := \frac{f_{T_0}(t)}{1-F_{T_0}(t)}$.
Let $T$ be the time to death with the underlying survival hazard using the Cox specification. Using standard calculations, the probability to be alive and unexposed corresponding to an a priori generation of the exposure time can be expressed as

$$\mathbb{P}(t < T, t < T_0) = \int_0^\infty \mathbb{P}(t < T, t < s | T_0 = s) dP^{T_0}(s) = \int_t^\infty \mathbb{P}(T > t | T_0 = s) f_{T_0}(s) ds \overset{s>t}{=} \int_t^\infty \exp(-A_{02}(t)) f_{T_0}(s) ds$$

$$= \exp(-A_{02}(t)) \cdot \underbrace{(1 - F_{T_0}(t))}_{\mathbb{P}(T_0 > t)} = \exp(-A_{02}(t) - A_{01}(t)),$$

where $A_{01}(t) = \int_0^t \alpha_{01}(u) du$

$\Rightarrow$ equivalent to the usual state occupation probability $\mathbb{P}(X(t) = 0)$ derived from the illness-death model with recovery with exposure hazard $\alpha_{01}(t)$, because we have $\mathbb{P}(X_0 = 0) = 1$
Similar arguments for $\mathbb{P}(T_0 < t < T)$

# Performance of bootstrapped CIs for state occupation probabilities (excerpt)

- Parametric hazards: $\alpha_{01}(t) \equiv 0.0005,\ \alpha_{02}(t) \equiv 0.0002\ \alpha_{10}(t) \equiv 0.002,\ \alpha_{12}(t) \equiv 0.0012$
- Initial distribution: $\pi_0 = 0.43,\ \pi_1 = 0.57$
- Sample sizes: $n \in \{50, 100, 251, 500\}$
- 'True' benchmarks: $P(X_t = \ell),\ \ell \in \{0, 1, 2\},\ t = 378, 500, 1000, 2700, 3200.$
- 1000 studies for each sample sizes via non-empirical simulation algorithm, within each study 1000 iterations using empirical algorithm
- 95% bootstrap CIs for the state occupation probabilities are set to the corresponding 2.5% and 97.5 quantile of the 1000 bootstrapped quantities

# Performance of bootstrapped CIs for state occupation probabilities (excerpt)

| $n$ | $t$ | Coverage Probability (%) | | |
|---|---|---|---|---|
| | | $P(X_t = 0)$ | $P(X_t = 1)$ | $P(X_t = 2)$ |
| 50 | 378 | 97.4 | 95.1 | 94.0 |
| | 500 | 97.4 | 94.5 | 94.9 |
| | 1000 | 95.5 | 93.1 | 94.8 |
| | 2700 | 90.3 | 66.8 | 90.9 |
| | 3200 | 89.1 | 68.7 | 91.2 |
| 100 | 378 | 97.2 | 94.7 | 94.2 |
| | 500 | 96.5 | 94.3 | 94.9 |
| | 1000 | 94.1 | 94.3 | 94.6 |
| | 2700 | 92.1 | 87.2 | 92.8 |
| | 3200 | 90.3 | 74.8 | 91.9 |
| 251 | 378 | 97.3 | 94.9 | 94.4 |
| | 500 | 95.4 | 94.5 | 95.9 |
| | 1000 | 96.7 | 95.0 | 96.4 |
| | 2700 | 92.8 | 89.8 | 94.0 |
| | 3200 | 92.3 | 87.6 | 93.2 |
| 500 | 378 | 96.8 | 95.3 | 96.4 |
| | 500 | 96.7 | 95.0 | 95.6 |
| | 1000 | 94.9 | 95.7 | 95.0 |
| | 2700 | 92.1 | 91.4 | 93.3 |
| | 3200 | 91.8 | 89.4 | 91.6 |

# Other recurrent event techniques

**Negative Binomial:** Fully parametric

- $\alpha_{01}(t; v, Z) = \alpha_{02}(t; v, Z) \ldots \equiv v \cdot \alpha_{01} \cdot \exp(\beta Z)$, where $v \sim \Gamma\left(\frac{1}{\theta}, \frac{1}{\theta}\right)$ is an (unobserved) random effect (frailty term)
- Markov assumption violated
- Dependence between recurrent events captured by $v$

**Joint Frailty Model:** Semi- or fully parametric

$$\begin{cases} \alpha_{(k-1)k}(t; v, Z) = v \cdot \alpha_0(t) \cdot \exp(\beta Z) & \text{(recurrent events)} \\ \alpha_{kD}(t; v, Z) = v^{\kappa} \cdot \alpha_{D;0}(t) \cdot \exp(\tilde{\beta} Z) & \text{(death)}, \end{cases}$$

where $v \sim \Gamma\left(\frac{1}{\theta}, \frac{1}{\theta}\right)$ is an (unobserved) random effect (frailty term)

- Markov assumption violated
- Dependence between recurrent events captured by $v$
- Frailty acts differently on the two hazards via $\kappa > 0$