Oncology clinical trial design based on a multistate model that jointly models PFS and OS

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Basel Biostatistics Community Forum, 13th March 2023

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Assuming that PFS and OS are independent when designing a trial does not make sense!

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Who

Meller *et al.* (2019):



Erdmann *et al.* (2023):



Power gains through exploiting correlations:

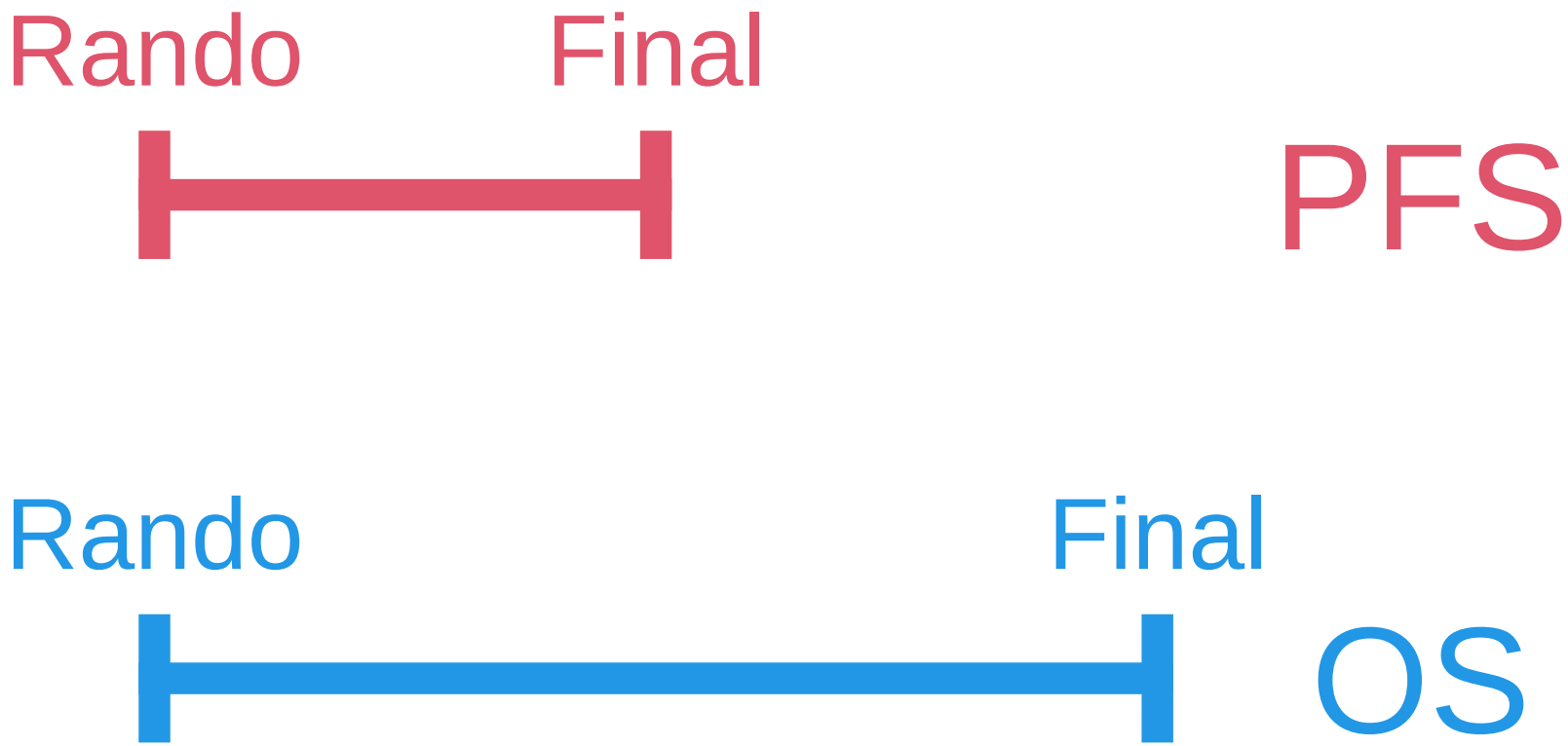
Group-sequential designs: over time.

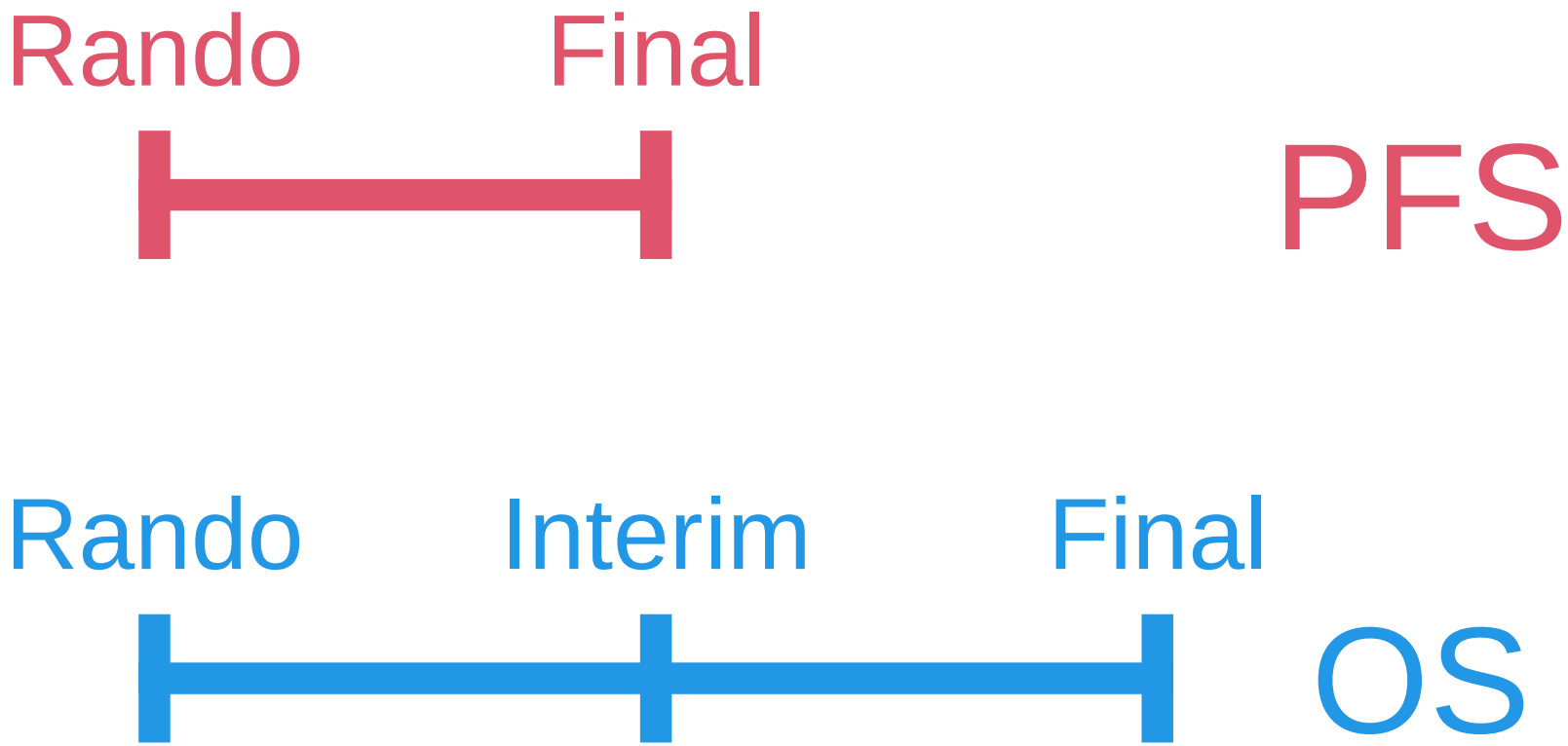
Enrichment designs:
over nested subpopulations.

Goal:

design trial with PFS and OS

Co-primary (win both) or multiple (win ≥ 1)


Rando
Final
PFS
Rando
Final
OS


Rando
Final
PFS
Rando
Interim
Final
OS

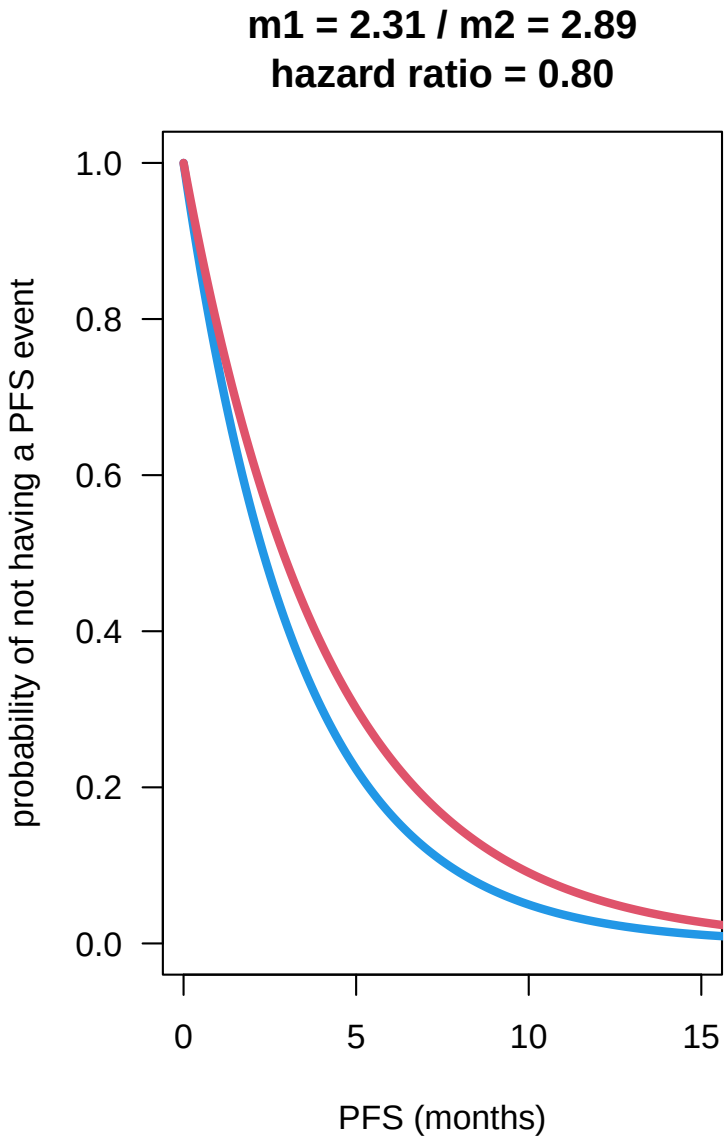
Typical approach:

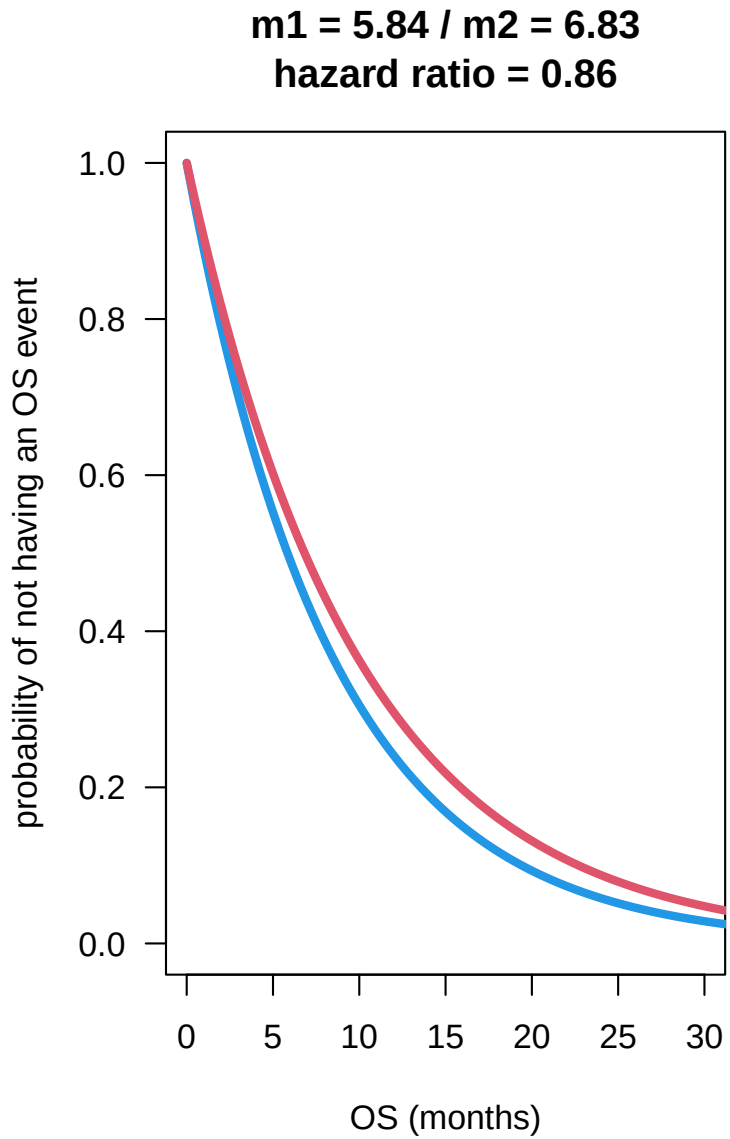
1) Split significance level

2) PFS: exponential, plan GSD

3) OS: exponential (or NPH), plan GSD, align OS interim with PFS final

Example: exponential for PFS and OS





Compute necessary #events based on α-split and GSD assumptions.

Why is this not necessarily optimal?

1) Ignores cor(PFS, OS).

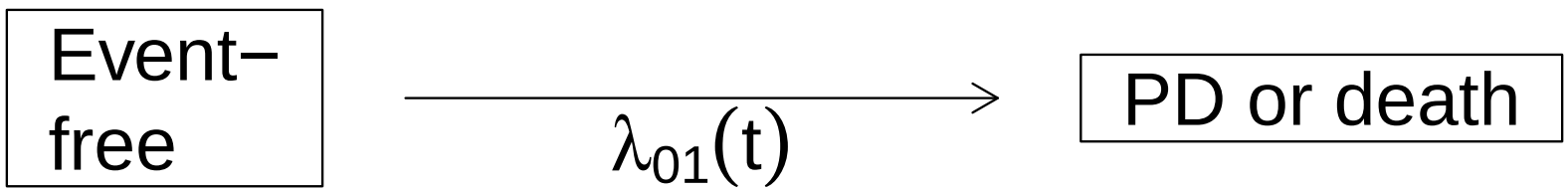
2) PFS + OS both involve death
$\Rightarrow$ OS not independent from PFS!

How can we fix that?

PFS and OS are connected through illness-death model. Use that!

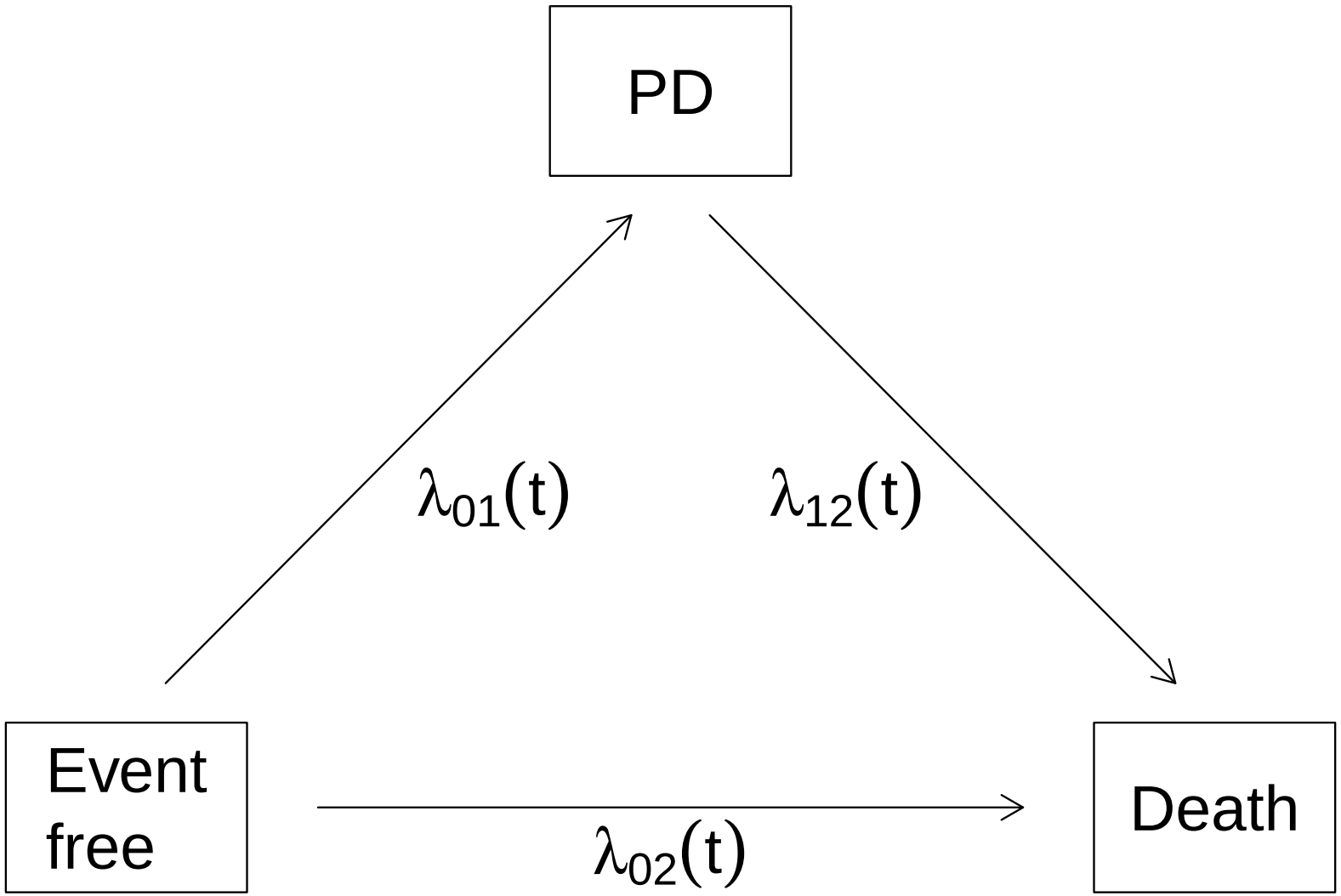
Multistate models

Canonical extension of survival analysis



Time-to-event modelling using random variables.

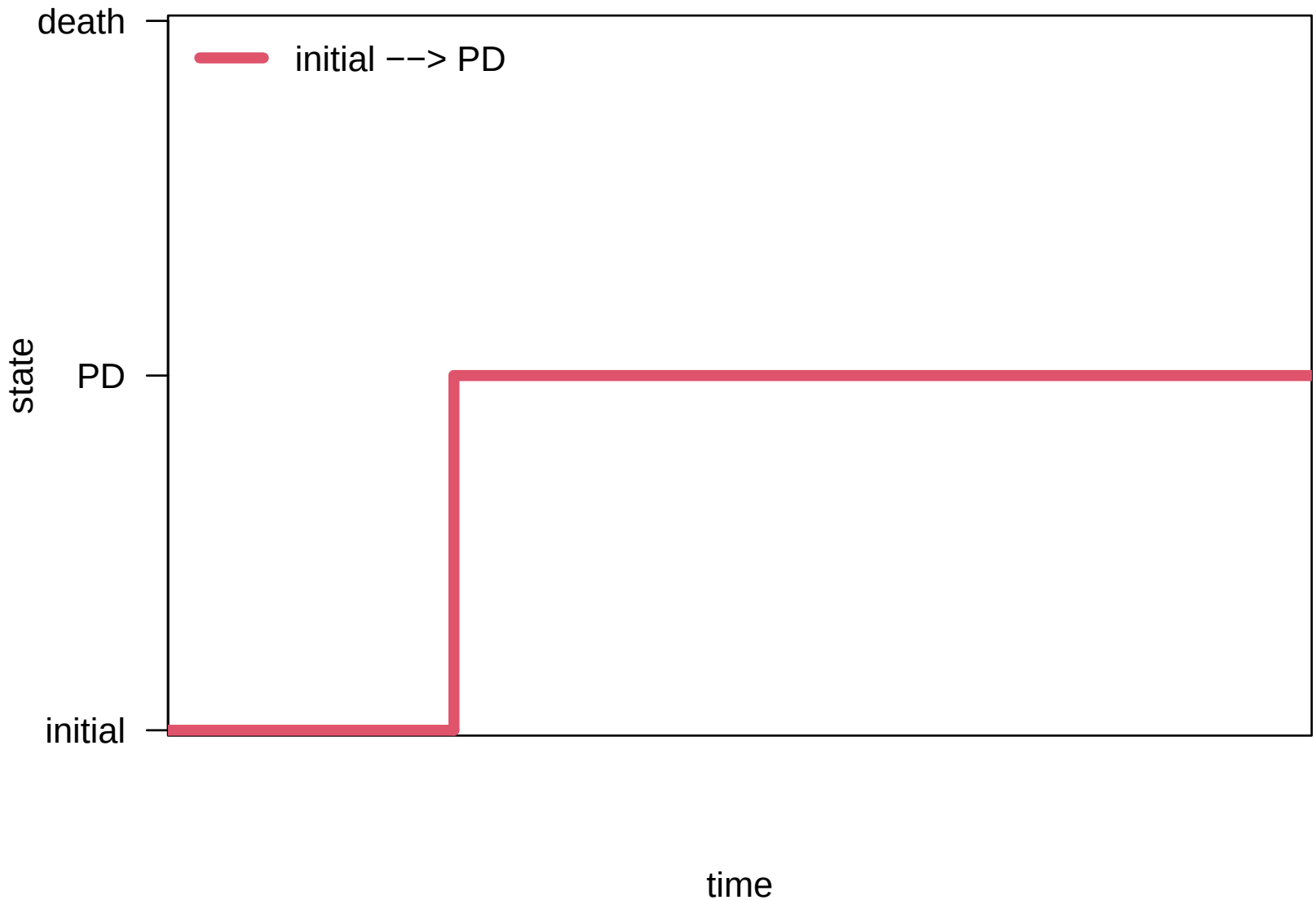
Canonical extension of survival analysis



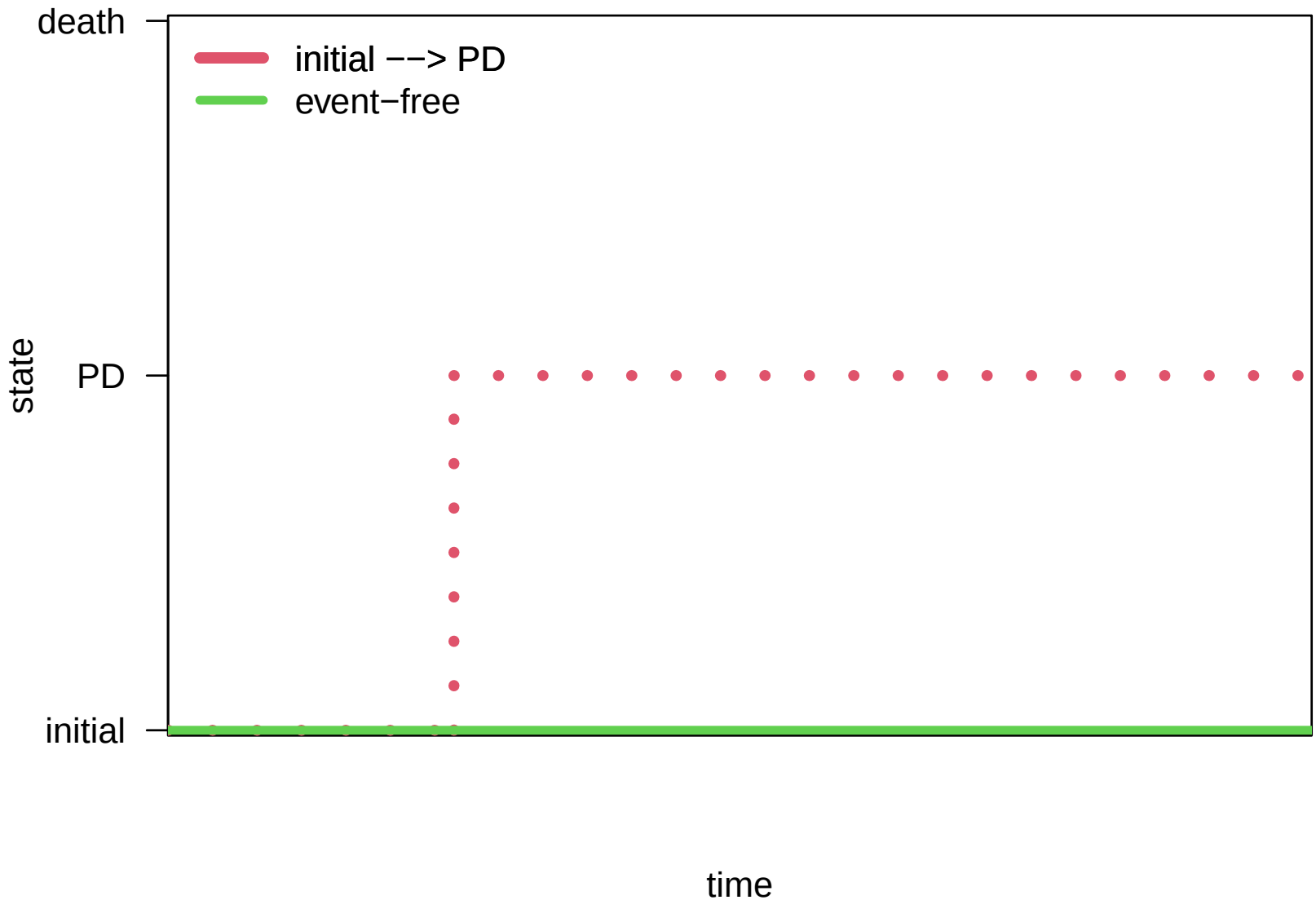
Track events over time using counting processes. Avoids metaphysics!

Multistate modeling using counting processes

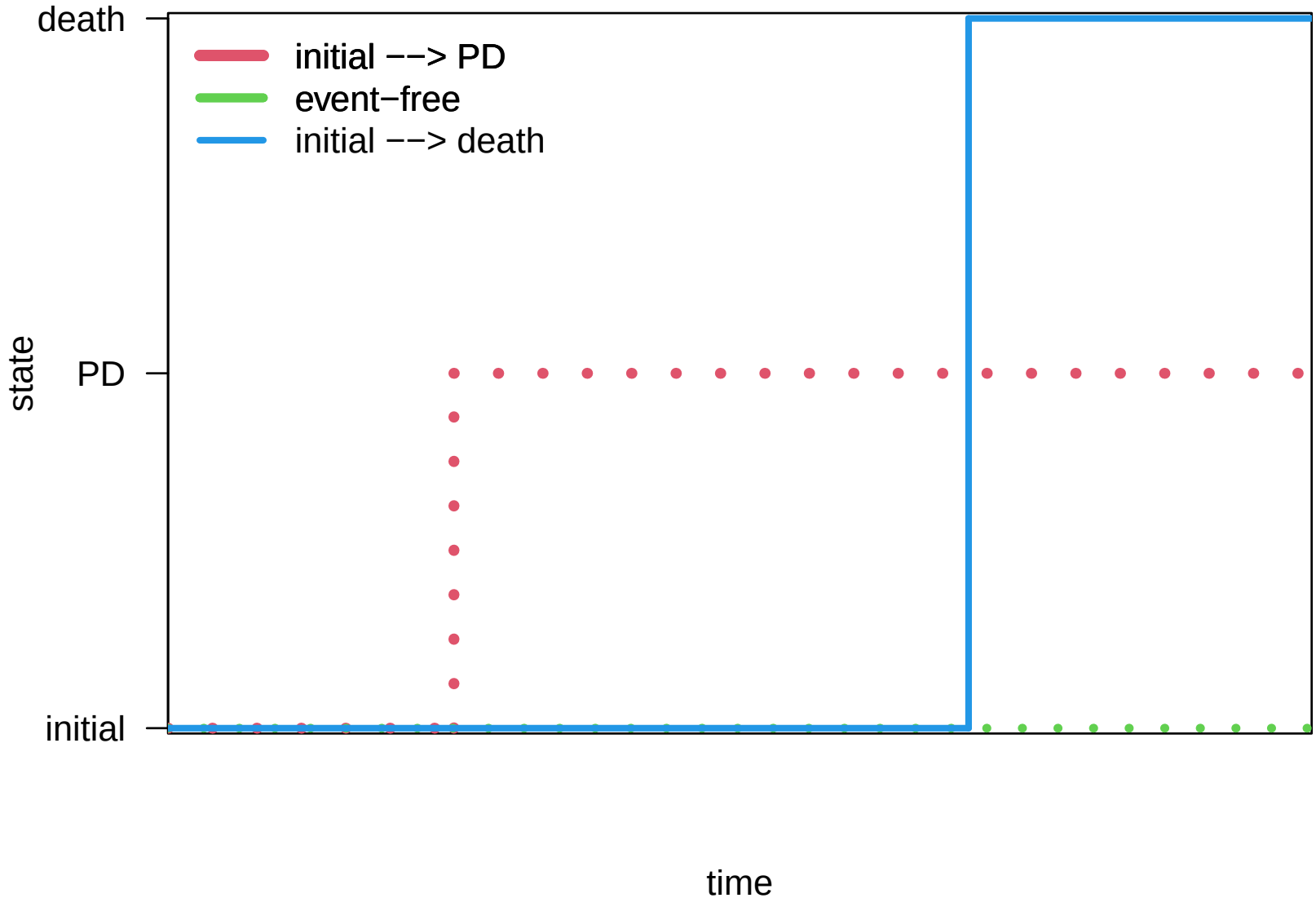
Multistate modeling using counting processes



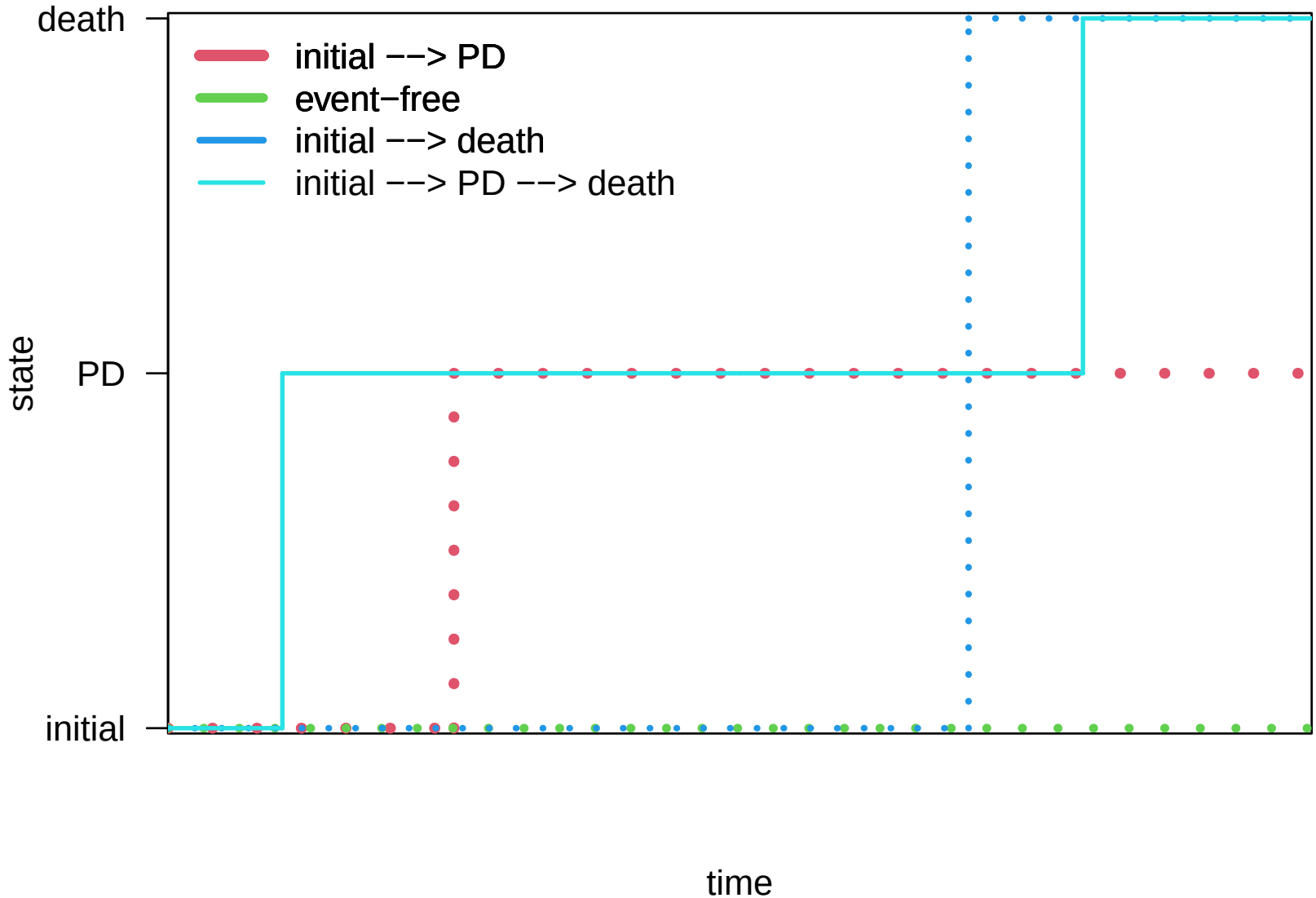
Multistate modeling using counting processes



Multistate modeling using counting processes



Multistate modeling using counting processes



Multistate models

General multistate models:

- **Transition probabilities**: (Markov) process $X(t)_{t\geq 0}$ with state space $\{0, 1, 2, ...\}$. Then,

$$P_{lm}(s,t) \quad := \quad P(X(t) = m | X(s) = l, \text{history}).$$

- Estimate P_{lm}'s **nonparametrically** by **Aalen-Johansen** estimator.
- 1-1 correspondence **hazard - probability** breaks down.

Illness-death multistate model for PFS and OS

Transition probabilities to move from state l at time s to state m at time t:

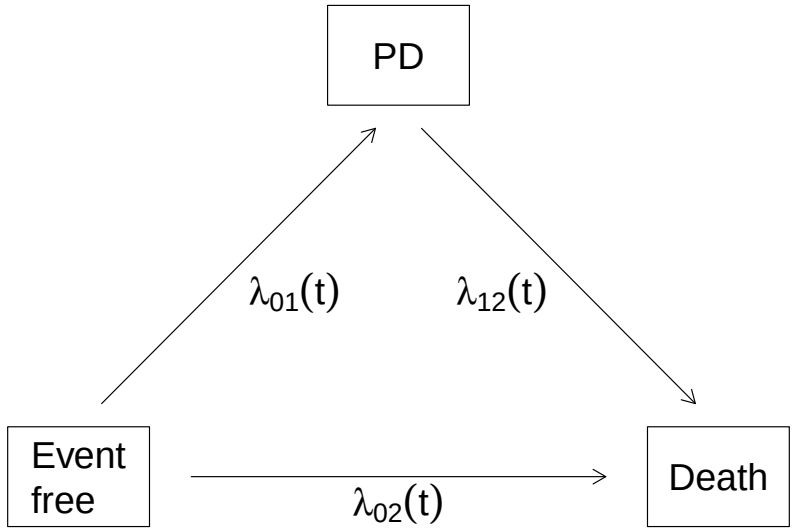
$$P_{lm}(s,t) \quad := \quad P(X(t) = m | X(s) = l, \text{history}).$$

Illness-death model w/o recovery, P_{lm} as functions of transition intensities, Aalen *et al.* (2008):

$$\begin{aligned}
P_{00}(s,t) &= \exp\left(-\int_s^t \lambda_{01}(u) + \lambda_{02}(u)\,\mathrm{d}u\right), \\
P_{11}(s,t;\mathbf{t_1}) &= \exp\left(-\int_s^t \lambda_{12}(u;\mathbf{t_1})\,\mathrm{d}u\right), \\
P_{22}(s,t) &= 1, \\
P_{01}(s,t) &= \int_s^t P_{00}(s,u_-)\lambda_{01}(u)P_{11}(u,t;u)\,\mathrm{d}u, \\
P_{12}(s,t;\mathbf{t_1}) &= 1 - P_{11}(s,t;\mathbf{t_1}), \\
P_{02}(s,t) &= 1 - \Big(P_{00}(s,t) + P_{01}(s,t)\Big).
\end{aligned}$$

If $X(t)$ non-Markov: P_{11} and P_{12} depend on **PFS time** t_1.

Illness-death model for PFS and OS



Marginal distributions:

- All patients in state 0 at time 0: $P(X(0) = 0) = 1$.
- PFS: waiting time in initial state 0, $\mathrm{PFS} = \inf\{t : X(t) \neq 0\}$.

$$S_{PFS}(t) \quad = \quad P(\mathrm{PFS} > t) \quad = \quad P_{00}(0, t).$$

- OS: time until reaching state 2, $\mathrm{OS} = \inf\{t : X(t) = 2\}$.

$$S_{OS}(t) \quad = \quad P(\mathrm{OS} > t) \quad = \quad P_{00}(0, t) + P_{01}(0, t).$$

Advantages of illness-death model for PFS and OS

Illness-death model:

- Assumptions on $X(t)$ **induce** properties of transition intensities, (joint) probabilities, survival functions of PFS and OS.
- Estimation of derived quantities straightforward by plugging in estimated intensities.
- Can reflect disease specifics and drug mode-of-action in transition hazards, see also Beyer et al. (2020).

(Non-)Proportional hazards

Induced survival functions

Meller *et al.* (2019):

$$\begin{aligned} S_{PFS}(t) &= P(\mathrm{PFS} > t) &&= P_{00}(0,t), \\ S_{OS}(t) &= P(\mathrm{OS} > t) &&= S_{PFS}(t) + P_{01}(0,t). \end{aligned}$$

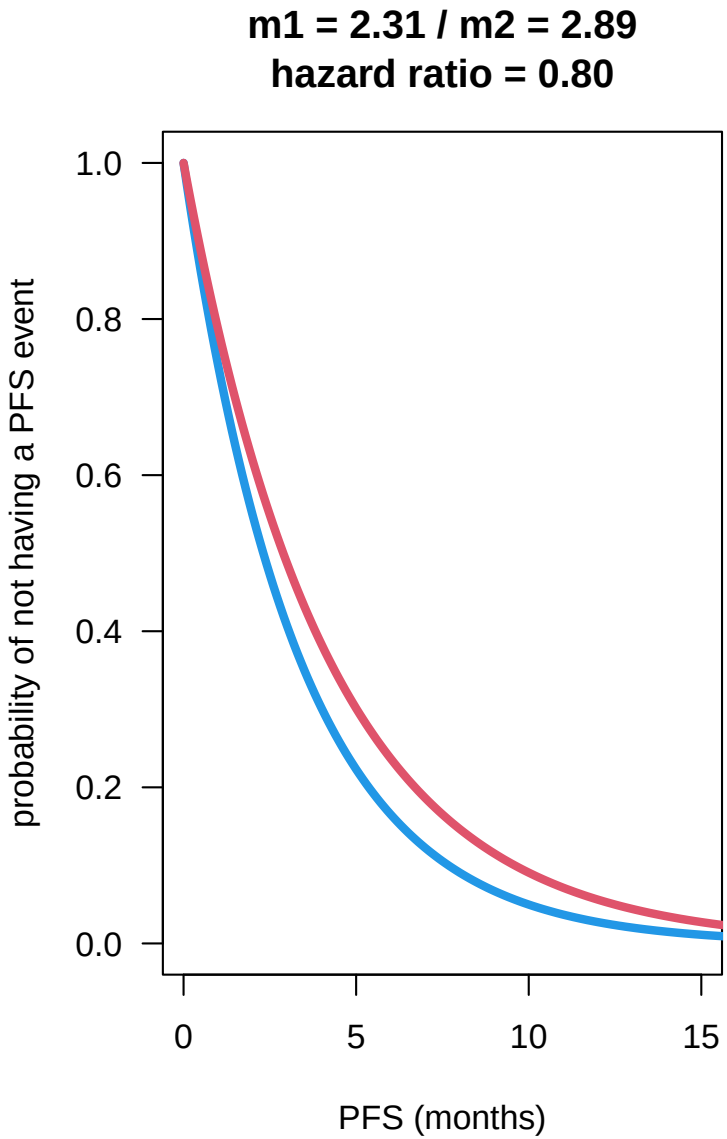
Assume constant transition hazards:

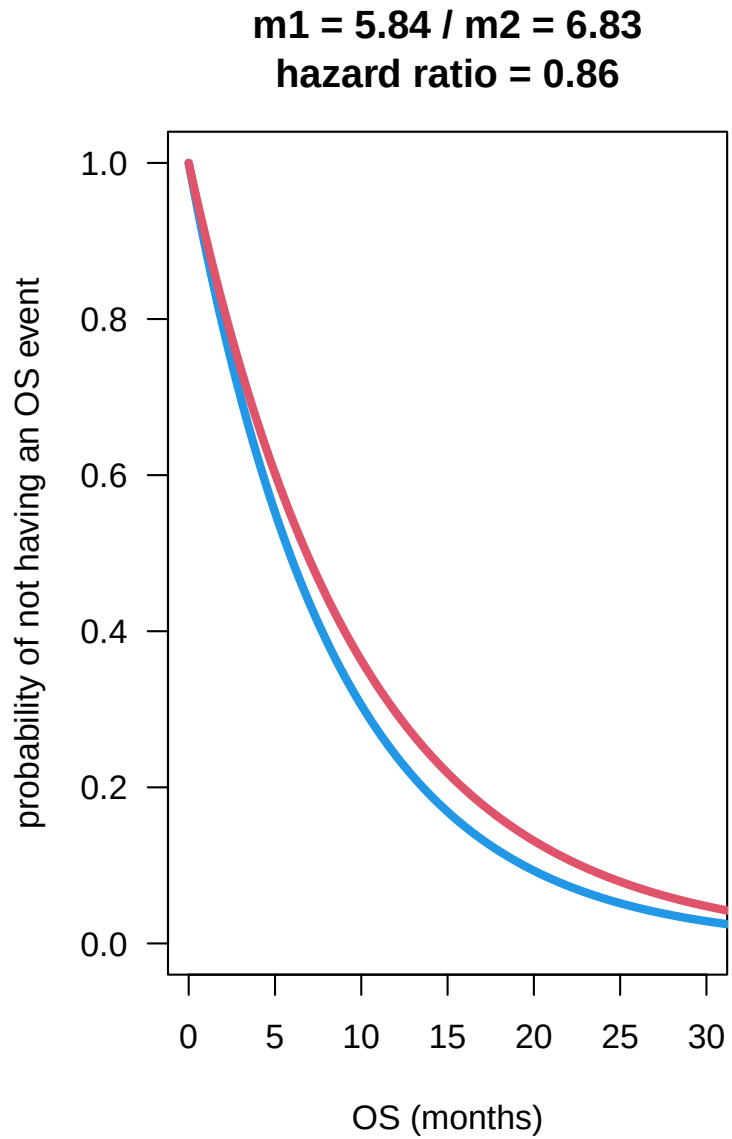
$$\begin{aligned} S_{PFS}(t) &= \exp\Big(-(\lambda_{01}+\lambda_{02})t\Big), \\ S_{OS}(t) &= \frac{S_{PFS}(t)}{\lambda_{012}}\Big(\lambda_{12}-\lambda_{02}-\lambda_{01}\exp(-\lambda_{012}t)\Big) \end{aligned}$$

with abbreviation $\lambda_{012} := \lambda_{12} - \lambda_{01} - \lambda_{02}$.

Hazard functions via $h(t) = -S'(t)/S(t)$.

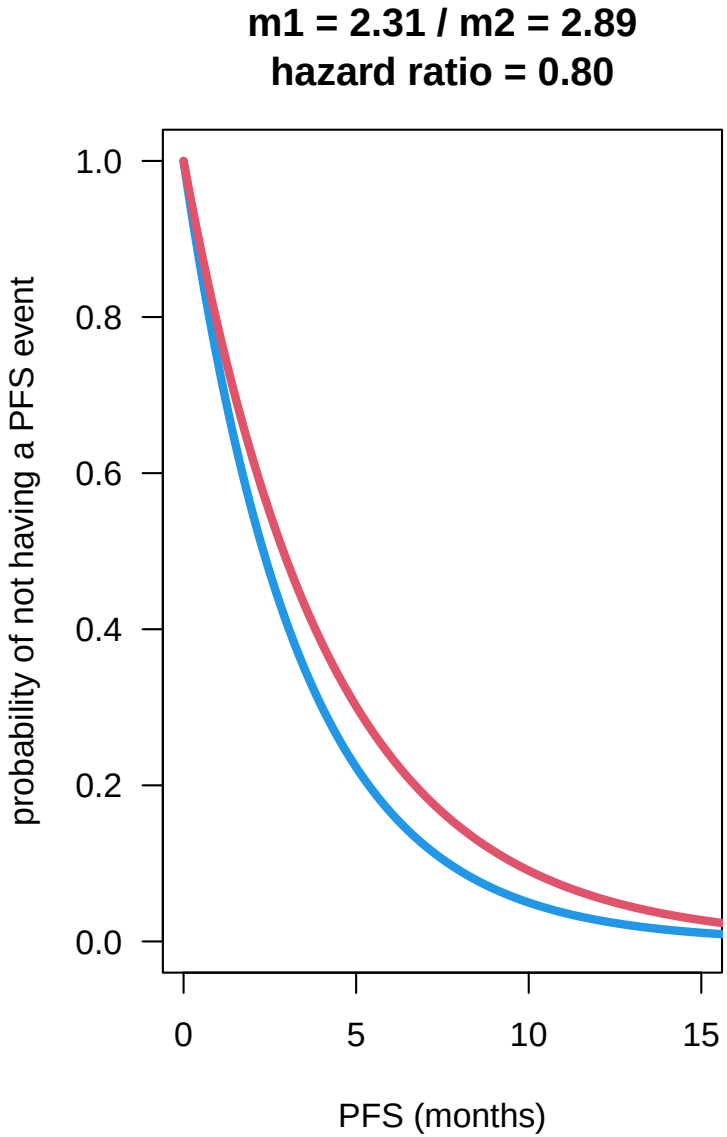
Example: exponential for PFS and OS

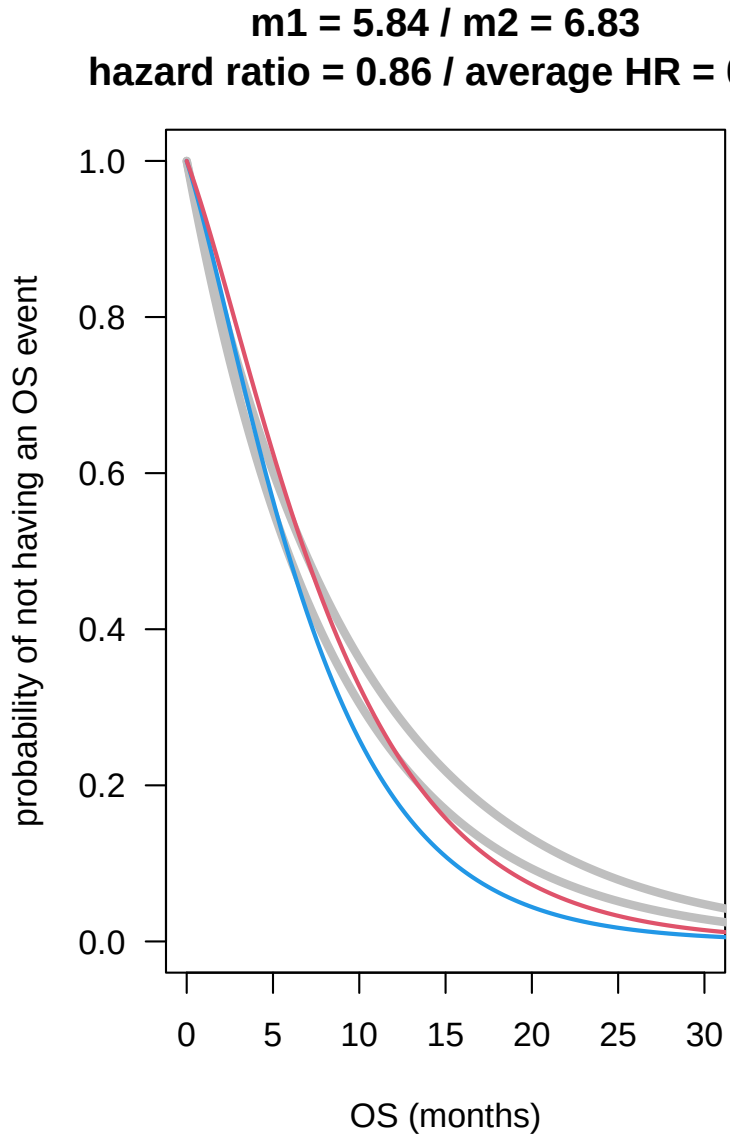




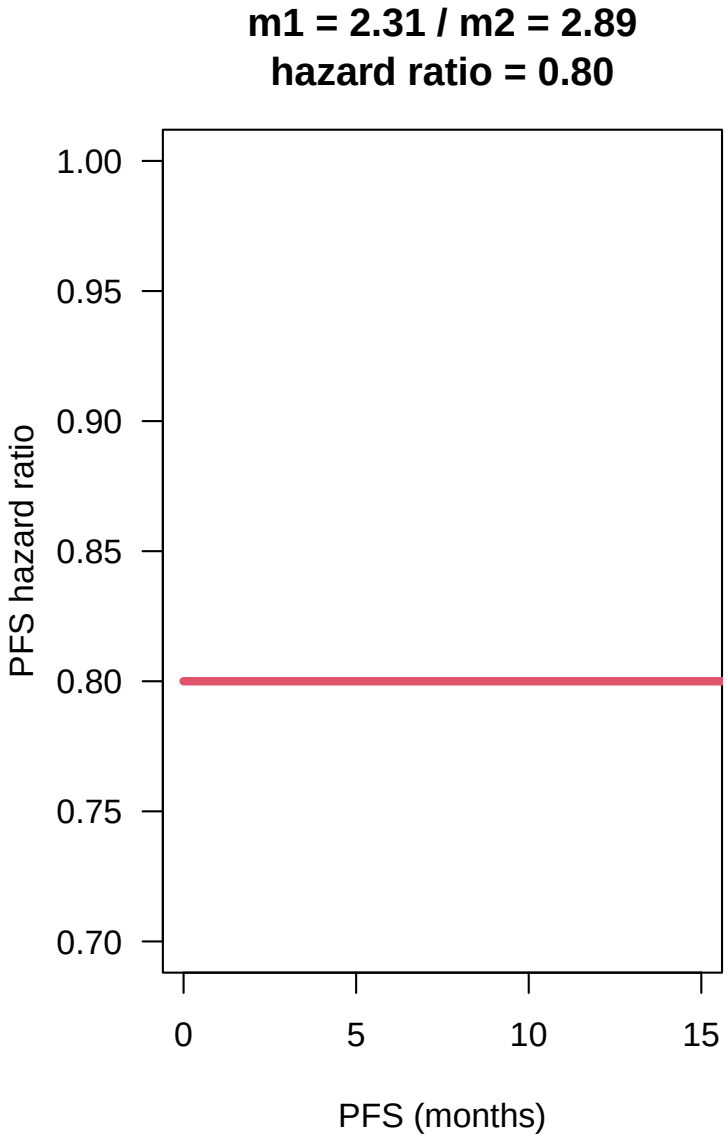
Compute necessary #events based on α-split and GSD assumptions.

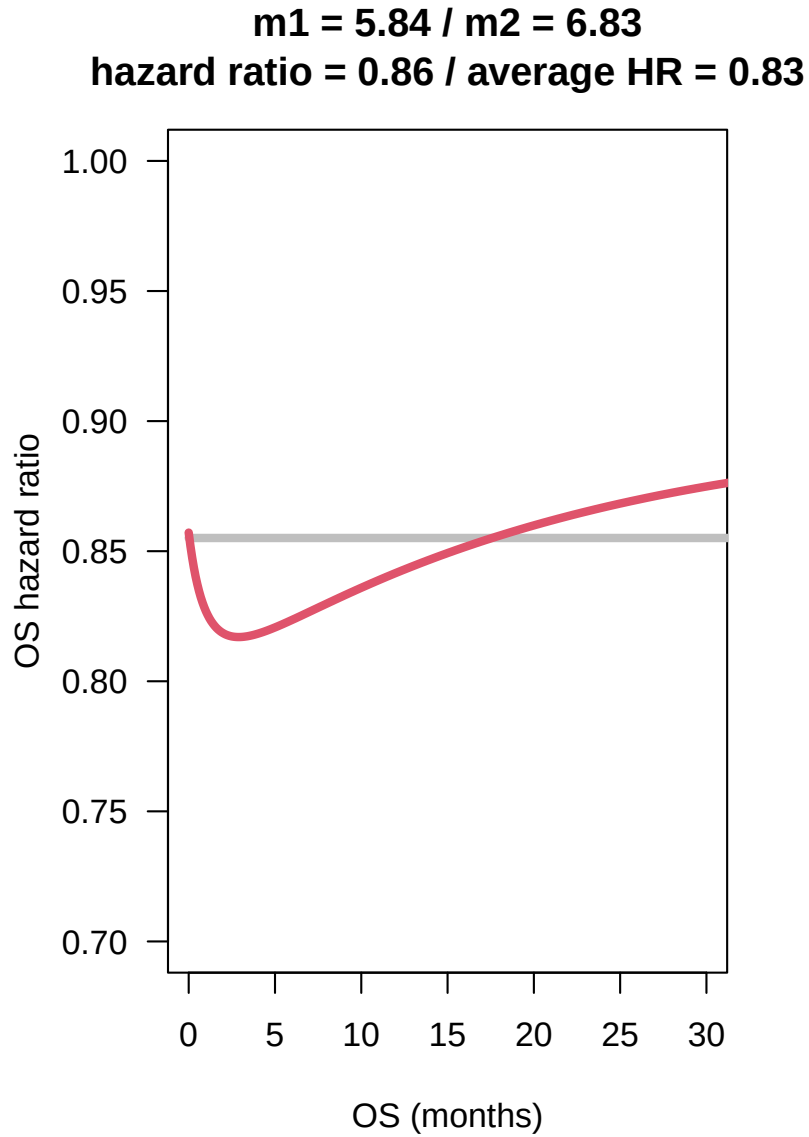
Example: median-matching survival functions induced by IDM





Example: hazard ratio as function of time - mind y-axis!





Induced hazard ratios

Hazard and hazard ratio for PFS:

$$\begin{aligned} h_{PFS}(t) &= \lambda_{01} + \lambda_{02}. \\ \theta_{PFS}(t) &= \frac{\lambda_{01,A} + \lambda_{02,A}}{\lambda_{01,B} + \lambda_{02,B}}. \end{aligned}$$

Constant as function of $t \Rightarrow$ **PH for PFS** for time-homogeneous transition hazards.

Hazard and hazard ratio for OS:

$$\begin{aligned} h_{OS}(t) &= \frac{(\lambda_{12} - \lambda_{02})(\lambda_{01} + \lambda_{02}) - \lambda_{01}\lambda_{12}\exp(-\lambda_{012}t)}{(\lambda_{12} - \lambda_{02}) - \lambda_{01}\exp(-\lambda_{012}t)}. \\ \theta_{OS}(t) &= h_{OS,A}(t)/h_{OS,B}(t). \end{aligned}$$

Proportional hazards for OS

Hazard ratio for OS:

$$\begin{aligned} h_{OS}(t) &= \frac{(\lambda_{12}-\lambda_{02})(\lambda_{01}+\lambda_{02})-\lambda_{01}\lambda_{12}\exp(-\lambda_{012}t)}{(\lambda_{12}-\lambda_{02})-\lambda_{01}\exp(-\lambda_{012}t)}. \\ \theta_{OS}(t) &= h_{OS,A}(t)/h_{OS,B}(t). \end{aligned}$$

When is $\theta_{OS}(t)$ independent of t?

- $\lambda_{12} = \lambda_{02}$ **in both groups**: progression has no impact on death hazard.
- $\lambda_{01} = 0$ **in both groups**: no progression occurs.
- $\lambda_{012} := \lambda_{12} - \lambda_{01} - \lambda_{02} = 0$: denominator of h_{OS} equal to 0.

Assumption that we have PH for PFS AND OS
unrealistic to hold in real clinical trial.

Clinical trial design via simulation from IDM

Clinical trial planning

- Type I error: P(reject **at least** one H_0 irrespective of which are true).
- Power: assume ≥ 1 H_1 is true:
  - **Endpoint-specific**: P(reject H_0) for each endpoint separately.
  - **At least**: P(reject ≥ 1 H_0 of **PFS and OS**).
  - **Joint**: P(reject both H_0 for **PFS and OS**).

Clinical trial design

Design feature	Standard approach	Illness-death model
Assumptions to make	Control medians and hazard ratios for PFS and OS	Transition-specific hazards
#quantities	4	6
Cor(PFS, OS)	Not exploited	Explicitly modelled through IDM
Proportional hazards	Assumed for OS, although not met	NPH properly induced through IDM
α allocation	Bonferroni	Bonferroni
Number of events	Schoenfeld's formula	Tune through simulation
Power	Disjoint per endpoint	Any type of power

Simulation of PFS - OS

Simulation of PFS and OS on patient level

In the past when simulating PFS and OS how did you make sure...

- ...PFS $\leq$ OS for each patient,
- ...PFS $=$ OS possible,
- ...association between PFS and OS transparent.

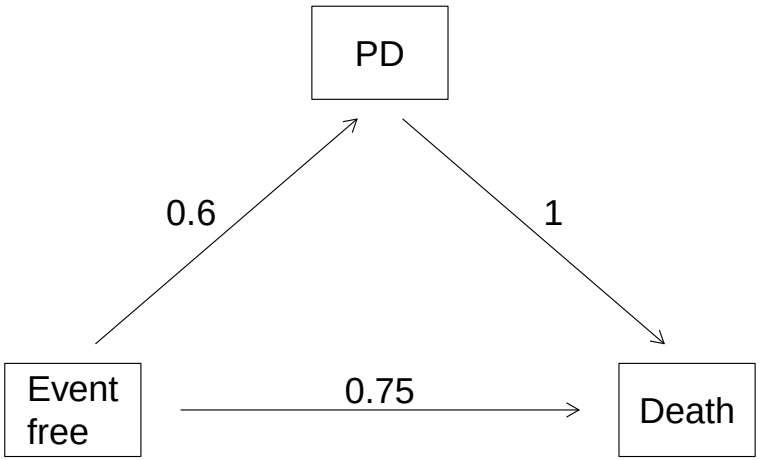
Simulation of (Markov) MSM:

- **Nested series of competing risk experiments**.
- MSM trajectors of individual in IDM can generated:
  1. Waiting time t_0 in initial state: Generated from CDF $F(t) = 1 - P_{00}(0, t)$.
  2. State entered at t_0: binomial experiment which decides with probability $\frac{\lambda_{01}(t_0)}{\lambda_{01}(t_0)+\lambda_{02}(t_0)}$ on State 1. If death $\Rightarrow$ stop,
  3. otherwise waiting time t_1 in State 1 is generated from CDF $F(t) = 1 - \exp(-\int_{t_0}^{t_0+s} \lambda_{12}(u)\ \mathrm{d}u)$.
  4. Death will happen at time $t_0 + t_1$.
- Add **drop-out** (random censoring) and **administrative censoring**.
- Non-Markov: model λ_{12} as function of entry time t_0 and time since time origin in Step 3 above.
- All implemented in **simIDM** on github and CRAN.

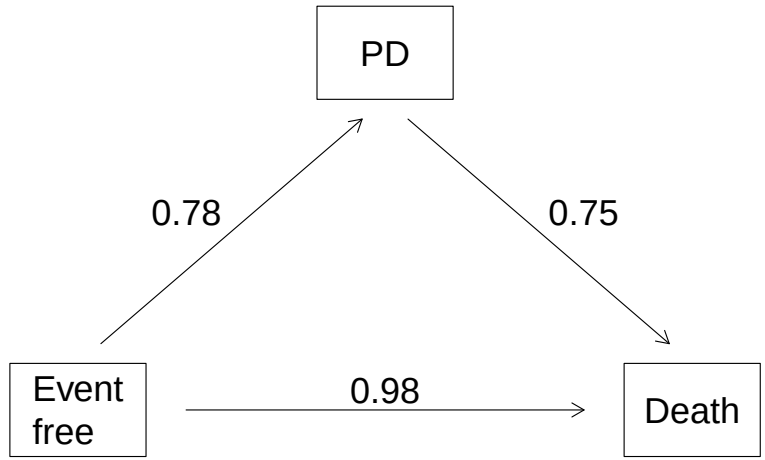
Scenarios

Scenarios

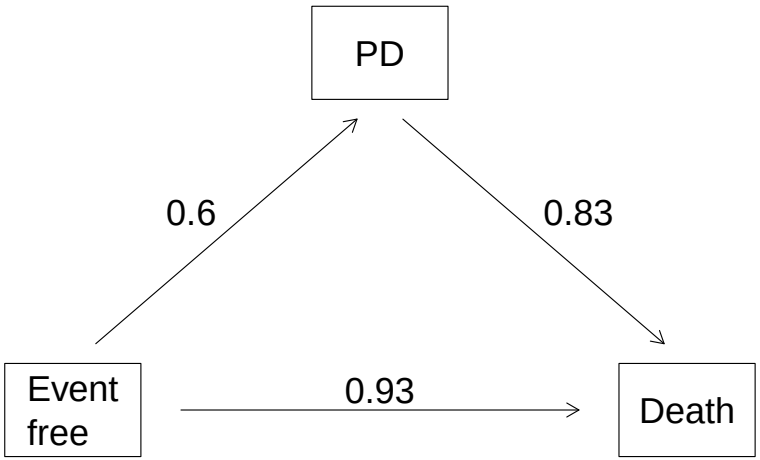
Scenario 1



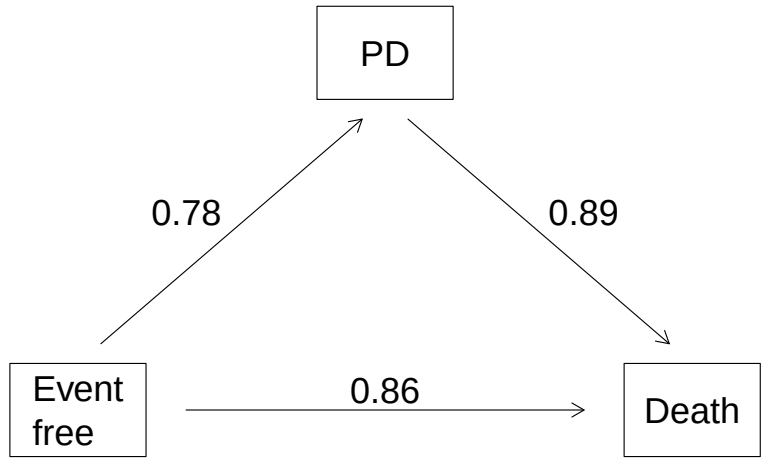
Scenario 3



Scenario 2



Scenario 4



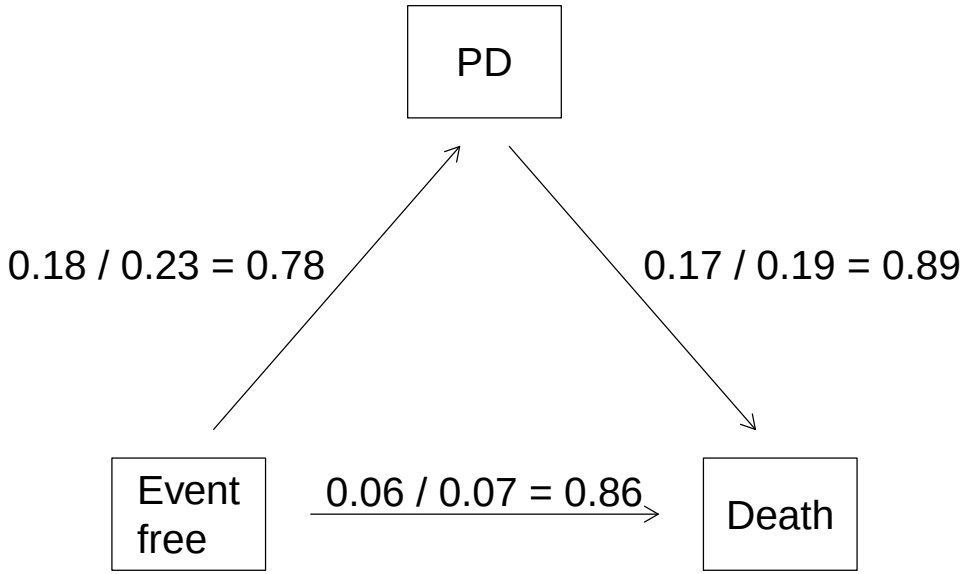
Paper

Results in paper:

- Plots of hazards.
- Plots of survival functions for PFS and OS.
- Comparison to exponential OS survival functions with same median.
- Plots of OS hazard ratio as function of time.
- Necessary number of events for PFS and OS for two scenarios:
  - Co-primary PFS and OS, one analysis each.
  - Co-primary PFS and OS, **OS interim at PFS final**.

Illustration using Scenario 4.

Scenario 4



Features:

- Drug effect on all transitions.
- PFS HR $= 0.8$.
- Average hazard ratio for OS: 0.832. Slightly different from paper.

How to plan a trial?

Co-primary endpoints PFS and OS, one analysis each

Global significance level: 0.05.

Design feature	**PFS**	**OS**
Local significance level	0.01	0.04
Critical value	2.576	2.054
Hazard ratio	0.80	0.832 (AHR)
Power	80%	80%
Events using Schoenfeld	939	992
Simulate from IDM under H_0	Empirical type I error: 0.0499	
Joint power of Schoenfeld sample size with these critical values	Joint power: 0.708	
Tune number of events to get endpoint-specific power of 80%	939	905
Empirical power per endpoint	0.797	0.801
Empirical joint power	Joint power: 0.686	

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Empirical joint power	Joint power: 0.686	

Before you ask...

...let me make a few comments

NPH for OS: should we use something else than logrank test and hazard ratio?

- Hypothesis test and effect quantification **independent** of MSM.
- adaptR tutorial "Sample size computation for two-sample time-to-event data using alternative methods to the log-rank test" (needs VPN).

What is role of the **Markov** assumption?

- Markov assumption: probability of future transition only depends on (i) state currently occupied and (ii) time t.
- If violated: individual transition hazards random quantities through dependence on history.
- S_{PFS}, S_{OS}: estimation straightforward even if X non-Markov.
- Meller *et al.* (2019): joint distribution of PFS and OS for non-Markov. Can be leveraged.

...let me make a few comments

Do we always **gain power** for OS? **No!**

Power for OS depends on:

- **Knowledge of PFS to "predict" OS**.
- **Induced shape** of survival functions. Relative effect can be smaller than, e.g., that of median-matching exponential survival functions.

Interim analysis for OS: see paper.

Does the IDM approach make some "regulatory-incompatible" assumptions?

- In our opinion **not at all**.
- Need to assume 6 transition-specific hazards. Maybe more uncommon to inform, but **conceptually no different** from PFS / OS medians.
- Current approach: assumes PH for OS $\Rightarrow$ we know can't be true!
- $\pm$ Markov.

Conclusions

Conclusions and outlook

Conclusions:

- Illness-death model for PFS and OS:
  - Properly account for **induced** $\theta_{OS}(t)$ for OS.
  - Exploit correlation between PFS and OS.
- Sample size for OS might **decrease** or **increase**!
- **Proper simulation** of PFS and OS on patient-level.

Outlook:

- **Broadly applicable**: surrogacy, interim decisions based on PFS, OS prediction, ...
- Combine subpopulation + illness-death model for PFS - OS. **Tira trials**.
- Extendable to more states, Beyer et al. (2020).

Resources

Resources

Resources:

- Meller et al., Meller *et al.* (2019).
- Paper on arxiv.
- Package **simIDM** on github and CRAN. Exponential, Weibull, piecewise exponential transition hazards.
- Linkedin post.
- Further MSM resources:
  - Beyer et al. on use of MSMs for early-phase decision-making, Beyer et al. (2020).
  - MS example.
  - Material of BBS seminar "Competing Risks and Multi-State Models".
  - oncomsm: R package by Boehringer colleagues, "Bayesian Multi-State Models for Early Oncology".

Thank you for your attention.

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http://go.roche.com/dss-mco

http://www.kasparrufibach.ch

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Backup

Multistate model formulation

Transition probabilities:

- **Full description** of multistate model by only assuming existence of intensities $\lambda_{01}, \lambda_{02}$ and λ_{12}.
- Formulas, even for **non-Markov** case: Aalen *et al.* (2008).

Meller *et al.* (2019):

- Embed PFS and OS in multistate model framework,
- formulas for P_{lm}'s assuming **Weibull** transition hazards for time-inhomogeneous Markov and semi-Markov (explicit),
- inference via **counting process likelihood**,
- $P(\mathrm{PFS} \leq u, \mathrm{OS} \leq v)$ for X non-Markov (generic).

Allows derivation of any functional of PFS and OS.

Assumptions for multistate model

Multistate model **sufficiently smooth** so that following intensities exist:

$$\begin{aligned}
\lambda_{0j}(t) &= \lim_{\Delta t \searrow 0} \frac{P(\mathrm{PFS} \in [t, t+\Delta t), X(\mathrm{PFS}) = j \,|\, \mathrm{PFS} \geq t)}{\Delta t}, \; j = 1, 2, \\
\lambda_{12}(t; t_1) &= \lim_{\Delta t \searrow 0} \frac{P(X(t+\Delta t) = 2 \,|\, X(t-) = 1, \mathrm{PFS} = t_1)}{\Delta t} \\
&= \lim_{\Delta t \searrow 0} \frac{P(\mathrm{OS} - \mathrm{PFS} \in [t - t_1, t - t_1 + \Delta t) \,|\, \mathrm{OS} \geq t, \mathrm{PFS} = t_1)}{\Delta t} \quad \text{for } \mathbf{t_1 < t}.
\end{aligned}$$

t_1: observed PFS time, i.e. time when leaving state 0.

Assumptions for multistate model

$X(t)$ **Markov**:

- **Time-inhomogeneous**: intensity of death after progression does not depend on time of progression, $\lambda_{12}(t; t_1) = \lambda_{12}(t)$ for all $t_1 < t$.
- **Homogeneous**: intensities are time-constant, i.e. **Exponential**, $\lambda_{ij}(t) = \lambda_{ij}, i, j = 0, 1, 2$.

$X(t)$ **non-Markov** (= semi-Markov for illness-death model without recovery):

- Intensities depend on state patient is in at s and entire history $\leq s$, i.e. all transitions.
- Relevant for $1 \to 2$ transition only, as $0 \to 1, 2$ are rooted in initial state 0.

As soon as a quantity depends on $1 \to 2$ **transition** we need to be specific about assumption on $X(t)$.

Illness-death multistate model for PFS and OS

Transition probabilities to move from state l at time s to state m at time t:

$$P_{lm}(s,t) \quad := \quad P(X(t) = m | X(s) = l, \text{history}).$$

Illness-death model w/o recovery, P_{lm} as functions of transition intensities, Aalen *et al.* (2008):

$$\begin{aligned}
P_{00}(s,t) &= \exp\left(-\int_s^t \lambda_{01}(u) + \lambda_{02}(u)\,\mathrm{d}u\right), \\
P_{11}(s,t;\mathbf{t_1}) &= \exp\left(-\int_s^t \lambda_{12}(u;t_1)\,\mathrm{d}u\right), \\
P_{22}(s,t) &= 1, \\
P_{01}(s,t) &= \int_s^t P_{00}(s,u_-)\lambda_{01}(u)P_{11}(u,t;u)\,\mathrm{d}u, \\
P_{12}(s,t;\mathbf{t_1}) &= 1 - P_{11}(s,t;\mathbf{t_1}), \\
P_{02}(s,t) &= 1 - \Big(P_{00}(s,t) + P_{01}(s,t)\Big).
\end{aligned}$$

If $X(t)$ non-Markov:

- P_{11} and P_{12} depend on **PFS time** t_1.
- Although P_{01}, P_{02} depend on λ_{12} they **do not depend on** t_1.

Intuition behind transition probabilities

$P_{00}(s,t)$, $P_{11}(s,t;t_1)$: exp of cumulative hazards $\Rightarrow$ standard survival functions.

$P_{01}(s,t) = \int_s^t P_{00}(s,u_-)\lambda_{01}(u)P_{11}(u,t;u)\,\mathrm{d}u$: integral of

- $P_{00}(s,u_-)\lambda_{01}(u)$: "infinitesimal probabilities" to move from 0 to 1 at time u, $u \in (s,t]$,
- $P_{11}(u,t;u)$: subsequently stay in state 1 until at least time t, with progression happened in u.

Multistate model for PFS and OS

Joint distribution:

$$\begin{aligned} P(\mathrm{PFS} \leq u, \mathrm{OS} \leq v) &= P(X(u) \in \{1,2\}, X(v) = 2) \\ &= P(X(v) = 2 | X(u) = 1) \cdot P_{01}(0,u) + P_{02}(0,u). \end{aligned}$$

X **inhomogeneous Markov**: $P(X(v) = 2|X(u) = 1) = P_{12}(u,v)$ independent of progression time $t_1 \leq u$.

X **non-Markov**:

- Integrate $P_{12}(u,v;t_1)$ over conditional distribution of all possible progression times $t_1 \leq u$.
- Formula tedious (see Meller *et al.* (2019)) $\Rightarrow$ **simulate** in applications.

Doing now what patients need next

R version and packages used to generate these slides:

R version: R version 4.2.3 (2023-03-15 ucrt)

Base packages: stats / graphics / grDevices / utils / datasets / methods / base

Other packages: checkmate / survival / rpact / reporttools / xtable / prodlim / simIDM

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