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Tutorial on survival analysis and its application to the assessment of competing risks in clinical data analysis.

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Objectives

- **Part 1: Fundamentals**. The theory of survival analysis including competing risks (Andy).

- **Part 2: Application.** Multistate models and patient benefit (Joachim).

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Acknowledgments

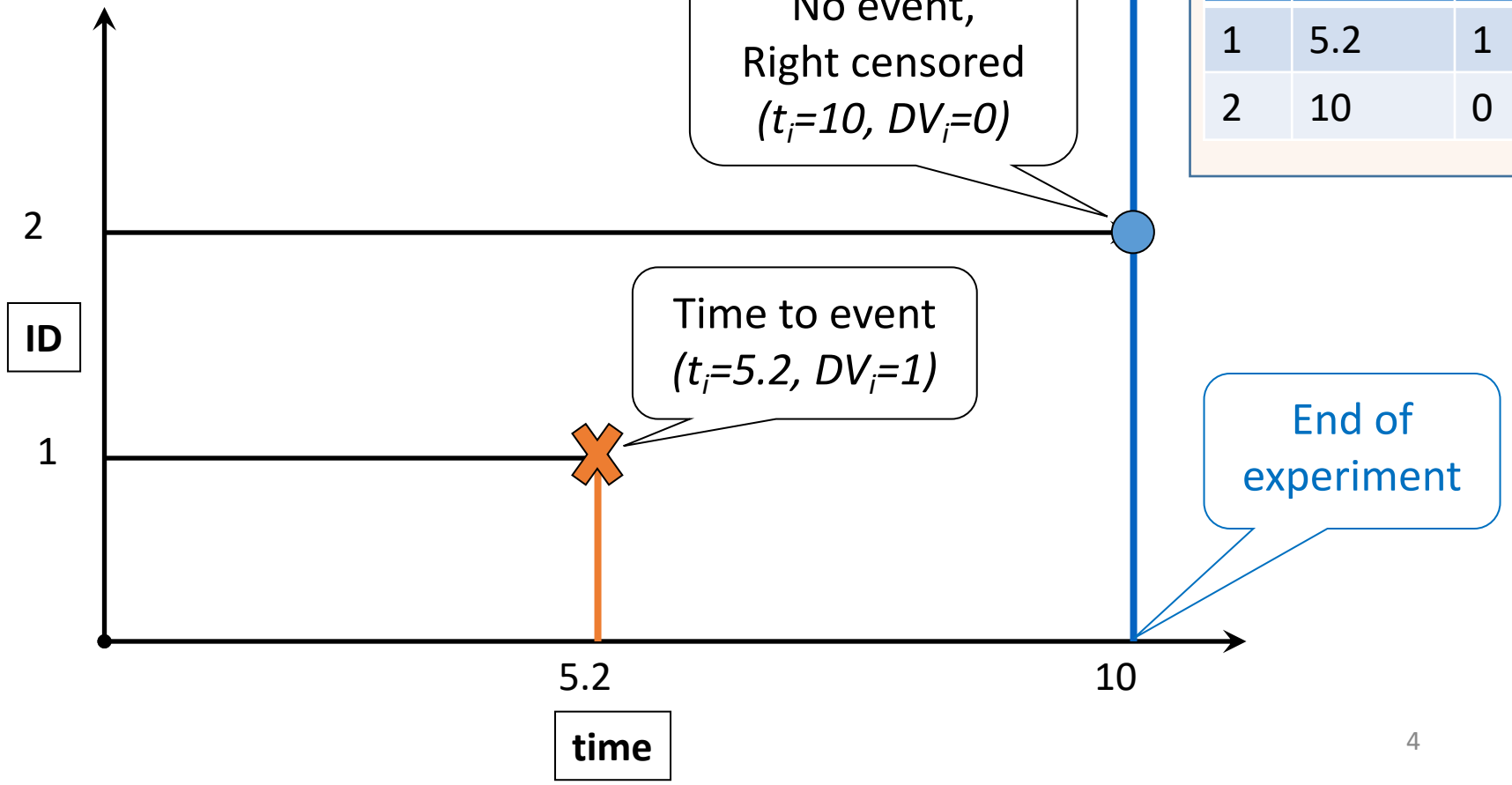
Many of these slides are derived from a set of slides developed by myself and:

- Ulrika Simonsson, Uppsala University
- Mats Karlsson, Uppsala University

Survival analysis based on time-to-event (TTE)

Event examples

- Death
- Cardiovascular death
- Drop-out from study
- A side effect (e.g. nausea)
- Progression (cancer, HIV/AIDS)
- Discharge from hospital



Dataset

ID	TIME	DV
1	5.2	1
2	10	0

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Survival assessment

- **Survival function= S(t)**: the probability of individual survival beyond time *t*

$$S(t) = \Pr(T > t)$$

t is some time
T is a random variable denoting the TTE

- **Cumulative distribution function F(t)**: The probability of individual having an event before, or at, time t

$$F(t) = \Pr(T \leq t) = 1 - S(t)$$

Non-parametric estimates of S(t)

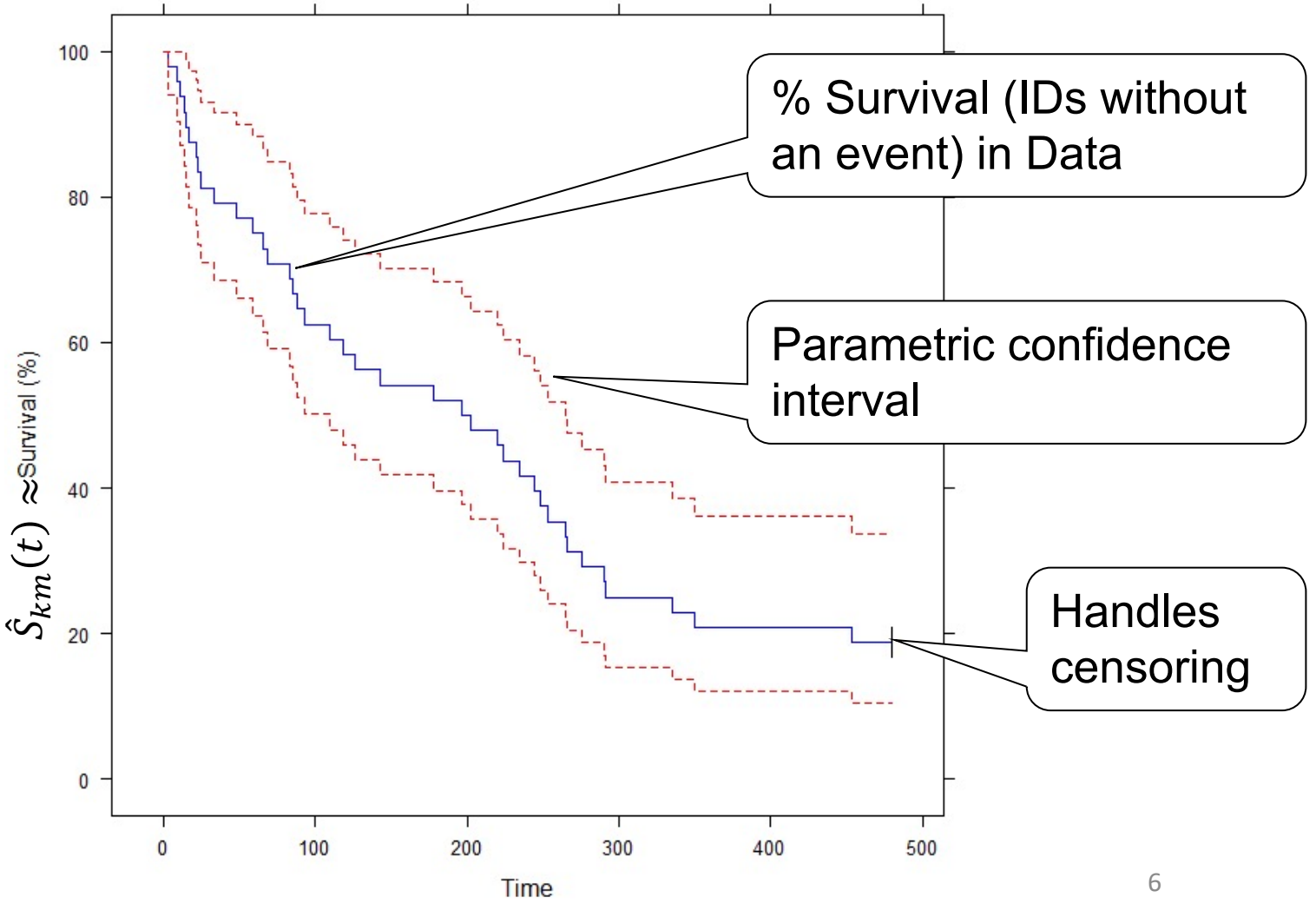
Kaplan-Meier estimator

$$\hat{S}_{km}(t) = \prod_{i:\, T_i \leq t} \left(1 - \frac{ne_i}{n_i}\right)$$

ne_i : The number of events at T_i

n_i : The number of individuals who have not had an event or censoring at or before T_i

Implicitly assumes that censored observations will have events in the future



Models for survival functions

- Often based on the hazard function h(t): The instantaneous rate of demise at time t, conditional on survival to that time

$$h(t) = \lim_{\Delta t \to 0} \frac{\Pr[(t \le T < t + \Delta t) \mid T \ge t]}{\Delta t}$$

To build a likelihood

Dataset

ID	TIME	DV
1	5.2	1
2	10	0

Probability of surviving beyond a time t (right censored data, t=T, DV =0):

$$S(t) = \exp(-\int_0^t h(u)\, \partial u)$$

Probability density function for having an event at time t (t=T, DV =1):

$$\mathrm{f}(t) = \lim_{\Delta t \longrightarrow 0} \frac{\Pr(t \le T < t + \Delta t)}{\Delta t} = h(t)S(t)$$

As long as h(t)>0 then $\lim_{t\to\infty} S(t) = 0$. Censored observations will have events in the future

Common hazard modeling approaches

- **Semi-parametric**: Cox proportional hazard model

$$h(t) = HR = \frac{h_1(t)}{h_2(t)} = \frac{h_0(t)e^{\beta x_1}}{h_0(t)e^{\beta x_2}} = e^{\beta(x_1 - x_2)}$$

Model Parameters

Covariates

  - Estimates hazard ratios (HR) … relative risk between groups

- **Parametric**: Absolute risk, baseline is modeled.

$$h(t) = h_0(t) \cdot h_a(x, \beta)$$

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Pharmacometric survival analysis?

- Typically fully parametric (modeled baseline)
  - Can more easily handle time-varying covariates (e.g. exposure instead of AUC)

$$h_0(t) = \lambda\alpha(\lambda t)^{\alpha-1}$$

$$h_a(t) = h_0 \cdot (1 - \frac{Cp}{Cp + C50})$$

  - Clinical trial simulations

- Joint models: Shared parameters with other models
  - E.g. failure to include dropout may introduce bias in parameter estimates

- Repeated events (traditionally not handled in standard analysis)

Designs can be optimized using these parametric models.

- Optimization of dose levels, number of individuals in each group.
- Adaptive procedures allow for fewer assumptions about model structure.

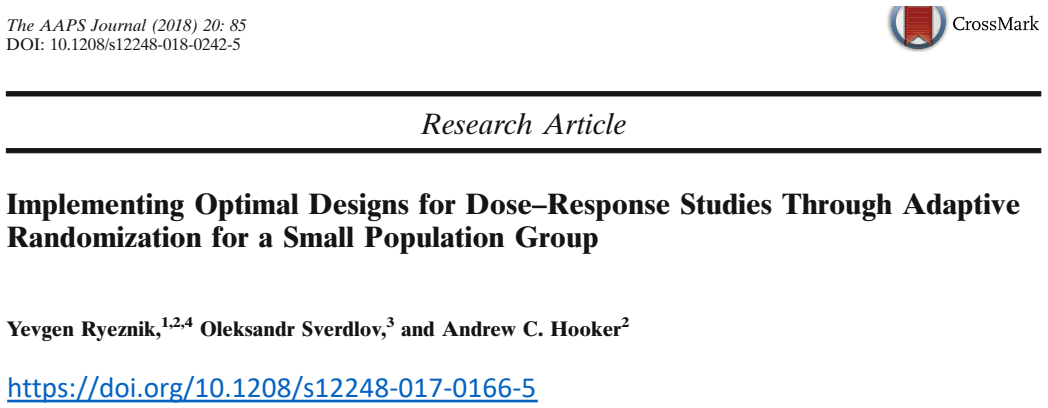
The AAPS Journal (2018) 20: 24
DOI: 10.1208/s12248-017-0166-5

Research Article

Adaptive Optimal Designs for Dose-Finding Studies with Time-to-Event Outcomes

Yevgen Ryeznik,[1,2,4] Oleksandr Sverdlov,[3] and Andrew C. Hooker[2]

https://doi.org/10.1208/s12248-017-0166-5



The AAPS Journal (2018) 20: 85
DOI: 10.1208/s12248-018-0242-5

Research Article

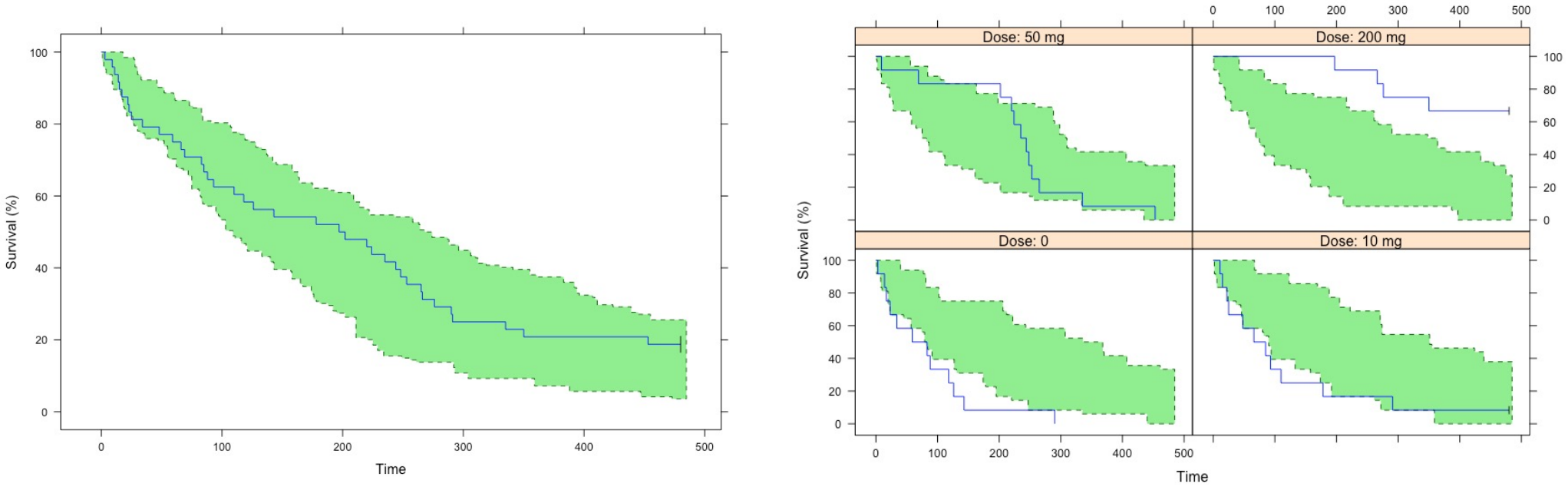
Implementing Optimal Designs for Dose–Response Studies Through Adaptive Randomization for a Small Population Group

Yevgen Ryeznik,[1,2,4] Oleksandr Sverdlov,[3] and Andrew C. Hooker[2]

https://doi.org/10.1208/s12248-017-0166-5

Goodness-of-fit for parametric survival analysis models

Visual Predictive Check



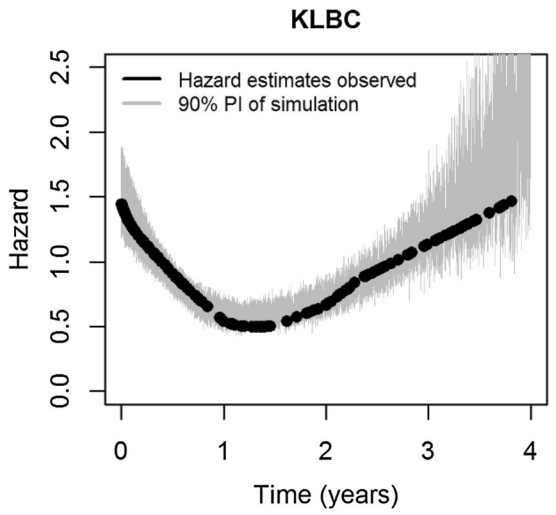
Kaplan-Meier plot of data (blue line) and 95% prediction intervals of the Kaplan-Meier plot (green area, 100 simulations).

May also see VPCs for the cumulative distribution function F(t):
The probability of individual having an event before, or at, time t

$$F(t) = \Pr(T \le t) = 1 - S(t)$$

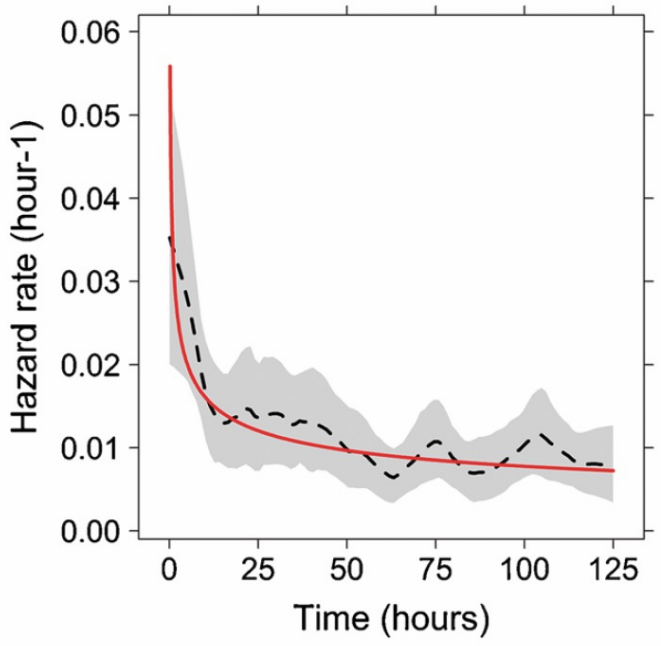
Model building tools

Hazard assessment: Hazard based visual predictive check



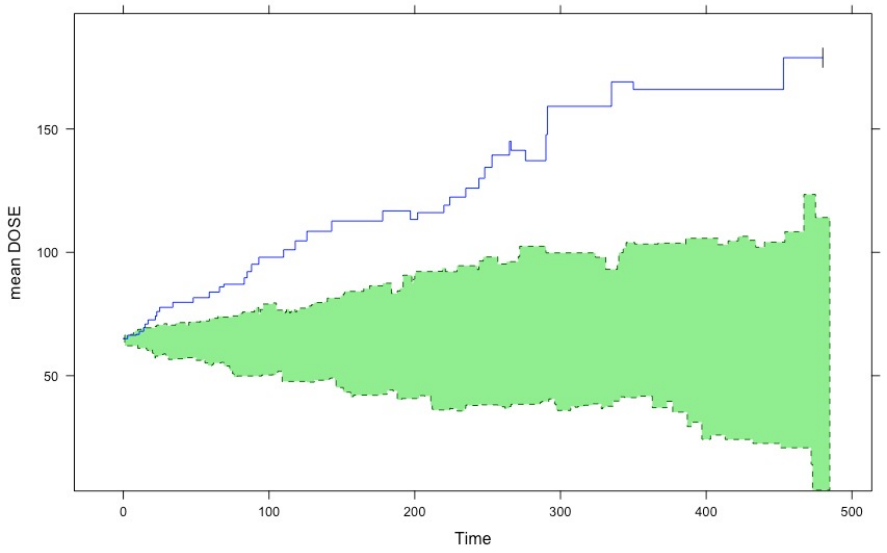
[Huh, Hutmacher, JPKPD, 2016]

Hazard assessment: Kernel-Based Visual Hazard Comparison (kbVHC)



[Goulooze et al, AAPS J, 2018]

Covariate assessment: The Kaplan-Meier Mean Covariate plot (KMMC)



[Hooker, Karlsson, PAGE, 2012]

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Other tutorials on survival analysis

Holford & Lavielle, PAGE, 2011

Citation: CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e43; doi:10.1038/psp.2013.18

www.nature.com/psp

TUTORIAL

A Time to Event Tutorial for Pharmacometricians

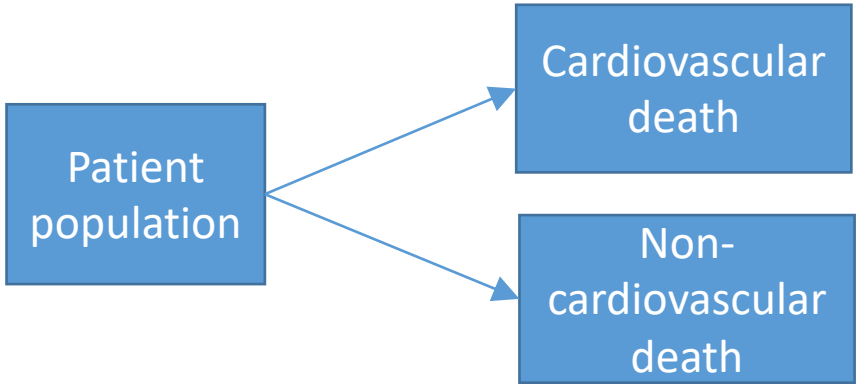
Nick Holford[1]

Models for time to event provide the link between standard pharmacokinetic–dynamic models disease progression, and clinical outcome events. The biological basis for events may be expressed quantitatively in terms of a hazard function. This tutorial explains hazards and how doses can be linked to events predicted from hazard functions.
CPT: Pharmacometrics & Systems Pharmacology (2013) **2**, e43; doi:10.1038/psp.2013.18; advance online publication 15 May 2013

https://dx.doi.org/10.1038%2Fpsp.2013.18

A Hiccup: competing risks

- Assume we want to study time to death attributable to a cardiovascular cause



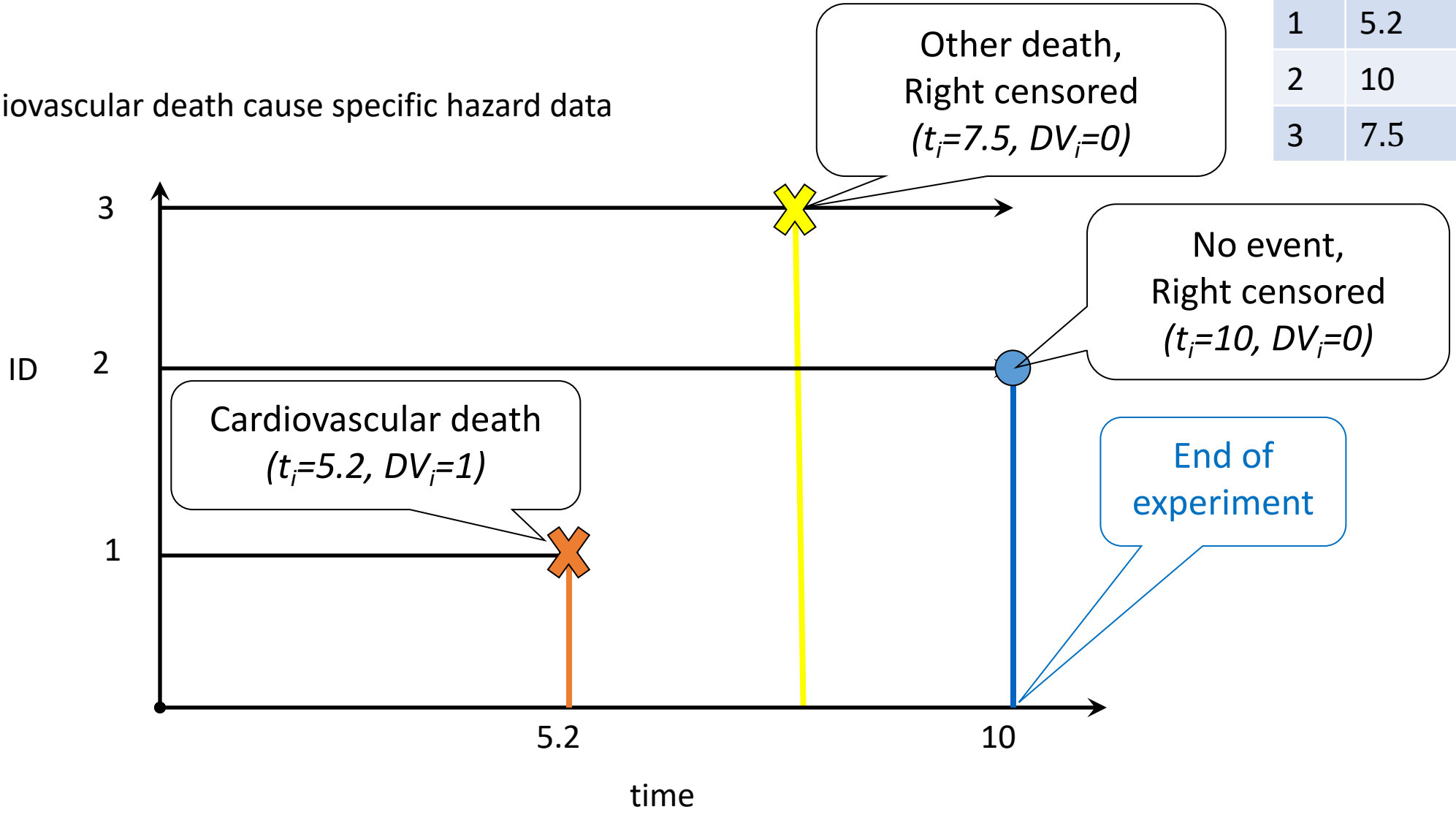
If non-cardiovascular death occurs, cardiovascular death will never occur

- Standard methods would separate the two causes and treat events of the other type as censoring events (for Kaplan-Meier and semi-parametric and parametric cause-specific hazard modeling).
  - Assumes that censored observations will have events in the future! (this is wrong)
  - This may overestimate the size of the hazard! (this is bad)

Cause specific hazard function

ID	TIME	DV
1	5.2	1
2	10	0
3	7.5	0

Cardiovascular death cause specific hazard data



An solution for competing events: The Cumulative Incidence Function (CIF)

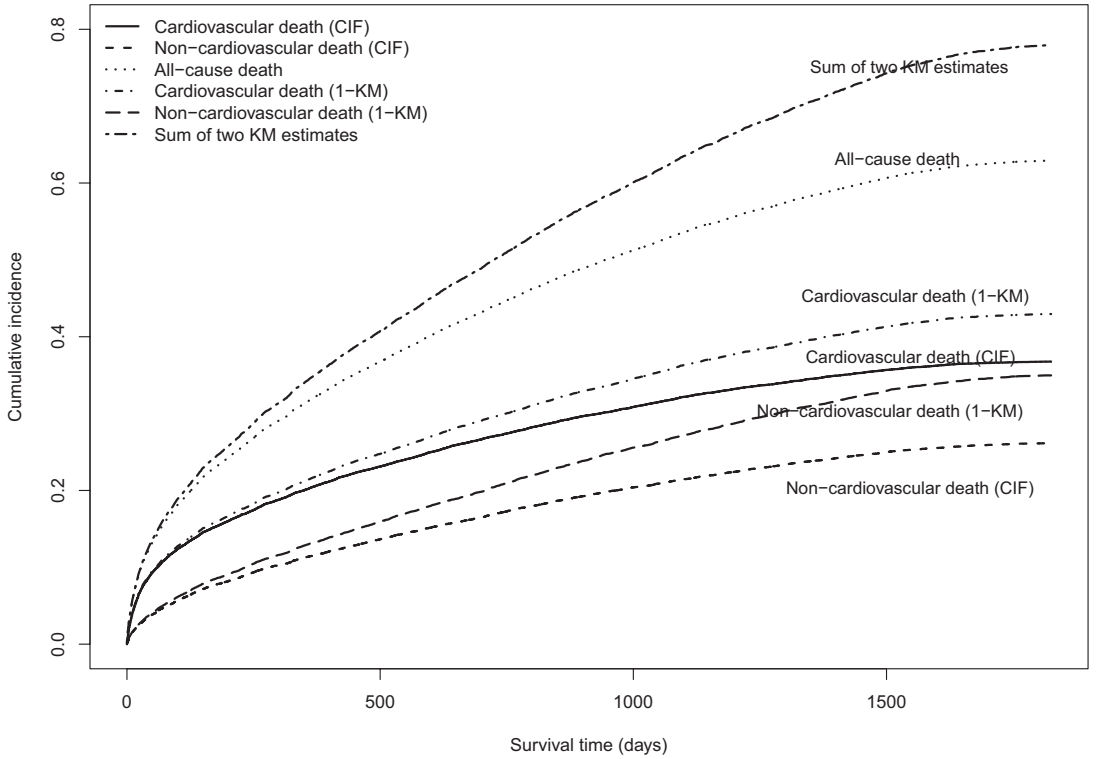
- The probability of experiencing the event k before time t and before the occurrence of a different type of event.

$$CIF_k(\mathrm{t}) = \Pr(\mathrm{T} \leq \mathrm{t}, \mathrm{D} = \mathrm{k})$$

- *Non-parametric estimator*

$$\widehat{CIF}_{\mathrm{np},k}(t) = \sum_{i:\, T_i \leq t} \hat{S}_{\mathrm{km},\, all\ causes}(t)\, \frac{ne_{\mathrm{k},i}}{n_i}$$

$ne_{k,i}$: The number of events of type k at T_i
n_i : total number of observations at risk at time T_i



Austin et al, Circulation, 2016

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Semi-parametric method for modeling the CIF

- Fine-Gray model: A Proportional Hazards Model for the Subdistribution of a Competing Risk
- Proportional Hazard model to describe a hazard derived from CIF

$$h_{k,CIF}(t) = -\frac{d}{dt}\ln(1 - CIF_k(\mathrm{t}))$$

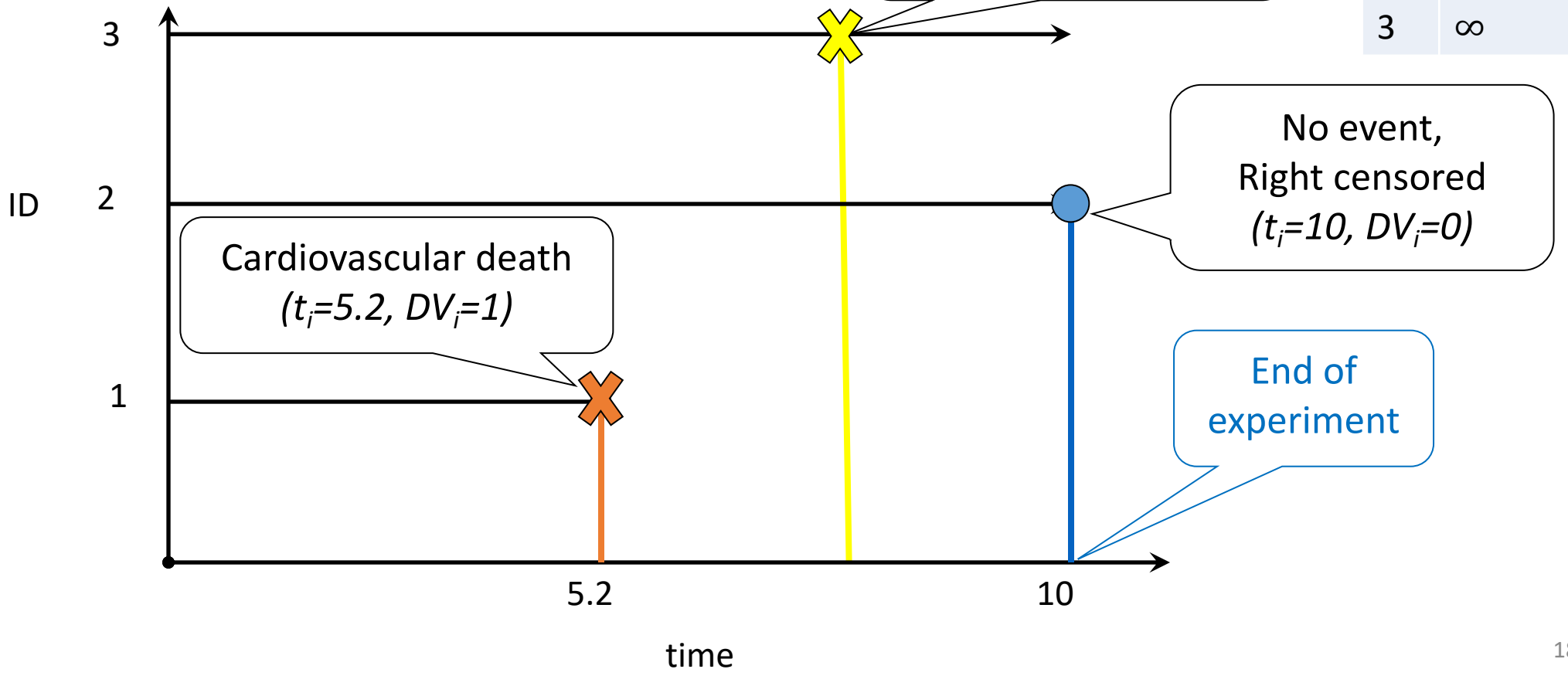
- This is called a “subdistribution hazard”: instantaneous risk of failure from the *kth* event type in subjects who have not yet experienced an event of type *k (including* those who have previously experienced a competing event).

Fine & Gray, JASA, 1999. Langenhorst et al, Blood advances, 2019

Modeling the subdistribution hazard function parametrically

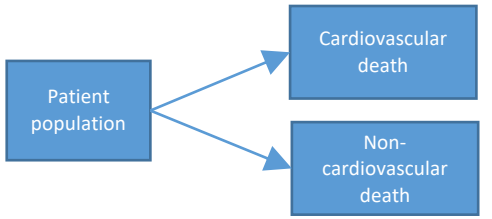
instantaneous risk of failure from the *k*th event in subjects who have not yet experienced an event of type *k (including* those who have previously experienced a competing event).

ID	TIME	DV
1	5.2	1
2	10	0
3	7.5	0
3	∞	1

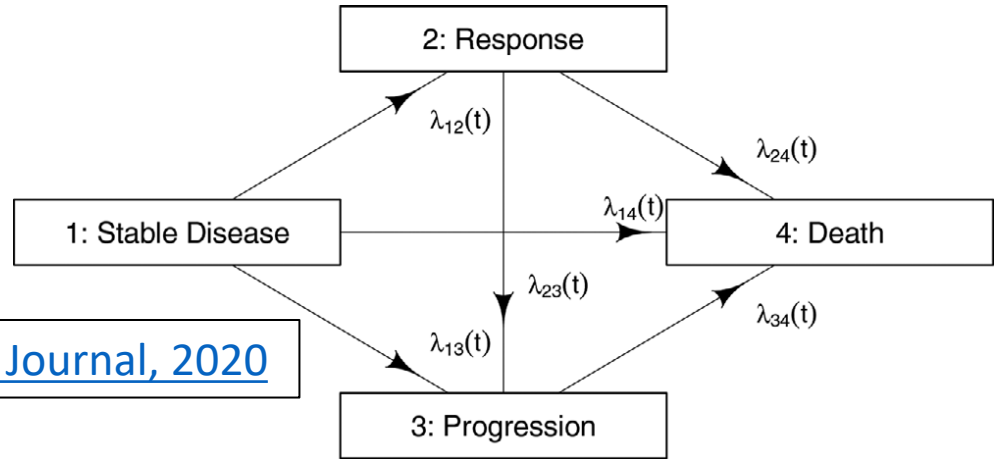


An alternative approach: Multi-state models for survival analysis

- Potentially a more natural representation of the system



- Events prior to the event(s) of interest may substantially change the risk of the event of interest to occur.



Beyer et al, Biometrical Journal, 2020

Ibrahim et al, PAGE 2019

Krishnan et al, CPT:PSP, 2021
Krishnan et al, PAGE, 2021

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Conclusions

- Survival analysis can be very useful but will typically not account for competing events, which may bias the analysis.
- Methods that account for competing events exist and should be used when competing events are present.