To use a cure model or not, is that the question ?

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Joint work with Aurélie Bertrand

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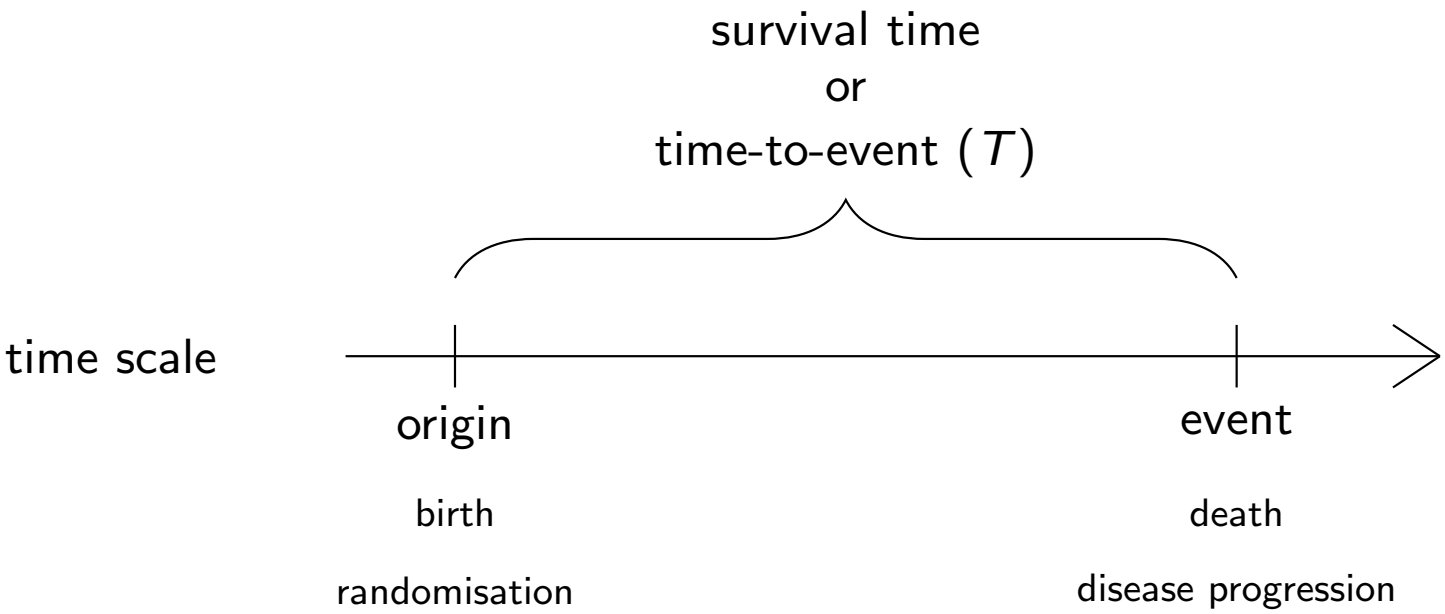
DISCLAIMER: A special thanks to M. Amico from whom I have stolen several introductory slides!!

So, what are we talking about ?

- Time-to-event or survival data analysis



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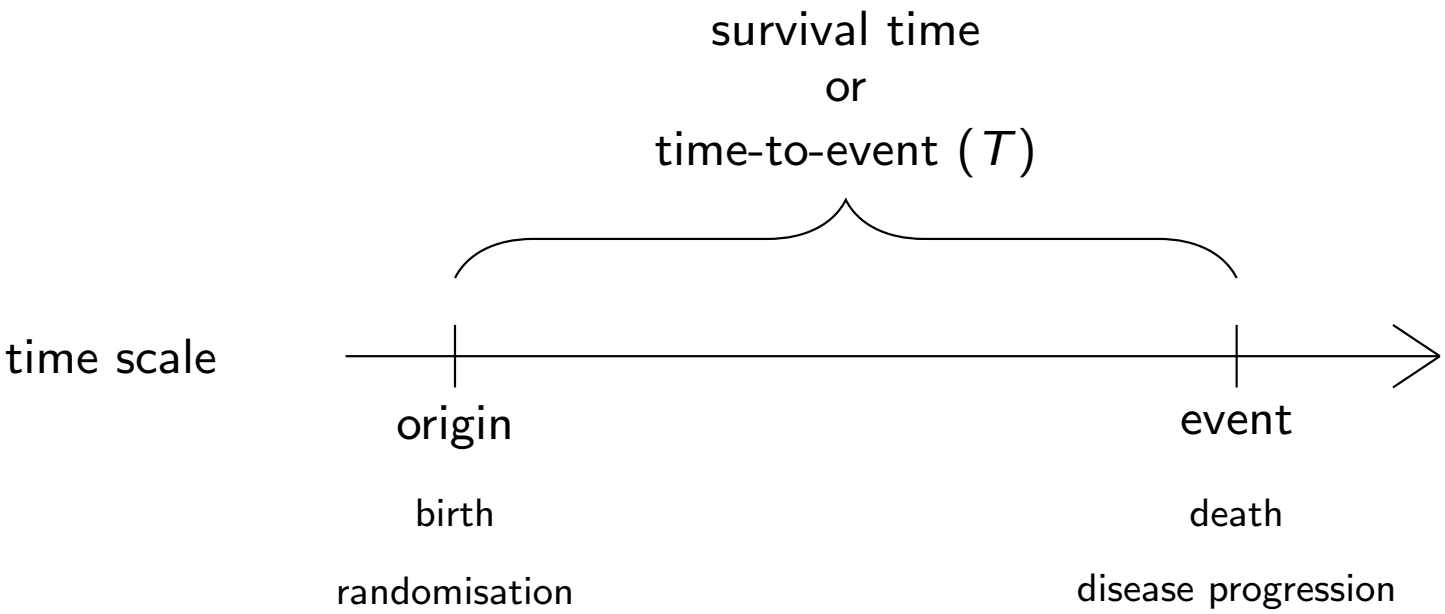
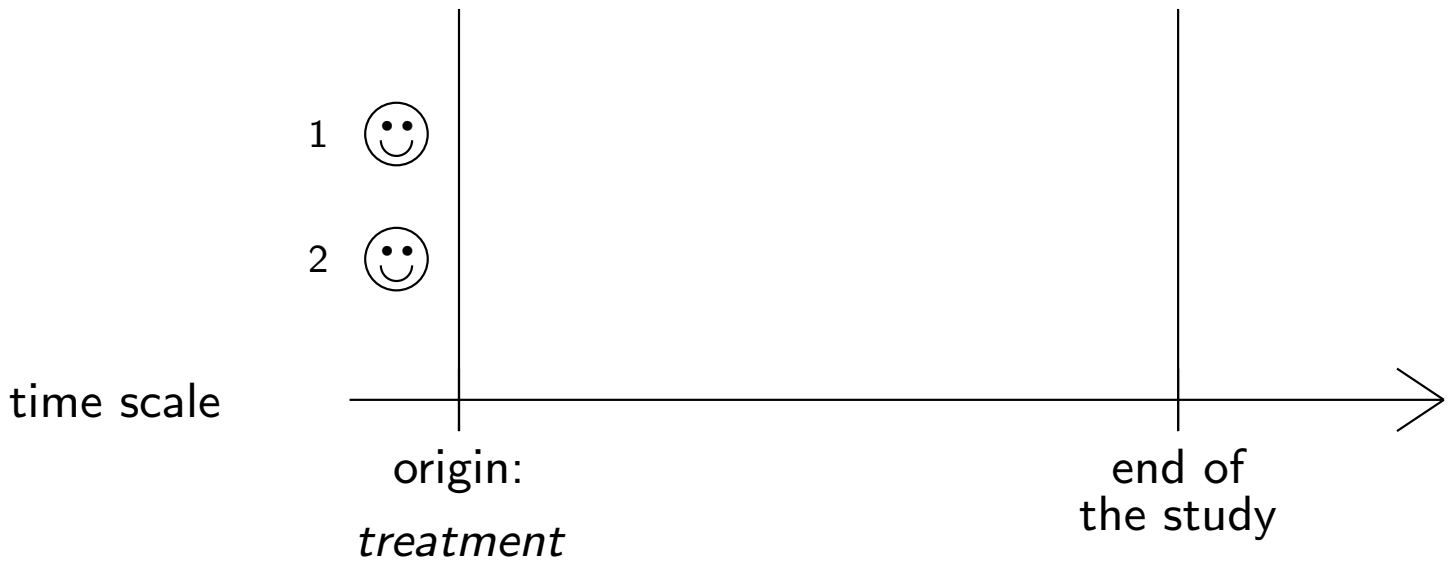


- Main function of interest:

$$S(t) = 1 - F(t) = P(T > t)$$

A well-known phenomenon: right-censoring

In practice: it is not possible to follow all observations until the occurence of the event of interest



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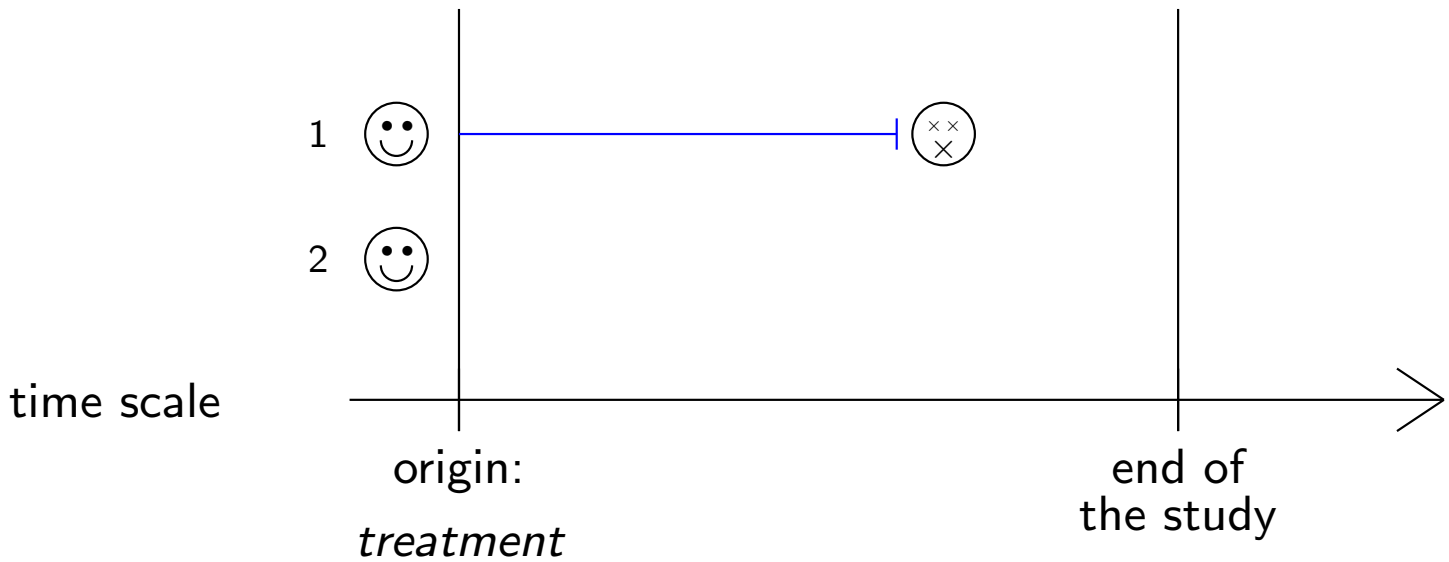

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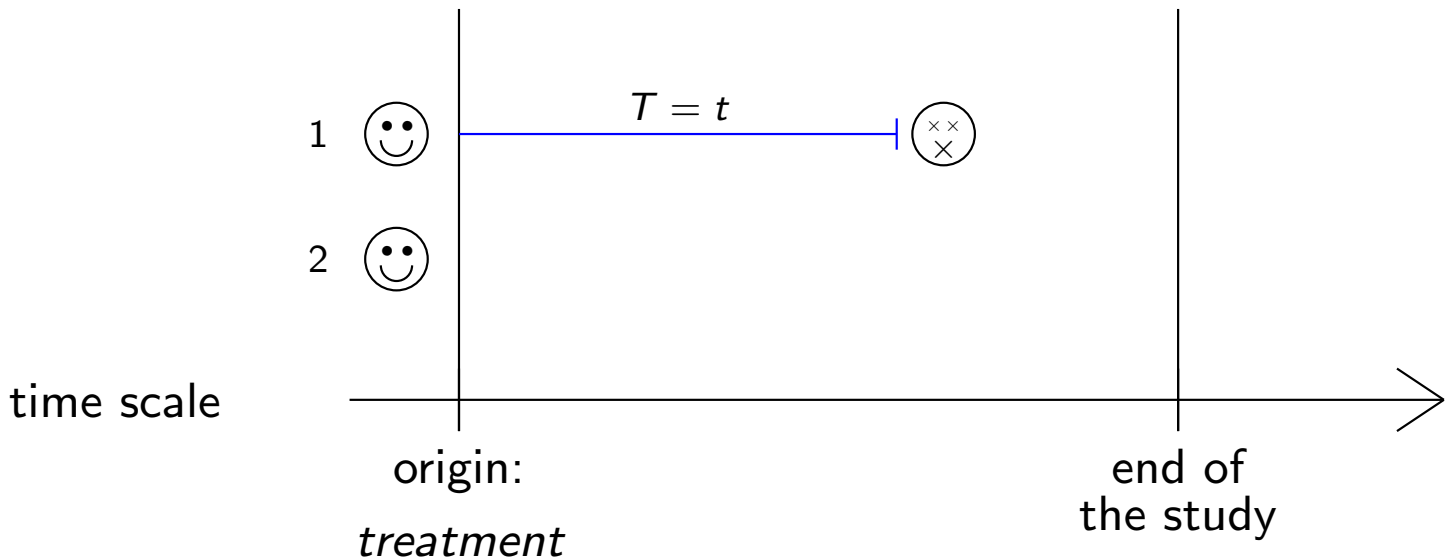

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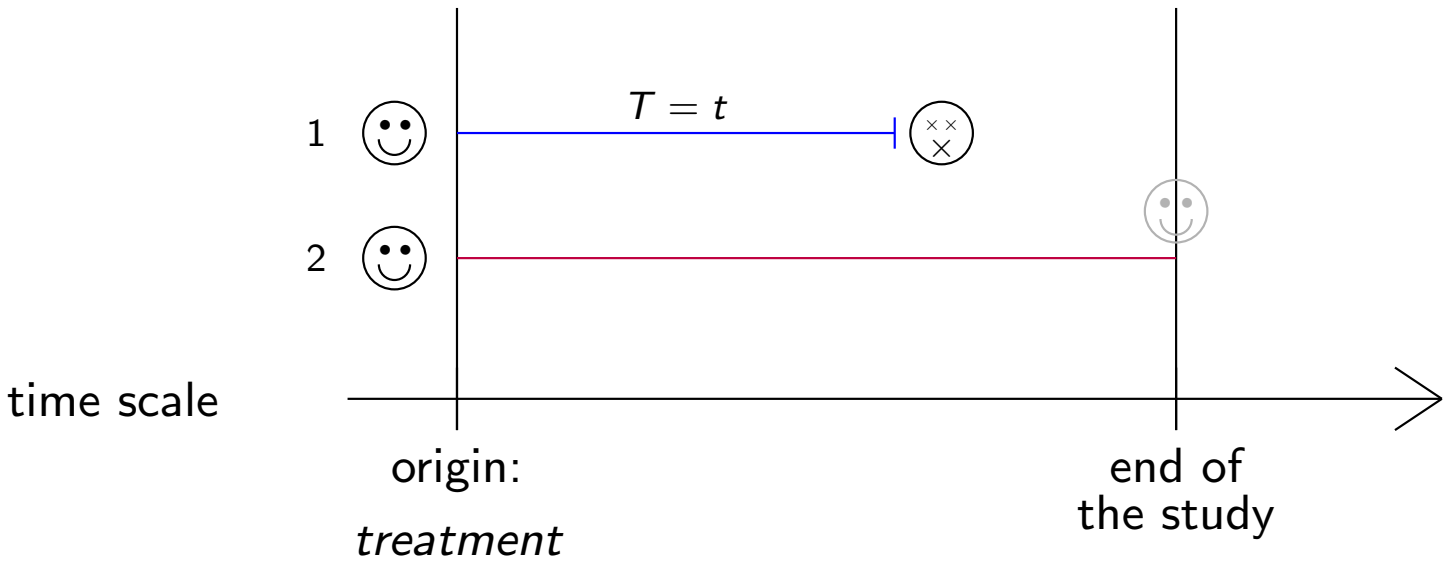

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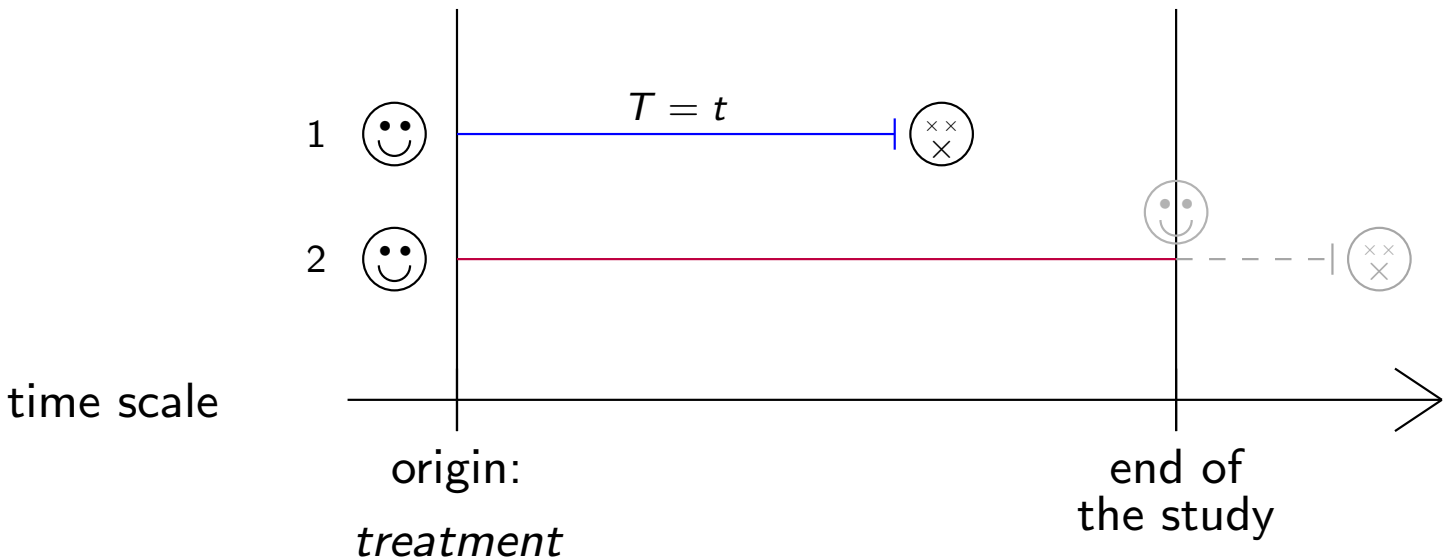

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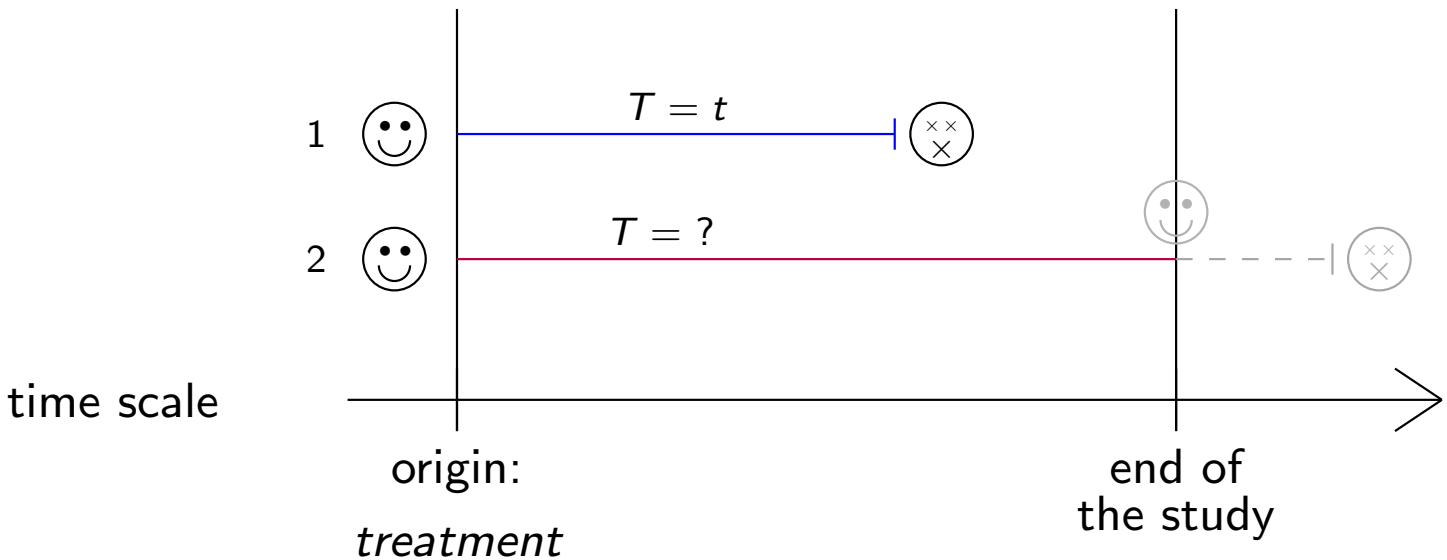

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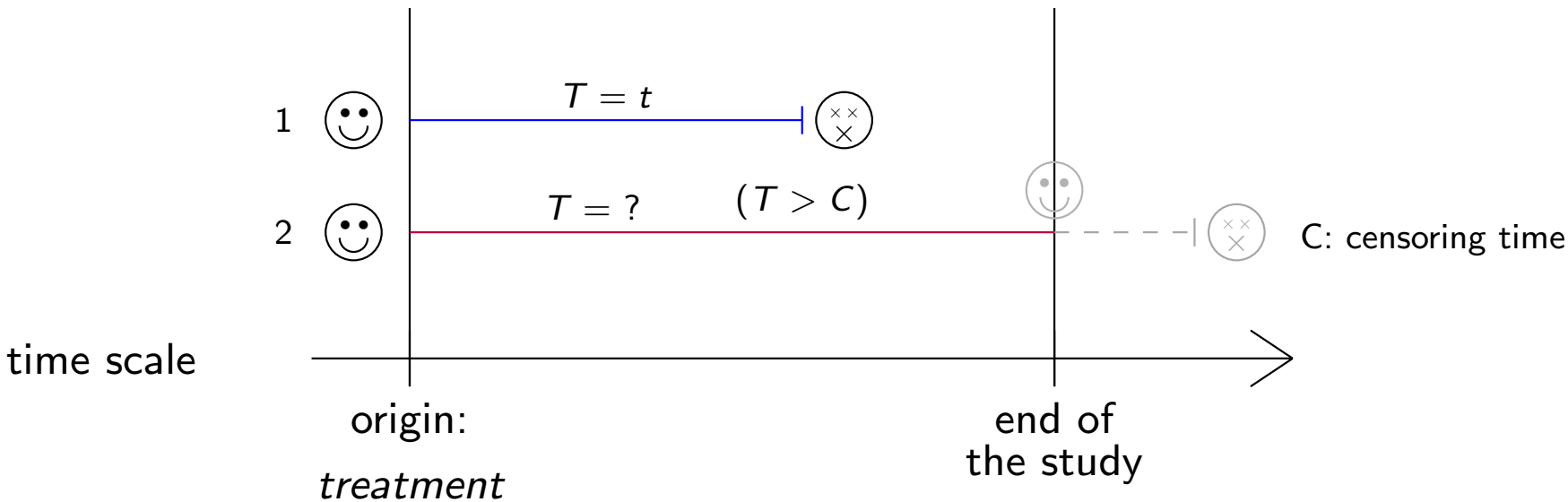

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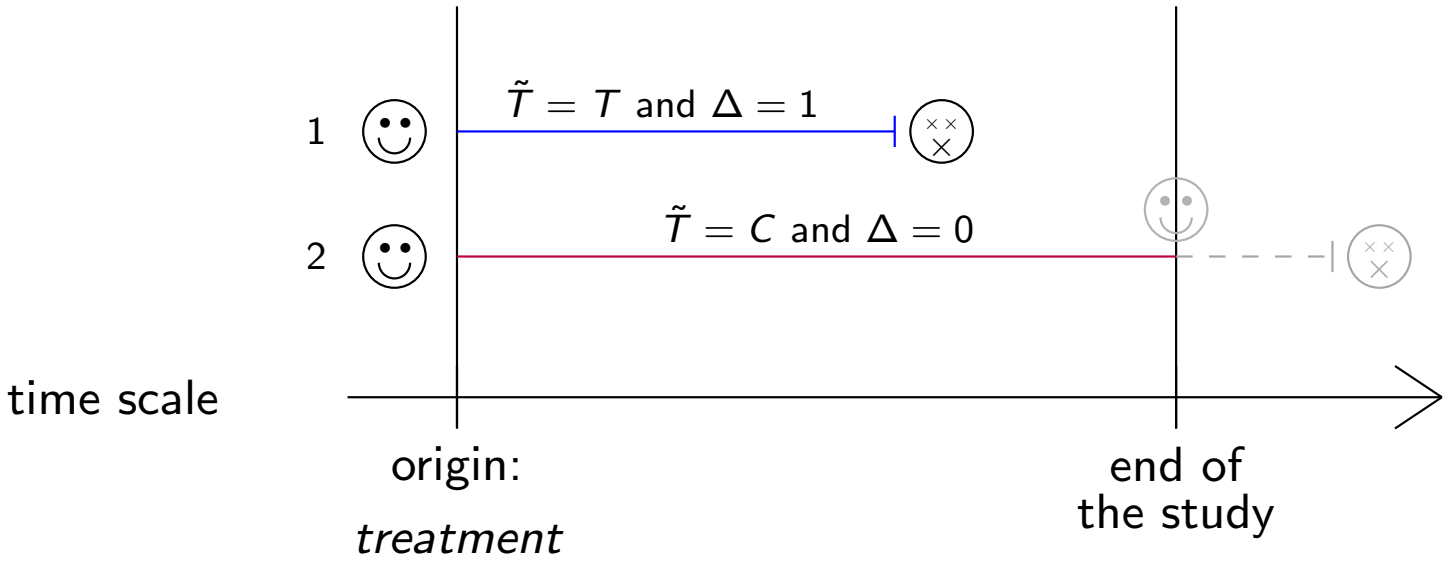

- Observed data:
  - Follow-up time: $\tilde{T} = \min(T, C)$
  - Censoring indicator: $\Delta = I(T \leq C)$

The concept of cure in survival analysis

"Classical" survival analysis supposes that all observations are susceptible to the event.

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- **Time-to-relapse for a curable disease**: patients who are cured from the disease will never relapse
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Observations that do not experience the event : cured, non-susceptible or long-term survivors, ...

$\Rightarrow$ Survival data are said to contain a **cure fraction**.

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Since survival data are subject to censoring, the presence of a **cure fraction** is **not observed**.

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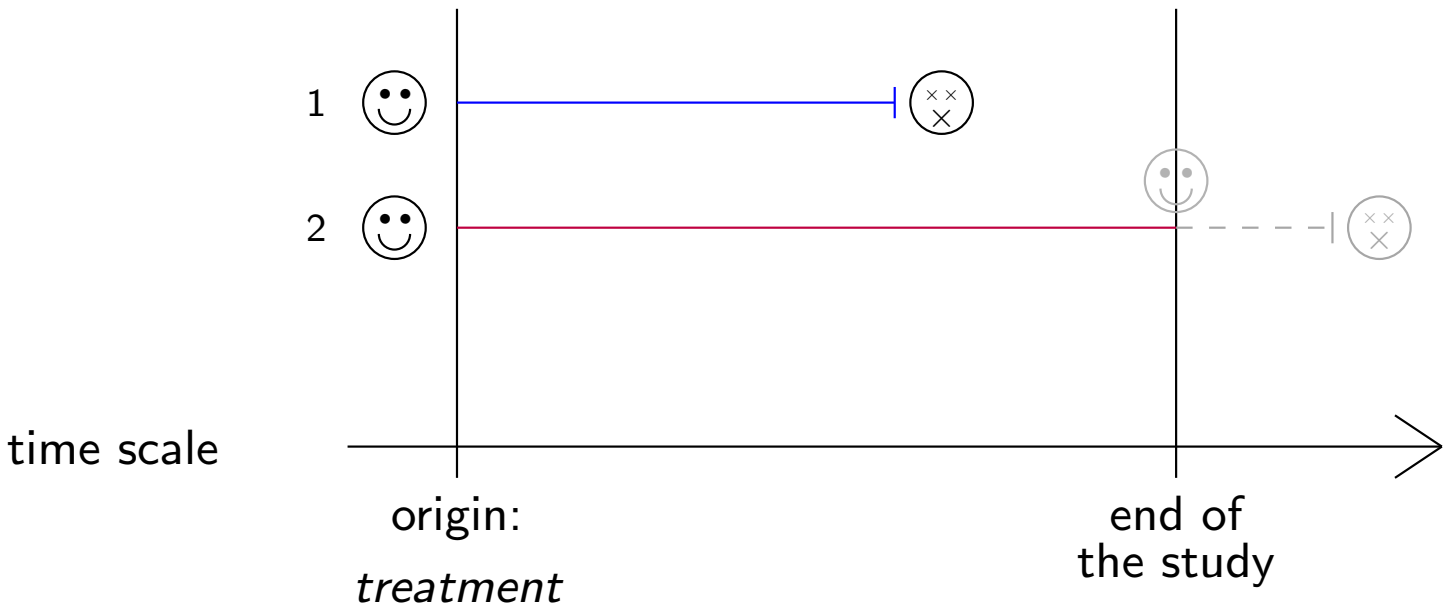

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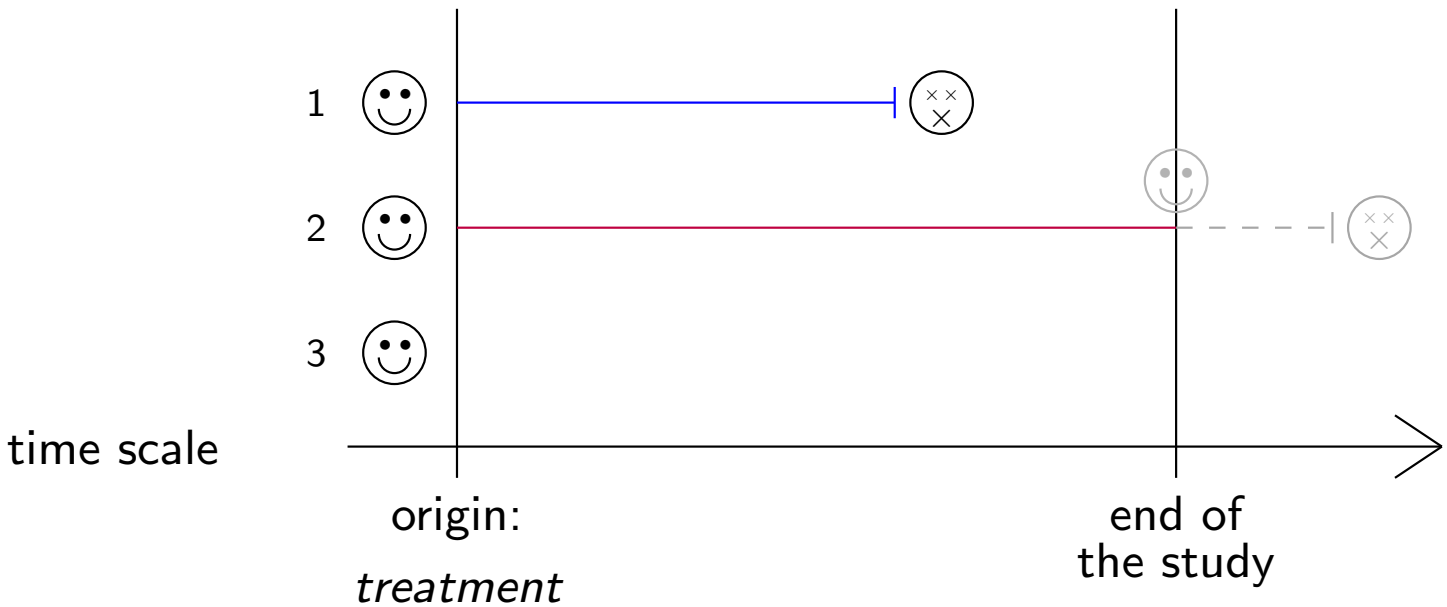

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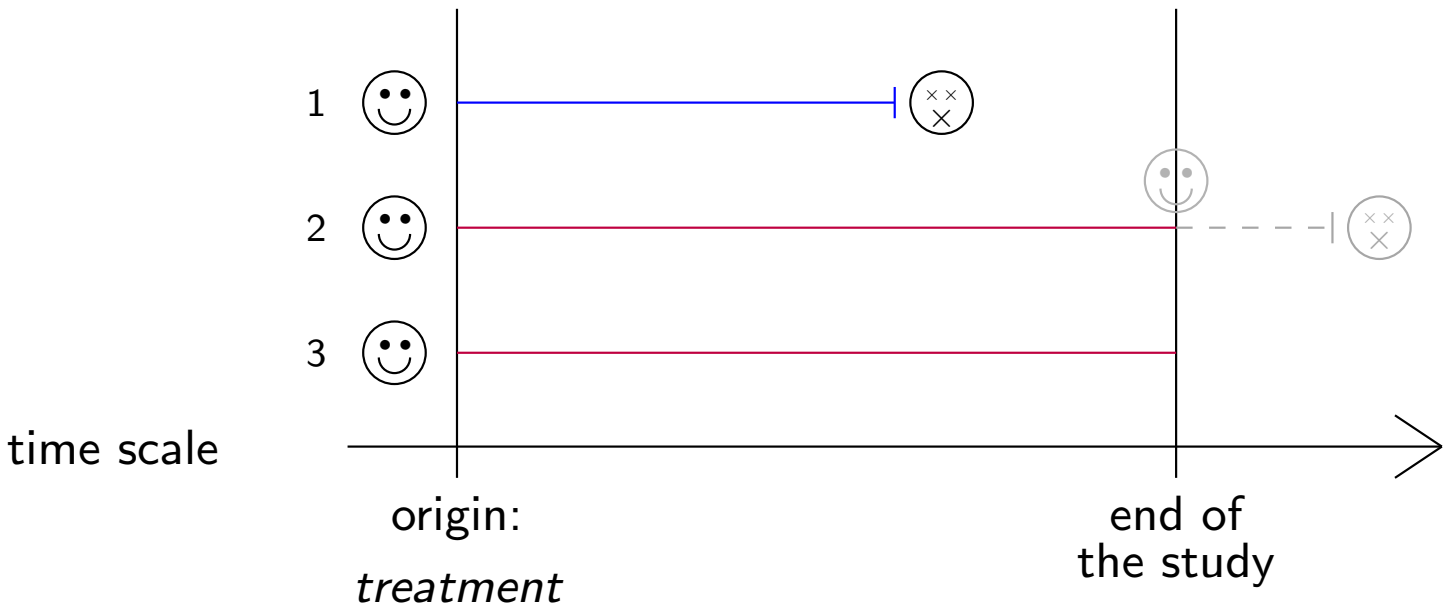

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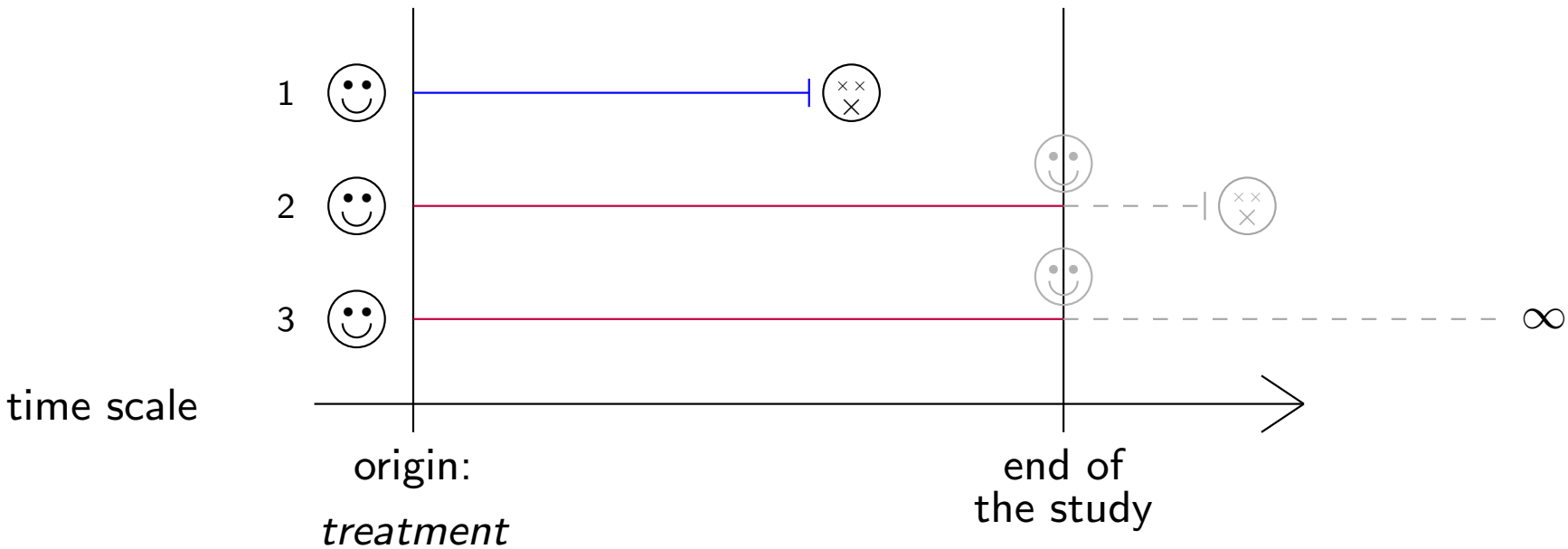

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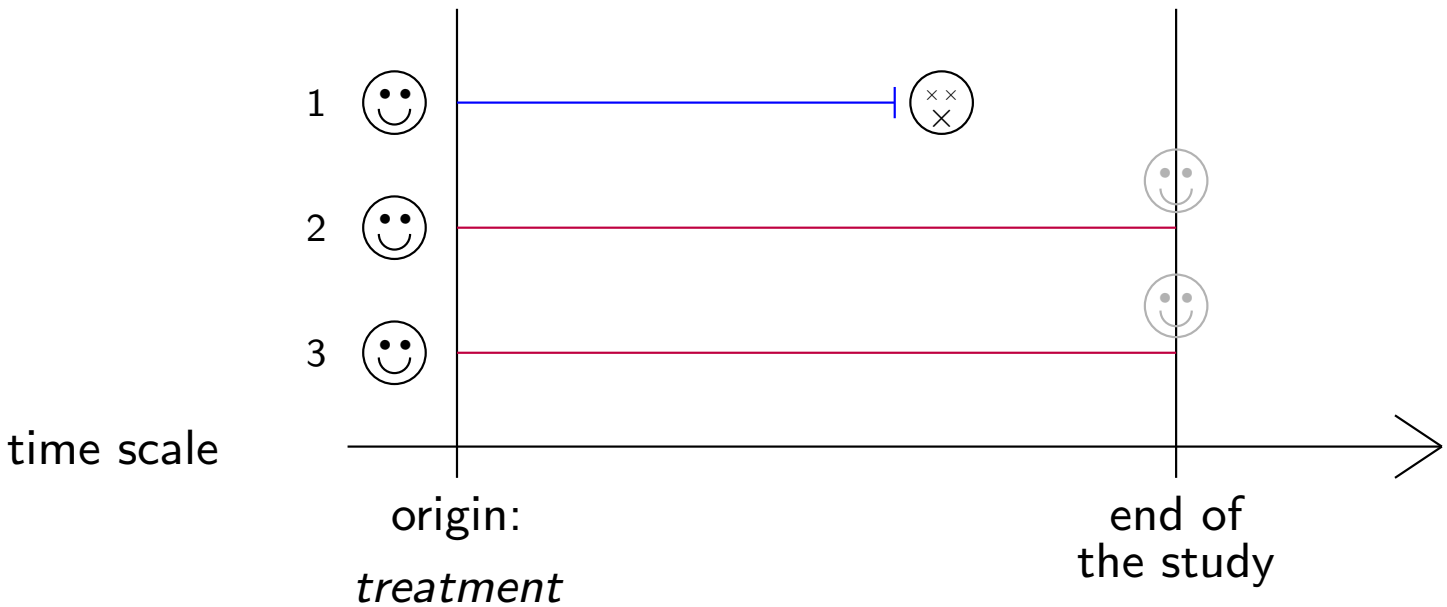

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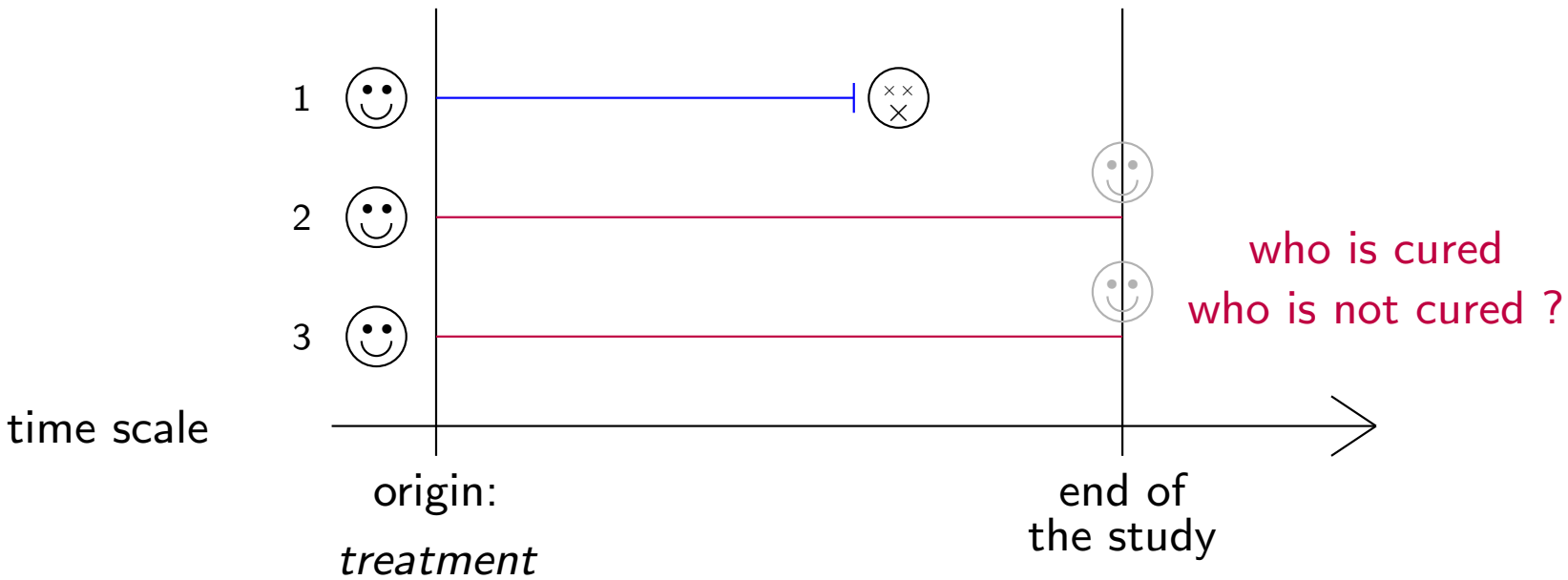
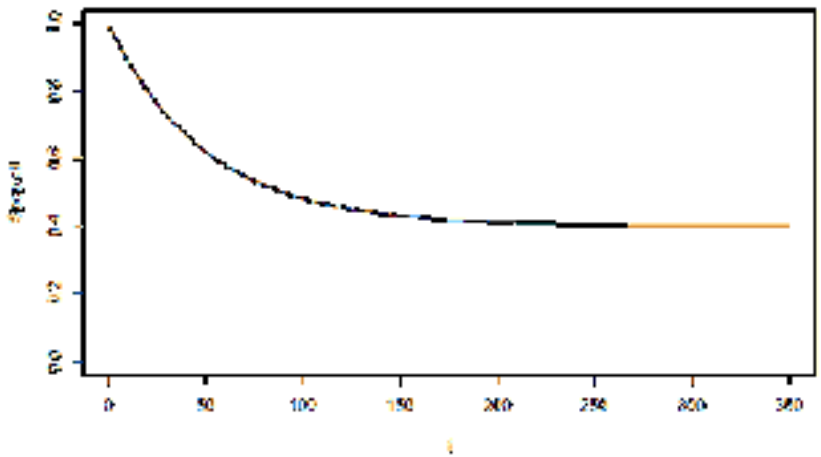


Survival analysis with a cure fraction

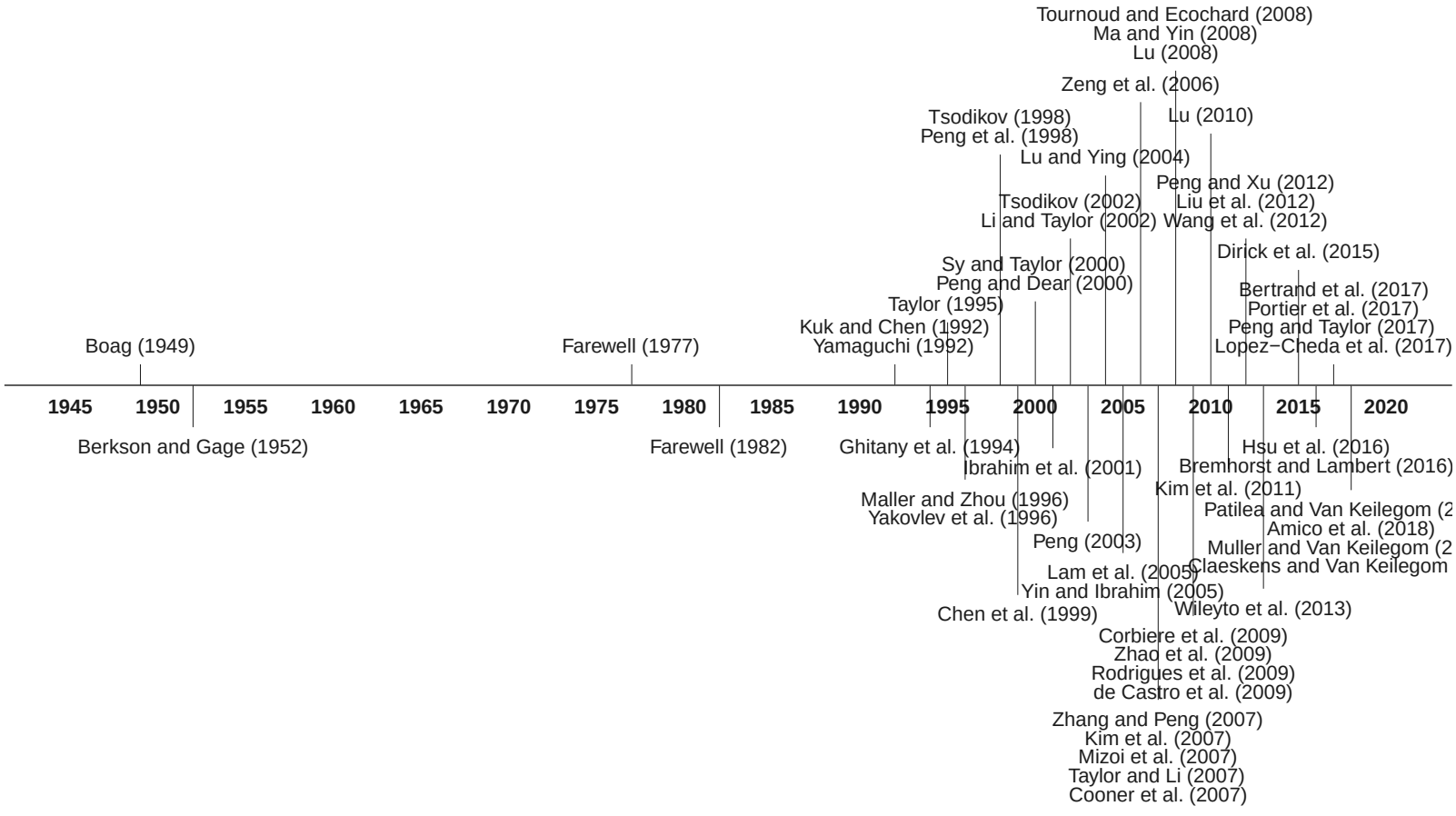
$\hookrightarrow$ Due to the presence of a cure fraction, the survival function "levels up" at some value



Cure models:

- Extension of survival analysis to take the presence of a cure fraction into account.
- Two main families of cure models:
  - Mixture cure models
  - Promotion time cure models

Cure Models: a Literature Review (Amico and Van Keilegom, 2018)



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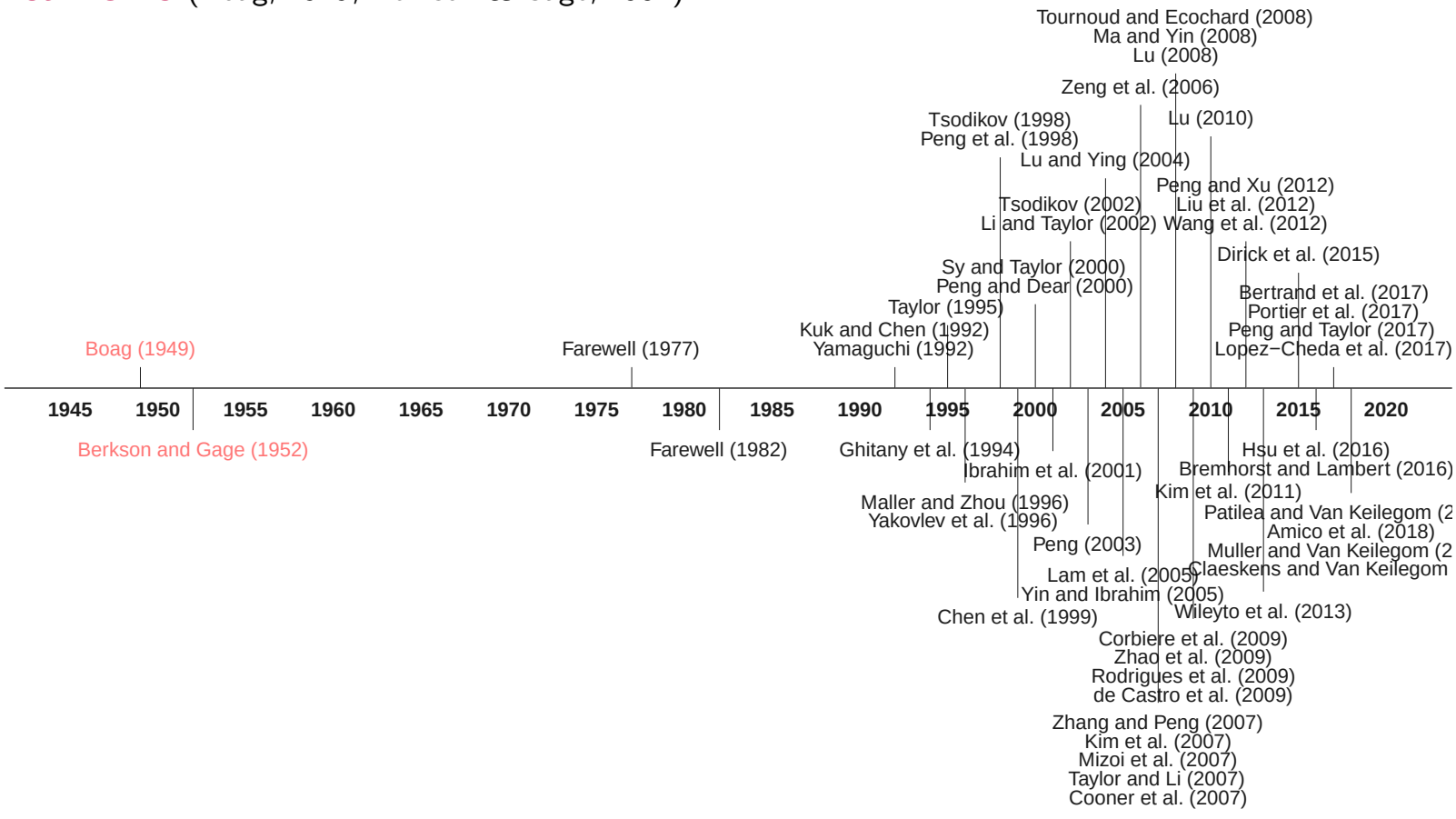

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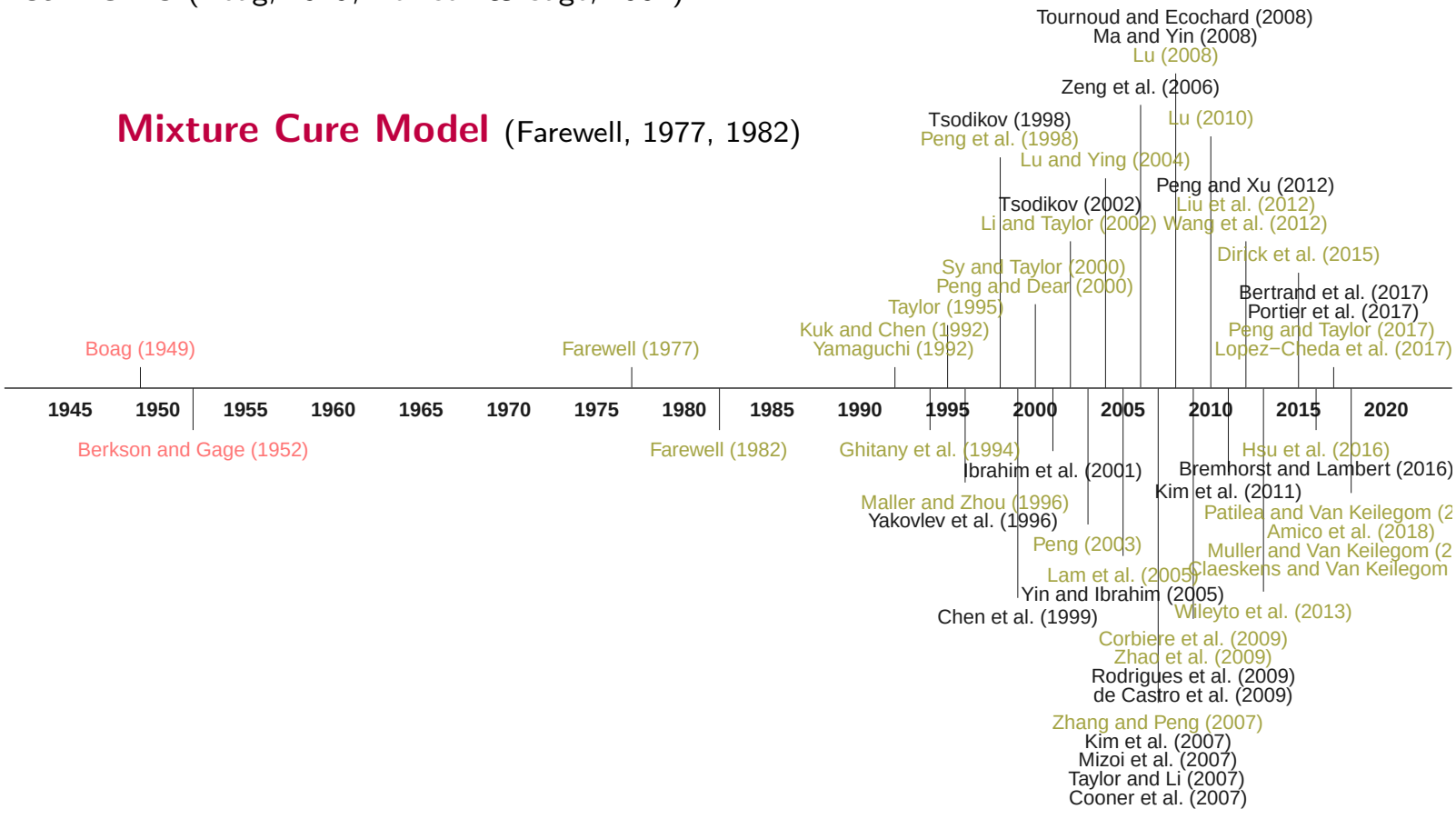

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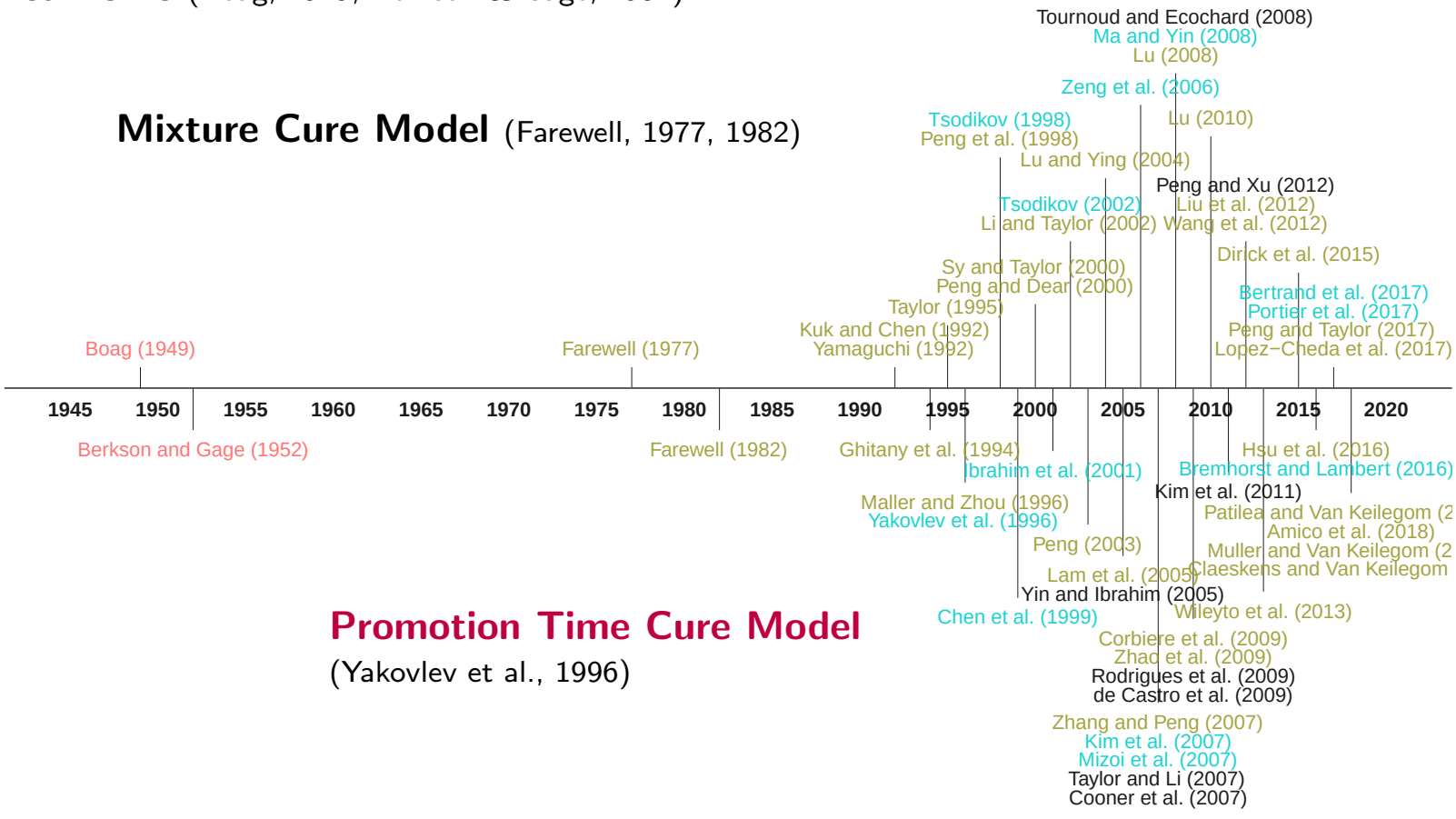

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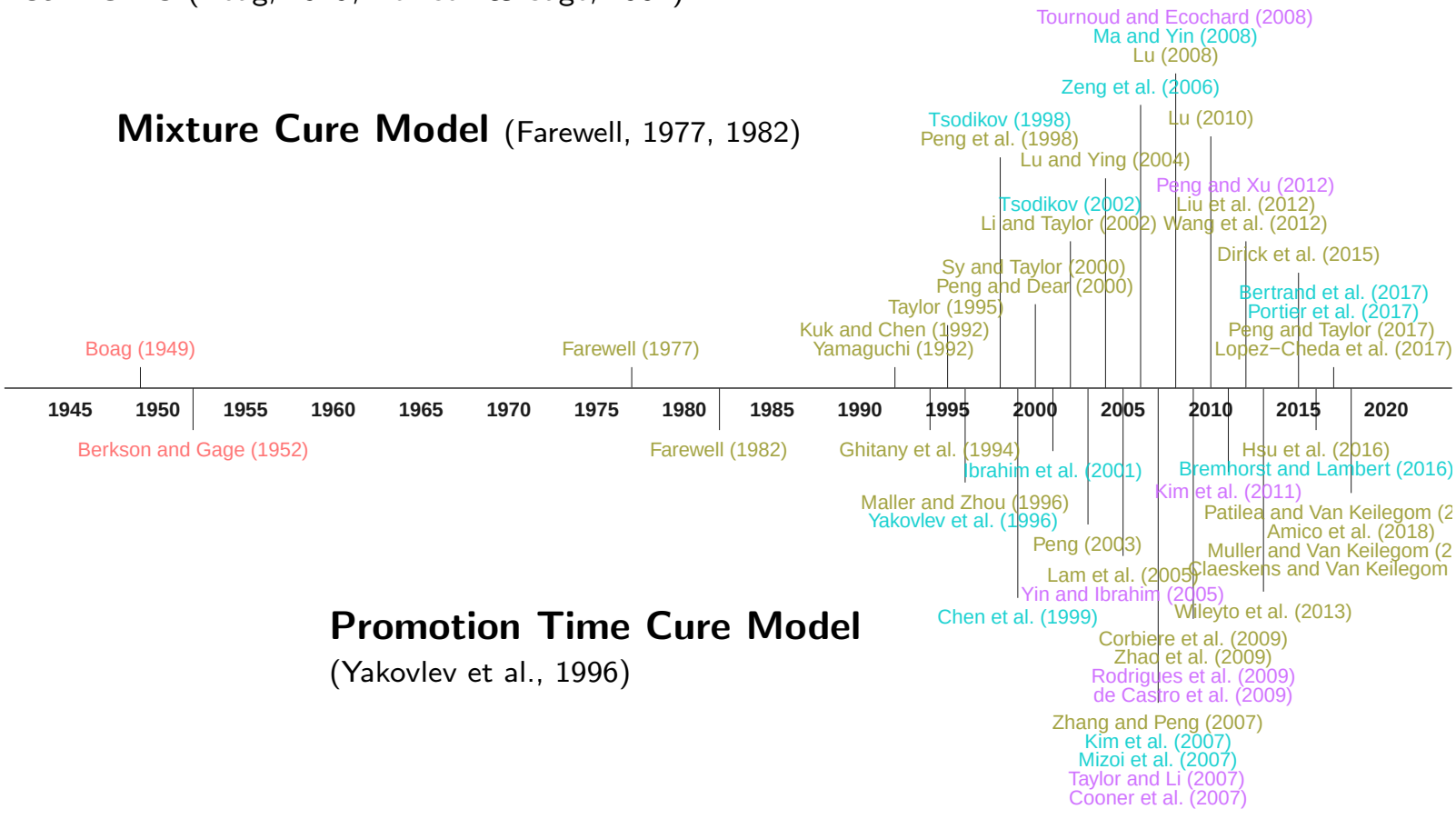
Unifying Models
(Yin & Ibrahim, 2005)



The Mixture Cure Model

Let Y denotes the uncure status, such that $Y = 1$ for a uncured (susceptible) subject and $Y = 0$ for a cured subject.

The mixture cure model writes

$$S_{pop}(t|\mathbf{x}, \mathbf{z}) = \{1 - p(\mathbf{x})\} + p(\mathbf{x})\ S_u(t|\mathbf{z}),$$

where

$p(\mathbf{x}) = P(Y = 1|\mathbf{X} = \mathbf{x})$ for some vector of covariates $\mathbf{X}$

$\longrightarrow$ incidence

$S_u(t|\mathbf{z}) = P(T > t|Y = 1, \mathbf{Z} = \mathbf{z})$ for some vector of covariates $\mathbf{Z}$

$\longrightarrow$ latency

Cure rate: $lim_{t\to\infty} S_{pop}(t|\mathbf{x}, \mathbf{z}) = 1 - p(x)$

The Mixture Cure Model

$$S_{pop}(t|\mathbf{x}, \mathbf{z}) = \{1 - p(\mathbf{x})\} + p(\mathbf{x})\ S_u(t|\mathbf{z}),$$

Advantage: allows to disentangle the effects of covariates on the incidence and on the latency

- e.g. for treatment: long-term *curative* treatment effect and short-term *life-prolonging* treatment effect
- in lines with intuition that patient/disease related factors associated with short and long-term effects are not necesarily the same

Most often: (semi-)parametric logistic / PH mixture cure model

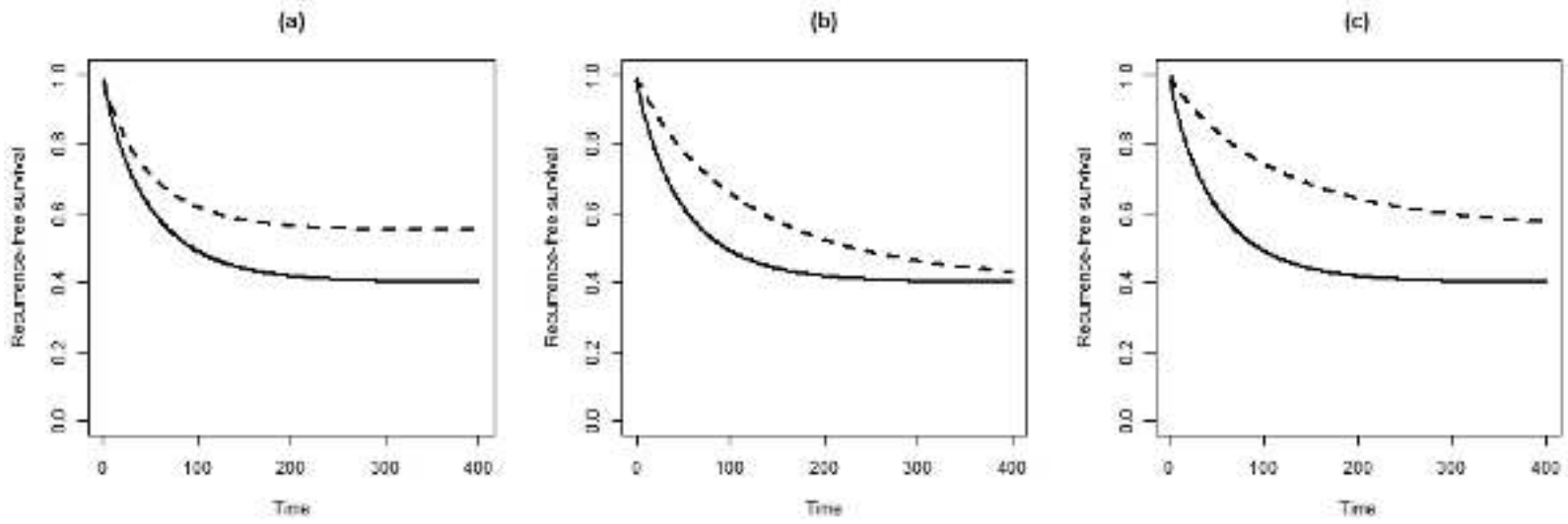
- incidence: logistic regression
- latency: (semi-)parametric PH model

But other approaches have been proposed in the literature (mainly for the latency)

The Mixture Cure Model

The (semi-)parametric logistic / PH mixture cure model:

- PH assumption in the uncured sub-population
- **no PH assumption at the level of the population**



The Mixture Cure Model: Estimation

$\longrightarrow$ cure status only known for the uncensored observations

Fully parametric model:

- maximisation of the likelihood function [`smcure, PSPMCM`]
- asymptotic std errors can be obtained by inverting the Fisher information matrix

Logistic incidence and semi-parametric (Cox/AFT) latency:

- Partial likelihood method does not work
- Other approaches
  - EM algorithm [`smcure, PSPMCM`] (Peng and Dear, 2000; Sy and Taylor, 2000)
  - Marginal likelihood (MC approximation) (Kuk and Chen, 1992)
  - Penalized likelihood approach (splines) (Corbieres et al., 2009)
- **zero-tail constraint**

Other (less parametric) models:

- ad-hoc methods

The Promotion Time Cure Model

The Promotion Time Cure Model writes

$$S_{pop}(t|\mathbf{x}) = \exp\{-\theta(x)F(t)\}$$

where

$F(t)$ is a proper distribution function

$\rightarrow$ can be parametric or non parametric

$\theta(x)$ is a known link function with an intercept

$\rightarrow$ can be parametric or non parametric

Cumulative hazard function: $\theta(x)F(t)$ is bounded

$\Rightarrow$ *bounded cumulative hazard models*

Cure rate: $lim_{t\rightarrow\infty} S_{pop}(t|\mathbf{x}) = \exp\{-\theta(x)\}$

The Promotion Time Cure Model

- The promotion time cure model possesses the PH property (at the population level):

$$\frac{h(t \mid x_i)}{h(t \mid x_j)} = \frac{\theta(x_i)}{\theta(x_j)}$$

- The semi-parametric promotion time cure model with an exponential link function can actually be seen as a generalization of the Cox PH model (Portier et al., 2017)

$$\begin{aligned} S_{pop}(t|\mathbf{x}) &= \exp\{-\exp(\beta_0 + x^t\beta)F(t)\} \\ &= \exp\{-\exp(x^t\beta)\exp(\beta_0)F(t)\} \\ &= \exp\{-\exp(x^t\beta)H(t)\} \end{aligned}$$

So, in practice

$$\begin{aligned} \hat{\beta}_{PT} &= \hat{\beta}_{PH} \\ \exp(\hat{\beta}_{0,PT}) &= \hat{H}_{PH}(T_{(n)}) \\ \exp(\hat{\beta}_{0,PT})\hat{F}_{PT}(t) &= \hat{H}_{PH}(t) \end{aligned}$$

The Promotion Time Cure Model

Consequences: When the exponential link function is used and F(.) is left unspecified

- estimates of the promotion time model can be obtained from fitting a Cox PH model
- as long as the PH assumption is met, Cox P model provides reliable results even in the presence of a non-negligible cure fraction but parameters should be interpreted accordingly

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...no need for cure models since the Cox PH model does the job ...

The Promotion Time Cure Model

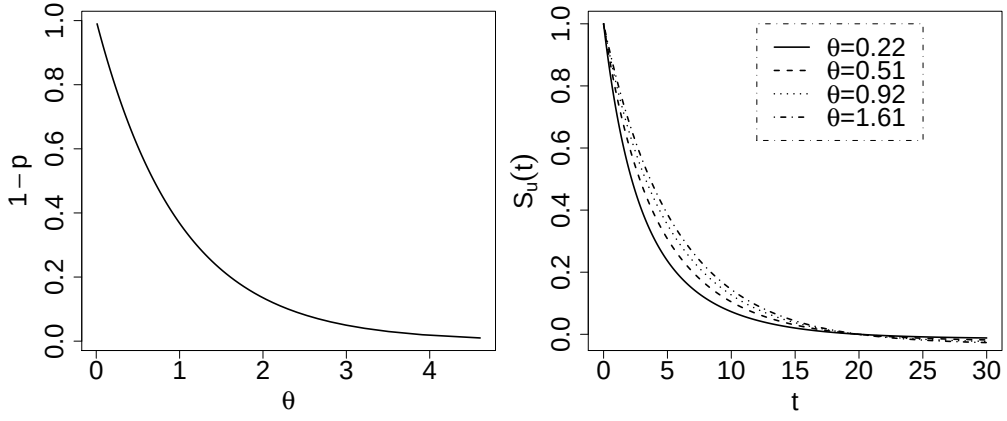
$$S_{pop}(t|\mathbf{x}) = \exp\{-\theta(x)F(t)\}$$

Advantage:

- Seminal biological interpretation of the model: modeling cancer relapse from N_i carcinogenic cells left
  - $N_i \sim Poisson(\theta(X_i))$
  - Promotion times $W_{ik}, i = 1, ..., n_k$ iid with distribution $F(t)$
  - Time until relapse $T_i = \min(W_1, ..., W_{N_i})$

Interpretation:

- Covariates X affect both the probability of being cured and the survival of uncured subjects



The Promotion Time Cure Model: Estimation

Mainly studied in a Bayesian context

Different frequentist approaches for the semi-parametric model

- maximisation of a profile likelihood (Tsodikov, 1998)
- maximisation of the full likelihood through a profiling approach (Zeng et al., 2006)
- maximisation of the full likelihood through a backfitting approach [`miCoPTCM`] (Ma and Yin, 2008)
- as a Cox model (if exponential link) [`coxph`]

OK, but ...cure or not cure ?

When should we use a cure model to analyse our data ?

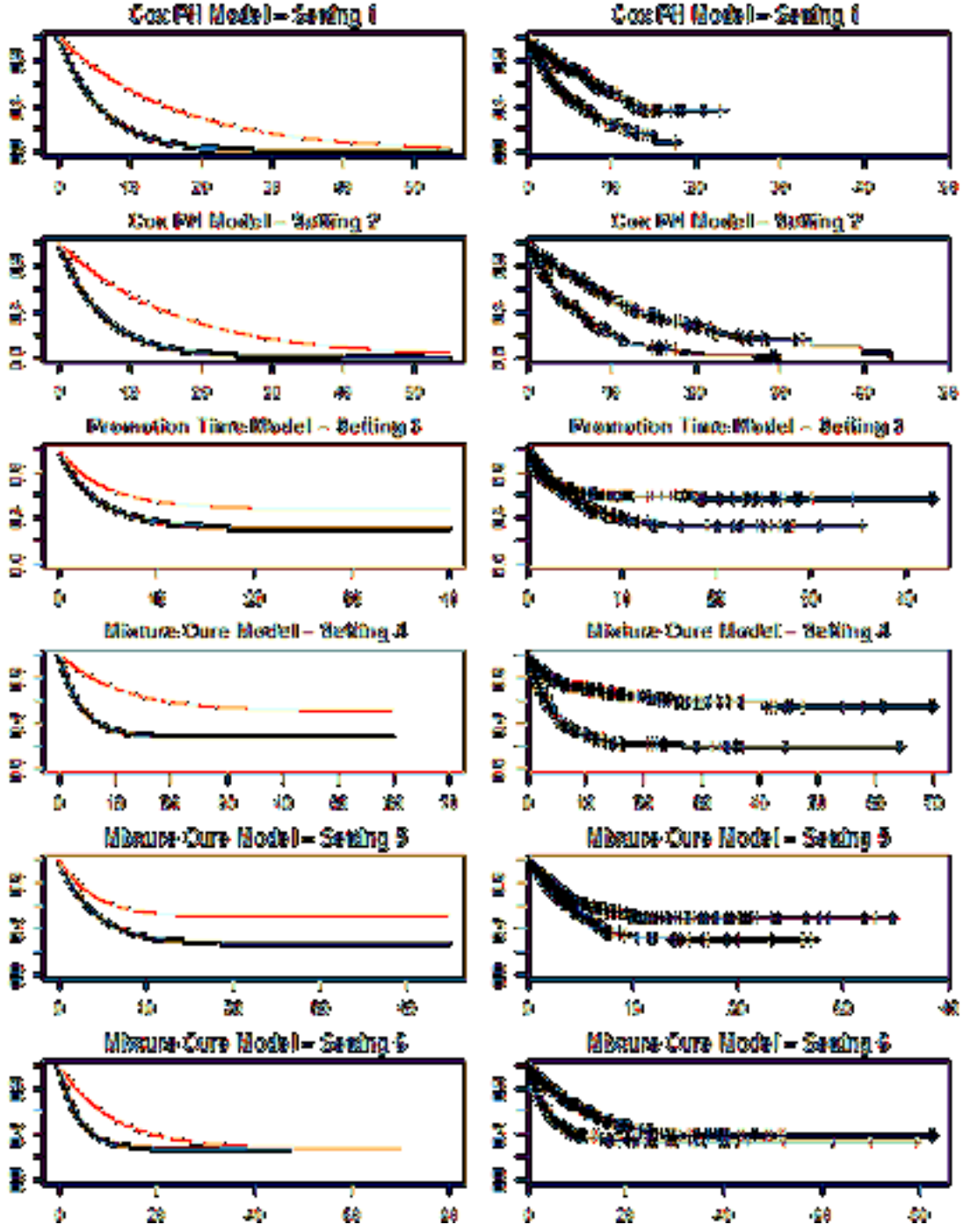
... and if indeed we have to, do we use a mixture cure model or a promotion time model ?

OK, but ...cure or not cure ?

Simulation study

- 500 datasets of 500 patients
- include a binary covariate for treatment
- 6 differents settings

1	Parametric PH	no cure	53% censoring
2	Parametric PH	no cure	27% censoring
3	Parametric PTM	29% and 48%	57% censoring
4	Parametric MTM (both)	27% and 50%	54% censoring
5	Parametric MTM (incidence)	27% and 50%	56% censoring
6	Parametric MTM (latency)	38% and 38%	54% censoring


Cox PH Model – Setting 1
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Cox PH Model – Setting 2
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Promotion Time Model – Setting 3
Promotion Time Model – Setting 3
Mixture Cure Model – Setting 4
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$\Rightarrow$ The consequences of a model misspecification can vary largely, depending on the true model underlying the data, and on the focus of the estimation: cure probability, conditional survival function, treatment effect size and signifiance.

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Full results: see our upcoming book chapter !

OK, but ...cure or not cure ?

If no cure:

- treatment effect is well recovered by the PTM and quite well by the MCM when the censoring is not too high
- estimated coefficients in the incidence part of the MCM are largely biased and accompanied by a very large s.e.
- ability of the models to acknowledge the absence of cure is highly dependent on the amount of censoring
- zero-tail constraint: leads to a positive bias in the estimation of the cure probability, and a negative bias in the estimation of the survival function of the uncured patients.

OK, but ...cure or not cure ?

If cure: Pay attention to PH assumption !

if PH holds, e.g. data generated from a PTM or from a MCM with a trt affecting only the incidence

- although we can not formally compare their coefficients, PTM and MCM seem to recover the trt effect
- PTM does not allow us to disentangle the short- and the long-term effects
- estimation of the cure rate in each arm and of the conditional survival curve for the uncured is nearly unbiased with both PTM and MCM

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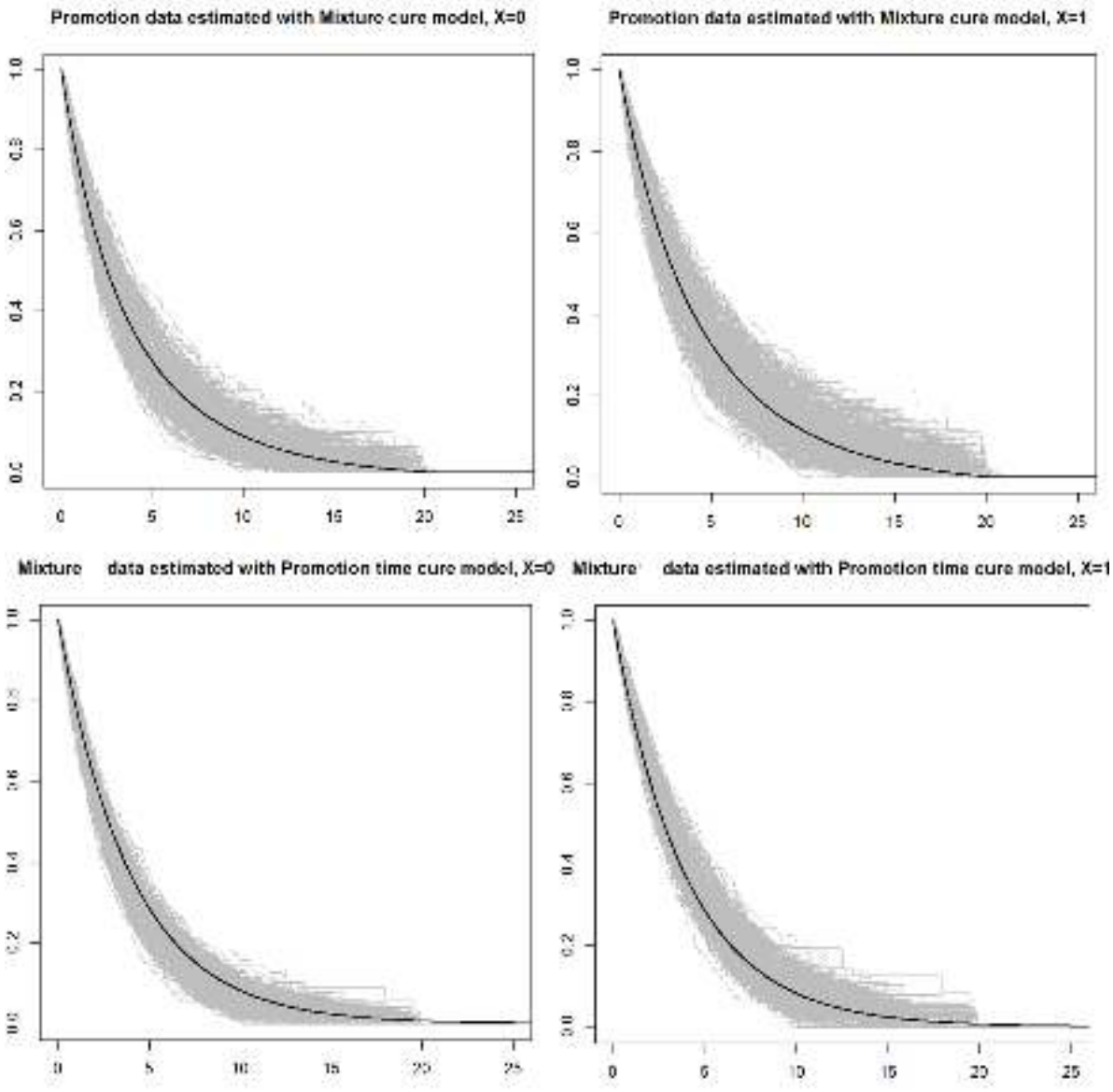

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OK, but ...cure or not cure ?

If cure: Pay attention to PH assumption!

if PH does not hold, e.g. data generated from a MCM with a trt affecting the latency (and the incidence)

- PTM seems to recover some part of trt effect but
  - the estimated cure rate is biased (downwards in the control arm and upward in the treatment arm)
  - the estimated conditional survival is biased (upwards in the control arm and downward in the treatment arm)
- no problem when using the appropriate model (as expected)

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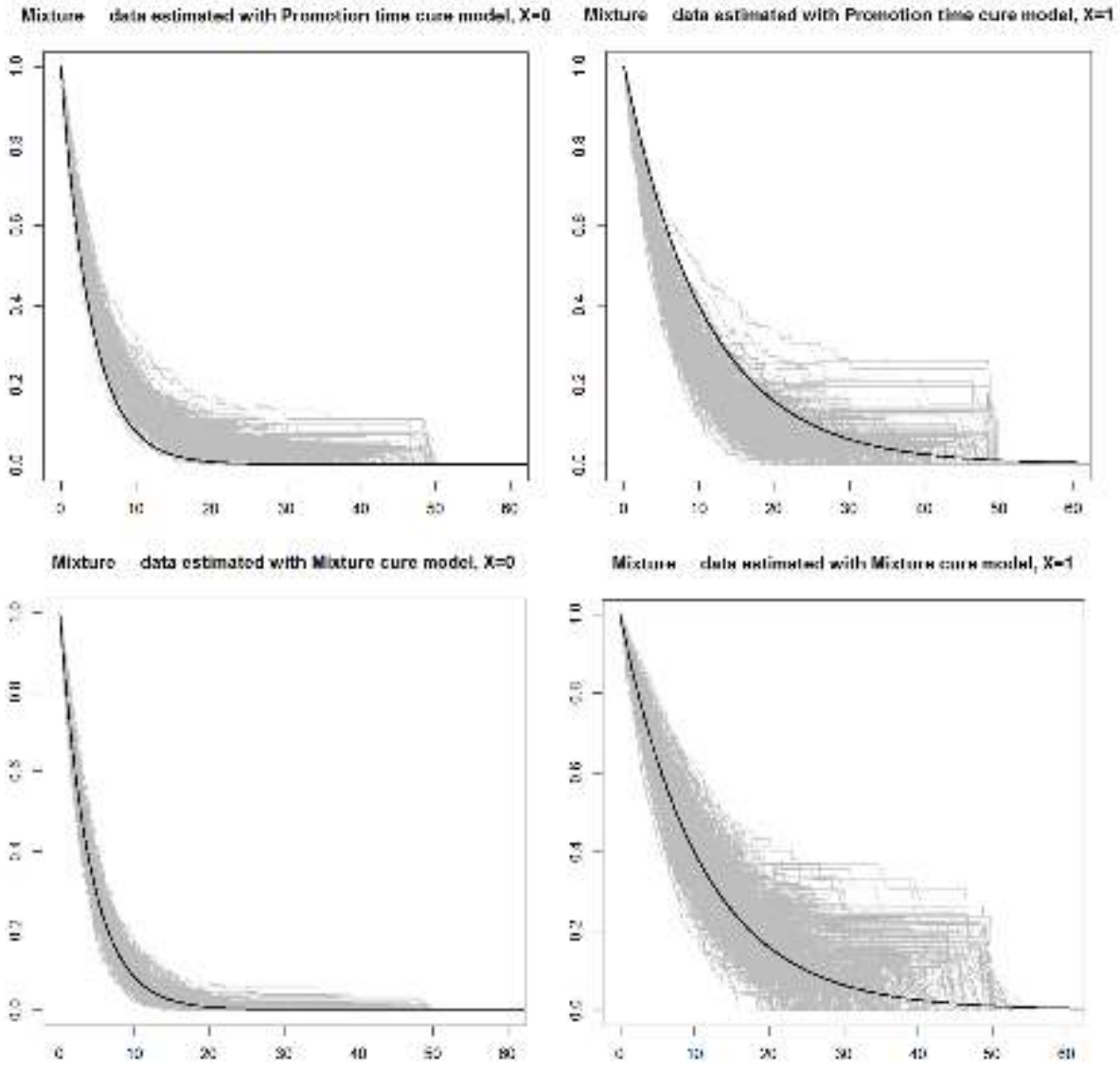

CONCLUSIONS

For some types of cancer, cure is now a reality for patients and MDs

- When there is a fraction of cure, the proportion of patients being cure is a useful piece of information in the evaluation of cure treatment
- **As long as the PH assumption is met**, CM provides reliable estimates of the treatment effect (but PTM preferable if cure)
- **If the PH assumption is not met**, don't use PTM nor CM
- **If the PH assumption is not met due to the presence of a cure fraction**, use MCM

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- **If the PH assumption is not met for another reason** ... then ask the two other speakers what to do!

CONCLUSIONS

Be careful with the statement *"As long as one can assume that not all patients will experience the event of interest, a cure model should be preferred"*

- Must have evidence of cure fraction, via sufficient follow-up
- We recommend not using cure model to estimate the proportion of cure when there is no evidence of such a fraction of cure
- If PH holds and not need to separate short- and long-term effect, CM is indeed ok
- MCM will allow to disentangle short-term (life-prolonging effect) from long-term (life-saving effect) of a treatment

Main references

Peng Y. and Taylor J.M.G. Cure models. Book chapter in *Handbook of Survival Analysis*, pages 113-134. Editors: Klein J., van Houwelingen H., Ibrahim J.G., and Scheik, T.H. Chapman and Hall, Boca raton, FL, USA, 2014

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Legrand C. and Bertrand A. Cure models in cancer clinical trials. Book chapter in it Textbook of Clinical Trials in Oncology.. Editors: Halabi S. and Michiels S. Chapman and Hall,CRC Press. To appear (July 2019).