Sciences Economiques et Sociales de la Santé
& Traitement de l'Information Médicale

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Pr. Catherine LEGRAND

Institute of Statistics, Biostatistics and
Actuarial Sciences (ISBA-LIDAM), UCLouvain, Louvain-la-Neuve, Belgium

On the use of cure models in cancer clinical trials.

mars 2020

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On the use of cure models in cancer clinical trials

Prof. Catherine Legrand

Joint work with Aurélie Bertrand

ISBA - LIDAM, UCLouvain, Belgium

Webinar QuanTIM - March 20, 2020

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

Setting the scene ... (randomized) clinical trials

- How do we establish that a new treatment is indeed better than what we actually use to treat (or prevent) a given disease

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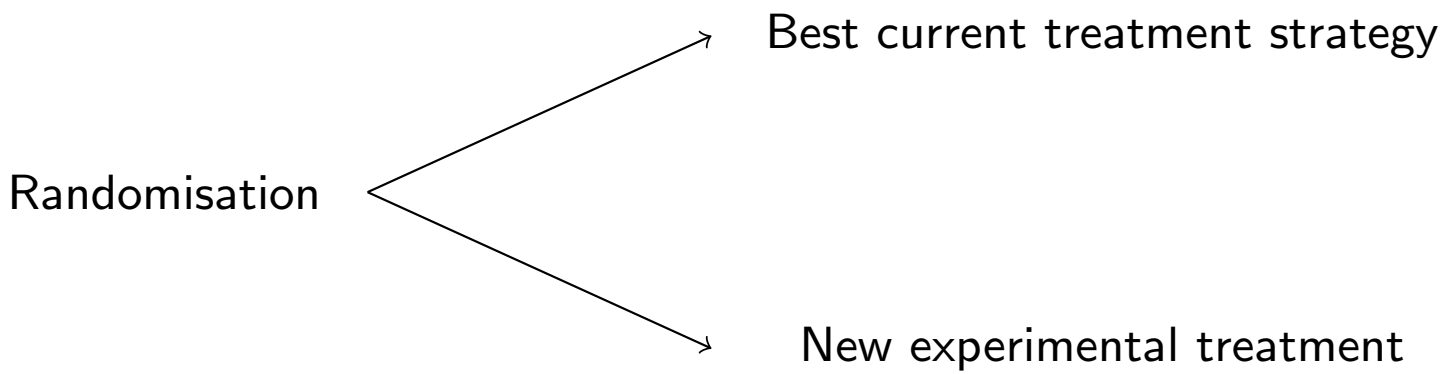
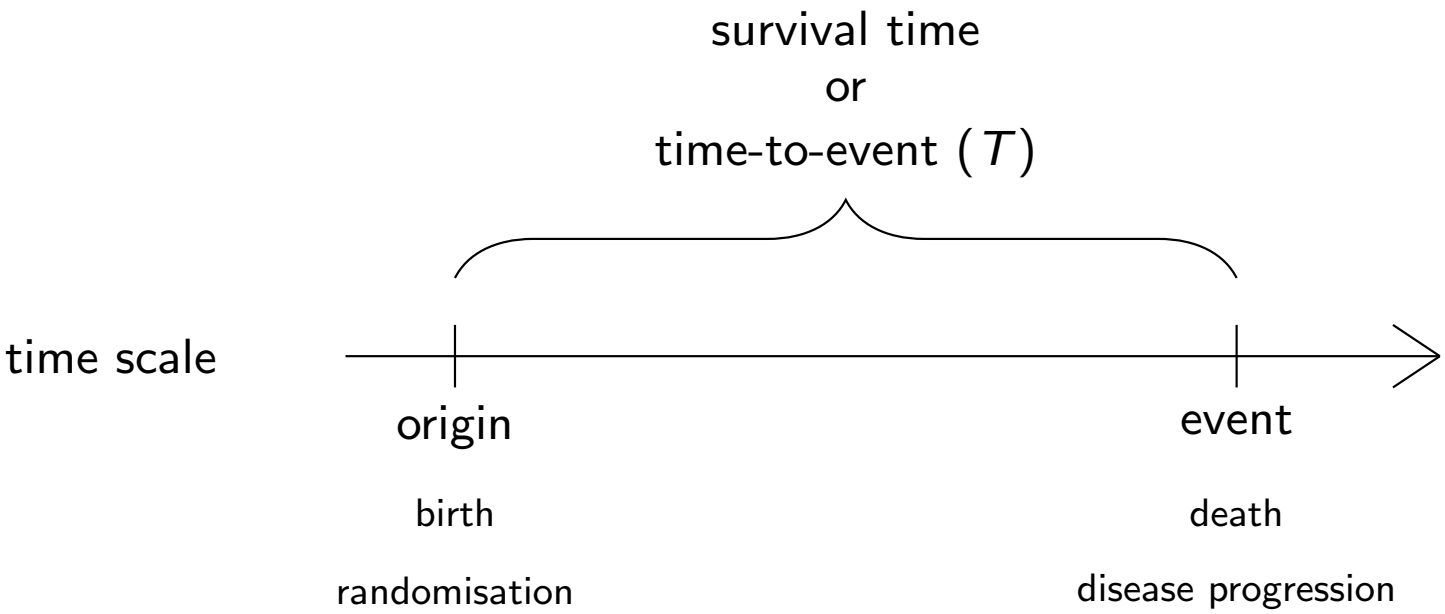


Setting the scene ... survival outcome

- Time-to-event or survival data analysis



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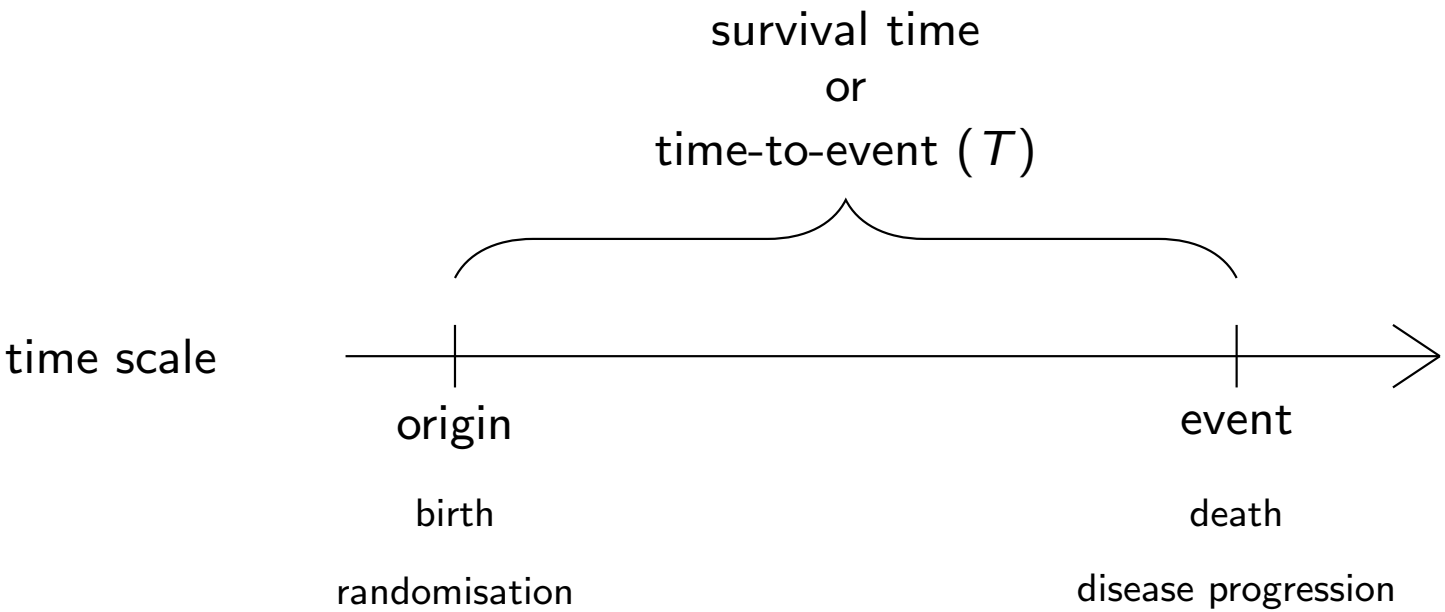
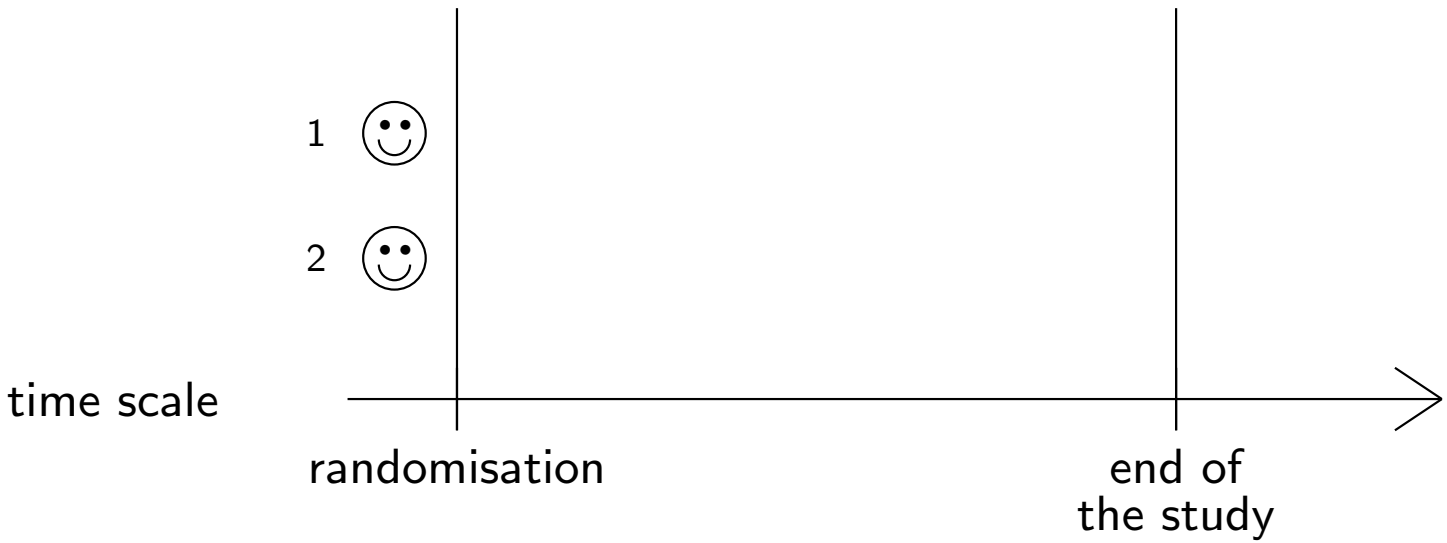


- Main function of interest:

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

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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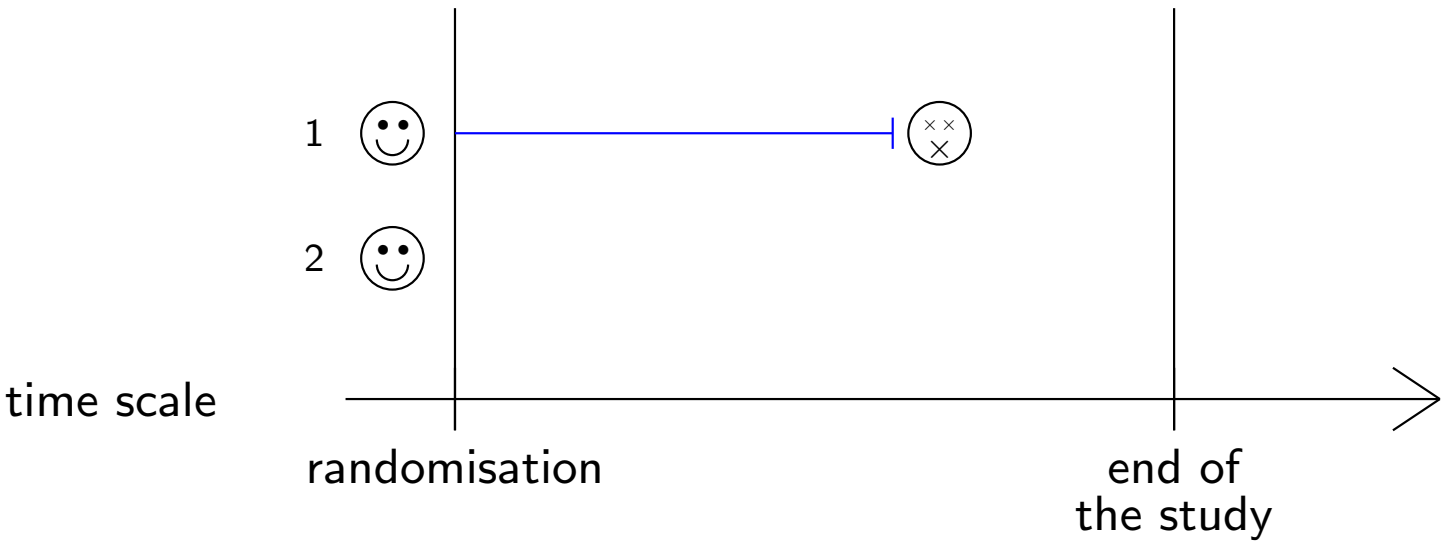

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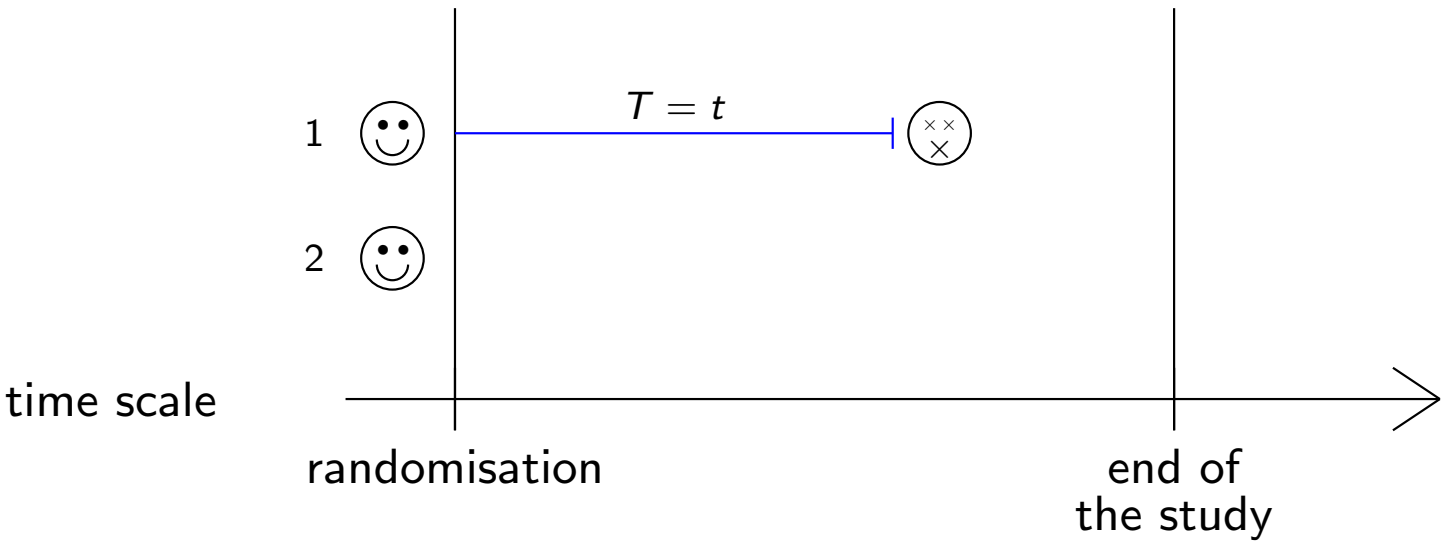

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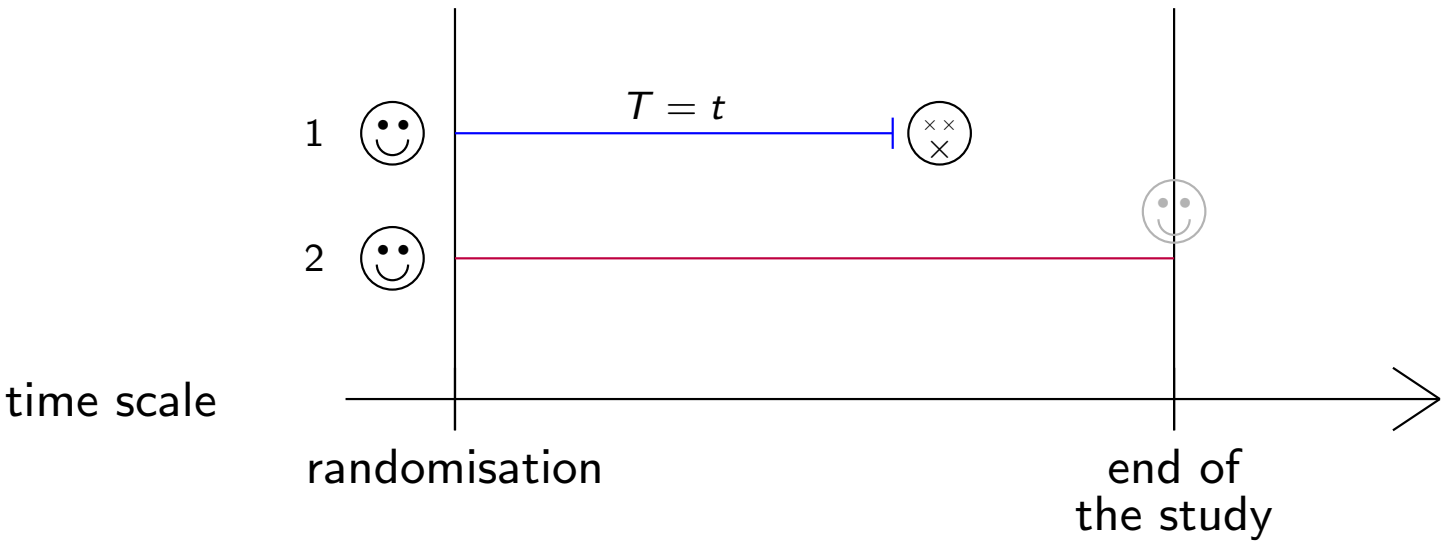

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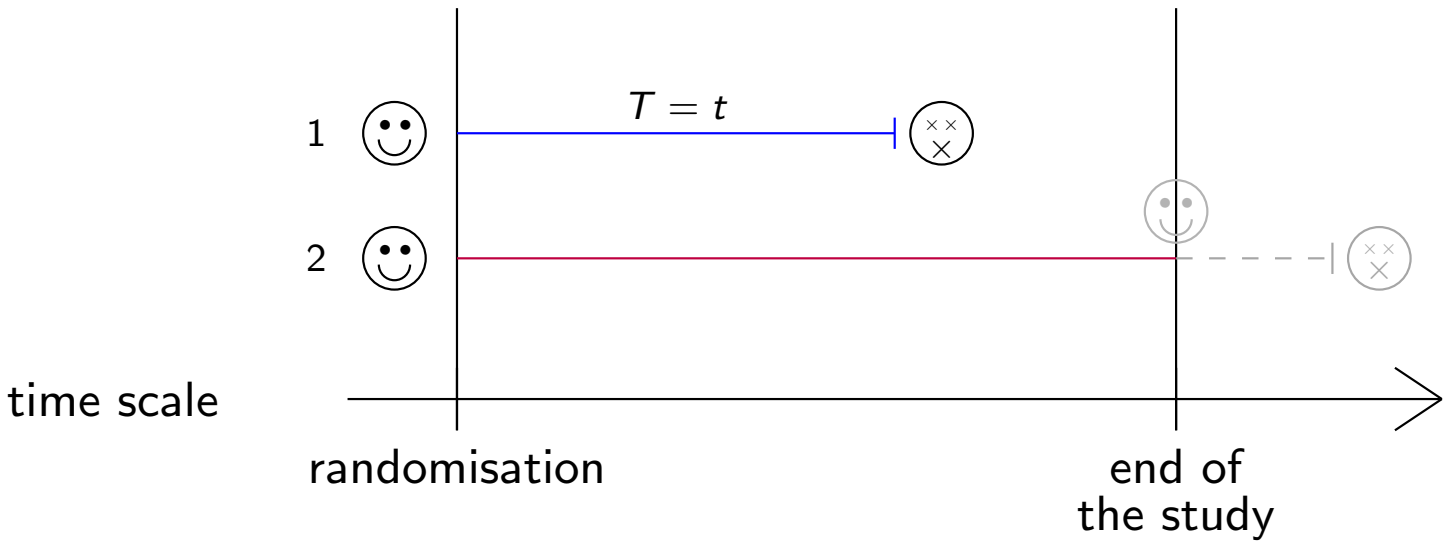

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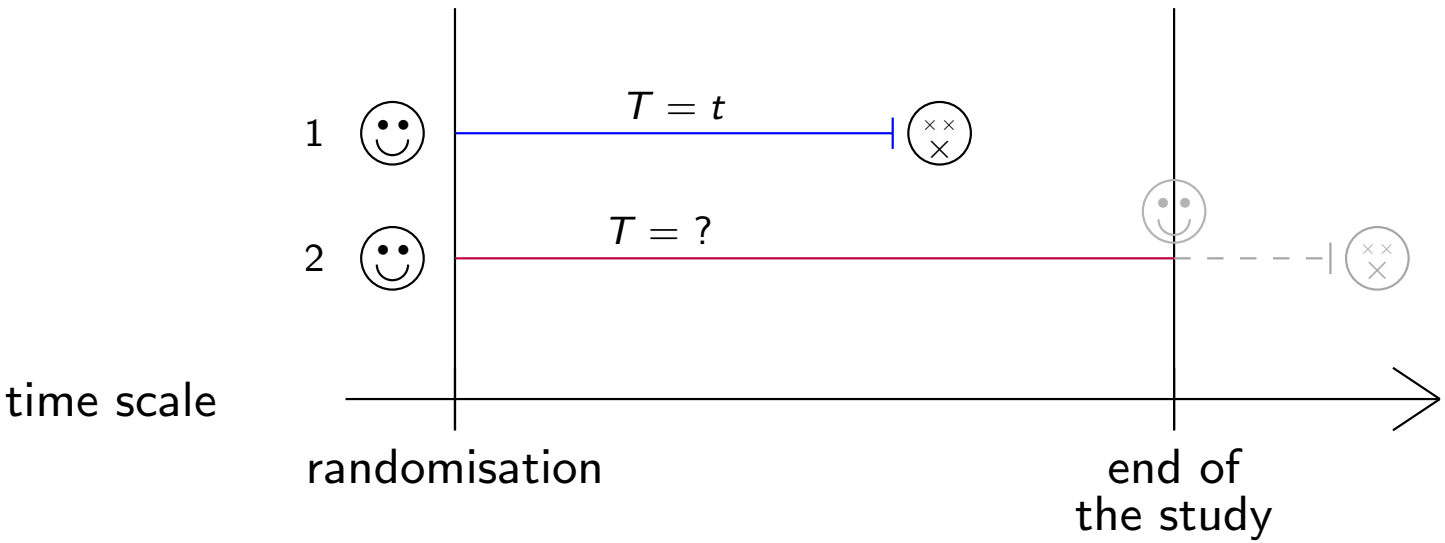

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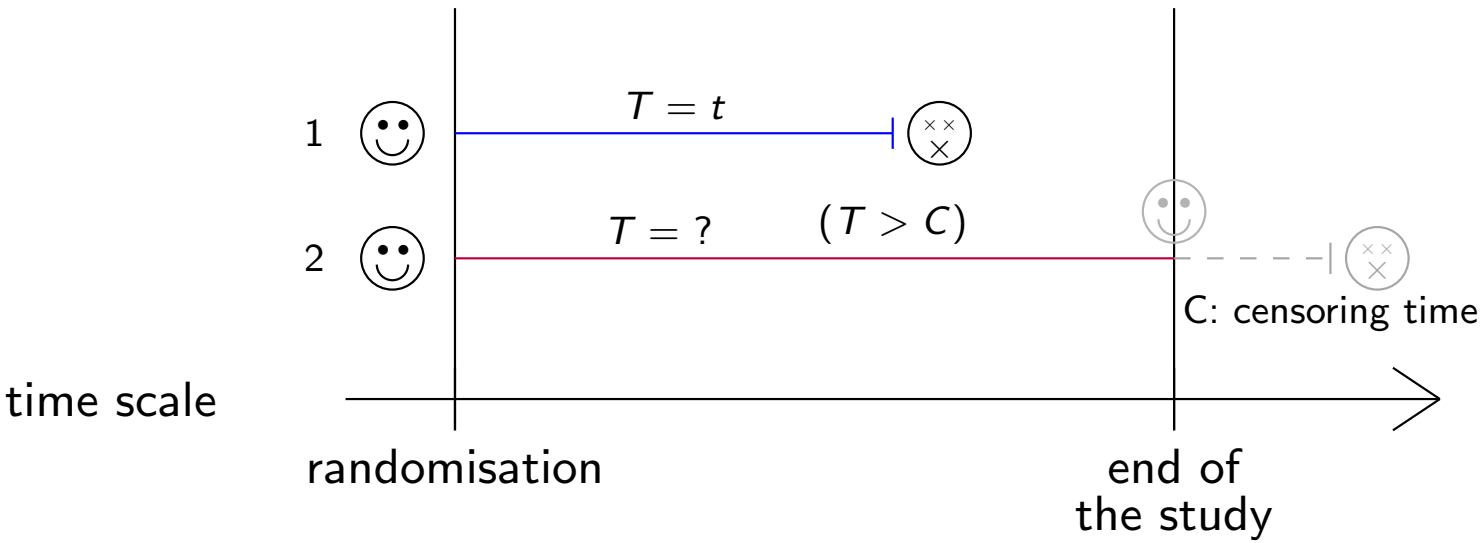

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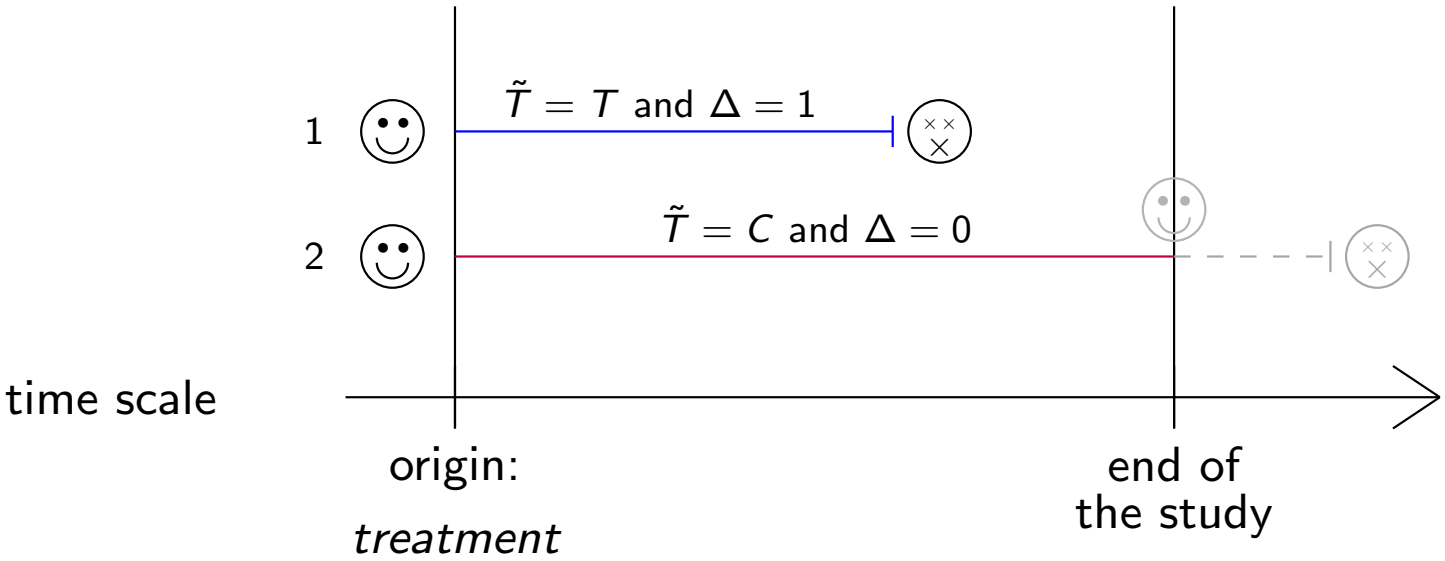
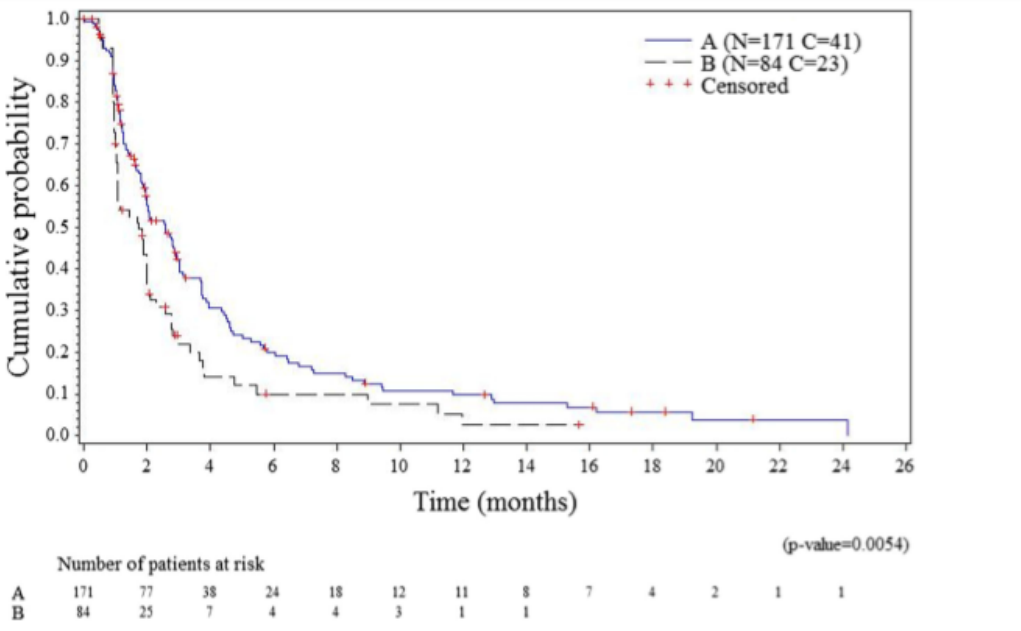


- Observed data:
  - Follow-up time: $\tilde{T} = \min(T, C)$
  - Censoring indicator: $\Delta = I(T \leq C)$

Several analysis techniques are available

Assuming independent/non-informative censoring, the most often used methods are

- **Kaplan-Meier estimator**: non-parametric estimation of the survival distribution $S(t)$



Spicka et al., Annals of Hematology, 2019

Several analysis techniques are available

Assuming independent/non-informative censoring, the most often used methods are

- **Cox Proportional Hazards (PH) model**: semi-parametric model for the hasard function

$$h(t) = h_0(t) \exp(\mathbf{X}^t \beta)$$

where

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t \mid T \geq t)}{\Delta t}$$

We also have

$$S(t) = \exp\left(- \int h_0(t) \exp(\mathbf{X}^t \beta)\, dt \right) = \exp\left(-H_0(t) \exp(\mathbf{X}^t \beta) \right)$$

Several analysis techniques are available

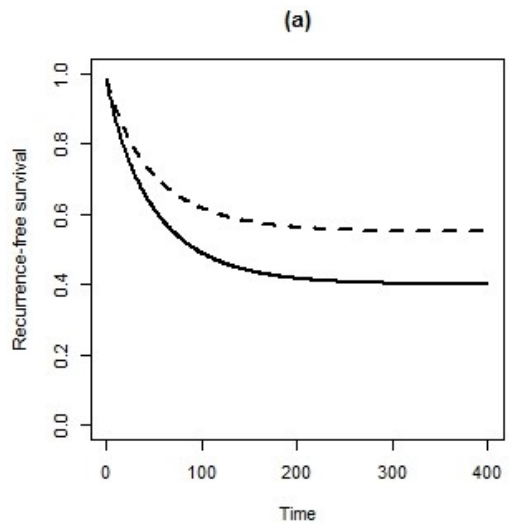
Assuming independent/non-informative censoring, the most often used methods are

- **Cox Proportional Hazards (PH) model**: semi-parametric model for the hasard function

$$h(t \mid \mathbf{X}) = h_0(t) \exp(\mathbf{X}^t \beta)$$

Important assumption: proportional hazards

$$\frac{h(t \mid \mathbf{X_1})}{h(t \mid \mathbf{X_2})} = \frac{\exp(\mathbf{X_1}^t \beta)}{\exp(\mathbf{X_2}^t \beta)}$$



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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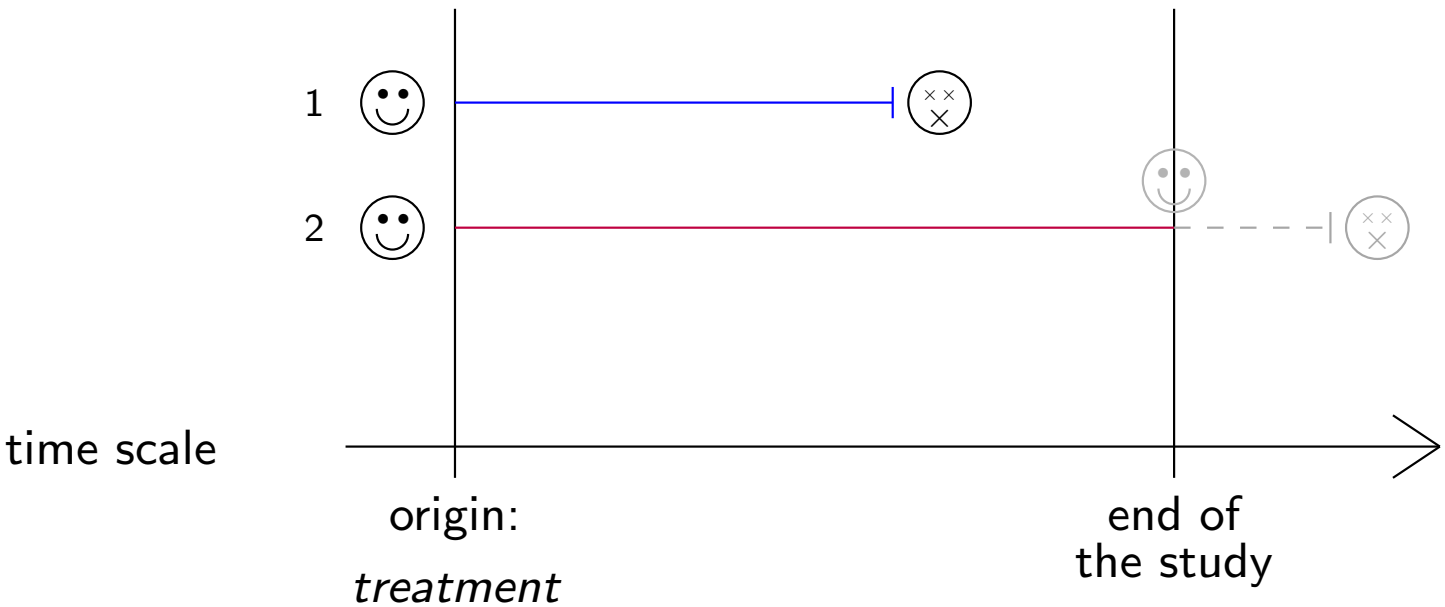
Example: Curable disease - time to relapse



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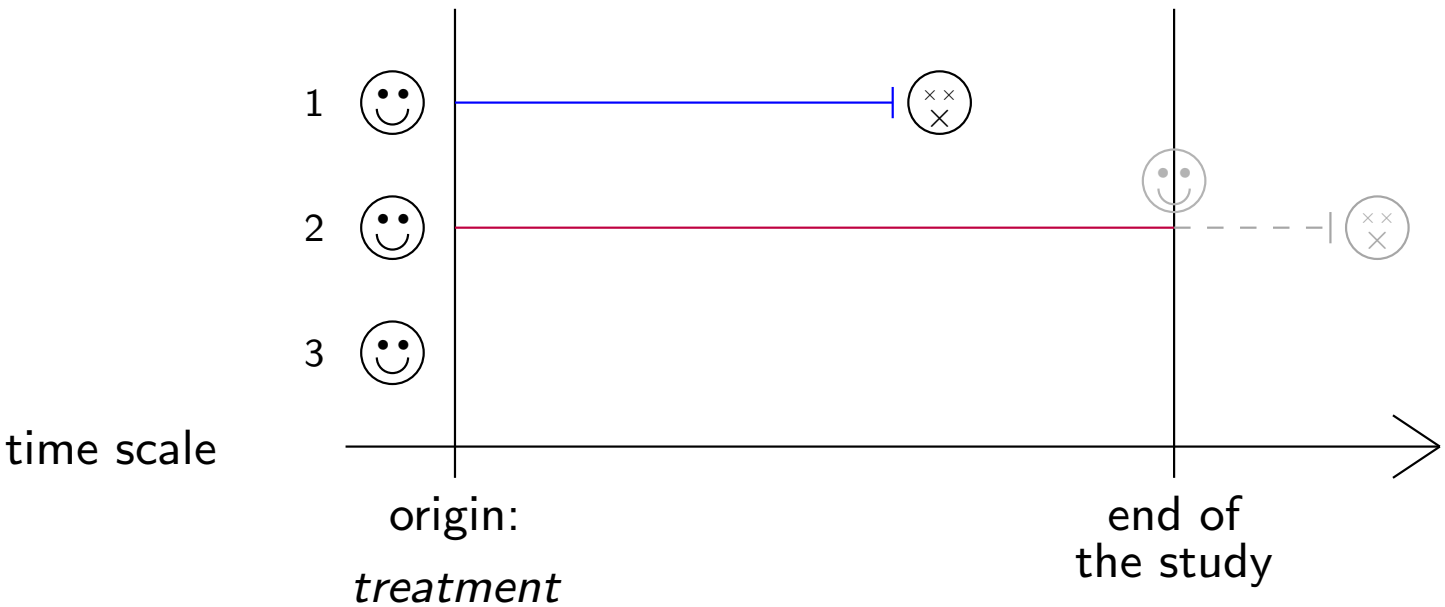

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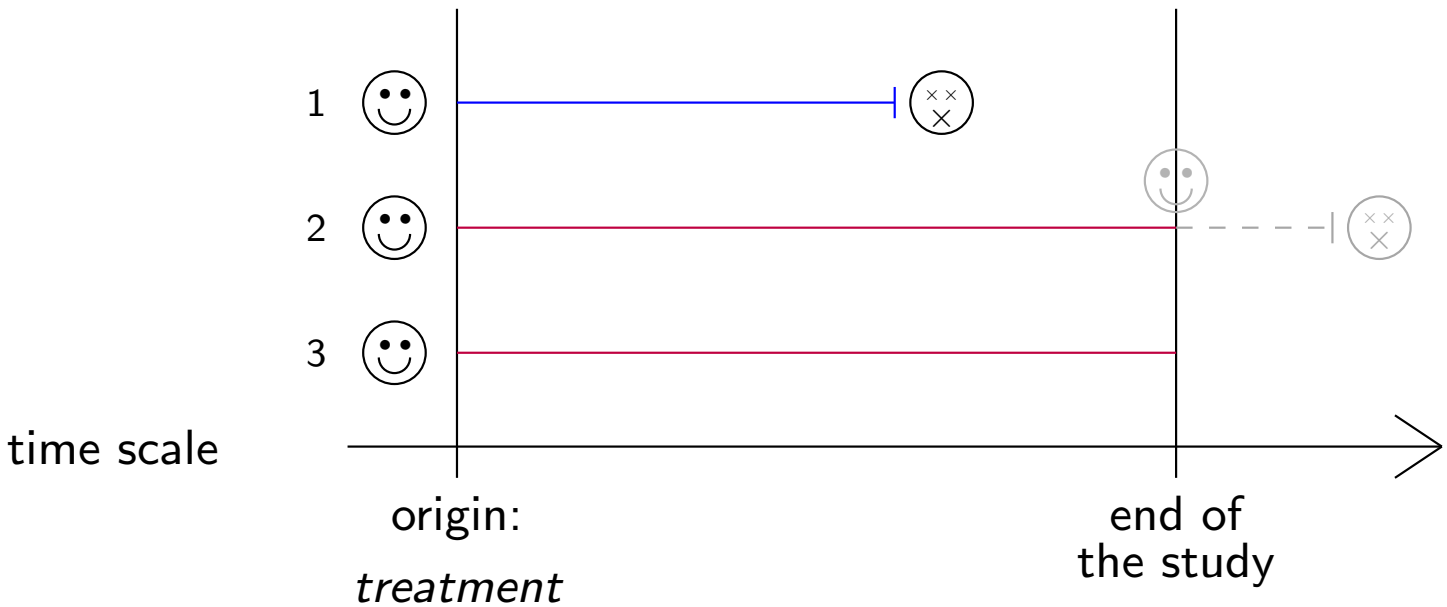

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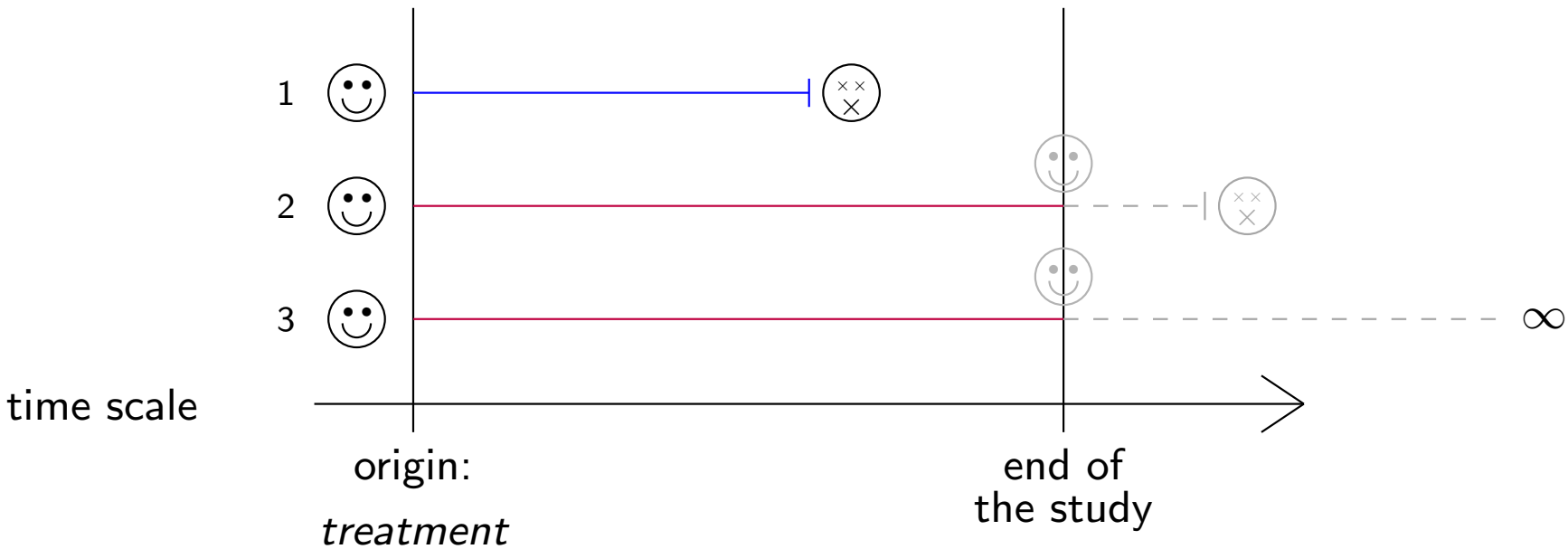

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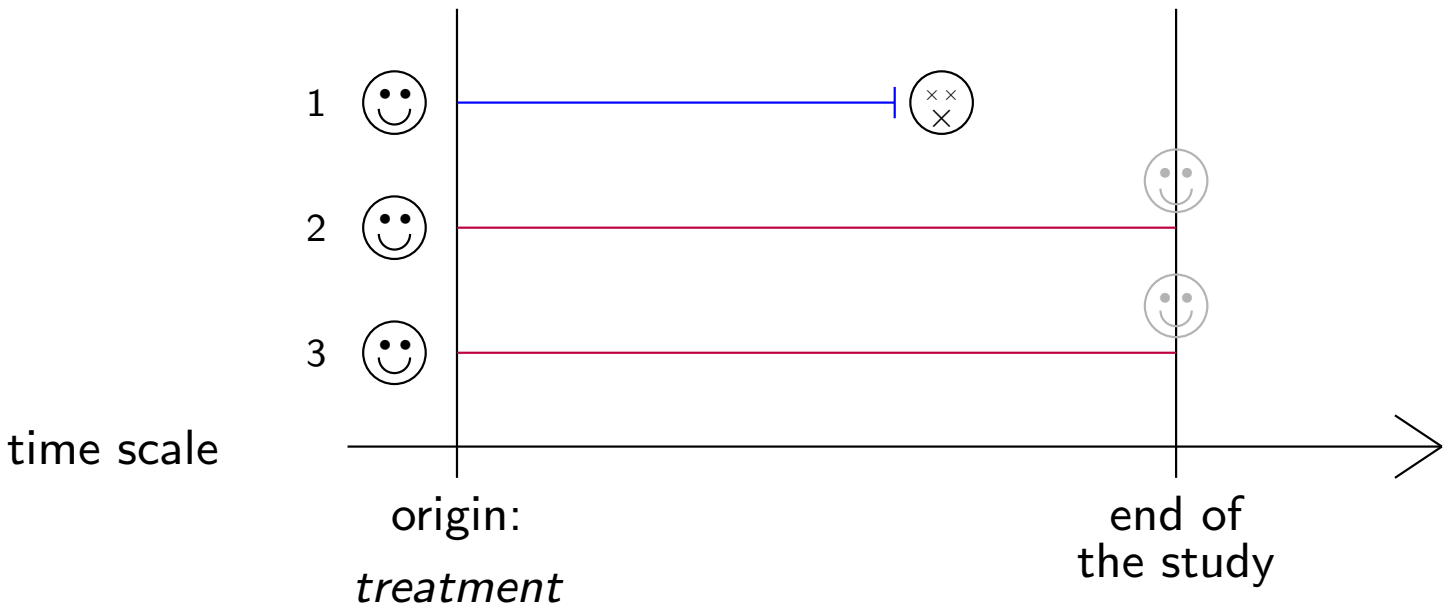

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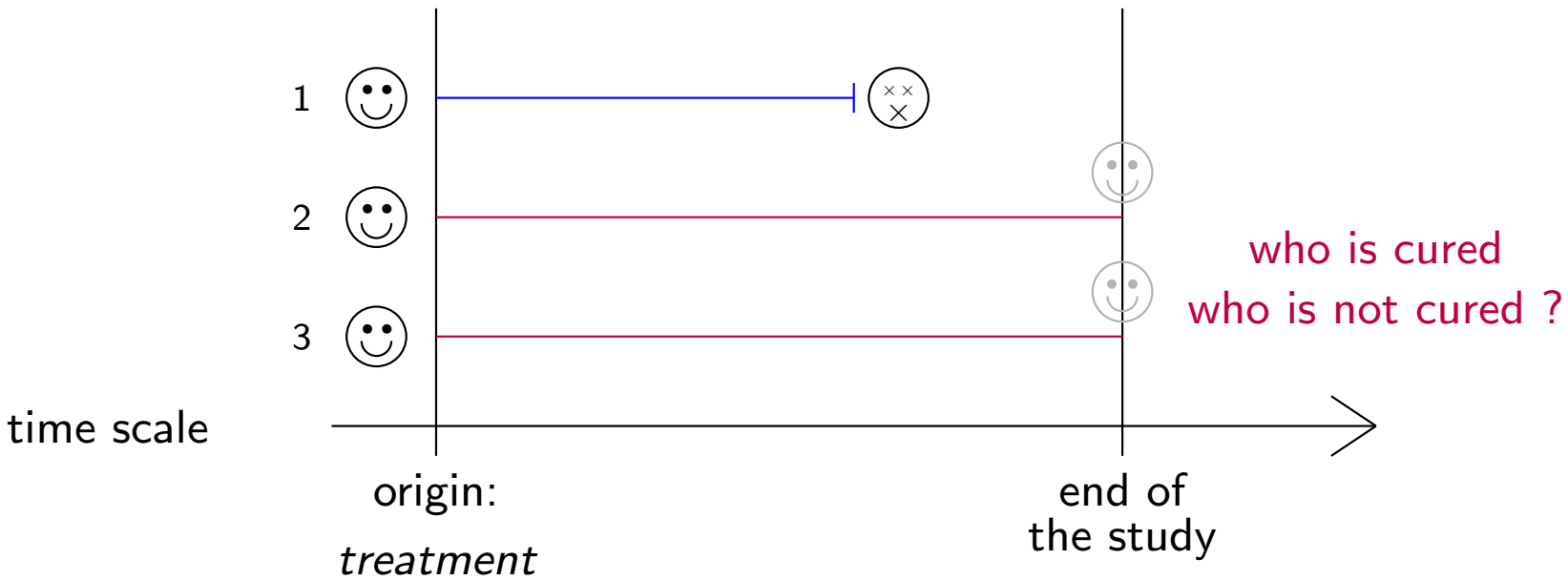
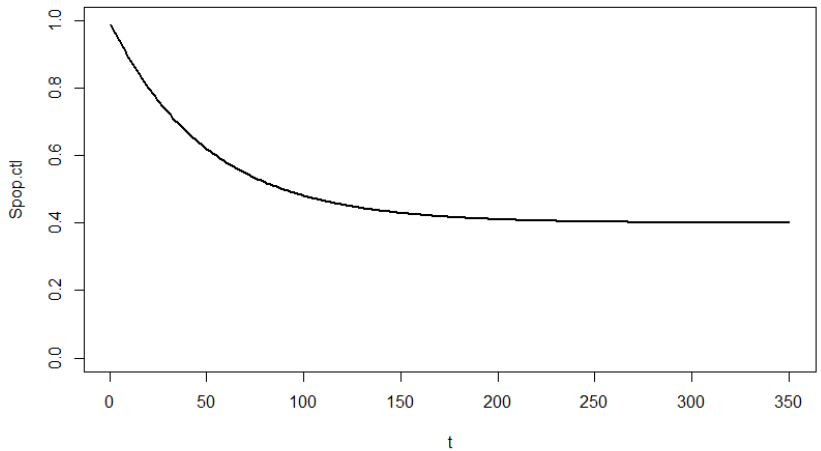


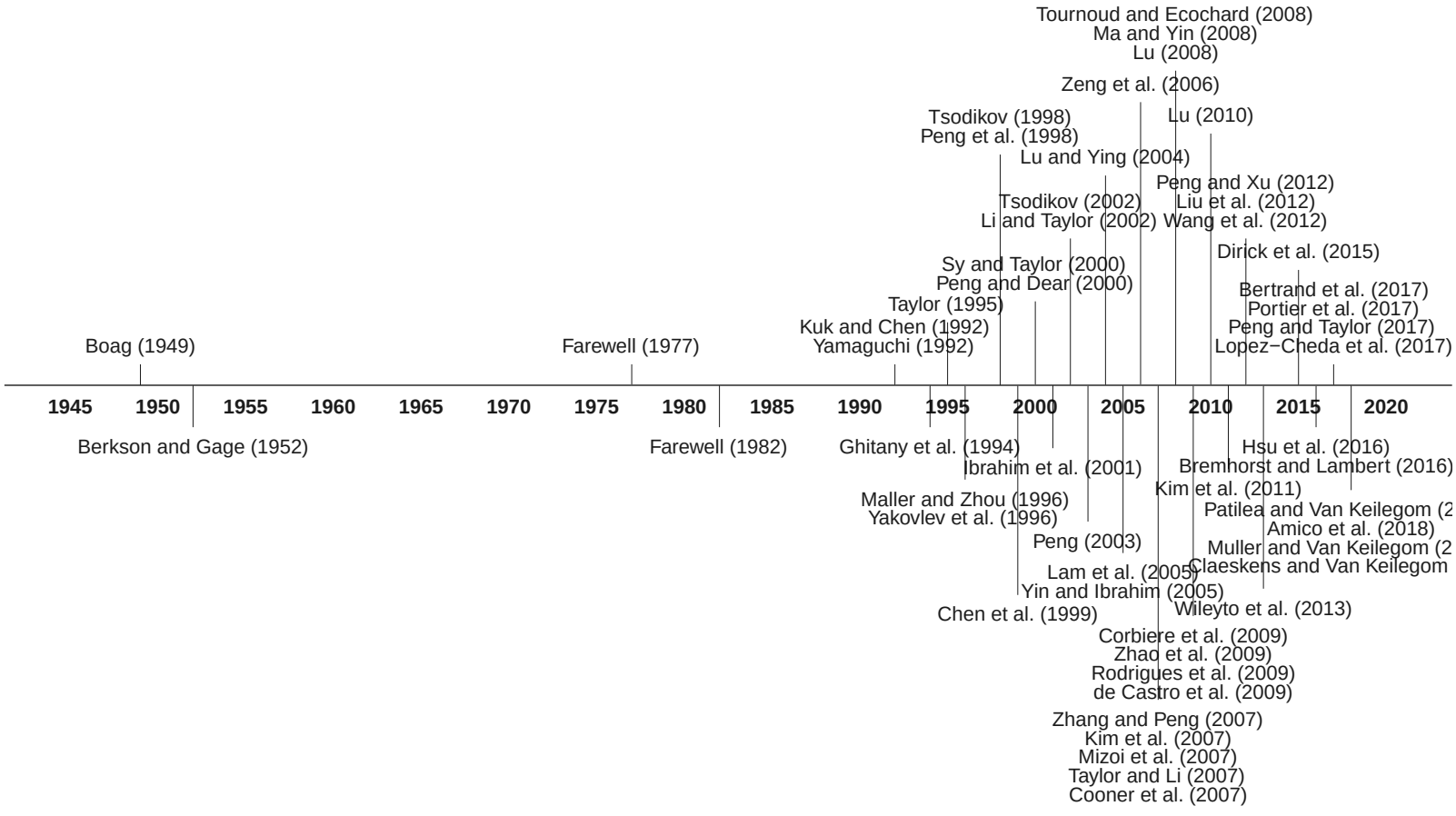
$\hookrightarrow$ Due to the presence of a cure fraction, the survival function "levels up" at some value



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,



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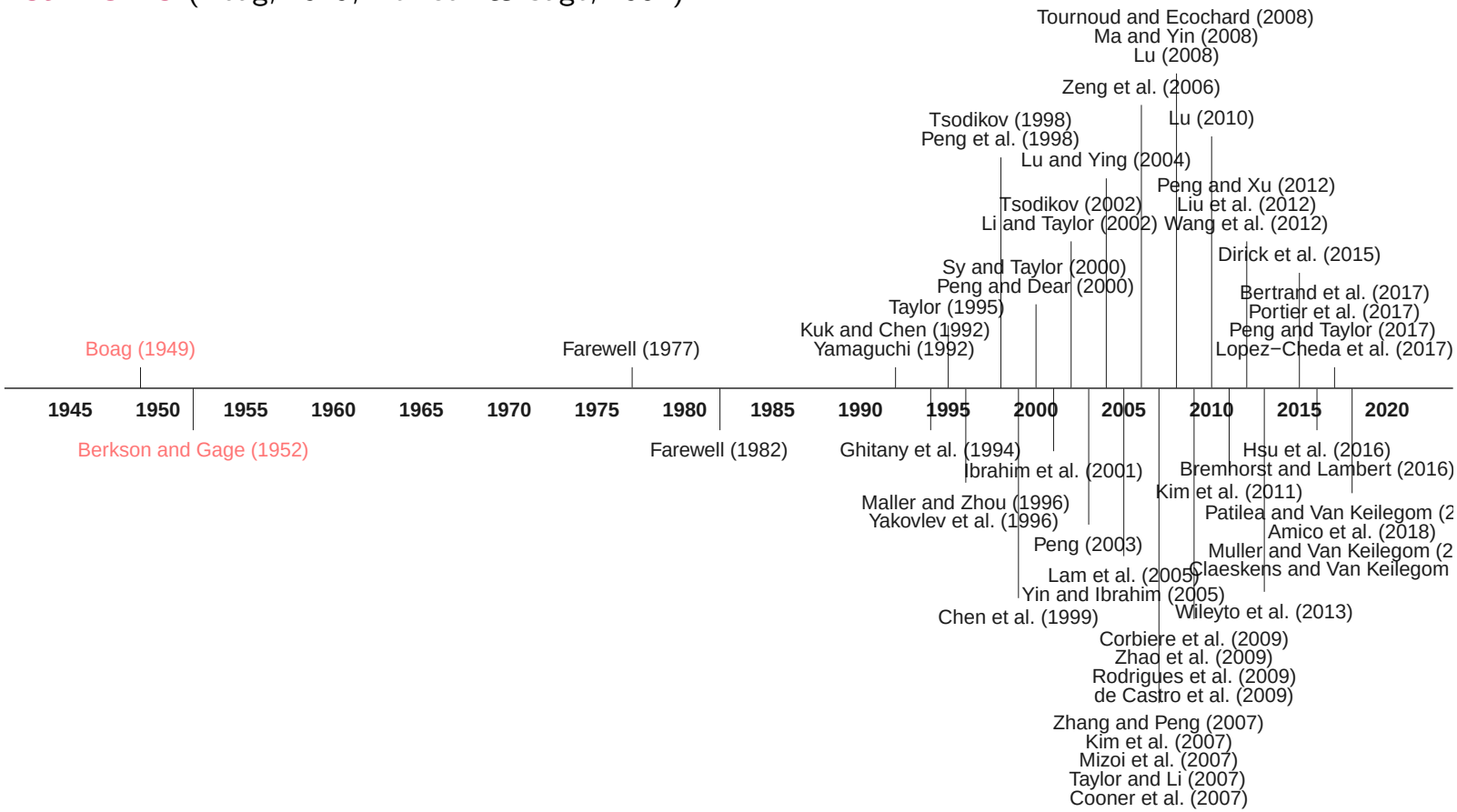

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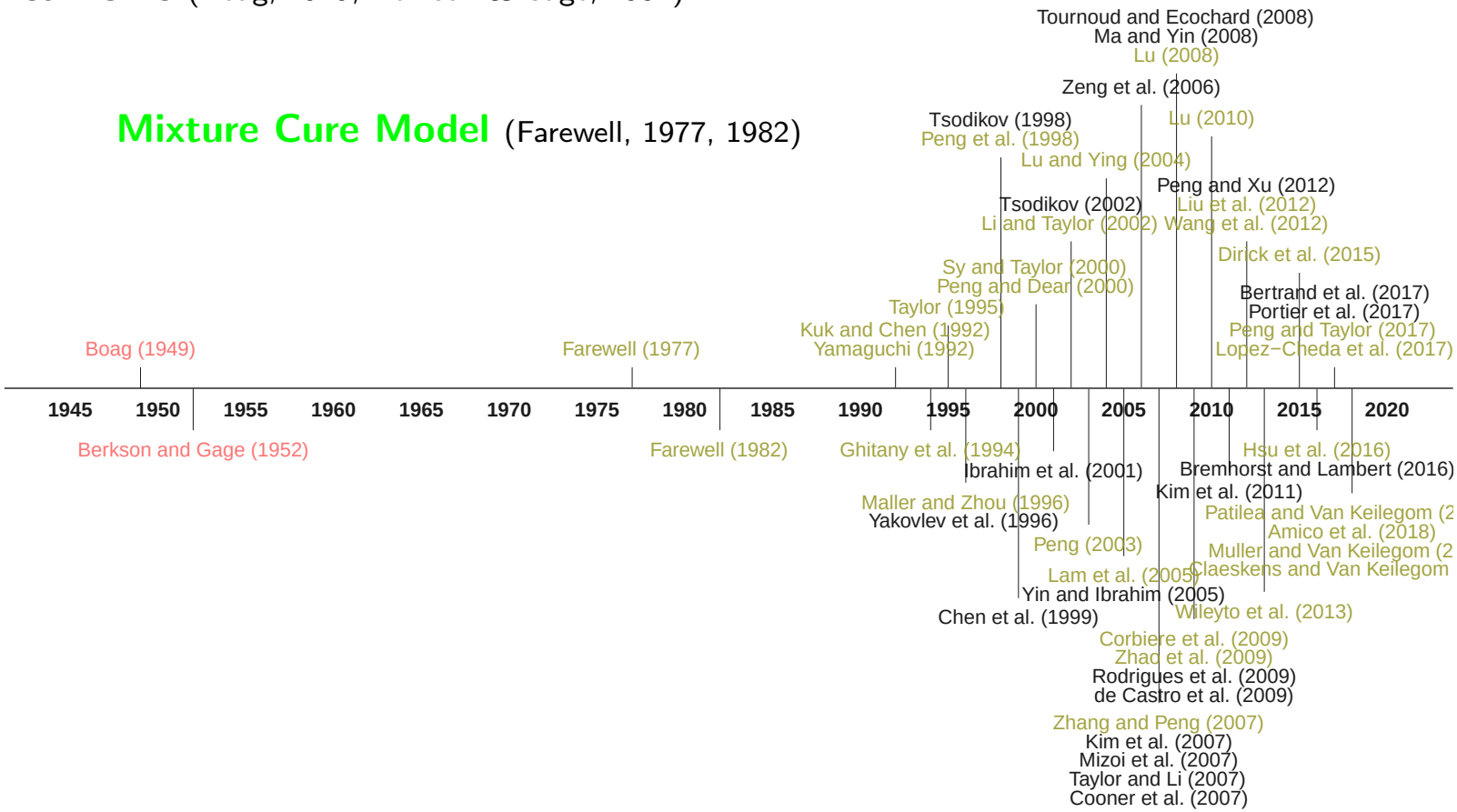

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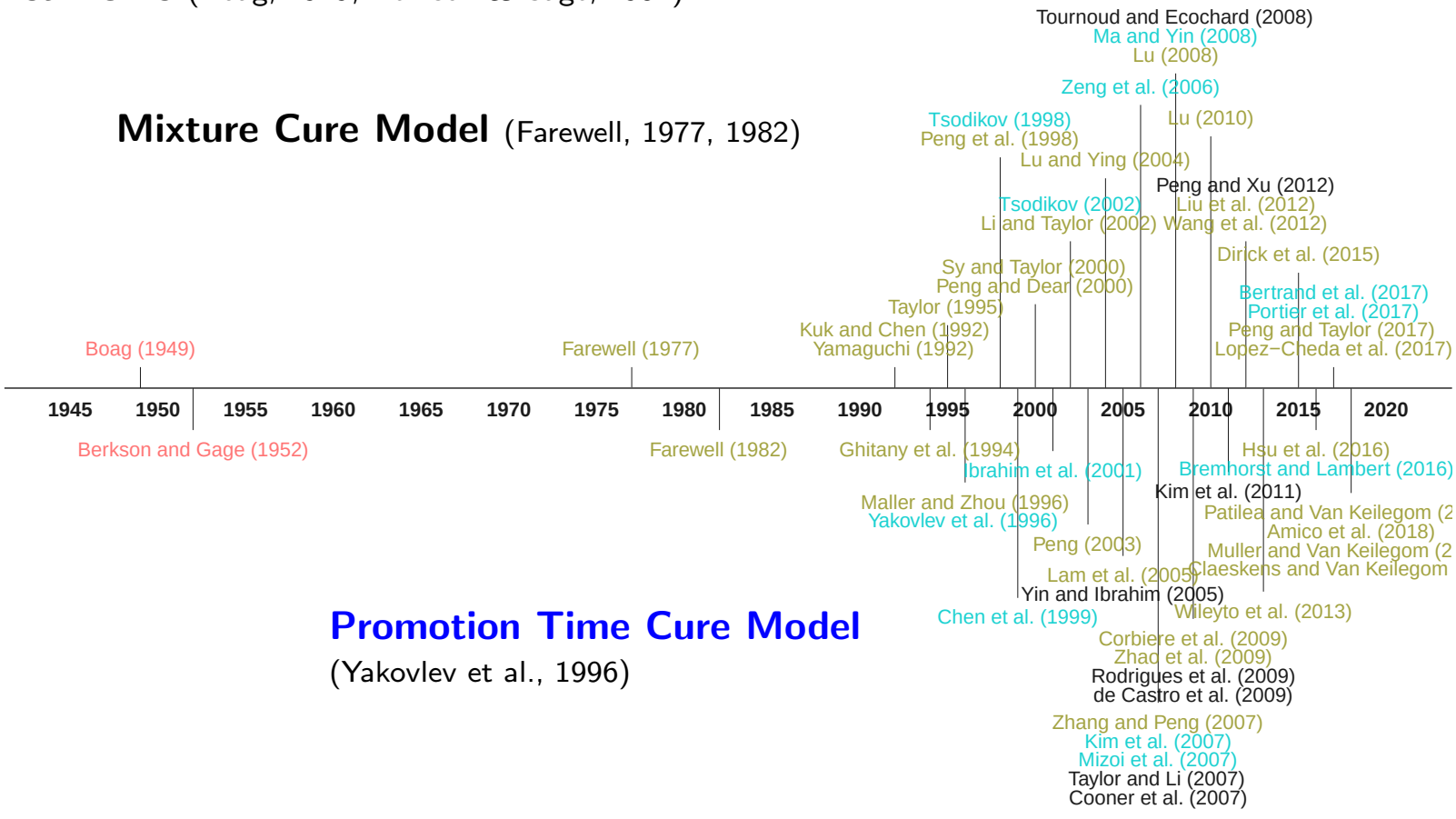

Promotion Time Cure Model

(Yakovlev et al., 1996)

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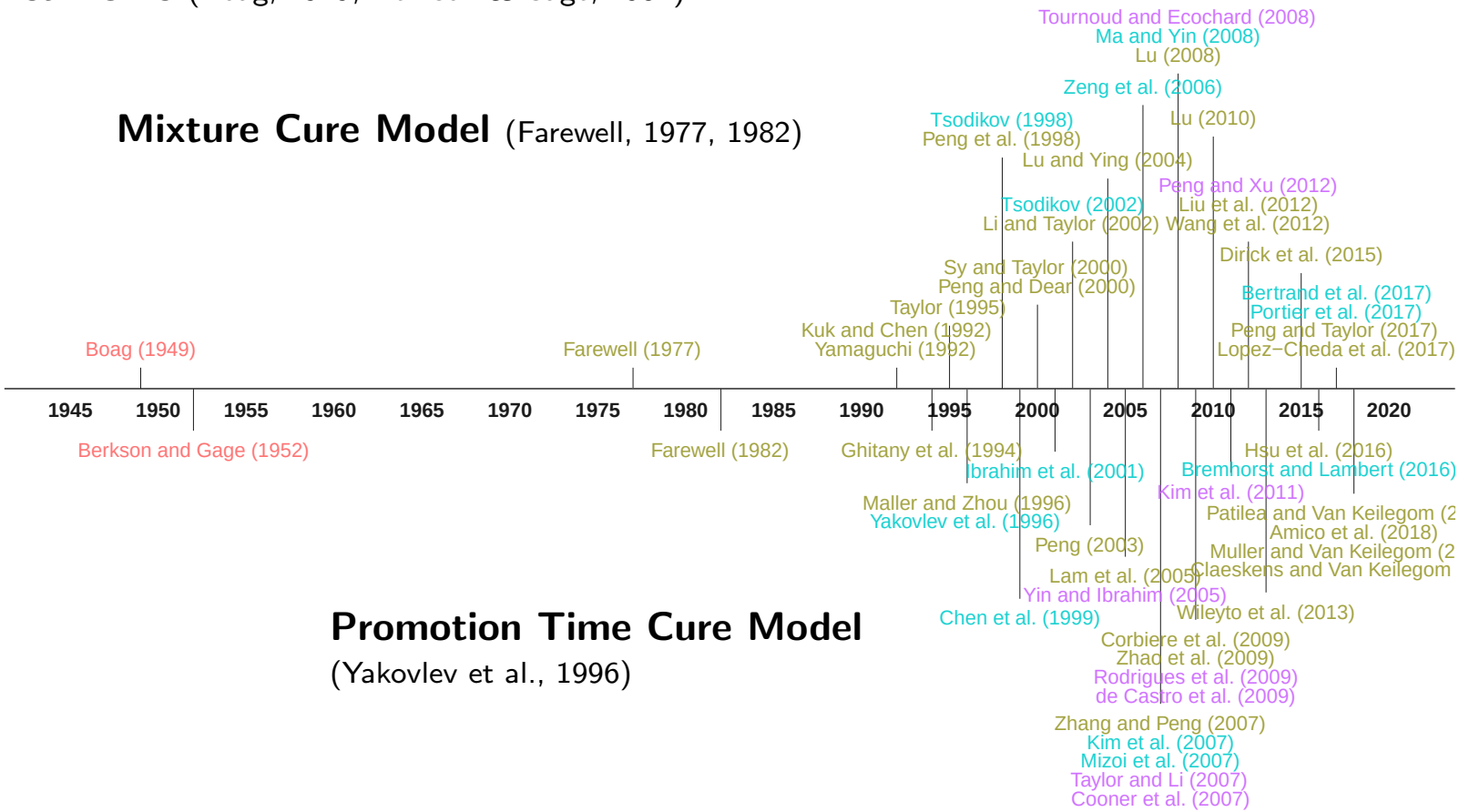


Promotion Time Cure Model

(Yakovlev et al., 1996)

Unifying Models

(Yin & Ibrahim, 2005)

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

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

where

$\pi(\mathbf{x}) = P(Y = 1|\mathbf{X} = \mathbf{x})$ 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: $lim_{t\to\infty} S_{pop}(t|\mathbf{x}, \mathbf{z}) = 1 - \pi(x)$

The Mixture Cure Model

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

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

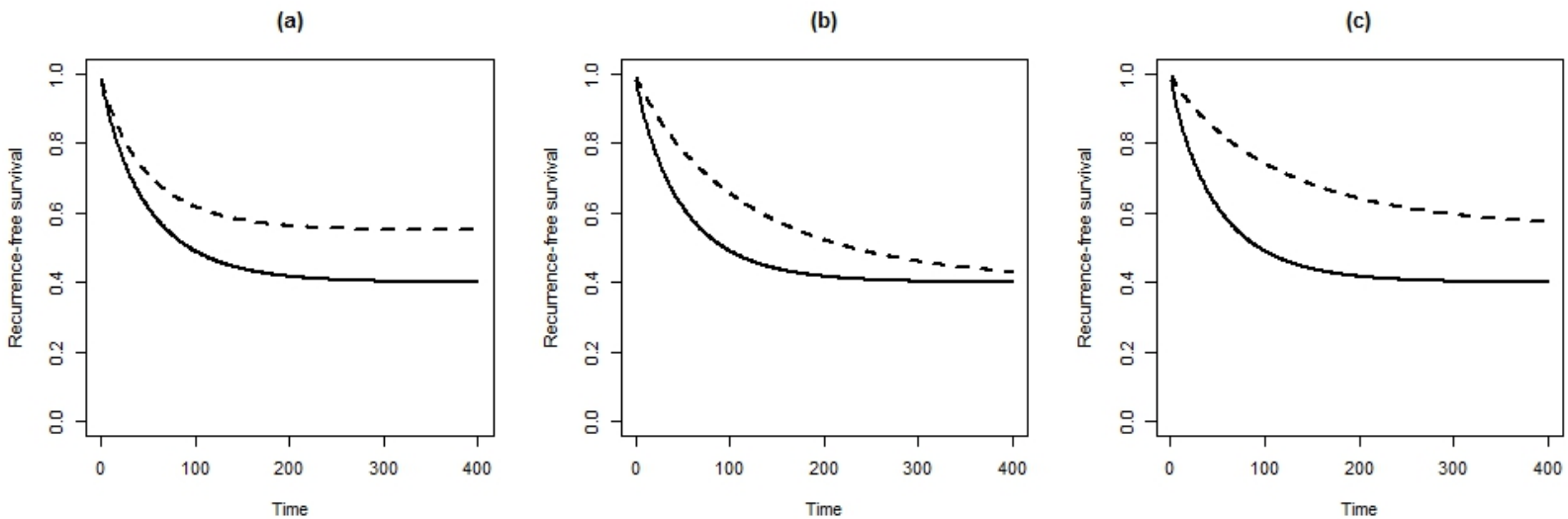
- incidence: logistic regression
- latency: (semi-)parametric PH model

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**



$\longrightarrow$ 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) 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

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

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

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

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

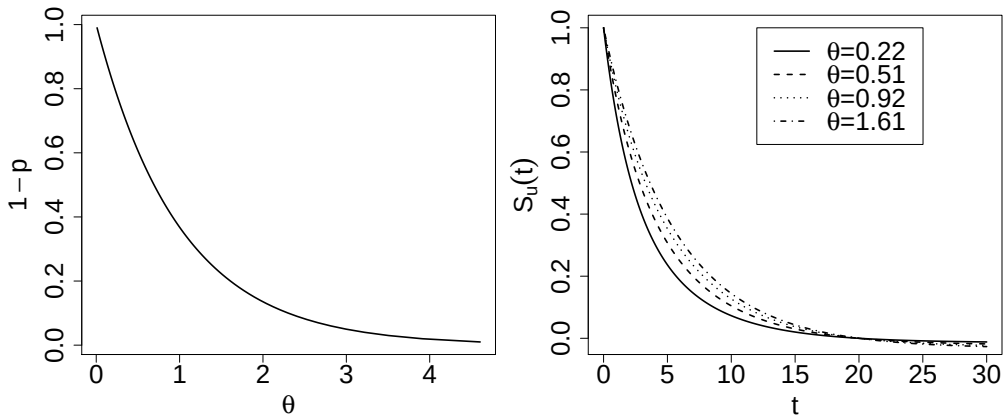
$$S_{pop}(t|\mathbf{x}) = \exp\{-\theta(x)F(t)\}$$

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 ?

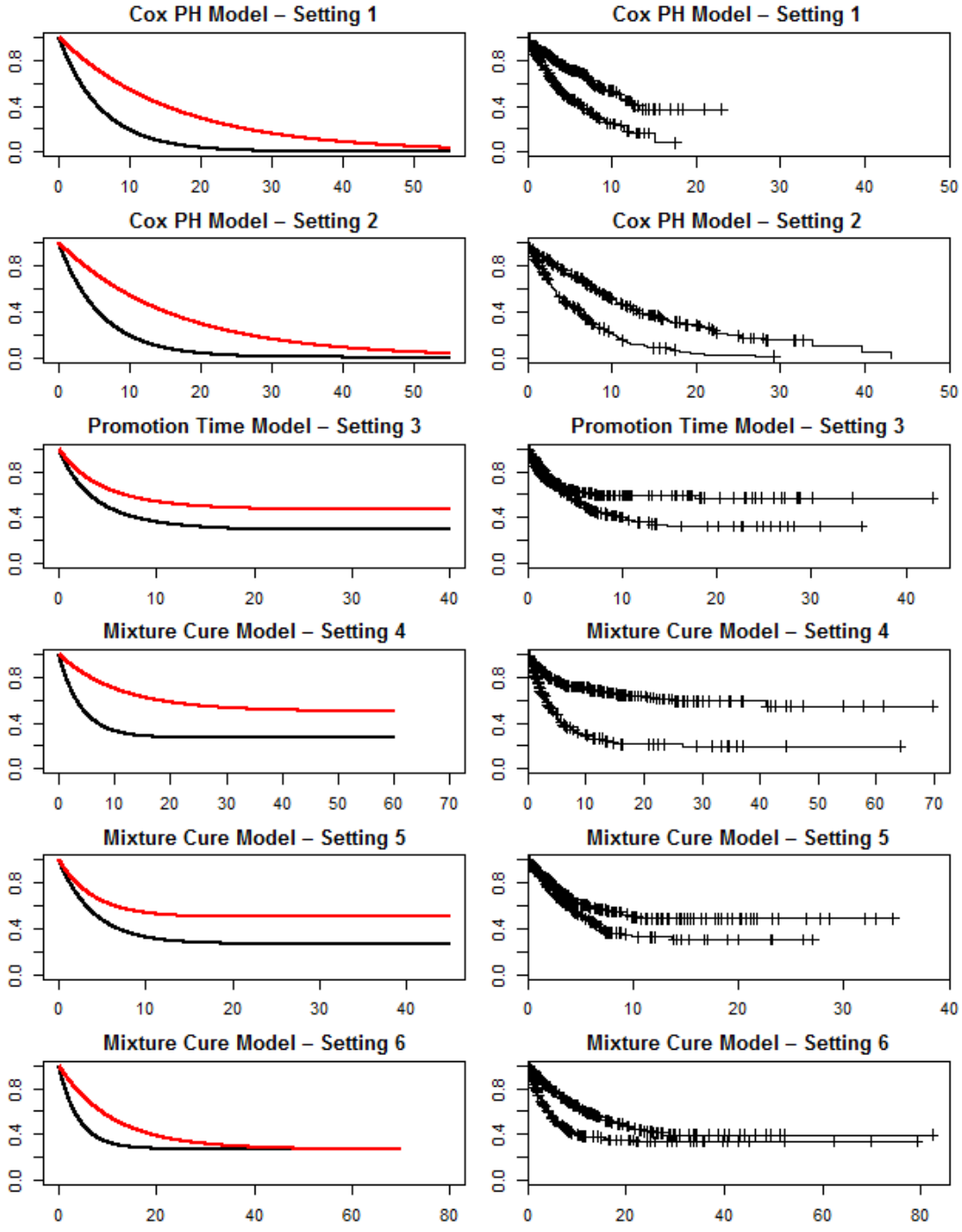
... and if indeed we have to, do we use a mixture cure model or a promotion time model ?

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 MCM (both)	27% and 50%	54% censoring
5	Parametric MCM (incidence)	27% and 50%	56% censoring
6	Parametric MCM (latency)	38% and 38%	54% censoring


Cox PH Model – Setting 1
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Cox PH Model – Setting 2
Cox PH Model – Setting 2
Promotion Time Model – Setting 3
Promotion Time Model – Setting 3
Mixture Cure Model – Setting 4
Mixture Cure Model – Setting 4
Mixture Cure Model – Setting 5
Mixture Cure Model – Setting 5
Mixture Cure Model – Setting 6
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OK, but ...cure or not cure ?

$\Rightarrow$ 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.

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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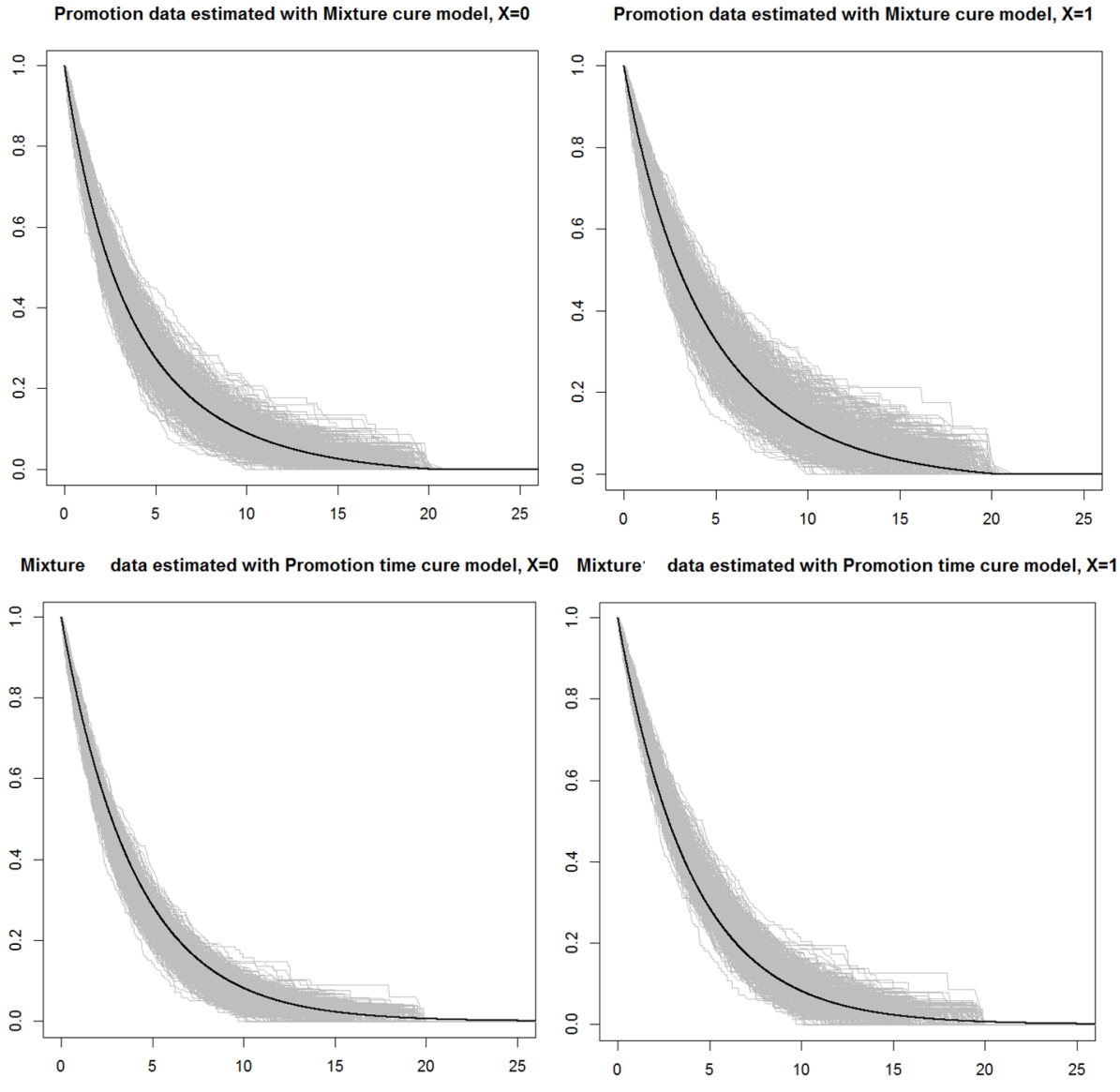

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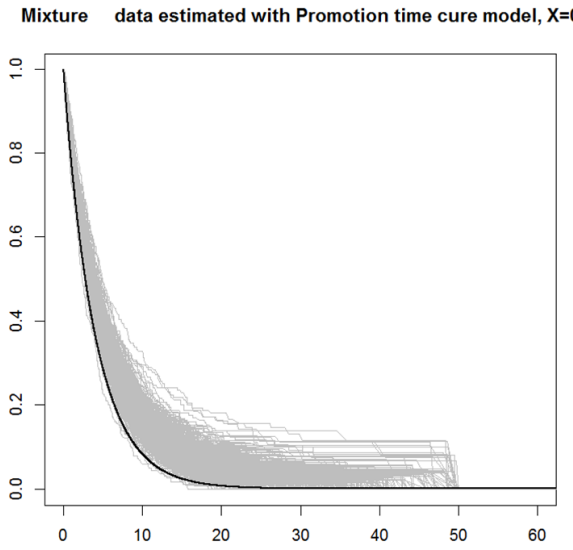
OK, but ...cure or not cure ?

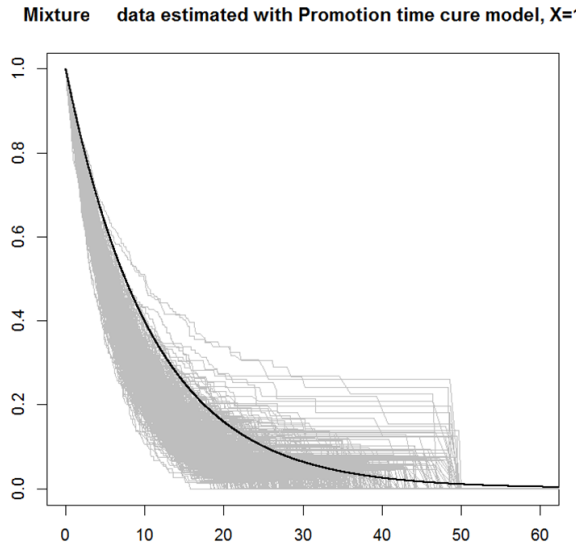
If cure: Pay attention to PH assumption!

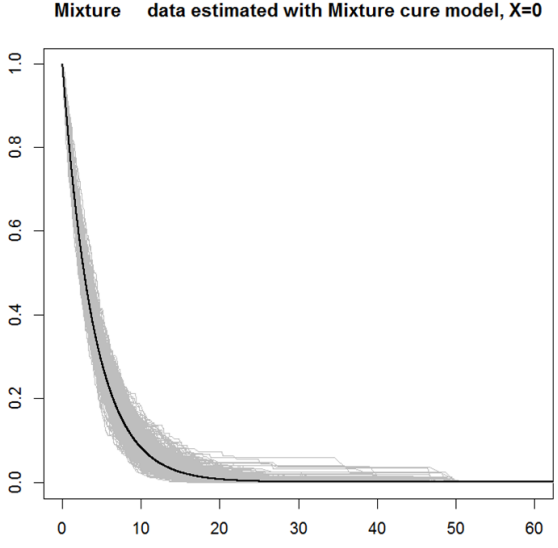
if PH does not hold, e.g. data generated from a MCM with a trt affecting the latency (and the incidence)

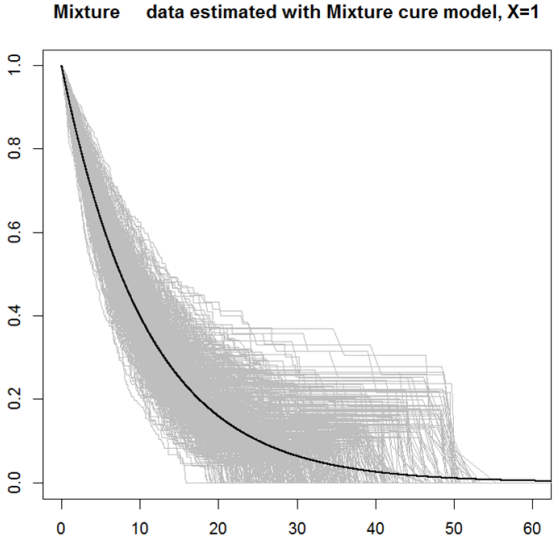
- PTM seems to recover some part of trt effect but
  - the estimated cure rate is biased (downwards in the control arm and upward in the treatment arm)
  - the estimated conditional survival is biased (upwards in the control arm and downward in the treatment arm)
- no problem when using the appropriate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

OK, but ...cure or not cure ?









CONCLUSIONS

For some types of cancer (as well as other diseases), 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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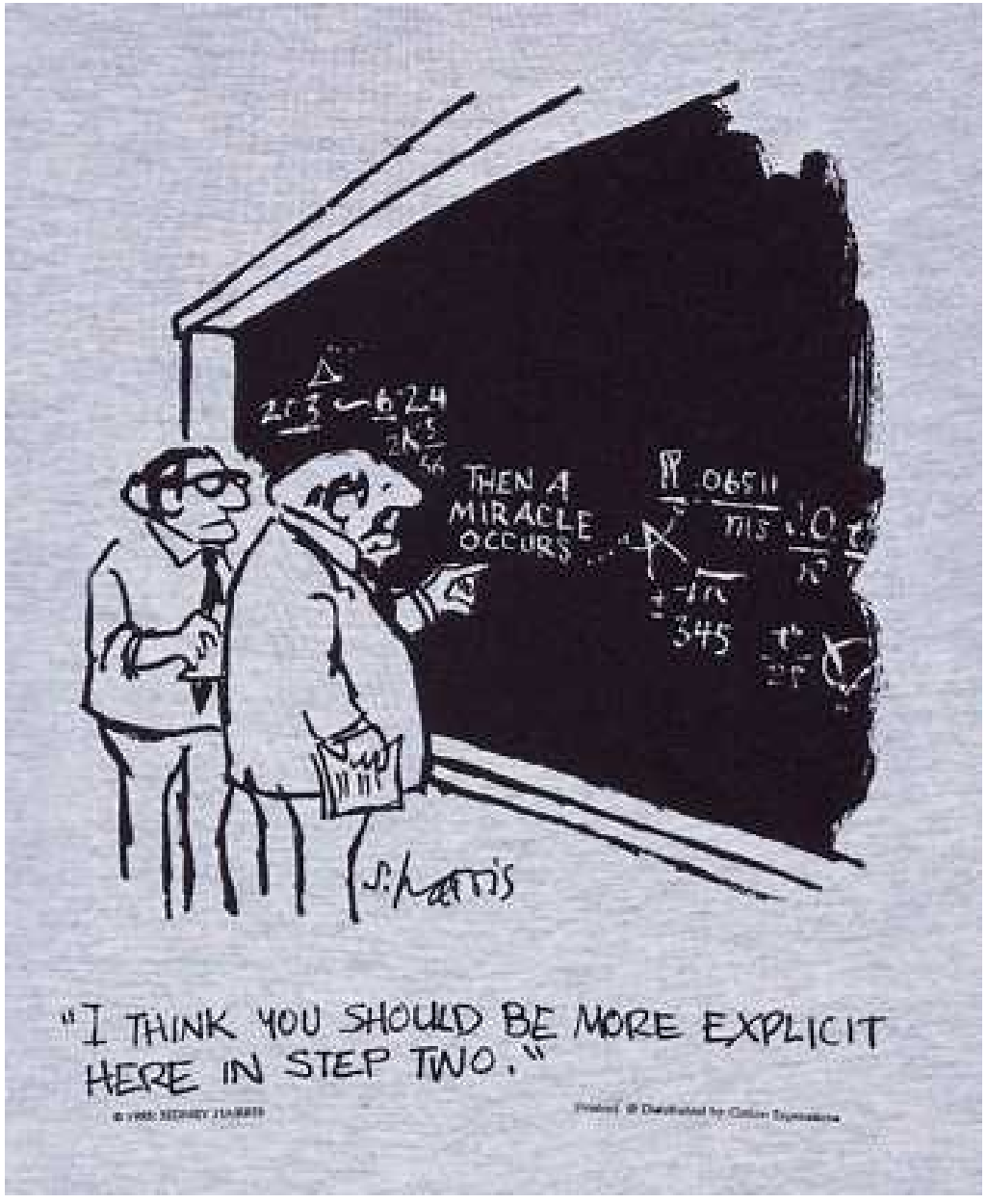
- **If the PH assumption is not met**, don't use PTM nor CM
- **If the PH assumption is not met due to the presence of a cure fraction**, use MCM
- **If the PH assumption is not met for another reason** ... then ask someone else what to do!

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

Any questions ?



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

Amico M. and Van Keilegom I. Cure models in survival analysis. Annual Review of Statistics and Its Application, 5(1), 2018

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