Introduction to Survival analysis

The DARTH Workgroup

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17/3/2020

Overview

- Motivation and introduction in Survival analysis
- Survival modeling
- Non-parametric modeling
- Semi-Parametric modeling
- Fully Parametric modeling
- Multistate models
- Advanced topiics
  - Mixture cure models
  - External evidence in survival models

Introduction

So far we worked with :

- continuous data (linear modeling)
- binary/categorical/ count data (generalized linear modeling)
- . . . but what about data that measure time until an event of interest? (Survival time data /Duration data)

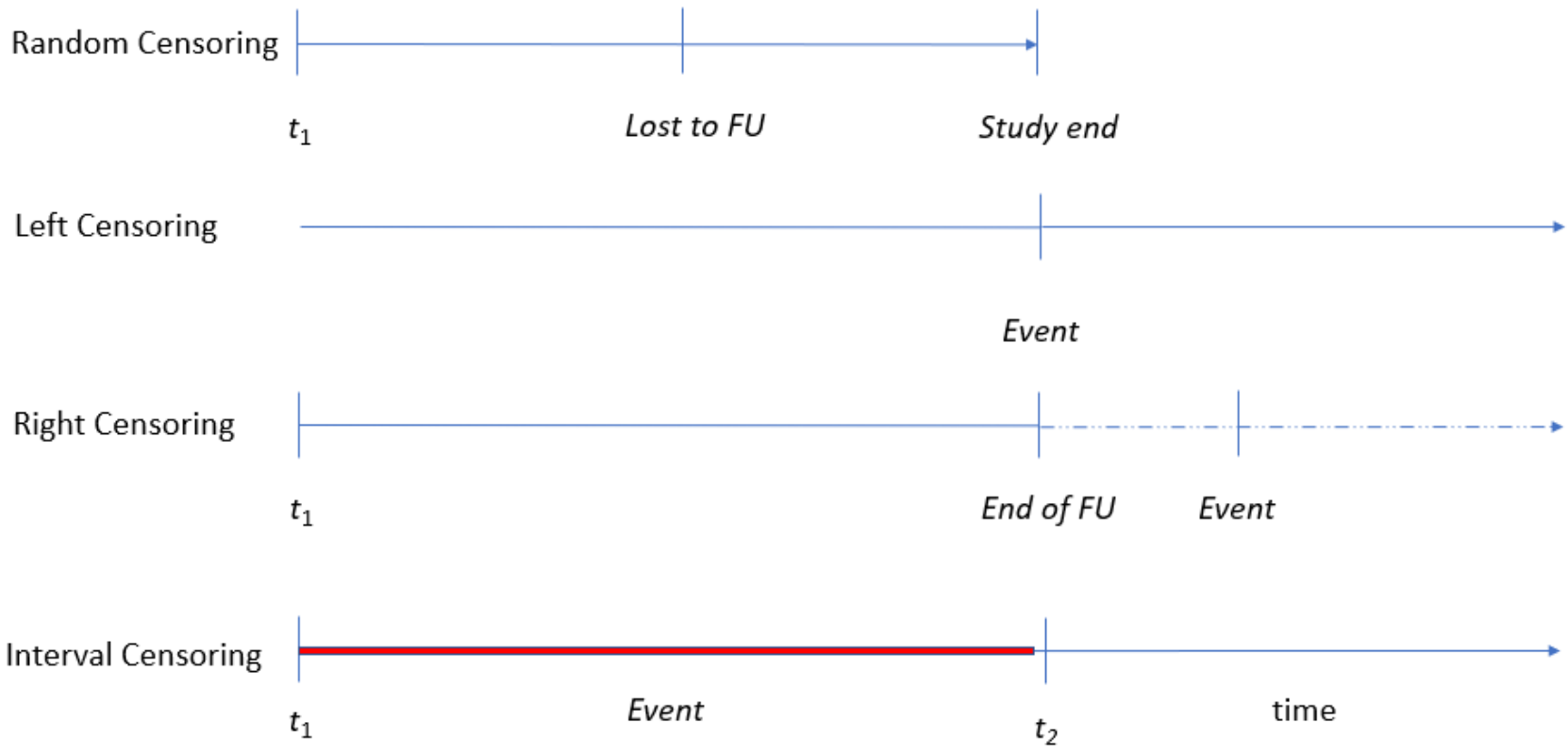
It's all about the data!

- RCT evidence often not sufficient for Health Technology Assesment (HTA)
  - Short follow up
  - Patients lost during follow up
  - Often not reflective of real world
  - Right skewed
  - Information "flowing" over intervals
  - Extrapolation often necessary

Bonus challenges in Oncology RCTs

- Overall Survival (OS), Progression-Free Survival (PFS)
- Trials powered to show differences on PFS and not OS
- Cross-over
- PFS and OS data are correlated
- Access to patient level OS data not always the case

Censoring


Random Censoring
t_1
Lost to FU
Study end
Left Censoring
Event
Right Censoring
t_1
End of FU
Event
Interval Censoring
t_1
Event
t_2
time

Infromative Censoring

The case where survival time is dependent with whatever causes the censoring. Example: A patient in a community study is censored because they are hospitalized (hospitalization indicates severity)

In most of the examples throughout we will make the assumption of non-informative censoring

What is survival analysis

- Set of statistical methods that can handle:
  - Data skewness
  - Censoring
  - (Time-dependent) Covariates
  - State transition processes
  - Recurrent events
  - The expectation of cure
- Used for both inference and extrapolation

Key Concepts in survival analysis

- survival time T: the random variable capturing time since the beginning of the event.
- Survival: the probability of not experiencing an event unit some time t $S(t) = Pr(T > t) = 1 - Pr(T \leq t)$
- Cumulative density function:

$$F(t) = Pr(T \leq t)$$

$$F(t) = 1 - S(t)$$

- Hazard function (the instantaneous rate of the event): $h(t) = \lim_{\delta t \to 0} \frac{1}{\delta t} \frac{F(t+\delta t) - F(t)}{S(t)}$

turns out $h(t) = \frac{f(t)}{S(t)}$

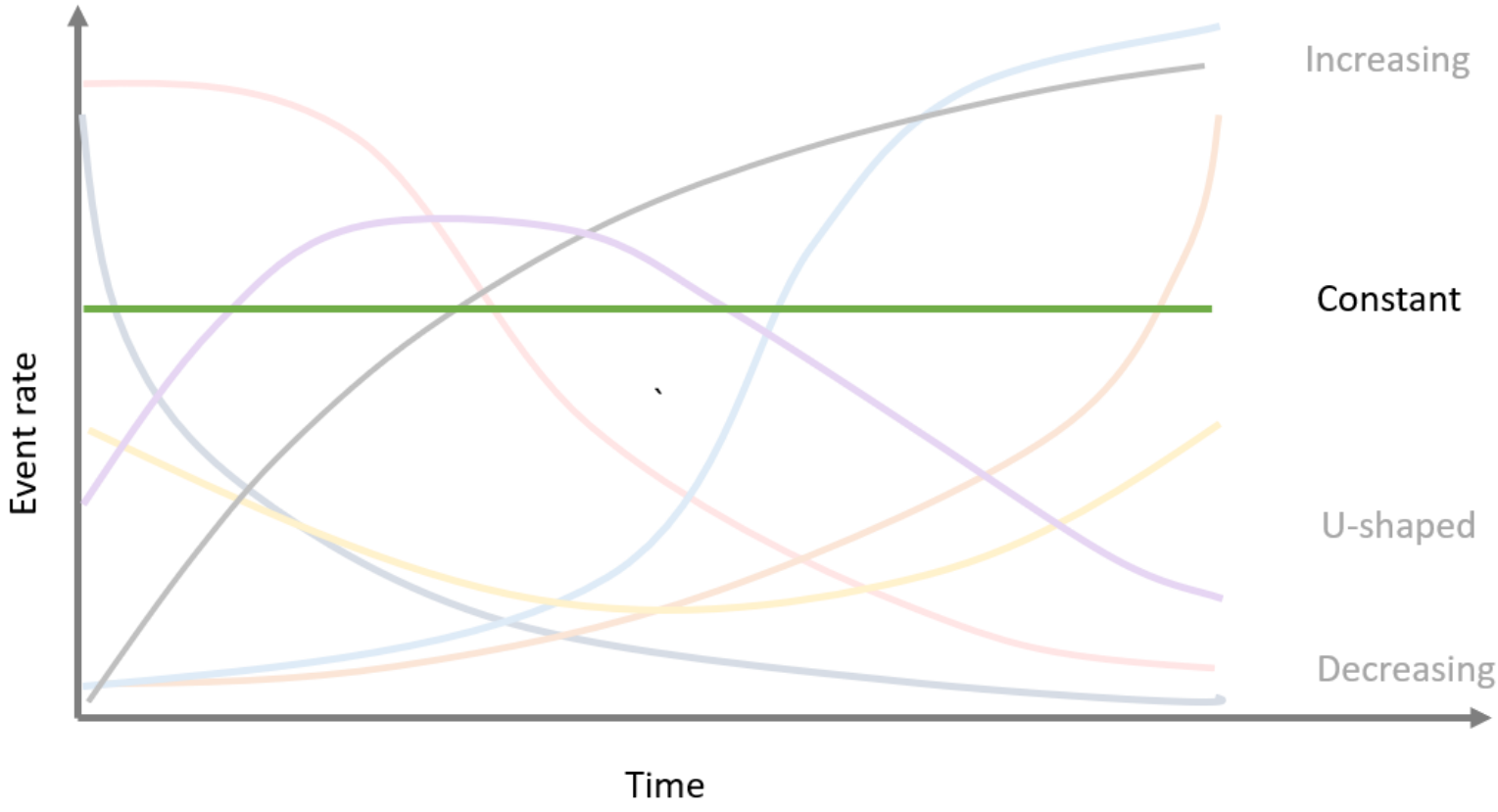
- Cumulative hazard $H(t) \int_0^t h(x)dx$

as well as $S(t) = e^{-H(t)}$

Example: the exponential distribution

- $H(t) = \lambda t$
- $S(t) = exp(-\lambda t)$
- $f(t) = \lambda exp(-\lambda t)$
- Weibull , gamma, lognormal etc. . .

Some shapes of hazards

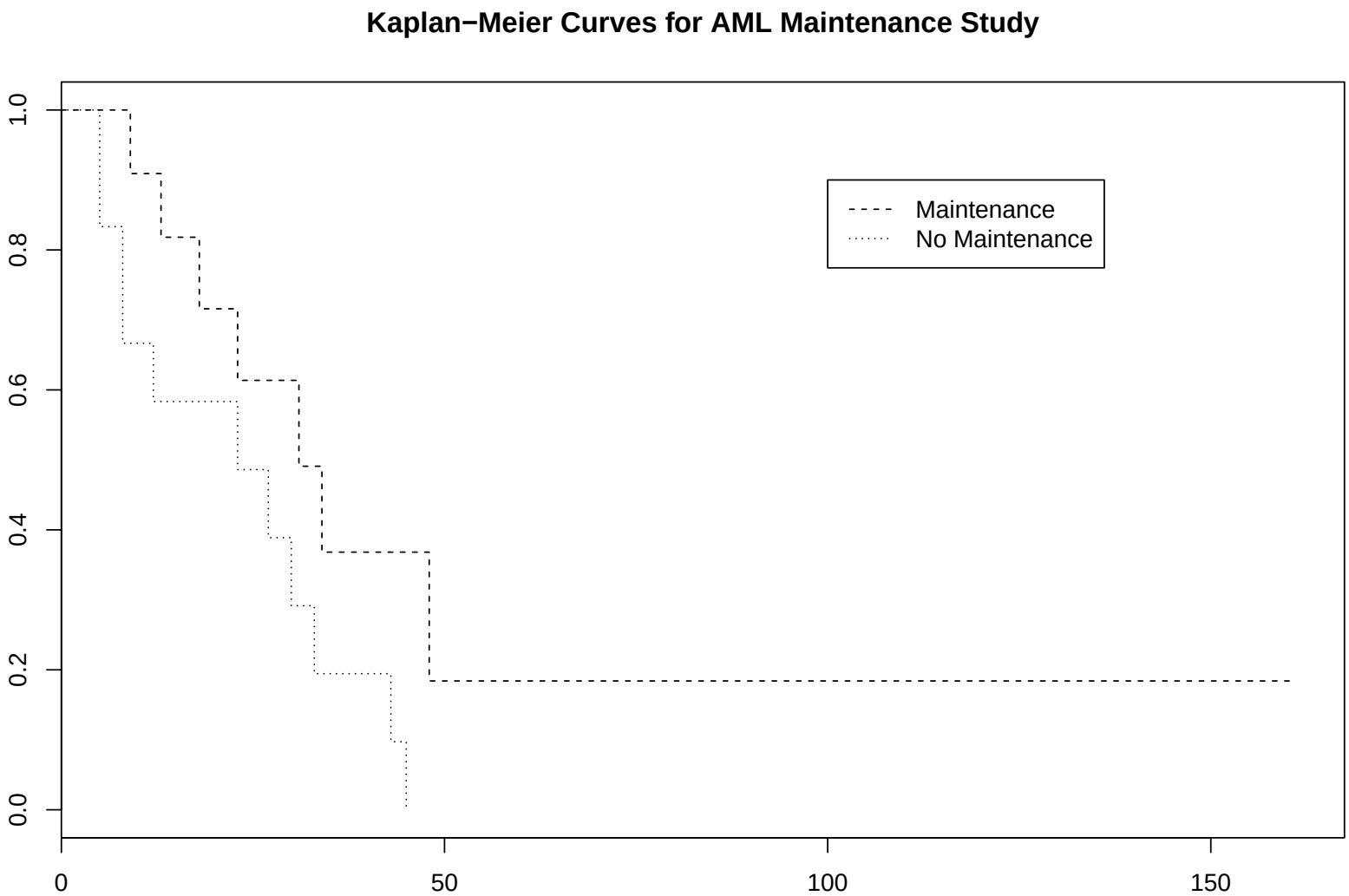


Types of survival analysis models

- Non-parametric models (e.g. Kaplan Meier)
- Semi-Parametric models (e.g. Cox Proportional Hazard)
- Parametric models (e.g. Accelerated Failure Time)

Non-Parametric models

- known as the "product-limit" estimator. The most used survival analysis method
- makes no parametric assumption on the data



Non-Parametric models

```
## Call: survfit(formula = Surv(time, status) ~ x, data = a
##
##                 x=Maintained
##  time n.risk n.event survival std.err lower 95% CI upper
##     9     11       1    0.909  0.0867        0.7541
##    13     10       1    0.818  0.1163        0.6192
##    18      8       1    0.716  0.1397        0.4884
##    23      7       1    0.614  0.1526        0.3769
##    31      5       1    0.491  0.1642        0.2549
##    34      4       1    0.368  0.1627        0.1549
##    48      2       1    0.184  0.1535        0.0359
##
##                 x=Nonmaintained
##  time n.risk n.event survival std.err lower 95% CI upper
##     5     12       2   0.8333  0.1076        0.6470
##     8     10       2   0.6667  0.1361        0.4468
##    12      8       1   0.5833  0.1423        0.3616
##    23      6       1   0.4861  0.1481        0.2675
```

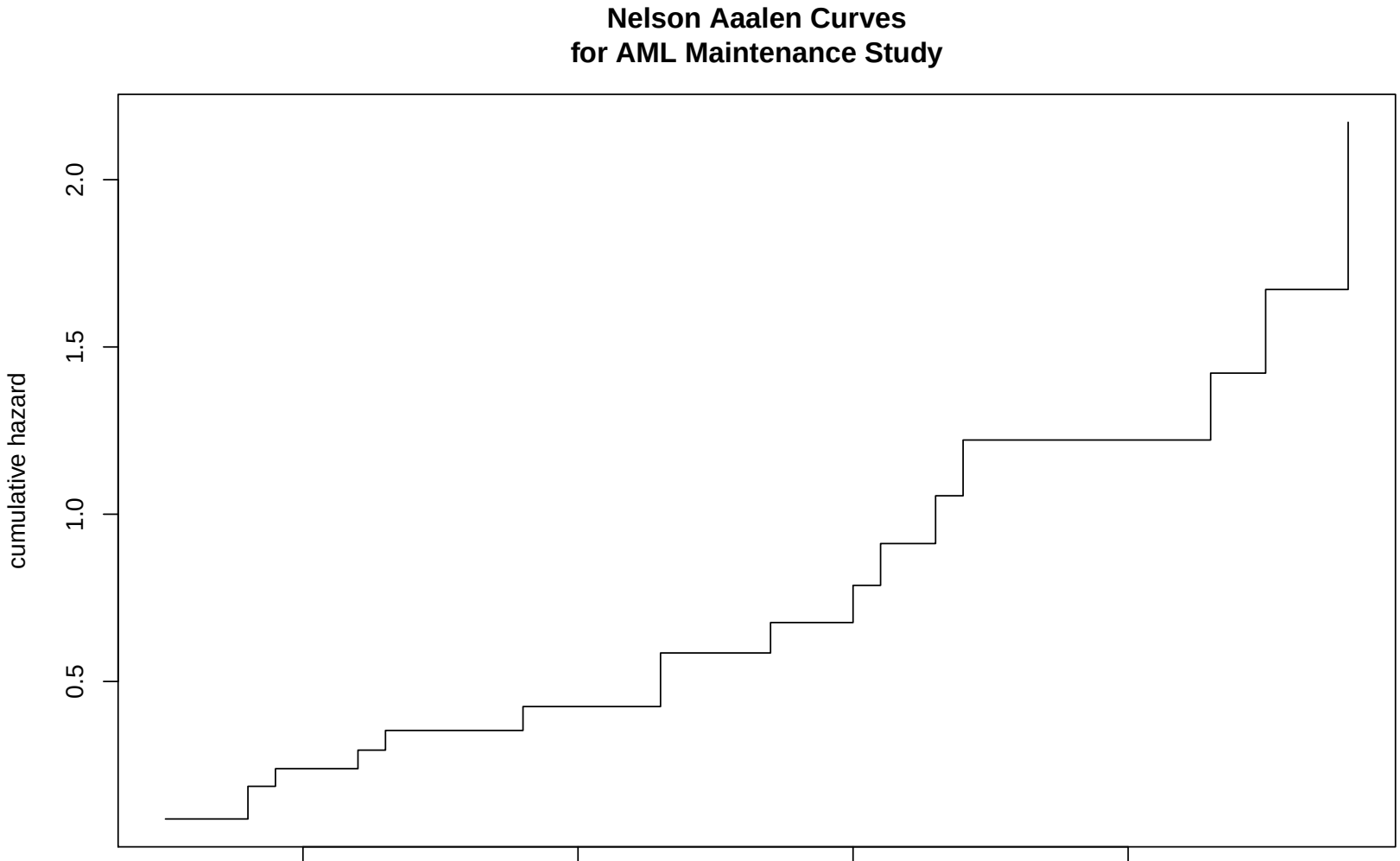
Non-Parametric models - testing

- We can use a non parametric test to understand if group A lives longer than group B
- long-rank test: is the difference in survival times statistically different?
- relying on a χ^2 distribution

```
## Call:
## survdiff(formula = Surv(time, status) ~ x, data = aml)
##
##                  N Observed Expected (O-E)^2/E (O-E)^2/V
## x=Maintained    11        7    10.69      1.27       3.4
## x=Nonmaintained 12       11     7.31      1.86       3.4
##
##  Chisq= 3.4  on 1 degrees of freedom, p= 0.07
```

Non-Parametric models

- Often, more intuitive to look at the results on the cumulative hazard rate
- Nelson Aalen cumulative hazard is the most common non parametric estimator



Semi- Parametric models

- Cox proportional hazard model
  - Hazard: the instantaneous risk of an event at time t, conditional on survival to that time.
- Semi:
  - Baseline hazard modelled non parametrically (i.e effect of time)
  - Covariate effects (β 's) modelled parametrically (like in a regression model)

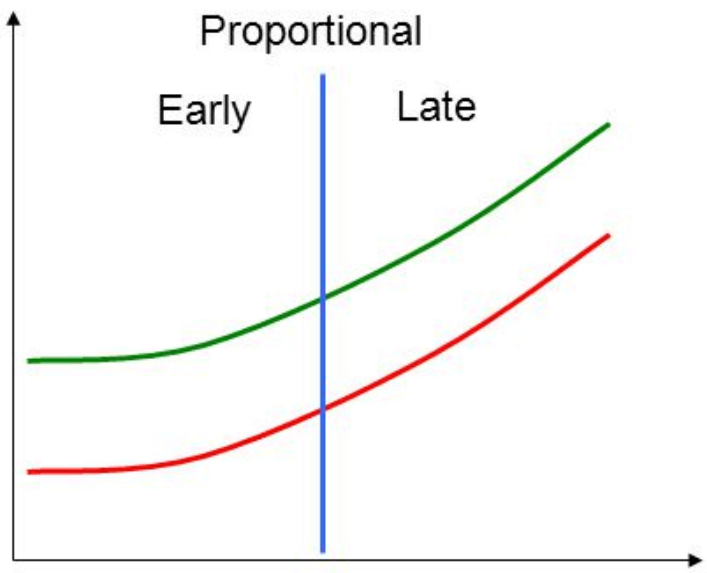
$h(t) = h_0(t)exp(X\beta)$ where $h_0(t)$ is estimated non-parametrically

Notice that the effect of the covariates is proportional on the baseline hazard..(that's why "proportional hazard" model)

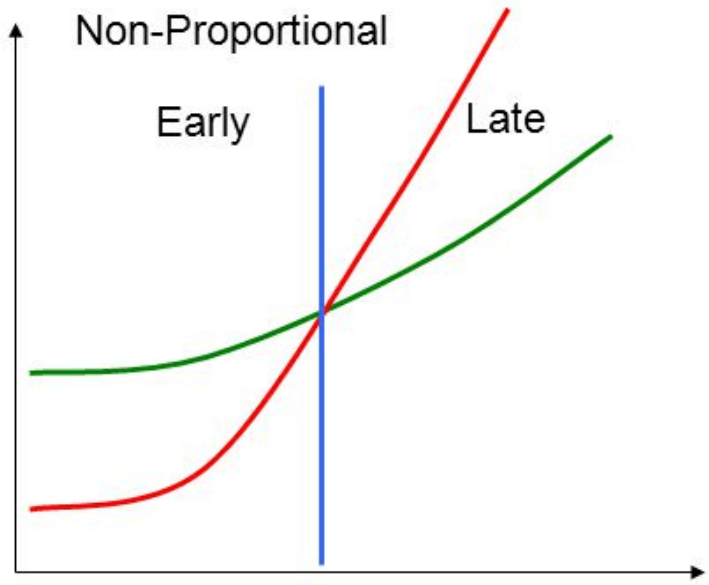
The assumption of proportional hazards

Proportional Hazard Assumption

- In a piecewise model, coefficients would differ in non-proportional models



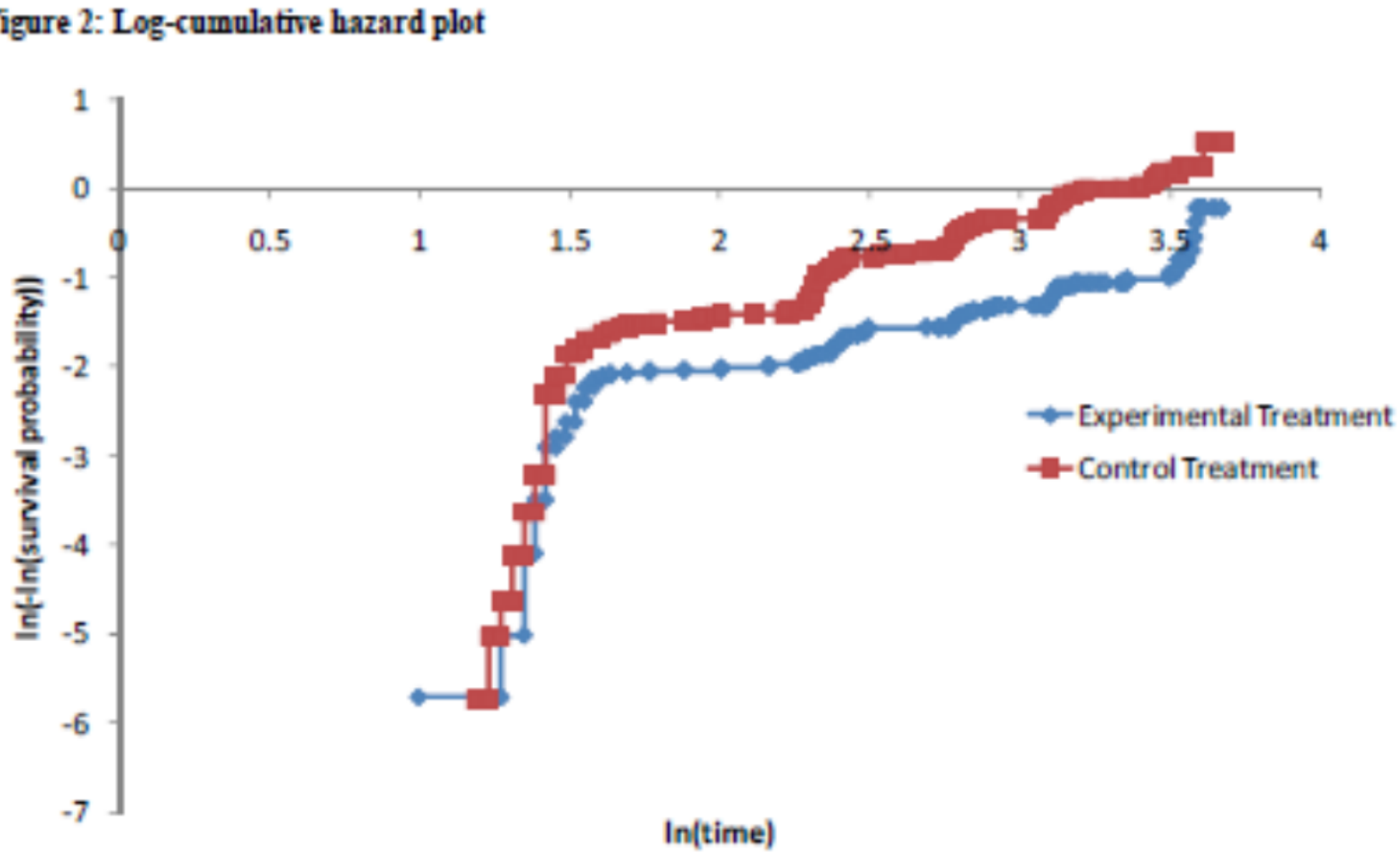
Here, the effect is the same in both time periods



Here, the effect is negative in the early period and positive in the late period

Assessing the proportionality assumption

The assumption can be assessed number of ways : visually



http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf

Testing the non-zero slope of the Schoenfeld residuals (more in the

Fully Parametric models (Accelerated Failure Time models)

- Usually model time-to-event directly rather than hazard
- Resemble a regression model but can capture censoring
- Fit a distribution to the (observed) time-to-event data
  - 1 parameter : exponential
  - 2 parameter : Weibull, lognormal, gamma etc
  - 3, 4 parameter: Gen. gamma , Gen F etc
- Assumption that censored patients will follow similar patterns to the observed.
- Temporal extrapolation possible !

AFT and covariates

- We can incorporate covariates in a sort of similar way as we would do in a linear regression model $log(T) = \beta_0 + X\beta_1 + \epsilon$

T	$\log(T)$
Exponential	Extreme value
Weibull	Extreme value
Log-logistic	Logistic
Lognormal	Normal

Choosing the "right" distribution

- Statistical considerations of goodness-of-fit
- Clinical plausibility
  - in-sample
  - extrapolations
  - out-of-sample

Goodness of fit metrics

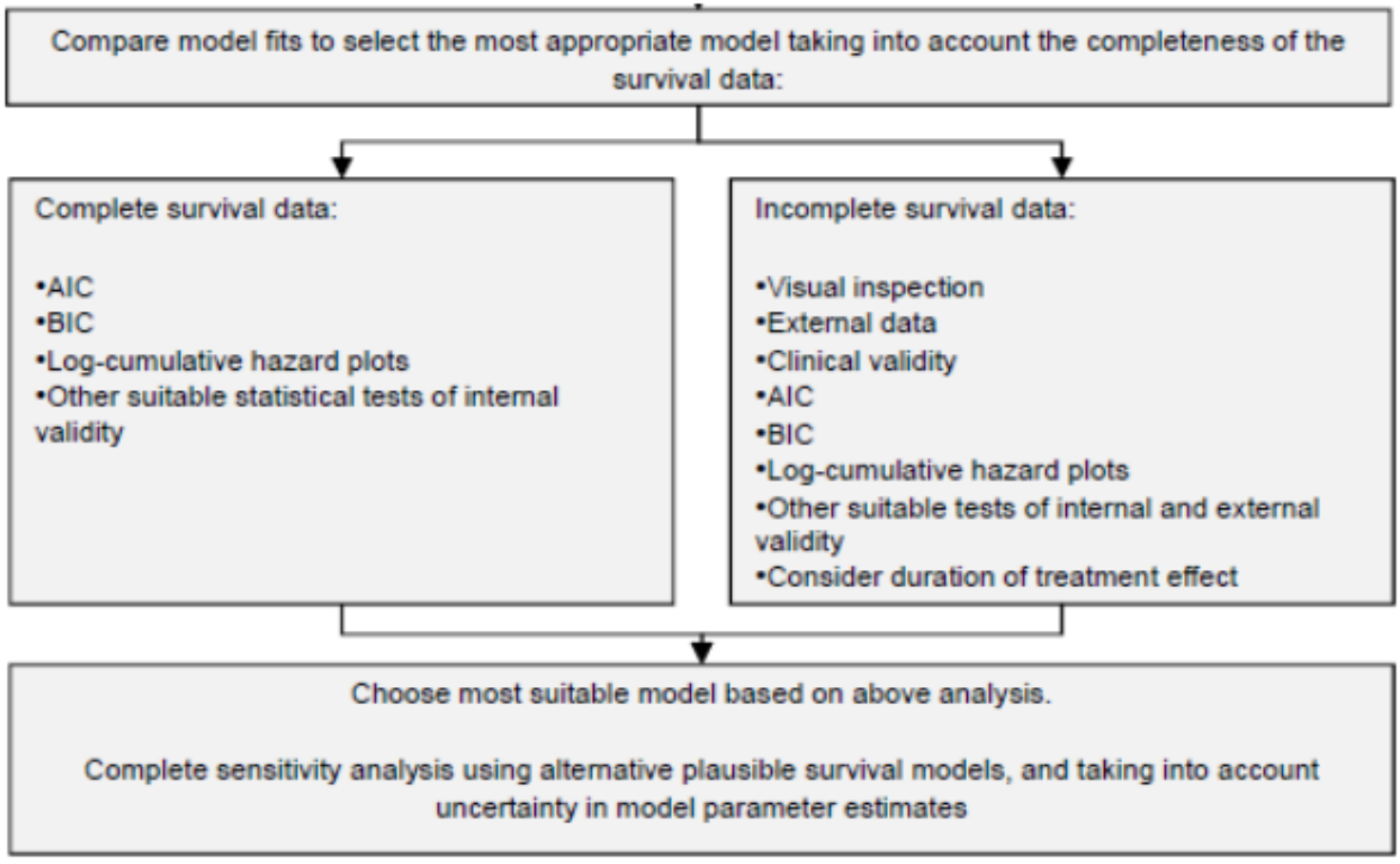
- Likelihood based metrics
- Akaike Information Criterion (AIC)
- Bayesian Information Criterion (BIC)
- Performance based metrics
- Sensitivity , Specificity
- (time dependent) Receiver Operating characteristic (ROC) curve
- Area Under the Curve (AUC)
- c- statistic

Choosing the "right" distribution

- NICE Decision Support Unit
- Latimer et al 2011 : Survival Analysis For Economic Evaluations Alongside Clinical Trials - Extrapolation with Patient-Level Data
  - **Survival Model Selection Process algorithm**:
    - *recommendations for how survival analysis can be undertaken more systematically. This involves fitting and testing a range of survival models and comparing these based upon internal validity (how well they fit to the observed trial data) and external validity (how plausible their extrapolated portions are)*

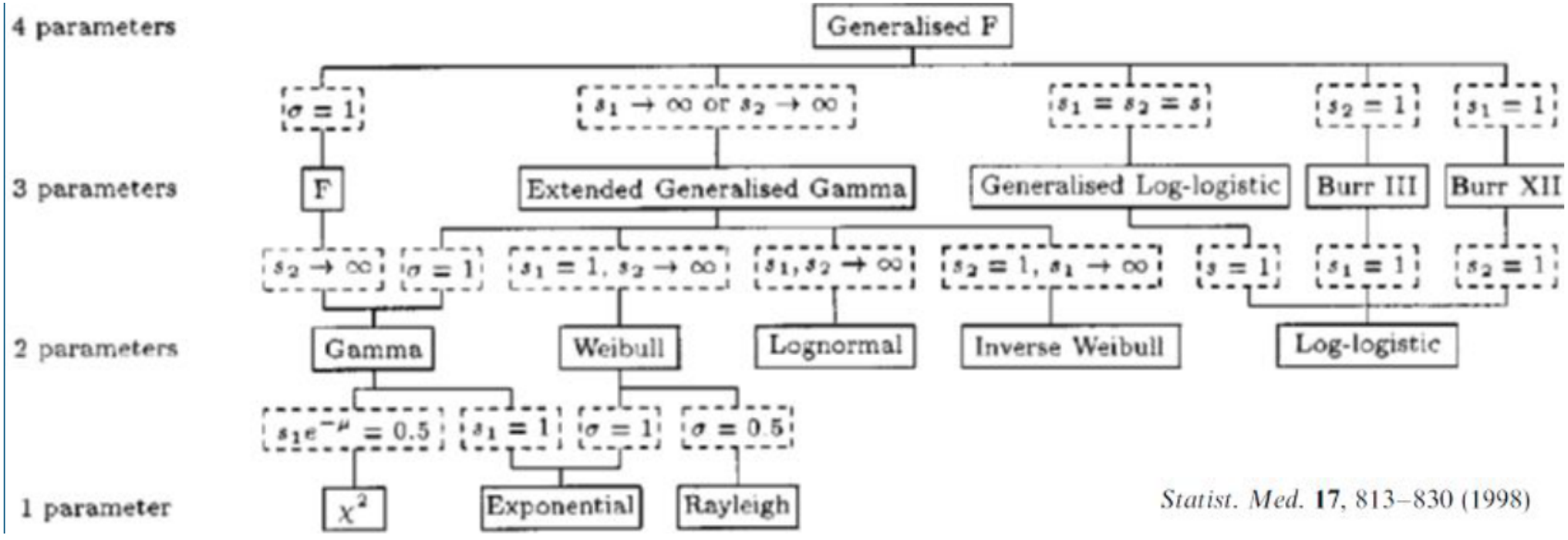
Choosing the "right" distribution

Latimer et al 2011 (DSU 14)



Flexible Survival models

- Multi - parameter distributions
  - Generalized Gamma
  - Generalized F
  - Data hungry - possibiliy of overfitting
  - Hypothesis testing possible



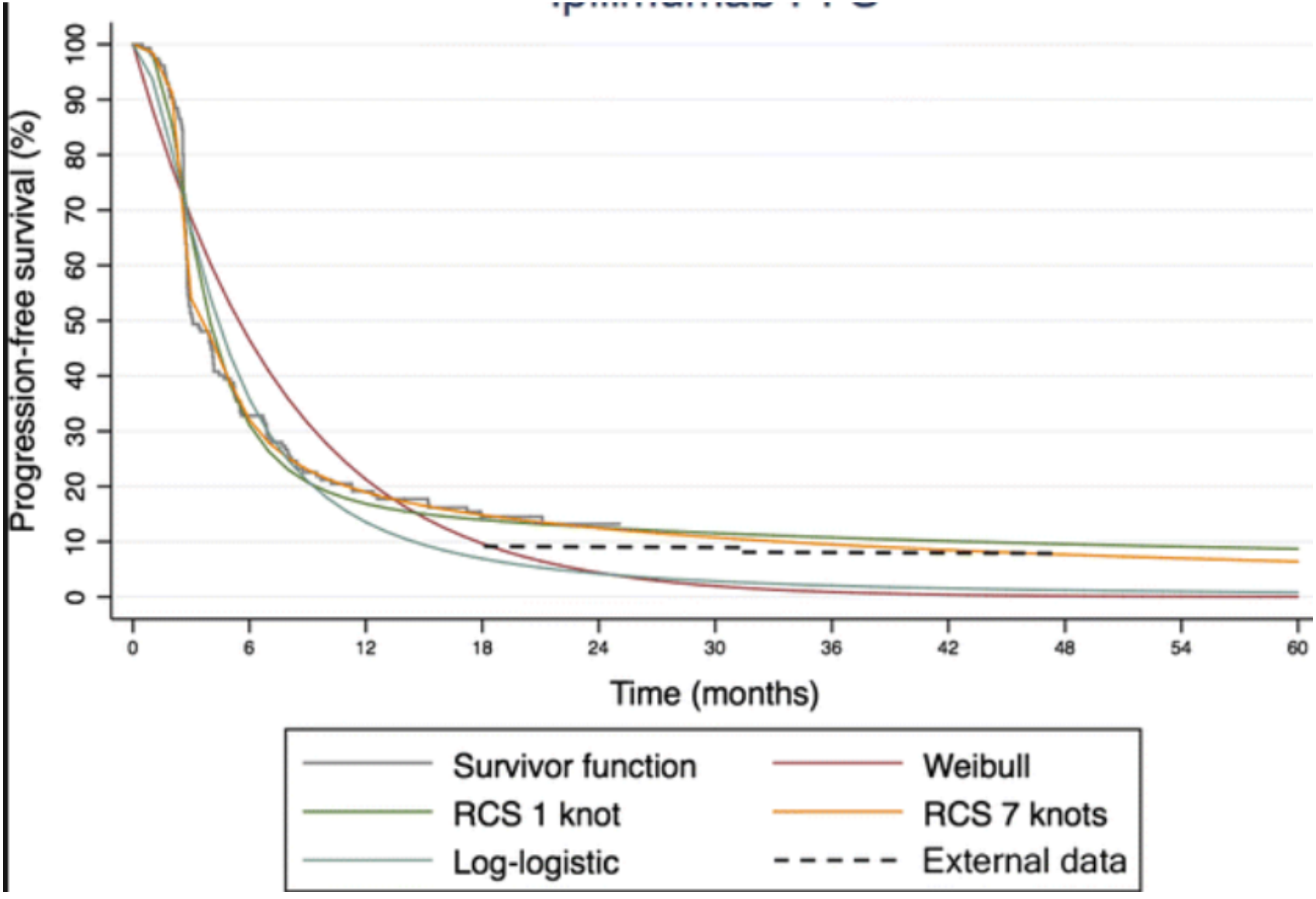
Statist. Med. **17**, 813–830 (1998)

Spline Survival models

- Survival models where the underlying hazard of an event is modelled as a smooth, piecewise polynomial function of time.
- Extrapolation of hazard possible
- Non-linear relation of time and hazard
- Conventionally *knots* are evenly spread on the (log)-time axis
- Overfitting with too many knots possible -sensitivity analysis
- AIC, BIC valid GoF tests

Spline Survival models

Gibson et al (Pharmacoeconomics, 2017)



Spline Survival models

From Gibson et al (Pharacoeconomcs, 2017)

Spline-based models using a limited number of knots can provide an acceptable fit to trial data and generate extrapolated estimates supported by longer term evidence, with results that are stable in response to changes in knot placement.

Approaches in extrapolation

Modeler faced with a more decisions: - Extrapolate using KM and "fitted" tails - Extrapolate using the fitted curve

- Fit seperate curves to the data
- Extrapolate treatment effect as relative
- What is the behaviour of the relative effect post trial?

Approaches in extrapolation

The Ends Justify the Mean: Outcome Measures for Estimating the Value of New Cancer Therapies

Andrew Davies, MSc[a], Andrew Briggs, DPhil[b], John Schneider, PhD[b], Adrian Levy, PhD[c], Omar Ebeid, MPH[b], Samuel Wagner, PhD[d], Srividya Kotapati, PharmD[d], Scott Ramsey, MD, PhD[e]

Approaches in extrapolation

- Extrapolate using KM and "fitted" tails

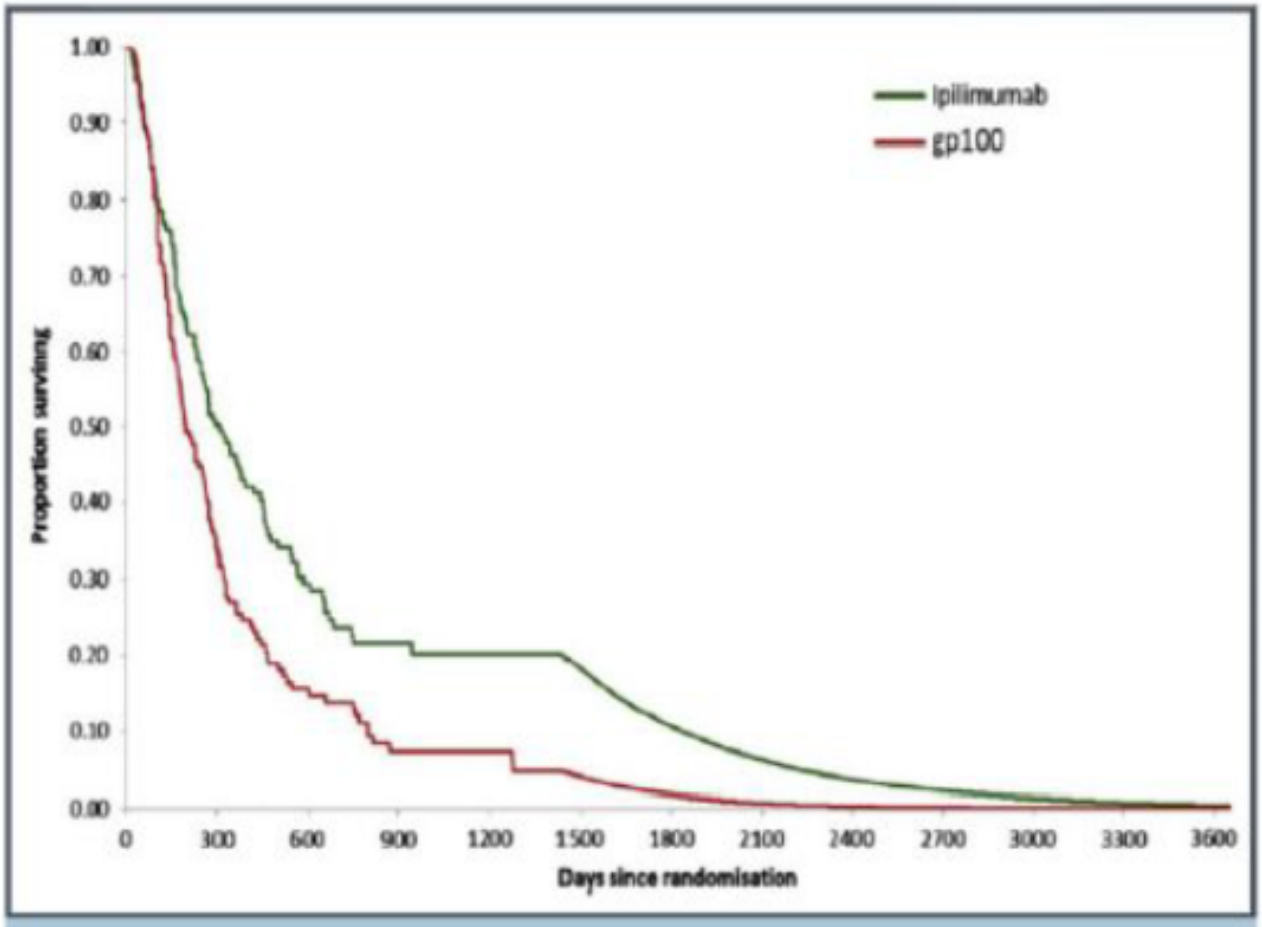


FIGURE 4: Case study showing empiric Kaplan-Meier curves and exponential extrapolation.

- Extrapolate using the fitted curve

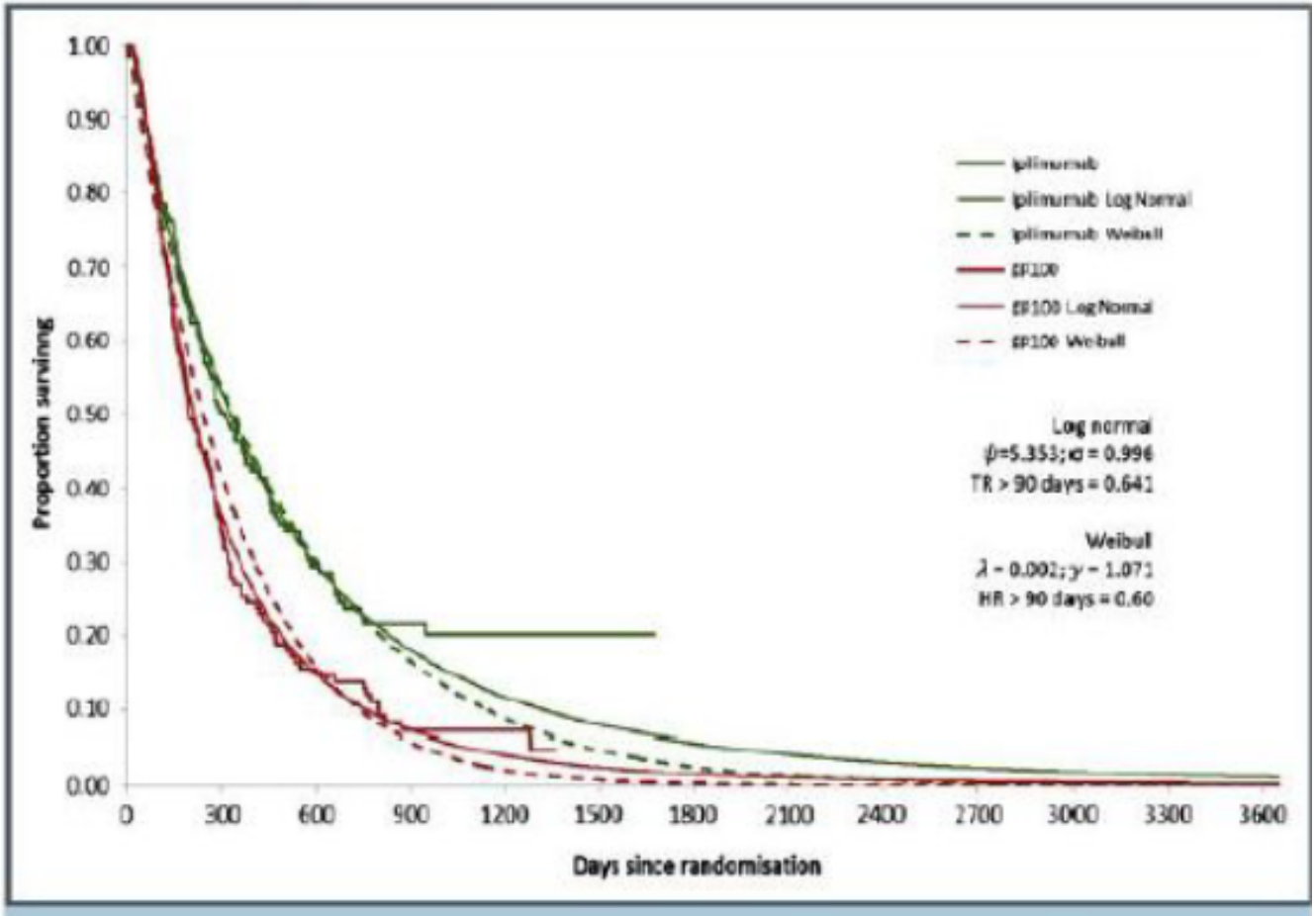
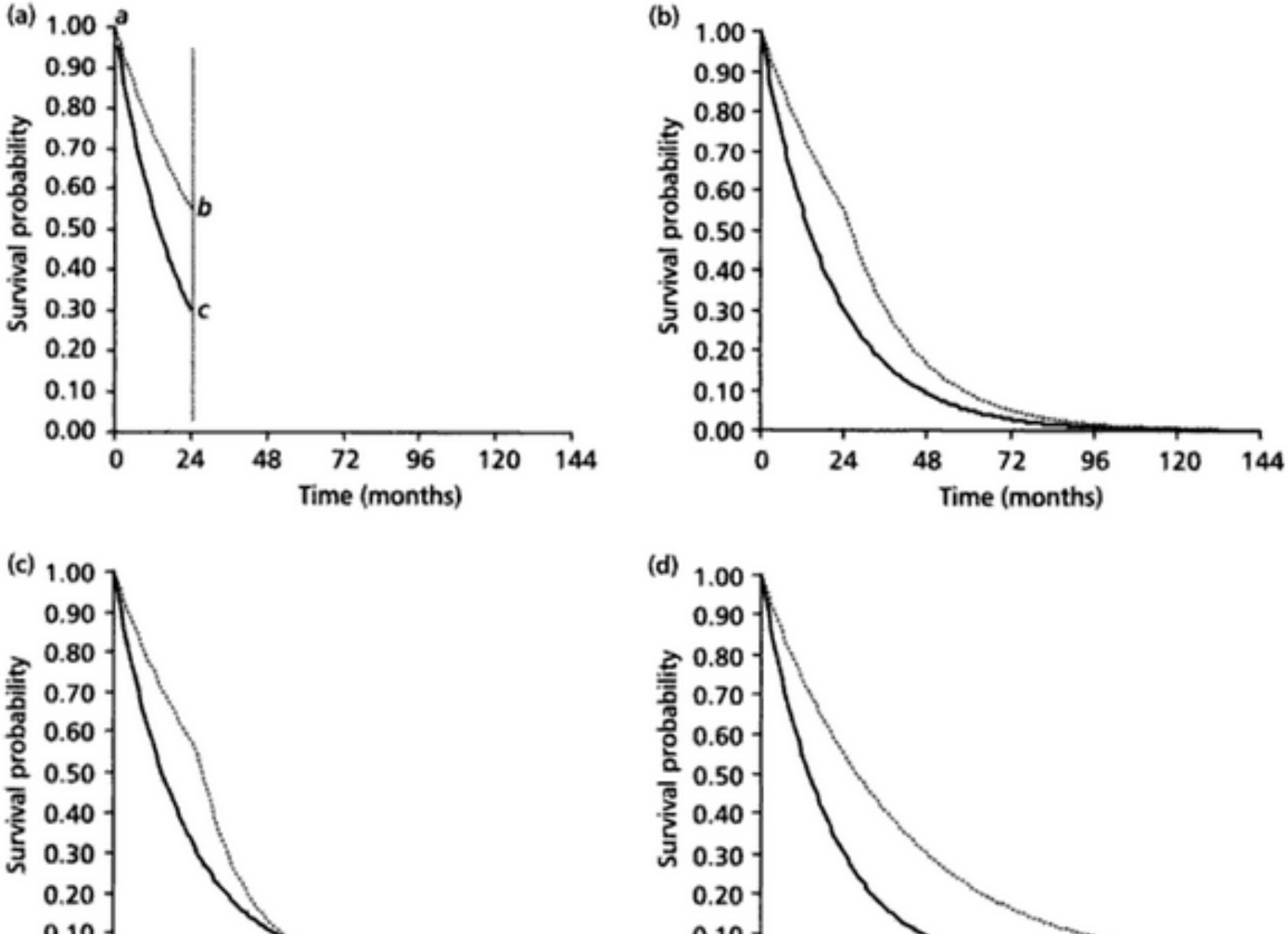


FIGURE 7: Case study showing empiric Kaplan-Meier curves and log-normal survivor functions.

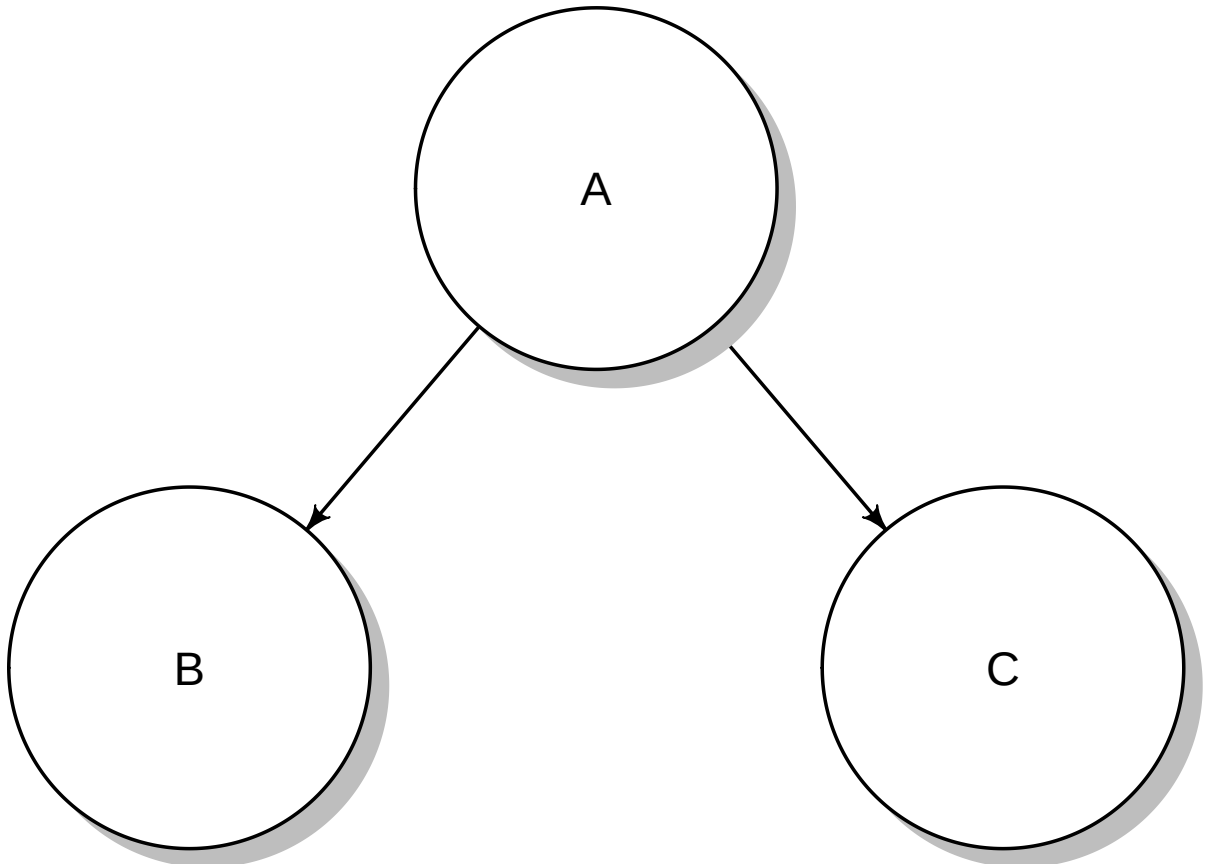
Extrapolating a relative treatment effect

Drummond, et al (2015). Methods for the economic evaluation of health care programmes. Oxford university press.



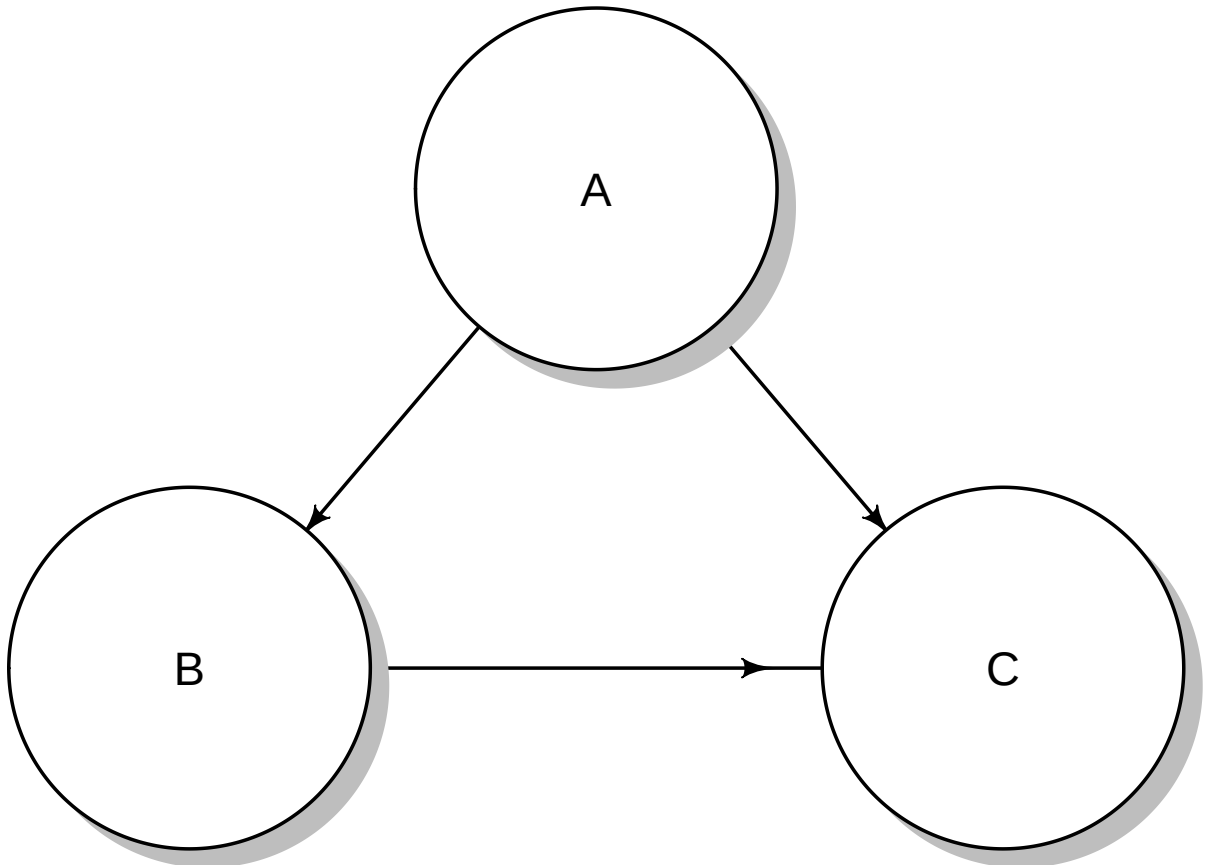
Competing Risks

- Underlying assumption in survival analysis:
  - If we could follow censored individuals long enough they would experience the event of interest.
- Event B (progression) affecs population size at risk for the competing event C


A
B
C

Multistate modeling

- Extended form of competing risks
- Multivariate survival analysis



Multistate modeling

- Extended form of competing risks
- Multivariate survival analysis
- Can incorporate:
  - Transition specific covariates
  - Recurrent events
- Can work with
  - Patient-level data (best)
  - Digitized / interval censored data (. . . not best)

Multistate modeling

Fitted in two ways:

1. separate models for each trasition

- recurrent events
- covariates
- seperate dataset for each (non-saturating) state
- "naive" assumption of censoring when competing event occurs
- easy to fit in R `flexsurv` and `mstate`

Multistate modeling

Fitted in two ways:

2. Joint multivariate model for all transitions - Powerfull!
   - Mislclassification errors
   - Latent states
   - Interval censoring
   - Continuous time

Drawbacks: - Difficult to converge - Limited options wrt assumed distributions (exponential)

Can be fitted through `msm` and `flexsurv`

Multistate modeling

Journal of Statistical Software

May 2016, Volume 70, Issue 8. *doi: 10.18637/jss.v070.i08*

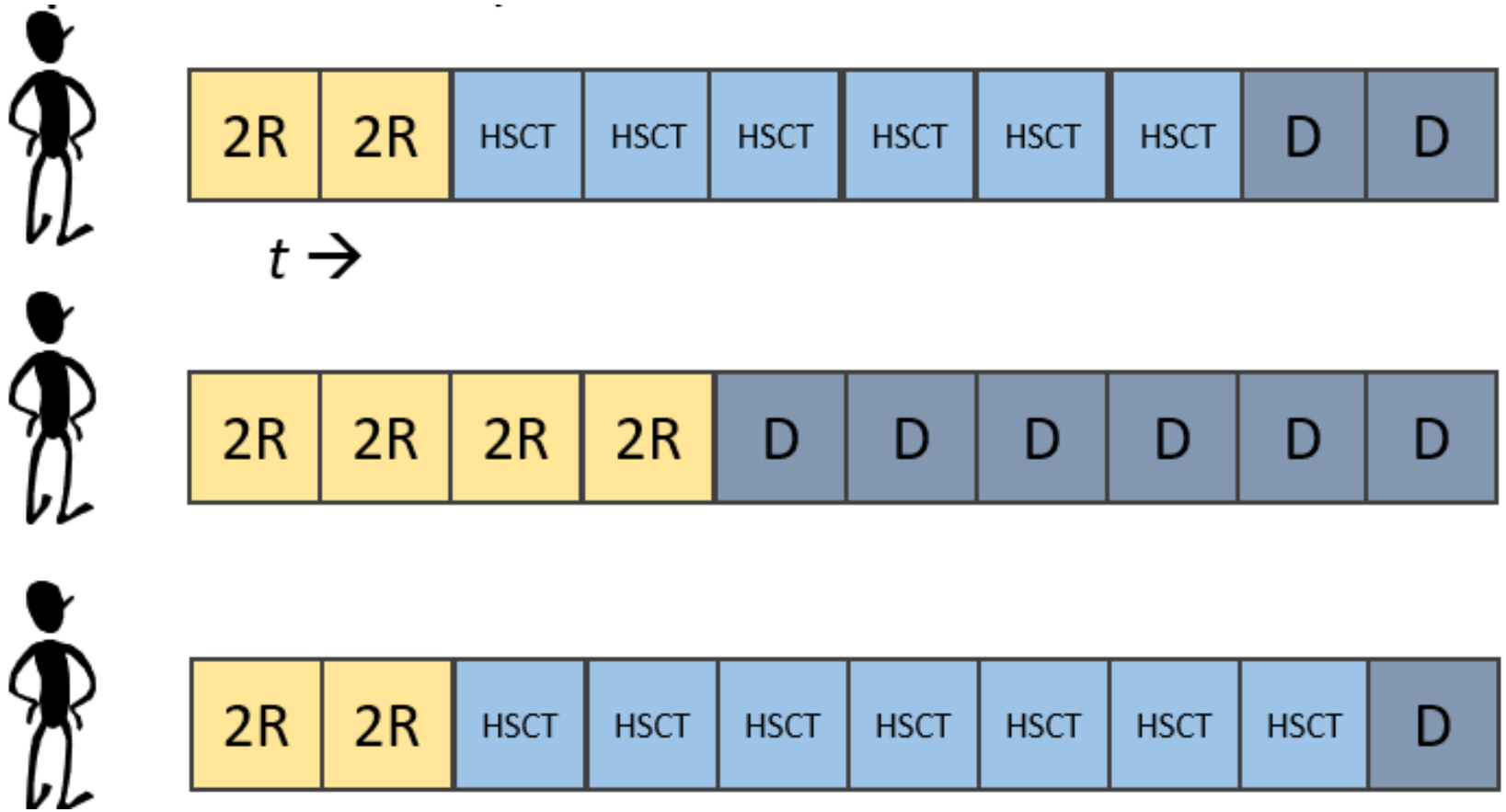
flexsurv: A Platform for Parametric Survival Modeling in R

Christopher H. Jackson
MRC Biostatistics Unit

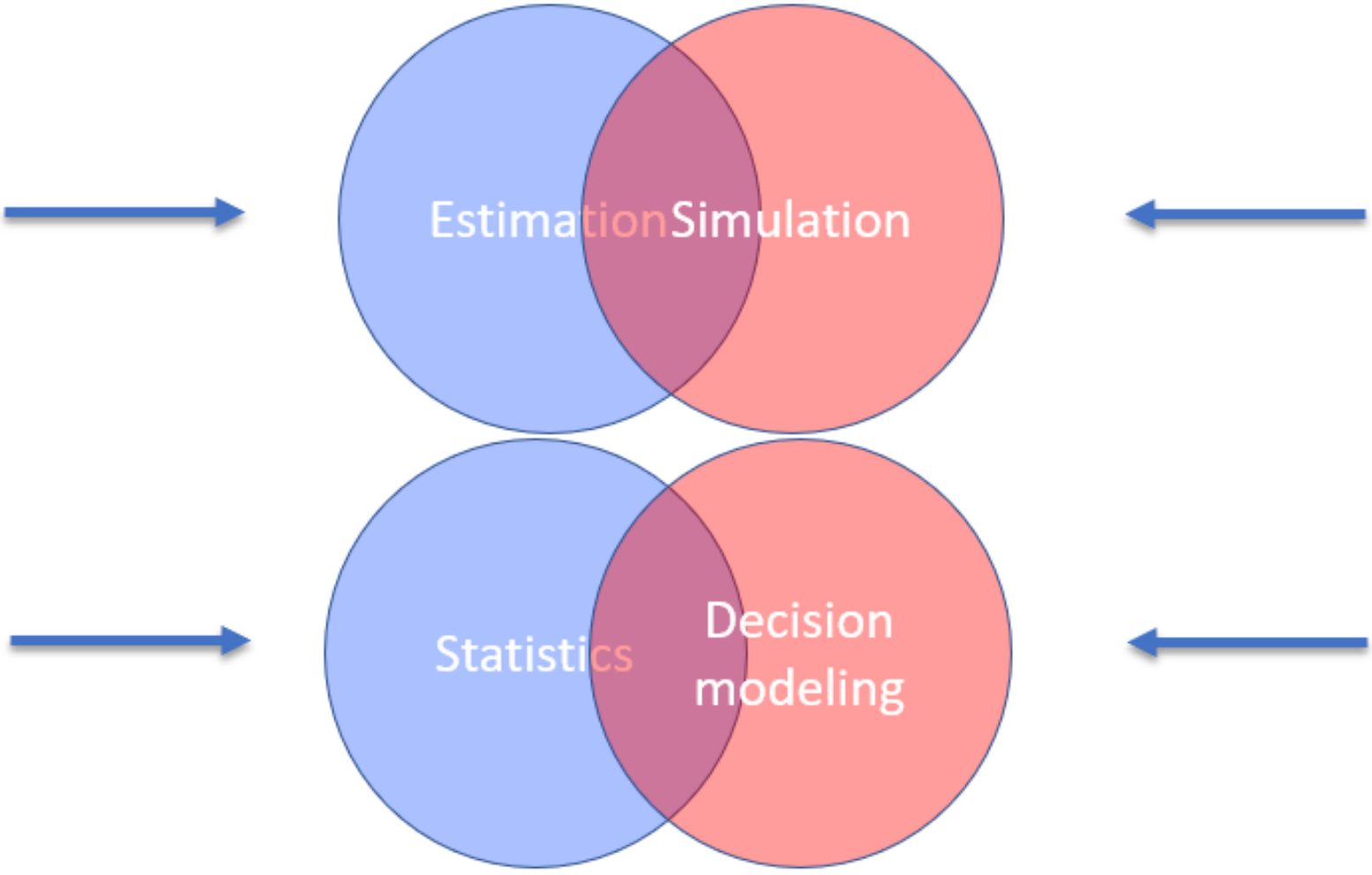
Great resource for both survival fitting and multistate models

Multistate & microsimulation

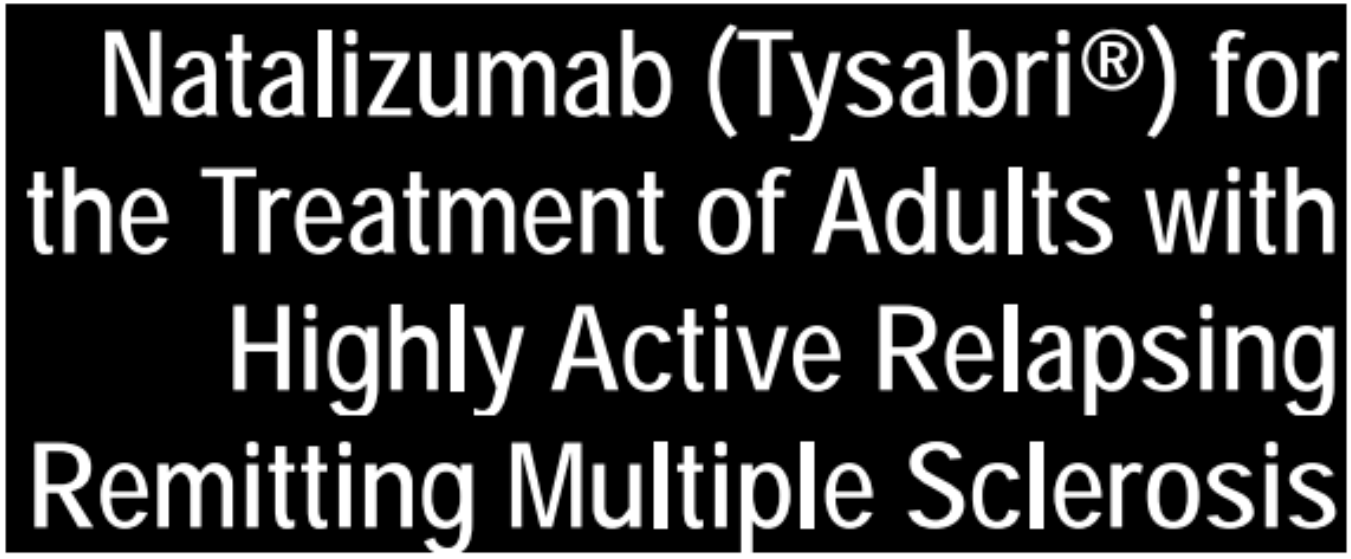
- Multistate models allow for time-dependent transition probabilities
- When dependence on time-in-state partioned survival / markov models are inadequate
- Necessary solution: Individual level simulation modeling



Multistate modeling



Multistate modeling



Biogen Idec Single Technology Appraisal (STA) Submission to The National Institute for Health and Clinical Excellence

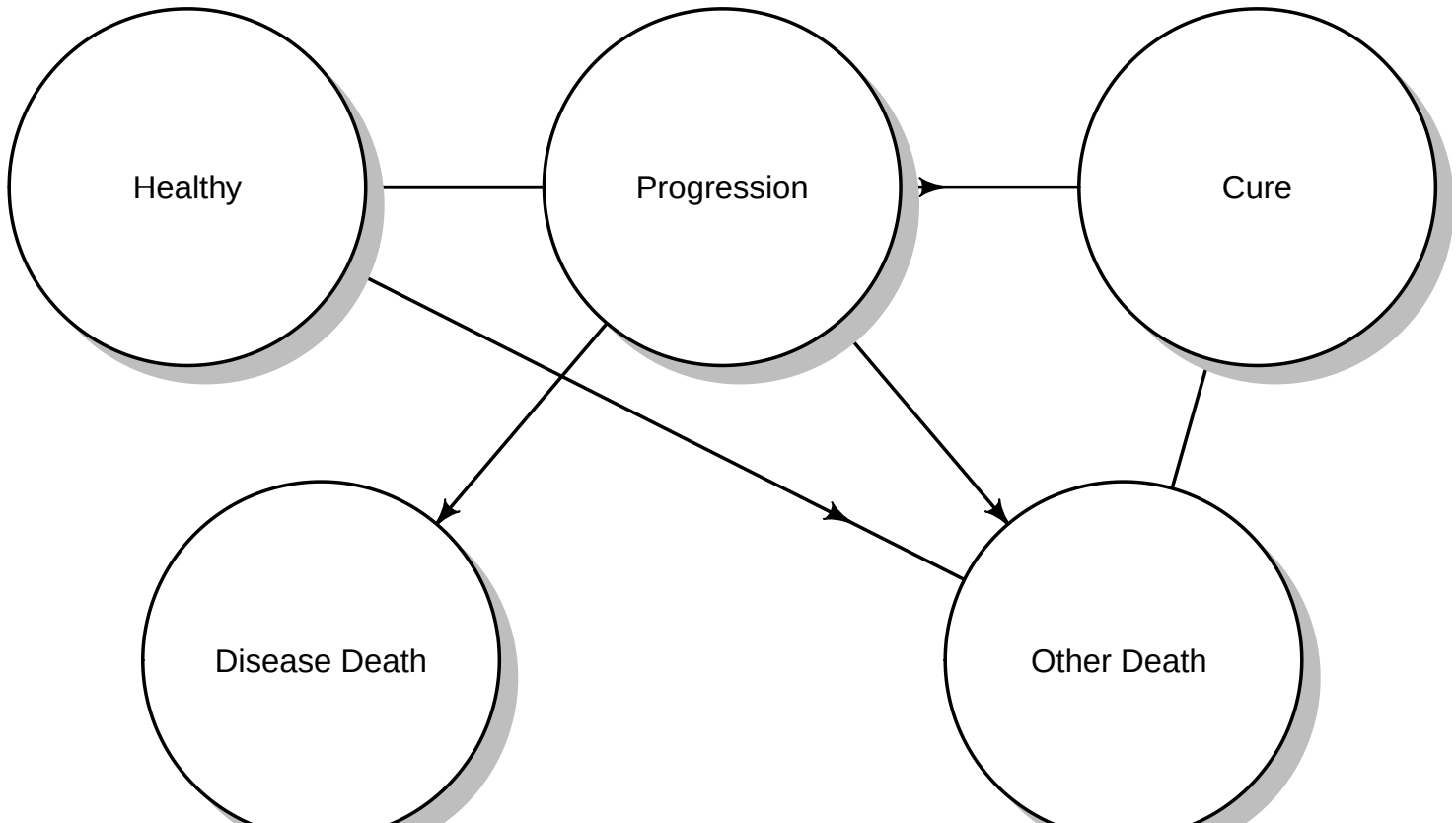
Document name:	Natalizumab in HARRMS_FINAL.doc
Product:	Tysabri® (natalizumab)
Manufacturer:	Biogen Idec
Document written by:	Biogen Idec, Heron Evidence Development
Document customer:	The National Institute for Health and Clinical Excellence (NICE)
Document purpose:	To present the clinical and cost-effectiveness of natalizumab in highly active relapsing remitting multiple sclerosis to NICE
Confidential Information:	Note that all confidential information within the submission has been

Mixture Cure Models - Main Points

- Therapies with the possibility of cure pose a modeling challenge
- e.g. plateau on immotherapy survival curves
- Extrapolation challenging without external information
- Traditional methods: Underestimation more likely than over estimation of the effect

Mixture Cure Models - Main Points

- extension of survival models where a proportion of the population is assumed to be “cured”
  - non-cured fraction at risk of progression and death informed by the trial
  - cured fraction at risk of death informed by external data.



Mixture Cure Models - Estimation

- Cure rate models a promising solution but the cure faction difficult to estimate
- Can be fitted in both R and SAS
- Guidance is lacking but given the popularity soon to come!