

Fitting and extrapolating survival curves for cost-effectiveness models in R

Ash Bullement, abullement@deltahat.co.uk

Delta Hat, Nottingham, UK

Contents

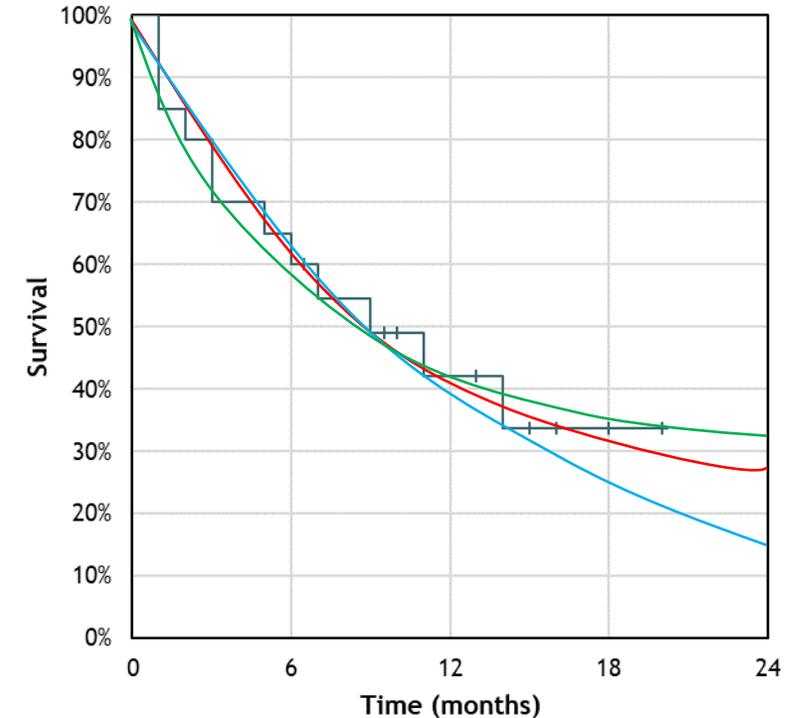


- Introduction to survival analysis
- Commonly-used extrapolation methods
- Extrapolation method selection
- Relevant packages in *R*
- Example
- References

Introduction to survival analysis



- Survival analysis is concerned with the interpretation of time-to-event data
 - Used to describe a range of possible events, the most well-known within the field of health economics being death (i.e. overall survival)
- Time-to-event data may not be complete for all patients, and so some observations may be censored
 - To illustrate this, time-to-event data are commonly presented as a Kaplan-Meier curve (right)
 - Censored patients are marked by dashes
- We often wish to understand the pattern of survival over time, including the period after which data are unavailable
 - Different models may predict very different longer-term survival, and so a robust approach to selecting appropriate models is highly important



Commonly used extrapolation methods



- Approaches used in practice include:
 - **Parametric survival models** (exponential, gamma, generalised gamma, Gompertz, log-logistic, lognormal, Weibull)
 - **Piecewise models** (two or more components “stitched” together at a specific point in time)
 - **Royston and Parmar spline-based models** (smoothed, piecewise polynomials that are extensions to parametric models)
 - **Mixture models** (blend of two or more models used to inform a weighted-average estimate of survival over time, which may account for a group of “cured” patients)
 - **Landmark models** (use of a time point and corresponding outcome measure to inform the estimation of a piecewise/ mixture model for specific groups, also known as a response-based model)

Discussed at length in NICE TSD 14, easy to implement, may not be considered flexible enough for some situations

Proposed as a pragmatic approach where there is a notable, abrupt change in the hazard of death and/or to easily utilise data from multiple sources

Avoids issues with “implausible” changes in hazards seen with piecewise models, yet requires the estimation of a relatively large number of parameters

Able to directly address concerns with heterogeneity, yet the specification of mixture models may be challenging with respect to clinical plausibility

Leverages additional within-trial evidence with the intention of improving accuracy of survival extrapolation, but may be considered biased

Extrapolation method selection



- Selecting the most appropriate survival model should be based on a comprehensive assessment of available information, including:
 - **Statistical goodness-of-fit** (e.g. Akaike's information criterion [AIC], Bayesian information criterion [BIC], amongst others)
 - **Visual goodness-of-fit** (which may be aided by further inspection of the underlying hazard function)
 - **Clinical plausibility** (e.g. comparison to historical estimates)
- Some recent studies have attempted to retrospectively assess best-fitting models, using a combination of point estimate survival accuracy and restricted mean survival times (RMST) estimates (see Bullement et al., [2019] and Ouwens et al., [2019])

A note on AIC and BIC

Prevailing opinion is that both AIC and BIC should be considered when comparing statistical goodness-of-fit, and it is generally understood that BIC applies a larger penalty for model complexity versus AIC (provided $\ln(\text{sample size}) > 2$). AIC and BIC also only provide information regarding the goodness of fit within the observed period of data collection.

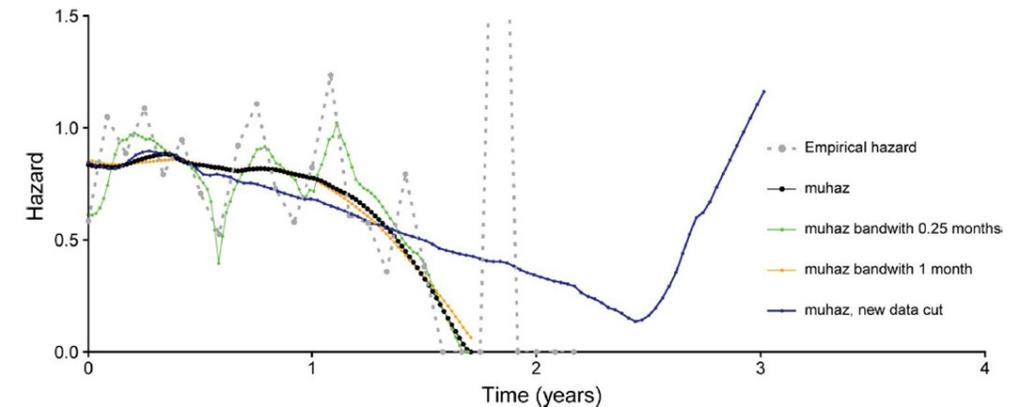
However, it is noted in literature (see Burnham [2002]) that the AIC and BIC aim to address two associated yet distinct aims. The AIC aims to minimise the Kullback-Leibler divergence (difference between the fitted model and the 'true' model); whereas the BIC aims to select the true model from a set of candidate models. Interpretation of AIC and BIC scores should therefore be approached with caution, as the BIC may not be appropriate if none of the candidate models are considered to be close to the 'true' model.

Relevant packages in R



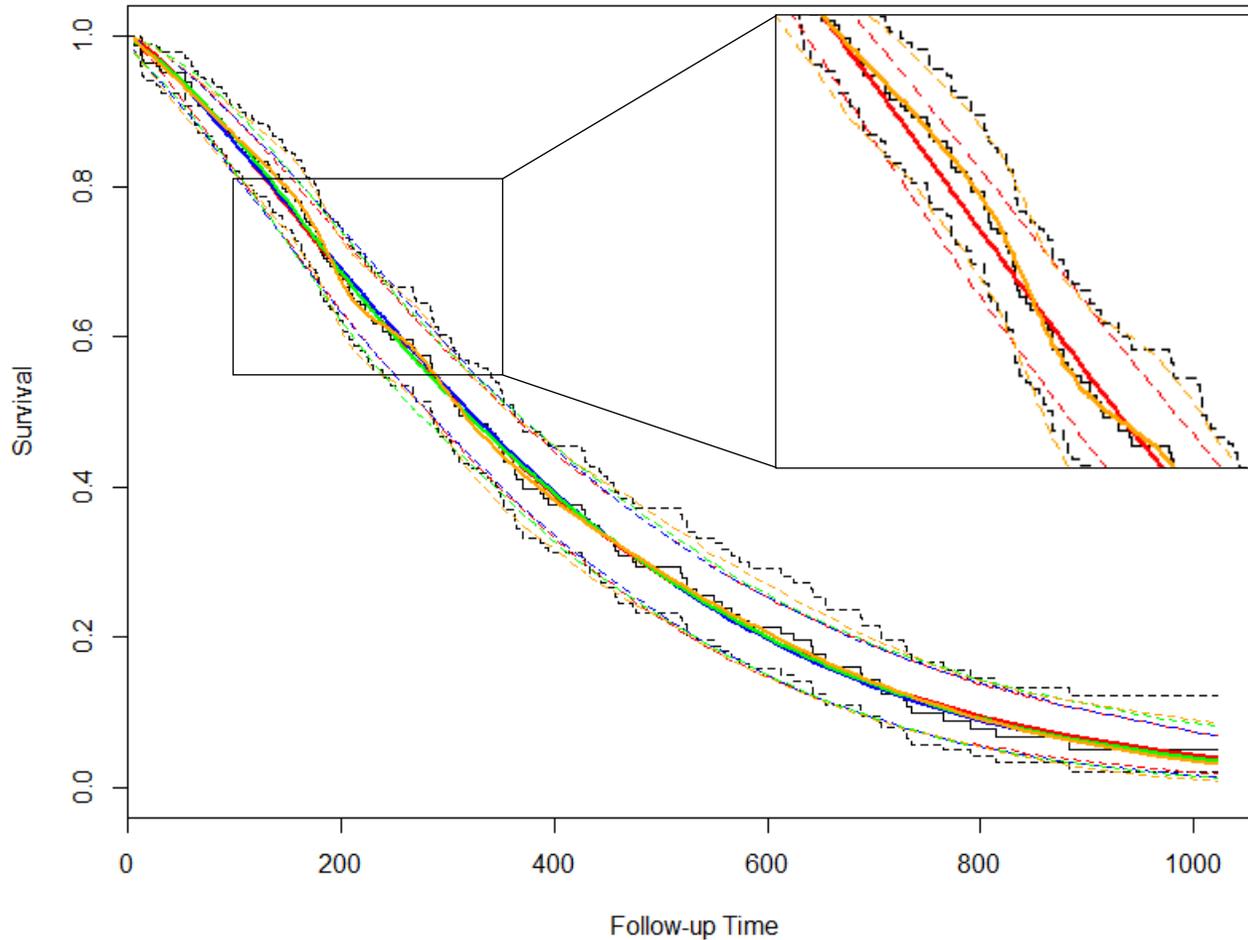
Some potentially useful R packages:

- **flexsurv** - allows for specification of common parametric approaches, including spline-based models using the function *flexsurvspline*
- **flexsurvcure** - allows fitting of parametric cure models (noting that specification of background mortality is an ongoing area of research)
- **survHE** - allows for ease of running simple parametric models using a frequentist (i.e. per *flexsurv*) or Bayesian approach
- **rjags** - may be used as an interface for JAGS when fitting Bayesian models, such as a mixture-Weibull model
- **muhaz** - can be used to produce smoothed-hazard plots to aid model selection



Estimated hazard plot extracted from Ouwens *et al.* (2019)

Example - survival



Black - Kaplan-Meier curve

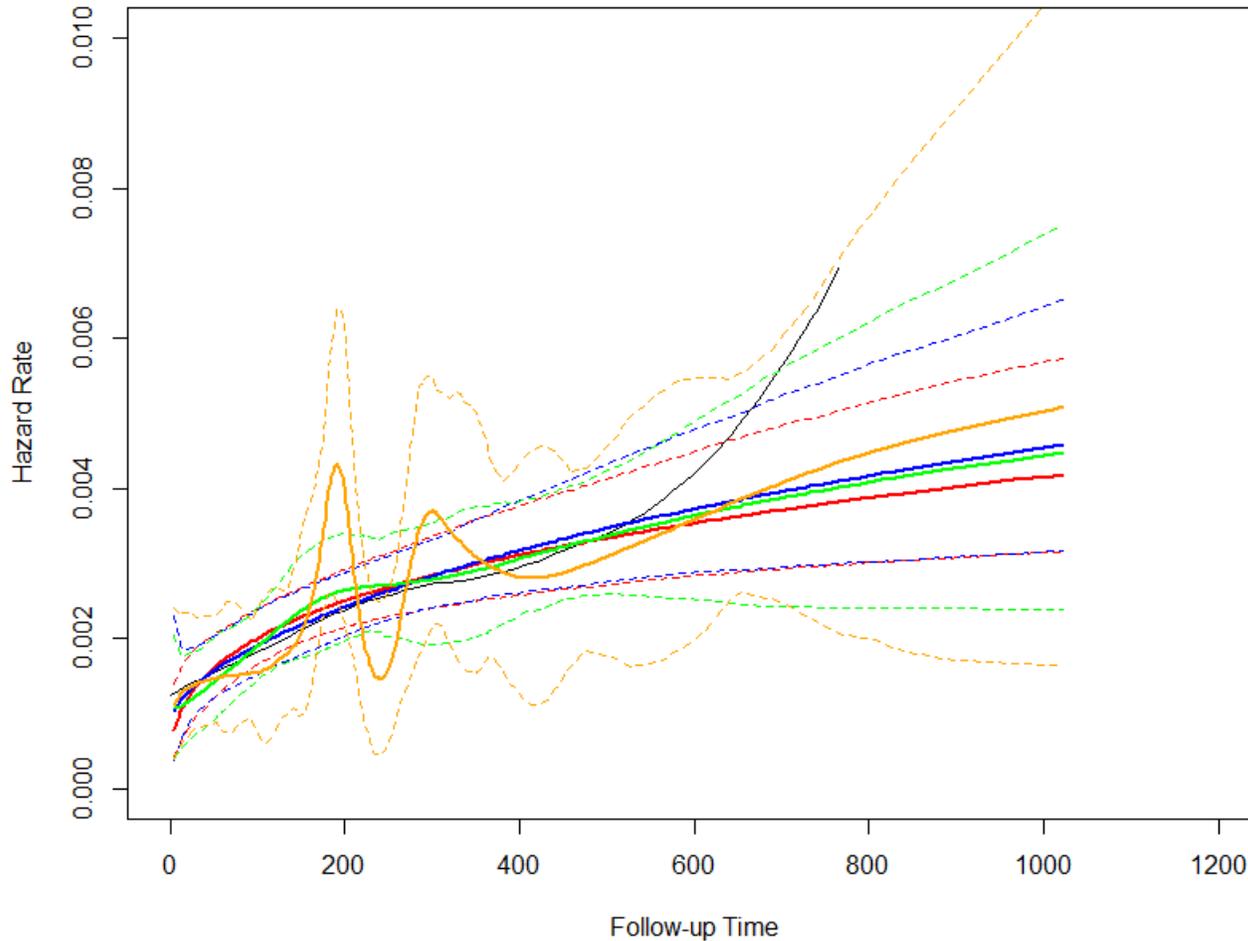
Red - Weibull model

Blue - one-knot hazard-based spline model

Green - three-knot hazard-based spline model

Orange - ten-knot hazard-based spline model

Example - hazard (*muhaz* default)



Black - Kaplan-Meier curve

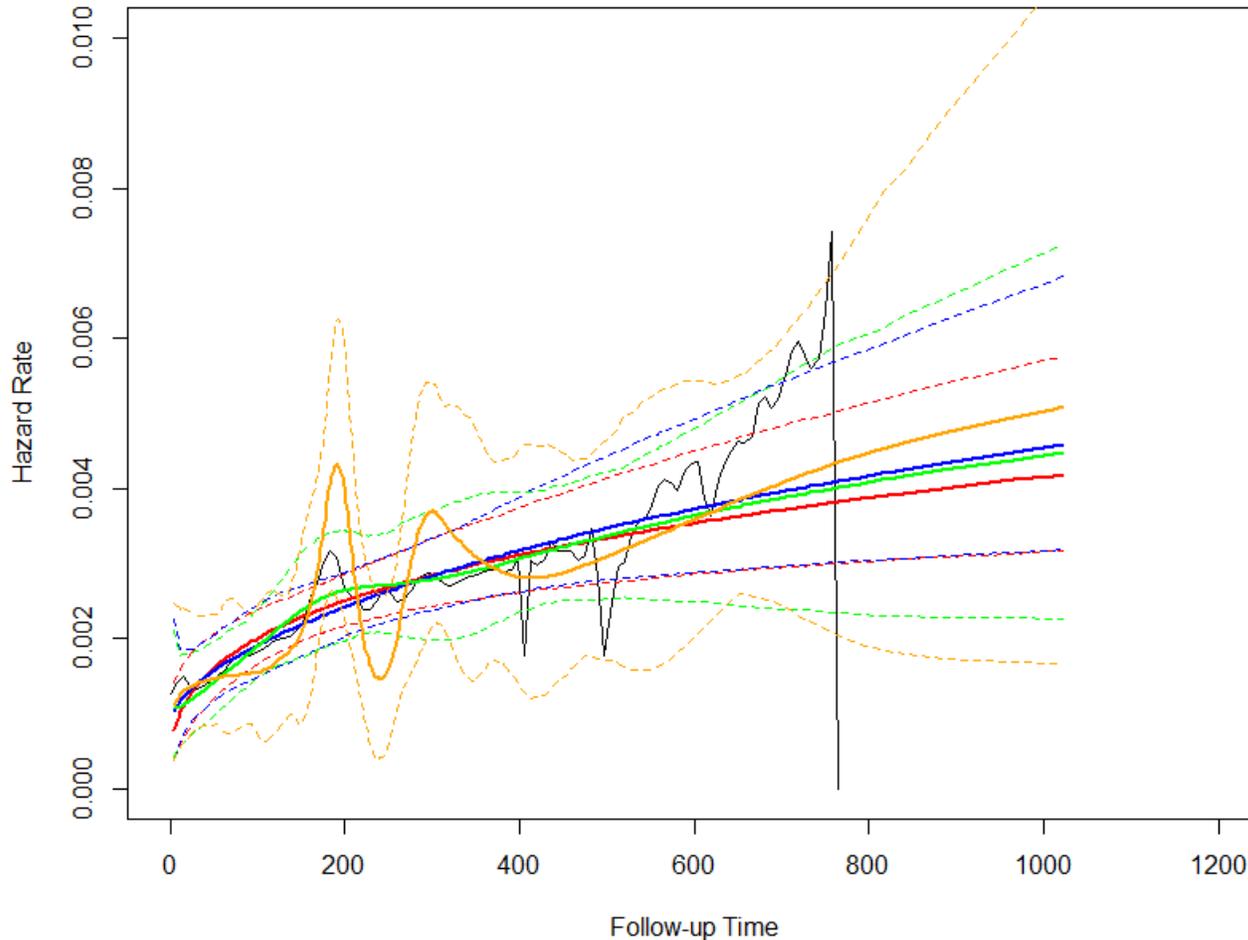
Red - Weibull model

Blue - one-knot hazard-based spline model

Green - three-knot hazard-based spline model

Orange - ten-knot hazard-based spline model

Example - hazard (*muhaz* shorter bandwidth)



Black - Kaplan-Meier curve

Red - Weibull model

Blue - one-knot hazard-based spline model

Green - three-knot hazard-based spline model

Orange - ten-knot hazard-based spline model

Note on estimated hazard plots

The confidence interval around the predicted hazard function is estimated using bootstrapping methods, hence minor fluctuations are to be expected

Example - code



- Hazard plot R code:

```
library(flexsurv)
library(muhaz)
data(lung)
test <- survfit(Surv(time,status)~1,data=lung)
plot(test)

test_muhaz_default <- muhaz(times = lung$time, delta = lung$status-1)
test_muhaz_shorter <- muhaz(times = lung$time, delta = lung$status-1, bw.smooth=17.2046)
weib <- flexsurvreg(Surv(time,status-1)~1,data=lung,dist="weibull")
one_k_hazard_spline <- flexsurvspline(formula=Surv(time,status-1)~1,data=lung,k = 1, scale = "hazard")
three_k_hazard_spline <- flexsurvspline(formula=Surv(time,status-1)~1,data=lung,k = 3, scale = "hazard")
ten_k_hazard_spline <- flexsurvspline(formula=Surv(time,status-1)~1,data=lung,k = 10, scale = "hazard")

plot(test,ylab="Survival",xlab="Follow-up Time")
lines(weib, col="red")
lines(one_k_hazard_spline, col="blue")
lines(three_k_hazard_spline, col="green")
lines(ten_k_hazard_spline, col="orange")

plot(test_muhaz_default,ylim=c(0,0.01),xlim=c(0,1200))
lines(weib, type="hazard",col="red")
lines(one_k_hazard_spline, type="hazard", col="blue")
lines(three_k_hazard_spline, type="hazard", col="green")
lines(ten_k_hazard_spline, type="hazard", col="orange")

plot(test_muhaz_shorter,ylim=c(0,0.01),xlim=c(0,1200))
lines(weib, type="hazard",col="red")
lines(one_k_hazard_spline, type="hazard", col="blue")
lines(three_k_hazard_spline, type="hazard", col="green")
lines(ten_k_hazard_spline, type="hazard", col="orange")

plot(test_muhaz_shorter,ylim=c(0,0.01),xlim=c(0,1200))
lines(weib, type="hazard",col="red",ci=FALSE,lty=1)
lines(one_k_hazard_spline, type="hazard", col="blue",ci=FALSE,lty=1)
lines(three_k_hazard_spline, type="hazard", col="green",ci=FALSE,lty=1)
lines(ten_k_hazard_spline, type="hazard", col="orange",ci=FALSE,lty=1)
```

References



- Published studies:
 - Bullement A, Latimer NR, Bell Gorrod H. Survival Extrapolation in Cancer Immunotherapy: A Validation-Based Case Study. Value Health. 2019 Mar;22(3):276-283.
 - Burnham KP, Anderson DR. Model Selection and Multimodel Inference : a practical information-theoretic approach. Second Ed. United States of America: Springer-Verlag New York, Inc.; 2002.
 - Gibson E, Koblbauer I, Begum N, et al. Modelling the Survival Outcomes of Immuno-Oncology Drugs in Economic Evaluations: A Systematic Approach to Data Analysis and Extrapolation. Pharmacoeconomics. 2017 Dec;35(12):1257-1270
 - Latimer NR. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. June 2011. Last updated March 2013. Available at: <http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf>
 - Ouwens MJNM, Mukhopadhyay P, Zhang Y, et al. Estimating Lifetime Benefits Associated with Immuno-Oncology Therapies: Challenges and Approaches for Overall Survival Extrapolations. Pharmacoeconomics. 2019 May 18.
- R packages:
 - survHE: <https://cran.r-project.org/web/packages/survHE/survHE.pdf>
 - flexsurv: <https://cran.r-project.org/web/packages/flexsurv/flexsurv.pdf>
 - flexsurvcure: <https://cran.r-project.org/web/packages/flexsurvcure/flexsurvcure.pdf>
 - muhaz: <https://cran.r-project.org/web/packages/muhaz/muhaz.pdf>
 - rjags: <https://cran.r-project.org/web/packages/rjags/rjags.pdf>