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blendR: An R package for blending survival curves

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Summary

The goal of `blendR` is to provide functionality to *blend* two survival curves together from one to the other according to some defined blending function.

Survival extrapolation is essential in cost-effectiveness analysis to quantify the lifetime survival benefit associated with a new intervention, due to the restricted duration of randomized controlled trials (RCTs). Current approaches of extrapolation often assume that the treatment effect observed in the trial can continue indefinitely, which is unrealistic and may have a significant impact on decisions for resource allocation.

Blended survival curves are a possible solution to alleviate the problem of survival extrapolation with heavily censored data from clinical trials. The main idea is to mix a flexible model (e.g., Cox semiparametric model) to fit as well as possible the observed data and a parametric model encoding assumptions on the expected behaviour of underlying long-term survival. The two are "blended" into a single survival curve that is identical with the first model over the range of observed times and gradually approaching the parametric model over the extrapolation period based on a weight function. The weight function regulates the way two survival curves are blended, determining how the internal and external sources contribute to the estimated survival over time. Long-term extrapolation from immature trial data may lead to significantly different estimates with various modelling assumptions. The blending approach provides sufficient flexibility, allowing a wide range of plausible scenarios to be considered as well as the inclusion of external information, based, for example, on hard data or expert opinion.

Statement of need

Interim analyses of trials with limited follow-up are often subject to high degrees of administrative censoring, which may result in implausible long-term extrapolations using standard approaches (Latimer et al., 2013). Implementing an innovative methodology based on "blending" survival curves to relax the traditional proportional hazard assumption and simultaneously incorporate external information can guide the extrapolation (Che et al., 2022). The `blendR` package provides a simple and powerful means to allow a careful consideration of a wide range of plausible scenarios, accounting for model fit to the short-term data as well as the plausibility of long-term extrapolations. `blendR` was designed to be used by statisticians, health economists, healthcare professionals and other users of survival data.

Method

The *blending* idea is to consider two separate processes to describe the long-term horizon survival. The first one is driven exclusively by the observed data. Similar to a *standard* health technology assessments (HTA), this is used to determine an estimate over the entire time horizon of a survival curve, termed $S_{obs}(t \mid \boldsymbol{\theta}_{obs})$, a function of the relevant parameters $\boldsymbol{\theta}_{obs}$.

A simple parametric model could be chosen, or alternatively, some other more complex model, with the main objective to produce the *best* fit possible to the observed information. Unlike in a standard modelling exercise where the issue of overfitting is potentially critical, achieving a very close approximation to the observed dynamics has much less important implications in the case of blending, as explained further below. Common packages available in R for this step include `survHE` (Baio, 2020) and `flexsurv` (Jackson, 2016).

For the second component of the blending process, consider a separate *external* survival curve, $S_{ext}(t \mid \boldsymbol{\theta}_{ext})$. This is a parametric model that is not informed by the observed data - for instance, "hard" " information could be used, e.g. derived from a different data source (such as registries or observational studies), or construct a model that is purely based on subjective knowledge elicited from experts, or possibly a combination of the two. Either way, $S_{ext}(t \mid \boldsymbol{\theta}_{ext})$ will typically be less concerned with the observed portion of the time horizon, but is instrumental to produce a reasonable and realistic *long-term* estimate for the survival probabilities.

The *blended* survival curve is defined as

$$S_{ble}(t \mid \boldsymbol{\theta}) = S_{obs}(t \mid \boldsymbol{\theta}_{obs})^{1-\pi(t;\alpha,\beta,a,b)} \times S_{ext}(t \mid \boldsymbol{\theta}_{ext})^{\pi(t;\alpha,\beta,a,b)} \tag{1}$$

where $\boldsymbol{\theta} = \{\boldsymbol{\theta}_{obs}, \boldsymbol{\theta}_{ext}, \alpha, \beta, a, b\}$ is the vector of model parameters. Here, $\pi(\cdot)$ is a weight function that controls the extent to which the two survival curves $S_{obs}(\cdot)$ and $S_{ext}(\cdot)$ are blended together. Technically, define $\pi(\cdot)$ as the cumulative distribution function of a Beta random variable with parameters $\alpha, \beta > 0$, evaluated at the point $(t-a)/(b-a)$.

$$\pi(t;\alpha,\beta,a,b) = \Pr\left(T \leq \frac{t-a}{b-a} \mid \alpha,\beta\right) = F_{\text{Beta}}\left(\frac{t-a}{b-a} \mid \alpha,\beta\right),$$

for $t \in [0, T^*]$, where T^* is the upper end of the interval of times over which to perform our evaluation. This means that the weighting function $\pi(\cdot)$ varies over the time horizon, which in turn allows us to give different weight to the two components at different times t. The range $[a, b] \in (0, T^*)$ is the *blending interval*, i.e. a subset of the life-time horizon in which $S_{obs}(\cdot)$ and $S_{ext}(\cdot)$ are blended into a single survival curve.

Figure Figure 1 depicts this process graphically. In this case, it is assumed that the trial data span over the interval $[0, a]$, which is labelled in the graph as the "Follow-up". The dashed curve is the Kaplan-Meier (KM) estimate of the observed data (for simplicity, but without loss of generality, consider here a single arm). The curve labelled as S_{obs} results from a suitable model fitted to the observed data, in order to capture the known features of the data generating process almost to perfection - as is possible to appreciate in the graph, the KM curve is basically identical with the model obtained with S_{obs}.

The blue curve, indicated as S_{ext} should be used to give information about the expected long-term behaviour of the survival process. While it may be difficult to directly access hard data to inform this it is often possible and generally desirable to so. For example, experts may have individual level data from a registry based on use of a drug with a similar mechanism to the one they are assessing in the trial; or perhaps they have elicited clinical knowledge or expert opinion to identify that survival at a certain time point is not expected to exceed a certain threshold. Notice in particular that S_{ext} can deviate substantially from the observed data, as shown in Figure Figure 1.

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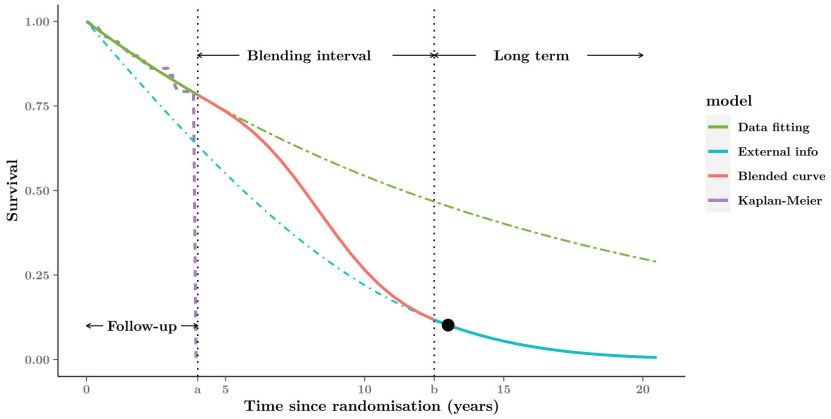


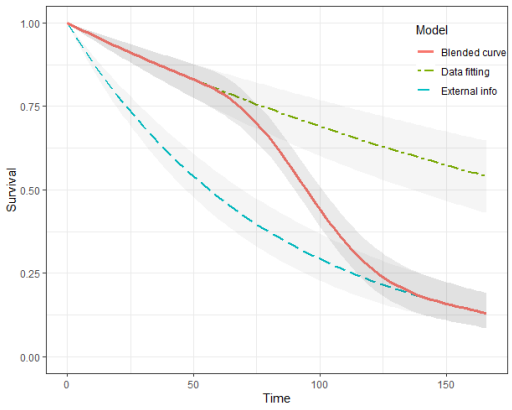
Figure 1: Graphical representation of the blended curve method. The whole time-horizon is partitioned into three parts: Follow-up, Blending interval and Long term. The blended survival is equivalent to the model fitted to the short-term data (purple Kaplan-Meier curve) within Follow-up period (green curve); then gradually approaching the external estimate in the Blending interval (red curve); eventually consistent with the expected behaviour (blue curve) in the Long term. The black point in the Long term is an example of external information about 10% expected survival at the 13 years from experts.

Example

We present a basic example which demonstrates how to solve a common problem. Using the *TA174_FCR* data set contained in the `blendR` package, we fit exponential distribution survival models with no covariates using the `fit.models()` function from the `survHE` package (Baio, 2020). This employs the Hamiltonian Monte Carlo (HMC) sampler from Stan behind the scenes (Carpenter et al., 2017). The *external* or *long-term* data are obtained from an heuristic approach to simulating data consistent with user-defined constraints. The results are then blended into a single survival curve using the `blendsurv()` function.

```
library(blendR)
library(survHE)

## trial data
data("TA174_FCR", package = "blendR")

## externally estimated data
data_sim <- ext_surv_sim(t_info = 144,
                         S_info = 0.05,
                         T_max = 180)

# observed survival model
obs_Surv <- survHE::fit.models(formula = Surv(death_t, death) ~ 1,
                               data = dat_FCR,
                               distr = "exponential",
                               method = "hmc")

# external survival model
ext_Surv <- survHE::fit.models(formula = Surv(time, event) ~ 1,
                               data = data_sim,
                               distr = "exponential",
                               method = "hmc")

blend_interv <- list(min = 48, max = 150)
```

```r
beta_params <- list(alpha = 3, beta = 3)

# blended survival model
ble_Surv <- blendsurv(obs_Surv, ext_Surv, blend_interv, beta_params)

plot(ble_Surv)
```



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