

flexsurv: flexible parametric survival modelling in R

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Abstract

flexsurv is an R package for fully-parametric modelling of survival data. Any parametric time-to-event distribution may be fitted if the user supplies at minimum a probability density or hazard function. Many standard survival distributions are built in, and also the three and four-parameter generalized gamma and F models. Any parameter of the distribution can be modelled as a linear or log-linear function of covariates. Another built-in model is the spline model of Royston and Parmar, in which both baseline survival and covariate effects can be arbitrarily flexible parametric functions of time.

The main model-fitting function, **flexsurvreg**, uses the familiar syntax of **survreg** from the standard **survival** package — censoring or left-truncation are specified in **Surv** objects. Estimates and confidence intervals for any function of the model parameters can be printed or plotted. **flexsurv** also enhances the **mstate** package (Putter et al) by providing cumulative incidences for fully-parametric multi-state models.

This article explains the methods and design principles of the package, giving several worked examples of its use.

Keywords: ~survival.

1. Motivation and design

The Cox model for survival data is ubiquitous in medical research, since the effects of predictors can be estimated without needing to supply a baseline survival distribution that might be inaccurate. However, fully-parametric models have many advantages, and even the originator of the Cox model has expressed a preference for parametric modelling (Reid 1994). Fully-specified models help to understand the change in hazard through time, and help with prediction and extrapolation. For example, the mean survival $E(T) = \int_0^\infty S(t)$, used in health economic evaluations (Latimer 2013), needs the survivor function $S(t)$ to be fully-specified for all times t .

flexsurv allows parametric distributions of arbitrary complexity to be fitted to survival data, gaining the convenience of parametric modelling, while avoiding the risk of model misspecification. Built-in choices include splines with any number of knots (Royston and Parmar 2002) and 3–4 parameter generalized gamma and F distribution families. Any user-defined model may be employed by supplying at minimum an R function to compute the probability density or hazard, and ideally also its cumulative form. Any parameters may be modelled in terms of covariates, and any function of the parameters may be printed or plotted in model summaries.

flexsurv is intended as a general platform for survival modelling in R. It is similar in spirit to the Stata packages **stpm2** (Lambert and Royston 2009) for spline-based survival modelling, and **stgenreg** (Crowther and Lambert 2013) for fitting survival models with user-defined hazard functions using numerical integration. The **survreg** function in the R package **survival** (Therneau 2014) only supports two-parameter (location/scale) distributions, though users can supply their own distributions if they can be parameterised in this form. Many other contributed R packages can fit survival models, e.g. **eha** (Brostr m 2014), **VGAM** (Yee and Wild 1996), though these are either limited to specific distribution families, not specifically designed for survival analysis, or (**ActuDistns**, Nadarajah and Bakar (2013)) contain only the definitions of distribution functions. **flexsurv** enables distribution functions provided by such packages to be employed in models. An advantage over **stgenreg** is that numerical integration can be avoided if the analytic cumulative distribution or hazard can be supplied, and optimisation can also be speeded by supplying analytic derivatives. **flexsurv** also has features for multi-state modelling and interval censoring, and general output reporting. It employs functional programming to work with user-defined or existing R functions.

2. General parametric survival model

2.1. Definitions

The general model that **flexsurv** fits has probability density function

$$f(t|\mu(\mathbf{z}), \boldsymbol{\alpha}(\mathbf{z})), \quad t \geq 0 \quad (1)$$

The cumulative distribution function $F(t)$, survivor function $S(t) = 1 - F(t)$, cumulative hazard $H(t) = -\log S(t)$ and hazard $h(t) = f(t)/S(t)$ are also defined (suppressing the conditioning for clarity). $\mu = \alpha_0$ is the parameter of primary interest, which usually governs the mean or location of the distribution. Other parameters $\boldsymbol{\alpha} = \alpha_1, \dots, \alpha_R$ are called ‘‘ancillary’’ and determine the shape, variance or higher moments.

Covariates All parameters may depend on a vector of covariates \mathbf{z} through link-transformed linear models $g_0(\mu) = \boldsymbol{\beta}'_0 \mathbf{z}$ and $g_r(\alpha_r) = \boldsymbol{\beta}'_r \mathbf{z}$. $g(\cdot)$ will typically be $\log(\cdot)$ if the parameter is defined to be positive, or the identity function if the parameter is unrestricted. In all models, $\boldsymbol{\beta}$ includes at least an intercept, so that the full set of parameters is given by $\{\boldsymbol{\beta}_r : r = 0, \dots, R\}$. Suppose that the location, but not the ancillary parameters, depends on covariates. If the hazard function factorises as $h(t|\alpha, \mu(\mathbf{z})) = \mu(\mathbf{z})h_0(t|\alpha)$, then this is a *proportional hazards* (PH) model, so that the hazard ratio between two groups (defined by different values of \mathbf{z}) is constant over time.

Alternatively, if $S(t|\mu(\mathbf{z}), \alpha) = S(\mu(\mathbf{z})t|\alpha)$ then we have an *accelerated failure time* (AFT) model, so that the effect of covariates is to speed or slow the passage of time. For example, doubling the value of a covariate with coefficient $\beta = \log(2)$ would give half the expected survival time.

Data and likelihood Let $t_i : i = 1, \dots, n$ be a sample of times from individuals i . Let $c_i = 1$ if t_i is an observed death time, or $c_i = 0$ if t_i is a right-censoring time, thus the true

death time is known only to be greater than t_i . Also let s_i be corresponding left-truncation (or delayed-entry) times, meaning that individual i is only observed conditionally on having survived up to s_i , thus $s_i = 0$ if there is no left-truncation. Additionally let t_i^{max} be left-censoring times. If there is no left-censoring then these are infinite, so that $S(t_i^{max}) = 0$; or if the i th death time is interval-censored then $c_i = 0$ and t_i^{max} is finite.

The likelihood for the parameters β in model (1), given the corresponding data vectors, is

$$l(\{\beta_r\} | \mathbf{t}, \mathbf{c}, \mathbf{s}, \mathbf{t}^{max}) = \left\{ \prod_{i: c_i=1} f_i(t_i) \prod_{i: c_i=0} (S_i(t_i) - S_i(t_i^{max})) \right\} / \prod_i S_i(s_i) \quad (2)$$

Note that the individuals are independent, so that **flexsurv** does not currently support frailty, clustered or random effects models.

An example dataset used throughout this paper is from 686 patients with primary node positive breast cancer, available in the package as **bc**. This was originally provided with **stpm** Royston (2001), and analysed in much more detail by Royston and Parmar (2002) and Sauerbrei and Royston (1999).

3. Model fitting syntax

The main model-fitting function is called **flexsurvreg**. Its first argument is an R *formula* object. The left hand side of the formula gives the response as a survival object, using the **Surv** function from the **survival** package. Here, this indicates that the response variable is **recyrs**, and that these are observed death and censoring times when the variable **censrec** is 1 or 0 respectively. The covariate **group** is a factor representing prognostic score, with three levels "Good" (the baseline), "Medium" and "Poor". All of these variables are in the data frame **bc**.

```
> library(flexsurv)
> fs1 <- flexsurvreg(Surv(recyrs, censrec) ~ group, data=bc, dist="weibull")
```

If we also had left-truncation times in a variable called **start**, the response would be **Surv(start, recyrs, censrec)**. Or if all responses were interval-censored between lower and upper bounds **tmin** and **tmax**, then we would write **Surv(tmin, tmax, type="interval2")**.

If the argument **dist** is a string, this denotes a built-in survival distribution, in this case the Weibull. Printing the fitted model object gives estimates and confidence intervals for the model parameters and other useful information. Note that these are the *same parameters* as represented by the R distribution function **dweibull**: the **shape** α and the **scale** μ of the survivor function $S(t) = \exp(-(t/\mu)^\alpha)$.

```
> fs1
```

Call:

```
flexsurvreg(formula = Surv(recyrs, censrec) ~ group, data = bc, dist = "weibull")
```

Estimates:

	data	mean	est	L95%	U95%	se	exp(est)	L95%
--	------	------	-----	------	------	----	----------	------

shape	NA	1.3797	1.2548	1.5170	0.0668	NA	NA
scale	NA	11.4229	9.1818	14.2110	1.2728	NA	NA
groupMedium	0.3338	-0.6136	-0.8623	-0.3649	0.1269	0.5414	0.4222
groupPoor	0.3324	-1.2122	-1.4583	-0.9661	0.1256	0.2975	0.2326
U95%							
shape	NA						
scale	NA						
groupMedium	0.6943						
groupPoor	0.3806						

N = 686, Events: 299, Censored: 387
 Total time at risk: 2113.425
 Log-likelihood = -811.9419, df = 4
 AIC = 1631.884

The same model can be fitted using `survreg` in **survival**:

```
> survreg(Surv(recyrs, censrec) ~ group, data=bc, dist="weibull")
```

Call:

```
survreg(formula = Surv(recyrs, censrec) ~ group, data = bc, dist = "weibull")
```

Coefficients:

```
(Intercept) groupMedium groupPoor
  2.4356168  -0.6135892  -1.2122137
```

Scale= 0.7248206

```
Loglik(model)= -811.9   Loglik(intercept only)= -873.2
      Chisq= 122.53 on 2 degrees of freedom, p= 0
n= 686
```

The maximised log-likelihoods are the same, however the parameterisation is different: the first coefficient (`Intercept`) reported by `survreg` is $\log(\mu)$, and `survreg`'s "`scale`" is `dweibull`'s (thus `flexsurvreg`'s `1 / shape`). The covariate effects β , however, have the same "accelerated failure time" interpretation, as linear effects on $\log(\mu)$. The multiplicative effects $\exp(\beta)$ are provided in the output as `expest`.

3.1. Built-in survival models

`flexsurvreg`'s currently built-in distributions are listed in Table 1. In each case, the probability density $f()$ and parameters used in the fitted model are taken from an existing R function of the same name but beginning with the letter **d**. For the Weibull, exponential (`dexp`), gamma (`dgamma`) and log-normal (`dlnorm`), the density functions are provided with standard installations of R.

flexsurv provides some additional survival distributions, including a Gompertz distribution with unrestricted shape parameter (`dist="gompertz"`), and the three- and four-parameter

families described below. For all built-in distributions, **flexsurv** also defines functions beginning **h** giving the hazard, and **H** for cumulative hazard.

Generalized gamma This three-parameter distribution includes the Weibull, gamma and log-normal as special cases. The original parameterisation from Stacy (1962) is available as `dist="gengamma.orig"`, however the newer parameterisation (Prentice 1974) is preferred: `dist="gengamma"`. This has parameters (μ, σ, q) , and survivor function

$$\begin{aligned} 1 - I(\gamma, u) & \quad (q > 0) \\ 1 - \Phi(z) & \quad (q = 0) \end{aligned}$$

where $I(a, x) = \int_0^x t^{a-1} \exp(-t) / \Gamma(a)$ is the incomplete gamma function (the cumulative gamma distribution with shape a and scale 1), Φ is the standard normal cumulative distribution, $u = \gamma \exp(|q|z)$, $z = (\log(t) - \mu) / \sigma$, and $\gamma = q^{-2}$. The Prentice (1974) parameterisation extends the original one to include a further class of models with negative q , and survivor function $I(\gamma, u)$, where z is replaced by $-z$. This stabilises estimation when the distribution is close to log-normal, since $q = 0$ is no longer near the boundary of the parameter space. In R notation,¹ the parameter values corresponding to the three special cases are

```
dgengamma(x, mu, sigma, Q=0)      == dlnorm(x, mu, sigma)
dgengamma(x, mu, sigma, Q=1)      == dweibull(x, shape=1/sigma, scale=exp(mu))
dgengamma(x, mu, sigma, Q=sigma) == dgamma(x, shape=1/sigma^2,
                                             rate=exp(-mu) / sigma^2)
```

The generalized gamma model is fitted to the breast cancer survival data. The first `fs2` is an AFT model, where only the parameter μ depends on the prognostic covariate `group`. In a second model `fs3`, the first ancillary parameter `sigma` also depends on this covariate, giving a model with a time-dependent effect that is neither PH nor AFT. The second ancillary parameter `Q` is still common between prognostic groups.

```
> fs2 <- flexsurvreg(Surv(recyrs, censrec) ~ group, data=bc, dist="gengamma")
> fs3 <- flexsurvreg(Surv(recyrs, censrec) ~ group + sigma(group),
+                   data=bc, dist="gengamma")
```

SHOW IT FITS BETTER, LIKS, AIC, PLOTS

Generalized F This four-parameter distribution includes the generalized gamma, and also the log-logistic, as special cases. The variety of hazard shapes that can be represented is discussed by Cox (2008). It is provided here in alternative “original” (`dist="genf.orig"`) and “stable” parameterisations (`dist="genf"`) as presented by Prentice (1975). See `help(GenF)` and `help(GenF.orig)` in the package documentation for the exact definitions.

3.2. Plotting outputs

The `plot()` method for `flexsurvreg` objects is used as a quick check of model fit. By default, this draws a Kaplan-Meier estimate of the survivor function $S(t)$, one for each combination

¹The parameter called q here and in previous literature is called Q in `dgengamma` and related functions, since the first argument of a cumulative distribution function is conventionally named `q`, for quantile, in R.

	Parameters	Density R function	dist
Exponential	rate	dexp	"exp"
Weibull	shape, scale	dweibull	"weibull"
Gamma	shape, rate	dgamma	"gamma"
Log-normal	meanlog, sdlog	dlnorm	"lnorm"
Gompertz	shape, rate	dcompertz	"gompertz"
Generalized gamma (Prentice 1975)	mu, sigma, Q	dgengamma	"gengamma"
Generalized gamma (Stacy 1962)	shape, scale, k	dgengamma.orig	"gengamma.orig"
Generalized F (stable)	mu, sigma, Q, P	dgenf	"genf"
Generalized F (original)	mu, sigma, s1, s2	dgenf.orig	"genf.orig"

Table 1: Built-in parametric survival distributions in **flexsurv**

of categorical covariates, or just a single “population average” curve if there are no categorical covariates. The corresponding estimates from the fitted model are overlaid. Fitted values from further models can be added with the `lines()` method. `scale="hazard"` can be used to plot hazards from parametric models against kernel density estimates (obtained from **muhaz**; citetmuhaz,mueller:wang). This shows more clearly why the Weibull model is inadequate: the hazard must be increasing or decreasing — while the generalized gamma can represent the increase and subsequent decline in hazard seen in the data.

Similarly, `scale="cumhaz"` plots cumulative hazards. In fact any function of the parameters can be plotted, see **EXAMPLE**.

For more customisable plots, it is advised to set up the axes beforehand, and use the `lines()` method. Or for even more flexibility, the data underlying the plots is available from the `summary.flexsurvreg()` method.

In this example, there is only a single categorical covariate, and the `plot` and `summary` methods return one observed and fitted trajectory for each level of that covariate. For more complicated models, users should specify exactly what covariate values they want summaries for, rather than relying on the default ². This is done by

EXAMPLE

3.3. Supplying custom distributions

flexsurv is not limited to its built-in distributions. Any survival model of the form (1–2) can be fitted if we can provide either the density function $f()$ or the hazard $h()$. Many contributed R packages provide probability density and cumulative distribution functions for positive distributions. Though survival models may be more naturally characterised by their hazard function, representing the changing risk of death through time. For example, for survival following major surgery we may want a “U-shaped” hazard curve, representing a high risk soon after the operation, which then decreases, but increases naturally as survivors grow older.

To supply a custom distribution, the `dist` argument to `flexsurvreg` is defined to be an R

²If there are only factor covariates, all combinations are plotted. If there are any continuous covariates, these methods by default return a “population average” curve, with the linear model design matrix set to its average values, including the 0/1 contrasts defining factors, which doesn’t represent a meaningful covariate combination.

```
> plot(fs1, col="gray", lwd.obs=2)
> lines(fs2, col="red", lty=2)
> lines(fs3, col="red")
```

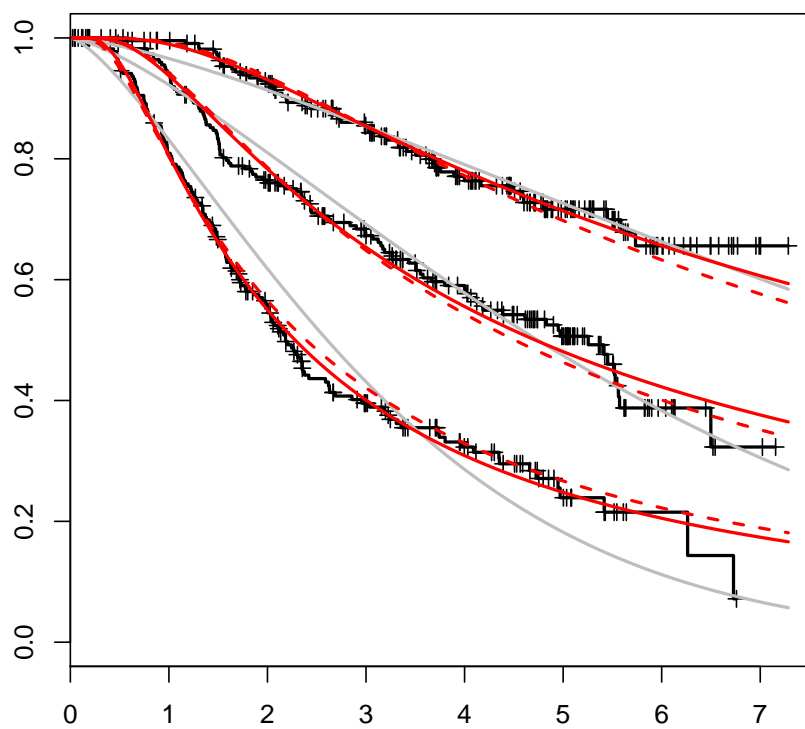


Figure 1: Estimated survival from parametric models and Kaplan-Meier estimates.

```
> plot(fs1, type="hazard", col="gray", lwd.obs=2)
> lines(fs2, type="hazard", col="red", lty=2)
> lines(fs3, type="hazard", col="red")
```

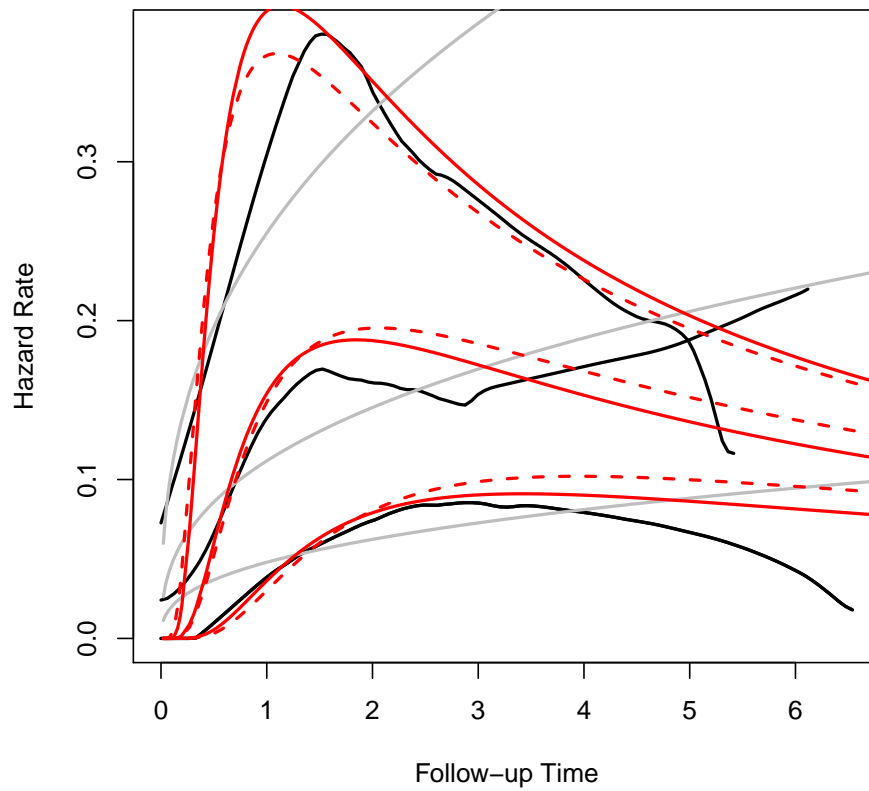


Figure 2: Estimated hazards from parametric models and kernel density estimates.

list object, rather than a character string. The list has the following elements.

name Name of the distribution. For example, if this is "llogis" then there are assumed to be at least either a function called **d** to compute the probability density or **h** to compute the hazard. Ideally there will also be a function called **p** for the cumulative distribution (if **d** is given), or **H** for the cumulative hazard (to complement **h**). These functions must be *vectorised*, and the density function must also accept an argument **log**, which when TRUE, returns the log density. See the examples below.

pars Character vector naming the parameters of the distribution $\mu, \alpha_1, \dots, \alpha_R$.

location Quoted name of the location parameter μ .

transforms A list of functions $g()$ which transform the parameter from its natural range to the real line, for example, `c(log, identity)`³

inv.transforms List of corresponding inverse functions.

inits A function which returns initial values of the parameters for maximum likelihood estimation. TRICKY

Example: Using functions from a contributed package The following custom model uses the log-logistic distribution function (**dllogis** and **pllogis**) available in the package **eha**. The survivor function is $S(t|\mu, \alpha) = 1/(1 + (t/\mu)^\alpha)$, so that the odds $(1 - S(t))/S(t)$ are a linear function of log time.

```
> library(eha)
> custom.llogis <- list(name="llogis", pars=c("shape","scale"), location="scale",
+                       transforms=c(log, log), inv.transforms=c(exp, exp),
+                       inits=function(t){ c(1, median(t)) })
> fs4 <- flexsurvreg(Surv(recyrs, censrec) ~ group, data=bc, dist=custom.llogis)
```

This fits the breast cancer data better than the Weibull, since it can represent a peaked hazard, but less well than the generalized gamma. Proportional odds. ANY SPACE FOR A HIGHLIGHTED PLOT

Example: Wrapping functions from a contributed package Sometimes there may be probability density and similar functions in a contributed package, but in a different format. For example, **eha** also provides a three-parameter Gompertz-Makeham distribution with density **dmakeham**, and hazard $h(t|\mu, \alpha_1, \alpha_2) = \alpha_2 + \alpha_1 \exp(t/\mu)$ whose shape parameters $((\alpha_1, \alpha_2))$ are provided as a vector of length two. However, **flexsurvreg** expects its distribution functions to have one argument for each parameter. Therefore we write our own functions that wrap around the third-party functions.

³Note this is a *list*, not an *atomic vector* of functions, so if the distribution only has one parameter, we should write `transforms=c(log)` or `transforms=list(log)`, not `transforms=log`

```
> dmakeham3 <- function(x, shape1, shape2, scale, ...) {
+   dmakeham(x, shape=c(shape1, shape2), scale=scale, ...)
+ }
> pmakeham3 <- function(q, shape1, shape2, scale, ...) {
+   pmakeham(q, shape=c(shape1, shape2), scale=scale, ...)
+ }
```

`flexsurvreg` also requires these functions to be *vectorized*, as the standard distribution functions in R are. That is, we can supply a vector of alternative values for one or more arguments, and expect a vector of the same length to be returned. The R base function `Vectorize` can be used to do this here.

```
> dmakeham3 <- Vectorize(dmakeham3)
> pmakeham3 <- Vectorize(pmakeham3)
```

and this allows us to write, for example,

```
> pmakeham3(c(0, 1, 1, Inf), 1, c(1, 1, 2, 1), 1)

[1] 0.0000000 0.9340120 0.9757244 1.0000000
```

We could then use `dist=list(name="makeham3", pars=c("shape1","shape2","scale"),...)` in a `flexsurvreg` model⁴.

Example: Changing the parameterisation of a distribution We may want to parameterise the Weibull distribution as $S(t) = \exp(-\mu t^\alpha)$, so that the covariate effects reported in the printed `flexsurvreg` object can be interpreted as hazard ratios or log hazard ratios without any further transformation. Here instead of the density and cumulative distribution functions, we provide the hazard and cumulative hazard.⁵

```
> detach("package:eha")
> hweibullPH <- function(x, shape, scale = 1, log=FALSE){
+   hweibull(x, shape=shape, scale=scale^{-1/shape}, log=log)
+ }
> HweibullPH <- function(x, shape, scale=1, log=FALSE){
+   Hweibull(x, shape=shape, scale=scale^{-1/shape}, log=log)
+ }
> custom.weibullPH <- list(name="weibullPH", pars=c("shape","scale"), location="scale",
+   transforms=c(log, log), inv.transforms=c(exp, exp),
+   inits = function(t){
+     c(1, exp(median(log(t[t>0]))) / log(2)))
+   })
> fs6 <- flexsurvreg(Surv(recyrs, censrec) ~ group, data=bc, dist=custom.weibullPH)
> 1 / fs1$res["scale","est"]^fs1$res["shape","est"]
```

⁴though the second shape parameter appears to be not identifiable in the breast cancer example

⁵The `eha` package needs to be detached first so that `flexsurv`'s built-in `hweibull` is used, which returns `NaN` if the parameter values are zero, rather than failing as `eha`'s does

```
[1] 0.03472474
```

```
> 1 / exp(fs1$res["groupMedium", "est"]) ^ fs1$res["shape", "est"]
```

```
[1] 2.331564
```

The fitted model is the same as `fs1`, therefore the maximised likelihood is the same, and the parameter estimates of `fs1` can be transformed to those of `fs6` as shown.

Crowther and Lambert (2013) discuss using the `stgenreg` Stata package to construct a proportional hazards parameterisation of the generalised gamma. A similar trick can be used in R. A four-parameter custom distribution is created by defining its hazard (and cumulative hazard) functions. These are obtained by multiplying the built-in functions `hgengamma` and `Hgengamma` by a dummy parameter, which is used as the location parameter of the new distribution. The intercept of this parameter is fixed at 1, so that the new model is no more complex than the generalized gamma AFT model `fs3`, but covariate effects on the dummy parameter are now interpreted as hazard ratios.

```
> hgengammaPH <- function(x, dummy, mu=0, sigma=1, Q){
+   dummy * hgengamma(x=x, mu=mu, sigma=sigma, Q=Q)
+ }
> HgengammaPH <- function(x, dummy, mu=0, sigma=1, Q){
+   dummy * Hgengamma(x=x, mu=mu, sigma=sigma, Q=Q)
+ }
> custom.gengammaPH <- list(name="gengammaPH", pars=c("dummy", "mu", "sigma", "Q"), location=
+   transforms=c(log, identity, log, identity),
+   inv.transforms=c(exp, identity, exp, identity),
+   inits=function(t){
+     lt <- log(t[t>0])
+     c(1, mean(lt), sd(lt), 0)
+   })
> fs7 <- flexsurvreg(Surv(recyrs, censrec) ~ group, data=bc, dist=custom.gengammaPH, fixed=
```

Example: Omitting the cumulative distribution or hazard If there is no analytic form for $F(t)$ or $H(t)$ as the integral of the density or hazard respectively, then `flexsurv` can compute these internally by numerical integration, though this will substantially slow down the computation. The default options of the built-in R routine `integrate` for adaptive quadrature are used, though these may be changed using the `integ.opts` argument to `flexsurvreg`.

In Section [4.2](#)

3.4. Computation

The likelihood is maximised using the optimisation methods available through the standard R `optim` function. By default, this is the "BFGS" method ((Nash 1990)) which can use the analytic derivatives of the likelihood with respect to the model parameters, if these are available, to improve the speed of convergence to the maximum.

For custom distributions, the user can optionally supply functions with names beginning "DLd" and "DLS" respectively (e.g. `DLdweibull`, `DLSweibull`) to calculate the derivatives of the log density and log survivor functions with respect to the transformed parameters γ .

Initial values are difficult: ideally two would come from moments of the distribution, then defaults that reduce to simpler distributions. example

Demo on at least one dataset: `stgenreg` uses bc example i think

3.5. Output functions

`summary.flexsurvreg` calculates the estimated survival, hazard or cumulative hazard at a series of times and for specified covariate values. Confidence intervals are produced by simulating a large sample from the asymptotic normal distribution of the maximum likelihood estimates γ OR WHATEVER, via the function `normboot.flexsurvreg`. The default `plot` method for `flexsurvreg` objects graphs these fitted trajectories against non-parametric estimates based on Kaplan-Meier or kernel estimation (REF `muhaz`), while the `lines` method adds lines to an existing plot. REFER TO EXAMPLE FIGURE

Any user-defined function of the basic model parameters γ OR WHATEVER and time can also be summarised in the same way. For example, in a non-proportional hazards model, the hazard ratio between two groups of interest varies through time. To plot this trajectory, and confidence intervals. EXAMPLE FROM SPLINE.

Restricted mean survival: say of interest. ref royston + parmar

4. Any-dimension models

flexsurv also supports models where the number of parameters is arbitrary. In the models discussed previously, the number of parameters in the model family is fixed (e.g. three for the generalized gamma). Here the model complexity can be chosen by the user. We may want to represent more irregular hazard curves by more flexible functions, or use bigger models if a bigger sample size makes it feasible to estimate more parameters.

4.1. Royston and Parmar spline model

In the spline-based survival model of [Royston and Parmar \(2002\)](#), a transformation $g(S(t, z))$ of the survival function is modelled as a natural cubic spline function of log time, $x = \log(t)$, plus linear effects of covariates z . This is available here as the function `flexsurvspline`, and is also available in the Stata package `stpm2` ([Lambert and Royston 2009](#)) (and historically `stpm`, [Royston \(2001, 2004\)](#)).

$$g(S(t, z)) = s(x, \gamma)$$

Typically we use $g(S(t, \mathbf{z})) = \log(-\log(S(t, \mathbf{z}))) = \log(H(t, \mathbf{z}))$, the log cumulative hazard, giving a proportional hazards model.

Spline parameterisation The complexity of the model, thus the dimension of γ , is governed by the number of *knots* m in the spline function $s()$. Natural cubic splines are piecewise

Model	$g(S(t, \mathbf{z}))$	In <code>flexsurvspline</code>	With $m = 0$
Proportional hazards	$\log(-\log(S(t, \mathbf{z})))$ (log cumulative hazard)	<code>scale="hazard"</code>	Weibull
Proportional odds	$\log(S(t, \mathbf{z})^{-1} - 1)$ (log cumulative odds)	<code>scale="odds"</code>	Log-logistic
Normal / probit	$\Phi^{-1}(S(t, \mathbf{z}))$ (inverse normal CDF, <code>qnorm</code>)	<code>scale="normal"</code>	Log-normal

Table 2: Alternative modelling scales for `flexsurvspline`

cubic polynomials defined to be continuous, with continuous first and second derivatives at the knots, and also constrained to be linear beyond boundary knots k_{min}, k_{max} . As well as the boundary knots there may be up to $m \geq 0$ *internal* knots k_1, \dots, k_m . Various spline parameterisations exist — the one used here is from [Royston and Parmar \(2002\)](#).

$$s(x, \boldsymbol{\gamma}) = \gamma_0 + \gamma_1 x + \gamma_2 v_1(x) + \dots + \gamma_{m+1} v_m(x) \quad (3)$$

where $v_j(x)$ is the j th *basis* function

$$v_j(x) = (x - k_j)_+^3 - \lambda_j (x - k_{min})_+^3 - (1 - \lambda_j) (x - k_{max})_+^3, \quad \lambda_j = \frac{k_{max} - k_j}{k_{max} - k_{min}}$$

and $(x - a)_+ = \max(0, x - a)$. If $m = 0$ then there are only two parameters γ_0, γ_1 — in fact if $g()$ is the log cumulative hazard, this is equivalent to a Weibull model (PARAMETERS / DPQR STATEMENT). Table 2 explains two alternative choices of $g()$.

Covariates on spline parameters Covariates can be placed on any parameter γ through a linear model (with identity link function). Most straightforwardly we can let the intercept γ_0 vary with covariates \mathbf{z} , giving a proportional hazards or odds model (depending on $g()$).

$$g(S(t, z)) = s(x, \boldsymbol{\gamma}) + \boldsymbol{\beta}^T \mathbf{z}$$

FLEXSURVSPLINE COMMAND

The spline coefficients $\gamma_j : j = 1, 2, \dots$, the "ancillary parameters", may also be modelled as linear functions of covariates \mathbf{z} , as

$$\gamma_j(\mathbf{z}) = \gamma_{j0} + \gamma_{j1} z_1 + \gamma_{j2} z_2 + \dots$$

giving a model where the effects of covariates are arbitrarily flexible functions of time: a non-proportional hazards or odds model.

FLEXSURVSPLINE COMMAND

Demo on at least one dataset

DPQR STATEMENTS

4.2. General-dimension models

The spline model above is an example of the general parametric form (1), but the number of parameters ($R + 1$ in (1), $m + 2$ in (3)) is arbitrary. **flexsurv** has the tools to deal with any model of this form. **flexsurvspline** works internally by building a custom distribution and then calling **flexsurvreg**. Similar models may in principle be built by users using the same method. This relies on a functional programming trick.

Creating distribution functions dynamically The R distribution functions supplied to custom models are expected to have a fixed number of arguments, one for each scalar parameter. However, the distribution functions for the spline model (e.g. **dsurvspline**) have an argument **gamma** representing the vector of parameters γ .

To convert it into the correct form, **flexsurv** provides the utility **unroll.function**. This converts a function with one (or more) vector parameters (matrix arguments) to a function with an arbitrary number of scalar parameters (vector arguments).

Note the scalar *parameters* can be supplied to the function as correspond to vector *arguments*, and vector parameters supplied as *matrix* arguments.

That is, **x,shape** and **scale** in **dweibull(x,shape,scale)** could actually be vectors representing alternative values for the **x** or the parameters. Similarly **gamma** in **dsurvspline(x, gamma, ...)** could be a matrix, whose rows represent alternative sets of values for γ .

Due to vectorisation: EXAMPLE

Example: splines on alternative scales **stgenreg** has demo of spline modelling on the log hazard scale. Can we do this using a generic distribution? (advantage: when there are multiple time dependent effects, the interpretation of the time-dependent hazard ratios is simplified as they do not depend on values of other covariates, which is the case when modelling on the cumulative hazard scale (Royston and Lambert 2011)).

Example: fractional polynomials relation to fractional polynomials (Royston and Altman 1994)

Note that both splines and fractional polynomials have only been used here to express how risk changes through time — they can also be used for expressing non-linear effects of any continuous predictor, see e.g. Sauerbrei, Royston, and Binder (2007), and several other publications by the same authors, for a discussion and comparison. This may be achieved here by using a suitable basis function of the covariate EXAMPLE in the model formula.

Polyhazard models (Louzada-Neto 1999) are another potential application of this technique. These express an overall hazard as a sum of latent cause-specific hazards, although they may suffer from lack of identifiability. cite nikos, me

5. Multi-state models

A *multi-state model* represents how an individual moves between multiple states through time. Survival analysis is a special case of multi-state modelling with two states “alive” and “dead”. Suppose an individual is in state $S(t)$ at time t . The next state to which the individual moves, and the time of the change, are governed by a set of *transition intensities* $q_{rs}(t)$ for states

$r, s = 1, \dots, R$, which for a survival model are equivalent to the hazard $h(t)$. The intensity represents the instantaneous risk of moving from state r to state s .

Suppose our data consist of a series of event times t_1, \dots, t_n , the last of these may be an observed event or censoring. Any software to fit survival models can also fit multi-state models to this kind of data, provided it can deal with left-truncation or *counting process* data.

For more discussion of the theory see [Putter, Fiocco, and Geskus \(2007\)](#). ref also Andersen for CP data

Counting process data For each permitted $r \rightarrow s$ transition in the multi-state model (ILLUSTRATION) there is a corresponding *time-to-event model*, with cause-specific hazard rates defined by $q_{rs}(t)$. To enable estimation of these hazards, the data are expressed as a series of times to events which are potentially censored: $dt_j = t_{j+1} - t_j : j = 1, \dots, n-1$. For a patient who moves into state s at time t_j , their next event at t_{j+1} is defined by the model structure (FIGURE) to be one of a set of competing events $s_1^*, \dots, s_{n_s}^*$.

For example, in state EXAMPLE, the next state must either be EXAMPLE or EXAMPLE so $n_s = EG$. The time of the event which actually occurs at t_{j+1} is *observed*, and the times of the *competing* events from this set (which have not occurred by this time) are *censored*. Each dt_j contributes an *observed* time to one of the EG transition-specific models, and a *censored* time to each of the models for the competing events.

FLEXSURVREG EXAMPLE

The **mstate** R package ([deWreede, Fiocco, and Putter 2010, 2011](#)) has a utility **msprep** to produce data of this form from “wide-format” datasets where rows represent individuals, and times of different events appear in different columns, and **mstate** has a utility **msm2Surv** for illustrates Cox models flexible parametric multi-state models

Prediction from multi-state models Define cumulative incidence functions

The **mstate** package is designed to work with piecewise-constant cumulative incidence functions baseline hazards are estimated non-parametrically ([deWreede et al. 2010, 2011](#))

function **msfit** that produces the cumulative incidences for each transition and a given covariate category, and their covariances, given a Cox model fitted using **coxph** from the **survival** package.

Aalen-Johansen estimator, simulation

contrast Markov and semi-Markov models

Multi-state models for panel data Note the contrast with multi-state models for *panel data*, that is, observations of the state of the process at a series of times ([Kalbfleisch and Lawless 1985](#)). In panel data, we do not necessarily know the time of each transition, or even whether a transitions of a certain type have occurred at all between a pair of observations. Such models can be fitted with the **msm** package for R, but are restricted to (piecewise) exponentially-distributed event times.

survSplit function in **survival**

6. Potential extensions

relative survival frailty many extensions may come from user-contributed models

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