

Analysis of time-to-event data with mexhaz

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Abstract

This vignette provides a description of the R package **mexhaz** and its use. It is adapted from an article accepted for publication in the *Journal of Statistical Software* (Charvat and Belot 2020). The **mexhaz** package allows for fitting flexible hazard-based regression models with the possibility to add time-dependent effects of covariates and to account for a two-level hierarchical structure in the data through the inclusion of a normally distributed random intercept (i.e., a log-normally distributed shared frailty). Moreover, **mexhaz**-based models can be fitted within the excess hazard setting by allowing the specification of an expected hazard in the model. These models are of common use in the context of the analysis of population-based cancer registry data.

Follow-up time can be entered in the right-censored or counting process input style, the latter allowing models with delayed entries. The logarithm of the baseline hazard can be flexibly modelled with B-splines or restricted cubic splines of time. Parameters estimation is based on likelihood maximisation: in deriving the contribution of each observation to the cluster-specific conditional likelihood, Gauss-Legendre quadrature is used to calculate the cumulative hazard; the cluster-specific marginal likelihoods are then obtained by integrating over the random effects distribution, using adaptive Gauss-Hermite quadrature. Functions to compute and plot the predicted (excess) hazard and (net) survival (possibly with cluster-specific predictions in the case of random effect models) are provided. We illustrate the use of the different options of the **mexhaz** package with practical examples.

Keywords: adaptive Gauss-Hermite quadrature, excess hazard, flexible models, frailty models, time-dependent effects, C.

1. Introduction

In the context of the analysis of time-to-event data, parametric and semi-parametric hazard regression models are widely used when the interest lies in estimating the impact of covariates on the time to occurrence of the event of interest. The semi-parametric Cox proportional hazard model is still widely used, even if its creator himself argued that parametric models should be used more often in practice, due to powerful features for in- and out-sample predictions, as well as the advantage of allowing statistical inference using maximum likelihood theory (see Reid 1994). However, using parametric regression models requires the assumption of a particular distribution for the observed survival times, and this assumption may sometimes be considered as too restrictive (e.g., constant or monotonic hazard for the exponential and Weibull distribution, respectively). One possibility to take advantage of parametric models without making unrealistic assumptions on the shape of the hazard (and on the corresponding

survival) is to use flexible functions, such as fractional polynomials or regression splines. The correct modelling of the data might also require the inclusion of time-dependent effects of some of the covariates. Indeed, it has been shown in many studies that the effects of covariates such as age may vary with time since diagnosis, especially in cancer epidemiology, so that the proportional hazard assumption does no longer hold (Quantin *et al.* 1999; Bossard *et al.* 2007).

Another aspect one might have to deal with is the presence of a hierarchical structure in the data: individuals from the same cluster share common characteristics (e.g., cancer patients from the same geographical area may have similar access to therapeutical resources) so that the assumption of independence of the survival times no longer holds and taking account of this hierarchical structure is necessary for correct statistical inference. In such a case, shared frailty models (also called multilevel or mixed-effect survival models) have been shown to provide a satisfactory and convenient theoretical framework by allowing the introduction of a random effect defined at the cluster level that accounts for the inter-cluster heterogeneity (Duchateau and Janssen 2008; Wienke 2010).

In population-based cancer research, it is generally of interest to disentangle the cancer-specific mortality from the mortality from other causes, mainly because cancer patients are usually old and, as a consequence, more prone to die from diseases other than their cancer (these other diseases thus act as competing causes of death). The general principle is to assume that the observed mortality hazard can be split into two components, one representing the mortality from cancer and the other one representing the impact of other causes of death. When information on the cause of death is available for each individual, this can be achieved by estimating cause-specific mortality hazards (Putter *et al.* 2007; Belot *et al.* 2010; Haller *et al.* 2013). However, when using population-based cancer registry data, the cause of death is usually unavailable or inaccurate (it might even be difficult to define a cause of death for elder patients with multiple diseases). Thus specific methods have been developed (Estève *et al.* 1990; Giorgi *et al.* 2003; Nelson *et al.* 2007; Remontet *et al.* 2007; Pohar Perme *et al.* 2012) that rely on the same general principle than in the cause-specific setting (i.e., the overall mortality rate is seen as the sum of two components), but it requires the additional assumption that the mortality hazard for other causes of death can be approximated by the mortality hazard of the general population (for a given set of demographic characteristics observed on each cancer patient). These methods allow the estimation of the so-called excess mortality hazard, which can be interpreted as the cancer-specific mortality hazard. The net survival, i.e., the survival that would be observed if cancer patients could only die from their cancer, can then be obtained from the estimated excess mortality hazard (Belot *et al.* 2019).

Within the R software environment, different packages have been developed for fitting flexible hazard models based on a full or penalised likelihood framework. In the full likelihood framework, the contributed R package **flexsurv** (Jackson 2016) uses specific distributions for the survival time, including the generalized gamma and F distribution families and also spline-based models. Facilities are also proposed to fit excess hazard regression models. Another R package named **flexrsurv** (Clerc-Urmès *et al.* 2017) has been developed for fitting two types of flexible hazard regression models (Remontet *et al.* 2007; Mahboubi *et al.* 2011) in the excess hazard setting. It is also worth mentioning the **relsurv** package (Pohar Perme and Pavlič 2018; Pohar and Stare 2006, 2007) which, although primarily aimed at non-parametric net survival estimation, can also be used to fit excess hazard regression models with either a baseline hazard described by piecewise constant functions (full likelihood framework) or with

a baseline hazard left unspecified (in the same spirit as the Cox model) using an expectation-maximisation algorithm for parameter estimation (Pohar Perme *et al.* 2009). However, neither **flexsurv**, **flexrsurv** nor **reلسurv** has the possibility to account for correlated survival times. The package **rstpm2** (Clements and Liu 2019) allows flexible modelling on the cumulative hazard scale, in the same spirit as the Royston-Parmar model (Royston and Parmar 2002), using either a fully parametric or a penalised approach. Excess hazard models can be fitted and clustered data can be accounted for by the inclusion of a Gamma or log-normally distributed frailty.

Regarding other existing R packages allowing the inclusion of random effects to analyse correlated survival times, **frailtypack** is probably the most developed (Rondeau *et al.* 2012), with functions for fitting shared and nested frailty models as well as joint modelling of multiple time-to-event processes. Users can specify either a Gamma or a log-normal frailty distribution, and estimated parameters are obtained by using a penalized likelihood framework. In the full likelihood framework, the **parfm** package has been developed for shared frailty models with a parametric distribution associated to the time-to-event (Munda *et al.* 2012), with many choices supported for the frailty distributions and parametric baseline hazards. Other R packages developed for fitting random-effect models on time-to-event data include **survival** (Therneau 2019b) (via the `frailty()` element that can be added to the formula of `survreg()`) for parametric survival regression model, and, for semi-parametric hazard models, the **coxme** (Therneau 2019a) and **frailtyEM** (Balan and Putter 2019) packages, among others. However, these packages do not offer functionalities for excess hazard regression modelling.

The **mexhaz** package allows for both flexible specification of the hazard and shared frailty modelling in the excess hazard setting, thus complementing the existing R packages. Besides the Weibull model, models using piecewise constant functions or splines (B-splines and restricted cubic splines) to describe the logarithm of the hazard are implemented. Time-dependent effects of covariates and delayed entry times can be accounted for and clustered data can be modelled through the inclusion of a log-normally distributed frailty. Table 1 summarizes the functionalities offered by **mexhaz** compared to some of the packages already cited.

As regards the domain of application, the **rstpm2** package is the one that most closely matches **mexhaz**'s capabilities. However, while **rstpm2** proposes a flexible modelling on the cumulative hazard scale, **mexhaz** offers modelling on the hazard scale. These equally valid approaches have advantages and limitations: modelling on the cumulative hazard scale is usually faster because there is no need for integration of the hazard; on the other hand, it might suffer from problems due to the instability of numerical differentiation. Besides, the interpretation of results from models defined on the cumulative hazard scale can present difficulties when multiple time-dependent effects are included (see section 7.6.3 in Royston and Lambert 2011). It should also be noted that different modelling choices result in different constraints: models of the logarithm of the cumulative excess hazard (as in **rstpm2**) impose a constraint of positivity for the overall hazard, so that the excess hazard can become negative, while modelling the logarithm of the excess hazard, as is performed in **mexhaz**, imposes positivity of the excess hazard.

The aim of this paper is to present the full likelihood-based approach implemented in **mexhaz** for fitting flexible regression models defined on the hazard scale. The package allows the user to deal with i) time-dependent effects of covariates, ii) correlated survival times and iii) estimation of the disease-specific mortality hazard without relying on cause of death

information (excess hazard model). In the first section, we present the general framework of flexible hazard-based regression models and describe their extension to excess hazard and mixed-effect (possibly, excess) hazard models. We then proceed to illustrate the use of the package in the second section.

2. Flexible parametric hazard-based regression model

2.1. General framework

In the following, we are concerned with time-to-event data, i.e., data recording the occurrence of an event (death, disease, relapse, etc.) along time. In this context, 'survival at time t ' refers to the state of not having presented the event by time t . The observed survival time, t , of an individual can then be seen as the realisation of a non-negative random variable T . If we denote by f the probability density function of T , the cumulative probability function, F , is defined by the relationship:

$$F(t) = P(T \leq t) = \int_0^t f(u) du \quad (1)$$

The survival at time t , representing the probability of being 'alive' (free of the event) at t , is then defined as $S(t) = 1 - F(t)$.

Besides, a central quantity in survival analysis is the hazard, λ , representing the instantaneous failure rate (expressed as a number of events per person-time) and defined formally as:

$$\lambda(t) = \lim_{dt \rightarrow 0} \frac{P(t \leq T < t + dt | T \geq t)}{dt} \quad (2)$$

The hazard is linked to f and S through the following relationship:

$$\lambda(t) = \frac{f(t)}{S(t)} \quad (3)$$

from which we can derive:

$$S(t) = \exp\left\{-\int_0^t \lambda(u) du\right\} \quad (4)$$

Due to the presence of right censoring and left truncation, most methods developed for the analysis of time-to-event data are based on the hazard (Cox and Oakes 1984; Geskus 2015), and we will focus in this paper on hazard-based regression models.

Derivation of the likelihood

First of all, let us define some notations. For each individual j , $j = 1, \dots, n$, let t_{0j} denote the time at entry, t_j the observed failure time (which is defined as the minimum between the survival time and the censoring time), and δ_j an indicator variable taking the value 1 in case of occurrence of the event at t_j and 0 in case of censoring.

Suppose that we want to describe the hazard in the study population by a function of time and of a vector of covariates (such as age, gender, etc.) parameterized by $\boldsymbol{\beta}$, the vector of parameters to be estimated. Under the hypothesis of non-informative censoring, the contribution of the unknown censoring distribution can be omitted from the likelihood function and we can thus write the likelihood for individual j with covariates \mathbf{x}_j as (Kalbfleisch and Prentice 2002):

$$\begin{aligned} L_j(\boldsymbol{\beta}) &= \frac{f(t_j, \mathbf{x}_j)^{\delta_j} S(t_j, \mathbf{x}_j)^{1-\delta_j}}{S(t_{0j}, \mathbf{x}_j)} \\ &= \lambda(t_j, \mathbf{x}_j)^{\delta_j} \exp\left\{-\int_{t_{0j}}^{t_j} \lambda(u, \mathbf{x}_j) du\right\} \end{aligned} \quad (5)$$

Thus, the log-likelihood function for the whole population is obtained as the sum of the individual contributions:

$$\begin{aligned} \ell(\boldsymbol{\beta}) &= \sum_{j=1}^n \log(L_j(\boldsymbol{\beta})) \\ &= \sum_{j=1}^n \left\{ \delta_j \log(\lambda(t_j, \mathbf{x}_j)) - \int_{t_{0j}}^{t_j} \lambda(u, \mathbf{x}_j) du \right\} \end{aligned} \quad (6)$$

Note that if $t_{0j} = 0$ for all individuals (no late entries), the log-likelihood can be written:

$$\ell(\boldsymbol{\beta}) = \sum_{j=1}^n \left\{ \delta_j \log(\lambda(t_j, \mathbf{x}_j)) - \Lambda(t_j, \mathbf{x}_j) \right\} \quad (7)$$

where $\Lambda(t) = \int_0^t \lambda(u) du$ is the cumulative hazard.

2.2. Extension to net survival analysis: Excess hazard regression model

In the context of the analysis of the mortality of cancer patients, we usually want to take into account the following situation: cancer patients may die from their cancer (either directly as a consequence of the natural progression of the disease, or indirectly as a consequence of the treatment) but they might also die from other causes like individuals sharing the same characteristics (age, gender, birth cohort, etc.) but not diagnosed with cancer. In other words, we would like to quantify the excess mortality that cancer patients experience because of their disease. One possible way to answer this question is to use the so-called excess hazard approach: it is based on the idea that the overall hazard may be decomposed into a sum of two hazards, one taking into account the excess mortality that can be attributed to the disease under study, λ_e , and the other that takes care of all the other possible causes of death, λ_{oth} . The objective is then to estimate λ_e while considering λ_{oth} as known. Provided that the prevalence of the disease under study (or at least, that the mortality from this disease) is reasonably low in the general population, λ_{oth} can be approximated by the population (or expected) mortality hazard, λ_p , usually obtained from national statistics institutes and

described as a function of demographic variables, such as sex, age, year, etc. This results in the following model:

$$\lambda(t, \mathbf{x}, \tilde{\mathbf{z}}) = \lambda_e(t, \mathbf{x}) + \lambda_p(a + t, y + t, \tilde{\mathbf{z}}) \quad (8)$$

where a and y represent age at diagnosis and year of diagnosis, respectively, \mathbf{x} is a vector of covariates and $\tilde{\mathbf{z}}$ a vector of demographic variables used to define the population mortality ($\tilde{\mathbf{z}}$ is usually a subset of \mathbf{x}) excluding age and year of diagnosis. In practice, λ_p is obtained from population mortality tables and depends on age, year of diagnosis and other variables such as gender, county of residence (Estève *et al.* 1990; Remontet *et al.* 2007; Pohar Perme *et al.* 2012). In the following, we define $\mathbf{z} = (a, y, \tilde{\mathbf{z}})$ and write conveniently λ_p as a function of t and \mathbf{z} .

The excess hazard model consists in modelling λ_e by a function of time and covariates parameterized by $\boldsymbol{\beta}$. The log-likelihood is obtained by replacing λ in Equation 6 by its expression under the excess hazard assumption (Equation 8):

$$\ell(\boldsymbol{\beta}) = \sum_{j=1}^n \left\{ \delta_j \log(\lambda_e(t_j, \mathbf{x}_j) + \lambda_p(t_j, \mathbf{z}_j)) - \int_{t_{0j}}^{t_j} (\lambda_e(u, \mathbf{x}_j) + \lambda_p(u, \mathbf{z}_j)) du \right\} \quad (9)$$

The quantity $\sum_{j=1}^n \int_{t_{0j}}^{t_j} \lambda_p(u, \mathbf{z}_j) du$ does not depend on the parameters to be estimated and is usually dropped when maximising the likelihood. This implies that only the value of the population hazard λ_p at the end of follow-up for each individual is necessary to specify the likelihood.

Also note that if we set λ_p to 0 for all individuals, Equation 8 simplifies to Equation 6 and specifies a model for the overall hazard.

2.3. Extension to hierarchical survival data: Mixed-effect excess hazard regression model

Now suppose that individuals come from different clusters (e.g., geographical areas): we thus have a two-level hierarchical structure with individuals nested in clusters. People from the same cluster share common characteristics so that their survival times are correlated. In order to take this structure into account, one possibility is to extend our previous model by including a random effect at the cluster level.

First of all, let us refine our notations. For each individual j , $j = 1, \dots, n_i$ from cluster i , $i = 1, \dots, D$, let t_{ij} denote the observed failure time and δ_{ij} an indicator variable taking the value 1 in case of an event and 0 in case of censoring. Our mixed-effect excess hazard regression model can be written as:

$$\lambda(t, \mathbf{x}, \mathbf{z}, w) = \lambda_{me}(t, \mathbf{x}, w) + \lambda_p(t, \mathbf{z}) \quad (10)$$

with

$$\lambda_{me}(t, \mathbf{x}, w) = \lambda_e(t, \mathbf{x}) \exp(w) \quad (11)$$

where w is a random effect assumed to be normally distributed with mean 0 and variance σ^2 . Note that this model can be parameterized in terms of $u = \exp\{w\}$, a quantity known as the

shared frailty ("shared frailty models" is an equivalent term for designing mixed-effect hazard models): the distributional assumption of our model thus corresponds to a log-normally distributed shared frailty.

In the case of non-left truncated data (i.e., $t_{0ij} = 0$ for all individuals), the likelihood for a single observation j from cluster i conditional on the value of the random effect is:

$$L_{ij}^C(\boldsymbol{\beta}|w_i) = \{\lambda_{me}(t_{ij}, \mathbf{x}_{ij}, w_i) + \lambda_p(t_{ij}, \mathbf{z}_{ij})\}^{\delta_{ij}} S(t_{ij}, \mathbf{x}_{ij}, \mathbf{z}_{ij}, w_i) \quad (12)$$

with

$$S(t_{ij}, \mathbf{x}_{ij}, \mathbf{z}_{ij}, w_i) = \exp\{-\Lambda_{me}(t_{ij}, \mathbf{x}_{ij}, w_i) - \Lambda_p(t_{ij}, \mathbf{z}_{ij})\} \quad (13)$$

In practice, the last term of the exponential in Equation 13 is omitted from the estimation procedure because it has no impact on the maximization of the likelihood. The conditional likelihood for cluster i is:

$$L_i^C(\boldsymbol{\beta}|w_i) = \prod_{j=1}^{n_i} L_{ij}^C(\boldsymbol{\beta}|w_i) \quad (14)$$

Then, the marginal likelihood for cluster i is obtained by integrating the conditional likelihood over the distribution of the random effect:

$$L_i^M(\boldsymbol{\beta}, \sigma) = \int_{-\infty}^{\infty} L_i^C(\boldsymbol{\beta}|w_i) \phi(w_i, 0, \sigma) dw_i \quad (15)$$

where $\phi(x, \mu, \sigma) = \frac{1}{\sqrt{2\pi}\sigma} \exp\left\{-\frac{1}{2}\left(\frac{x-\mu}{\sigma}\right)^2\right\}$.

The model parameters $(\boldsymbol{\beta}^\top, \sigma)^\top$ can then be estimated by maximizing the full log-likelihood:

$$\ell(\boldsymbol{\beta}, \sigma) = \sum_{i=1}^D \log\{L_i^M(\boldsymbol{\beta}, \sigma)\} \quad (16)$$

Note once again that we obtain the likelihood for a standard mixed-effect hazard model when λ_p is set to 0 (which corresponds to modelling the overall hazard).

In the presence of left truncation, the formulation of the likelihood must take account of the fact that the delayed entry times are conditional on the value of the frailty (defined at $t = 0$). Indeed, individuals with a lower value of the frailty are more likely to be alive up to a given time, so that the distribution of the frailty in a population with delayed entry times differs from the distribution of the frailty in the original population (Wienke 2010; van den Berg and Drepper 2016; Crowther *et al.* 2016). The marginal likelihood for cluster i then becomes:

$$L_i^M(\boldsymbol{\beta}, \sigma) = \frac{\int_{-\infty}^{\infty} L_i^C(\boldsymbol{\beta}|w_i) \phi(w_i, 0, \sigma) dw_i}{\int_{-\infty}^{\infty} \prod_{j=1}^{n_i} \{S(t_{0ij}, \mathbf{x}_{ij}, \mathbf{z}_{ij}, w_i)\} \phi(w_i, 0, \sigma) dw_i} \quad (17)$$

where t_{0ij} is the delayed entry time for individual j from cluster i . Also note that, here again, when modelling the excess mortality hazard, the denominator involves a term related to the expected hazard that can be omitted from the likelihood maximisation procedure.

2.4. Model specificities

Model parametrisation: Functional forms for the baseline hazard and the time-dependent effects

In **mexhaz**, the hazard, λ (in the classical setting), or the excess hazard, λ_e (in the excess hazard setting), is modelled as a function of time and some covariates depending on a vector of parameters β . In the following, we will use the generic notation $\tilde{\lambda}$ to refer to either λ or λ_e depending on the setting.

The user can choose between the so-called Weibull model and flexible parametric models of the hazard based on either a piecewise constant function, B-splines (up to degree 3) or restricted cubic splines.

Concerning the Weibull model, the general expression of the hazard, $\tilde{\lambda}$, as a function of time t and covariates \mathbf{x} (assuming that the first N variables are modelled with a proportional effect and the M following are modelled with a time-dependent effect), is:

$$\tilde{\lambda}(t, \mathbf{x}) = \rho(\mathbf{x})\theta(\mathbf{x})t^{\theta(\mathbf{x})-1} \quad (18)$$

with ρ and θ respectively the scale and shape parameters of the Weibull function depending on \mathbf{x} through the relationships:

$$\begin{cases} \rho(\mathbf{x}) = \exp\left\{\gamma_0 + \sum_{k=1}^{M+N} \gamma_k x_k\right\} \\ \theta(\mathbf{x}) = \exp\left\{\xi_0 + \sum_{m=N+1}^{M+N} \xi_m x_m\right\} \end{cases} \quad (19)$$

where

- γ_0 is the logarithm of the constant scale parameter,
- the γ_k 's ($k \in \{1, \dots, N\}$) are the coefficients corresponding to the variables modelled with a proportional effect,
- the γ_k 's ($k \in \{N+1, \dots, M+N\}$) are the coefficients corresponding to the non-time dependent part of the effect of the variables modelled with a time-dependent effect,
- ξ_0 is the logarithm of the constant shape parameter,
- the ξ_m 's ($m \in \{N+1, \dots, M+N\}$) are the coefficients corresponding to the time-dependent part of the effect of the variables modelled with a time-dependent effect.

For the piecewise constant- and spline-based models, the user is free to choose the number of knots and specify their locations. The time-dependent effects of covariates are parametrised as interaction terms between the covariates and the baseline hazard, thus leading to the same functional form for the time-dependent effect than the one used for the baseline hazard. So for example, if the baseline hazard is modelled using a quadratic B-spline with one knot at 1 year, then the time-dependent effect of a covariate will be parametrised using a quadratic B-spline with one knot at 1 year.

With the same conventions as for the Weibull model, the general expression of the hazard is now:

$$\tilde{\lambda}(t, \mathbf{x}) = \exp \left\{ \underbrace{\gamma_0 + \sum_{k=1}^{M+N} \gamma_k x_k}_{\text{Time-fixed part}} + \underbrace{\sum_{l=1}^L \left(\xi_{l0} + \sum_{m=N+1}^{M+N} \xi_{lm} x_m \right) \text{FT}_l(t)}_{\text{Time-dependent part}} \right\} \quad (20)$$

where

- FT_l are the basis functions of time used to describe the baseline hazard and the time-dependent effects of covariates. In practice, **mexhaz** allows the use of i) B-splines of degree 1 to 3 (in which case L is the sum of the degree of the spline and of the number of interior knots), ii) restricted cubic B-splines (in which case L is equal to 1 plus the number of interior knots), and iii) piecewise constant functions, in which case L is equal to 1 plus the number of interior knots;
- γ_0 is the coefficient corresponding to the constant term (or 'intercept') of the model,
- the γ_k 's ($k \in \{1, \dots, N\}$) are the coefficients corresponding to the variables modelled with a proportional effect,
- the γ_k 's ($k \in \{N+1, \dots, M+N\}$) are the coefficients corresponding to the non-time dependent part of the effect of the variables modelled with a time-dependent effect,
- the ξ_{l0} 's are the coefficients corresponding to the spline modelling the logarithm of the baseline hazard,
- the ξ_{lm} 's ($m > N$) are the coefficients corresponding to the modelling of the time-dependent effect of the variables (obtained by considering interaction terms with the function used to model the baseline hazard).

For example, for a model in which the baseline hazard is described with a quadratic B-spline with two knots (i.e., requiring four basis functions, named here $\text{BS}_1, \dots, \text{BS}_4$, in addition to the intercept), with the variable x_1 modelled with a proportional (i.e, constant in time) effect, and the variable x_2 modelled with a time-dependent effect, Equation 20 becomes:

$$\begin{aligned} \tilde{\lambda}(t, x_1, x_2) &= \exp \left\{ \gamma_0 + \gamma_1 x_1 + \gamma_2 x_2 + \sum_{l=1}^4 \xi_{l0} \text{BS}_l(t) + x_2 \sum_{l=1}^4 \xi_{l2} \text{BS}_l(t) \right\} \\ &= \underbrace{\exp \left\{ \gamma_0 + \sum_{l=1}^4 \xi_{l0} \text{BS}_l(t) \right\}}_{\lambda_0(t)} \exp \left\{ \gamma_1 x_1 + \underbrace{\left(\gamma_2 + \sum_{l=1}^4 \xi_{l2} \text{BS}_l(t) \right)}_{f(t)} x_2 \right\} \quad (21) \end{aligned}$$

That is, the hazard can be expressed in the form:

$$\tilde{\lambda}(t, x_1, x_2) = \lambda_0(t) \exp(\gamma_1 x_1 + f(t) x_2) \quad (22)$$

with the restriction that f be based on the same basis functions of time as the ones used to model the logarithm of the baseline hazard.

Calculation of the cumulative hazard

Computation of the log-likelihood requires the calculation of the cumulative hazard (see Equations 6, 9 or 13). Depending on the choice of function used to describe the hazard, the `mexhaz()` function computes the cumulative hazard in different ways:

- for the Weibull model, or when the logarithm of the hazard is described by a piecewise constant function or a B-spline of degree 1, the calculation is based on the analytical formula for the cumulative hazard;
- when the log-hazard is described by a quadratic or cubic B-spline or by a restricted cubic spline, the cumulative hazard is obtained by numerical integration, more precisely by Gauss-Legendre quadrature.

The Gauss-Legendre quadrature is a numerical integration technique which approximates the integral of a function defined on $[-1, 1]$ by a weighted sum using G pre-specified weights and nodes (Mathews and Fink 1998). The G -point Gauss-Legendre rule is exact for polynomials functions of degree less or equal than $2G - 1$. By applying a simple change of variable, the Gauss-Legendre quadrature rule can be used for approximating the integral of functions defined on the interval $[t_0, t_1]$ according to the general formula:

$$\int_{t_0}^{t_1} \tilde{\lambda}(u) du \approx \frac{t_1 - t_0}{2} \sum_{g=1}^G w_g \tilde{\lambda}\left(\frac{t_0 + t_1}{2} + \frac{t_1 - t_0}{2} z_g\right) \quad (23)$$

where w_g and z_g are the weights and nodes for the G -point GL rule, respectively. Those G weights and nodes are available in the `statmod` R package.

In the `mexhaz()` function, we apply the Gauss-Legendre quadrature rule on subintervals defined by the interior knots used to define the spline bases. More precisely, to integrate the hazard on $[t_0, t_1]$, supposing that this interval contains K of the knots used to define the spline and renumbering for convenience these knots so that $k_0 = t_0, \dots, k_{K+1} = t_1$, we write:

$$\int_{t_0}^{t_1} \tilde{\lambda}(u) du = \sum_{j=0}^K \int_{k_j}^{k_{j+1}} \tilde{\lambda}(u) du \quad (24)$$

and apply the G -point Gauss-Legendre quadrature rule to each $\int_{k_j}^{k_{j+1}} \tilde{\lambda}(u) du$. By default in `mexhaz()`, G is set to 20.

Computation of the marginal cluster-specific likelihoods

The marginal likelihood L_i^M in Equation 15 as well as the numerator and denominator of Equation 17 do not have a closed analytical form. It is thus necessary to use numerical methods to approximate their value.

The Gauss-Hermite quadrature is a numerical integration technique that allows the evaluation of integrals of the form:

$$\int_{-\infty}^{\infty} f(x) \exp(-x^2) dx \quad (25)$$

by computing a weighted sum of the function f evaluated at particular points called the quadrature nodes:

$$\int_{-\infty}^{\infty} f(x) \exp(-x^2) dx \approx \sum_{q=1}^Q \rho_q^H f(x_q^H) \quad (26)$$

The Q nodes x_q^H and weights ρ_q^H are computed from the zeros of the Q -th order Hermite polynomial and in the context of our work, were obtained through the use of the R package **statmod** which makes use of an algorithm previously developed by [Golub and Welsch \(1969\)](#).

With a simple transformation of the weights and nodes, the same principle can be used to evaluate integrals of the form:

$$\int_{-\infty}^{\infty} f(x) \phi(x, \mu, \sigma) dx \approx \sum_{q=1}^Q \rho_q^N f(x_q^N(\mu, \sigma)) \quad (27)$$

The transformed nodes, x_q^N , are now functions of μ and σ , respectively the mean and the standard deviation of the normal density function ϕ . In particular, these nodes and weights do not depend on the function f appearing in the integrand. This means that the positions of the nodes might not cover adequately the region of variation of the function resulting in i) a poor approximation of the integral and ii) the necessity of using a large number of nodes to try to improve that approximation.

Note also that, by defining the function $g(x, \mu, \sigma) = f(x)\phi(x, \mu, \sigma)$, we can rewrite Equation 27 as follows:

$$\int_{-\infty}^{\infty} g(x, \mu, \sigma) dx \approx \sum_{q=1}^Q \rho_q^* g(x_q^*, \mu, \sigma) \quad (28)$$

with

$$\begin{cases} x_q^*(\mu, \sigma) = \mu + \sigma\sqrt{2} x_q^H \\ \rho_q^* = \frac{1}{\sqrt{\pi}} \exp\{(x_q^H)^2\} \rho_q^H \end{cases} \quad (29)$$

This last formulation is seldom presented but it makes the comparison with the adaptive Gauss-Hermite quadrature more straightforward.

The idea of the adaptive Gauss-Hermite quadrature ([Liu and Pierce 1994](#); [Pinheiro and Bates 1995](#)) is to transform the integrand in order to obtain a new quadrature formula in which the nodes and corresponding weights depend on the function f : the nodes are translated and rescaled so that they cover the region where the integrand varies most, that is, around its mode. These specific nodes and weights depend on the location and the shape of the integrand of Equation 15, and are defined by using a Laplace approximation. More precisely,

the adaptive Gauss-Hermite quadrature method requires, for each cluster, the computation of the mode of the integrand, μ_i , and σ_i defined as the negative of the inverse of the second derivative of the logarithm of the integrand evaluated at μ_i . These values are then used to transform the nodes and weights according to the following relationships:

$$\begin{cases} x_q^A(\mu_i, \sigma_i) = \mu_i + \sigma_i \sqrt{2} x_q^H \\ \rho_q^A(\sigma_i) = \sigma_i \sqrt{2} \exp\{(x_q^H)^2\} \rho_q^H \end{cases} \quad (30)$$

This transformation results in a much better approximation of the integral with a small number of quadrature points at the cost of extra computational time because of the evaluation of the cluster-specific μ_i 's and σ_i 's, which requires calculations involving the first and second derivatives of the integrand.

When applying Gauss-Hermite quadrature to the approximation of the cluster-specific marginal likelihood, we obtain:

$$L_i^M(\boldsymbol{\beta}, \sigma) \approx \sum_{q=1}^Q \rho_q^A(\sigma_i) L_i^C(\boldsymbol{\beta}, \sigma | x_q^A(\mu_i, \sigma_i)) \phi(x_q^A(\mu_i, \sigma_i), 0, \sigma) \quad (31)$$

In **mexhaz**, the cluster-specific μ_i 's and σ_i 's are estimated at each iteration of the optimisation algorithm, and by default, the number of quadrature points Q is set to 10.

Optimisation procedure

Once the full log-likelihood according to the context of the study (overall or excess mortality hazard, with or without a hierarchical structure) has been defined (as in Equations 6, 9, or 16), the **nlm** function is used by default in **mexhaz** to estimate the parameters $\hat{\boldsymbol{\theta}} = (\hat{\boldsymbol{\beta}}^\top, \hat{\sigma}^\top)^\top$. However, the user can alternatively choose the **optim** function, with all the different optimisation algorithms proposed. The estimated covariance matrix, $\hat{\Sigma}_{\boldsymbol{\theta}}$, is obtained as the inverse of the negative of the Hessian matrix, the standard errors of the parameters being the square root of the diagonal elements.

Because the Hessian matrix returned by the optimization algorithm might not be very accurate, the user can ask for a better approximation via the **numHess=TRUE** option of the **mexhaz()** function. In that case, the Hessian is evaluated through the function **hessian()** from the **numDeriv** R package (numerical derivation based on the Richardson method).

Shrinkage estimates

The cluster-specific random effects, commonly called 'shrinkage estimates' or 'empirical Bayes estimates', can be obtained as the modes of the integrand appearing in Equation 15 evaluated at the maximum likelihood value of the parameters:

$$\mu_i = \frac{1}{\hat{\sigma} \sqrt{2\pi}} \operatorname{argmax}_w \left(L_i^C(\hat{\boldsymbol{\beta}} | w) \exp\left\{-\frac{w^2}{2\hat{\sigma}^2}\right\} \right) \quad (32)$$

An approximate variance for these shrinkage estimates is obtained by the following formula

(Booth and Hobert 1998):

$$\text{Var}(\mu_i) \approx \sigma_i^2 + \left(\frac{\partial \mu_i}{\partial \boldsymbol{\theta}}(\hat{\boldsymbol{\theta}}) \right)^\top \hat{\Sigma}_{\boldsymbol{\theta}} \left(\frac{\partial \mu_i}{\partial \boldsymbol{\theta}}(\hat{\boldsymbol{\theta}}) \right) \quad (33)$$

where σ_i is the inverse of minus the second derivative of the logarithm of the integrand appearing in Equation 15 evaluated at μ_i and $\left(\frac{\partial \mu_i}{\partial \boldsymbol{\theta}}(\hat{\boldsymbol{\theta}}) \right)$ is the gradient of μ_i , i.e., the vector of partial derivatives of μ_i relative to the model parameters, evaluated at the maximum likelihood value of these parameters.

The approximate covariances between μ_i and the fixed effect parameters $\boldsymbol{\beta}$ are given by:

$$\text{Cov}(\mu_i, \boldsymbol{\beta}) \approx \left(\frac{\partial \mu_i}{\partial \boldsymbol{\beta}}(\hat{\boldsymbol{\beta}}) \right)^\top \hat{\Sigma}_{\boldsymbol{\beta}} \quad (34)$$

And the approximate covariance between two cluster-specific random effects μ_i and μ_j is given by:

$$\text{Cov}(\mu_i, \mu_j) \approx \left(\frac{\partial \mu_i}{\partial \boldsymbol{\theta}}(\hat{\boldsymbol{\theta}}) \right)^\top \hat{\Sigma}_{\boldsymbol{\theta}} \left(\frac{\partial \mu_j}{\partial \boldsymbol{\theta}}(\hat{\boldsymbol{\theta}}) \right) \quad (35)$$

Predictions and confidence intervals

In **mexhaz**, we provide tools to predict and plot the modelled hazard and the corresponding survival. In particular, in the excess hazard setting, these will correspond to the excess hazard and net survival if the population mortality rate is specified, and to the overall hazard and the overall survival if this population mortality rate is omitted from the model specification. To derive the corresponding confidence intervals, the user has the possibility to use either the Delta Method or a Monte-Carlo simulation-based method. For the Monte-Carlo method, the user can specify the number of simulations used.

3. Illustration

3.1. Introduction

The main function used for model fitting, **mexhaz()**, requires the following arguments:

- **formula**: a formula with the response on the left of the \sim operator, and the linear predictor on the right. The response must be of the form **Surv(time, event)**, following the classical survival model formulation popularised by the R package **survival**;
- **data**: the name of the dataset;
- **base**: the functional form that should be used to model the baseline hazard. Selection can be made between the following options: **"weibull"** for a Weibull hazard, **"exp.bs"** for a hazard described by the exponential of a B-spline (only B-splines of degree 1, 2 or 3 are accepted), **"exp.ns"** for a hazard described by the exponential of a restricted cubic spline (also called 'natural spline'), **"pw.cst"** for a piecewise constant hazard;
- **degree**: specifies the degree of the B-spline;

- **knots**: if `base="exp.bs"` or `"exp.ns"`, `knots` is the vector of interior knots of the spline. If `base="pw.cst"`, `knots` is the vector defining the endpoints of the time intervals on which the hazard is assumed to be constant. By default, `knots=NULL` (that is, it produces a B-spline with no interior knots if `base="exp.bs"`, a linear B-spline with no interior knots if `base="exp.ns"`, or a constant hazard over the whole follow-up period if `base="pw.cst"`);
- **expect**: name of the variable (from the dataset) defining the expected hazard (for excess hazard model estimation). By default `expect=NULL`, corresponding to a standard hazard regression model (which is a model for the overall hazard);
- **random**: name of the variable defining the cluster membership (for mixed effect hazard model estimation). By default `random=NULL`, corresponding to a fixed effect survival model.

The reader is referred to the help page of the function for more details on the arguments of `mexhaz()`.

Two simulated datasets (Charvat *et al.* 2016) provided as part of our package are used in this section in order to illustrate the various functionalities of the `mexhaz()` function.

The `simdatn1` dataset has 4000 rows and 8 columns and contains the following variables:

- **age**: Age at diagnosis (continuous);
- **agecr**: Centred and rescaled age variable corresponding to $(age-70)/100$;
- **depindex**: Deprivation index (continuous) defined at the cluster level;
- **IsexH**: Gender (0 = Female, 1 = Male);
- **clust**: ID number of the cluster;
- **vstat**: Vital status (0 = Censored, 1 = Dead);
- **timesurv**: Follow-up time (year), administratively censored after 10 years;
- **popmrate**: Population (expected) mortality rate at the time of censoring or death. This was based on French population mortality tables depending on sex, age and calendar year.

The `simdatn2` dataset has the same structure and contains the same variables but data have been generated so that gender has a time-dependent effect.

For convenience, we define a new variable named `agec`, corresponding to the age centred around 70 years.

```
R> data("simdatn1", package="mexhaz")
R> data("simdatn2", package="mexhaz")
R> simdatn1$agec <- simdatn1$age-70
R> simdatn2$agec <- simdatn2$age-70
R> head(simdatn1,3)
```

```

      age      agecr  depindex IsexH clust vstat  timesurv  popmrate
1 37.47094 -0.3252906  1.4995788     1    29     1 0.1650722 0.002166154
2 37.43171 -0.3256829 -0.7932424     1    39     1 0.3027221 0.002166154
3 38.23911 -0.3176089  1.2784658     1    17     1 0.2277427 0.002361141
      agec
1 -32.52906
2 -32.56829
3 -31.76089

```

```
R> head(simdatn2,3)
```

```

      age      agecr  depindex IsexH clust vstat  timesurv  popmrate
1 30.15893 -0.3984107 -0.1930792     1    15     1 0.61613832 0.001472332
2 32.44655 -0.3755345  0.4983286     1    36     1 0.95682302 0.001639670
3 34.15436 -0.3584564  1.9553450     1    39     1 0.04132608 0.001730233
      agec
1 -39.84107
2 -37.55345
3 -35.84564

```

3.2. Flexible hazard-based regression models

Model fitting

Using the simulated dataset `simdatn1`, we show how to fit four models in which the overall mortality (i.e., without taking account of the population mortality rate) is described as a function of age at diagnosis (`agecr`) and gender (`IsexH`). The effect of these variables is assumed to be proportional (i.e., constant over time) but the baseline hazard is described by a different function in each model: Weibull hazard; piecewise-constant hazard with knots at 1, 2, 4, 6 and 8 years of follow-up; hazard described by the exponential of a cubic B-spline with knots at 1 and 5 years; and hazard described by the exponential of a restricted B-spline with knots at 1 and 5 years (in that case, the B-spline is constrained to be linear before 0 and after 10, which corresponds to the default boundary knots defined as 0 and the maximum of the observed follow-up times).

For convenience, we first define the model formula:

```
R> Form1 <- Surv(time=timesurv, event=vstat) ~ agec + IsexH
```

And then fit the four models described above:

```

R> ModWb <- mexhaz(formula=Form1, data=simdatn1, base="weibull")
R> ModPw <- mexhaz(formula=Form1, data=simdatn1, base="pw.cst",
+                 knots=c(1,2,4,6,8))
R> ModBs <- mexhaz(formula=Form1, data=simdatn1, base="exp.bs",
+                 degree=3, knots=c(1,5))
R> ModNs <- mexhaz(formula=Form1, data=simdatn1, base="exp.ns",
+                 knots=c(1,5))

```

We obtain the following results:

	agec	IsexH	-2*log-lik	N Param	AIC
Weibull	0.052	0.914	-6245.740	4	12499.48
Piecewise Cst	0.053	0.953	-6411.072	8	12838.15
Restricted Spline	0.052	0.924	-6329.249	6	12670.50
B-Spline	0.052	0.920	-6283.951	8	12583.90

Not surprisingly, the model which provides the best fit (according to the Akaike Information Criterion) is the Weibull model as the data were simulated using a Weibull hazard. Among the three other models, we note that the model in which the baseline hazard is described by the exponential of a cubic B-spline with two interior knots also provides a good fit. The question of how to choose adequately the number and position of knots of spline functions is still open: the most frequently used methods consist in i) choosing the knots based on prior knowledge of the data-generating mechanism, or ii) determining the knots as the predefined percentiles of the distribution of the survival times of individuals who presented the event (Charvat *et al.* 2016). From an empirical point of view, the fit can also be checked a posteriori by comparing the average of the predicted survival curves in the study population with a non-parametric estimator of survival (or net survival in the excess hazard setting).

Prediction

The output of the `mexhaz()` function is an object of class `mexhaz`. A `predict` method is defined for objects of class `mexhaz`: it allows the computation of hazard and survival estimates for a given time and a given vector of covariate values (see the help page of `predict.mexhaz()` for more details). More precisely, we can use `predict.mexhaz()` to predict both the survival and the corresponding hazard for i) several individuals with specific set of covariates at one pre-specified time, or ii) at several time points for one individual.

We illustrate these possibilities using the previously fitted models. The object `P.bs.10` corresponds to the prediction at 10 years (argument `time.pts`) for both female and male aged 70 years at diagnosis (`IsexH=c(0,1)` and `agec=0`).

```
R> MyTime <- seq(0,10,le=1001)
R> MyData <- data.frame(agec=0, IsexH=c(0,1))
R> P.bs.10 <- predict(ModBs, time.pts=10, data.val=MyData)
R> round(P.bs.10$results,3)
```

	time.pts	agec	IsexH	hazard	hazard.inf	hazard.sup	surv	surv.inf	surv.sup
1	10	0	0	0.089	0.061	0.131	0.243	0.224	0.262
2	10	0	1	0.223	0.152	0.329	0.029	0.023	0.035

The objects `P.bs0` and `P.bs1` correspond to predictions from `ModBs` for female (`Isex=0`) and male (`Isex=1`) aged 70 years at diagnosis from 0 to 10 years by increments of 0.01 years. They are used in the following section for graphical representation purposes.

```
R> P.bs0 <- predict(ModBs, time.pts=MyTime, data.val=MyData[1,])
R> P.bs1 <- predict(ModBs, time.pts=MyTime, data.val=MyData[2,])
```


By default, the confidence intervals are based on the Delta method, assuming the normality of the logarithm of the cumulative hazard. The function `predict.mexhaz()` allows the user to get the components of the gradient of the logarithm of the hazard and cumulative hazard through the `include.gradient=TRUE` argument. This might be useful for example if one is interested in estimating the confidence interval for a weighted sum of individual-specific survival curves.

Graphical results

The output of `predict.mexhaz()` is an object of class `predMexhaz` that can be used by the functions `plot.predMexhaz()`, `lines.predMexhaz()` and `points.predMexhaz()` to plot the hazard and survival functions. By default, confidence intervals are also plotted (if present in the `predMexhaz` object). The following examples (corresponding to the graphical representation of the hazard and survival curves for men and women aged 70 based on the previously fitted models, see Figure 1), show how some of the standard arguments of the plotting functions can be used (see the help page of the package functions for more details).

```
R> plot(P.bs1, which="hazard", ylim=c(0,1.5), lwd=2.5, col="blue",
+ main="Mortality hazard")
R> lines(P.bs0, which="hazard", lwd=2.5, col="red")
R> plot(P.bs1, which="surv", ylim=c(0,1), lwd=2.5, col="blue",
+ main="Overall survival")
R> lines(P.bs0, which="surv", lwd=2.5, col="red")
```

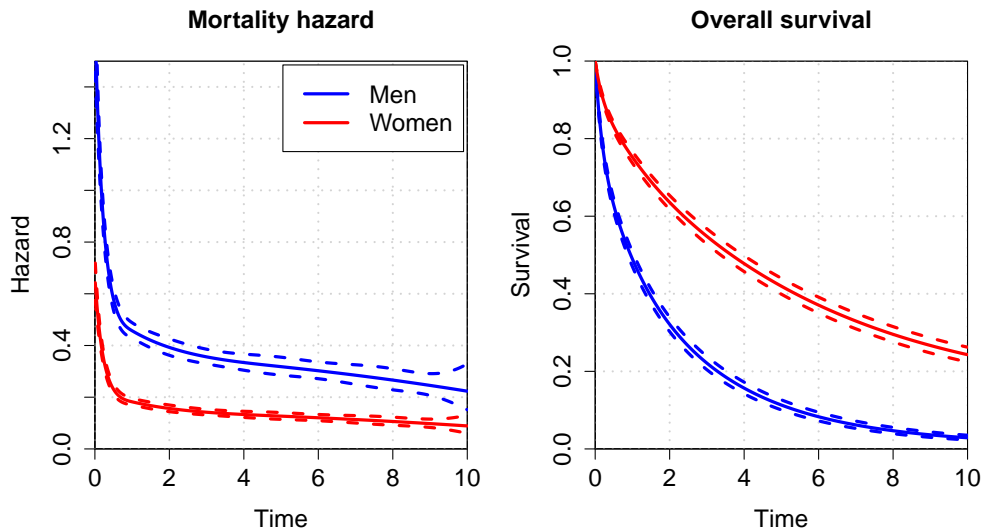


Figure 1: Mortality hazard and corresponding survival estimated for men and women aged 70.

In Figure 2, we represent the hazard and survival functions for women aged 70 years based on three of the previously fitted models. We can see that, although the hazards seem different, the survival estimates (as well as their confidence intervals, not shown here) are very similar.

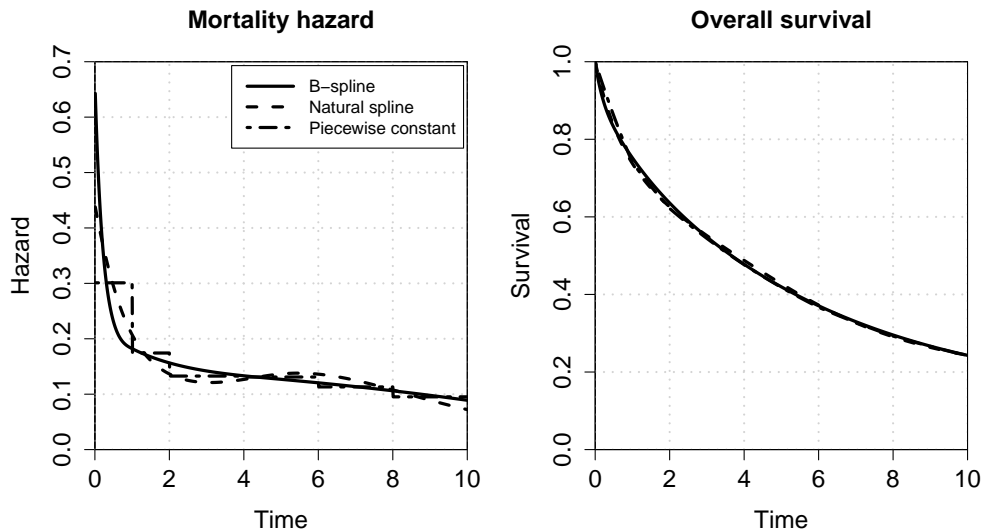


Figure 2: Mortality hazard and corresponding survival estimated by three different models.

Time-dependent effect

One of most commonly used assumption in survival analysis, mainly due to the popularity of the Cox model, is the proportionality of the hazards obtained for different values of the covariates. In other terms, the effects of the covariates, measured by the hazard ratio, is assumed to be constant over time, and the hazard for a specific value of a covariate is obtained by multiplying the baseline hazard by this constant. Although this assumption makes sense in many situations and greatly simplifies the estimation and interpretation of hazard-based survival models, there is sometimes no reason to think that the effect of a covariate should be constant over time.

The modelisation of non-proportional effects of covariates is possible with the `mexhaz()` function, through the use of the `nph()` option in the model formula, and a graphical example is shown in Figure 3. In the current state of development of the package, non-proportional effects are modelled as interaction terms between the covariates and the baseline hazard. It is planned in future versions to allow for more flexibility through the specification of different time functions for each non-proportional effect.

```
R> ModBs2.Nph <- mexhaz(Surv(time=timesurv, event=vstat) ~ agec + IsexH +
+ nph(IsexH), data=simdatn2, base="exp.bs",
+ degree=2, knots=c(1,5))
```

Note on the modelling of non-linear effects of variables

For the purpose of illustrating the general syntax of the `mexhaz()` function, in this section and the following, we have modelled the effect of the continuous variable `agec` as linear (on the logarithm of the hazard). In real application, care should of course be taken about how

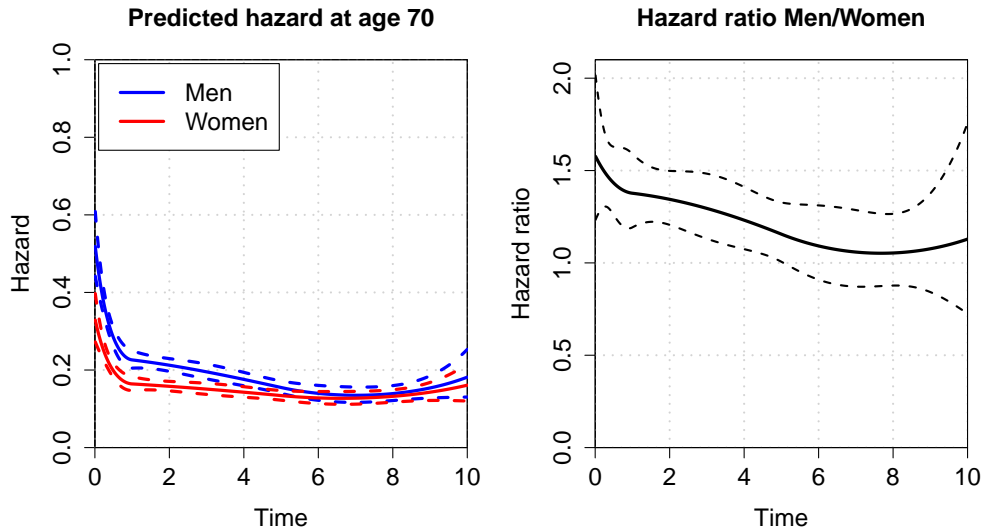


Figure 3: Example of time-dependent effect of gender.

to model the effect of such a variable by introducing, if necessary, non-linear terms. This can be done, as with most other R functions for regression models, by either i) creating new variables in the dataset corresponding to non-linear functions of the variable of interest, ii) using the `I()` operator within the model formula to generate these variables directly during model fitting, or iii) using functions such as `bs()` or `ns()` directly within the model formula.

3.3. Excess hazard regression model

General syntax

As we saw previously, the excess hazard regression approach to net survival estimation requires only the knowledge of the population mortality rate at the end of follow-up for each individual (in order to specify the likelihood). This is in contrast with non-parametric methods (such as the Pohar-Perme estimator) that require information on the population hazard at each event time.

As a consequence, unlike functions implementing non-parametric methods (such as the `rs.surv()` function from the `relsurv` package) for which the full lifetable has to be provided in the form of a `ratetable` object, the `mexhaz()` function only requires an extra variable (which has to be included in the dataset) corresponding to the population mortality rate at the end of follow-up.

The syntax for fitting an excess mortality hazard model with the `mexhaz()` function is thus simply obtained by specifying the name of the dataset variable containing the expected mortality rate through the `expected` argument:

```
R> ModBsExc <- mexhaz(Surv(timesurv, vstat) ~ agec + IsexH +
+   npH(IsexH), data=simdatn1, base="exp.bs",
```

```
+ degree=3, knots=c(1,5), expected="popmrate")
```

```
R> summary(ModBsExc)
```

```
Call:
```

```
mexhaz(formula = Surv(timesurv, vstat) ~ agec + IsexH + npH(IsexH),
        data = simdatn1, expected = "popmrate", base = "exp.bs",
        degree = 3, knots = c(1, 5))
```

```
Coefficients:
```

	Estimate	StdErr	t.value	p.value	
Intercept	-0.4329343	0.1028774	-4.2083	2.630e-05	***
BS3.1	-1.3962071	0.1871848	-7.4590	1.064e-13	***
BS3.2	-1.6915795	0.1839224	-9.1972	< 2.2e-16	***
BS3.3	-1.6158372	0.3494209	-4.6243	3.877e-06	***
BS3.4	-2.5209196	0.3721655	-6.7737	1.440e-11	***
BS3.5	-2.5145466	0.4139937	-6.0739	1.365e-09	***
agec	0.0453846	0.0018422	24.6364	< 2.2e-16	***
IsexH	0.9680385	0.1215462	7.9644	2.148e-15	***
IsexH*BS3.1	0.2032594	0.2272727	0.8943	0.3712	
IsexH*BS3.2	0.0530386	0.2474255	0.2144	0.8303	
IsexH*BS3.3	-0.7926945	0.5140445	-1.5421	0.1231	
IsexH*BS3.4	0.6032433	0.5599749	1.0773	0.2814	
IsexH*BS3.5	-0.0896992	0.6223925	-0.1441	0.8854	

```
---
```

```
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
Hazard ratios (for proportional effect variables):
```

	Coef	HR	CI.lower	CI.upper
agec	0.0454	1.0464	1.0427	1.0502
IsexH	0.9680	2.6328	2.0745	3.3412

```
log-likelihood: -5812.5676 (for 13 degree(s) of freedom)
```

```
number of observations: 4000, number of events: 3237
```

The parameter estimates now pertain to the effect of the covariates on the excess mortality hazard that patients are subject to because of their disease: from these parameters, excess hazard ratios can be calculated.

A note on the population mortality rate variable

In the previous example, the population mortality rate variable `popmrate` was already provided as part of the example dataset. However, it is usually necessary to create this variable from population mortality tables. We show here how this can be done using data from the `rstpm2` package, namely the `colon` dataset that contains 15,564 observations on colon cancer patients, and the `popmort` dataset that provides the corresponding population mortality rates.

```
R> data("colon", package="rstpm2")
R> data("popmort", package="rstpm2")
R> head(colon, 3)
```

	sex	age	stage	mmdx	yydx	surv_mm	surv_yy	status
1	Female	77	Distant	9	1977	16.5	1.5	Dead: cancer
2	Female	78	Localised	10	1978	82.5	6.5	Dead: other
3	Male	78	Distant	12	1978	1.5	0.5	Dead: cancer

	subsite	year8594	agegrp	dx	exit
1	Transverse	Diagnosed 75-84	75+	1977-09-07	1979-01-22
2	Coecum and ascending	Diagnosed 75-84	75+	1978-10-07	1985-08-22
3	Descending and sigmoid	Diagnosed 75-84	75+	1978-12-07	1979-01-22

```
R> head(popmort, 3)
```

	sex	prob	rate	age	year
1	1	0.96429	0.036363177	0	1951
2	1	0.99639	0.003616547	1	1951
3	1	0.99783	0.002172384	2	1951

The general principle is to compute from the available variables the age and year reached at the end of follow-up for each individual and then retrieve from the mortality table the value of the mortality rate corresponding to each individual-specific sex, age at exit and year at exit. It should be noted that the variables available (e.g., complete birth date versus age given as an integer) and the extension of the lifetables (e.g., ages are available until 99 years whereas some individuals in the dataset are 100 years or older at the end of follow-up) might introduce some differences in the selection of the appropriate mortality rate. For example, for an individual diagnosed in December 2015 at age 40 years and 8 months and censored after 6 months (i.e., in May 2016 at age 41 years and 2 months), the correct population mortality rate at end of follow-up corresponds to the mortality rate for year 2016 and age 41. However, if age and year of diagnosis are only available as integer (i.e., the diagnosis is made in 2015 at age 40), we can only compute an approximate age at exit of 40.5 years and a year at exit of 2015.5, which in terms of attained age and year at exit, corresponds to 40 years and 2015, thus leading to the selection of a different population mortality rate.

Because our objective here is not to enter these technical details, we will use the syntax provided in the vignette of the **rstpm2** package without questioning the choices made in terms of calculation of time periods.

The following lines of code create a new dataset `colon2` containing amongst others the variables `exitage` and `exityear` (respectively, age and calendar year at the end of follow-up), as well as `sex`, that will be used to get the appropriate mortality rate.

```
R> colon2 <- within(rstpm2::colon, {
+   status <- ifelse(surv_mm > 120.5, 1, status)
+   tm <- pmin(surv_mm, 120.5)/12
+   exit <- dx + tm*365.25
+   sex <- as.numeric(sex)
```

```
+     exitage <- pmin(floor(age + tm), 99)
+     exityear <- floor(yydx + tm)
+   })
```

Now, we can create the variable `rate` by merging `colon2` with `popmort`:

```
R> colon2 <- merge(colon2, popmort, by.x=c("sex", "exitage", "exityear"),
+                 by.y=c("sex", "age", "year"))
R> head(colon2[, c("sex", "age", "stage", "status",
+                 "exitage", "exityear", "tm", "rate")], 3)
```

	sex	age	stage	status	exitage	exityear	tm	rate
1	1	12	Distant	2	13	1991	1.6250000	0.0002300408
2	1	16	Regional	2	16	1987	0.7083333	0.0009003758
3	1	17	Distant	2	17	1979	0.1250000	0.0010305587

This dataset will be used later to compare `mexhaz()` to functions for excess hazard estimation from other packages.

Note that population lifetables for many countries can be accessed through the Human Mortality Database website (<http://www.mortality.org/>). In general, the mortality rate is expressed in number of events per person-year: it might be rescaled (e.g., number of events per person-month) to match the time scale chosen in a particular application but there is no need to convert it to a specific scale, as is for example the case when using the `relSurv` package (all time variables having to be expressed in days).

3.4. Mixed-effect excess hazard regression model

In order to fit a (possibly, excess) hazard regression model with a random effect, the argument `random` is used to specify the name of the covariate defining the cluster. By default in `mexhaz`, the number of nodes of adaptive Gauss-Hermite quadrature (AGHQ) is set to 10 but it can be modified through the argument `n.aghq`.

Here are the results obtained when fitting a mixed-effect excess hazard model with 10 quadrature nodes:

Call:

```
mexhaz(formula = Surv(timesurv, vstat) ~ agec + IsexH + nph(IsexH),
       data = simdatn1, expected = "popmrate", base = "exp.bs",
       degree = 3, knots = c(1, 5), random = "clust", n.aghq = 10)
```

Coefficients:

	Estimate	StdErr	t.value	p.value
Intercept	-0.4742698	0.1087197	-4.3623	1.319e-05 ***
BS3.1	-1.3784399	0.1870137	-7.3708	2.051e-13 ***
BS3.2	-1.6597091	0.1838144	-9.0293	< 2.2e-16 ***
BS3.3	-1.5328453	0.3492171	-4.3894	1.166e-05 ***
BS3.4	-2.4781726	0.3718693	-6.6641	3.027e-11 ***

```

BS3.5          -2.4239934  0.4101604  -5.9099 3.710e-09 ***
agec           0.0470502  0.0018874  24.9280 < 2.2e-16 ***
IsexH          0.9820957  0.1218117   8.0624 9.801e-16 ***
IsexH*BS3.1    0.2137447  0.2271847   0.9408  0.3468
IsexH*BS3.2    0.1252103  0.2477386   0.5054  0.6133
IsexH*BS3.3   -0.7965804  0.5146900  -1.5477  0.1218
IsexH*BS3.4    0.6929658  0.5605545   1.2362  0.2165
IsexH*BS3.5   -0.0590359  0.6212609  -0.0950  0.9243
clust [log(sd)] -1.4182882  0.1363752 -10.3999 < 2.2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

Hazard ratios (for proportional effect variables):

	Coef	HR	CI.lower	CI.upper
agec	0.0471	1.0482	1.0443	1.0521
IsexH	0.9821	2.6700	2.1028	3.3903

log-likelihood: -5776.5972 (for 14 degree(s) of freedom)

number of observations: 4000, number of events: 3237

Using less quadrature points will decrease the time needed to compute the cluster-specific marginal likelihood but may result in a poor approximation of the total likelihood: this might in turn increase time to convergence and sometimes even hamper the convergence of the model.

	agec	clust (sd)	log-lik	AIC	time (sec)	nlm code
1Quad-P	0.047	0.242	-5776.649	11581.30	118.38	1
5Quad-P	0.047	0.242	-5776.598	11581.19	68.28	1
10Quad-P	0.047	0.242	-5776.597	11581.19	71.06	1

When a random effect model is fitted, the object returned by `mexhaz()` includes an estimate of the logarithm of the standard deviation of the random effect (`clust [log(sd)]`) in the `coefficients` slot and the predicted cluster-specific shrinkage factors can be found in the `mu.hat` slot. These shrinkage factors are used by the `predict.mexhaz()` function to calculate cluster-specific hazard and survival values. If no cluster name is given, predictions are made for the value 0 of random effect (but it should be reminded that hazard and survival predictions at the mean value of the random effect are different from the marginal hazard and survival values obtained by integrating over the distribution of the random effect).

For example, the following lines of code show how to obtain the baseline excess hazard for men aged 70 in cluster 15:

```

R> PBsExcR.c15 <- predict(ModBsExc.10n, time.pts=MyTime,
+ data.val=MyData[2,], cluster="15")

```

And for men aged 70 with the value 0 for the random effect:

```
R> PBsExcR.0 <- predict(ModBsExc.10n, time.pts=MyTime,
+ data.val=MyData[2,])
```

3.5. Convergence issues in practice

A common problem encountered by users of statistical package in the process of constructing a regression model is that of non convergence, i.e., the algorithm is not able to find the values of the parameters corresponding to the specified model. Although there might be structural reasons explaining why "the model does not converge" (such as non-identifiability or collinearity between covariates), we list here a few problems that can be encountered when using `mexhaz()` and that may be solved either by modifying some of the arguments of the function or by changing the parametrisation of the model.

First of all, it is a fact that there is generally no algorithm that works for all optimisation problems. The R statistical software includes various optimisation algorithms, the most commonly used being `nlm()` and `optim()` (the latter allows the user to choose among several methods such as Nelder-Mead or BFGS). In order to take advantage of the availability of these different optimisation procedure, the `mexhaz()` function allows the user to choose between these options through the arguments `fnoptim` (which can take values "nlm" and "optim"). The `method` argument takes as possible values the names of the different methods available in `optim` (as there is only one method for `nlm`). Moreover, it is possible to add extra-arguments to `mexhaz()` to further customise the calls to `nlm` or `optim` (e.g., maximal number of iterations, gradient tolerance, etc.). Information on the convergence of the model is provided in the output of our function (slot `code`). It is worth noticing here that the value of `code` is the one returned by the optimisation method chosen by the user. Consequently, convergence is indicated by `code=1` when `nlm` (the default) is used and by `code=0` when `optim` is used.

Among the frequent causes of non convergence is the choice of initial values. Indeed, the likelihood function might present local extrema or be almost flat in some regions of the parameter space so that depending on the initial values, the algorithm might find itself stuck in such an area. Sensitivity to initial values is more likely to happen when the complexity of the model increases: we showed for example that the mixed-effect excess mortality hazard models were sensitive to initial values (Charvat *et al.* 2016). In such cases, a common (and usually effective) practice is to fit a simple model first and use the estimated parameters (possibly rounded) as initial values for more complex models. Based on this practice, it appears that the convergence of mixed-effect excess hazard models can be greatly improved by first fitting a fixed-effect excess hazard model and then use the rounded estimated values as initial values (setting the initial value of the standard deviation of the random effect at a reasonably small positive value such as 0.5). Initial values are specified through the argument `init`.

Another problem that one might be faced with is related to the numerical approximation of the likelihood. If this approximation is too crude, the algorithm might fail to locate the maximum of the likelihood function (or this maximum might not exist for the approximated likelihood). In mixed-effect hazard models fitted with the `mexhaz()` function, two possible causes of inadequate approximation of the likelihood function are i) the approximation of the cumulative hazard for each individual by Gauss-Legendre quadrature (when B-splines of degree 2 or 3, or restricted cubic splines, are used to model the logarithm of the baseline hazard) and ii) the approximation of the cluster-specific marginal likelihood by adaptive

Gauss-Hermite quadrature. The user can modify the number of Gauss-Legendre nodes (argument `n.gleg`) and of Gauss-Hermite nodes (argument `n.aghq`): increasing the number of nodes will allow better convergence of the models but will require more computational time (especially for the adaptive Gauss-Hermite quadrature).

In the specific context of excess hazard models, convergence problems might also be encountered if the total hazard observed in the study population is lower than the expected hazard (obtained through population mortality tables). Indeed, the excess hazard should become negative, which is not permitted by its parameterisation (i.e., the excess hazard is constrained to be a positive function of time). In that very particular case, there is no other solution than to drop the expected hazard term and fit a model for the total hazard, as assuming an excess hazard on this population does not sound appropriate.

The last problem we will mention in this section is related to the scale of the variables used in the model, whether it be i) the time scale or ii) the scale of the covariates used in the linear predictor.

Concerning the time scale, it should be adapted to the event-generating mechanism: if only a few dozen cases happen each year, and time is expressed in days or months, the hazard rate will be very small. Consequently, a regression model based on such a time scale might fail to estimate correctly the hazard because optimisation algorithms might not be able to find a correct step size to reach the maximum likelihood value of the parameters. A simple solution to this problem is of course to rescale time so that the hazard is expressed on a meaningful scale: invariance of the likelihood function towards model reparameterisation insures that we are estimating the same model. One should notice that such problems are specific to parametric and flexible hazard models: with the semi-parametric Cox model, only the order of the events is used in the estimation procedure so that the time scale is of no importance.

A similar problem occurs with covariates taking very large (age expressed in days, age squared, etc.) or very small values (e.g., concentration of biomarkers expressed in g/L). Remembering that parameter estimates corresponds to a one unit increase of the variable of interest, it is easy to imagine that the effect of age expressed in days is likely to be very small in most applications. Consequently, the associated parameter will be very small and, as before, the optimisation algorithm might have problem to deal with parameters of widely different magnitude and find its way in the parameter space towards the maximum likelihood. Once again, a possible solution to this problem is to rescale the variables.

3.6. Model parameterisation in `mexhaz` compared to other packages

We focus here on the two main extensions proposed in our package, namely the possibility to include time-dependent effects and a random effect, in comparison with two existing tools proposed in R by default, `mgcv` (Wood 2017) and `nlme` (Pinheiro *et al.* 2018). In our model parameterisation (see equation 20), a time-dependent effect for a given covariate is defined as an interaction between the functional form defining the baseline hazard and that covariate. The user can specify that time-dependent effects are to be fitted by using the special term `nph()` in the model formula. The `nph()` term takes as argument the names of the covariates (separated by a plus operator) for which a time-dependent effect is assumed; because this time-dependent effect uses that same function of time as the baseline hazard, there is no need for further model specification. This is one difference with, for example, the smoother functions `s()` in the package `mgcv` where the user can specify a different degree and a different number

of knots for each covariate. One planned extension of our package is to allow for different functions of time for each time-dependent effect.

Regarding the inclusion of a random effect, we used a specific argument `random` which contains the name of the variable defining the cluster level within quotes, following the essence of `nlme`, even though the `mexhaz()` function does not require a formula syntax (because it currently allows only one random effect). It is planned to extend the `mexhaz()` function so that it allows for several random effects.

4. Discussion and conclusion

The `mexhaz` package combines different tools to model time-to-event data based on maximum likelihood theory, from flexible parametric models up to flexible parametric excess hazard model including a random effect to analyse clustered data. Its implementation is efficient, computationally robust and compares very well with different existing packages devoted to some of the implemented features. The spline functions are powerful tools to provide smooth estimates for either the baseline hazard or the time-dependent effect of covariates, such effects being particularly important in areas such as cancer epidemiology. Even if the R code provided in the examples use a single time-dependent effect, extension to multiple time-dependent effects is straightforward. One feature of the package that we have not detailed here is the fact that the output of the `mexhaz()` and `predict.mexhaz()` functions can be used to derive other survival-related indicators. For example, Kipourou et al. show an example of use of `mexhaz` to derive the (adjusted) cumulative incidence functions with their confidence intervals in a competing risk setting (Kipourou *et al.* 2019).

We focused here on the free R software environment, but tools in `Stata` and `SAS` are also available for fitting (excess) hazard regression models with the possible inclusion of random effects. In `Stata`, the user-written commands `stpm2` (Lambert and Royston 2009) and `strcs` (Bower *et al.* 2016) can be used to fit flexible models defined on the cumulative hazard scale (the Royston-Parmar model) or the log-hazard scale, respectively, for both the overall mortality hazard and the excess mortality hazard. The commands `streg` and `mestreg` allow the user to fit parametric mixed-effect survival model with either a gamma or a lognormally distributed frailty, respectively (the command `mestreg` being however not restricted to two-level mixed effect models), while `stcox` allows the user to fit Cox proportional hazard models with a shared gamma frailty through the option `shared()`. The user-written `stmixed` (Crowther 2019) command provides a complementary programme for fitting multilevel parametric survival models defined on the cumulative hazard scale, with the possibility to perform excess hazard modelling. In `SAS`, the procedure `PHREG` includes a `RANDOM` statement for specifying a shared frailty, the `DIST` option allowing this frailty to be gamma or lognormally distributed. Besides, the `SAS` procedure `NLMIXED` is an extremely powerful tool for developing two-level random effect models and can be used to construct shared frailty hazard-based regression model, where one can assume either a parametric distribution for the time-to-event (such as Weibull (Liu and Huang 2008; Kong *et al.* 2010)) or different kinds of specification of the baseline hazard (such as piecewise constant (Dupont *et al.* 2013) or splines (Belot *et al.* 2014)).

The current development of `mexhaz` allows the analysis of two-level hierarchical time-to-event data through the use of a random effect defined at the cluster level. Based on adaptive Gauss-

Hermite quadrature, we showed that our approach provides reasonable estimates of the effects of the covariates defined either at the individual or cluster level, as long as enough clusters are present in the data (50 or more) (Charvat *et al.* 2016).

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Package name	mexhaz	rstpm2	flexsurv	frailtypack	parfm	Survival
Function name	mexhaz	stpm2; pstpm2	flexsurvreg; flexsurvspline	frailtyPenal	parfm	coxph; survreg
Parametric models	Exponential, Weibull	Weibull, generalized Gamma	Built-in or user-defined distributions	Exponential, Weibull	Exponential, Weibull, Gompertz, log-normal and log-logistic	Built-in or user-defined distributions
Flexible modelling of the (log-)hazard	Log-hazard scale: piecewise constant, B-splines (up to cubic), natural cubic splines	-	-	Hazard scale: penalized cubic M-splines	-	-
Flexible modelling of the log-cumulative hazard	-	Smoothed functions implemented in R (e.g., natural cubic splines)	Natural cubic splines	-	-	-
Position of spline knots	User-defined	Quantile of the event distribution; user-defined	Quantile of the event distribution; user-defined	Quantile of the event distribution; equispaced knots	-	-
Time-dependent effects	Yes	Yes	Yes	Yes	No	Yes
Shared frailty model for left-truncated data	Yes	No	No	Yes	Yes	No
Shared frailty distribution	log-normal	Gamma, log-normal	-	Gamma, log-normal	Gamma, log-normal, positive stable, inverse Gaussian	Gamma, log-normal, log-t
Excess hazard modelling	Yes	Yes	Yes	No	No	No

Available outputs

Prediction of the hazard / survival function	Yes	Yes	Yes	Yes	No	Yes
Gradient of the predicted values	Yes	No	No	No	No	No
Empirical Bayes estimates	Yes	No	-	Yes (with their variance only for Gamma frailty)	Yes (but not their variance)	Yes

Table 1: Comparison of the functionalities provided by **mexhaz** and other R packages for hazard regression modelling with excess hazard or shared frailty.