



## Fitting regression models to interval-censored observations of illness-death models

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### Abstract

The irreversible illness-death model describes the pathway from an initial state to an absorbing state either directly or through an intermediate state. This model is frequently used in medical applications where the intermediate state represents illness and the absorbing state represents death. In many studies, disease onset times are not known exactly. This happens for example if the disease status of a patient can only be assessed at regular visits. In this situation the disease onset times are interval-censored. This article presents the **SmoothHazard** package for R. It implements algorithms for simultaneously fitting regression models to the three transition intensities of an illness-death model where the transition times to the intermediate state may be interval-censored and the all event times can be right censored. The program parses the individual data structure of the subjects in a data set to find the individual contributions to the likelihood. The three baseline hazard functions are modelled by Weibull distributions, alternatively in a semi-parametric approach by an M-spline approach. For a given set of covariates, the estimated transition intensities can be combined into predictions of cumulative event probabilities and life expectancies.

*Keywords:* illness-death model, interval-censored data, left-truncated data, survival model, proportional regression models, smooth transition intensities, Weibull, penalized likelihood, M-splines.

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## 1. Introduction

The irreversible illness-death model is a multi-state model which has many applications in various areas of research, for example in the medical field. The model describes the transitions from an initial state (e.g., alive and disease-free) to an absorbing state (e.g., death) either directly or via an intermediate state (e.g., disease) (Figure 1). The transition intensities  $\alpha_{01}$ ,  $\alpha_{02}$ , and  $\alpha_{12}$  are positive functions of time which can also depend on covariates.

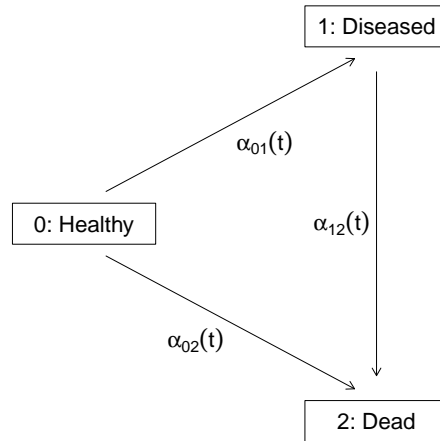


Figure 1: The irreversible illness-death model

In some applications it happens for some or all subjects that the transition times from the initial state to the intermediate state are interval censored. This occurs for example when the status of the intermediate state can only be determined at a sequence of visit times. In this case, if a subject is diagnosed as diseased at one of the visit times, say  $R$ , then it is only known that the subject was last seen disease-free at the previous visit time, say  $L$ , and hence the time of the onset of the disease is interval censored between  $L$  and  $R$  for this subject. Furthermore, both the process of visit times and the observation of the time of the transition into the absorbing state are usually right censored, i.e., limited to the individual followup period of the subjects. This yields a rather complex general observational pattern, because for a subject who died without being diagnosed as diseased at earlier visit times, it may or it may not be possible to determine retrospectively if and when the subject became diseased between the last visit time and the time of death.

The **SmoothHazard** package provides estimates of the transition intensities and of covariate effects when the data fall into one of the 6 cases that are displayed in Figure 2. Thus, the case of left-truncated event times (delayed entry) is covered, as well as the case where for some subjects the transition time into the intermediate state is observed exactly and for others it is interval censored. Finally, the special case is covered where for some or all subjects no intermediate information is available about the disease status such that it is only known whether or not the subjects became diseased between the start and the end of followup. The latter occurs in Figure 2 when  $E = L$  and  $R = \min(T, C)$  in cases 2. or 4.

To estimate covariate effects on the three transition intensities, implemented are regression models which assume proportional transition intensities and a non-homogeneous Markov process. The user chooses between a fully parametric model where each of the baseline intensities is described by the parameters of a Weibull distribution and a semi-parametric model where the baseline intensities are left unspecified and approximated by M-splines. For the parametric model, the regression coefficients and Weibull parameters are estimated by maximising the likelihood, for the semi-parametric model, the coefficients of the M-splines and the regression coefficients are estimated by maximising a penalized likelihood.

If the exact transition times are observed, standard procedures like those implemented, e.g.

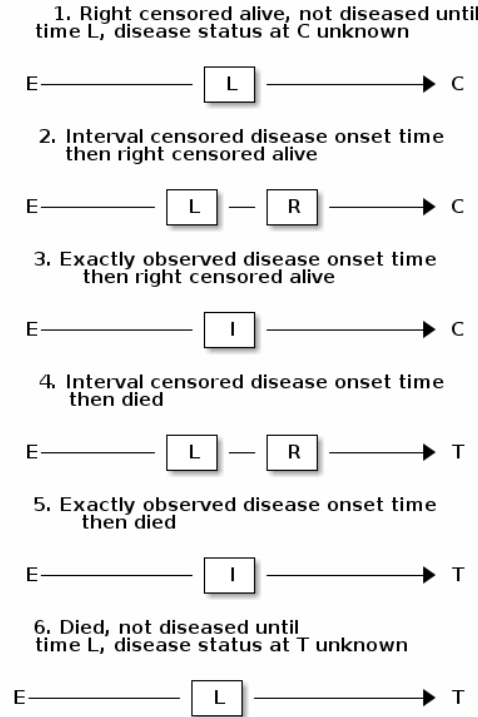


Figure 2: Observational patterns that are recognized by **SmoothHazard**. The letters I and T denote the transition times into the intermediate and absorbing state, respectively. The letters E and C denote the start and end of followup, respectively, and the letters L and R the visit times between which the transition into the intermediate happened.

in the packages **survival**, **rms**, **etm**, **mstate** can be used to estimate transition intensities, regression coefficients and functionals thereof (see [de Wreede et al. 2011](#); [Beyersmann et al. 2011](#)). In particular, the regression coefficients can be estimated using Cox partial likelihood ([Cox 1975](#)) without the need to model the baseline intensities. However, when transition times to the intermediate event are interval censored, it is generally not possible to arrive at consistent estimates with the software provided by the packages listed above. There are several adhoc approaches. For example one can artificially end the followup for subject who died with unknown disease status at the last time they were seen without disease and subsequently treat them as right-censored. Or, one can try to impute the onset time of disease for diseased subjects, for example simply by using the middle of the interval censored observation. However, these approaches can lead to a systematic bias in the estimates of transition intensities and of regression coefficients ([Joly et al. 2002](#); [Leffondré et al. 2013](#)). The bias will be especially pronounced if the risk of death is higher for diseased subjects than the risk of death for disease-free subjects.

The **msm** package ([Jackson 2011](#)) allows to fit Markov multi-state models to panel data where the status of the subjects is known at a finite series of inspection times. As a special case the setting includes the illness-death model and it can be used with interval-censored disease times and exact death times. However, in this package the likelihood is calculated using the

Kolmogorov differential equations that relate the transition probabilities and the transition intensities and to make this work a time-homogeneity assumption is made where all transition intensities are constant or piecewise-constant.

The package **intcox** provides estimates of the Cox regression model based on interval-censored event times. However, presently the functions are restricted to the simple survival model with a single event and it does not seem to provide estimates of the standard errors which could be used to construct confidence limits and p-values.

### *Outline*

The main functions of **SmoothHazard** are

- **shr** : for fitting survival regression models based on possibly interval-censored event times.
- **idm** : for fitting illness-death regression models based on possibly interval-censored disease times and right censored death times;
- **predict.idm** : ???
- **lifexpect** : ???

The R functions are essentially an interface between the user and FORTRAN programs which constitute the heart of the package **SmoothHazard**. A fitted illness-death model as produced by **idm** can be used to calculate predictions for a given set of covariates: transition probabilities, cumulative event probabilities, life expectancies.

Section 2 presents the model and the likelihood. Section 3 presents the estimation methods. Section 4 briefly presents predictions that can be made in an illness-death model. Section 5 provides some examples illustrating **SmoothHazard**.

## 2. Model and likelihood

We consider an illness-death process  $X = (X(t), t \geq 0)$  which takes values in  $\{0, 1, 2\}$  (Figure 1). Subjects are initially disease-free ( $X(0) = 0$ ) and may become diseased (transition  $0 \rightarrow 1$ ) and die (transition  $1 \rightarrow 2$ ), or die directly without disease (transition  $0 \rightarrow 2$ .)  $X$  is assumed to be a non-homogeneous Markov process which means that the future evolution of the process  $\{X(t), t > s\}$  depends on the current time  $s$  and only on the current state  $X(s)$ . Thus, the distribution of  $X$  is fully characterized by the set of transition probabilities:

$$p_{hl}(s, t) = \mathbb{P}(X(t) = l | X(s) = h) \quad hl \in \{01, 02, 12\}.$$

The transition probabilities are related to the instantaneous transition intensities  $\alpha_{hl}$  shown in Figure 1 by the relation:

$$\alpha_{hl}(t) = \frac{p_{hl}(t, t + \Delta t)}{\Delta t}.$$

We introduce covariate effects separately for each transition through proportional transition intensities regression models which are a natural extension of the Cox proportional hazard model:

$$\alpha_{hl}(t | Z_{hli}) = \alpha_{0,hl}(t) \exp\{\beta_{hl}^T Z_{hli}\}; \quad hl \in \{01, 02, 12\}. \quad (1)$$

Here  $\alpha_{0,hl}$  are baseline transition intensities,  $Z_{hli}$  are covariate vectors for subject  $i$  and  $\beta_{hl}$  are vectors of regression parameters for transition  $hl$ .

In the situation where the time to disease and the time to death are not interval censored but either observed exactly or right censored, the regression coefficients can be estimated by the partial likelihood method without the need to specify and estimate the baseline hazard functions  $\alpha_{0,hl}(t)$ . For interval-censored transition times to the intermediate state the situation is more complex. It turns out that we have to estimate all parameters simultaneously and that we need a model for the baseline transition intensity functions. This can be seen by inspecting the likelihood function.

For subject  $i$ , denote the conditional disease-free survival function by

$$S(t|Z_{01i}, Z_{02i}) = e^{-A_{01}(t|Z_{01i}) - A_{02}(t|Z_{02i})}$$

where  $A_{hl}(\cdot|Z_{hli})$  is the conditional cumulative intensity function of transition  $hl$ :

$$A_{hl}(t|Z_{hli}) = \int_0^t \alpha_{hl}(u|Z_{hli}) du.$$

Note that if subject  $i$  has entered the intermediate state, the conditional survival function in the intermediate state between times  $s$  and  $t$  is given by:

$$\frac{e^{-A_{12}(t|Z_{12i})}}{e^{-A_{12}(s|Z_{12i})}}.$$

We allow that the event times are left truncated, i.e., that subjects enter the study at the delayed entry time  $E > 0$ . The left truncation condition  $X(E_i) = 0$  implies that subject  $i$  has survived in state 0 until time  $E_i$ . This is taken into account by dividing the above likelihood contributions by the term  $S(E_i|Z_{01i}, Z_{02i})$ .

In addition to the covariate vectors  $Z_{01i}, Z_{02i}, Z_{12i}$  we observe the vector  $(E_i, L_i, R_i, \delta_{1i}, \tilde{T}_i, \delta_{2i})$  where  $\tilde{T}_i = \min(T_i, C_i)$  is the minimum between the transition time into the absorbing state  $T_i$  and the right censoring time  $C_i$  and  $\delta_{2i} = 1\{T_i \leq C_i\}$ . Also,  $\delta_{1i} = 1$  if we know for sure that subject  $i$  was diseased between  $E_i$  and  $\tilde{T}_i$  and  $\delta_{1i} = 0$  otherwise. The visit times  $L_i$  and  $R_i$  are defined by  $E_i \leq L_i \leq R_i \leq \tilde{T}_i$  if  $\delta_{1i} = 1$  and by  $E_i \leq L_i \leq \tilde{T}_i, R_i = \infty$  if  $\delta_{1i} = 0$ . When the transition time into the intermediate state is observed exactly, we have  $\delta_{1i} = 1$  and  $L_i = R_i$ . In the latter case we also denote  $I_i$  for the transition time into the intermediate state.

We now detail the likelihood contributions according to the different observational patterns shown in Figure 2:

$$\begin{aligned}
\text{case 1: } \mathcal{L}_i &= S(C_i|Z_{01i}, Z_{02i}) + \int_{L_i}^{C_i} S(u|Z_{01i}, Z_{02i})\alpha_{01}(u|Z_{01i})\frac{e^{-A_{12}(C_i|Z_{12i})}}{e^{-A_{12}(u|Z_{12i})}}du \\
\text{case 2: } \mathcal{L}_i &= \int_{L_i}^{R_i} S(u|Z_{01i}, Z_{02i})\alpha_{01}(u|Z_{01i})\frac{e^{-A_{12}(C_i|Z_{12i})}}{e^{-A_{12}(u|Z_{12i})}}du \\
\text{case 3: } \mathcal{L}_i &= S(I_i|Z_{01i}, Z_{02i})\alpha_{01}(I_i|Z_{01i})\frac{e^{-A_{12}(C_i|Z_{12i})}}{e^{-A_{12}(I_i|Z_{12i})}} \\
\text{case 4: } \mathcal{L}_i &= \int_{L_i}^{R_i} S(u|Z_{01i}, Z_{02i})\alpha_{01}(u|Z_{01i})\frac{e^{-A_{12}(T_i|Z_{12i})}}{e^{-A_{12}(u|Z_{12i})}}\alpha_{12}(T_i|Z_{12i})du \\
\text{case 5: } \mathcal{L}_i &= S(I_i|Z_{01i}, Z_{02i})\alpha_{01}(I_i|Z_{01i})\frac{e^{-A_{12}(T_i|Z_{12i})}}{e^{-A_{12}(I_i|Z_{12i})}}\alpha_{12}(T_i|Z_{12i}) \\
\text{case 6: } \mathcal{L}_i &= S(T_i|Z_{01i}, Z_{02i})\alpha_{02}(T_i|Z_{02i}) \\
&\quad + \int_{L_i}^{T_i} S(u|Z_{01i}, Z_{02i})\alpha_{01}(u|Z_{01i})\frac{e^{-A_{12}(T_i|Z_{12i})}}{e^{-A_{12}(u|Z_{12i})}}\alpha_{12}(T_i|Z_{12i})du
\end{aligned}$$

Indeed, subject  $i$  has survived in state 0 until some time  $u$  between  $L_i$  and  $R_i$  and moved to state 1 at time  $u$ . Then, he has survived in state 1 between times  $u$  and time  $T_i$  and died at time  $T_i$  if  $\delta_{2i} = 1$ .

- If subject  $i$  has never been seen diseased, let us denote the last time he has been observed disease-free by  $R_i$ . The likelihood contribution for subject  $i$  is:

$$\begin{aligned}
\mathcal{L}_i &= S(T_i|Z_{01i}, Z_{02i})(\alpha_{02}(T_i|Z_{02i}))^{\delta_{2i}} + \\
&\quad \int_{R_i}^{T_i} S(u|Z_{01i}, Z_{02i})\alpha_{01}(u|Z_{01i})\frac{e^{-A_{12}(T_i|Z_{12i})}}{e^{-A_{12}(u|Z_{12i})}}(\alpha_{12}(T_i|Z_{12i}))^{\delta_{2i}}du \quad (2)
\end{aligned}$$

Indeed, if subject  $i$  has not died at  $T_i$  ( $\delta_{2i}=0$ ), he may have survived in state 0 (term at the left side of the plus sign) or he may have become diseased between  $R_i$  and  $T_i$  (term at the right side of the plus sign); if subject  $i$  has died at  $T_i$ , he may have moved directly from state 0 to state 2 (term at the right side of the plus sign) or he may have become diseased at some time between  $R_i$  and  $L_i$  and then died (term at the right side of the plus sign).

If time to disease and time to death are both right-censored at the same time, we have  $L_i = R_i = T_i$  and the integral value in (2) is zero.

### 3. Estimation

The `idm` function computes estimates for the three baseline transition intensities and for the regression parameters using likelihood-based estimation methods. In the parametric method and in the semi-parametric method, respectively the likelihood and the penalized likelihood are maximized using the Levenberg-Marquardt's algorithm ([Levenberg 1944](#); [Marquardt 1963](#)) which is a combination of a Newton-Raphson algorithm and a gradient descent algorithm (also

known as the steepest descent algorithm). This algorithm has the advantage of being more robust than the Newton-Raphson algorithm while preserving its fast convergence property.

### 3.1. Parametric estimation

In the default estimation method of function `idm`, a Weibull parametrization for the baseline transition intensities is assumed:

$$\alpha_{0,hl}(t) = a_{hl} b_{hl}^{a_{hl}} t^{a_{hl}-1}; \quad hl \in \{01, 02, 12\}.$$

where  $a_{hl}$  and  $b_{hl}$  are shape and scale parameters. The Weibull parameters  $a_{hl}$  and  $b_{hl}$  and the vectors of regression parameter  $\hat{\beta}_{hl}$  are obtained simultaneously by maximizing the log-likelihood.

Confidence intervals for the regression parameters are obtained using estimated standard errors estimated by inverting the Hessian matrix of the log-likelihood. Confidence bands for the baseline transition intensities are obtained using a simulation-based approach explained below (section 4.1).

### 3.2. Semi-parametric estimation

In situations where it is suspected that the Weibull distribution does not fit the data very well one can think of extending the model and to leave the baseline intensity functions completely unspecified, as in the Cox regression model. Unfortunately, in interval censored data there is no direct analogue to the partial likelihood and the Breslow estimator of the Cox model in right censored data. To approximate the likelihood simultaneously for the regression coefficients and the baseline intensities the function `idm` implements a semi-parametric model where the three baseline transition intensities are approximated by linear combinations of M-splines. In this section we explain the basic steps of the approach.

#### *The penalized likelihood*

To control the smoothness of the estimated intensity functions, we penalize the log-likelihood by a term which specifies the curvature of the intensity functions. It is given by the square of the second derivatives. The penalized log-likelihood ( $pl$ ) is defined as:

$$pl = l - \kappa_{01} \int \alpha_{01}''^2(u|Z_{01})du - \kappa_{02} \int \alpha_{02}''^2(u|Z_{02})du - \kappa_{12} \int \alpha_{12}''^2(u|Z_{12})du \quad (3)$$

where  $l$  is the log-likelihood and  $\kappa_{01}$ ,  $\kappa_{02}$  and  $\kappa_{12}$  are three positive parameters which control the trade-off between the data fit and the smoothness of the functions. It is proposed that the penalization parameters are chosen by maximizing a cross-validated likelihood score. Here, leave-one-out is appealing as the result does not depend on the random seed as it would, e.g., for 10-fold cross-validation. However, since leave-one-out requires as many computations of the likelihood as there are subjects in the data set, this can be computationally very expensive. To avoid extremely long run times we have implemented the following algorithm:

Step 1. We ignore the covariates and use a grid search method to find the values for  $(\kappa_{01}, \kappa_{02}, \kappa_{12})$  based on an approximation of the marginal leave-one-out log-likelihood score. The approximation is equivalent to one step of the Newton-Raphson algorithm and reduces the number of calculations considerably. This approach was proposed by O'Sullivan (1988)

for survival models and extended and studied by Joly *et al.* (2002) in a multi-state model with interval censored data.

Step 2. We use the results of Step 1, i.e. the optimized value of  $(\kappa_{01}, \kappa_{02}, \kappa_{12})$  to maximize the penalized likelihood (3) with covariates. The parameters being maximized are the regression coefficients and the coefficients of the linear combination of the M-splines defined below.

### *M-splines*

A family of M-spline functions of order  $k$ ,  $M_1, \dots, M_n$  is defined by a set of  $m$  knots where  $n = m + k - 2$  (Ramsay 1988). We consider only cubic M-splines of order  $k = 4$ . Denote by  $t_{01} = (t_{01,1}, \dots, t_{01,m_{01}})$  a sequence of  $m_{01}$  knots used for  $\hat{\alpha}_{0,01}$ , and by  $t_{02} = (t_{02,1}, \dots, t_{02,m_{02}})$  and  $t_{12} = (t_{12,1}, \dots, t_{12,m_{12}})$  similar sequences of knots for  $\hat{\alpha}_{0,02}$  and  $\hat{\alpha}_{0,12}$ , respectively. We denote by  $M_{hl}^T = M_{hl,1}, \dots, M_{hl,n_{hl}}$  the families of  $n_{hl}$  cubic M-splines, with  $n_{hl} = m_{hl} + 2$  and for  $hl \in \{01, 02, 12\}$ . The estimator  $\hat{\alpha}_{hl}$  is approximated using the following linear combination:

$$\tilde{\alpha}_{0,hl}(t) = \sum_{i=1}^{n_{hl}} (a_{hl,i})^2 M_{hl,i}(t)$$

where  $a_{hl,i}$  are unknown parameters. The  $n_{hl}$  M-splines are integrated in order to produce a family of monotone splines, these are called I-splines. Thus, with each M-spline  $M_{hl,i}$  we associate an I-spline  $I_{hl,i}$ :

$$I_{hl,i}(t) = \int_{t_{hl,1}}^t M_{hl,i}(u) du.$$

For given values of the parameters  $a_{hl,i}$ , we can approximate the cumulative baseline transition intensities  $A_{hl}$  by a linear combination of I-splines:

$$\tilde{A}_{0,hl}(t) = \sum_{i=1}^{n_{hl}} (a_{hl,i})^2 I_{hl,i}(t).$$

Because M-splines are non-negative, the positivity constraint on  $a_{hl,i}$  ensures that  $\tilde{A}_{0,hl}$  is monotone increasing.

Confidence intervals of the regression parameters are obtained using estimated standard errors which are obtained by inverting the Hessian matrix of the log-likelihood. Confidence intervals for the transition intensities  $\alpha_{hl}(t)$  are obtained using the Bayesian approach proposed in O'Sullivan (1988) for survival analysis where the standard errors are estimated by  $M_{hl}(t)^T H^{-1} M_{hl}(t)$  where  $H$  denotes the Hessian matrix of the penalized log-likelihood.

## 4. Predictions

Often in illness-death models the functions of interest are the transition intensities. However, other quantities which can be expressed in terms of the transition intensities (Touraine *et al.* 2013) may provide additional information and have a more natural interpretation.

For example, given a set of covariates  $Z_{01,i}, Z_{02,i}, Z_{12,i}$  for a subject  $i$  who is diseased at time  $s$ , one could be interested in probability to be still alive at some time  $t > s$ , or in life expectancy; given a set of covariates  $Z_{01,j}, Z_{02,j}, Z_{12,j}$  for a subject  $j$  who is diseased-free at time  $s$ , one could be interested in lifetime risk of disease or in healthy life expectancy



(expected remaining sojourn time in state 0). Since these quantities can be written in terms of the transition intensities, **SmoothHazard** provides estimates of them using estimates of the transition intensities. Confidence intervals of these quantities are calculated using the simulation-based method immediately following.

#### 4.1. Confidence regions

A simulation based approach (?) is used to calculate confidence intervals for the transition intensities  $\alpha_{hl}(t)$  in the parametric approach and for the quantities of interest (transition probabilities, cumulative probabilities and life expectancies) in both parametric and semi-parametric approaches.

We assume the asymptotic normality for the estimator  $\hat{\theta}$  (either for the regression parameters and the distribution parameters in the parametric approach, or for the regression parameters and the spline parameters in the semi-parametric approach). We denote by  $\hat{V}_{\hat{\theta}}$  the estimated covariance matrix of  $\hat{\theta}$ . We consider a multivariate normal distribution with the parameters estimates as expectation and  $\hat{V}_{\hat{\theta}}$  as covariance matrix. We generate  $n$  vectors ( $n = 2000$  in practice) from this distribution:  $\theta^{(1)}, \dots, \theta^{(n)}$ . Based on them, we can calculate  $n$  values for the transition intensities:  $\alpha_{hl}^{(1)}(t), \dots, \alpha_{hl}^{(n)}(t)$ , and therefore  $n$  values for any quantity of interest written in terms of the transition intensities. The  $n$  values reflecting the sample variation (?), we order them and the 2.5<sup>th</sup> and the 97.5<sup>th</sup> empirical percentiles are then used as lower and upper confidence bounds for 95% confidence intervals. This procedure can be repeated for any  $t$ , so we can obtain pointwise confidence bands for  $\alpha_{hl}(\cdot)$ .

## 5. Using SmoothHazard

### 5.1. How to prepare the data

Case	Description	$\delta_1$	$\delta_2$	L	R	T	Remark
1	Right censored, disease-free	0	0	$L_i$	$L_i$	$C_i$	Requires $L_i \leq C_i$
2	Interval censored ill time, right censored death time	1	0	$L_i$	$R_i$	$C_i$	$L_i < R_i$ ; requires $R_i \leq C_i$
3	Exact ill time, right censored death time	1	0	$L_i$	$L_i$	$C_i$	Requires $L_i \leq C_i$
4	Interval censored ill time, death time observed	1	1	$L_i$	$R_i$	$T_i$	$L_i < R_i$ ; requires $R_i \leq T_i$
5	Exact ill time, death time observed	1	1	$L_i$	$L_i$	$T_i$	Requires $L_i \leq T_i$
6	No illness observed, death time observed	0	1	$L_i$	$L_i$	$T_i$	Requires $L_i \leq T_i$

Table XX shows how the program interpretes the structure of the data set. Some more details are necessary to distinguish the case where the ill status is diagnosed at the last follow-up time for death from the case where this is not possible.

- In case 1, if  $L_i < C_i$  then it is assumed that the subject may become ill between  $L_i$  and  $C_i$ . If  $L_i = C_i$  it is assumed that the subject is disease-free at time  $C_i$ . In the latter case the second part of the likelihood in equation EE equals zero.

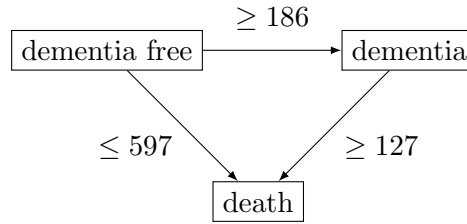


Figure 3: The exact number of transitions in the illness-death model with interval-censored time to disease is unknown.

- In case 6, if  $L_i < T_i$  then it is assumed that the subject may become ill between  $L_i$  and  $T_i$ . If  $L_i = T_i$  it is assumed that the subject is disease-free at time  $T_i$ . In the latter case the second part of the likelihood in equation OO equals zero.
- In all cases,  $L_i$  may be equal to the entry time.

## 5.2. Paquid study

In order to illustrate the functionality of the package we provide a random subset containing data from 1000 subjects that were enrolled in the Paquid study ([Letenneur et al. 1999](#)), a large cohort study on mental and physical aging.

```

1 library(SmoothHazard)
2 data(Paq1000)

```

The population consists of subjects aged 65 years and older living in Southwestern France. The event of interest is dementia and death without dementia is a competing risk. Furthermore, the time to dementia onset is interval censored between the diagnostic visit and the previous one and demented subjects are at risk of death. Thus, subjects who died without being diagnosed as demented at their last visit may have become demented between last visit and death.

In this subset 186 subjects are diagnosed as demented and 724 died from whom 597 without being diagnosed as demented before. Because of interval censoring more than 186 should have been demented, more than 127 should have been dead with dementia and less than 597 should have been dead without dementia (see Figure 5.2).

Age is chosen as the basic time scale and subjects are dementia-free (and alive) at entry into study. Consequently, we need to deal with left-truncated event times.

```

1 head(round(Paq1000,1))

```

	dementia	death	t0	l	r	t	certif	gender
1	1	1	72.3	82.3	84.7	87.9	0	0
2	0	1	77.9	78.9	78.9	79.6	0	1
3	0	1	79.9	79.9	79.9	80.9	0	0

4	0	1	74.7	78.6	78.6	82.9	1	1
5	0	1	76.7	76.7	76.7	79.2	0	1
6	0	0	66.2	71.4	71.4	84.2	1	0

Each row in the data corresponds to one subject. The variables **dementia** and **death** are the status variables (1 if an event occurred, 0 otherwise) for dementia and death, respectively. The variable **t0** contains ages of subjects at entry into study. The variables **l** and **r** contain the left and right endpoints of the censoring intervals. For demented subjects, **r** is the age at the diagnostic visit and **l** is the age at the previous one. For non demented subjects, **l** and **r** are the age at the latest visit without dementia ( $l=r$ ). The variable **t** is the age at death or at latest news on vital status. There are two binary covariates: **certif** for primary school diploma (762 with diploma and 238 without diploma) and **gender** (578 women and 422 men).

The function **idm** computes estimates for the three transition intensities  $\alpha_{01}(\cdot)$ ,  $\alpha_{02}(\cdot)$ ,  $\alpha_{12}(\cdot)$  which are age-specific incidence rate of dementia, age-specific mortality rate of dementia-free subjects and age-specific mortality rate of demented subjects, respectively. Proportional transition intensities regression models allow for covariates on each transition. Covariates are specified independently for the regression models of the three transition intensities by the right hand side of the respective formula **formula01**, **formula02** and **formula12**.

Interval censoring and left truncation must be specified at the left side of the formula arguments using the **Hist** function. For left-truncated data, the **entry** argument of **Hist** must contain the vector of delayed entry times. For interval-censored data, the **time** argument of **Hist** must contain a list of the left and right endpoints of the intervals. The **data** argument contains the data frame in which to interpret the variables of **formula01**, **formula02** and **formula12**. The left side of **formula12** argument does not need to be filled because all the data informations are already contained in **formula01** and **formula02**. The left side of **formula12** argument is required only if we want the covariates impacting transition 12 different from those impacting transition 02.

### 5.3. Fitting the illness-death model based on interval-censored data

The main function **idm** computes estimates for the three baseline transition intensities and for the regression parameters of an illness-death model. The **intensities** argument by specifying the form of the transition intensities allows to select either a parametric or a semi-parametric estimation method :

- With the default value **"Weib"**, a Weibull distribution is assumed for the baseline transition intensities and the parameters are estimated by maximizing the log-likelihood;
- With the **"Splines"** value, the estimation is conducted by maximizing a penalized log-likelihood where the transition intensities estimators are approximated by linear combinations of M-splines.

We stop the iterations of the maximization algorithm when the differences between two consecutive parameters values, log-likelihood values, and gradient values is small enough. The default convergence criteria are  $10^{-5}$ ,  $10^{-5}$  and  $10^{-3}$  and can be changed by means of the **eps** argument.

We now illustrate how to fit the illness-death model to the Paq1000 data set, based on interval-censored dementia times and exact death times.

In the following call, a Weibull parametrization is used for the three baseline transition intensities and we include two covariates on the transition to dementia, one covariate on the transition from no dementia to death and no covariates on the transition from dementia to death. Note that in case of missing formula12 argument the covariates on the  $1 \rightarrow 2$  transition are the same as the ones specified in the formula02 argument.

```
1 fit.weib <- idm(formula01=Hist(time=list(l,r),event=dementia,entry=t0)~certif+
  gender,
2     formula02=Hist(time=t,event=death,entry=t0)~gender,
3     formula12= ~ 1,
4     data=Paq1000)
5 fit.weib
```

Call:

```
idm(formula01 = Hist(time = list(l, r), event = dementia, entry = t0) ~
  certif + gender, formula02 = Hist(time = t, event = death,
  entry = t0) ~ gender, formula12 = ~1, data = Paq1000)
```

Illness-death model: Results of Weibull regression for the intensity functions.

```
number of subjects: 1000
number of events '0-->1': 186
number of events '0-->2' or '0-->1-->2': 724
number of covariates: 2 1 0
```

	coef	SE.coef	HR	CI	Wald	p.value
certif_01_01	-0.4117	0.1827	0.6625	[0.46;0.95]	5.077537	0.02424
gender_01_01	-0.2621	0.1561	0.7694	[0.57;1.04]	2.818281	0.09320
gender_02_02	0.6712	0.1144	1.9565	[1.56;2.45]	34.449070	< 0.0001

	Without cov	With cov
Log likelihood	-3075.308	-3053.648

Parameters of the Weibull distribution: 'S(t) = exp(-(b\*t)^a)'

	alpha01	alpha02	alpha12
a	11.12344747	8.82268030	6.44006723
b	0.01102198	0.01074539	0.01381268

----

Model converged.

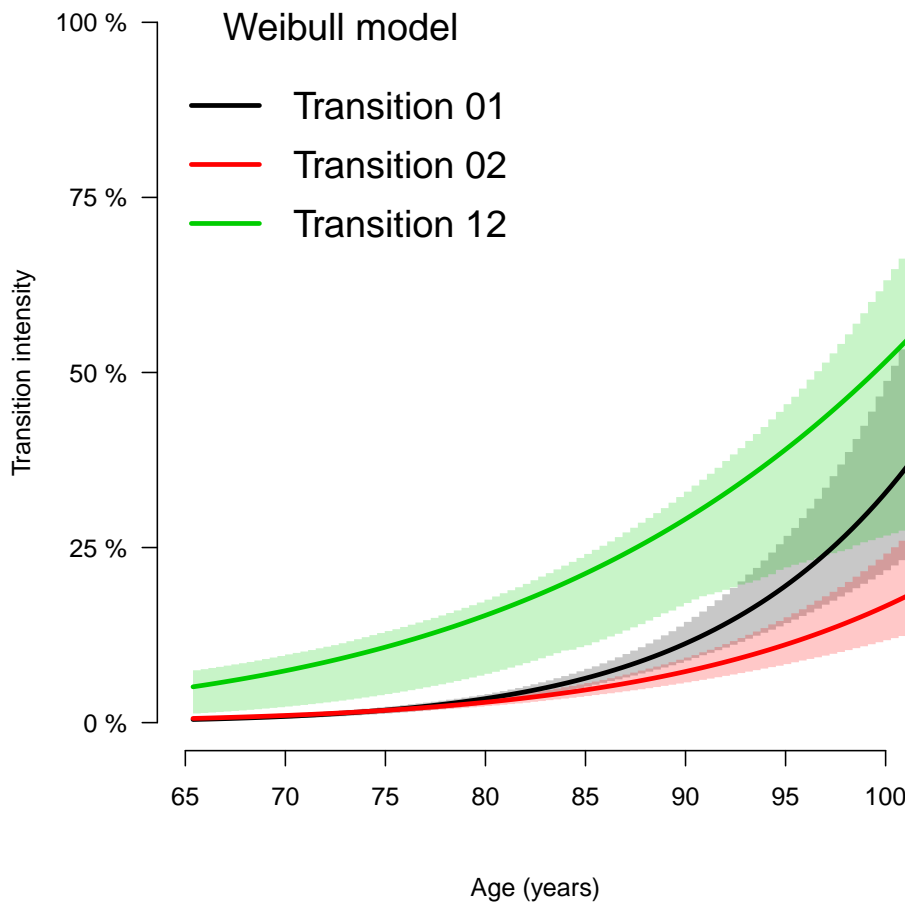
number of iterations: 7

convergence criteria: parameters= 0.00000000011  
: likelihood= 0.0000000023  
: second derivatives= 0.0000000000008

The hazard ratios  $HR(e^{\text{coef}})$  have the usual interpretation, as in a parametric Cox regression model.

The three baseline transition intensity functions can be displayed as functions of time, functions of age in our illustrative example (Figure 3).

```
1 par(mgp=c(4,1,0),mar=c(5,5,5,5))
2 plot(fit.weib,conf.int=TRUE,lwd=3,citype="shadow",xlim=c(65,100), axis2.las=2,
      axis1.at=seq(65,100,5),xlab="Age (years)")
```



The other estimation option in the function `idm` permits to relax the strict parametric assumptions of the Weibull regression models. With the option `intensities="Splines"`, linear combinations of M-splines are used to approximate the three baseline transition intensities. Although this option implies a considerable amount of extra computations (see Section 3.2), the call and the printed output are very similar to the Weibull model:

```
1 fit.splines <- idm(formula01=Hist(time=list(l,r),event=dementia,entry=t0)~certif+
  gender,
2   formula02=Hist(time=t,event=death,entry=t0)~gender,
```

```

3     formula12= ~ 1,
4     intensities="Splines",data=Paq1000)
5 fit.splines

```

Call:

```

idm(formula01 = Hist(time = list(l, r), event = dementia, entry = t0) ~
    certif + gender, formula02 = Hist(time = t, event = death,
    entry = t0) ~ gender, formula12 = ~1, data = Paq1000, intensities = "Splines")

```

Illness-death regression model using M-spline approximations  
of the baseline transition intensities.

```

number of subjects: 1000
number of events '0-->1': 186
number of events '0-->2' or '0-->1-->2': 724
number of subjects: 1000
number of covariates: 2 1 0

```

Smoothing parameters:

	transition01	transition02	transition12
knots	7	7	7
kappa	800000	200000	50000

	coef	SE.coef	HR	CI	Wald	p.value
certif_01_01	-0.3762	0.1853	0.6865	[0.48;0.99]	4.123243	0.0423
gender_01_01	-0.2297	0.1580	0.7948	[0.58;1.08]	2.112681	0.1461
gender_02_02	0.6529	0.1119	1.9211	[1.54;2.39]	34.038890	<0.0001

	Without cov	With cov
Penalized log likelihood	-3072.464	-3052.046

----

Model converged.

number of iterations: 9

convergence criteria: parameters= 0.000000028

: likelihood= 0.00000064

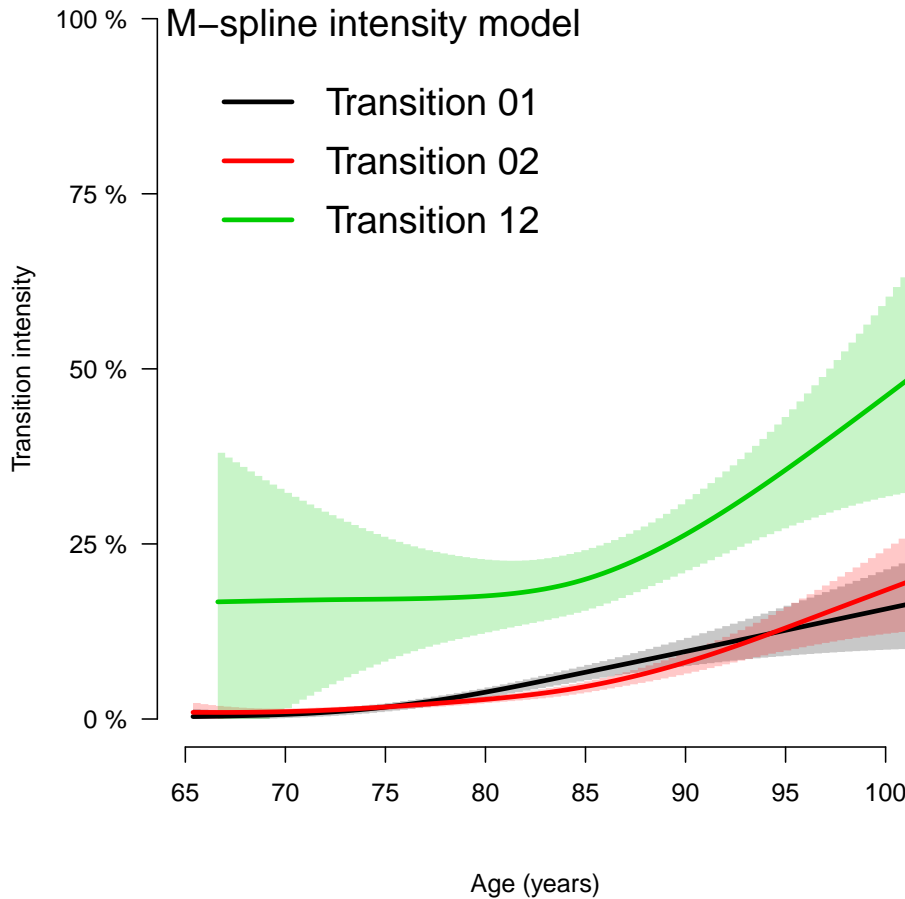
: second derivatives= 0.0000000016

Again, the estimated baseline transition intensities can conveniently be visualized in a joint graph (Figure 4).

```

1 par(mgp=c(4,1,0),mar=c(5,5,5,5))
2 plot(fit.splines,conf.int=TRUE,lwd=3,citype="shadow",xlim=c(65,100), axis2.las=2,
    axis1.at=seq(65,100,5),xlab="Age (years)")

```



*Semi-parametric estimation method: choice of smoothing parameters*

Some optional arguments are specific to the semi-parametric approach (when using the option `intensities="Splines"`):

- `n.knots` contains a vector (by default `c(7,7,7)`) specifying the number of knots on the  $0 \rightarrow 1$ ,  $0 \rightarrow 2$  and  $1 \rightarrow 2$  transitions, respectively;
- `knots` contains the choice of the knots placement (equidistant by default or quantile-based placement) or a list of sequences of knots for transitions  $0 \rightarrow 1$ ,  $0 \rightarrow 2$  and  $1 \rightarrow 2$ , respectively, to be specified by the user;
- `CV` (FALSE by default) is set to TRUE for using approximate leave-one-out cross-validation score to choose the smoothing parameters  $\kappa_{01}$ ,  $\kappa_{02}$ ,  $\kappa_{12}$ ;
- `kappa` contains the smoothing parameters if `CV=FALSE` (arbitrary choice of the smoothing parameters  $\kappa_{01}$ ,  $\kappa_{02}$ ,  $\kappa_{12}$ ); the initial smoothing parameters for the grid search method which maximize the approximate leave-one-out cross-validation score if `CV=TRUE`.

By default the function `idm` selects equidistant sequences of 7 knots between the minimal and maximal event times (`t0`, 1 and `r` for `Paq1000`). There must be a knot before or at the first time from which there are subjects at risk and after or at the last time of transition. The current implementation of our program requires a minimum of 4 knots for each transition intensity.

Consequently, the semi-parametric approach requires much more information than the parametric one to achieve convergence. The number of parameters to be estimated is larger, and enough observation times on each transition are required to fit the splines. In particular, in data sets where few  $1 \rightarrow 2$  transitions times are observed, we this approach is not recommended. Increasing the number of knots does not deteriorate the estimates of the transition intensities: this is because the degree of smoothing in the penalized likelihood method is tuned by the smoothing parameters  $\kappa_{01}$ ,  $\kappa_{12}$  and  $\kappa_{02}$ . On the other hand, once a sufficient number of knots is established, there is no advantage in adding more. Moreover, the more knots, the longer the running time. Some numerical problem can arise, particularly for a large number of knots. That is why the maximum number of knots is limited to 25. So it is recommended to start with a small number of knots (e.g. 5 or 7) and increase the number of knots until the graph of the transition intensities function remains unchanged (from our own experience rarely more than 12 knots).

The default values for the smoothing parameters are suitable for the `Paq1000` data set. However, these values can be expected to be very different depending on time scale, number of subjects and number of knots. The cross-validation option can be used to find appropriate smoothing parameters. However, the running time with cross-validation is very long and an empirical technique can be preferred. It consists in repeating the `idm` running trying different smoothing parameters. After each estimation, the transition intensities are plotted. This can be done with the `plot` function. If the curves seem too smooth it may be useful to reduce the associated smoothing parameter. Similarly, if the curves are too wiggly, the associated smoothing parameter may be increased.

## 5.4. Making predictions

The function `idm` returns an “`idmWeib`” or “`idmSplines`” class object depending on the parametrization of the transition intensities (Weibull or splines). A object as returned by the `idm` function can be used in argument of the `predict` function in order to obtain transition probabilities, cumulative probabilities of event and life expectancies with confidence intervals. For example, the following call give predictions regarding a 70 years-old female subject who do not have primary school diploma, over a 10 years horizon:

```
1 pred <- predict(fit.weib,s=70,t=80,Z01=c(1,1),Z02=1)
2 pred
```

`$p00`

```
[1] 0.6351952 0.5886665 0.6765563
```

`$p01`

```
[1] 0.04764996 0.03273026 0.07278779
```

`$p11`



```
[1] 0.333767 0.261300 0.683898
```

```
$p12
```

```
[1] 0.666233 0.316102 0.738700
```

```
$p02_0
```

```
[1] 0.2872955 0.2441831 0.3336892
```

```
$p02_1
```

```
[1] 0.02985929 0.01166756 0.04572470
```

```
$p02
```

```
[1] 0.3171548 0.2745690 0.3575900
```

```
$F01
```

```
[1] 0.07750924 0.05108109 0.11451963
```

```
$F0.
```

```
[1] 0.3648048 0.3234437 0.4113335
```

The covariates values must be specified in the Z01, Z02 and Z12 arguments in the same order as they were entered in the preceding `idm` call.

The output attributes are:

- for a dementia-free 70 years-old subject:
  - the probability of being still alive and dementia-free 10 years later  $p_{00}(70, 80)$ ,
  - the probability of being still alive but demented 10 years later  $p_{01}(70, 80)$ ,
  - the probability of dying in the next 10 years  $p_{02}(70, 80)$  having been demented before ( $p_{02}^1(70, 80)$ ) or not ( $p_{02}^0(70, 80)$ ),
  - the absolute risk of dementia in the 10 years (10 years later, the subject may have die or not)  $F_{01}(s, t)$ ,
  - the absolute risk of exit from state 0 in the 10 years  $F_{0\bullet}(s, t)$  (due to either dementia or death);
- for a demented 70 years-old subject: the probability of dying in the next 10 years  $p_{12}(s, t)$  or not  $p_{11}(s, t)$ .

The following calls give life expectancies regarding a 70 years-old female subject who do not have primary school diploma based on the transition intensities estimates from respectively the parametric approach and the semi-parametric approach:

```
1 LE.weib <- lifexpect(fit.weib,s=80,Z01=c(1,0),Z02=0)
2 LE.weib
```

```
$life.in.0.expectancy
```

```
[1] 8.868163 7.947171 9.820537
```

```
$life.expectancy.nondis
```

```
[1] 10.445056 9.746877 11.639649
```

```
$life.expectancy.dis
```

```
[1] 4.890873 4.427345 7.990467
```

```
1 LE.splines <- lifexpect(fit.splines,s=80,Z01=c(1,0),Z02=0,CI=FALSE)
2 LE.splines
```

```
$life.in.0.expectancy
```

```
[1] 8.817877
```

```
$life.expectancy.nondis
```

```
[1] 10.41731
```

```
$life.expectancy.dis
```

```
[1] 4.908891
```

The confidence intervals calculation may take time, especially using the splines estimates of the transition intensities. To suppress this calculation the `CI` argument must be set to `FALSE` (see above). The number of the simulations for calculating confidence intervals can also be modified using the `nsim` argument (by default 2000 for the `predict` function and 1000 for the `lifexpect` function).

The output attributes of the `lifexpect` function are:

- for a dementia-free 80 years-old subject:
  - the life expectancy in state 0 (healthy life expectancy),
  - the life expectancy;
- for a demented 80 years-old subject: the life expectancy.

### *Warnings regarding predictions*

Predictions using the splines estimates of the transition intensities are not possible if involving times prior to the first knot or times beyond the last knot. Moreover, the life expectancies are calculated using integration until infinity using the Weibull estimates and until the last knot using the splines estimates. Consequently, to calculate life expectancies using the splines estimates, we implicitly assume that the last knot time is the maximal time of death. The above life expectancies calculating from the Weibull estimates or the splines estimates of the transition intensities are very close because the follow-up period of the **Paq1000** data set is long. However, in other data sets this assumption may not hold anymore. Finally, to avoid numerical problem in the predictions calculations, the first and last knots must be the same or very close on each transition.

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