SemiCompRisks: An R Package for Independent and Cluster-Correlated Analyses of Semi-Competing Risks Data

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Abstract

Semi-competing risks refer to the setting where primary scientific interest lies in estimation and inference with respect to a non-terminal event, the occurrence of which is subject to a terminal event. In this paper, we present the R package SemiCompRisks that provides functions to perform the analysis of independent/clustered semi-competing risks data under the illness-death multi-state model. The package allows the user to choose the specification for model components from a range of options giving users substantial flexibility, including: accelerated failure time or proportional hazards regression models; parametric or non-parametric specifications for baseline survival functions; parametric or non-parametric specifications for random effects distributions when the data are cluster-correlated; and, a Markov or semi-Markov specification for terminal event following non-terminal event. While estimation is mainly performed within the Bayesian paradigm, the package also provides the maximum likelihood estimation for select parametric models. The package also includes functions for univariate survival analysis as complementary analysis tools.

Keywords: illness-death models, multi-state models, semi-competing risks, survival analysis.


1 Introduction

Semi-competing risks refer to the general setting where primary scientific interest lies in estimation and inference with respect to a non-terminal event (e.g., disease diagnosis), the occurrence of which is subject to a terminal event (e.g., death) (Fine et al., 2001; Jazić et al., 2016). When there is a strong association between two event times, naïve application of a univariate survival model for non-terminal event time will result in overestimation of outcome rates as the analysis treats the terminal event as an independent censoring mechanism (Haneuse and Lee, 2016). The semi-competing risks analysis framework appropriately treats the terminal event as a competing event and considers the dependence between non-terminal and terminal events as part of the model specification.

Toward formally describing the structure of semi-competing risks data, let $T_1$ and $T_2$ denote the times to the non-terminal and terminal events, respectively. From the modeling perspective, the focus in the semi-competing risks setting is to characterize the distribution $T_1$ and its potential relationship with the distribution of $T_2$, i.e. the joint distribution of $(T_1, T_2)$. For example, from an initial state (e.g., transplantation), as time progresses, a subject could make a transition into the non-terminal or terminal state (see Figure 1.a). In the case of a transition into the non-terminal state, the subject could subsequently transition into the terminal state even if these transitions cannot occur in the reverse order. The main disadvantage of the competing risks framework (see Figure 1.b) to the study of non-terminal event is that it does not utilize the information on the occurrence and timing of terminal event following the non-terminal event, which could be used to understand the dependence between the two events.

The current literature for the analysis of semi-competing risks data is composed of three approaches: methods that specify the dependence between non-terminal and terminal events via a copula (Fine et al., 2001; Wang, 2003; Jiang et al., 2005; Ghosh, 2006; Peng and Fine, 2007; Lakhal et al., 2008; Hsieh et al., 2008; Fu et al., 2013); methods based on multi-state models, specifically the so-called illness-death model (Liu et al., 2004; Putter et al., 2007; Ye et al., 2007; Kneib and Hennerfeind, 2008; Zeng and Lin, 2009; Xu et al., 2010; Zeng et al., 2012; Han et al., 2014; Zhang et al., 2014; Lee et al., 2015, 2016); and methods built upon the principles of causal inference (Zhang and Rubin, 2003; Egleston et al., 2007; Tchetgen Tchetgen, 2014; Varadhan et al., 2014).

The SemiCompRisks package is designed to provide a comprehensive suite of functions for
the analysis of semi-competing risks data based on the illness-death model, together with, as a complementary suite of tools, functions for the analysis of univariate time-to-event data. While Bayesian methods are used for estimation and inference for all available models, maximum likelihood estimation is also provided for select parametric models. Furthermore, SemiCompRisks offers flexible parametric and non-parametric specifications for baseline survival functions and cluster-specific random effects distributions under accelerated failure time and proportional hazards models. The functionality of the package covers methods proposed in a series of recent papers on the analysis of semi-competing risks data (Lee et al., 2015, 2016, 2017c).

The remainder of the paper is organized as follows. Section 2 summarizes existing R packages that provide methods for multi-state modeling, and explains the key contributions of the SemiCompRisks package. Section 3 introduces an on-going study of stem cell transplantation and provides a description of the data available in the package. Section 4 presents different specifications of models and estimation methods implemented in our package. Section 5 summarizes the core components of the SemiCompRisks package, including datasets, functions for fitting models, functions, the structure of output provided to analysts. Section 6 illustrates the usage of the main functions in the package through three semi-competing risks analyses of the stem cell transplantation data. Finally, Section 7 concludes with discussion and an overview of the
extensions we are working on.

2 Other packages and their features

As we elaborate upon below, the illness-death model for semi-competing risks, that is the focus on the SemiCompRisks package, is a special case of the broader class of multi-state models. Currently, there are numerous R packages that permit estimation and inference for a multi-state model and that could conceivably be used to analyze semi-competing risks data.

The mvna package computes the Nelson-Aalen estimator of the cumulative transition hazard for arbitrary Markov multi-state models with right-censored and left-truncated data, but it does not compute transition probability matrices (Allignol et al., 2008). The TPmsm implements non-parametric and semi-parametric estimators for the transition probabilities in 3-state models, including the Aalen-Johansen estimator and estimators that are consistent even without Markov assumption or in case of dependent censoring (Araújo et al., 2014). The p3state.msm package performs inference in an illness-death model (Meira-Machado and Roca-Pardiñas, 2011). Its main feature is the ability for obtaining non-Markov estimates for the transition probabilities. The etm package calculates the empirical transition probability matrices and corresponding variance estimates for any time-inhomogeneous multi-state model with finite state space and data subject to right-censoring and left-truncation, but it does not account for the influence of covariates (Allignol et al., 2011). The msm package is able to fit time-homogeneous Markov models to panel count data and hidden Markov models in continuous time (Jackson, 2011). The time-homogeneous Markov approach could be a particular case of the illness-death model, where interval-censored data can be considered. The tdc.msm package may be used to fit the time-dependent proportional hazards model and multi-state regression models in continuous time, such as Cox Markov model, Cox semi-Markov model, homogeneous Markov model, non-homogeneous piecewise model, and non-parametric Markov model (Meira-Machado et al., 2007). The SemiMarkov package performs parametric (Weibull or exponentiated Weibull specification) estimation in a homogeneous semi-Markov model (Król and Saint-Pierre, 2015). Moreover, the effects of covariates on the process evolution can be studied using a semi-parametric Cox model for the distributions of sojourn times. The flexsurv package provides functions for fitting and predicting from fully-parametric multi-state models with Markov or semi-Markov specification (Jackson, 2016). In addition, the multi-state models implemented in flexsurv give
the possibility to include interval-censoring and some of them also left-truncation. The `msSurv` package calculates non-parametric estimation of general multi-state models subject to independent right-censoring and possibly left-truncation (Ferguson et al., 2012). This package also computes the marginal state occupation probabilities along with the corresponding variance estimates, and lower and upper confidence intervals. The `mstate` package can be applied to right-censored and left-truncated data in semi-parametric or non-parametric multi-state models with or without covariates and it may also be used to competing risk models (Wreede et al., 2011). Specifically for Cox-type illness-death models to interval-censored data, we highlight the packages `coxinterval` (Boruvka and Cook, 2015) and `SmoothHazard` (Touraine et al., 2017), where the latter also allows that the event times to be left-truncated. Finally, the `frailtypack` package permits the analysis of correlated data under select clusterings, as well as the analysis of left-truncated data, through a focus on frailty models using penalized likelihood estimation or parametric estimation (Rondeau et al., 2012).

While these packages collectively provide broad functionality, each of them is either non-specific to semi-competing risks or only permits consideration of a narrow model specifications. In developing the `SemiCompRisks` package, the goal was to provide a single package within which a broad range of models and model specifications could be entertained. The `frailtypack` package, for example, can also be used to analyze cluster-correlated semi-competing risks data but it is restricted to the proportional hazards model with either patient-specific or cluster-specific random effects but not both (Liquet et al., 2012). Furthermore, estimation/inference is within the frequentist framework so that estimation of hospital-specific random effects, of particular interest in health policy applications (Lee et al., 2016), together with the quantification of uncertainty is incredibly challenging. This, however, is (relatively) easily achieved through the functionality of `SemiCompRisks` package. Given the breadth of the functionality of the package, in addition to the usual help files, we have developed a series of modelspecific vignettes which can be accessed through the CRAN (Lee et al., 2017b) or R command `vignette("SemiCompRisks")`, covering a total of 12 distinct model specifications.

3 CIBMTR data

The example dataset used throughout this paper was obtained from the Center for International Blood and Marrow Transplant Research (CIBMTR), a collaboration between the National Mar-
row Donor Program and the Medical College of Wisconsin representing a worldwide network of transplant centers (Lee et al., 2017a). For illustrative purposes, we consider a hypothetical study in which the goal is to investigate risk factors for grade III or IV acute graft-versus-host disease (GVHD) among 9,651 patients who underwent the first allogeneic hematopoietic cell transplant (HCT) between January 1999 and December 2011.

As summarized in Table 1, after administratively censoring follow-up at 365 days post-transplant, each patient can be categorized according to their observed outcome information into four groups: (i) acute GVHD and death; (ii) acute GVHD and censored for death; (iii) death without acute GVHD; and (iv) censored for both. Furthermore, for each patient, the following covariates are available: gender (Male, Female); age (<10, 10-19, 20-29, 30-39, 40-49, 50-59, 60+); disease type (AML, ALL, CML, MDS); disease stage (Early, Intermediate, Advanced); and HLA compatibility (Identical sibling, 8/8, 7/8).

We note that due to confidentiality considerations the original study outcomes ($time_1, time_2, event_1, event_2$: times and censoring indicators to the non-terminal and terminal events) are not available in SemiCompRisks package. As such we provide the five original covariates together with estimates of parameters from the analysis of CIBMTR data, so that one could simulate semi-competing risks outcomes (see the simulation procedure in Appendix B). Based on this, the data shown in Table 1 reflects simulated outcome data using 1405 as the seed.

4 The illness-death models for semi-competing risks data

We offer three flexible multi-state illness-death models for the analysis of semi-competing risks data: accelerated failure time (AFT) models for independent data; proportional hazards regression (PHR) models for independent data; and PHR models for cluster-correlated data. These models accommodate parametric or non-parametric specifications for baseline survival functions as well as a Markov or semi-Markov assumptions for terminal event following non-terminal event.

4.1 AFT models for independent semi-competing risks data

In the AFT model specification, we directly model the connection between event times and covariates (Wei, 1992). For the analysis of semi-competing risks data, we consider the following
|                        | N    | %    | Both acute GVHD & death | Acute GVHD & censored for death | Death without acute GVHD | Censored for both |
|------------------------|------|------|--------------------------|----------------------------------|--------------------------|------------------|
| Total subjects         | 9,651| 100.0| 9.5                      | 8.9                             | 28.8                     | 52.8             |
| Gender                 |      |      |                          |                                  |                          |                  |
| Male                   | 5,366| 55.6 | 9.7                      | 9.5                             | 28.1                     | 52.7             |
| Female                 | 4,285| 44.4 | 9.1                      | 8.3                             | 29.7                     | 52.9             |
| Age, years             |      |      |                          |                                  |                          |                  |
| <10                    | 653  | 6.8  | 5.0                      | 11.9                            | 23.4                     | 59.7             |
| 10-19                  | 1,162 | 12.0 | 8.0                      | 11.4                            | 24.0                     | 56.6             |
| 20-29                  | 1,572 | 16.3 | 9.7                      | 9.9                             | 27.4                     | 53.0             |
| 30-39                  | 1,581 | 16.4 | 9.8                      | 10.7                            | 28.5                     | 51.0             |
| 40-49                  | 2,095 | 21.7 | 11.0                     | 9.6                             | 29.7                     | 49.7             |
| 50-59                  | 2,008 | 20.8 | 9.8                      | 5.1                             | 32.3                     | 52.8             |
| 60+                    | 580  | 6.0  | 9.9                      | 4.8                             | 33.1                     | 52.2             |
| Disease type           |      |      |                          |                                  |                          |                  |
| AML                    | 4,919 | 51.0 | 8.2                      | 8.0                             | 30.3                     | 53.5             |
| ALL                    | 2,071 | 21.5 | 9.9                      | 9.0                             | 29.3                     | 51.8             |
| CML                    | 1,525 | 15.8 | 12.1                     | 11.3                            | 22.2                     | 54.4             |
| MDS                    | 1,136 | 11.8 | 11.0                     | 10.0                            | 30.0                     | 49.0             |
| Disease status         |      |      |                          |                                  |                          |                  |
| Early                  | 4,873 | 50.5 | 8.4                      | 11.0                            | 23.6                     | 57.0             |
| Intermediate           | 2,316 | 24.0 | 9.7                      | 8.5                             | 30.1                     | 51.7             |
| Advanced               | 2,462 | 25.5 | 11.5                     | 5.4                             | 37.7                     | 45.4             |
| HLA compatibility      |      |      |                          |                                  |                          |                  |
| Identical sibling      | 3,941 | 40.8 | 7.4                      | 8.5                             | 26.3                     | 57.8             |
| 8/8                    | 4,100 | 42.5 | 10.5                     | 9.7                             | 30.3                     | 49.5             |
| 7/8                    | 1,610 | 16.7 | 12.2                     | 8.1                             | 30.9                     | 48.8             |

Table 1: Covariate and simulated outcome information for 9,651 patients who underwent the first HCT between 1999-2011 with administrative censoring at 365 days.

AFT model specifications under the illness-death modeling framework (Lee et al., 2017c):

\[
\log(T_{i1}) = x_{i1}^\top \beta_1 + \gamma_i + \epsilon_{i1}, \quad T_{i1} > 0,
\]

\[
\log(T_{i2}) = x_{i2}^\top \beta_2 + \gamma_i + \epsilon_{i2}, \quad T_{i2} > 0,
\]

\[
\log(T_{i2} - T_{i1}) = x_{i3}^\top \beta_3 + \gamma_i + \epsilon_{i3}, \quad T_{i2} > T_{i1},
\]

where \(T_{i1}\) and \(T_{i2}\) denote the times to the non-terminal and terminal events, respectively, from subject \(i = 1, \ldots, n\), \(x_{i\cdot}\) is a vector of transition-specific covariates, \(\beta_g\) is a corresponding vector of transition-specific regression parameters, and \(\epsilon_{i\cdot}\) is a transition-specific random variable whose distribution determines that of the corresponding transition time, \(g \in \{1, 2, 3\}\). Finally, in
each of (1)-(3), $\gamma_i$ is a study subject-specific random effect that induces positive dependence between the two event times. We assume that $\gamma_i$ follows a Normal$(0, \theta)$ distribution and adopt a conjugate inverse Gamma distribution, denoted by $\text{IG}(a(\theta), b(\theta))$ for the variance component $\theta$. For regression parameters $\beta_g$, we adopt non-informative flat prior on the real line.

From models (1)-(3), we can adopt either a fully parametric or a semi-parametric approach depending on the specification of the distributions for $\epsilon_{i1}$, $\epsilon_{i2}$, $\epsilon_{i3}$. We build a parametric modeling based on the log-Normal formulation, where $\epsilon_{ig}$ follows a Normal($\mu_g, \sigma^2_g$) distribution. As an alternative, a semi-parametric framework can be considered by adopting independent non-parametric Dirichlet process mixtures (DPM) of $M_g$ Normal($\mu_{gr}, \sigma^2_{gr}$) distributions, $r \in \{1, \ldots, M_g\}$, for each $\epsilon_{ig}$. Following convention in the literature, we refer to each component Normal distribution as being specific to some “class” (Neal, 2000). Since the class-specific $(\mu_{gr}, \sigma^2_{gr})$ are unknown, they are assumed to be draws from a so-called the centering distribution. Specifically, we take a Normal distribution centered at $\mu_{g0}$ with a variance $\sigma^2_{g0}$ for $\mu_{gr}$ and an $\text{IG}(a_{gr}, b_{gr})$ for $\sigma^2_{gr}$. Furthermore, since the “true” class membership for any given study subject is unknown, we let $p_{gr}$ denote the probability of belonging to the $r$th class for transition $g$ and $\mathbf{p}_g = (p_{g1}, \ldots, p_{gM_g})^T$ the collection of such probabilities. In the absence of prior knowledge regarding the distribution of class memberships for the $n$ subjects across the $M_g$ classes, $\mathbf{p}_g$ is assumed to follow a conjugate symmetric Dirichlet($\tau_g/M_g, \ldots, \tau_g/M_g$) distribution, where $\tau_g$ is referred to as the precision parameter (for more details, see Lee et al., 2017c).

Our AFT modeling framework can also handle interval-censored and/or left-truncated semi-competing risks data. Suppose that subject $i$ was observed at follow-up times $\{c_{i1}, \ldots, c_{imi}\}$ and let $c^*_i$ and $L_i$ denote the time to the end of study (or administrative right-censoring) and the time at study entry (i.e., the left-truncation time), respectively. Considering interval-censoring for both events, $T_{i1}$ and $T_{i2}$, for $i = 1, \ldots, n$, satisfy $c_{ij} \leq T_{i1} < c_{ij+1}$ for some $j$ and $c_{ik} \leq T_{i2} < c_{ik+1}$ for some $k$, respectively. Therefore, the observed outcome information for interval-censored and left-truncated semi-competing risks data for the subject $i$ can be represented by $\{L_i, c_{ij}, c_{ij+1}, c_{ik}, c_{ik+1}\}$.

### 4.2 PHR models for independent semi-competing risks data

We consider an illness-death multi-state model with proportional hazards assumptions characterized by three hazard functions (see Figure 1.a) that govern the rates at which subjects...
transition between the states: a cause-specific hazard for non-terminal event, \( h_1(t_{i1}) \); a cause-specific hazard for terminal event, \( h_2(t_{i2}) \); and a hazard for terminal event conditional on a time for non-terminal event, \( h_3(t_{i2} \mid t_{i1}) \). We consider the following specification for hazard functions (Xu et al., 2010; Lee et al., 2015):

\[
\begin{align*}
  h_1(t_{i1} \mid \gamma_i, x_{i1}) &= \gamma_i h_{01}(t_{i1}) \exp(x_{i1}^\top \beta_1), \quad t_{i1} > 0, \quad (4) \\
  h_2(t_{i2} \mid \gamma_i, x_{i2}) &= \gamma_i h_{02}(t_{i2}) \exp(x_{i2}^\top \beta_2), \quad t_{i2} > 0, \quad (5) \\
  h_3(t_{i2} \mid t_{i1}, \gamma_i, x_{i3}) &= \gamma_i h_{03}(z(t_{i1}, t_{i2})) \exp(x_{i3}^\top \beta_3), \quad t_{i2} > t_{i1}, \quad (6)
\end{align*}
\]

where \( h_{0g} \) is an unspecified baseline hazard function and \( \beta_g \) is a vector of log-hazard ratio regression parameters associated with the covariates \( x_{ig} \). Finally, in each of (4)-(6), \( \gamma_i \) is a study subject-specific shared frailty following a Gamma(\( \theta^{-1}, \theta^{-1} \)) distribution, parametrized so that \( E[\gamma_i] = 1 \) and \( V[\gamma_i] = \theta \). The model (6) is referred to as being Markov or semi-Markov depending on whether we assume \( z(t_{i1}, t_{i2}) = t_{i2} \) or \( z(t_{i1}, t_{i2}) = t_{i2} - t_{i1} \), respectively.

The Bayesian approach for models (4)-(6) requires the specification of prior distributions for unknown parameters. For the regression parameters \( \beta_g \), we adopt a non-informative flat prior distribution on the real line. For the variance in the subject-specific frailties, \( \theta \), we adopt a Gamma(\( a(\theta), b(\theta) \)) for the precision \( \theta^{-1} \). For the parametric specification for baseline hazard functions, we consider a Weibull model: \( h_{0g}(t) = \alpha_g \kappa_g t^{\alpha_g-1} \). We assign a Gamma(\( a_g^{(\alpha)}, b_g^{(\alpha)} \)) for \( \alpha_g \) and a Gamma(\( c_g^{(\kappa)}, d_g^{(\kappa)} \)) for \( \kappa_g \). As an alternative, a non-parametric piecewise exponential model (PEM) is considered for baseline hazard functions based on taking each of the log-baseline hazard functions to be a flexible mixture of piecewise constant function. Let \( s_{g,\text{max}} \) denote the largest observed event time for each transition and construct a finite partition of the time axis, \( 0 = s_{g,0} < s_{g,1} < s_{g,2} < \ldots < s_{g,K_g+1} = s_{g,\text{max}} \). Letting \( \lambda_g = (\lambda_{g,1}, \ldots, \lambda_{g,K_g}, \lambda_{g,K_g+1})^\top \) denote the heights of the log-baseline hazard function on the disjoint intervals based on the time splits \( s_g = (s_{g,1}, \ldots, s_{g,K_g+1})^\top \), we assume that \( \lambda_g \) follows a multivariate Normal distribution (MVN), \( \text{MVN}(\mu_{\lambda_g}, \Sigma_{\lambda_g}) \), where \( \mu_{\lambda_g} \) is the overall mean, \( \sigma_{\lambda_g}^2 \) represents a common variance component for the \( K_g + 1 \) elements, and \( \Sigma_{\lambda_g} \) specifies the covariance structure these elements. We adopt a flat prior on the real line for \( \mu_{\lambda_g} \) and a conjugate Gamma(\( a_g^{(\sigma)}, b_g^{(\sigma)} \)) distribution for the precision \( \sigma_{\lambda_g}^{-2} \). In order to relax the assumption of fixed partition of the time scales, we adopt a Poisson(\( a_g^{(K)} \)) prior for the number of splits, \( K_g \), and conditioned on the number of splits, we
consider locations, \( s_g \), to be a priori distributed as the even-numbered order statistics:

\[
\pi(s_g | K_g) \propto \frac{(2K_g + 1)! \prod_{k=1}^{K_g+1} (s_{g,k} - s_{g,k-1})}{(s_g, K_g + 1)^{2K_g + 1}}.
\]

Note that the prior distributions of \( K_g \) and \( s_g \) jointly form a time-homogeneous Poisson process prior for the partition \((K_g, s_g)\). For more details, see Lee et al. (2015).

### 4.3 PHR models for cluster-correlated semi-competing risks data

Lee et al. (2016) proposed hierarchical models that accommodate correlation in the joint distribution of the non-terminal and terminal events across patients for the setting where patients are clustered within hospitals. The hierarchical models for cluster-correlated semi-competing risks data build upon the illness-death model given in (4)-(6). Let \( T_{ji1} \) and \( T_{ji2} \) denote the times to the non-terminal and terminal events for the \( i \)-th subject in the \( j \)-th cluster, respectively, for \( i = 1, \ldots, n_j \) and \( j = 1, \ldots, J \). The general modeling specification is given by:

\[
\begin{align*}
    h_1(t_{ji1} | \gamma_{ji}, x_{ji1}, V_{j1}) &= \gamma_{ji} h_{01}(t_{ji2}) \exp(x_{ji1}^\top \beta_1 + V_{j1}), \ t_{ji1} > 0, \\
    h_2(t_{ji2} | \gamma_{ji}, x_{ji2}, V_{j2}) &= \gamma_{ji} h_{02}(t_{ji2}) \exp(x_{ji2}^\top \beta_2 + V_{j2}), \ t_{ji2} > 0, \quad (8) \\
    h_3(t_{ji2} | t_{ji1}, \gamma_{ji}, x_{ji3}, V_{j3}) &= \gamma_{ji} h_{03}(z(t_{ji1}, t_{ji2})) \exp(x_{ji3}^\top \beta_3 + V_{j3}), \ t_{ji2} > t_{ji1}, \quad (9)
\end{align*}
\]

where \( h_{0g} \) is an unspecified baseline hazard function and \( \beta_g \) is a vector of log-hazard ratio regression parameters associated with the covariates \( x_{jig} \). A study subject-specific shared frailty \( \gamma_{ji} \) is assumed to follow a Gamma(\( \theta^{-1}, \theta^{-1} \)) distribution and \( V_j = (V_{j1}, V_{j2}, V_{j3})^\top \) is a vector of cluster-specific random effects, each specific to one of the three possible transitions.

From a Bayesian perspective for models (8)-(10), we can adopt either a parametric Weibull or non-parametric PEM specification for baseline hazard functions \( h_{0g} \) with their respective configurations of prior distributions analogous to those outlined in Section 4.2. For the parametric specification of cluster-specific random effects, we assume that \( V_j \) follows MVN\(_3\)(0, \( \Sigma_V \)) distribution. We adopt a conjugate inverse-Wishart(\( \Psi_v, \rho_v \)) prior for the variance-covariance matrix \( \Sigma_V \). For the non-parametric specification, we adopt a DPM of MVN distributions with a centering distribution, \( G_0 \), and a precision parameter, \( \tau \). Here we take \( G_0 \) to be a multivariate Normal/inverse-Wishart (NIW) distribution for which the probability density function can be expressed as the product:

\[
f_{\text{NIW}}(\mu, \Sigma | \Psi_0, \rho_0) = f_{\text{MVN}}(\mu | 0, \Sigma) \times f_{\text{inverse-Wishart}}(\Sigma | \Psi_0, \rho_0), \quad (11)
\]
where $\Psi_0$ and $\rho_0$ are the hyperparameters of $f_{\text{NIW}}(\cdot)$. We assign a Gamma($a_\tau, b_\tau$) prior distribution for $\tau$. Finally, for $\beta_g$ and $\theta$, we adopt the same priors as those adopted for the model in Section 4.2. For more details, see Lee et al. (2016).

### 4.4 Estimation and inference

Bayesian estimation and inference is available for all models in the SemiCompRisks. Additionally, one may also choose to use maximum likelihood estimation for the parametric Weibull PHR model described in Section 4.2.

To perform Bayesian estimation and inference, we use a random scan Gibbs sampling algorithm to generate samples from the full posterior distribution. Depending on the complexity of the model adopted, the Markov chain Monte Carlo (MCMC) scheme may also include additional strategies, such as Metropolis-Hastings and reversible jump MCMC (Metropolis-Hastings-Green) steps. Specific details of each implementation can be seen in the online supplemental materials of Lee et al. (2015, 2016, 2017c).

### 5 Package description

The SemiCompRisks package contains three key functions, FreqID_HReg, BayesID_HReg and BayesID_AFT, focused on models for semi-competing risks data as well as the analogous univariate survival models, FreqSurv_HReg, BayesSurv_HReg and BayesSurv_AFT. It also provides two auxiliary functions, initiate.startValues_HReg and initiate.startValues_AFT, that can be used to generate initial values for Bayesian estimation; simID and simSurv functions for simulating semi-competing risks and univariate survival data, respectively; five covariates and parameter estimates from CIBMTR data; and the BMT dataset referring to 137 bone marrow transplant patients.

#### 5.1 Summary of functionality

Table 2 shows the modeling options implemented in the SemiCompRisks package for both semi-competing risks and univariate analysis. Specifically, we categorize the approaches based on the analysis type (semi-competing risks or univariate), the survival model (AFT or PHR), data type (independent or clustered), accommodation to left-truncation and/or interval-censoring in addition to right-censoring, and also statistical paradigms (frequentist or Bayesian).
| Analysis          | Model | Data type | L-T and/or I-C | Statistical paradigm |
|-------------------|-------|-----------|----------------|----------------------|
| Semi-competing    | AFT   | Independent | No             | B                    |
|                   |       | Yes        | Yes             | B                    |
|                   |       | No         | x               |                      |
|                   |       | Yes        | x               |                      |
|                   | PHR   | Independent | No             | B & F                |
|                   |       | Yes        | x               |                      |
|                   |       | No         | B               |                      |
|                   |       | Yes        | x               |                      |
|                   | AFT   | Independent | No             | B                    |
|                   |       | Yes        | B               |                      |
|                   |       | Cl�usted | No             | B                    |
|                   |       | Yes        | x               |                      |
|                   | PHR   | Independent | No             | B & F                |
|                   |       | Yes        | x               |                      |
|                   |       | Clusteded | No             | B                    |
|                   |       | Yes        | x               |                      |
| Univariate        | AFT   | Independent | No             | B                    |
|                   |       | Yes        | B               |                      |
|                   |       | Clusteded | No             | x                    |
|                   |       | Yes        | x               |                      |
|                   | PHR   | Independent | No             | B & F                |
|                   |       | Yes        | x               |                      |
|                   |       | Clusteded | No             | B                    |
|                   |       | Yes        | x               |                      |

L-T: left-truncation; I-C: interval-censoring; B: Bayesian; F: frequentist; x: not available

Table 2: Models implemented in the SemiCompRisks package.

The full description of functionality of the SemiCompRisks package can be accessed through the R command `help("SemiCompRisks")` or `vignette("SemiCompRisks")` which provides in detail the specification of all models implemented in the package. Below we describe the input data format and some crucial arguments for defining and fitting a model for semi-competing risks data using the SemiCompRisks package.

5.1.1 Model specification

From a semi-competing risks dataset, we jointly define the outcomes and covariates in a `Formula` object. Here we use the simCIBMTR dataset, obtained from the simulation procedure presented in Appendix B:

```r
R> form <- Formula(time1 + event1 | time2 + event2 ~ dTypeALL + dTypeCML +
+                     dTypeMDS + sexP | dTypeALL + dTypeCML + dTypeMDS | dTypeALL +
+                     dTypeCML + dTypeMDS)
```

The outcomes `time1`, `time2`, `event1` and `event2` denote the times and censoring indicators to the non-terminal and terminal events, respectively, and the covariates of each hazard function
are separated by | (vertical bar).

The specification of the Formula object varies slightly if the semi-competing risks model accommodates left-truncated and/or interval-censored data (see vignette documentation Lee et al. (2017b)).

### 5.1.2 Critical arguments

Most functions for semi-competing risks analysis in the **SemiCompRisks** package take common arguments. These arguments and their descriptions are shown as follows:

- **id**: a vector of cluster information for \( n \) subjects, where cluster membership corresponds to one of the positive integers 1, \ldots, \( J \).

- **model**: a character vector that specifies the type of components in a model. It can have up to three elements depending on the model specification. The first element is for the assumption on \( h_3 \): “semi-Markov” or “Markov”. The second element is for the specification of baseline hazard functions for PHR models - “Weibull” or “PEM” - or baseline survival distribution for AFT models - “LN” (log-Normal) or “DPM”. The third element needs to be set only for clustered semi-competing risks data and is for the specification of cluster-specific random effects distribution: “MVN” or “DPM”.

- **hyperParams**: a list containing vectors for hyperparameter values in hierarchical models.

- **startValues**: a list containing vectors of starting values for model parameters.

- **mcmcParams**: a list containing variables required for MCMC sampling.

Hyperparameter values, starting values for model parameters, and MCMC arguments depend on the specified Bayesian model and the assigned prior distributions. For a list of illustrations, see vignette documentation Lee et al. (2017b).

### 5.2 FreqID_HReg

The function **FreqID_HReg** fits Weibull PHR models for independent semi-competing risks data, as in (4)-(6), based on maximum likelihood estimation. Its default structure is given by

\[
\text{FreqID_HReg(Formula, data, model="semi-Markov", frailty=TRUE),}
\]
where Formula represents the outcomes and the linear predictors jointly, as presented in Section 5.1; data is a data frame containing the variables named in Formula; model is one of the critical arguments of the SemiCompRisks package (see Section 5.1), in which it specifies the type of model based on the assumption on $h_3(t_{i2} \mid t_{i1}, \cdot)$ in (6). Here, model can be “Markov” or “semi-Markov”. Finally, frailty is a logical value (TRUE or FALSE) to determine whether to include the subject-specific shared frailty term $\gamma$ into the illness-death model.

5.3 BayesID_HReg

The function BayesID_HReg fits parametric and semi-parametric PHR models for independent or cluster-correlated semi-competing risks data, as in (4)-(6) or (8)-(10), based on Bayesian inference. Its default structure is given by

BayesID_HReg(Formula, data, id=NULL, model=c("semi-Markov","Weibull"), hyperParams, startValues, mcmcParams, path=NULL)

Formula and data are analogous to the previous case; id, model, hyperParams, startValues, and mcmcParams are all critical arguments of the SemiCompRisks package (see Section 5.1), where id indicates the cluster that each subject belongs to (for independent data, id=NULL); model allows us to specify either “Markov” or “semi-Markov” assumption, whether the priors for baseline hazard functions are parametric (“Weibull”) or non-parametric (“PEM”), and whether the cluster-specific random effects distribution is parametric (“MVN”) or non-parametric (“DPM”). The third element of model is only required for models for clustered-correlated data given in (8)-(10).

The hyperParams argument defines all model hyperparameters: theta (a numeric vector for hyperparameters, $a^{(\theta)}$ and $b^{(\theta)}$, in the prior of subject-specific frailty variance component), WB (a list containing numeric vectors for Weibull hyperparameters $(a^{(\alpha)}_g, b^{(\alpha)}_g)$ and $(c^{(\kappa)}_g, d^{(\kappa)}_g)$ for $g \in \{1,2,3\}$: WB.ab1, WB.ab2, WB.ab3, WB.cd1, WB.cd2, WB.cd3), PEM (a list containing numeric vectors for PEM hyperparameters $(a^{(\sigma)}_g, b^{(\sigma)}_g)$, and $\alpha^{(K)}_g$ for $g \in \{1,2,3\}$: PEM.ab1, PEM.ab2, PEM.ab3, PEM.alpha1, PEM.alpha2, PEM.alpha3); and for the analysis of clustered semi-competing risks data, additional components are required: MVN (a list containing numeric vectors for MVN hyperparameters $\Psi_v$ and $\rho_v$: Psi_v, rho_v), DPM (a list containing numeric vectors for DPM hyperparameters $\Psi_0$, $\rho_0$, $a_\tau$, and $b_\tau$: Psi0, rho0, aTau, bTau).
The `startValues` argument specifies initial values for model parameters. This specification can be done manually or through the auxiliary function `initiate.startValues_HReg`. The `mcmcParams` argument sets the information for MCMC sampling: `run` (a list containing numeric values for setting for the overall run: `numReps`, total number of scans; `thin`, extent of thinning; `burninPerc`, the proportion of burn-in), `storage` (a list containing numeric values for storing posterior samples for subject- and cluster-specific random effects: `nGam.save`, the number of \( \gamma \) to be stored; `storeV`, a vector of three logical values to determine whether all the posterior samples of \( V_j \), for \( j = 1, \ldots, J \) are to be stored), `tuning` (a list containing numeric values relevant to tuning parameters for specific updates in Metropolis-Hastings-Green (MHG) algorithm: `mhProp_theta_var`, the variance of proposal density for \( \theta \); `mhProp_Vg_var`, the variance of proposal density for \( V_j \) in DPM models; `mhProp_alphag_var`, the variance of proposal density for \( \alpha_g \) in Weibull models; `Cg`, a vector of three proportions that determine the sum of probabilities of choosing the birth and the death moves in PEM models (the sum of the three elements should not exceed 0.6); `delPertg`, the perturbation parameters in the birth update in PEM models (the values must be between 0 and 0.5); `rj.scheme`: if `rj.scheme=1`, the birth update will draw the proposal time split from \( 1:s_g{\max} \) and if `rj.scheme=2`, the birth update will draw the proposal time split from uniquely ordered failure times in the data. For PEM models, additional components are required: `kg_max`, the maximum number of splits allowed at each iteration in MHG algorithm for PEM models; `time_lambda1`, `time_lambda2`, `time_lambda3`, time points at which the posterior distribution of log-hazard functions are calculated. Finally, `path` indicates the name of directory where the results are saved. For more details and examples, see Lee et al. (2017b).

5.4 BayesID_AFT

The function `BayesID_AFT` fits parametric and semi-parametric AFT models for independent semi-competing risks data, given in (1)-(3), based on Bayesian inference. Its default structure is given by

\[
\text{BayesID_AFT(} \text{Formula, data, model="LN", hyperParams, startValues, mcmcParams, path=NULL)}
\]

where `data, startValues` (auxiliary function `initiate.startValues_AFT`), and `path` are analogous to functions described in previous sections. Here, `Formula` has a different structure.
of outcomes, since the AFT model accommodates more complex censoring, such as interval-censoring and/or left-truncation (see Section 4.1). It takes the generic form \( h(t_i \mid y_1 L + y_1 U \mid y_2 L + y_2 U \quad \text{cov1} \mid \text{cov2} \mid \text{cov3}) \), where \( LT \) represents the left-truncation time, \((y_1 L, y_1 U)\) and \((y_2 L, y_2 U)\) are the interval-censored times to the non-terminal and terminal events, respectively, and \( \text{cov1}, \text{cov2} \) and \( \text{cov3} \) are covariates of each linear regression. The \texttt{model} argument specifies whether the baseline survival distribution is parametric (“LN”) or non-parametric (“DPM”). The \texttt{hyperParams} argument defines all model hyperparameters: \texttt{theta} is for hyperparameters \((a(\theta), b(\theta))\); \texttt{LN} is a list containing numeric vectors, \texttt{LN.ab1}, \texttt{LN.ab2}, \texttt{LN.ab3}, for log-Normal hyperparameters \((a_g, b_g)\) with \( g \in \{1, 2, 3\} \); \texttt{DPM} is a list containing numeric vectors, \texttt{DPM.mu1}, \texttt{DPM.mu2}, \texttt{DPM.mu3}, \texttt{DPM.sigSq1}, \texttt{DPM.sigSq2}, \texttt{DPM.sigSq3}, \texttt{DPM.ab1}, \texttt{DPM.ab2}, \texttt{DPM.ab3}, \texttt{Tau.ab1}, \texttt{Tau.ab2}, \texttt{Tau.ab3} for DPM hyperparameters \((\mu_g, \sigma^2_g), (a_g, b_g)\) with \( g \in \{1, 2, 3\} \). The \texttt{mcmcParams} argument sets the information for MCMC sampling: \texttt{run} (see Section 5.3), \texttt{storage} (\texttt{nGam.save}; \texttt{nY1.save}, the number of \( y_1 \) to be stored; \texttt{nY2.save}, the number of \( y_2 \) to be stored; \texttt{nY1.NA.save}, the number of \( y_1==\text{NA} \) to be stored), \texttt{tuning} (\texttt{betag.prop.var}, the variance of proposal density for \( \beta_g \); \texttt{mug.prop.var}, the variance of proposal density for \( \mu_g \); \texttt{zetag.prop.var}, the variance of proposal density for \( 1/\sigma^2_g \); \texttt{gamma.prop.var}, the variance of proposal density for \( \gamma \)).

5.5 Univariate survival data analysis

The functions \texttt{FreqSurv.HReg}, \texttt{BayesSurv.HReg} and \texttt{BayesSurv.AFT} provide the same flexibility as functions \texttt{FreqID.HReg}, \texttt{BayesID.HReg} and \texttt{BayesID.AFT}, respectively, but in a univariate context (i.e., a single outcome).

The function \texttt{FreqSurv.HReg} fits a Weibull PHR model based on maximum likelihood estimation. This model is described by:

\[
h(t_i \mid x_i) = \alpha \kappa t_i^{\alpha - 1} \exp(x_i^\top \beta), \quad t_i > 0.
\]

The function \texttt{BayesSurv.HReg} implements Bayesian PHR models given by:

\[
h(t_{ji} \mid x_{ji}) = h_0(t_{ji}) \exp(x_{ji}^\top \beta + V_j), \quad t_i > 0,
\]

We can adopt either a parametric Weibull or a non-parametric PEM specification for \( h_0 \). Cluster-specific random effects \( V_j, j = 1, \ldots, J \), can be assumed to follow a parametric Normal distribution or a non-parametric DPM of Normal distributions.
Finally, the function `BayesSurv_AFT` implements Bayesian AFT models expressed by:

$$\log(T_i) = x_i^\top \beta + \epsilon_i, \quad T_i > 0, \quad (14)$$

where we can adopt either a fully parametric log-Normal or a non-parametric DPM specification for $\epsilon_i$.

5.6 Summary output

The functions presented in Sections 5.2, 5.3 and 5.4 return objects of classes `Freq_HReg`, `Bayes_HReg` and `Bayes_AFT`, respectively. Each of these objects represents results from its respective semi-competing risks analysis. These results can be visualized using several R methods, such as `print`, `summary`, `predict`, `plot`, `coef`, and `vcov`.

The function `print` shows the estimated parameters and, in the Bayesian case, also the MCMC description (number of chains, scans, thinning, and burn-in) and the potential scale reduction factor (PSRF) convergence diagnostic for each model parameter (Gelman and Rubin, 1992; Brooks and Gelman, 1998). If the PSRF is close to 1, a group of chains have mixed well and have converged to a stable distribution. The function `summary` presents the regression parameters in exponential format (hazard ratios) and the estimated baseline hazard function components.

Functions `predict` and `plot` complement each other. The former uses the fitted model to predict an output of interest (survival or hazard) at a given time interval from new covariates. From the object created by `predict`, `plot` displays survival (`plot.est="Surv"`) or hazard (`plot.est="Haz"`) functions with their respective 95% confidence/credibility intervals.

Additionally, `SemiCompRisks` provides the standard functions `coef` (model coefficients) and `vcov` (variance-covariance matrix for a fitted frequentist model). For examples with more details, see Lee et al. (2017b).

5.7 Simulation of semi-competing risks data

The function `simID` simulates semi-competing risks outcomes from independent or cluster-correlated data (for more details of the simulation algorithm, see Appendix A). The simulation is based on a semi-Markov Weibull PHR modeling and, in the case of the cluster-correlated approach, the cluster-specific random effects follow a MVN distribution. We provide a simulation example of independent semi-competing risks data in Appendix B.
Analogously, the function simSurv simulates univariate independent/cluster-correlated survival data under a Weibull PHR model with cluster-specific random effects following a Normal distribution.

5.8 Datasets

CIBMTR data. It is composed of 5 covariates that come from a study of acute GVHD with 9,651 patients who underwent the first allogeneic hematopoietic cell transplant between January 1999 and December 2011 (see Section 3).

BMT data. It refers to a well-known study of bone marrow transplantation for acute leukemia (Klein and Moeschberger, 2003). This data frame contains 137 patients with 22 variables and its description can be viewed from the R command help(BMT).

6 Illustration: Stem Cell Transplantation data

In our first example we employ the modeling (4)-(6) for independent data, semi-Markov assumption and Weibull baseline hazards. Here, Formula (form) is defined as in Section 5.1. We fit the model using the function FreqID_HReg, described in Section 5.2, and visualize the results through the function summary:

6.1 Frequentist analysis

6.1.1 Independent semi-Markov PHR model with Weibull baseline hazards

In our first example we employ the modeling (4)-(6) for independent data, semi-Markov assumption and Weibull baseline hazards. Here, Formula (form) is defined as in Section 5.1. We fit the model using the function FreqID_HReg, described in Section 5.2, and visualize the results through the function summary:

R> fitFreqPHR <- FreqID_HReg(form, data=simCIBMTR, model="semi-Markov")
R> summary(fitFreqPHR)

Analysis of independent semi-competing risks data
semi-Markov assumption for h3

Hazard ratios:

| beta1 | LL   | UL   | beta2 | LL   | UL   | beta3 | LL   | UL   |
|-------|------|------|-------|------|------|-------|------|------|
| dTypeALL | 1.49 | 1.20 | 1.8   | 1.37 | 1.09 | 1.7   | 0.99 | 0.78 | 1.3   |
| dTypeCML | 1.78 | 1.41 | 2.3   | 0.83 | 0.64 | 1.1   | 1.30 | 0.99 | 1.7   |
| dTypeMDS | 1.64 | 1.26 | 2.1   | 1.39 | 1.04 | 1.9   | 1.49 | 1.09 | 2.0   |
sexP 0.89 0.79 1.0 NA NA NA NA NA NA

Variance of frailties:
  Estimate  LL  UL
theta  7.8  7.3  8.4

Baseline hazard function components:
  h1-PM  LL  UL   h2-PM  LL  UL   h3-PM  LL  UL
Weibull: log-kappa -6.14 -6.4 -5.90 -11.33 -10.93 -6.873 -7.189 -6.557
Weibull: log-alpha  0.15  0.1  0.21  0.86  0.82  0.91  0.022 -0.033  0.077

As shown in Section 5.6, summary provides estimates of all model parameters. Using the auxiliary functions predict (default option x1new=x2new=x3new=NULL which corresponds to the baseline specification) and plot, we can graphically visualize the results:

R> pred <- predict(fitFreqPHR, time=seq(0,365,1), tseq=seq(from=0,to=365,by=30))
R> plot(pred, plot.est="Surv")
R> plot(pred, plot.est="Haz")

Figure 2 displays estimated baseline survival and hazard functions (solid line) with their corresponding 95% confidence intervals (dotted line).

6.2 Bayesian analysis
6.2.1 Independent semi-Markov PHR model with PEM baseline hazards

Our second example is also based on the models (4)-(6) adopting a semi-Markov assumption for $h_3$, but now we use the non-parametric PEM specification for baseline hazard functions. Again, Formula is defined as in Section 5.1. Here we employ the Bayesian estimation by means of the function BayesID_HReg, described in Section 5.3. The first step is to specify initial values for model parameters through the startValues argument using the auxiliary function initiate.startValues:

R> startValues <- initiate.startValues_HReg(form, data=simCIBMTR, +   model=c("semi-Markov","PEM"), nChain=3)

The nChain argument indicates the number of Markov chains that will be used in the MCMC algorithm. Next step is to define all model hyperparameters using the hyperParams argument:

R> hyperParams <- list(theta=c(0.5,0.05), PEM=list(PEM.ab1=c(0.5,0.05), +   PEM.ab2=c(0.5,0.05), PEM.ab3=c(0.5,0.05), PEM.alpha1=10, +   PEM.alpha2=10, PEM.alpha3=10))

To recall what prior distributions are related to these hyperparameters, see Section 4.3. Now we set the MCMC configuration for the mcmcParams argument, more specifically defining the overall run, storage, and tuning parameters for specific updates:

R> sg_max <- c(max(simCIBMTR$time1[simCIBMTR$event1==1]), +   max(simCIBMTR$time2[simCIBMTR$event1==0 & simCIBMTR$event2==1]), +   max(simCIBMTR$time2[simCIBMTR$event1==1 & simCIBMTR$event2==1]))
Figure 2: Estimated baseline survival (top) and hazard (bottom) functions from the above analysis.

R> mcmcParams <- list(run=list(numReps=5e6, thin=1e3, burninPerc=0.5),
+   storage=list(nGam_save=0, storeV=rep(FALSE,3)),
+   tuning=list(mhProp_theta_var=0.05, Cg=rep(0.2,3), delPertg=rep(0.5,3),
+     rj.scheme=1, Kg_max=rep(50,3), sg_max=sg_max, time_lambda1=seq(1,sg_max[1],1),
+     time_lambda2=seq(1,sg_max[2],1), time_lambda3=seq(1,sg_max[3],1))

As shown above, we set \( \text{sg.max} \) to the largest observed failure times for \( g \in \{1,2,3\} \). For more details of each item of \texttt{mcmcParams}, see Section 5.3.
Given this setup, we fit the PHR model using the function `BayesID_HReg`:

```r
R> fitBayesPHR <- BayesID_HReg(form, data=simCIBMTR, model=c("semi-Markov","PEM"),
+ startValues=startValues, hyperParams=hyperParams, mcmcParams=mcmcParams)
```

We note that, depending on the complexity of the model specification (e.g. if PEM baseline hazards are adopted) and the size of the dataset, despite the functions having been written in C and compiled for R, the MCMC scheme may require a large number of MCMC scans to ensure convergence. As such, some models may take a relatively long time to converge. The example we present below, for example, took 45 hours on a Windows laptop with an Intel(R) Core(TM) i5-3337U 1.80GHz processor, 2 cores, 4 logical processors, 4GB of RAM and 3MB of cache memory to cycle through the 6 millions scans for 3 chains. In lieu of attempting to reproduce the exact results we present here, while readers are of course free to do, Appendix C provides the code for this same semi-competing risks model and its respective posterior summary, but based on a reduced number of scans of the MCMC scheme (specifically 50,000 scans for 3 chains). Based on the full set of scans, the `print` method for object returned by `BayesID_HReg`, yields:

```r
R> print(fitBayesPHR, digits=2)
```

**Analysis of independent semi-competing risks data**

**semi-Markov assumption for h3**

- **Number of chains:** 3
- **Number of scans:** 5e+06
- **Thinning:** 1000
- **Percentage of burnin:** 50%

```
# Potential Scale Reduction Factor

Variance of frailties, theta:
1

Regression coefficients:
  beta1 beta2 beta3
dTypeALL    1    1    1
dTypeCML    1    1    1
dTypeMDS    1    1    1
sexP        1    NA   NA

Baseline hazard function components:

lambda1: summary statistics
       Min. 1st Qu. Median Mean 3rd Qu. Max.
       1.00  1.00   1.00  1.00  1.00   1.01

lambda2: summary statistics
       Min. 1st Qu. Median Mean 3rd Qu. Max.
```
lambda3: summary statistics

|       | Min.  | 1st Qu. | Median | Mean  | 3rd Qu. | Max. |
|-------|-------|---------|--------|-------|---------|------|
| h1    | 1.00  | 1.00    | 1.00   | 1.00  | 1.01    | 1.01 |
| h2    | 1.00  | 1.00    | 1.00   | 1.00  | 1.01    | 1.01 |
| h3    | 1.00  | 1.00    | 1.00   | 1.00  | 1.01    | 1.01 |

mu

| sigmaSq | 1 | 1 | 1 |
| K       | 1 | 1 | 1 |

... Note that all parameters obtained PSRF close to 1, indicating that the chains have converged well (see Section 5.6). Convergence can also be assessed graphically through a trace plot:

R> plot(fitBayesPHR$chain1$theta.p, type="l", col="red",
+     xlab="iteration", ylab=expression(theta))
R> lines(fitBayesPHR$chain2$theta.p, type="l", col="green")
R> lines(fitBayesPHR$chain3$theta.p, type="l", col="blue")

Figure 3: Convergence diagnostic via trace plot of multiple chains.

Figure 3 shows convergence diagnostic for $\theta$ (subject-specific frailty variance component), where the three chains have mixed and converged to a stable distribution. Any other model parameter could be similarly evaluated. Analogous to the frequentist example, we can also visualize the results through the function summary:

R> summary(fitBayesPHR)
Analysis of independent semi-competing risks data
semi-Markov assumption for h3

#####

Hazard ratios:

|                | dTypeALL | dTypeCML | dTypeMDS | sexP |
|----------------|----------|----------|----------|------|
| exp(beta1) LL UL | 1.45 1.18 1.8 | 1.73 1.39 2.2 | 1.61 1.26 2.1 | 0.89 0.79 1.0 |
| exp(beta2) LL UL | 1.32 1.07 1.6 | 0.81 0.63 1.0 | 1.36 1.04 1.8 | 1.61 1.26 2.1 |
| exp(beta3) LL UL | 0.99 0.77 1.3 | 1.26 0.97 1.6 | 1.45 1.07 1.9 | NA NA NA |

Variance of frailties:

| theta LL UL | 6.7 6.1 7.3 |

Baseline hazard function components:

| h1-PM LL UL | h2-PM LL UL | h3-PM LL UL |
|-------------|-------------|-------------|
| mu          | -5.60 -6.003 -5 | -5.2 -9.6 -2.3 | -6.75 -7.048 -6.5 |
| sigmaSq     | 0.21 0.027 2 | 7.2 2.5 24.3 | 0.13 0.018 2.4 |
| K           | 11.00 5.000 17 | 15.0 11.0 21.0 | 10.00 4.000 17.0 |

Here we provide estimates of all model parameters with their respective 95% credible intervals.

6.2.2 Independent AFT model with log-Normal baseline survival distribution

Our last example is based on AFT models (1)-(3) adopting a semi-Markov assumption for $h_3$ and the parametric log-Normal specification for baseline survival distributions. Here we apply the Bayesian framework via function BayesID_AFT. As pointed out in Section 5.4, Formula argument for AFT models takes a specific form:

```R
R> simCIBMTR$LT <- rep(0,dim(simCIBMTR)[1])
R> simCIBMTR$y1L <- simCIBMTR$y1U <- simCIBMTR[,1]
R> simCIBMTR$y2L[w]hich(simCIBMTR[,2]==0) <- Inf
R> simCIBMTR$y2U[w]hich(simCIBMTR[,3]==0] <- Inf
R> formAFT <- Formula(LT | y1L + y1U | y2L + y2U ~ dTypeALL + dTypeCML + dTypeMDS +
+       sexP | dTypeALL + dTypeCML + dTypeMDS | dTypeALL + dTypeCML + dTypeMDS)
```

Recall that LT represents the left-truncation time, and (y1L, y1U) and (y2L, y2U) are the interval-censored times to the non-terminal and terminal events, respectively. Next step is to set the initial values for model parameters through the startValues argument, but now using the auxiliary function initiate.startValues_AFT:

```R
R> startValues <- initiate.startValues_AFT(formAFT, data=simCIBMTR,
+       model="LN", nChain=3)
```

23
Again, we considered three Markov chains (nChain=3). Using the hyperParams argument we specify all model hyperparameters:

```r
R> hyperParams <- list(theta=c(0.5,0.05), LN=list(LN.ab1=c(0.5,0.05),
+ LN.ab2=c(0.5,0.05), LN.ab3=c(0.5,0.05)))
```

Each pair of hyperparameters defines shape and scale of an inverse Gamma prior distribution (see Section 4.1). Similar to the previous example, we must specify overall run, storage, and tuning parameters for specific updates through the mcmcParams argument:

```r
R> mcmcParams <- list(run=list(numReps=5e6, thin=1e3, burninPerc=0.5),
+ storage=list(nGam_save=0, nY1_save=0, nY2_save=0, nY1.NA_save=0),
+ tuning=list(betag.prop.var=rep(0.01,3), mug.prop.var=rep(0.01,3),
+ zetag.prop.var=rep(0.01,3), gamma.prop.var=0.01))
```

Analogous to the previous Bayesian model, a large number of scans are also required here to achieve the convergence of the Markov chains. Again, for a quickly reproducible example, the code for the AFT model with simplified MCMC setting is provided in Appendix C. For more details of each item of mcmcParams, see Section 5.4. Finally, we fit the AFT model using the function BayesID_AFT and analyze the convergence of each parameter through the function print:

```r
R> fitBayesAFT <- BayesID_AFT(formAFT, data=simCIBMTR, model="LN",
+ startValues=startValues, hyperParams=hyperParams, mcmcParams=mcmcParams)
R> print(fitBayesAFT, digits=2)
```

Analysis of independent semi-competing risks data

Number of chains: 3
Number of scans: 5e+06
Thinning: 1000
Percentage of burnin: 50%

#####
Potential Scale Reduction Factor

Variance of frailties, theta:

1

Regression coefficients:

- beta1 beta2 beta3
dTypeALL 1 1 1
dTypeCML 1 1 1
dTypeMDS 1 1 1
sexP 1 NA NA

Baseline survival function components:

- g=1 g=2 g=3
mu 1 1.1 1
Again, the PSRF for each parameter indicates the convergence. As a last step, we visualize the estimate of each parameter and their respective 95% credible intervals through the function `summary`:

\[
\text{R> summary(fitBayesAFT)}
\]

Analysis of independent semi-competing risks data

###

Acceleration factors:

|            | exp(beta1) | LL  | UL  | exp(beta2) | LL  | UL  | exp(beta3) | LL  | UL  |
|------------|------------|-----|-----|------------|-----|-----|------------|-----|-----|
| dTypeALL   | 0.68       | 0.55| 0.85| 0.95       | 0.86| 1.0 | 1.09       | 0.86| 1.4 |
| dTypeCML   | 0.53       | 0.42| 0.67| 1.27       | 1.11| 1.4 | 0.91       | 0.71| 1.2 |
| dTypeMDS   | 0.58       | 0.44| 0.76| 0.89       | 0.78| 1.0 | 0.78       | 0.59| 1.0 |
| sexP       | 1.16       | 0.99| 1.36| NA         | NA  | NA | NA         | NA  | NA  |

Variance of frailties:

| theta | LL  | UL  |
|-------|-----|-----|
| 2.6   | 2.5 | 2.8 |

Baseline survival function components:

| g=1: | PM  | LL  | UL  | g=2: | PM  | LL  | UL  | g=3: | PM  | LL  | UL  |
|------|-----|-----|-----|------|-----|-----|-----|------|-----|-----|-----|
| log-Normal: mu | 8.2 | 8.0 | 8.4 | 6.274| 6.226| 6.323| 6.5 | 6.4 | 6.7 |
| log-Normal: sigmaSq | 7.1 | 6.4 | 8.0 | 0.014| 0.006| 0.038| 1.7 | 1.5 | 2.0 |

7 Discussion

This paper discusses the implementation of a comprehensive R package **SemiCompRisks** for the analyses of independent/cluster-correlated semi-competing risks data. The package allows to fit parametric or semi-parametric models based on either accelerated failure time or proportional hazards regression approach. It is also flexible in that one can adopt either a Markov or semi-Markov specification for terminal event following non-terminal event. The estimation and inference are mostly based on the Bayesian paradigm, but parametric PHR models can also be fitted using the maximum likelihood estimation. Users can easily obtain numerical and graphical presentation of model fits using R methods, as illustrated in the stem cell transplantation example in Section 6. In addition, the package provides functions for performing univariate survival analysis. We would also like to emphasize that the vignette documentation (Lee et al., 2017b) provides a list of detailed examples applying each of the implemented models in the package.

**SemiCompRisks** provides researchers with valid and practical analysis tools for semi-competing risks data. The application examples in this paper were run using version v3.0 of the
package, available from the CRAN at https://cran.r-project.org/package=SemiCompRisks. We plan to constantly update the package to incorporate more functionality and flexibility to the models for semi-competing risks analysis.

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References

A. Allignol, J. Beyersmann, and M. Schumacher. mvna: An R package for the Nelson-Aalen estimator in multistate models. *R News*, 8(2):48–50, 2008.

A. Allignol, M. Schumacher, and J. Beyersmann. Empirical transition matrix of multi-state models: The etm package. *Journal of Statistical Software*, 38(4):1–15, 2011.

A. Araújo, L. Meira-Machado, and J. Roca-Pardiñas. TPmsm: Estimation of the transition probabilities in 3-state models. *Journal of Statistical Software*, 62(4):1–29, 2014.

A. Boruvka and R. J. Cook. *coxinterval: Cox-type models for interval-censored data*, 2015. URL https://cran.r-project.org/package=coxinterval. R package version 1.2.

S. P. Brooks and A. Gelman. General methods for monitoring convergence of iterative simulations. *Journal of Computational and Graphical Statistics*, 7(4):434–455, 1998.

B. L. Egleston, D. O. Scharfstein, E. E. Freeman, and S. K. West. Causal inference for non-mortality outcomes in the presence of death. *Biostatistics*, 8(3):526–545, 2007.

N. Ferguson, S. Datta, and G. Brock. msSurv: An R package for nonparametric estimation of multistate models. *Journal of Statistical Software*, 50(14):1–24, 2012.

J. P. Fine, H. Jiang, and R. Chappell. On semi-competing risks data. *Biometrika*, 88(4):907–919, 2001.

H. Fu, Y. Wang, J. Liu, P. M. Kulkarni, and A. S. Melemed. Joint modeling of progression-free survival and overall survival by a Bayesian normal induced copula estimation model. *Statistics in Medicine*, 32(2):240–254, 2013.

A. Gelman and D. B. Rubin. Inference from iterative simulation using multiple sequences. *Statistical Science*, 7(4):457–472, 1992.

D. Ghosh. Semiparametric inferences for association with semi-competing risks data. *Statistics in Medicine*, 25(12):2059–2070, 2006.
B. Han, M. Yu, J. J. Dignam, and P. J. Rathouz. Bayesian approach for flexible modeling of semicompeting risks data. *Statistics in Medicine*, 33(29):5111–5125, 2014.

S. Haneuse and K. H. Lee. Semi-competing risks data analysis: Accounting for death as a competing risk when the outcome of interest is nonterminal. *Circulation: Cardiovascular Quality and Outcomes*, 9(3):322–331, 2016.

J. J. Hsieh, W. Wang, and A. A. Ding. Regression analysis based on semicompeting risks data. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 70(1):3–20, 2008.

C. H. Jackson. Multi-state models for panel data: The msm package for R. *Journal of Statistical Software*, 38(8):1–28, 2011.

C. H. Jackson. flexsurv: A platform for parametric survival modeling in R. *Journal of Statistical Software*, 70(8):1–33, 2016.

I. Jazić, D. Schrag, D. J. Sargent, and S. Haneuse. Beyond composite endpoints analysis: Semi-competing risks as an underutilized framework for cancer research. *Journal of the National Cancer Institute*, 108(12):djw154, 2016.

H. Jiang, J. P. Fine, and R. Chappell. Semiparametric analysis of survival data with left truncation and dependent right censoring. *Biometrics*, 61(2):567–575, 2005.

J. P. Klein and M. L. Moeschberger. *Survival analysis: Techniques for censored and truncated data*. Springer-Verlag New York, 2nd edition, 2003.

T. Kneib and A. Hennerfeind. Bayesian semi parametric multi-state models. *Statistical Modelling*, 8(2):169–198, 2008.

A. Król and P. Saint-Pierre. SemiMarkov: An R package for parametric estimation in multi-state semi-Markov models. *Journal of Statistical Software*, 66(6):1–16, 2015.

L. Lakhal, L. P. Rivest, and B. Abdous. Estimating survival and association in a semicompeting risks model. *Biometrics*, 64(1):180–188, 2008.

C. Lee, S. J. Lee, and S. Haneuse. Time-to-event analysis when the event is defined on a finite time interval. *Submitted*, 2017a.

K. H. Lee, S. Haneuse, D. Schrag, and F. Dominici. Bayesian semiparametric analysis of semicompeting risks data: Investigating hospital readmission after a pancreatic cancer diagnosis. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, 64(2):253–273, 2015.

K. H. Lee, F. Dominici, D. Schrag, and S. Haneuse. Hierarchical models for semicompeting risks data with application to quality of end-of-life care for pancreatic cancer. *Journal of the American Statistical Association*, 111(515):1075–1095, 2016.
K. H. Lee, C. Lee, D. Alvares, and S. Haneuse. *SemiCompRisks: Hierarchical models for parametric and semi-parametric analyses of semi-competing risks data*, 2017b. URL https://cran.r-project.org/web/packages/SemiCompRisks/vignettes/SemiCompRisks.pdf. R package version 3.0.

K. H. Lee, V. Rondeau, and S. Haneuse. Accelerated failure time models for semi-competing risks data in the presence of complex censoring. *Biometrics*, 73(4):1401–1412, 2017c.

B. Liquet, J. F. Timsit, and V. Rondeau. Investigating hospital heterogeneity with a multi-state frailty model: Application to nosocomial pneumonia disease in intensive care units. *BMC Medical Research Methodology*, 12(1):1–14, 2012.

L. Liu, R. A. Wolfe, and X. Huang. Shared frailty models for recurrent events and a terminal event. *Biometrics*, 60(3):747–756, 2004.

L. Meira-Machado and J. Roca-Pardiñas. p3state.msm: Analyzing survival data from an illness-death model. *Journal of Statistical Software*, 38(3):1–18, 2011.

L. Meira-Machado, C. Cadarso-Suárez, and J. Uña-Álvarez. tdc.msm: AnR library for the analysis of multi-state survival data. *Computer Methods and Programs in Biomedicine*, 86: 131–140, 2007.

R. M. Neal. Markov chain sampling methods for Dirichlet process mixture models. *Journal of Computational and Graphical Statistics*, 9(2):249–265, 2000.

L. Peng and J. P. Fine. Regression modeling of semicompeting risks data. *Biometrics*, 63(1): 96–108, 2007.

H. Putter, M. Fiocco, and R. B. Geskus. Tutorial in biostatistics: Competing risks and multi-state models. *Statistics in Medicine*, 26(11):2389–2430, 2007.

V. Rondeau, Y. Mazroui, and J. R. Gonzalez. frailtypack: An R package for the analysis of correlated survival data with frailty models using penalized likelihood estimation or parametrical estimation. *Journal of Statistical Software*, 47(4):1–28, 2012.

E. J. Tchetgen Tchetgen. Identification and estimation of survivor average causal effects. *Statistics in Medicine*, 33(21):3601–3628, 2014.

C. Touraine, T. A. Gerds, and P. Joly. SmoothHazard: An R package for fitting regression models to interval-censored observations of illness-death models. *Journal of Statistical Software*, 79 (7):1–22, 2017.

R. Varadhan, Q. L. Xue, and K. Bandeen-Roche. Semicompeting risks in aging research: Methods, issues and needs. *Lifetime Data Analysis*, 20(4):538–562, 2014.
W. Wang. Estimating the association parameter for copula models under dependent censoring. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 65(1):257–273, 2003.

L. J. Wei. The accelerated failure time model: A useful alternative to the Cox regression model in survival analysis. *Statistics in Medicine*, 11(14-15):1871–1879, 1992.

L. C. Wreede, M. Fiocco, and H. Putter. mstate: An R package for the analysis of competing risks and multi-state models. *Journal of Statistical Software*, 38(7):1–30, 2011.

J. Xu, J. D. Kalbfleisch, and B. Tai. Statistical analysis of illness-death processes and semicompeting risks data. *Biometrics*, 66(3):716–725, 2010.

Y. Ye, J. D. Kalbfleisch, and D. E. Schaubel. Semiparametric analysis of correlated recurrent and terminal events. *Biometrics*, 63(1):78–87, 2007.

D. Zeng and D. Y. Lin. Semiparametric transformation models with random effects for joint analysis of recurrent and terminal events. *Biometrics*, 65(3):746–752, 2009.

D. Zeng, Q. Chen, M. H. Chen, and J. G. Ibrahim. Estimating treatment effects with treatment switching via semicompeting risks models: An application to a colorectal cancer study. *Biometrika*, 99(1):167–184, 2012.

J. L. Zhang and D. B. Rubin. Estimation of causal effects via principal stratification when some outcomes are truncated by “death”. *Journal of Educational and Behavioral Statistics*, 28(4):353–368, 2003.

Y. Zhang, M. H. Chen, J. G. Ibrahim, D. Zeng, Q. Chen, Z. Pan, and X. Xue. Bayesian gamma frailty models for survival data with semi-competing risks and treatment switching. *Lifetime Data Analysis*, 20(1):76–105, 2014.
A Simulation algorithm for semi-competing risks data

The SemiCompRisks package contains a function, \texttt{simID}, for simulating independent or cluster-correlated semi-competing risks data. In this section, we provide the details on the simulation algorithm used in \texttt{simID} for generating cluster-correlated semi-competing risks data based on a parametric Weibull-MVN semi-Markov illness-death model, as presented in Section 4.3, where the baseline hazard functions are defined as

\[ h_{0g}(t) = \alpha_g \kappa_g t^{\alpha_g - 1}, \quad \text{for } g \in \{1, 2, 3\}. \]

The step by step algorithm is given as follows:

1. Generate \( V_j = (V_{j1}, V_{j2}, V_{j3})^\top \) from a \( \text{MVN}(0, \Sigma_V) \), for \( j = 1, \ldots, J \).

2. For each \( j \), repeat the following steps for \( i = 1, \ldots, n_j \).
   a) Generate \( \gamma_{ji} \) from a \( \text{Gamma}(\theta - 1, \theta - 1) \).
   b) Calculate \( \eta_{jig} = \log(\gamma_{ji}) + x_{jig}^\top \beta_g + V_{jg} \), for \( g \in \{1, 2, 3\} \).
   c) Generate \( t^*_{1i} \) from a \( \text{Weibull}(\alpha_1, \kappa_1 e^{\eta_{j1i}}) \) and \( t^*_{2i} \) from a \( \text{Weibull}(\alpha_2, \kappa_2 e^{\eta_{j2i}}) \).
      - If \( t^*_{1i} \leq t^*_{2i} \), generate \( t^* \) from a \( \text{Weibull}(\alpha_3, \kappa_3 e^{\eta_{j3i}}) \) and set \( t_{ji1} = t^*_{1i}, \ t_{ji2} = t^*_{1i} + t^* \).
      - Otherwise, set \( t_{ji1} = \infty, \ t_{ji2} = t^*_{2i} \).
   d) Generate a censoring time \( c_{ji} \) from \( \text{Uniform}(c_L, c_U) \).
   e) Set the observed outcome information (\texttt{time1, time2, event1, event2}) as follows:
      - \((t_{ji1}, t_{ji2}, 1, 1), \) if \( t_{ji1} < t_{ji2} < c_{ji} \).
      - \((t_{ji1}, c_{ji}, 1, 0), \) if \( t_{ji1} < c_{ji} < t_{ji2} \).
      - \((t_{ji2}, c_{ji}, 0, 1), \) if \( t_{ji1} = \infty \) and \( t_{ji2} < c_{ji} \).
      - \((c_{ji}, c_{ji}, 0, 0), \) if \( t_{ji1} > c_{ji} \) and \( t_{ji2} > c_{ji} \).

We note that the function \texttt{simID} is flexible in that one can set the \( \theta \) argument as zero (\texttt{theta.true}=0) to simulate the data under the model without the subject-specific shared frailty term \( (\gamma_{ji}) \), which is analogous to the model proposed by Liquet et al. (2012). One can generate independent semi-competing risks data outlined in Section 4.2 by setting the \texttt{id} and \texttt{SigmaV.true} arguments as nulls (\texttt{cluster=NULL} and \texttt{SimgaV.true=NULL}).

B Simulating outcomes using CIBMTR covariates

The true values of model parameters are set to estimates obtained by fitting a semi-Markov Weibull PHR model to the original CIBMTR data.

```r
R> data(CIBMTR_Params)
R> beta1.true <- CIBMTR_Params$beta1.true
R> beta2.true <- CIBMTR_Params$beta2.true
R> beta3.true <- CIBMTR_Params$beta3.true
R> alpha1.true <- CIBMTR_Params$alpha1.true
R> alpha2.true <- CIBMTR_Params$alpha2.true
```
R> alpha3.true <- CIBMTR_Params$alpha3.true
R> kappa1.true <- CIBMTR_Params$kappa1.true
R> kappa2.true <- CIBMTR_Params$kappa2.true
R> kappa3.true <- CIBMTR_Params$kappa3.true
R> theta.true <- CIBMTR_Params$theta.true
R> cens <- c(365, 365)

The next step is to define the covariates matrices and then simulate outcomes using the simID function, available in the SemiCompRisks package.

R> data(CIBMTR)
# Sex (M: reference category)
R> CIBMTR$sexP <- as.numeric(CIBMTR$sexP)-1

# Age (LessThan10: reference category)
R> CIBMTR$ageP20to29 <- as.numeric(CIBMTR$ageP=="20to29")
R> CIBMTR$ageP30to39 <- as.numeric(CIBMTR$ageP=="30to39")
R> CIBMTR$ageP40to49 <- as.numeric(CIBMTR$ageP=="40to49")
R> CIBMTR$ageP50to59 <- as.numeric(CIBMTR$ageP=="50to59")
R> CIBMTR$ageP60plus <- as.numeric(CIBMTR$ageP=="60plus")

# Disease type (AML: reference category)
R> CIBMTR$dTypeALL <- as.numeric(CIBMTR$dType=="ALL")
R> CIBMTR$dTypeCML <- as.numeric(CIBMTR$dType=="CML")
R> CIBMTR$dTypeMDS <- as.numeric(CIBMTR$dType=="MDS")

# Disease status (Early: reference category)
R> CIBMTR$dStatusInt <- as.numeric(CIBMTR$dStatus=="Int")
R> CIBMTR$dStatusAdv <- as.numeric(CIBMTR$dStatus=="Adv")

# HLA compatibility (HLA_Id_Sib: reference category)
R> CIBMTR$donorGrp8_8 <- as.numeric(CIBMTR$donorGrp=="8_8")
R> CIBMTR$donorGrp7_8 <- as.numeric(CIBMTR$donorGrp=="7_8")

# Covariate matrix
R> x1 <- CIBMTR[,c("sexP", "ageP20to29", "ageP30to39", "ageP40to49",
+ "ageP50to59", "ageP60plus", "dTypeALL", "dTypeCML", "dTypeMDS",
+ "dStatusInt", "dStatusAdv", "donorGrp8_8", "donorGrp7_8")]

R> x2 <- CIBMTR[,c("sexP", "ageP20to29", "ageP30to39", "ageP40to49",
+ "ageP50to59", "ageP60plus", "dTypeALL", "dTypeCML", "dTypeMDS",
+ "dStatusInt", "dStatusAdv", "donorGrp8_8", "donorGrp7_8")]

R> x3 <- CIBMTR[,c("sexP", "ageP20to29", "ageP30to39", "ageP40to49",
+ "ageP50to59", "ageP60plus", "dTypeALL", "dTypeCML", "dTypeMDS",
+ "dStatusInt", "dStatusAdv", "donorGrp8_8", "donorGrp7_8")]

R> set.seed(1405)
C Code for illustrative Bayesian examples

In order to encourage the reproducibility of the results obtained through our R package in a reasonable computational time, Bayesian analyses contained in Section 6.2 are illustrated below using a reduced number of scans (numReps) and extent of thinning (thin). Given the complexity of these Bayesian models, the reduction of scans/thinning results in non-convergence of the Markov chains, but at least it is possible to reproduce the results quickly.

C.1 Independent semi-Markov PHR model with PEM baseline hazards

```R
form <- Formula(time1 + event1 | time2 + event2 ~ dTypeALL + dTypeCML +
                dTypeMDS + sexP | dTypeALL + dTypeCML + dTypeMDS | dTypeALL +
                dTypeCML + dTypeMDS)

startValues <- initiate.startValues_HReg(form, data=simCIBMTR,
                                         model=c("semi-Markov","PEM"), nChain=3)

hyperParams <- list(theta=c(0.5,0.05), PEM=list(PEM.ab1=c(0.5,0.05),
                     PEM.ab2=c(0.5,0.05), PEM.ab3=c(0.5,0.05), PEM.alpha1=10,
                     PEM.alpha2=10, PEM.alpha3=10))

sg_max <- c(max(simCIBMTR$time1[simCIBMTR$event1==1]),
            max(simCIBMTR$time2[simCIBMTR$event1==0 & simCIBMTR$event2==1]),
            max(simCIBMTR$time2[simCIBMTR$event1==1 & simCIBMTR$event2==1]))

mcmcParams <- list(run=list(numReps=5e4, thin=5e1, burninPerc=0.5),
                    storage=list(nGam_save=0, storeV=rep(FALSE,3)),
                    tuning=list(mhProp_theta_var=0.05, Cg=rep(0.2,3), delPertg=rep(0.5,3),
                    rj.scheme=1, Kg_max=rep(50,3), sg_max=sg_max, time_lambda1=seq(1,sg_max[1],1),
                    time_lambda2=seq(1,sg_max[2],1), time_lambda3=seq(1,sg_max[3],1))

fitBayesPHR <- BayesID_HReg(form, data=simCIBMTR, model=c("semi-Markov","PEM"),
                            startValues=startValues, hyperParams=hyperParams, mcmcParams=mcmcParams)

print(fitBayesPHR, digits=2)
```

Analysis of independent semi-competing risks data
semi-Markov assumption for h3

32
Number of chains: 3
Number of scans: 50000
Thinning: 50
Percentage of burnin: 50%

########
Potential Scale Reduction Factor

Variance of frailties, theta:
3.4

Regression coefficients:

| dType  | beta1 | beta2 | beta3 |
|--------|-------|-------|-------|
| dTypeALL | 1.8   | 1.6   | 1.8   |
| dTypeCML | 1.9   | 1.8   | 2.1   |
| dTypeMDS | 1.8   | 2.0   | 2.0   |
| sexP    | 1.1   | NA    | NA    |

Baseline hazard function components:

lambda1: summary statistics

| Min.  | 1st Qu. | Median | Mean  | 3rd Qu. | Max.  |
|-------|---------|--------|-------|---------|-------|
| 1.1   | 2.9     | 3.2    | 3.2   | 3.6     | 4.3   |

lambda2: summary statistics

| Min.  | 1st Qu. | Median | Mean  | 3rd Qu. | Max.  |
|-------|---------|--------|-------|---------|-------|
| 1.0   | 3.3     | 4.0    | 3.7   | 4.5     | 5.8   |

lambda3: summary statistics

| Min.  | 1st Qu. | Median | Mean  | 3rd Qu. | Max.  |
|-------|---------|--------|-------|---------|-------|
| 1.8   | 2.2     | 2.5    | 2.5   | 2.7     | 3.2   |

h1     h2   h3
mu     1.3  2.2  1.5
sigmaSq 1.0  1.1  1.0
K       1.1  1.0  1.0

########
Estimates

Variance of frailties, theta:

| Estimate | SD   | LL   | UL  |
|----------|------|------|-----|
|          | 0.8  | 9.4  | 12  |

Regression coefficients:

| Estimate | SD   | LL   | UL  |
|----------|------|------|-----|
C.2 Independent AFT model with log-Normal baseline survival distribution

R> simCIBMTR$LT <- rep(0, dim(simCIBMTR)[1])
R> simCIBMTR$y1L <- simCIBMTR$y1U <- simCIBMTR[,1]
R> simCIBMTR$y1U[which(simCIBMTR[,2]==0)] <- Inf
R> simCIBMTR$y2L <- simCIBMTR$y2U <- simCIBMTR[,3]
R> simCIBMTR$y2U[which(simCIBMTR[,4]==0)] <- Inf

R> formAFT <- Formula(LT | y1L + y1U | y2L + y2U ~ dTypeALL + dTypeCML + dTypeMDS +
+ sexP | dTypeALL + dTypeCML + dTypeMDS | dTypeALL + dTypeCML + dTypeMDS)

R> startValues <- initiate.startValues_AFT(formAFT, data=simCIBMTR,
+ model="LN", nChain=3)

R> hyperParams <- list(theta=c(0.5,0.05), LN=list(LN.ab1=c(0.5,0.05),
+ LN.ab2=c(0.5,0.05), LN.ab3=c(0.5,0.05)))

R> mcmcParams <- list(run=list(numReps=5e4, thin=5e1, burninPerc=0.5),
+ storage=list(nGam_save=0, nY1_save=0, nY2_save=0, nY1.NA_save=0),
+ tuning=list(beta1.prop.var=rep(0.01,3), mug.prop.var=rep(0.01,3),
+ zetag.prop.var=rep(0.01,3), gamma.prop.var=0.01))

R> fitBayesAFT <- BayesID_AFT(formAFT, data=simCIBMTR, model="LN",
+ startValues=startValues, hyperParams=hyperParams, mcmcParams=mcmcParams)
R> print(fitBayesAFT, digits=2)

Analysis of independent semi-competing risks data

Number of chains: 3
Number of scans: 50000
Thinning: 50
Percentage of burnin: 50%

#####

Potential Scale Reduction Factor
Variance of frailties, theta:
1.7

Regression coefficients:
  beta1 beta2 beta3
dTypeALL 1 1.1 1.1
dTypeCML 1 1.0 1.0
dTypeMDS 1 1.1 1.0
sexP 1 NA NA

Baseline survival function components:
  g=1 g=2 g=3
mu 1.2 1.1 1.1
sigmaSq 1.4 1.7 1.2

#####
Estimates

Variance of frailties, theta:
  Estimate  SD  LL  UL
1.7  0.16 1.4 2

Regression coefficients:
  Estimate  SD  LL  UL
dTypeALL -0.42 0.13 0.52 0.83
dTypeCML -0.73 0.13 0.37 0.62
dTypeMDS -0.60 0.14 0.42 0.72
sexP 0.14 0.09 0.95 1.37
dTypeALL -0.02 0.06 0.87 1.09
dTypeCML 0.30 0.06 1.20 1.54
dTypeMDS -0.10 0.07 0.78 1.01
dTypeALL 0.04 0.13 0.81 1.31
dTypeCML -0.14 0.12 0.67 1.10
dTypeMDS -0.23 0.14 0.61 1.03