# Estimating Joint Models for Longitudinal and Time-to-Event Data with rstanarm

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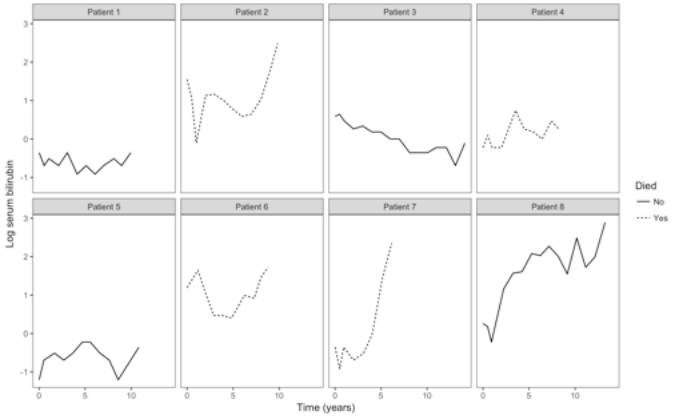
## Preamble

This vignette provides an introduction to the `stan_jm` modelling function in the **rstanarm** package. The `stan_jm` function allows the user to estimate a shared parameter joint model for longitudinal and time-to-event data under a Bayesian framework.

## Introduction

Joint modelling can be broadly defined as the simultaneous estimation of two or more statistical models which traditionally would have been separately estimated. When we refer to a shared parameter joint model for longitudinal and time-to-event data, we generally mean the joint estimation of: 1) a longitudinal mixed effects model which analyses patterns of change in an outcome variable that has been measured repeatedly over time (for example, a clinical biomarker) and 2) a survival or time-to-event model which analyses the time until an event of interest occurs (for example, death or disease progression). Joint estimation of these so-called "submodels" is achieved by assuming they are correlated via individual-specific parameters (i.e. individual-level random effects).

Over the last two decades the joint modelling of longitudinal and time-to-event data has received a significant amount of attention [1-5]. Methodological developments in the area have been motivated by a growing awareness of the benefits that a joint modelling approach can provide. In clinical or epidemiological research it is common for a clinical biomarker to be repeatedly measured over time on a given patient. In addition, it is common for time-to-event data, such as the patient-specific time from a defined origin (e.g. time of diagnosis of a disease) until a terminating clinical event such as death or disease progression to also be collected. The figure below shows observed longitudinal measurements (i.e. observed "trajectories") of log serum bilirubin for a small sample of patients with primary biliary cirrhosis. Solid lines are used for those patients who were still alive at the end of follow up, while dashed lines are used for those patients who died. From the plots, we can observe between-patient variation in the longitudinal trajectories for log serum bilirubin, with some patients showing an increase in the biomarker over time, others decreasing, and some remaining stable. Moreover, there is variation between patients in terms of the frequency and timing of the longitudinal measurements.




From the perspective of clinical risk prediction, we may be interested in asking whether the between-patient variation in the log serum bilirubin trajectories provides meaningful prognostic information that can help us differentiate patients with regard to some clinical event of interest, such as death. Alternatively, from an epidemiological perspective we may wish to explore the potential for etiological associations between changes in log serum bilirubin and mortality. Joint modelling approaches provide us with a framework under which we can begin to answer these types of clinical and epidemiological questions.

More formally, the motivations for undertaking a joint modelling analysis of longitudinal and time-to-event data might include one or more of the following:

- One may be interested in how *underlying changes in the biomarker influence the occurrence of the event*. However, including the observed biomarker measurements directly into a time-to-event model as time-varying covariates poses several problems. For example, if the widely used Cox proportional hazards model is assumed for the time-to-event model then biomarker measurements need to be available for all patients at all failure times, which is unlikely to be the case [3]. If simple methods of imputation are used, such as the "last observation carried forward" method, then these are likely to induce bias [6]. Furthermore, the observed biomarker measurements may be subject to measurement error and therefore their inclusion as time-varying covariates may result in biased and inefficient estimates. In most cases, the measurement error will result in parameter estimates

which are shrunk towards the null [7]. On the other hand, joint modelling approaches allow us to estimate the association between the biomarker (or some function of the biomarker trajectory, such as rate of change in the biomarker) and the risk of the event, whilst allowing for both the discrete time and measurement-error aspects of the observed biomarker.

- One may be interested primarily in the evolution of the clinical biomarker but *may wish to account for what is known as informative dropout*. If the value of future (unobserved) biomarker measurements are related to the occurrence of the terminating event, then those unobserved biomarker measurements will be "missing not at random" [8,9]. In other words, biomarker measurements for patients who have an event will differ from those who do not have an event. Under these circumstances, inference based solely on observed measurements of the biomarker will be subject to bias. A joint modelling approach can help to adjust for informative dropout and has been shown to reduce bias in the estimated parameters associated with longitudinal changes in the biomarker [1,9,10].
- Joint models are naturally suited to the task of *dynamic risk prediction*. For example, joint modelling approaches have been used to develop prognostic models where predictions of event risk can be updated as new longitudinal biomarker measurements become available. Taylor et al. [11] jointly modelled longitudinal measurements of the prostate specific antigen (PSA) and time to clinical recurrence of prostate cancer. The joint model was then used to develop a web-based calculator which could provide real-time predictions of the probability of recurrence based on a patient's up to date PSA measurements.

In this vignette, we describe the **rstanarm** package's `stan_jm` modelling function. This modelling function allows users to fit a shared parameter joint model for longitudinal and time-to-event data under a Bayesian framework, with the backend estimation carried out using Stan. In Section 2 we describe the formulation of the joint model used by `stan_jm` . In Section 3 we present a variety of examples showing the usage of `stan_jm` .

Note that some aspects of the estimation are covered in other vignettes, such as the priors vignette (priors.html) which contains details on the prior distributions available for regression coefficients.

## Technical details

# Model formulation

A shared parameter joint model consists of related submodels which are specified separately for each of the longitudinal and time-to-event outcomes. These are therefore commonly referred to as the *longitudinal submodel(s)* and the *event submodel*. The longitudinal and event submodels are linked using shared individual-specific parameters, which can be parameterised in a number of ways. We describe each of these submodels below.

## Longitudinal submodel(s)

We assume $y_{ijm}(t) = y_{im}(t_{ij})$ corresponds to the observed value of the $m^{th}$ $(m = 1, \ldots, M)$ biomarker for individual $i$ $(i = 1, \ldots, N)$ taken at time point $t_{ij}, j = 1, \ldots, n_{im}$ . We specify a (multivariate) generalised linear mixed model that assumes $y_{ijm}(t)$ follows a distribution in the exponential family with mean $\mu_{ijm}(t)$ and linear predictor

$$\eta_{ijm}(t) = g_m(\mu_{ijm}(t)) = \boldsymbol{x}_{ijm}^T(t)\boldsymbol{\beta}_m + \boldsymbol{z}_{ijm}^T(t)\boldsymbol{b}_{im}$$

where $\boldsymbol{x}_{ijm}^T(t)$ and $\boldsymbol{z}_{ijm}^T(t)$ are both row-vectors of covariates (which likely include some function of time, for example a linear slope, cubic splines, or polynomial terms) with associated vectors of fixed and individual-specific parameters $\boldsymbol{\beta}_m$ and $\boldsymbol{b}_{im}$ , respectively, and $g_m$ is some known link function. The distribution and link function are allowed to differ over the $M$ longitudinal submodels. We let the vector $\boldsymbol{\beta} = \{\boldsymbol{\beta}_m; m = 1, \ldots, M\}$ denote the collection of population-level parameters across the $M$ longitudinal submodels. We assume that the dependence across the different longitudinal submodels (i.e. the correlation between the different longitudinal biomarkers) is captured through a shared multivariate normal distribution for the individual-specific parameters; that is, we assume

$$\begin{pmatrix} \boldsymbol{b}_{i1} \\ \vdots \\ \boldsymbol{b}_{iM} \end{pmatrix} = \boldsymbol{b}_i \sim \text{Normal}\,(0, \boldsymbol{\Sigma})$$

for some unstructured variance-covariance matrix $\boldsymbol{\Sigma}$.

## Event submodel

We assume that we also observe an event time $T_i = \min\left(T_i^*, C_i\right)$ where $T_i^*$ denotes the so-called "true" event time for individual $i$ (potentially unobserved) and $C_i$ denotes the censoring time. We define an event indicator $d_i = I(T_i^* \leq C_i)$. We then model the hazard of the event using a parametric proportional hazards regression model of the form

$$h_i(t) = h_0(t; \boldsymbol{\omega})\exp\left(\boldsymbol{w}_i^T(t)\boldsymbol{\gamma} + \sum_{m=1}^{M}\sum_{q=1}^{Q_m} f_{mq}(\boldsymbol{\beta}, \boldsymbol{b}_i, \alpha_{mq}; t)\right)$$

where $h_i(t)$ is the hazard of the event for individual $i$ at time $t$, $h_0(t; \boldsymbol{\omega})$ is the baseline hazard at time $t$ given parameters $\boldsymbol{\omega}$, $\boldsymbol{w}_i^T(t)$ is a row-vector of individual-specific covariates (possibly time-dependent) with an associated vector of regression coefficients $\boldsymbol{\gamma}$ (log hazard ratios), $f_{mq}(.)$ are a set of known functions for $m = 1, \ldots, M$ and $q = 1, \ldots, Q_m$, and the $\alpha_{mq}$ are regression coefficients (log hazard ratios).

The longitudinal and event submodels are assumed to be related via an "association structure", which is a set of functions each $\{f_{mq}; m = 1, \ldots, M, q = 1, \ldots, Q_m\}$ that may each be conditional on the population-level parameters from the longitudinal submodel $\boldsymbol{\beta}$, the individual-specific parameters $\boldsymbol{b}_i$, and the population-level parameters $\alpha_{mq}$ for $m = 1, \ldots, M$ and $q = 1, \ldots, Q_m$. That is, the association structure of the joint model is captured via the $\sum_{m=1}^{M} \sum_{q=1}^{Q_m} f_{mq}(\boldsymbol{\beta}_m, \boldsymbol{b}_{im}, \alpha_{mq}; t)$ term in the linear predictor of the event submodel. The $\alpha_{mq}$ are referred to as the "association parameters" since they quantify the strength of the association between the longitudinal and event processes. The various ways in which the association structure can be are described in the next section.

The probability of individual $i$ still being event-free at time $t$, often referred to as the "survival probability", is defined as

$$S_i(t) = \text{Prob}\Big(T_i^* \geq t\Big) = \exp\Big(-H_i(t)\Big)$$

where $H_i(t) = \int_{s=0}^{t} h_i(s)ds$ is the cumulative hazard for individual $i$.

We assume that the baseline hazard $h_0(t; \boldsymbol{\omega})$ is modelled parametrically. In the `stan_jm` modelling function the baseline hazard be specified as either: an approximation using B-splines on the log hazard scale (the default); a Weibull distribution; or an approximation using a piecewise constant function on the log hazard scale (sometimes referred to as piecewise exponential). The choice of baseline hazard can be made via the `basehaz` argument. In the case of the B-splines or piecewise constant baseline hazard, the user can control the flexibility by specifying the knots or degrees of freedom via the `basehaz_ops` argument. (Note that currently there is slightly limited post-estimation functionality available for models estimated with a piecewise constant baseline hazard, so this is perhaps the least preferable choice).

## Association structures

As mentioned in the previous section, the dependence between the longitudinal and event submodels is captured through the association structure, which can be specified in a number of ways. The simplest association structure is likely to be

$$f_{mq}(\boldsymbol{\beta}, \boldsymbol{b}_{im}, \alpha_{mq}; t) = \alpha_{mq}\eta_{im}(t)$$

and this is often referred to as a *current value* association structure since it assumes that the log hazard of the event at time $t$ is linearly associated with the value of the longitudinal submodel's linear predictor also evaluated at time $t$. This is the most common association structure used in the joint modelling literature to date. In the situation where the longitudinal submodel is based on an identity link function and normal error distribution (i.e. a linear mixed model) the *current value* association structure can be viewed as a method for including the underlying "true" value of the biomarker as a time-varying covariate in the event submodel.[1]

However, other association structures are also possible. For example, we could assume the log hazard of the event is linearly associated with the *current slope* (i.e. rate of change) of the longitudinal submodel's linear predictor, that is

$$f_{mq}(\boldsymbol{\beta}, \boldsymbol{b}_i, \alpha_{mq}; t) = \alpha_{mq}\frac{d\eta_{im}(t)}{dt}$$

There are in fact a whole range of possible association structures, many of which have been discussed in the literature [14-16].

The `stan_jm` modelling function in the **rstanarm** package allows for the following association structures, which are specified via the `assoc` argument:

Current value (of the linear predictor or expected value)

$$f_{mq}(\boldsymbol{\beta}, \boldsymbol{b}_i, \alpha_{mq}; t) = \alpha_{mq}\eta_{im}(t)$$
$$f_{mq}(\boldsymbol{\beta}, \boldsymbol{b}_i, \alpha_{mq}; t) = \alpha_{mq}\mu_{im}(t)$$

Current slope (of the linear predictor or expected value)

$$f_{mq}(\boldsymbol{\beta}, \boldsymbol{b}_i, \alpha_{mq}; t) = \alpha_{mq}\frac{d\eta_{im}(t)}{dt}$$
$$f_{mq}(\boldsymbol{\beta}, \boldsymbol{b}_i, \alpha_{mq}; t) = \alpha_{mq}\frac{d\mu_{im}(t)}{dt}$$

Area under the curve (of the linear predictor or expected value)

$$f_{mq}(\boldsymbol{\beta}, \boldsymbol{b}_i, \alpha_{mq}; t) = \alpha_{mq}\int_0^t \eta_{im}(u)du$$
$$f_{mq}(\boldsymbol{\beta}, \boldsymbol{b}_i, \alpha_{mq}; t) = \alpha_{mq}\int_0^t \mu_{im}(u)du$$

Interactions between different biomarkers

$$f_{mq}(\boldsymbol{\beta}, \boldsymbol{b}_i, \alpha_{mq}; t) = \alpha_{mq}\eta_{im}(t)\eta_{im'}(t) \text{ for some } m = m' \text{ or } m \neq m'$$
$$f_{mq}(\boldsymbol{\beta}, \boldsymbol{b}_i, \alpha_{mq}; t) = \alpha_{mq}\eta_{im}(t)\mu_{im'}(t) \text{ for some } m = m' \text{ or } m \neq m'$$
$$f_{mq}(\boldsymbol{\beta}, \boldsymbol{b}_i, \alpha_{mq}; t) = \alpha_{mq}\mu_{im}(t)\mu_{im'}(t) \text{ for some } m = m' \text{ or } m \neq m'$$

Interactions between the biomarker (or it's slope) and observed data

$$f_{mq}(\boldsymbol{\beta}, \boldsymbol{b}_i, \alpha_{mq}; t) = \alpha_{mq} c_i(t) \eta_{im}(t) \text{ for some covariate value } c_i(t)$$
$$f_{mq}(\boldsymbol{\beta}, \boldsymbol{b}_i, \alpha_{mq}; t) = \alpha_{mq} c_i(t) \mu_{im}(t) \text{ for some covariate value } c_i(t)$$
$$f_{mq}(\boldsymbol{\beta}, \boldsymbol{b}_i, \alpha_{mq}; t) = \alpha_{mq} c_i(t) \frac{d\eta_{im}(t)}{dt} \text{ for some covariate value } c_i(t)$$
$$f_{mq}(\boldsymbol{\beta}, \boldsymbol{b}_i, \alpha_{mq}; t) = \alpha_{mq} c_i(t) \frac{d\mu_{im}(t)}{dt} \text{ for some covariate value } c_i(t)$$

As well as using lagged values for any of the above. That is, replacing $t$ with $t - u$ where $u$ is some lag time, such that the hazard of the event at time $t$ is assumed to be associated with some function of the longitudinal submodel parameters at time $t - u$.

Lastly, we can specify some time-independent function of the random effects, possibly including the fixed effect component. For example,

$$f_{mq}(\boldsymbol{\beta}, \boldsymbol{b}_i, \alpha_{mq}; t) = \alpha_{mq} \boldsymbol{b}_{im0}$$

or

$$f_{mq}(\boldsymbol{\beta}, \boldsymbol{b}_i, \alpha_{mq}; t) = \alpha_{mq} \left( \boldsymbol{\beta}_{m0} + \boldsymbol{b}_{im0} \right)$$

where $\boldsymbol{\beta}_{m0}$ is the population-level intercept for the $m^{th}$ longitudinal submodel and $\boldsymbol{b}_{im0}$ is the $i^{th}$ individual's random deviation from the population-level intercept for the $m^{th}$ longitudinal submodel.

Note that more than one association structure can be specified, however, not all possible combinations are allowed. Moreover, if you are fitting a multivariate joint model (i.e. more than one longitudinal outcome) then you can optionally choose to use a different association structure(s) for linking each longitudinal submodel to the event submodel. To do this you can pass a list of length $M$ to the `assoc` argument.

## Assumptions

Here we define a set of assumptions for the multivariate shared parameter joint model.

The so-called conditional independence assumption of the shared parameter joint model postulates

$$y_{im}(t) \perp y_{im'}(t) \mid \boldsymbol{b}_i, \boldsymbol{\theta}$$
$$y_{im}(t) \perp y_{im}(t') \mid \boldsymbol{b}_i, \boldsymbol{\theta}$$
$$y_{im}(t) \perp T_i^* \mid \boldsymbol{b}_i, \boldsymbol{\theta}$$

for some $m \neq m'$ and $t \neq t'$, and where $\boldsymbol{\theta}$ denotes the combined vector of all remaining population-level parameters in the model. That is, conditional on the individual-specific parameters $\boldsymbol{b}_i$ and population-level parameters $\boldsymbol{\theta}$, the following are assumed: (i) any biomarker measurement for individual $i$ is independent of that individual's true event time $T_i^*$; (ii) any two measurements of the $m^{th}$ biomarker taken on the $i^{th}$ individual at two distinct time points $t$ and $t'$ (i.e. longitudinal or repeated measurements) are independent of one another; and (iii) any two measurements of two different biomarkers, taken on the $i^{th}$ individual at some time point $t$ are independent of one another. These conditional independence assumptions allow for a convenient factorisation of the full likelihood for joint model into the likelihoods for each of the component parts (i.e. the likelihood for the longitudinal submodel, the likelihood for the event submodel, and the likelihood for the distribution of the individual-specific parameters), which facilitates the estimation of the model.

Moreover, we require two additional assumptions: (i) that the censoring process for the event outcome is independent of the true event time, that is $C_i \perp T_i^* \mid \boldsymbol{\theta}$ (i.e. uninformative censoring); and (ii) that the visiting process by which the observation times $t_{ijm}$ are determined is independent of the true event time $T_i^*$ and all missing future unobserved longitudinal biomarker measurements.

## Log posterior distribution

Under the conditional independence assumption, the log posterior for the $i^{th}$ individual can be specified as

$$\log p(\boldsymbol{\theta}, \boldsymbol{b}_i \mid \boldsymbol{y}_i, T_i, d_i) \propto \log \left[ \left( \prod_{m=1}^{M} \prod_{j=1}^{n_i} p(y_{ijm}(t) \mid \boldsymbol{b}_i, \boldsymbol{\theta}) \right) p(T_i, d_i \mid \boldsymbol{b}_i, \boldsymbol{\theta}) p(\boldsymbol{b}_i \mid \boldsymbol{\theta}) p(\boldsymbol{\theta}) \right]$$

where $\boldsymbol{y}_i = \{ y_{ijm}(t); j = 1, \ldots, n_i, m = 1, \ldots, M \}$ denotes the collection of longitudinal biomarker data for individual $i$ and $\boldsymbol{\theta}$ denotes all remaining population-level parameters in the model.

We can rewrite this log posterior as

$$\log p(\boldsymbol{\theta}, \boldsymbol{b}_i \mid \boldsymbol{y}_i, T_i, d_i) \propto \left( \sum_{m=1}^{M} \sum_{j=1}^{n_i} \log p(y_{ijm}(t) \mid \boldsymbol{b}_i, \boldsymbol{\theta}) \right) + \log p(T_i, d_i \mid \boldsymbol{b}_i, \boldsymbol{\theta}) + \log p(\boldsymbol{b}_i \mid \boldsymbol{\theta}) + \log p(\boldsymbol{\theta})$$

where $\sum_{j=1}^{n_{im}} \log p(y_{ijm} \mid \boldsymbol{b}_i, \boldsymbol{\theta})$ is the log likelihood for the $m^{th}$ longitudinal submodel, $\log p(T_i, d_i \mid \boldsymbol{b}_i, \boldsymbol{\theta})$ is the log likelihood for the event submodel, $\log p(\boldsymbol{b}_i \mid \boldsymbol{\theta})$ is the log likelihood for the distribution of the group-specific parameters (i.e. random effects), and $\log p(\boldsymbol{\theta})$ represents the log likelihood for the joint prior distribution across all remaining unknown parameters.[2]

We can rewrite the log likelihood for the event submodel as

$$\log p(T_i, d_i \mid \boldsymbol{b}_i, \boldsymbol{\theta}) = d_i * \log h_i(T_i) - \int_0^{T_i} h_i(s)ds$$

and then use Gauss-Kronrod quadrature with $Q$ nodes to approximate $\int_0^{T_i} h_i(s)ds$, such that

$$\int_0^{T_i} h_i(s)ds \approx \frac{T_i}{2} \sum_{q=1}^{Q} w_q h_i\left(\frac{T_i(1+s_q)}{2}\right)$$

where $w_q$ and $s_q$, respectively, are the standardised weights and locations ("abscissa") for quadrature node $q$ ($q = 1, \ldots, Q$) [17]. The default for the `stan_jm` modelling function is to use $Q = 15$ quadrature nodes, however if the user wishes, they can choose between $Q = 15, 11$, or $7$ quadrature nodes (specified via the `qnodes` argument).

Therefore, once we have an individual's event time $T_i$ we can evaluate the design matrices for the event submodel and longitudinal submodels at the $Q + 1$ necessary time points (which are the event time $T_i$ and the quadrature points $\frac{T_i(1+s_q)}{2}$ for $q = 1, \ldots, Q$) and then pass these to Stan's data block. We can then evaluate the log likelihood for the event submodel by simply calculating the hazard $h_i(t)$ at those $Q + 1$ time points and summing the quantities appropriately. This calculation will need to be performed each time we iterate through Stan's model block. A simplified example of the underlying Stan code used to fit the joint model can be found in Brilleman et al. (2018) (https://github.com/stan-dev/stancon_talks/blob/master/2018/Contributed-Talks/03_brilleman/notebook.pdf) [12].

# Model predictions

Before discussing the methods by which we can generate posterior predictions, first let us define some additional relevant quantities. Let $\mathcal{D} = \{\boldsymbol{y}_i, T_i, d_i; i = 1, \ldots, N\}$ be the entire collection of outcome data in the sample. We will refer to this sample as the "training data". Let $T_{max} = \max\{T_i; i = 1, \ldots, N\}$ denote the maximum event or censoring time across the $i = 1, \ldots, N$ individuals in our training data.

## Individual-specific predictions for in-sample individuals (for $0 \leq t \leq T_i$)

We can generate posterior predictions for the longitudinal and time-to-event outcomes in the following manner. For the $i^{th}$ individual in our training data, a predicted value for the $m^{th}$ longitudinal biomarker at time $t$, denoted $y^*_{im}(t)$, can be generated from the posterior predictive distribution

$$p\Big(y^*_{im}(t) \mid \mathcal{D}\Big) = \int\int p\Big(y^*_{im}(t) \mid \boldsymbol{\theta}, \boldsymbol{b}_i\Big) p\Big(\boldsymbol{\theta}, \boldsymbol{b}_i \mid \mathcal{D}\Big)\, d\boldsymbol{b}_i\, d\boldsymbol{\theta}$$

and, similarly, a predicted probability of the $i^{th}$ individual being event-free at time $t$, denoted $S^*_i(t)$, can be generated from the posterior predictive distribution

$$p\Big(S^*_i(t) \mid \mathcal{D}\Big) = \int\int p\Big(S^*_i(t) \mid \boldsymbol{\theta}, \boldsymbol{b}_i\Big) p\Big(\boldsymbol{\theta}, \boldsymbol{b}_i \mid \mathcal{D}\Big) d\boldsymbol{b}_i\, d\boldsymbol{\theta}$$

Note that for simplicity we have ignored the implicit conditioning on covariates; $\boldsymbol{x}_{im}(t)$ and $\boldsymbol{z}_{im}(t)$, for $m = 1, \ldots, M$, and $\boldsymbol{w}_i(t)$. Since individual $i$ is included in the training data, it is easy for us to approximate these posterior predictive distributions by drawing from $p(y^*_{im}(t) \mid \boldsymbol{\theta}^{(l)}, \boldsymbol{b}_i^{(l)})$ and $p(S^*_i(t) \mid \boldsymbol{\theta}^{(l)}, \boldsymbol{b}_i^{(l)})$ where $\boldsymbol{\theta}^{(l)}$ and $\boldsymbol{b}_i^{(l)}$ are the $l^{th}$ ($l = 1, \ldots, L$) MCMC draws from the joint posterior distribution $p(\boldsymbol{\theta}, \boldsymbol{b}_i \mid \mathcal{D})$.

These draws from the posterior predictive distributions can be used for assessing the fit of the model. For example,

- the draws from $p(y^*_{im}(t) \mid \mathcal{D})$ for $0 \leq t \leq T_i$ can be used to evaluate the fit of the longitudinal trajectory for the $m^{th}$ biomarker for the $i^{th}$ individual, and
- the draws from $p(S^*_i(t) \mid \mathcal{D})$ for $0 \leq t \leq T_{max}$ can be averaged across the $N$ individuals to obtain a standardised survival curve (discussed in greater detail in later sections) which can then be compared to the observed survival curve, for example, the Kaplan-Meier curve.

## Individual-specific predictions for in-sample individuals (for $t > C_i$)

However, given that we know the event or censoring time for each individual in our training data, it may make more sense to consider what will happen to censored individuals in our study when we look beyond their last known survival time (i.e. extrapolation).

For an individual $i$, who was in our training data, and who was known to be event-free up until their censoring time $C_i$, we wish to draw from the conditional posterior predictive distribution for their longitudinal outcome at some time $t > C_i$, that is

$$p\Big(y^*_{im}(t) \mid \mathcal{D}, t > C_i\Big) = \int\int p\Big(y^*_{im}(t) \mid \boldsymbol{\theta}, \boldsymbol{b}_i, t > C_i\Big) p\Big(\boldsymbol{\theta}, \boldsymbol{b}_i \mid \mathcal{D}\Big) d\boldsymbol{b}_i\, d\boldsymbol{\theta}$$

and the conditional posterior predictive distribution for their survival probability at some time $t > C_i$, that is

$$p\Big(S_i^*(t) \mid \mathcal{D}, t > C_i, T_i^* > C_i\Big) = \frac{p\Big(S_i^*(t) \mid \mathcal{D}\Big)}{p\Big(S_i^*(C_i) \mid \mathcal{D}\Big)} = \int\int \frac{p\Big(S_i^*(t) \mid \boldsymbol{\theta}, \boldsymbol{b}_i\Big)}{p\Big(S_i^*(C_i) \mid \boldsymbol{\theta}, \boldsymbol{b}_i\Big)} p\Big(\boldsymbol{\theta}, \boldsymbol{b}_i \mid \mathcal{D}\Big) d\boldsymbol{b}_i \, d\boldsymbol{\theta}$$

These draws from the conditional posterior predictive distributions can be used to extrapolate into the future for individual $i$, conditional on their longitudinal biomarker data collected between baseline and their censoring time $C_i$. For example,

- the draws from $p(y_{im}^*(t) \mid \mathcal{D}, t > C_i)$ for $C_i \leq t \leq T_{max}$ can be used to show the forecasted longitudinal trajectory for the $m^{th}$ biomarker for the $i^{th}$ individual, and
- the draws from $p(S_i^*(t) \mid \mathcal{D}, t > C_i, T_i^* > C_i))$ for $C_i \leq t \leq T_{max}$ can be used to show the estimated conditional probability of individual $i$ remaining event-free into the future.

## Individual-specific predictions for out-of-sample individuals (i.e. dynamic predictions)

**TBC.** Describe dynamic predictions under the framework of Rizopoulos (2011) [18]. These types of individual-specific predictions can be obtained using the `posterior_traj` and `posterior_survfit` functions by providing prediction data and specifying `dynamic = TRUE` (which is the default); see the examples provided below.

## Population-level (i.e. marginal) predictions

We can also generate posterior predictions for the longitudinal and time-to-event outcomes that do not require any conditioning on observed outcome data for a specific individual. Here, we will discuss two ways in which this can be done.

The first way is to "marginalise" over the distribution of the individual-specific parameters. We wish to generate a predicted value for the $m^{th}$ longitudinal biomarker at time $t$ for a new individual $k$ for whom we do not have any observed data. We will denote this prediction $y_{km}^*(t)$ and note that it can be generated from the posterior predictive distribution for the longitudinal outcome

$$p\Big(y_{km}^*(t) \mid \mathcal{D}\Big) = \int\int p\Big(y_{km}^*(t) \mid \boldsymbol{\theta}, \tilde{\boldsymbol{b}}_k\Big) p\Big(\boldsymbol{\theta}, \tilde{\boldsymbol{b}}_k \mid \mathcal{D}\Big) \, d\tilde{\boldsymbol{b}}_k \, d\boldsymbol{\theta} = \int\int p\Big(y_{km}^*(t) \mid \boldsymbol{\theta}, \tilde{\boldsymbol{b}}_k\Big) p\Big(\tilde{\boldsymbol{b}}_k \mid \boldsymbol{\theta}\Big) p\Big(\boldsymbol{\theta} \mid \mathcal{D}\Big) \, d\tilde{\boldsymbol{b}}_k \, d\boldsymbol{\theta}$$

and similiarly for the survival probability

$$p\Big(S_k^*(t) \mid \mathcal{D}\Big) = \int\int p\Big(S_k^*(t) \mid \boldsymbol{\theta}, \tilde{\boldsymbol{b}}_k\Big) p\Big(\boldsymbol{\theta}, \tilde{\boldsymbol{b}}_k \mid \mathcal{D}\Big) d\boldsymbol{b}_k \, d\boldsymbol{\theta} = \int\int p\Big(S_k^*(t) \mid \boldsymbol{\theta}, \tilde{\boldsymbol{b}}_k\Big) p\Big(\tilde{\boldsymbol{b}}_k \mid \boldsymbol{\theta}\Big) p\Big(\boldsymbol{\theta} \mid \mathcal{D}\Big) d\boldsymbol{b}_k \, d\boldsymbol{\theta}$$

We can obtain draws for $\tilde{\boldsymbol{b}}_k$ in the same manner as for the individual-specific parameters $\boldsymbol{b}_i$. That is, at the $l^{th}$ iteration of the MCMC sampler we draw $\tilde{\boldsymbol{b}}_k^{(l)}$ and store it[3]. However, individual $k$ did not provide any contribution to the training data and so we are effectively taking random draws from the posterior distribution for the individual-specific parameters. We are therefore effectively marginalising over the distribution of the group-specific coefficients when we obtain predictions using the draws $\tilde{\boldsymbol{b}}_k^{(l)}$ fro $l = 1, \ldots, L$. In other words, we are predicting for a new individual whom we have no information except that they are drawn from the same population as the $i = 1, \ldots, N$ individuals in the training data. Because these predictions will incorporate all the uncertainty associated with between-individual variation our 95% credible intervals are likely to be very wide. These types of marginal predictions can be obtained using the `posterior_traj` and `posterior_survfit` functions by providing prediction data and specifying `dynamic = FALSE`; see the examples provided below.

The second way is to effectively ignore the group-level structure in the model. That is, to only predict with only the population-level parameters contributing to the model. For example, under a identity link function and normal error distribution (i.e. linear mixed effect longitudinal submodel), we would obtain draws from the distribution $y_{km}^{(l)}(t) \sim N\Big(\boldsymbol{x}_{km}^T(t)\boldsymbol{\beta}_m^{(l)}, \sigma_m^{(l)}\Big)$ where $\boldsymbol{\beta}_m^{(l)}$ and $\sigma_m^{(l)}$ are the population-level parameters and residual error standard deviation, respectively, for the $l^{th}$ draw of the MCMC samples. However, referring to this as a "marginal" prediction is somewhat misleading since we are not explicitly conditioning on the individual-specific parameters but we are implicitly assuming that we know they are equal to zero with absolute certainty. That is, we are actually drawing from the posterior predictive distribution for the longitudinal outcome

$$p\Big(y_{km}^*(t) \mid \mathcal{D}\Big) = \int p\Big(y_{km}^*(t) \mid \boldsymbol{\theta}, \boldsymbol{b}_k = 0\Big) p\Big(\boldsymbol{\theta} \mid \mathcal{D}\Big) d\boldsymbol{\theta}$$

and similarly for the survival probability

$$p\Big(S_k^*(t) \mid \mathcal{D}\Big) = \int p\Big(S_k^*(t) \mid \boldsymbol{\theta}, \boldsymbol{b}_k = 0\Big) p\Big(\boldsymbol{\theta} \mid \mathcal{D}\Big) d\boldsymbol{\theta}$$

These types of so-called "marginal" predictions can not currently be obtained using the `posterior_traj` and `posterior_survfit` functions.

### Standardised survival probabilities

All of the previously discussed population-level (i.e. marginal) predictions assumed implicit conditioning on some covariate values for the longitudinal submodel, $\boldsymbol{x}_{im}(t)$ and $\boldsymbol{z}_{im}(t)$ for $m = 1, \ldots, M$, and for the event submodel, $\boldsymbol{w}_i(t)$. Even though we marginalise over the distribution of the individual-specific parameters we were still assuming that we obtained predictions for some known values of the covariates. However, sometimes we wish to marginalise (i.e. average) over the observed distribution of covariates as well. Here we discuss a method by which we can do that for the predicted survival probabilities.

At any time $t$, it is possible to obtain a standardised survival probability by averaging the individual-specific survival probabilities. That is, we can obtain

$$S^*(t) = \frac{\sum_{i=1}^{N^{pred}} S_i^*(t)}{N^{pred}}$$

where $S_i^*(t)$ is the predicted survival probability for individual $i$ ($i = 1, \ldots, N^{pred}$ at time $t$, and $N^{pred}$ is the number of individuals included in the prediction dataset. We refer to these predictions as *standardised survival probabilities*.

Note however, that if $N_{pred}$ is not sufficiently large (e.g. we pass new data with just 2 individuals, say) then marginalising over their covariate distribution may not be meaningful and, similarly, their joint random effects distribution may be a poor representation of the random effects distribution for the entire population. It is better to calculate these standardised survival probabilities using where, say, $N^{pred}$ is equal to the total number of individuals in the training data.

## Model extensions

### Delayed entry (left-truncation)

**TBC.**

### Multilevel clustering

**TBC.**

## Model comparison

### LOO/WAIC in the context of joint models

**TBC.**

### Usage examples

## Dataset used in the examples

We use the Mayo Clinic's primary biliary cirrhosis (PBC) dataset in the examples below. The dataset contains 312 individuals with primary biliary cirrhosis who participated in a randomised placebo controlled trial of D-penicillamine conducted at the Mayo Clinic between 1974 and 1984 [19]. However, to ensure the examples run quickly, we use a small random subset of just 40 patients from the full data.

These example data are contained in two separate data frames. The first data frame contains multiple-row per patient longitudinal biomarker information, as shown in

```
head(pbcLong)
```

```
  id      age sex trt      year     logBili albumin platelet
1  1 58.76523   f   1 0.0000000  2.67414865    2.60      190
2  1 58.76523   f   1 0.5256674  3.05870707    2.94      183
3  2 56.44627   f   1 0.0000000  0.09531018    4.14      221
4  2 56.44627   f   1 0.4982888 -0.22314355    3.60      188
5  2 56.44627   f   1 0.9993155  0.00000000    3.55      161
6  2 56.44627   f   1 2.1026694  0.64185389    3.92      122
```

while the second data frame contains single-row per patient survival information, as shown in

```
head(pbcSurv)
```

```
   id      age sex trt futimeYears status death
1   1 58.76523   f   1    1.095140      2     1
3   2 56.44627   f   1   14.151951      0     0
12  3 70.07255   m   1    2.770705      2     1
16  4 54.74059   f   1    5.270363      2     1
23  5 38.10541   f   0    4.120465      1     0
29  6 66.25873   f   0    6.852841      2     1
```

The variables included across the two datasets can be defined as follows:

- `age` in years
- `albumin` serum albumin (g/dl)
- `logBili` logarithm of serum bilirubin
- `death` indicator of death at endpoint
- `futimeYears` time (in years) between baseline and the earliest of death, transplantion or censoring
- `id` numeric ID unique to each individual
- `platelet` platelet count
- `sex` gender (m = male, f = female)
- `status` status at endpoint (0 = censored, 1 = transplant, 2 = dead)
- `trt` binary treatment code (0 = placebo, 1 = D-penicillamine)
- `year` time (in years) of the longitudinal measurements, taken as time since baseline)

A description of the example datasets can be found by accessing the following help documentation:

```
help("datasets", package = "rstanarm")
```

# Fitting the models

## Univariate joint model (current value association structure)

In this example we fit a simple univariate joint model, with one normally distributed longitudinal marker, an association structure based on the current value of the linear predictor, and B-splines baseline hazard. To fit the model we use the joint (longitudinal and time-to-event) modelling function in the **rstanarm** package: `stan_jm`. When calling `stan_jm` we must, at a minimum, specify a formula object for each of the longitudinal and event submodels (through the arguments `formulaLong` and `formulaEvent`), the data frames which contain the variables for each of the the longitudinal and event submodels (through the arguments `dataLong` and `dataEvent`), and the name of the variable representing time in the longitudinal submodel (through the argument `time_var`).

The formula for the longitudinal submodel is specified using the **lme4** package formula style. That is `y ~ x + (random_effects | grouping_factor)`. In this example we specify that log serum bilirubin (`logBili`) follows a subject-specific linear trajectory. To do this we include a fixed intercept and fixed slope (`year`), as well as a random intecept and random slope for each subject `id` (`(year | id)`).

The formula for the event submodel is specified using the **survival** package formula style. That is, the outcome of the left of the `~` needs to be of the format `Surv(event_time, event_indicator)` (`http://www.rdocumentation.org/packages/survival/topics/Surv`) for single row per individual data, or `Surv(start_time, stop_time, event_indicator)` (`http://www.rdocumentation.org/packages/survival/topics/Surv`) for multiple row per individual data. The latter allows for exogenous time-varying covariates to be included in the event submodel. In this example we assume that the log hazard of death is linearly related to gender (`sex`) and an indicator of treatment with D-penicillamine (`trt`).

```
library(rstanarm)
mod1 <- stan_jm (../reference/stan_jm.html)(formulaLong = logBili ~ sex + trt + year + (year | id),
                 dataLong = pbcLong,
                 formulaEvent = survival::Surv (http://www.rdocumentation.org/packages/survival/topi
                 dataEvent = pbcSurv,
                 time_var = "year",
                 chains = 1, refresh = 2000, seed = 12345)
```

```
Fitting a univariate joint model.

Please note the warmup may be much slower than later iterations!

SAMPLING FOR MODEL 'jm' NOW (CHAIN 1).

Gradient evaluation took 0.000548 seconds
1000 transitions using 10 leapfrog steps per transition would take 5.48 seconds.
Adjust your expectations accordingly!


Iteration:    1 / 2000 [  0%]  (Warmup)
Iteration: 1001 / 2000 [ 50%]  (Sampling)
Iteration: 2000 / 2000 [100%]  (Sampling)

 Elapsed Time: 36.4638 seconds (Warm-up)
               24.5074 seconds (Sampling)
               60.9712 seconds (Total)
```

The argument `refresh = 2000` was specified so that Stan didn't provide us with excessive progress updates whilst fitting the model. However, if you are fitting a model that will take several minutes or hours to fit, then you may wish to request progress updates quite regularly, for example setting `refresh = 20` for every 20 iterations (by default the refresh argument is set to 1/10th of the total number of iterations).

The fitted model is returned as an object of the S3 class `stanjm`. We have a variety of methods and postestimation functions available for this class, including: `print`, `summary`, `plot`, `fixef`, `ranef`, `coef`, `VarCorr`, `posterior_interval`, `update`, and more. Here, we will examine the most basic output for the fitted joint model by typing `print(f1)`:

```
stan_jm
 formula (Long1): logBili ~ sex + trt + year + (year | id)
 family  (Long1): gaussian [identity]
 formula (Event): survival::Surv(futimeYears, death) ~ sex + trt
 baseline hazard: bs
 assoc:           etavalue (Long1)
------

Longitudinal submodel: logBili
            Median MAD_SD
(Intercept)  0.269  0.598
sexf         0.485  0.581
trt         -0.161  0.411
year         0.208  0.037
sigma        0.354  0.018

Event submodel:
                Median MAD_SD exp(Median)
(Intercept)     -3.145  0.639  0.043
sexf            -0.340  0.642  0.712
trt             -0.752  0.448  0.472
Long1|etavalue   1.341  0.240  3.823
b-splines-coef1 -0.900  0.992     NA
b-splines-coef2  0.513  0.860     NA
b-splines-coef3 -1.871  1.219     NA
b-splines-coef4  0.479  1.634     NA
b-splines-coef5 -0.194  1.622     NA
b-splines-coef6 -0.761  1.795     NA

Group-level error terms:
 Groups Name              Std.Dev. Corr
 id     Long1|(Intercept) 1.2956
        Long1|year        0.1898   0.52
Num. levels: id 40

Sample avg. posterior predictive distribution
of longitudinal outcomes:
               Median MAD_SD
Long1|mean_PPD 0.588  0.030

------
For info on the priors used see help('prior_summary.stanreg').
```

The output tells us that for each one unit increase in an individual's underlying level of log serum bilirubin, their estimated log hazard of death increases by 36% (equivalent to a 3.9-fold increase in the hazard of death). The mean absolute deviation (MAD) is provided as a more robust estimate of the standard deviation of the posterior distribution. In this case the MAD_SD for the association parameter is 0.247, indicating there is quite large uncertainty around the estimated association between log serum bilirubin and risk of death (recall this is a small dataset containing only 40 patients!).

If we wanted some slightly more detailed output for each of the model parameters, as well as further details regarding the model estimation (for example computation time, number of longitudinal observations, number of individuals, type of baseline hazard, etc) we can instead use the `summary` method:

```
summary(mod1, probs = c(.025,.975))
```

```
Model Info:

 function:        stan_jm
 formula (Long1): logBili ~ sex + trt + year + (year | id)
 family  (Long1): gaussian [identity]
 formula (Event): survival::Surv(futimeYears, death) ~ sex + trt
 baseline hazard: bs
 assoc:           etavalue (Long1)
 algorithm:       sampling
 priors:          see help('prior_summary')
 sample:          1000 (posterior sample size)
 num obs:         304 (Long1)
 num subjects:    40
 num events:      29 (72.5%)
 groups:          id (40)
 runtime:         1 mins

Estimates:
                                              mean     sd       2.5%
Long1|(Intercept)                              0.272    0.603   -0.921
Long1|sexf                                     0.490    0.598   -0.686
Long1|trt                                     -0.158    0.433   -1.006
Long1|year                                     0.211    0.039    0.145
Long1|sigma                                    0.355    0.017    0.324
Long1|mean_PPD                                 0.587    0.030    0.526
Event|(Intercept)                             -3.164    0.623   -4.363
Event|sexf                                    -0.331    0.616   -1.438
Event|trt                                     -0.755    0.459   -1.663
Event|b-splines-coef1                         -1.000    1.048   -3.353
Event|b-splines-coef2                          0.476    0.870   -1.296
Event|b-splines-coef3                         -1.879    1.195   -4.189
Event|b-splines-coef4                          0.416    1.683   -3.095
Event|b-splines-coef5                         -0.149    1.689   -3.469
Event|b-splines-coef6                         -1.016    1.806   -5.091
Assoc|Long1|etavalue                           1.353    0.241    0.933
Sigma[id:Long1|(Intercept),Long1|(Intercept)]  1.679    0.433    1.063
Sigma[id:Long1|year,Long1|(Intercept)]         0.127    0.075    0.003
Sigma[id:Long1|year,Long1|year]                0.036    0.018    0.015
log-posterior                               -329.910   10.055 -349.931
                                              97.5%
Long1|(Intercept)                              1.527
Long1|sexf                                     1.699
Long1|trt                                      0.752
Long1|year                                     0.291
Long1|sigma                                    0.388
Long1|mean_PPD                                 0.645
Event|(Intercept)                             -2.013
Event|sexf                                     0.848
Event|trt                                      0.134
Event|b-splines-coef1                          0.818
Event|b-splines-coef2                          2.103
Event|b-splines-coef3                          0.430
Event|b-splines-coef4                          3.434
Event|b-splines-coef5                          3.207
Event|b-splines-coef6                          1.892
Assoc|Long1|etavalue                           1.849
Sigma[id:Long1|(Intercept),Long1|(Intercept)]  2.740
Sigma[id:Long1|year,Long1|(Intercept)]         0.306
Sigma[id:Long1|year,Long1|year]                0.078
```

```
log-posterior                                −310.239

Diagnostics:
                                           mcse  Rhat  n_eff
Long1|(Intercept)                          0.041 0.999  219
Long1|sexf                                 0.035 0.999  290
Long1|trt                                  0.041 1.008  110
Long1|year                                 0.003 1.002  154
Long1|sigma                                0.001 1.002  772
Long1|mean_PPD                             0.001 0.999 1110
Event|(Intercept)                          0.020 0.999  925
Event|sexf                                 0.020 0.999  963
Event|trt                                  0.015 1.001  909
Event|b-splines-coef1                      0.033 1.000 1037
Event|b-splines-coef2                      0.033 0.999  678
Event|b-splines-coef3                      0.048 1.000  631
Event|b-splines-coef4                      0.074 1.000  520
Event|b-splines-coef5                      0.072 1.000  548
Event|b-splines-coef6                      0.066 0.999  760
Assoc|Long1|etavalue                       0.008 0.999  856
Sigma[id:Long1|(Intercept),Long1|(Intercept)] 0.030 1.001  213
Sigma[id:Long1|year,Long1|(Intercept)]     0.006 0.999  156
Sigma[id:Long1|year,Long1|year]            0.001 0.999  164
log-posterior                              0.852 1.014  139

For each parameter, mcse is Monte Carlo standard error, n_eff is a crude measure of effective sampl
```

The easiest way to extract the correlation matrix for the random effects (aside from viewing the `print` output) is to use the `VarCorr` function (modelled on the `VarCorr` function from the **lme4** package). If you wish to extract the variances and covariances (instead of the standard deviations and correlations) then you can type the following to return a data frame with all of the relevant information:

```
as.data.frame(VarCorr (../reference/stanreg-methods.html)(mod1))
```

```
  grp             var1       var2       vcov     sdcor
1  id Long1|(Intercept)       <NA> 1.67863293 1.2956207
2  id        Long1|year       <NA> 0.03602176 0.1897940
3  id Long1|(Intercept) Long1|year 0.12685329 0.5158713
```

## Univariate joint model (current value and current slope association structure)

In the previous example we were fitting a shared parameter joint model which assumed that the log hazard of the event (in this case the log hazard of death) at time *t* was linearly related to the subject-specific expected value of the longitudinal marker (in this case the expected value of log serum bilirubin) also at time *t*. This is the default association structure, although it could be explicitly specified by setting the `assoc = "etavalue"` argument.

However, let's suppose we believe that the log hazard of death is actually related to both the *current value* of log serum bilirubin and the current *rate of change* in log serum bilirubin. To estimate this joint model we need to indicate that we want to also include the subject-specific slope (at time *t*) from the longitudinal submodel as part of the association structure. We do this by setting the `assoc` argument equal to a character vector `c("etavalue", "etaslope")` which indicates our desired association structure:

```
mod2 <- stan_jm (../reference/stan_jm.html)(formulaLong = logBili ~ sex + trt + year + (year | id),
                dataLong = pbcLong,
                formulaEvent = survival::Surv (http://www.rdocumentation.org/packages/survival/topi
                dataEvent = pbcSurv,
                assoc = c("etavalue", "etaslope"),
                time_var = "year",
                chains = 1, refresh = 2000, seed = 12345)
```

In this example the subject-specific slope is actually constant across time *t* since we have a linear trajectory. Note however that we could still use the `"etaslope"` association structure even if we had a non-linear subject specific trajectory (for example modelled using cubic splines or polynomials).

## Multivariate joint model (current value association structures)

Suppose instead that we were interested in *two* repeatedly measured clinical biomarkers, log serum bilirubin and serum albumin, and their association with the risk of death. We may wish to model these two biomarkers, allowing for the correlation between them, and estimating their respective associations with the log hazard of death. We will fit a linear mixed effects submodel (identity link, normal

distribution) for each biomarker with a patient-specific intercept and linear slope but no other covariates. In the event submodel we will include gender ( `sex` ) and treatment ( `trt` ) as baseline covariates. Each biomarker is assumed to be associated with the log hazard of death at time $t$ via it's expected value at time $t$ (i.e. a *current value* association structure).

The model we are going to fit can therefore be specified as:

$$y_{im}(t_{ijm}) \sim N(\mu_{im}(t_{ijm}), \sigma_m)$$

$$\eta_{im}(t) = \mu_{im}(t) = \beta_{0m} + \beta_{1m}t + b_{0mi} + b_{1mi}t$$

$$h_i(t) = h_0(t; \boldsymbol{\omega}) \exp(\gamma_1 w_{1i} + \gamma_2 w_{2i} + \alpha_{1i}\mu_{i1}(t) + \alpha_{2i}\mu_{i2}(t))$$

where $t$ is time in years, and $w_{1i}$ and $w_{2i}$ are, respectively, the gender and treatment indicators for individual $i$.

(Note that due to the very small sample size, the clinical findings from this analysis should not to be overinterpreted!).

```
mod3 <- stan_jm (../reference/stan_jm.html)(
    formulaLong = list(
        logBili ~ sex + trt + year + (year | id),
        albumin ~ sex + trt + year + (year | id)),
    formulaEvent = survival::Surv (http://www.rdocumentation.org/packages/survival/topics/Surv)(fut
    dataLong = pbcLong, dataEvent = pbcSurv,
    time_var = "year",
    chains = 1, refresh = 2000, seed = 12345)
```

```
Fitting a multivariate joint model.

Please note the warmup may be much slower than later iterations!

SAMPLING FOR MODEL 'jm' NOW (CHAIN 1).

Gradient evaluation took 0.000713 seconds
1000 transitions using 10 leapfrog steps per transition would take 7.13 seconds.
Adjust your expectations accordingly!


Iteration:    1 / 2000 [  0%]  (Warmup)
Iteration: 1001 / 2000 [ 50%]  (Sampling)
Iteration: 2000 / 2000 [100%]  (Sampling)

 Elapsed Time: 58.2278 seconds (Warm-up)
               59.3122 seconds (Sampling)
               117.54 seconds (Total)
```

We can now examine the output from the fitted model, for example

```
print(mod3)
```

```
stan_jm
 formula (Long1): logBili ~ sex + trt + year + (year | id)
 family  (Long1): gaussian [identity]
 formula (Long2): albumin ~ sex + trt + year + (year | id)
 family  (Long2): gaussian [identity]
 formula (Event): survival::Surv(futimeYears, death) ~ sex + trt
 baseline hazard: bs
 assoc:           etavalue (Long1), etavalue (Long2)
------

Longitudinal submodel 1: logBili
            Median MAD_SD
(Intercept)  0.185  0.527
sexf         0.541  0.520
trt         -0.019  0.367
year         0.220  0.040
sigma        0.354  0.017

Longitudinal submodel 2: albumin
            Median MAD_SD
(Intercept)  3.480  0.247
sexf         0.049  0.249
trt         -0.009  0.167
year        -0.153  0.022
sigma        0.290  0.013

Event submodel:
                Median  MAD_SD  exp(Median)
(Intercept)      6.863   2.815 955.917
sexf            -0.069   0.713   0.933
trt             -0.498   0.479   0.608
Long1|etavalue   0.789   0.262   2.202
Long2|etavalue  -3.079   0.872   0.046
b-splines-coef1 -0.990   1.161      NA
b-splines-coef2  0.494   0.894      NA
b-splines-coef3 -2.570   1.268      NA
b-splines-coef4 -0.640   1.711      NA
b-splines-coef5 -1.118   1.754      NA
b-splines-coef6 -2.811   1.780      NA

Group-level error terms:
 Groups Name              Std.Dev. Corr
 id     Long1|(Intercept) 1.24157
        Long1|year        0.18766   0.47
        Long2|(Intercept) 0.51959  -0.64 -0.47
        Long2|year        0.09497  -0.54 -0.80  0.42
Num. levels: id 40

Sample avg. posterior predictive distribution
of longitudinal outcomes:
               Median MAD_SD
Long1|mean_PPD 0.586  0.030
Long2|mean_PPD 3.345  0.023

------
For info on the priors used see help('prior_summary.stanreg').
```

or we can examine the summary output for the association parameters alone:

```
summary(mod3, pars = "assoc")
```

```
Model Info:

 function:        stan_jm
 formula (Long1): logBili ~ sex + trt + year + (year | id)
 family  (Long1): gaussian [identity]
 formula (Long2): albumin ~ sex + trt + year + (year | id)
 family  (Long2): gaussian [identity]
 formula (Event): survival::Surv(futimeYears, death) ~ sex + trt
 baseline hazard: bs
 assoc:           etavalue (Long1), etavalue (Long2)
 algorithm:       sampling
 priors:          see help('prior_summary')
 sample:          1000 (posterior sample size)
 num obs:         304 (Long1), 304 (Long2)
 num subjects:    40
 num events:      29 (72.5%)
 groups:          id (40)
 runtime:         2 mins

Estimates:
                       mean   sd     2.5%   25%    50%    75%    97.5%
Assoc|Long1|etavalue  0.806  0.278  0.271  0.627  0.789  0.992  1.374
Assoc|Long2|etavalue -3.141  0.935 -5.099 -3.691 -3.079 -2.516 -1.561

Diagnostics:
                     mcse  Rhat  n_eff
Assoc|Long1|etavalue 0.009 0.999 926
Assoc|Long2|etavalue 0.043 1.001 475

For each parameter, mcse is Monte Carlo standard error, n_eff is a crude measure of effective sampl
```

# Posterior predictions

We can also access the range of post-estimation functions (described in the `stan_jm` and related help documentation; see for example `help(posterior_traj)` or `help(posterior_survfit)`).

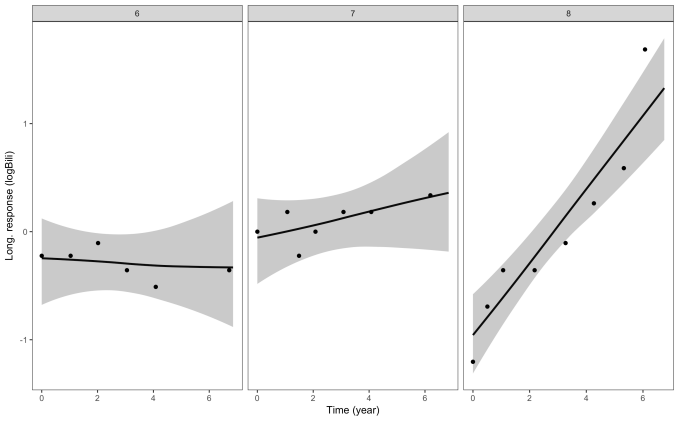
## Predicted individual-specific longitudinal trajectory for in-sample individuals

Predicted individual-specific biomarker values can be obtained using either the `posterior_traj` or `posterior_predict` function. The `posterior_traj` is preferable, because it can be used to obtain the biomarker values at a series of evenly spaced time points between baseline and the individual's event or censoring time by using the default `interpolate = TRUE` option. Whereas, the `posterior_predict` function only provides the predicted biomarker values at the observed time points, or the time points in the new data. Predicting the biomarker values at a series of evenly spaced time points can be convenient because they can be easily used for plotting the longitudinal trajectory. Moreover, by default the `posterior_traj` returns a data frame with variables corresponding to the individual ID, the time, the predicted mean biomarker value, the limits for the 95% credible interval (i.e. uncertainty interval for the predicted mean biomarker value), and limits for the 95% prediction interval (i.e. uncertainty interval for a predicted biomarker data point), where the level for the uncertainty intervals can be changed via the `prob` argument. Conversely, the `posterior_predict` function returns an $S$ by $N$ matrix of predictions where $S$ is the number of posterior draws and $N$ is the number of prediction time points (note that this return type can also be obtained for `posterior_traj` by specifying the argument `return_matrix = TRUE`).

As an example, let's plot the predicted individual-specific longitudinal trajectories for each of the two biomarkers (log serum bilirubin and serum albumin) in the multivariate joint model estimated above. We will do this for three individuals (IDs 6, 7 and 8) who were included in the model estimation.

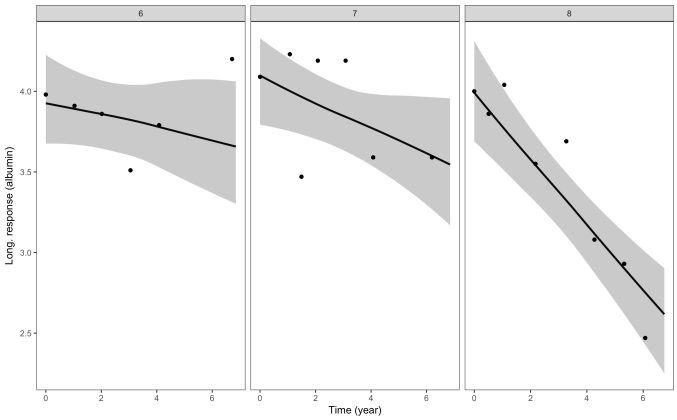
Here are the plots for log serum bilirubin:

```
p1 <- posterior_traj (../reference/posterior_traj.html)(mod3, m = 1, ids = 6:8)
pp1 <- plot(p1, plot_observed = TRUE)
pp1
```




and here are the plots for serum albumin:

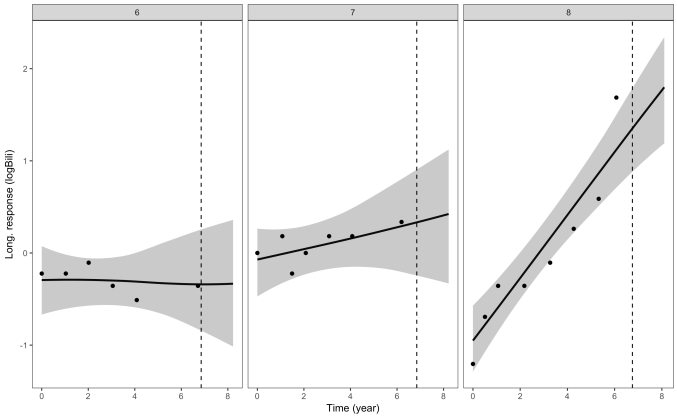
```
p2 <- posterior_traj (../reference/posterior_traj.html)(mod3, m = 2, ids = 6:8)
pp2 <- plot(p2, plot_observed = TRUE)
pp2
```




The `m` argument specifies which biomarker we want to predict for (only relevant for a multivariate joint model). The `ids` argument is optional, and specifies a subset of individuals for whom we want to predict. In the plotting method, the `plot_observed = TRUE` specifies that we want to include the observed biomarker values in the plot of the longitudinal trajectory.

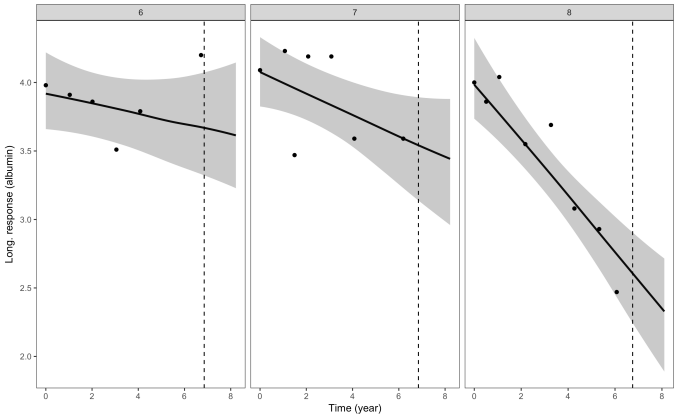
If we wanted to extrapolate the trajectory forward from the event or censoring time for each individual, then this can be easily achieved by specifying `extrapolate = TRUE` in the `posterior_traj` call. For example, here is the plot for log serum bilirubin with extrapolation:

```
p3 <- posterior_traj (../reference/posterior_traj.html)(mod3, m = 1, ids = 6:8, extrapolate = TRUE)
pp3 <- plot(p3, plot_observed = TRUE, vline = TRUE)
pp3
```




and for serum albumin with extrapolation:

```
p4 <- posterior_traj (../reference/posterior_traj.html)(mod3, m = 2, ids = 6:8, extrapolate = TRUE)
pp4 <- plot(p4, plot_observed = TRUE, vline = TRUE)
pp4
```




Here, we included the `vline = TRUE` which adds a vertical dashed line at the timing of the individual's event or censoring time. The interpolation and extrapolation of the biomarker trajectory can be further controlled through the `control` argument to the `posterior_traj` function; for example, we could specify the number of time points at which to predict, the distance by which to extrapolate, and so on.

We could customize these plots further, for example, by using any of the **ggplot2** functionality or using the additional arguments described in `help(plot.predict.stanjm)`.

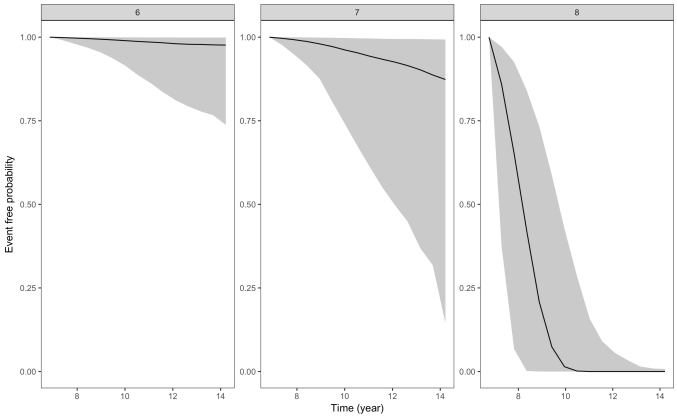
## Predicted individual-specific survival curves for in-sample individuals

Predicted individual-specific survival probabilities and/or survival curves can be obtained using the `posterior_survfit` function. The function by default returns a data frame with the individual ID, the time, and the predicted survival probability (posterior mean and limits for the 95% credible interval). The uncertainty level for the credible interval can be changed via the `prob` argument. By default, individual-specific survival probabilities are calculated *conditional* on the individual's last known survival time. When we are predicting survival probabilities for individuals that were used in the estimation of the model (i.e. in-sample individuals, where no new covariate data is provided), then the individual's "last known survival time" will be their event or censoring time. (Note that if we wanted didn't want to condition on the individual's last known survival time, then we could specify `condition = FALSE`, but we probably wouldn't want to do this unless we were calculating marginal or standardised survival probabilities, which are discussed later).

The default argument `extrapolate = TRUE` specifies that the individual-specific conditional survival probabilities will be calculated at evenly spaced time points between the individual's last known survival time and the maximum follow up time that was observed in the estimation sample. The behaviour of the extrapolation can be further controlled via the `control` argument. If we were to specify `extrapolate = FALSE` then the survival probabilities would only be calculated at one time point, which could be specified in the `times` argument (or otherwise would default to the individual's last known survival time).

As an example, let plot the predicted individual-specific conditional survival curve for the same three individual's that were used in the previous example. The predicted survival curve will be obtained under the multivariate joint model estimated above.

```
p5 <- posterior_survfit (../reference/posterior_survfit.html)(mod3, ids = 6:8)
pp5 <- plot(p5)
pp5
```

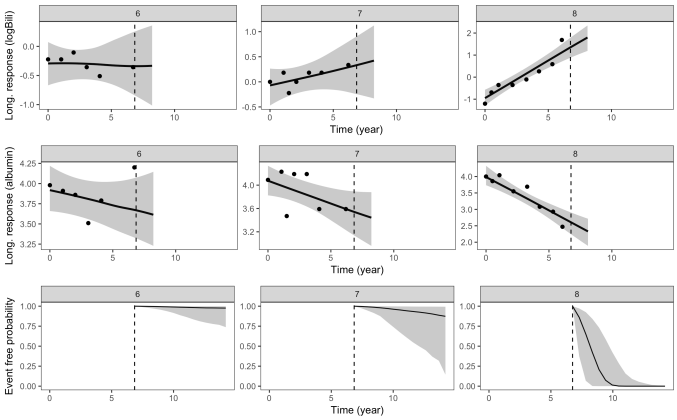



We could customize the plot further, for example, by using any of the **ggplot2** functionality or using the additional arguments described in `help(plot.survfit.stanjm)`.

## Combined plot of longitudinal trajectories and survival curves

The package also provides a convenience plotting function, which combines plots of the individual-specific longitudinal trajectories, and the individual-specific survival function. We can demonstrate this by replotting the predictions for the three individuals in the previous example:

```
plot_stack_jm (../reference/plot.survfit.stanjm.html)(yplot = list(pp3, pp4), survplot = pp5)
```




Here we can see the strong relationship between the underlying values of the biomarkers and mortality. Patient `8` who, relative to patients `6` and `7`, has a higher underlying value for log serum bilirubin and a lower underlying value for serum albumin at the end of their follow up has a far worse predicted probability of survival.

## Predicted individual-specific longitudinal trajectory and survival curve for out-of-sample individuals (i.e. dynamic predictions)

Let us take an individual from our training data, in this case the individual with subject ID value `8`. However, we will pretend this individual was not a member of our training data and rather that they are a new individual for whom we have obtained new biomarker measurements. Our goal is to obtain predictions for the longitudinal trajectory for this individual, and their conditional survival curve, given that we know they are conditional on their biomarker measurements we currently have available.

First, let's extract the data for subject `8` and then rename their subject ID value so that they appear to be an individual who was not included in our training dataset:

```
ndL <- pbcLong[pbcLong$id == 8, , drop = FALSE]
ndE <- pbcSurv[pbcSurv$id == 8, , drop = FALSE]
ndL$id <- paste0("new_patient")
ndE$id <- paste0("new_patient")
```

Note that we have both the longitudinal data and event data for this new individual. We require data for both submodels because we are going to generate *dynamic predictions* that require drawing new individual-specific parameters (i.e. random effects) for this individual conditional on their observed data. That means we need to evaluate the likelihood for the full joint model and that requires both the longitudinal and event data (note however that the status indicator `death` will be ignored, since it is assumed that the individual we are predicting for is still alive at the time we wish to generate the predictions).

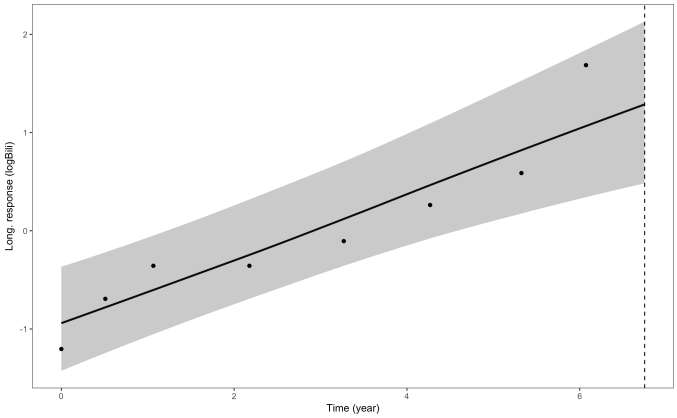
Now we can pass this data to the `posterior_traj` function in the same way as for the in-sample individuals, except we will now specify the `newdataLong` and `newdataEvent` arguments. We will also specify the `last_time` argument so that the function knows which variable in the event data specifies the individual's last known survival time (the default behaviour is to use the time of the last biomarker measurement).

Our predictions for this new individual for the log serum bilirubin trajectory can be obtained using:

```
p6 <- posterior_traj (../reference/posterior_traj.html)(mod3, m = 1,
                      newdataLong = ndL,
                      newdataEvent = ndE,
                      last_time = "futimeYears")
```

```
Drawing new random effects for 1 individuals. Monitoring progress:

  |
  |                                                              |   0%
  |
  |==============================================================| 100%
```

```
pp6 <- plot(p6, plot_observed = TRUE, vline = TRUE)
pp6
```

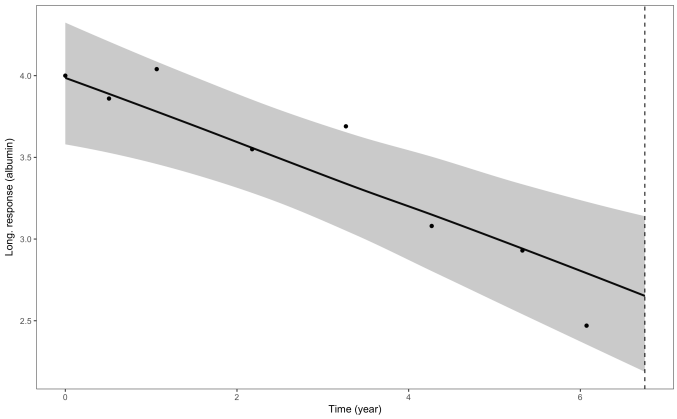



and for the serum albumin trajectory:

```
p7 <- posterior_traj (../reference/posterior_traj.html)(mod3, m = 2,
                      newdataLong = ndL,
                      newdataEvent = ndE,
                      last_time = "futimeYears")
```

```
Drawing new random effects for 1 individuals. Monitoring progress:

  |
  |                                                                |   0%
  |
  |================================================================| 100%
```

```
pp7 <- plot(p7, plot_observed = TRUE, vline = TRUE)
pp7
```

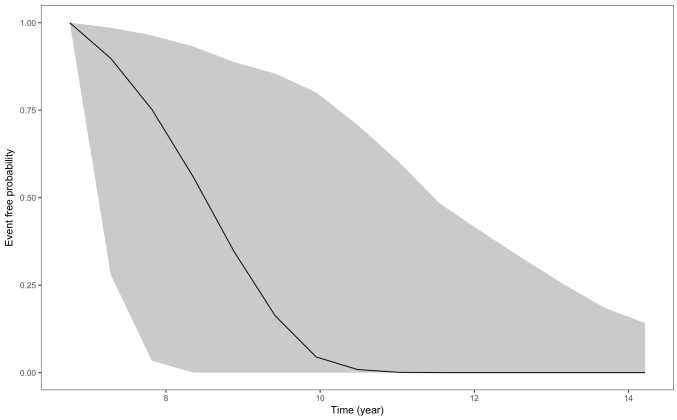



For the conditional survival probabilities we use similar information, provided to the `posterior_survfit` function:

```
p8 <- posterior_survfit (../reference/posterior_survfit.html)(mod3,
                         newdataLong = ndL,
                         newdataEvent = ndE,
                         last_time = "futimeYears")
```

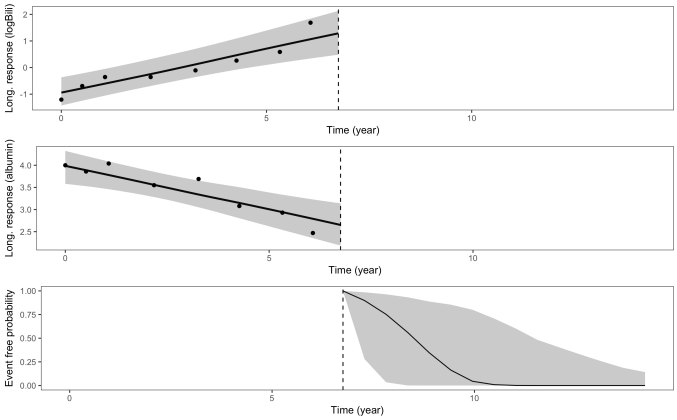
```
Drawing new random effects for 1 individuals. Monitoring progress:

  |
  |                                                                |   0%
  |
  |================================================================| 100%
```

```
pp8 <- plot(p8)
pp8
```




We can then use the `plot_stack_jm` function, as we saw in a previous example, to stack the plots of the longitudinal trajectory and the conditional survival curve:

```
plot_stack_jm (../reference/plot.survfit.stanjm.html)(yplot = list(pp6, pp7), survplot = pp8)
```




Here we see that the predicted longitudinal trajectories and conditional survival curve for this individual, obtained using the dynamic predictions approach, are similar to the predictions we obtained when we used their individual-specific parameters from the original model estimation. This is because in both situations we are conditioning on the same outcome data.

**Side note:** We can even compare the estimated individual specific parameters obtained under the two approaches. For example, here is the posterior mean for the estimated individual-specific parameters for individual `8` from the fitted model:

```
c(ranef (../reference/stanreg-methods.html)(mod3)[["Long1"]][["id"]][8,],
  ranef (../reference/stanreg-methods.html)(mod3)[["Long2"]][["id"]][8,])
```

```
$`(Intercept)`
[1] -1.67049

$year
[1] 0.1105815

$`(Intercept)`
[1] 0.4748229

$year
[1] -0.05140261
```

and here is the mean of the draws for the individual-specific parameters for individual `8` under the dynamic predictions approach:

```
colMeans(attr(p6, "b_new"))
```

```
b[Long1|(Intercept) id:new_patient]        b[Long1|year id:new_patient]
                         -1.66056250                          0.10688008
b[Long2|(Intercept) id:new_patient]        b[Long2|year id:new_patient]
                          0.46746097                         -0.04278264
```

## Predicted population-level longitudinal trajectory

Suppose we wanted to predict the longitudinal trajectory for each of the biomarkers, marginalising over the distribution of the individual-specific parameters. To do this, we can pass a new data frame with the covariate values we want to use in the predictions. Here, we will demonstrate this by obtaining the predicted trajectory for log serum bilirubin, under the multivariate joint model that was estimated previously. Our prediction data will require the variables `year`, `sex` and `trt`, since these were the covariates used in the longitudinal submodel.

We will predict the value of log serum bilirubin at years 0 through 10, for each combination of `sex` and `trt`. We also need to include the `id` variable in our prediction data because this is relevant to the longitudinal submodel. Since we want to marginalise over the individual-specific parameters (i.e. individual-level random effects) we need to note two things:

- First, the values for the `id` variable **must not** match any individual used in the model estimation. Here, we use the following `id` values: `"male_notrt"`, `"female_notrt"`, `"male_trt"`, and `"female_trt"`, since each individual in our prediction data represents a different combination of `sex` and `trt`. However, we could have given the individuals any `id` value just as long as is didn't match an individual who was used in the model estimation
- Second, we need to specify the argument `dynamic = FALSE` when calling `posterior_traj`. This specifies that we do not want to draw new individual-specific parameters conditional on outcome data observed up to some time $t$. Instead, we want predictions that marginalise over the distribution of individual-specific parameters and are therefore conditional *only on covariates* and not conditional on outcome data for the new individuals.

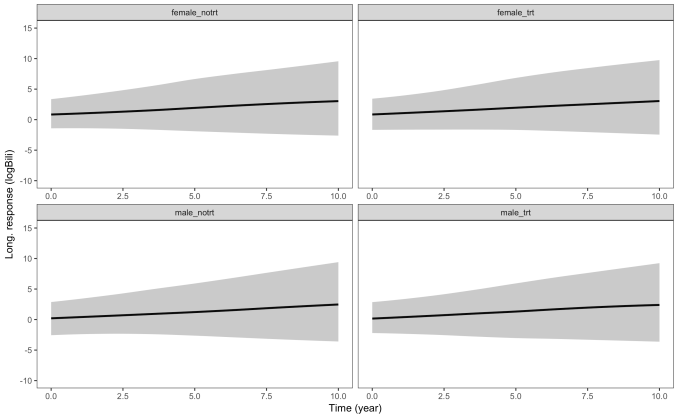
Here is our prediction data:

```
ndL <- expand.grid(year = seq(0, 10, 1),
                   sex = c("m", "f"),
                   trt = 0:1)
ndL$id <- rep(c("male_notrt", "female_notrt",
                "male_trt", "female_trt"), each = 11)
ndL <- ndL[, c(4,1,2,3)]
str(ndL)
```

```
'data.frame':   44 obs. of  4 variables:
 $ id  : chr  "male_notrt" "male_notrt" "male_notrt" "male_notrt" ...
 $ year: num  0 1 2 3 4 5 6 7 8 9 ...
 $ sex : Factor w/ 2 levels "m","f": 1 1 1 1 1 1 1 1 1 1 ...
 $ trt : int  0 0 0 0 0 0 0 0 0 0 ...
```

And to predict the marginal longitudinal trajectory for log serum bilirubin under each covariate profile and plot it we can type:

```
p1 <- posterior_traj (../reference/posterior_traj.html)(mod3, m = 1, newdataLong = ndL, dynamic = F
plot(p1) + ggplot2::coord_cartesian (http://www.rdocumentation.org/packages/ggplot2/topics/coord_ca
```




Because we are marginalising over the distribution of the individual-specific parameters, we are incorporating all the variation related to between-individual differences, and therefore the prediction interval is wide (shown by the shaded area around the marginal longitudinal trajectory). The magnitude of the effects of both `sex` and `trt` are relatively small compared to the population-level effect of `year` and the between-individual variation in the intercept and slope. For example, here are the point estimates for the population-level effects of `sex`, `trt`, and `year`:

```
fixef (../reference/stanreg-methods.html)(mod3)$Long1
```

```
(Intercept)        sexf         trt        year
 0.18533564  0.54101049 -0.01873875  0.21958678
```

and here are the standard deviations for the individual-level random effects:

```
VarCorr (../reference/stanreg-methods.html)(mod3)
```

```
 Groups Name              Std.Dev. Corr
 id     Long1|(Intercept) 1.241572
        Long1|year        0.187664  0.469
        Long2|(Intercept) 0.519592 -0.643 -0.473
        Long2|year        0.094967 -0.543 -0.799  0.418
```

This shows us that the point estimates for the population-level effects of `sex` and `trt` are 0.57 and -0.10, respectively, whereas the standard deviation for the individual-specific intercept and slope parameters are 1.24 and 0.19; hence, any differences due to the population-level effects of gender and treatment (i.e. differences in the black line across the four panels of the plot) are swamped by the width of the uncertainty intervals (i.e. the grey shaded areas).

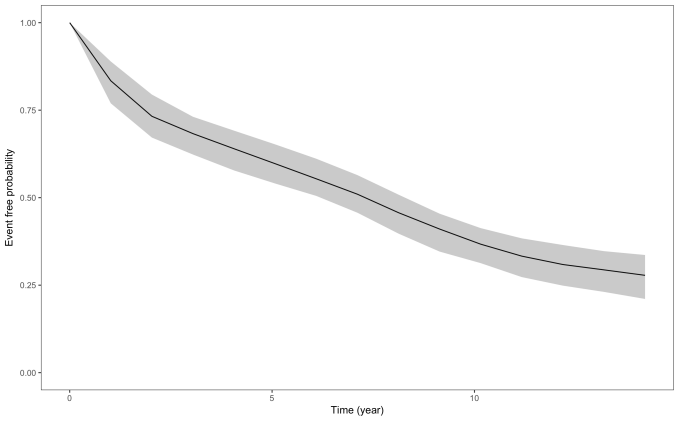
## Standardised survival curves

In this example we show how a standardised survival curve can be obtained, where the $i = 1, \ldots, N^{pred}$ individuals used in generating the standardised survival curve are the same individuals that were used in estimating the model. We will obtain the survival curve for the multivariate joint model estimated in an earlier example ( `mod3` ). The `standardise = TRUE` argument to `posterior_survfit` specifies that we want to obtain individual-specific predictions of the survival curve and then average these. Because, in practical terms, we need to obtain survival probabilities at time *t* for each individual and then average them we want to explicitly specify the values of *t* we want to use (and the same values of *t* will be used for individuals). We specify the values of *t* to use via the `times` argument; here we will predict the standardised survival curve at time 0 and then for convenience we can just specify `extrapolate = TRUE` (which is the default anyway) which will mean we automatically predict at 10 evenly spaced time points between 0 and the maximum event or censoring time.

```
p1 <- posterior_survfit (../reference/posterior_survfit.html)(mod3, standardise = TRUE, times = 0)
head(p1) # data frame with standardised survival probabilities
```

```
    year survpred  ci_lb  ci_ub
1 0.0000   1.0000 1.0000 1.0000
2 1.0154   0.8340 0.7696 0.8891
3 2.0307   0.7325 0.6717 0.7945
4 3.0461   0.6830 0.6233 0.7311
5 4.0614   0.6398 0.5778 0.6914
6 5.0768   0.5971 0.5405 0.6522
```

```
plot(p1) # plot the standardised survival curve
```

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1. By “true” value of the biomarker, we mean the value of the biomarker which is not subject to measurement error or discrete time observation. Of course, for the expected value from the longitudinal submodel to be considered the so-called “true” underlying biomarker value, we would need to have specified the longitudinal submodel appropriately! ↩
2. We refer the reader to the priors vignette (priors.html) for a discussion of the possible prior distributions. ↩
3. These random draws from the posterior distribution of the group-specific parameters are stored each time a joint model is estimated using `stan_glmer`, `stan_mvmer`, or `stan_jm`; they are saved under an ID value called `"_NEW_"` ↩