merlin: An R package for Mixed Effects Regression for Linear, Nonlinear and User-defined models

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Abstract

The R package merlin performs flexible joint modelling of hierarchical multi-outcome data. Increasingly, multiple longitudinal biomarker measurements, possibly censored time-to-event outcomes and baseline characteristics are available. However, there is limited software that allows all of this information to be incorporated into one model. In this paper, we present merlin which allows for the estimation of models with unlimited numbers of continuous, binary, count and time-to-event outcomes, with unlimited levels of nested random effects. A wide variety of link functions, including the expected value, the gradient and shared random effects, are available in order to link the different outcomes in a biologically plausible way. The accompanying predict.merlin function allows for individual and population level predictions to be made from even the most complex models. There is the option to specify user-defined families, making merlin ideal for methodological research. The flexibility of merlin is illustrated using an example in patients followed up after heart valve replacement, beginning with a linear model, and finishing with a joint multiple longitudinal and competing risks survival model.

Keywords: joint modelling, multi-outcome, mixed effects, survival, R, merlin.

1. Introduction

Software packages to fit joint and multi-state models are continuously being developed and updated to increase flexibility. However this flexibility is often limited in terms of outcome types, levels of nested random-effects, or the forms of linking functions between outcomes. We have developed merlin in order to address this lack of flexibility, allowing for a wide range of models to be estimated. With merlin it is possible to include any number of outcomes from a wide range of families, including Gaussian, Bernoulli, Poisson, a number of survival models including flexible parametric models, amongst others. It is also possible to custom
supply user defined families to allow for even greater flexibility and method development. This allows merlin to fit everything from a simple Weibull model to a multivariate joint model. Joint models can be defined using commonly chosen association structures (Gould, Boye, Crowther, Ibrahim, Quartey, Micallef, and Bois 2015), for example, shared random effects, the current value, gradient or area under the curve, and to provide even more customisation - user defined link functions. This R package is based on the recently released merlin package in Stata (Crowther 2017, Crowther (2018)).

Previous software released in R has some of the individual capabilities of merlin. Package JM (Rizopoulos 2010) fits a single normal longitudinal response jointly with a single survival outcome or competing risk outcomes, assuming a current value or current gradient link. There is also an extension JMBayes (Rizopoulos 2016) which fits similar models in a Bayesian framework. joineR (Philipson, Sousa, Diggle, Williamson, Kolamunnage-Dona, Henderson, and Hickey 2018) allows for the joint modelling of a single longitudinal response and a single time-to-event outcome or competing risk outcome. The extension joineRML (Hickey, Philipson, Jorgensen, and Kolamunnage-Dona 2018) additionally allows for multivariate longitudinal data. The frailtypack (Rondeau, Mazroui, and Gonzalez 2012) package fits shared, joint and nested frailty models, with one longitudinal response and multiple recurrent and terminal events.

New package merlin offers additional flexibility in how the joint model is specified. Multiple longitudinal responses can be specified and there is a wider range of models available to better describe the data, including splines and fractional polynomials. There is also a wider variety of survival models available compared to joineR which only allows Cox models, and JM and frailtypack which allow Cox, Weibull and limited spline based survival models. In addition to these models, merlin allows for exponential survival models, and a wider range of flexible spline based models such as Royston-Parmar models (Royston 2001). While it is possible to fit models with multiple shared random-effects, there are additional link functions available to describe the relationship between the longitudinal and time-to-event outcomes, including current expected value, or other functions of the longitudinal response, including derivatives and integrals. A number of packages exist which allow for multiple hierarchical levels of random-effects for either longitudinal responses (lme4 (Bates, Mächler, Bolker, and Walker 2015) or nlme (Pinheiro, Bates, DebRoy, Sarkar, and R Core Team 2019)) or time-to-event outcomes (coxme (Therneau 2019)). Each of the joint modelling packages described above only allow for one level of clustering, with the exception of frailtypack which allows for two, whereas merlin can incorporate any number of nested levels, which is particularly useful for big data such as electronic health records, which is often hierarchical.

Further flexibility is provided in merlin with the option of user-defined functions. This allows users to define their own likelihood functions, merlin is then used as a wrapper function to carry out the optimisation, similar to BAMLSS (Umlauf, Klein, and Zeileis 2017) which uses a modular “Lego brick” approach in a Bayesian framework. Allowing users to extend merlin via user-defined functions makes it a useful tool for the development of new methods.

In this paper we introduce the modular syntax employed by merlin which enables its flexibility. In order to illustrate this flexibility we will develop an example model using data from an observational study of patients following aortic valve replacement surgery (Lim, Ali, Theodorou, Sousa, Ashrafian, Chamageorgakis, Duncan, Henein, Diggle, and Pepper 2008). In Section 2 we explain the syntax to specify the model structure and use the predict function. In Section 3 we work through an illustrative example in patients following heart valve
replacement. Finally in Section 4 we discuss the advantages of using merlin and plans for future extensions.

2. Specifying model structure

2.1. Syntax

The syntax for merlin is modular in nature. The family is specified for each outcome, the linear predictor for each outcome can then be built from components such as an intercept, covariates and random effects.

merlin(model = list(model1, model2, ...),
       family = c("family1", "family2", ...),
       levels = "level1",
       data = data))

Where the syntax for each model is

model1 <- depvar ~ component1 + component2 + ..., model_options

Each component can be made up of a number of elements such as covariates, random effects, functions of time and expected values of other outcomes. Interactions between elements can be specified using : between different elements. By default a coefficient will be estimated for each component, the coefficient can be constrained to 1 using *1.

component1 <- element1 [:element2] [:element3] [...] [*1]

A number of model families are currently available, including

- **gaussian** - Gaussian distribution
- **bernoulli** - Bernoulli distribution
- **poisson** - Poisson distribution
- **beta** - beta distribution
- **negbinomial** - Negative binomial distribution

As well as a number of survival models

- **exponential** - exponential survival distribution
- **weibull** - Weibull distribution
- **gompertz** - Gompertz distribution
- **rp** - Royston-Parmar survival model, (complex predictor on the log cumulative hazard scale)
- **loghazard** - general log hazard model (complex predictor on the log hazard scale)

With two user-defined options

- **user** - which fits a user-defined model which can be written using merlin’s utility functions. The name of the user-defined function needs to be passed through using userf option
null - which is a convenience tool for defining additional complex predictors, that do not contribute to the log likelihood

2.2. Element types

Each element can take a number of different forms

- **varname** - the simplest form is a varname, which refers to a variable in the data set provided.
- **rcs** - a restricted cubic spline function,
  - **knots()** - allows the user to specify the location of the knots in the form of a vector.
  - **df()** - alternatively the number of degrees of freedom can be specified, in which case the boundary knots are assumed to be at the minimum and maximum of varname with the internal knots placed at evenly spaced centiles.
  - **orthog** - this option uses Gram-Schmidt orthogonalisation of the splines, specifying this can improve model convergence.
- **time functions** - such as powers of time and log time. In order to use time functions **timevar** must be specified as extra numerical integration may be required.
- **M[#] [cluster level]** - a random-effect at the cluster level, all random-effects must be named M followed by a number to enable the sharing of random effects between models
- **fp()** - specifies a fractional polynomial function, with order 1 or 2.
  - **powers()** - the powers of the the fractional polynomial function must be specified (up to second degree).
- **bhazard(varname)** - invokes a relative survival (excess hazard) model. varname specifies the expected hazard rate at the event time.
- **exposure(varname)** - include log(varname) in the linear predictor, with a coefficient of 1. For use with **family = "poisson"**.

Functions of longitudinal submodels can be included as covariates in other submodels using the following options

- **EV[depvar]** - the expected value of the response of a submodel
- **dEV[depvar]** - the first derivative with respect to time of the expected value of the response of a submodel
- **d2EV[depvar]** - the second derivative with respect to time of the expected value of the response of a submodel
- **iEV[depvar]** - the integral with respect to time of the expected value of the response of a submodel
- **XB[depvar]** - the expected value of the complex predictor of a submodel
- **dXB[depvar]** - the first derivative with respect to time of the expected value of the complex predictor of a submodel
- **d2XB[depvar]** - the second derivative with respect to time of the expected value of the complex predictor of a submodel
• $iXB[depvar]$ - the integral with respect to time of the expected value of the complex predictor of a submodel

2.3. Integration methods

There are a number of methods available for numerically integrating out the random-effects in order to calculate the likelihood for a mixed-effects model. The options for `intmethod` are:

• `ghermite` - for non-adaptive Gauss-Hermite quadrature;
• `halton` - for Monte Carlo integration using Halton sequences;
• `sobol` - for Monte Carlo integration using Sobol sequences;
• `mc` - for standard Monte Carlo integration using normal draws.

The default is `ghermite`. Level-specific integration techniques can be specified. Gauss-Hermite quadrature is widely considered the optimal numerical integration technique, however it doesn’t scale well for large numbers of random-effects. Therefore in a three level model example, we may use Gauss-Hermite quadrature at the highest level and the more efficient Monte-Carlo integration with Halton sequences at level 2, using `intmethod = c("ghermite", "halton")`.

2.4. Post estimation

A range of post estimation tools are available with `merlin` using the prediction function using the following syntax.

`predict(modelname, statistic, type, options)`

The currently available statistics options are

• `eta` - the expected value of the complex predictor
• `mu` - the expected value of the response variable
• `hazard` - the hazard function
• `chazard` - the cumulative hazard function
• `logchazard` - the log cumulative hazard function
• `survival` - the survival function
• `cif` - the cumulative incidence function
• `rmst` - calculates the restricted mean survival time, which is the integral of the survival function within the interval $[0,t]$, where $t$ is the time at which predictions are made. If multiple survival models have been specified in your `merlin` model, then it will assume all of them are cause-specific competing risks models, and include them in the calculation. If this is not the case, you can override which models are included by using the `causes` option. $\text{rmst} = t - \text{totaltimelost}$.
• `cifdifference` calculates the difference in `cif` predictions between values of a covariate specified using the `contrast` option.
• `hdivifference` calculates the difference in `hazard` predictions between values of a covariate specified using the `contrast` option.
• `rmstdifference` calculates the difference in `rmst` predictions between values of a covariate specified using the `contrast` option.
• **mudifference** calculates the difference in mu predictions between values of a covariate specified using the **contrast** option.
• **etadifference** calculates the difference in eta predictions between values of a covariate specified using the **contrast** option.
• **timelost** - calculates the time lost due to a particular event occurring, within the interval [0,t]. In a single event survival model, this is the integral of the cif between (0,t]. If multiple survival models are specified in the **merlin** model then by default all are assumed to be cause-specific event time models contributing to the calculation. This can be overridden using the **causes** option.
• **totaltimelost** - total time lost due to all competing events, within (0,t]. If multiple survival models are specified in the **merlin** model then by default all are assumed to be cause-specific event time models contributing to the calculation. This can be overridden using the **causes** option. **totaltimelost** is the sum of the **timelost** due to all causes.

**Prediction options include**

• **type** - specifies whether the predictions include fixed-effects only (**fixedonly**), or the marginal prediction is calculated marginally with respect to the latent variables. The **stat** is calculated by integrating the prediction function with respect to all the latent variables over their entire support.
• **predmodel** - specifies which model to predict from, default **predmodel=1**.
• **causes** - for use when calculating predictions from a competing risks model. By default, **cif, rmst, timelost** and **totaltimelost** assume that all survival models included in the **merlin** model are cause-specific hazard models contributing to the calculation. If this is not the case, then you can specify which models (indexed using the order they appear in your **merlin** model by using the **causes** option, e.g. **causes=c(1, 2)**).
• **at** - specifies covariate values for prediction. Fixed values of covariates should be specified in a list e.g. **at = c("trt" = 1, "age" = 50)**.
• **contrast** - specifies the values of a covariate to be used when comparing statistics, such as when using the **cifdifference** option to compare cumulative incidence functions, e.g. **contrast = c("trt" = 0, "trt" = 1)**.

### 3. Examples

A consequence of the flexibility of **merlin** is the syntax is arguably complex to allow for the generalisation. In order to illustrate the potential uses of **merlin** we fit a number of increasingly advanced models to data from an observational study which investigated the effects of aortic valve replacement with a stentless or a homograft valve (Lim et al. 2008). The study followed 300 patients who underwent aortic valve replacement between 1991 and 2001, all patients with at least one year of follow-up were included. A number of baseline measurements were available such as age, sex, preoperative body surface area and size of valve. The dataset also includes longitudinal measures of valve gradient, standardised left ventricular mass index and ejection fraction from an average of four follow-up appointments per patient. We will use the copy of the data set available from **R** package **joineRML** (Hickey et al. 2018) to illustrate.

```r
R> data(heart.valve, package = "joineRML")
```
As we are interested in fitting joint survival and longitudinal models, there must be at least one longitudinal biomarker measurement for each individual. We will primarily focus on valve gradient as our longitudinal outcome, therefore it is necessary to exclude any individual who doesn’t have at least one valve gradient observation.

```r
R> heart.valve <- heart.valve[!is.na(heart.valve$grad), ]
```

The data should be set out in wide format for submodel, with each outcome specified in a separate column. For survival data event time and status will appear in different columns, and should only be specified once per individual. However within a submodel long format is used, with each repeated measurement of a biomarker on a new row with a separate column specifying the timing of that observation. The current set up of the `heart.valve` data (shown below) needs some editing to allow modelling fitting with `merlin`, however once the data has been put into the correct format, all models can be fitted without any further editing being required.

```r
R> print(
R+ heart.valve[heart.valve$num %in% c(1:2, 13), 
R+ c(1:3, 25, 5:6, 4, 8, 10)], 
R+ row.names = FALSE
R+ )
```

| num | sex | age       | hs  | fuyrs | status | time   | log.grad | log.lvmi |
|-----|-----|-----------|-----|-------|--------|--------|----------|----------|
| 1   | 0   | 75.06027  | 4.956164 | 0     | 0.0109589 | 2.302585 | 4.778955 |
| 1   | 0   | 75.06027  | 4.956164 | 0     | 3.6794520 | 2.302585 | 4.778955 |
| 1   | 0   | 75.06027  | 4.956164 | 0     | 4.6958900 | 2.302585 | 4.924569 |
| 2   | 0   | 45.79452  | 9.663014 | 0     | 6.3643840 | 2.639057 | 4.744323 |
| 2   | 0   | 45.79452  | 9.663014 | 0     | 7.3041100 | 2.197225 | 4.698661 |
| 2   | 0   | 45.79452  | 9.663014 | 0     | 8.3013700 | 2.484907 | 5.058790 |
| 13  | 1   | 69.94247  | 5.186301 | 1     | 0.1369863 | 2.708050 | 5.305541 |
| 13  | 1   | 69.94247  | 5.186301 | 1     | 1.0575340 | 2.833213 | 5.283356 |
| 13  | 1   | 69.94247  | 5.186301 | 1     | 2.0547950 | 2.995732 | 4.794550 |
| 13  | 1   | 69.94247  | 5.186301 | 1     | 3.9726030 | 3.401197 | 4.993421 |

The event time (fuyrs) for each individual should only appear once in the data set, unless there are multiple events per individual, these should appear on separate lines. The `status` is the event indicator variable, coded 0 for censored (lost to follow-up) and 1 for died.

```r
R> heart.valve$id <- heart.valve$num
R> heart.valve$stime <- heart.valve$fuyrs
R> heart.valve$stime[duplicated(heart.valve$id)] <- NA
R> heart.valve$died <- heart.valve$status
R> heart.valve$died[duplicated(heart.valve$id)] <- NA
```

Binary variables, such as type of heart valve used, need to be converted to be numeric.

```r
R> heart.valve$type <- as.numeric(heart.valve$hs) - 1
```
A section of the correctly formatted data is shown below. Individual 1 has three longitudinal measurements for log valve gradient (log.grad) and log left ventricular mass index (log.lvmi), the timings of these measurements are given in the time column. In this case the different biomarkers were measured at the same time points, but this is not necessary, missing biomarker measurements should be recorded as NA. The survival information has been recorded on the first line for each individual. Baseline covariates such as sex should be specified on every line for that individual. All the models below are fitted to this data set.

```r
R> print(
R+   heart.valve[heart.valve$id %in% c(1:2, 13),
R+     c(26, 2:3, 29, 27:28, 8, 10, 4)],
R+   row.names = FALSE
R+ )

id sex   age type stime died log.grad log.lvmi time
1 0   75.06027 1   4.956164 0 2.302585 4.778955 0.0109589
1 0   75.06027 1   NA    NA 2.302585 4.778955 3.6794520
1 0   75.06027 1   NA    NA 2.302585 4.924569 4.6958900
2 0  45.79452 0   9.663014 0 2.197225 4.698661 7.3041100
2 0  45.79452 0   NA    NA 2.197225 4.698661 8.3013700
13 1   69.94247 0  5.186301 1 2.708050 5.305541 0.1369863
13 1   69.94247 0   NA    NA 2.995732 4.794550 2.0547950
13 1   69.94247 0   NA    NA 3.401197 4.993421 3.9726030
```

### 3.1. Linear regression

To begin with we will fit a simple linear regression of log of the valve gradient (log.grad) against time, with age and sex as covariates.

```r
R> library(merlin)
R> m1 <- merlin(
R+     model = log.grad ~ sex + age + time,
R+     family = "gaussian",
R+     data = heart.valve
R+ )
R> summary(m1)

Mixed effects regression model
Log likelihood = -651.4753

             Estimate  Std. Error     z  Pr(>|z|) [95% Conf. Interval]
sex         0.140489 0.059778 2.350 0.0188 0.023327 0.257651
age     -0.002212 0.002297-0.963 0.3356 -0.006714 0.002290
time     -0.013541 0.011958-1.132 0.2574 -0.036978 0.009895
```
The constant term for log valve gradient is estimated to be 2.772 (95% CI 2.457, 3.086) and this is estimated to change by -0.014 (95% CI -0.037, 0.010) for every year after valve replacement. The residual error is reported in the results table as the log of the standard deviation, meaning the residual standard error in this model is 0.682. To assess model fit we can calculate the residuals using the `predict` function to get the fitted values.

```
R> heart.valve$m1res <- heart.valve$log.grad - predict(m1, stat = "mu")
```

This shows that there seems to be some model misspecification, as the values at the beginning and end are generally under predicted, while values between 1 and 4 years are over predicted. To address this we can add further flexibility to the shape of the log valve gradient over time, using restricted cubic splines, with number degrees of freedom specified as above. The boundary knots will be assumed to be at the minimum and maximum of `log.grad` with the
internal knots at equally spaced centiles. Alternatively the locations of the knots can be specified by using the knots() option. The spline terms have been orthogonalised, which will impact on the interpretation of the intercept term. While the spline terms themselves have little meaningful interpretation they are reported to allow the model to be used to make external predictions.

```r
R> m2 <- merlin(
R+ model = log.grad ~ sex + age + rcs(time, df = 3, orthog = TRUE),
R+ timevar = "time",
R+ family = "gaussian",
R+ data = heart.valve
R+ )
R> summary(m2)

Mixed effects regression model
Log likelihood = -678.6148

Estimate Std. Error z Pr(>|z|) [95% Conf. Interval]
sex -0.09097 0.05792 -1.571 0.11625 -0.20449 0.022545
age 0.01674 0.00245 6.822 0.00000 0.01193 0.02155
rcs():1 -0.06781 0.02628 -2.580 0.00987 -0.11931 -0.01631
rcs():2 -0.21532 0.02590 -8.313 0.00000 -0.26609 -0.16455
rcs():3 0.09760 0.02567 3.801 0.00014 0.04728 0.14792
_cons 1.53205 0.15900 9.635 0.00000 1.22041 1.84369
log_sd(resid.) -0.44860 0.03034 -14.788 0.00000 -0.50805 -0.38914
```

When we plot the residuals for model m2 we can see there is less of a pattern over time, suggesting this model is a better fit to the data.

```r
R> heart.valve$m2res <- heart.valve$log.grad - predict(m2, stat = "mu")
R> ggplot(heart.valve, aes(x = time, y = m2res)) +
R+ geom_point() +
R+ geom_hline(yintercept = 0, color = "blue") +
R+ xlab("Time (years)") +
R+ ylab("Residual") +
R+ theme_classic()
```

We can further improve this model by accounting for the clustered nature of the log.grad measurements within patients (id). We can add a normally-distributed random intercept at the patient id level using the M# syntax below. Each random effect is given a name of this form to enable the sharing of random effects between models, which will be illustrated later. In the model below M1 specifies a random intercept and M2 specifies a random linear slope. By default the random-effects at each level are not assumed to be correlated (option covariance(identity)), however this can be relaxed and the correlation estimated by instead specifying covariance(unstructured). For mixed-effects models the levels must be specified using the level option. There is no limit to the number of levels which can be
fitted, but the levels must be be specified from highest to lowest, e.g. county > practice >
patient. By default all components in the model will have an estimated coefficient, however
the coefficient can be constrained to 1 using *1 notation, which would normally be the case
for random effects not shared between models. By default estimation of the likelihood is
done using Gauss-Hermite quadrature with 7 nodes, increasing this number using the ip option
will improve estimation of the likelihood, although this will increase computation time
considerably.

```r
R> m3 <- merlin(
R+   model = log.grad ~ sex + age + rcs(time, df = 3, orthog = TRUE) +
R+   M1[id] * 1 + time:M2[id] * 1,
R+   timevar = "time",
R+   level = "id",
R+   covariance = "unstructured",
R+   family = "gaussian",
R+   data = heart.valve
R+ )
R> summary(m3)
```

Mixed effects regression model
Log likelihood = -612.5806

|        | Estimate | Std. Error | z     | Pr(>|z|) | 95% Conf. Interval |
|--------|----------|------------|-------|--------|-------------------|
| sex    | 0.1559667| 0.0741357  | 2.104 | 0.0354 | 0.0106635 0.3012699|
merlin: Mixed Effects Regression

| Term       | Coefficient 1 | Coefficient 2 | Coefficient 3 | Coefficient 4 | Coefficient 5 | Coefficient 6 |
|------------|---------------|---------------|---------------|---------------|---------------|---------------|
| age        | 0.0057777     | 0.0030691     | 1.883         | 0.0598        | -0.0002377    | 0.0117931     |
| rcs():1    | -0.0331820    | 0.0332446     | -0.998        | 0.3182        | -0.0983402    | 0.0319762     |
| rcs():2    | -0.1828734    | 0.0262125     | -6.977        | 0.0000        | -0.2342490    | -0.1314978    |
| rcs():3    | 0.1294719     | 0.0233294     | 5.550         | 0.0000        | 0.0837471     | 0.1751967     |
| _cons      | 2.2338384     | 0.2030426     | 11.002        | 0.0000        | 1.8358823     | 2.6317945     |
| log_sd(resid.) | -0.7233108 | 0.0342331     | -21.129       | 0.0000        | -0.7904063    | -0.6562152    |
| log_sd(M1) | -1.0672644    | 0.1262396     | -8.454        | 0.0000        | -1.3146895    | -0.8198394    |
| log_sd(M2) | -0.7900452    | 0.1528337     | -5.169        | 0.0000        | -1.0895939    | -0.4904966    |
| atanh_corr(M2,M1) | -2.1512169 | 0.1571694     | -13.687       | 0.0000        | -2.4592632    | -1.8431706    |

Integration method: Non-adaptive Gauss-Hermite quadrature
Integration points: 7

Adding the random-effects terms at the id level greatly reduces the log-likelihood. The standard deviation for the random intercept is 0.344, and for the random slope is 0.454. The correlation between these random-effects is reported as the inverse hyperbolic tangent, to get the estimate of the correlation the tanh() function can be used, \( \tanh(-2.151) = -0.973 \) showing that these random-effects are highly correlated. Random-effects at multiple hierarchical levels can be included by changing the level variable in square brackets, and by specifying the levels from highest to lowest in the level option.

We can make predictions of the expected value of the response from mixed-effects model m3 using the predict function with the mu option. Predictions will only be made for non-missing values of the response. These predictions are marginal, calculated by integrating out the random-effects, giving population averaged predictions.

```r
R> ldata <- heart.valve[!is.na(heart.valve$log.grad), ]
R> ldata$pred1 <- predict(m3, stat = "mu", predmodel = 1, type = "marginal")
R> print(
R+ ldata[, c(1:2, 13), c("id", "time", "log.grad", "pred1"),
R+ row.names = FALSE
R+ )
```

| id    | time | log.grad | pred1   |
|-------|------|----------|---------|
| 1     | 0.0109589 | 2.302585 | 3.122391 |
| 1     | 3.6794520  | 2.302585 | 2.523278 |
| 1     | 4.6958900  | 2.302585 | 2.645854 |
| 2     | 6.3643840  | 2.639057 | 2.603468 |
| 2     | 7.3041100  | 2.197225 | 2.642733 |
| 2     | 8.3013700  | 2.484907 | 2.665921 |
| 13    | 0.1369863  | 2.708050 | 3.177508 |
| 13    | 1.0575340  | 2.833213 | 2.720037 |
| 13    | 2.0547950  | 2.995732 | 2.514966 |
| 13    | 3.9726030  | 3.401197 | 2.689035 |

3.2. User-defined model
As well as a wide range of standard models, merlin also allows users the flexibility to specify their own likelihood functions using the user family.

To help users to define their own likelihood there are a number of inbuilt utility functions.

- **merlin_util_depvar(M)** - returns the dependent variable for the current model. For time-to-event outcomes this will be a matrix with two columns, for event time and event-indicator.
- **merlin_util_xzb(M, t)** - returns the complex predictor for the current model, optionally evaluated at time \( t \).
- **merlin_util_xzb_deriv(M, t)** - returns the derivative with respect to time of the complex linear predictor for the current model, optionally evaluated at time \( t \).
- **merlin_util_xzb_deriv2(M, t)** - returns the second derivative with respect to time of the complex linear predictor for the current model, optionally evaluated at time \( t \).
- **merlin_util_xzb_integ(M, t)** - returns the integral with respect to time of the complex linear predictor for model \( M \), optionally evaluated at time \( t \).
- **merlin_util_expval(M, t)** - returns the expected value of the response for the current model, optionally evaluated at time \( t \).
- **merlin_util_expval_deriv(M, t)** - returns the derivative with respect to time of the expected value of the response for the current model, optionally evaluated at time \( t \).
- **merlin_util_expval_deriv2(M, t)** - returns the second derivative with respect to time of the expected value of the response for the current model, optionally evaluated at time \( t \).
- **merlin_util_expval_integ(M, t)** - returns the integral with respect to time of the expected value of the response for the current model, optionally evaluated at time \( t \).
- **merlin_util_ap(M,i)** - returns the \( i \)th ancillary parameter of the current model.
- **merlin_util_timevar(M)** - returns the time variable for the current model, specified by the timevar option.

These utility functions take a list as input, which has been referred to as \( \text{gml} \) below. This contains a merlin object, which should not then be edited by the user. The xzb or expval functions have a corresponding \(*\_mod()\) function, which allows users to specify an additional argument for which model to call, e.g. **merlin_util_xzb_mod(M,2)** will return the complex predictor for the second model in the merlin statement, allowing submodels to be linked.

The log-likelihood is specified as a function, giving the observation level log-likelihood contribution. As an example a simple linear model can be fitted using the function below.

```r
R> logl_gaussian <- function(gml) {
R+ y <- merlin_util_depvar(gml)
R+ xzb <- merlin_util_xzb(gml)
R+ se <- exp(merlin_util_ap(gml, 1))
R+ mu <- (sweep(xzb, 1, y, "-"))^2
R+ logl <- ((-0.5 * log(2 * pi) - log(se)) - (mu / (2 * se^2)))
R+ return(logl)
R+ }
```
To specify a user defined function, the family is given as `user`, the `userf` option must then be given the function above.

```r
R> m4 <- merlin(log.grad ~ sex + age + time + ap(1),
+ family = "user",
+ userf = "logl_gaussian",
+ data = heart.valve
+ )
R> summary(m4)
```

Mixed effects regression model
Log likelihood = -651.4753

|             | Estimate | Std. Error | z     | Pr(>|z|) | [95% Conf. Interval] |
|-------------|----------|------------|-------|----------|----------------------|
| sex         | 0.140489 | 0.059778   | 2.350 | 0.0188   | 0.023327 0.257651    |
| age         | -0.002212| 0.002297   | -0.963| 0.3356   | -0.006714 0.002290  |
| time        | -0.013541| 0.011958   | -1.132| 0.2574   | -0.036978 0.009895   |
| _cons       | 2.771597 | 0.160581   | 17.260| 0.0000   | 2.456863 3.086330    |
| _ap1        | -0.383205| 0.028194   | -13.592| 0.0000  | -0.438465 -0.327946  |

The parameter estimates from this model are the same as model M1 above, where `_ap1` is the ancillary residual error parameter. These user defined functions allows users to extend `merlin`, which is particularly useful for those doing methodological research.

### 3.3. Survival / time-to-event analysis

A number of standard time-to-event models are available in `merlin` such as Weibull, exponential and Gompertz models. Additionally a range of more flexible models are also available including Royston-Parmar models, and a model on the log hazard scale, for both a number of forms can be used for the baseline including restricted cubic splines, or fractional polynomials.

**Weibull proportional hazards model**

We will start by fitting a simple Weibull proportional hazard model for time-to-death, adjusting for age and type of aortic valve replacement. In order to fit a survival model a `Surv` object must be supplied with the time and event indicator variables.

```r
R> m5 <- merlin(
+ model = Surv(stime, died) ~ age + type,
+ family = "weibull",
+ data = heart.valve
+ )
R> summary(m5)
```

Mixed effects regression model
Log likelihood = -173.3746
The results table gives the coefficient for the factors in the model, which is the log of the hazard ratio. Therefore the hazard ratio for type of aortic valve replacement is $\exp(0.038) = 1.039$ showing that having a stentless valve replacement leads to worse survival than having a homograft valve replacement, although this is not statistically significant.

The survival function can be obtained using the predict function, with the survival option. Predictions will only be made for non-missing values of the response.

```r
R> p_50 <- predict(m5, stat = "survival", type = "fixedonly", at = c(age = 50, type = 1))
R> p_60 <- predict(m5, stat = "survival", type = "fixedonly", at = c(age = 60, type = 1))
R> p_70 <- predict(m5, stat = "survival", type = "fixedonly", at = c(age = 70, type = 1))
```

The predictions give the survival probability for each individual at their event time, depending on their age and type of valve replacement. We can use the at option to compare the survival functions for different levels of a covariate, while holding other covariates constant. As type of valve replacement has a smaller effect, we will instead look at the differences in survival prediction by age, assuming a stentless valve replacement.

```r
R> surv_pred <- data.frame(p_50, p_60, p_70, stime = heart.valve[!is.na(heart.valve$stime), "stime"],)
R> surv_pred <- melt(surv_pred, id.var = "stime")
```
Spline-based survival model

Further flexibility can be included in survival models by modelling the hazard function using splines. Royston-Parmar models use restricted cubic splines to model the baseline log cumulative hazard function. They allow flexibility in the shape of the baseline hazard and allow for time-dependent effects. The form of the baseline hazard is specified by adding the function to the linear predictor of the survival model. Here we fit a model using restricted cubic splines with 3 degrees of freedom in the baseline hazard. Using the `event = TRUE` option means the knots locations for the the splines are based on the event times only, ignoring censored time.
points.

\begin{verbatim}
R> m6 <- merlin(
R+   model = Surv(stime, died) ~ age + type +
R+   rcs(stime, df = 3, log = TRUE, event = TRUE),
R+   timevar = "stime",
R+   family = "rp",
R+   data = heart.valve
R+ )
R> summary(m6)

Mixed effects regression model
Log likelihood = -170.653

|        | Estimate | Std. Error | z       | Pr(>|z|) | [95% Conf. Interval] |
|--------|----------|------------|---------|----------|----------------------|
| age    | 0.101765 | 0.019528   | 5.211   | 0.0000   | 0.063491 0.140040    |
| type   | 0.025291 | 0.343717   | 0.074   | 0.9413   | -0.648381 0.698964   |
| rcs():1| 1.107442 | 0.143163   | 7.736   | 0.0000   | 0.826849 1.388036    |
| rcs():2| -0.274877| 0.089043   | -3.087  | 0.0020   | -0.449398 -0.100357  |
| rcs():3| -0.002397| 0.076386   | -0.031  | 0.9750   | -0.152112 0.147317   |
| _cons | -9.057037| 1.401644   | -6.462  | 0.0000   | -11.804210 -6.309865 |

The estimated age and treatment effects are very similar to the Weibull survival model \texttt{m5} above. We can compare the shape in baseline hazards between the Weibull and Royston-Parmar using the \texttt{hazard} option in the \texttt{predict} function.

\begin{verbatim}
R> base_m5 <- predict(m5, stat = "hazard", type="fixedonly",
R+   at = c(age = 0, type = 0))
R> base_m6 <- predict(m6, stat = "hazard", type="fixedonly",
R+   at = c(age = 0, type = 0))
R>
R> base_pred <- data.frame(stime = heart.valve[!is.na(heart.valve$stime), "stime"],
R+   base_m5,
R+   base_m6)
R> base_pred <- base_pred[!duplicated(base_pred$stime),]
R> base_pred <- melt(base_pred, id.var = "stime")

R> ggplot(base_pred, aes(x = stime, y = value, linetype = variable)) +
R+   geom_line(size = 0.6) +
R+   xlab("Time (years)") + ylab("Baseline hazard") +
R+   theme_classic() + theme(legend.position = c(0.2, 0.8)) +
R+   scale_linetype_discrete(name = "Model", labels = c("Weibull", "RP - 3df"))

Assess proportional-hazards

The survival models above assume proportional hazards. We can test this assumption in the effect of type aortic valve replacement by including the interaction between type and log time.
It is important to use the `timevar` option for this model, as time-dependent effects need to be differentiated with respect to time to calculate the hazard function.

```r
R> m7 <- merlin(
R+   model = Surv(stime, died) ~ age + type +
R+   type:fp(stime, powers = c(0)) +
R+   rcs(stime, df = 3, log = TRUE, event = TRUE),
R+   timevar = "stime",
R+   family = "rp",
R+   data = heart.valve
R+ )
R> summary(m7)
```

Mixed effects regression model
Log likelihood = -170.3792

|                | Estimate | Std. Error | z  | Pr(>|z|) | 95% Conf. Interval |
|----------------|----------|------------|----|----------|--------------------|
| age            | 0.10223  | 0.01956    | 5.226 | 0.0000   | 0.06389 0.14057    |
| type           | -0.62548 | 0.93454    | -0.669 | 0.5033   | -2.45714 1.20618   |
| type:fp()      | 0.34704  | 0.46673    | 0.744 | 0.4571   | -0.56773 1.26180   |
| rcs():1        | 0.96557  | 0.22712    | 4.251 | 0.0000   | 0.52044 1.41071    |
| rcs():2        | -0.24625 | 0.09397    | -2.620 | 0.0088   | -0.43044 -0.06207  |
| rcs():3        | -0.01036 | 0.07610    | -0.136 | 0.8917   | -0.15952 0.13880   |
The interaction term (type:fp()) is not significant, therefore accounting for time-dependent
effects on the type of aortic valve is not necessary.

**Non-linear effects**

In the above models the effect of age was assumed to be linear. We can investigate the non-
linear effect of age using fractional polynomials. Including \texttt{fp(age, powers = c(1, 1))}
specifies a second-order fractional polynomial. The first specified term is \texttt{stime} to the first
power, which in this case is a linear term. The second specified term is \texttt{stime} to the second
power multiplied by the natural log of \texttt{stime}.

```r
R> m8 <- merlin(R+ model = Surv(stime, died) ~ type +
R+     fp(age, powers = c(1, 1)) +
R+     rcs(stime, df = 3, log = TRUE, event = TRUE),
R+     timevar = "stime",
R+     family = "rp",
R+     data = heart.valve
R+ )
R> summary(m8)

Mixed effects regression model
Log likelihood = -170.7799

| Estimate  | Std. Error | z  | Pr(>|z|) | [95% Conf. Interval] |
|-----------|------------|----|----------|---------------------|
| type 0.038219 | 0.350542   | 0.109       | 0.9132 | -0.648830 0.725268 |
| fp():1 -0.596800 | 0.392650   | -1.520      | 0.1285 | -1.366380 0.172780 |
| fp():2 0.133596 | 0.072833   | 1.834       | 0.0666 | -0.009154 0.276345 |
| rcs():1 1.114711 | 0.143890   | 7.747       | 0.0000 | 0.832692 1.396731 |
| rcs():2 -0.277742 | 0.089596   | -3.100      | 0.0019 | -0.453347 -0.102137 |
| rcs():3 -0.003194 | 0.076810   | -0.042      | 0.9668 | -0.153740 0.147351 |
| _cons 0.007325 | 5.537987   | 0.001       | 0.9989 | -10.846930 10.861580 |

The hazard ratios for linear age (0.551) and linear age multiplied by log age (1.143) are both
significant, suggesting the effect of age is non-linear. We could go on to investigate whether
the proportional hazard assumption is valid for this non-linear function of age by fitting an
interaction between the age function and log time.

### 3.4. Wrapper functions

The syntax for relatively simple one outcome models such as those above can be simplified
using available wrapper functions, which use the powerful \texttt{merlin} function underneath. For example the \texttt{mlsurv} wrapper fits parametric survival models, with \texttt{exponential}, \texttt{weibull},
\texttt{gompertz}, \texttt{rp}, \texttt{logchazard}, and \texttt{loghazard} model options. To illustrate, the Weibull model
in \texttt{m5} above can fitted using the wrapper \texttt{mlsurv}, with simplified syntax.
Proportional hazards regression model
Weibull baseline hazard
Data: data

Coefficients:

|      | age | type  | _cons | log(gamma) |
|------|-----|-------|-------|------------|
|      | 0.09719 | 0.03778 | -11.67541 | 0.63998 |

3.5. Competing risks

Competing risk analysis can be framed as a multiple outcome survival model by specifying cause-specific hazard models. As this data set only contains all cause survival information, to illustrate fitting a competing risks model we randomly assign the deaths to either cardiovascular disease (cardio) or other causes (other).

```
R> set.seed(6342)
R> heart.valve$cardio[!is.na(heart.valve$died)] <- rbinom(length(heart.valve$died[!is.na(heart.valve$died)]), 1, 0.6)
R> heart.valve$other <- 1 - heart.valve$cardio
R> heart.valve$cardio[heart.valve$died == 0 & !is.na(heart.valve$died)] <- 0
R> heart.valve$other[heart.valve$died == 0 & !is.na(heart.valve$died)] <- 0
```

We can then fit a model with cardio as one outcome and other as a second outcome. Both event types have been fitted using a Royston-Parmar model with 3 degrees of freedom, however it is possible to use different survival model types for each event. As there are two outcomes the model now needs to be specified as a list.

```
R> m9 <- merlin(
R+   model = list(
R+     Surv(stime, cardio) ~ type +
R+     rcs(stime, df = 3, log = TRUE, event = TRUE),
R+     Surv(stime, other) ~ type +
R+     rcs(stime, df = 3, log = TRUE, event = TRUE)
R+   ),
R+   timevar = c("stime", "stime"),
R+   family = c("rp", "rp"),
R+   data = heart.valve
R+ )
R> summary(m9)
```
Mixed effects regression model
Log likelihood = -232.9797

| Estimate | Std. Error | z    | Pr(>|z|) | [95% Conf. Interval] |
|----------|------------|------|----------|----------------------|
| type     | -0.004186  | 0.412139 | -0.010   | 0.9919               |
| rcs():1  | 1.098643   | 0.186195 | 5.901    | 0.0000               |
| rcs():2  | -0.415694  | 0.101863 | -4.081   | 0.0000               |
| rcs():3  | -0.149017  | 0.100844 | -1.478   | 0.1395               |
| _cons    | -2.836043  | 0.351496 | -8.068   | 0.0000               |
| type     | -0.408162  | 0.364551 | -1.120   | 0.2629               |
| rcs():1  | 2.480418   | 0.792595 | 3.129    | 0.0018               |
| rcs():2  | 1.362926   | 0.631493 | 2.158    | 0.0309               |
| rcs():3  | -0.178580  | 0.124901 | -1.430   | 0.1528               |
| _cons    | -2.405594  | 0.323577 | -7.434   | 0.0000               |

The hazard ratio for type of graft is 0.996 for death from cardiovascular disease, suggesting in this simulated example having a stentless valve replacement increases the risk of death due to cardiovascular disease compared to having a homograft valve replacement. The effect is in the same direction for death from other causes, although the hazard ratio of 0.665 suggests the effect is much smaller.

Hazard ratios describe the relative differences in hazard between groups. In the case of competing risks the cause-specific cumulative incidence function, which is the probability of failure from the event of interest in the presence of other competing events, may be more useful. We can calculate the cause-specific cumulative incidence function for each of the causes in the model using the `predict` function, by specifying which submodel to predict from using the `predmodel` option. Predictions are for each valve type at a given age, specified using the `at` option.

```r
R> card_homo <- predict(m9, stat = "cif", type = "fixedonly",
                       predmodel = 1, at = c(age = 50, type = 0))
```

To create stacked cumulative incidence plots for both types of valve replacements we then calculate further predictions as below for stentless grafts, and for death from other causes.

```r
R> card_stent <- predict(m9, stat = "cif", type = "fixedonly",
                         predmodel = 1, at = c(age = 50, type = 1))
R> other_homo <- predict(m9, stat = "cif", type = "fixedonly",
                         predmodel = 2, at = c(age = 50, type = 0))
R> other_stent <- predict(m9, stat = "cif", type = "fixedonly",
                         predmodel = 2, at = c(age = 50, type = 1))
```

We can then plot the stacked cumulative incidence plots, allowing us to compare between the two types of valve replacement. They show that for both types the cumulative incidence for cardiovascular disease starts to flatten over time, whereas it continues to increase for death from other causes.
Figure 5: Stacked cumulative incidence functions for death from cardiovascular disease and death from other causes, by type of valve replacement (model m9)

```r
R> stime = rep(heart.valve$stime[!is.na(heart.valve$stime)], 4)
R> pred = c(card_homo, card_stent, other_homo, other_stent)
R> valve = rep(c(rep("Homograft valve", length(card_homo)),
R+ rep("Stentless valve", length(card_stent))), 2)
R> cod = c(rep("cardio", length(card_homo) * 2),
R+ rep("other", length(card_stent) * 2))
R> pred_comp <- data.frame(stime, pred, valve, cod)
R> pred_comp <- pred_comp[!duplicated(pred_comp[, c(1, 3, 4)]),]
R> ggplot(pred_comp, aes(x = stime, y = pred, fill = cod)) +
R+ geom_area() +
R+ xlab("Time (years)") +
R+ ylab("Cumulative Incidence") +
R+ theme_classic(base_size = 10) +
R+ theme(legend.position = c(0.19, 0.83)) +
R+ scale_fill_discrete(name = "Cause of death",
R+ labels = c("Other", "Cardiovascular disease"),
R+ guide = guide_legend(reverse = TRUE)) +
R+ facet_grid(. ~ valve)
```

3.6. Multiple-outcome models
We can also use merlin to fit joint longitudinal survival models. This can firstly be done through shared random-effects. In merlin shared random-effects are specified by using the same name for the random-effects that are to be shared. When using shared-random effects it is possible to allow for an association factor, which explains the relationship between the individual-specific random intercept of the biomarker and their survival. To estimate the association parameter the *1 is dropped from one of the random-effects terms, removing the constraint and allowing a coefficient to be estimated.

```r
R> m10 <- merlin(
R+ model = list(
R+ Surv(stime, died) ~ type + M1[id],
R+ log.grad ~ sex + age + time + M1[id] * 1
R+ ),
R+ timevar = c("stime", "time"),
R+ levels = c("id"),
R+ family = c("weibull", "gaussian"),
R+ data = heart.valve
R+ )
R> summary(m10)
```

Mixed effects regression model

|              | Estimate | Std. Error | z     | Pr(>|z|) | 95% Conf. Interval |
|--------------|----------|------------|-------|----------|-------------------|
| type         | 0.6198651 | 0.3254017  | 1.905 | 0.0568   | -0.0179105, 1.2576408 |
| M1           | 1.8384968 | 0.8677693  | 2.119 | 0.0341   | 0.1377002, 3.5392934 |
| _cons        | -5.0586043 | 0.5317924  | -9.512 | 0.0000   | -6.1008982, -4.0163104 |
| log(gamma)   | 0.5320193 | 0.1265303  | 4.205 | 0.0000   | 0.2840245, 0.7800141 |
| sex          | 0.1466814 | 0.0745633  | 1.967 | 0.0492   | 0.0005401, 0.2928228 |
| age          | -0.0051930 | 0.0030689  | -1.692 | 0.0906   | -0.0112078, 0.0008219 |
| time         | -0.0017929 | 0.0124788  | -0.144 | 0.8858   | -0.0262510, 0.0226652 |
| _cons        | 2.9499413 | 0.2081879  | 14.170 | 0.0000   | 2.5419006, 3.3579820 |
| log_sd(resid.) | -0.5013162 | 0.0340641  | -14.717 | 0.0000   | -0.5680806, -0.4345517 |
| log_sd(M1)   | -1.0821441 | 0.1140678  | -9.487 | 0.0000   | -1.3057129, -0.8585752 |

Integration method: Non-adaptive Gauss-Hermite quadrature
Integration points: 7

The parameter estimates from the survival submodel are reported first, followed by the estimates from the longitudinal model, then the random-effect estimates. Here the random effect M1 is shared between the longitudinal and survival submodels. In the longitudinal model M1 is a random intercept, therefore this model is relating an individuals baseline valve gradient to their survival. The standard deviation for the random effect is 0.339. The association between the random-effect on the intercept and survival is given in row M1 in the results table, a value of 1.838 suggests that higher baseline valve gradient leads to worse survival.

Alternatively it is possible to to use current value parameterisation, linking the time-dependent expected value of the biomarker to survival using the EV[] option. In order to do this the
timevar() must be supplied, as integration over time is required for the survival model likelihood contribution.

```r
R> m11 <- merlin(
R+  model = list(
R+    Surv(stime, died) ~ type + EV[log.grad],
R+    log.grad ~ sex + age + time + M1[id] * 1,
R+  ),
R+  timevar = c("stime", "time"),
R+  levels = c("id"),
R+  family = c("weibull", "gaussian"),
R+  data = heart.valve
R+ )
R> summary(m11)
```

Mixed effects regression model

```
Mixed effects regression model
Log likelihood = -826.1898

             Estimate  Std. Error z value Pr(>|z|) [95% Conf. Interval]
type          0.814597   0.322574   2.525  0.0116     0.182363 1.446831
EV[]          0.785010   0.810309   0.969  0.3327    -0.803168 2.373187
_cons         -6.747273   2.315188  -2.914  0.0036    -11.284959 -2.209587
log(gamma)    0.403767   0.131396   3.073  0.0021     0.146236 0.661298
sex           0.174081   0.074095   2.349  0.0188     0.028858 0.319305
age          -0.003442   0.003240  -1.062  0.2882    -0.009793 0.002909
time      -0.011135   0.013790  -0.807  0.4194    -0.038163 0.015893
_cons        2.856742   0.226865  12.592  <2e-16   2.412094 3.301390
log_sd(resid.) -0.512929   0.033856 -15.150  <2e-16  -0.579286 -0.446572
log_sd(M1)    -1.106644   0.114632 -9.654  <2e-16  -1.331319 -0.881969

Integration method: Non-adaptive Gauss-Hermite quadrature
Integration points: 7
```

Now the association term EV[] describes the effect of the current expected value of the biomarker log.grad on survival. The hazard ratio is 2.192, meaning for every unit increase in log valve gradient the hazard is 2.192 times higher.

The form of the association between the the longitudinal biomarker model and survival is flexible. For example, if there was instead a random slope term we could link the trend in the repeatedly measured biomarker to survival by using the gradient of the longitudinal model dEV[].

```r
R> m12 <- merlin(
R+  model = list(
R+    Surv(stime, died) ~ type + dEV[log.grad],
R+    log.grad ~ sex + age + time + time:M1[id] * 1
R+  ),
R+  timevar = c("stime", "time"),
R+  levels = c("id"),
R+  family = c("weibull", "gaussian"),
R+  data = heart.valve
R+ )
R> summary(m12)
```

Mixed effects regression model

```
Mixed effects regression model
Log likelihood = -819.4677

             Estimate  Std. Error z value Pr(>|z|) [95% Conf. Interval]
```
Mixed effects regression model

Log likelihood = -840.1187

| Estimate | Std. Error | z     | Pr(>|z|) | [95% Conf. Interval] |
|----------|------------|-------|----------|----------------------|
| type     | 0.834296   | 0.331631 | 2.516    | 0.0119 | 0.184312 | 1.484281 |
| dEV[]    | 1.835397   | 39.467308 | 0.047    | 0.9629 | -75.519105 | 79.189898 |
| _cons    | -5.018370  | 0.719250 | -6.977   | 0.0000 | -6.428074 | -3.608665 |
| log(gamma)| 0.517752 | 0.124721 | 4.151    | 0.0000 | 0.273304 | 0.762200 |
| sex      | 0.141272   | 0.061993 | 2.279    | 0.0227 | 0.019767 | 0.262777 |
| age      | -0.001734  | 0.003074 | -0.564   | 0.5727 | -0.007758 | 0.004290 |
| time     | -0.017077  | 0.021456 | -0.796   | 0.4261 | -0.059131 | 0.024977 |
| _cons    | 2.748958   | 0.198092 | 13.877   | 0.0000 | 2.360704 | 3.137211 |
| log_sd(resid.) | -0.401866   | 0.034755 | -11.563 | 0.0000 | -0.469985 | -0.333748 |
| log_sd(M1)| -3.337529  | 0.660043 | -5.057   | 0.0000 | -4.631190 | -2.043867 |

Integration method: Non-adaptive Gauss-Hermite quadrature
Integration points: 7

The hazard ratio for the gradient of the longitudinal model is 6.268 (exp(dEV[])), this large hazard ratio suggests an increase in log of the valve gradient leads to greater hazard. However the confidence intervals are wide, which may be due to the small standard deviation of 0.036 in the linear slope, leading to issues in the estimation of its effect.

Other available links include the second derivative d2EV[] and the cumulative exposure iEV[].
We can extend the previous model to investigate possible non-linearities in the associations and time dependent effects by including the interaction between the expected value of the biomarker and log time.

R> m13 <- merlin(
R+ model = list(
R+ Surv(stime, died) ~ type +
R+ EV[log.grad] +
R+ EV[log.grad]:fp(stime, powers = c(0)),
R+ log.grad ~ time + M1[id] * 1
R+ ),
R+ timevar = c("time", "time"),
R+ levels = c("id"),
R+ family = c("weibull", "gaussian"),
R+ data = heart.valve
R+ )
R> summary(m13)
Mixed effects regression model

Log likelihood = -827.7168

|          | Estimate | Std. Error | z     | Pr(>|z|) | [95% Conf. Interval] |
|----------|----------|------------|-------|----------|----------------------|
| type     | 0.67433  | 0.31513    | 2.140 | 0.0324   | 0.05669 1.29197      |
| EV[]     | 0.24692  | 1.03307    | 0.239 | 0.8111   | -1.77786 2.27170     |
| EV[]:fp()| -0.17456 | 0.38326    | -0.455| 0.6488   | -0.92574 0.57661     |
| _cons    | -5.85705 | 3.03192    | -1.932| 0.0534   | -11.79950 0.08539    |
| log(gamma)| 0.77284 | 0.46006    | 1.680 | 0.0930   | -0.12885 1.67453     |
| time     | -0.01275 | 0.01273    | -1.002| 0.3163   | -0.03770 0.01219     |
| _cons    | 2.66026  | 0.04662    | 57.058| 0.0000   | 2.56888 2.75164      |
| log_sd(resid.)| -0.50952 | 0.03478  | -14.652| 0.0000  | -0.57768 -0.44136   |
| log_sd(M1)| -1.13669 | 0.12899   | -8.812| 0.0000   | -1.38949 -0.88388    |

Integration method: Non-adaptive Gauss-Hermite quadrature
Integration points: 7

The parameter estimate for the interaction (EV[]:fp() in the results table) suggests that over time a unit increase in the current value of the log valve gradient has a reduced effect on hazard, however this is not significant.

3.7. A final model

For illustrative purposes we will now show how flexible merlin is by bringing together the previous examples, with some new model options, in one final model. Binary outcomes can be included using the bernoulli family. To illustrate this we will create a new binary variable catef from the ejection fraction variable ef.

\[
R> heart.valve$catef <- 0 \\
R> heart.valve$catef[heart.valve$ef > 70] <- 1
\]

Model m14 includes the two survival models for the competing risks of death (cardiovascular disease and other causes) from model m9. Continuous log valve gradient over time is described using restricted cubic splines as in model m6 with random intercept term (M1). Binary catef over time is also modelled with a random intercept term (M2). Both survival outcomes are described using Weibull models, the effect of the type of valve replacement on both causes of death is estimated. The effect of type of valve replacement is assumed to be time dependent in the time to death from other causes model. The random intercept for valve gradient M1 is shared with the time-to-death from other causes model, while the random intercept for categorical ejection fraction M2 is shared with the time-to-death from cardiovascular disease model. The expected value of valve gradient is included in the time-to-death from cardiovascular disease model.

\[
R> m14 <- merlin( \\
R+ model = list( \\
R+ Surv(stime, cardio) ~ type + EV[log.grad] + M2[id], \\
R+ Surv(stime, other) ~ type + type:fp(stime, powers = c(0)) + M1[id],
\]

\begin{verbatim}
R> log.grad ~ age + type + rcs(time, df = 3, orthog = TRUE) + M1[id] * 1,
R> catef ~ fp(time, powers = c(1)) + M2[id] * 1
R+ timevar = c("stime", "stime", "time", "time"),
R+ levels = c("id"),
R+ covariance = "unstructured",
R+ family = c("weibull", "weibull", "gaussian", "bernoulli"),
R+ data = heart.valve,
R+ control = list(ip = 9)
R+ )
R> summary(m14)
Mixed effects regression model
Log likelihood = -1409.455

                      Estimate Std. Error  z  Pr(>|z|) [95% Conf. Interval]
  type              1.713733   0.741166 2.312  0.0208  0.261074  3.166392
   EV[]            -1.206885   2.351814 -0.513  0.6078 -5.816356  3.402585
     M2             -0.069736   0.119881 -0.582  0.5608 -0.304699  0.165228
     _cons          -8.339090   5.046409 -1.652  0.0984 -18.229870  1.551689
     log(gamma)      1.429550   0.153848 9.292  0.0000  1.128013  1.731087
      type           11.132882   1.326384  8.393  0.0000  8.533217 13.732548
   type:fp()        -4.097624   0.684881 -5.983  0.0000 -5.439969 -2.755282
       M1            2.813494   0.158675 17.731  0.0000  2.502497  3.124491
     _cons          -13.450441   1.494459 -9.000  0.0000 -16.379527 -10.521355
     log(gamma)      1.590105   0.138583 11.474  0.0000  1.318488  1.861722
       age           -0.013361   0.003780 -3.535  0.0004 -0.020769 -0.005953
     type             0.911158   0.071653 12.716  0.0000  0.770720  1.051596
    rcs():1          -0.007336   0.028614 -0.256  0.7977 -0.063419  0.048747
   rcs():2           -0.159499   0.032838 -4.857  0.0000 -0.223860 -0.095138
   rcs():3            0.126317   0.026191  4.823  0.0000  0.074983  0.177651
     _cons           3.283403   0.223338 14.701  0.0000  2.845668  3.721138
   log_sd(resid.)     -0.578881   0.036576 -15.827  0.0000 -0.650569 -0.507193
     fp()            -0.117359   0.072014 -1.630  0.1032 -0.258503  0.023785
     _cons           1.377721   0.550711  2.502  0.0124  0.298348  2.457094
   log_sd(M2)        1.125207   0.182159  6.177  0.0000  0.768182  1.482232
   log_sd(M1)        0.297373   0.240480  1.237  0.2162 -0.173959  0.768704
  atanh_corr(M1,M2) -1.524655   0.257312 -5.925  0.0000 -2.028978 -1.020332

Integration method: Non-adaptive Gauss-Hermite quadrature
Integration points: 9
\end{verbatim}

The parameters are reported in the results table in the order the submodels were specified. This model is complex, and it would not be possible to fit it in the other joint modelling software discussed. This complexity of the model means it is computationally intensive to
estimate, taking approximately 29 minutes on a 2-core laptop with 8 Gb of RAM.

4. Discussion

The example above illustrates the flexibility of merlin and the wide rage of models it is able to fit, the cost of this flexibility is computational time, more complex models with multiple random effects can be slow. For particular models it may be possible to calculate the likelihood more efficiently, which cannot be done here due to the generalised way merlin has been built. By default the likelihood is estimated using Gauss-Hermite quadrature to integrate out the random-effects. For every random effect the likelihood has to be estimated at each of the quadrature points, meaning for \( r \) random effects, and \( n \) quadrature points the likelihood has to be estimated \( n^r \) times. Alternatively the option to use Monte-Carlo integration is available, which is more efficient, especially for large numbers of random effects, improving computation time.

A further cost of the flexibility of merlin is the relatively complex syntax which is necessary to enable the fitting of all possible models. Whilst the syntax allows for a wide range of models to be fitted, it could lead to confusion and mistakes in model specification being made. To address this we have written inbuilt wrapper functions, such as \texttt{mlsurv} shown in Section 3.4, and \texttt{mlrcs}, to fit specific types of models, which will use the underlying merlin package, but will have simplified syntax to make them more user-friendly.

The merlin package is constantly evolving, with many further updates to merlin planned in line with the Stata package. Planned updates include implementation of fully adaptive Gauss-Hermite quadrature, allowing for left truncated survival data, and empirical Bayes predictions of the random effects.

Overall the flexibility of merlin will allow it to be used to fit a wide range of new models which cannot be implemented in other software packages. Its modular nature will allow for the easy addition of further components and families of outcomes, and the ability to incorporate user-defined functions means that there are many directions merlin can be taken in which have not yet been considered.

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