Examples of joint models for a longitudinal process and a multi-state process

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Contents

Import two databases which contain longitudinal and survival data:

```
load("data.RData")
ls()
```

```
## [1] "data_long" "data_surv"
```

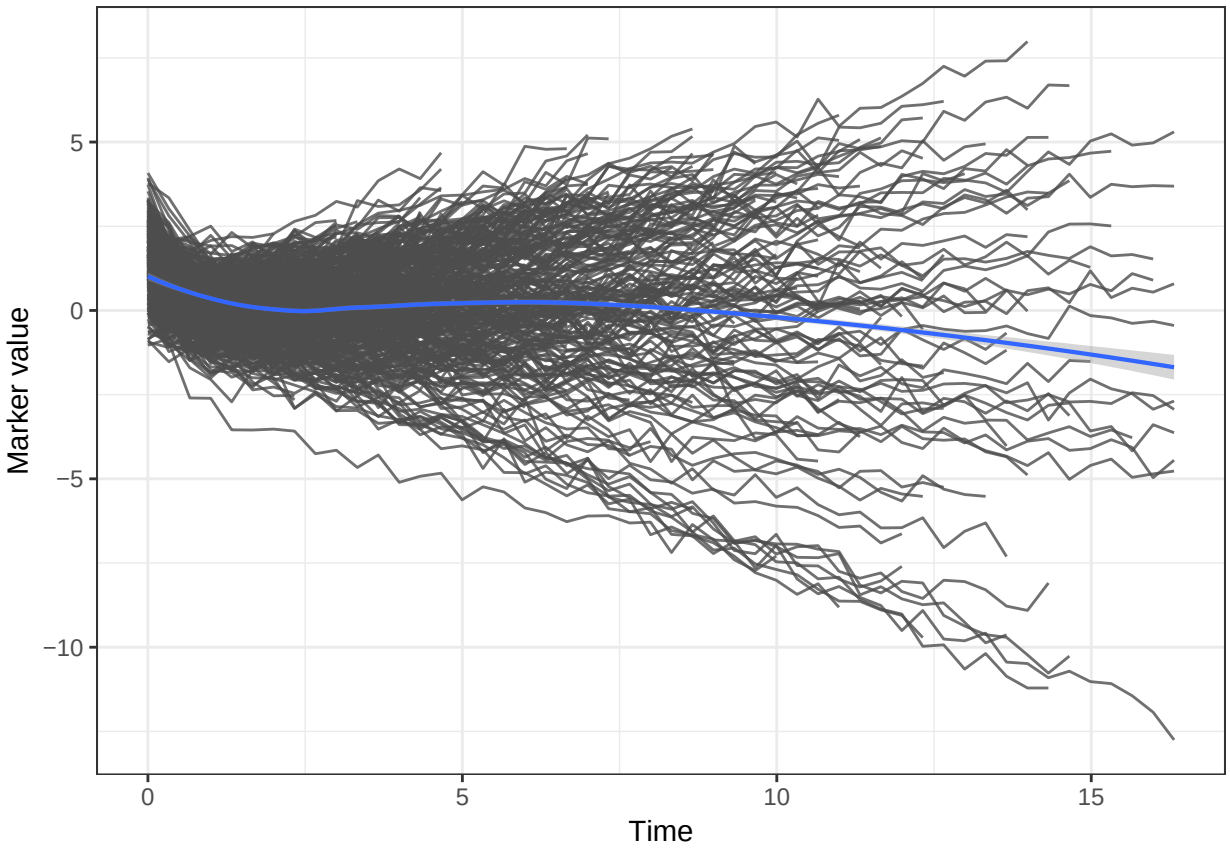
Load the packages and the function to estimate joint multi-state models:

```
library(mstate) # Please use the version 0.2.7
library(JM)
source("JMstateModel.R")
```

Longitudinal sub-part

Plot the individual trajectories of the longitudinal responses:

```
library(ggplot2)
plot_long <- (ggplot(data_long) +
                geom_line(aes(x = times, y = Y, group = id), color = "grey30", alpha = 0.8) +
                stat_smooth(aes(x = times, y = Y), method = "loess", size = 0.75) +
                theme_bw() +
                xlab("Time") +
                ylab("Marker value"))
plot_long
```



Fit the longitudinal responses using a linear mixed model:

```
lmeFit <- lme(fixed = Y ~ (times + I((1 + times)^(-1.2) - 1)) * X,
              data = data_long,
              random = ~ (times + I((1 + times)^(-1.2) - 1)) | id,
              method = "REML",
              control = list(opt = "optim"))
```

Multi-state sub-part

Construct the 3*3 matrix of transitions:

```
tmat <- matrix(NA, 3, 3)
tmat[1, 2:3] <- 1:2
tmat[2, 3] <- 3
dimnames(tmat) <- list(from = c("State_0", "State_1", "State_2"),
                       to = c("State_0", "State_1", "State_2"))
tmat
```

```
##          to
## from      State_0 State_1 State_2
##   State_0      NA       1       2
##   State_1      NA      NA       3
##   State_2      NA      NA      NA
```

The transition '0 -> 1' is called '1','0 -> 2' is called '2' and '1 -> 2' is called '3'.

Define the covariate(s) in the multi-state sub-part:

```
covs <- "X"
```

The *msprep()* function divides the survival database in order to have one line per transition at risk for each subject, with 'Tstart' the entry time in the current state, and 'Tstop' the time of transition or censorship; 'status' denotes if the transition has been performed:

```
data_mstate <- msprep(time = c(NA, "t_State_1", "t_State_2"),
                      status = c(NA, "State_1", "State_2"),
                      data = data_surv,
                      trans = tmat,
                      keep = covs,
                      id = "id")
```

expand.covs() permits to define the set of covariates which impact each transition:

```
data_mstate <- expand.covs(data_mstate, covs,
                           append = TRUE, longnames = FALSE)
head(data_mstate)
```

```
## An object of class 'msdata'
##
## Data:
##   id from to trans Tstart     Tstop      time status        X      X.1
## 1  1    1  2     1      0 10.756110 10.756110      0 1.358953 1.358953
## 2  1    1  3     2      0 10.756110 10.756110      1 1.358953 0.000000
## 3  2    1  2     1      0  3.064827  3.064827      0 1.833495 1.833495
## 4  2    1  3     2      0  3.064827  3.064827      1 1.833495 0.000000
## 5  3    1  2     1      0  4.742421  4.742421      0 2.224321 2.224321
## 6  3    1  3     2      0  4.742421  4.742421      0 2.224321 0.000000
##        X.2 X.3
## 1 0.000000   0
## 2 1.358953   0
## 3 0.000000   0
## 4 1.833495   0
## 5 0.000000   0
## 6 2.224321   0
```

The *events()* function indicates the number of observed transitions and their percentages.

```
events(data_mstate)
```

```
## $Frequencies
##          to
## from      State_0 State_1 State_2 no event total entering
##   State_0       0     164     157      179           500
##   State_1       0       0      99       65           164
##   State_2       0       0       0        0             0
##
## $Proportions
##          to
## from        State_0   State_1   State_2  no event
##   State_0 0.0000000 0.3280000 0.3140000 0.3580000
##   State_1 0.0000000 0.0000000 0.6036585 0.3963415
##   State_2
```

Multi-state model with transition-specific proportional intensities:

```
coxFit <- coxph(Surv(Tstart, Tstop, status) ~ X.1 + X.2 + X.3 + strata(trans),
                data = data_mstate, method = "breslow", x = TRUE, model = TRUE)
```

Joint multi-state sub-part

Define the derived of the fixed and random parts in the mixed model, and indicate which covariates are kept:

```
dForm <- list(fixed = ~ 1 + I((-1.2) * ((1 + times)^(-2.2))) +
                X + I((-1.2) * ((1 + times)^(-2.2))):X,
              indFixed = c(2:3 ,5:6),
              random = ~ 1 + I((-1.2) * ((1 + times)^(-2.2))),
              indRandom = 2:3)
```

Joint multi-state model with:

- true current level and true current slope of the biomarker as dependence function,
- cubic B-splines with 1 internal knot for each log-baseline intensity,
- 15 Gauss-Kronrod quadrature points to approximate the integral over time (default),
- 3 Gauss-Hermite quadrature points in the pseudo-adaptative numerical integration to approximate the integral over random effects.

```
jointFit_1step_GHk3 <-
  JMstateModel(lmeObject = lmeFit,
               survObject = coxFit,
               timeVar = "times",
               parameterization = "both",
               method = "spline-PH-aGH",
               interFact = list(value = ~ strata(trans) - 1,
                                slope = ~ strata(trans) - 1,
                                data = data_mstate),
               derivForm = dForm,
               Mstate = TRUE,
               data.Mstate = data_mstate,
               ID.Mstate = "id",
               control = list(GHk = 3, lng.in.kn = 1),
               verbose = TRUE)
summary(jointFit_1step_GHk3)
```

```
##
## Call:
## JMstateModel(lmeObject = lmeFit, survObject = coxFit, timeVar = "times",
##     parameterization = "both", method = "spline-PH-aGH", interFact = list(value = ~strata(trans) -
##         1, slope = ~strata(trans) - 1, data = data_mstate), derivForm = dForm,
##     control = list(GHk = 3, lng.in.kn = 1), Mstate = TRUE, data.Mstate = data_mstate,
##     ID.Mstate = "id", verbose = TRUE)
##
## Data Descriptives:
## Longitudinal Process     Event Process
## Number of Observations: 10065    Number of Events: 420 (84%)
## Number of Groups: 500
##
## Joint Model Summary:
## Longitudinal Process: Linear mixed-effects model
## Event Process: Stratified relative risk model with spline-approximated
```

```
##      baseline risk function
## Parameterization: Time-dependent + time-dependent slope
##
##    log.Lik      AIC      BIC
##  -5205.735 10485.47 10641.41
##
## Variance Components:
##                             StdDev    Corr
## (Intercept)                 0.6329  (Intr)   times
## times                       0.4092  0.0700
## I((1 + times)^(-1.2) - 1)  1.3482  0.4650  0.5444
## Residual                    0.2750
##
## Coefficients:
## Longitudinal Process
##                                Value Std.Err z-value p-value
## (Intercept)                 -0.2572  0.0900 -2.8580  0.0043
## times                       -0.1872  0.0245 -7.6402 <0.0001
## I((1 + times)^(-1.2) - 1)    0.6501  0.1810  3.5921  0.0003
## X                            0.7922  0.0408 19.4192 <0.0001
## times:X                      0.2585  0.0105 24.5103 <0.0001
## I((1 + times)^(-1.2) - 1):X  1.0553  0.0819 12.8876 <0.0001
##
## Event Process
##                                  Value Std.Err z-value p-value
## X.1                             0.1003  0.1267  0.7914  0.4287
## X.2                            -0.0437  0.1300 -0.3365  0.7365
## X.3                            -0.3084  0.1497 -2.0598  0.0394
## Assoct:strata(trans)trans=1     0.4020  0.0939  4.2802 <0.0001
## Assoct:strata(trans)trans=2    -0.0042  0.0487 -0.0858  0.9316
## Assoct:strata(trans)trans=3     0.1102  0.0863  1.2775  0.2014
## Assoct.s:strata(trans)trans=1  2.9994  0.4216  7.1138 <0.0001
## Assoct.s:strata(trans)trans=2  0.6959  0.3873  1.7969  0.0724
## Assoct.s:strata(trans)trans=3 -0.1406  0.8724 -0.1612  0.8720
## bs1(trans=1)                  -5.6826  0.8127 -6.9926 <0.0001
## bs2(trans=1)                  -4.1077  0.6221 -6.6026 <0.0001
## bs3(trans=1)                  -4.9324  0.9457 -5.2158 <0.0001
## bs4(trans=1)                  -6.5011  1.2782 -5.0863 <0.0001
## bs5(trans=1)                  -2.2499  1.6199 -1.3889  0.1649
## bs1(trans=2)                  -4.6128  0.7468 -6.1768 <0.0001
## bs2(trans=2)                  -3.3328  0.5570 -5.9839 <0.0001
## bs3(trans=2)                  -2.9346  0.7582 -3.8706  0.0001
## bs4(trans=2)                  -1.1341  0.7486 -1.5150  0.1298
## bs5(trans=2)                  -0.0159  0.7233 -0.0220  0.9825
## bs1(trans=3)                  -4.2656  4.7031 -0.9070  0.3644
## bs2(trans=3)                  -2.2203  1.2937 -1.7163  0.0861
## bs3(trans=3)                  -2.9859  1.2400 -2.4080  0.0160
## bs4(trans=3)                  -0.1892  1.0354 -0.1828  0.8550
## bs5(trans=3)                  -0.1480  0.9793 -0.1512  0.8798
##
## Integration:
## method: (pseudo) adaptive Gauss-Hermite
## quadrature points: 3
##
```

```
## Optimization:
## Convergence: 0
```

Same joint multi-state model with:

- 9 Gauss-Hermite quadrature points in the pseudo-adaptative numerical integration to approximate the integral over random effects.

```
jointFit_1step_GHk9 <-
  JMstateModel(lmeObject = lmeFit,
               survObject = coxFit,
               timeVar = "times",
               parameterization = "both",
               method = "spline-PH-aGH",
               interFact = list(value = ~ strata(trans) - 1,
                                slope = ~ strata(trans) - 1,
                                data = data_mstate),
               derivForm = dForm,
               Mstate = TRUE,
               data.Mstate = data_mstate,
               ID.Mstate = "id",
               control = list(GHk = 9, lng.in.kn = 1),
               verbose = TRUE)
summary(jointFit_1step_GHk9)
```

```
##
## Call:
## JMstateModel(lmeObject = lmeFit, survObject = coxFit, timeVar = "times",
##     parameterization = "both", method = "spline-PH-aGH", interFact = list(value = ~strata(trans) -
##         1, slope = ~strata(trans) - 1, data = data_mstate), derivForm = dForm,
##     control = list(GHk = 9, lng.in.kn = 1), Mstate = TRUE, data.Mstate = data_mstate,
##     ID.Mstate = "id", verbose = TRUE)
##
## Data Descriptives:
## Longitudinal Process     Event Process
## Number of Observations: 10065    Number of Events: 420 (84%)
## Number of Groups: 500
##
## Joint Model Summary:
## Longitudinal Process: Linear mixed-effects model
## Event Process: Stratified relative risk model with spline-approximated
##      baseline risk function
## Parameterization: Time-dependent + time-dependent slope
##
##    log.Lik      AIC      BIC
##  -5206.105 10486.21 10642.15
##
## Variance Components:
##                             StdDev    Corr
## (Intercept)                 0.6336  (Intr)   times
## times                       0.4084  0.0686
## I((1 + times)^(-1.2) - 1)  1.3450  0.4665  0.5399
## Residual                    0.2750
##
## Coefficients:
## Longitudinal Process
```

```
##                                Value Std.Err z-value p-value
## (Intercept)                 -0.2525  0.0907 -2.7842  0.0054
## times                       -0.1833  0.0457 -4.0079  0.0001
## I((1 + times)^(-1.2) - 1)    0.6754  0.1936  3.4880  0.0005
## X                            0.7909  0.0411 19.2313 <0.0001
## times:X                      0.2618  0.0177 14.7720 <0.0001
## I((1 + times)^(-1.2) - 1):X  1.0521  0.0872 12.0698 <0.0001
##
## Event Process
##                                  Value Std.Err z-value p-value
## X.1                             0.1110  0.1265  0.8776  0.3802
## X.2                            -0.0478  0.1301 -0.3672  0.7135
## X.3                            -0.3503  0.1492 -2.3471  0.0189
## Assoct:strata(trans)trans=1     0.4039  0.0943  4.2846 <0.0001
## Assoct:strata(trans)trans=2    -0.0024  0.0487 -0.0495  0.9605
## Assoct:strata(trans)trans=3     0.0789  0.0851  0.9264  0.3543
## Assoct.s:strata(trans)trans=1  2.9858  0.4229  7.0601 <0.0001
## Assoct.s:strata(trans)trans=2  0.6949  0.3870  1.7954  0.0726
## Assoct.s:strata(trans)trans=3  0.0539  0.8677  0.0621  0.9505
## bs1(trans=1)                   -5.8254  0.8252 -7.0598 <0.0001
## bs2(trans=1)                   -4.0261  0.6251 -6.4409 <0.0001
## bs3(trans=1)                   -5.2064  0.9596 -5.4258 <0.0001
## bs4(trans=1)                   -6.0947  1.3033 -4.6764 <0.0001
## bs5(trans=1)                   -3.1122  1.8580 -1.6750  0.0939
## bs1(trans=2)                   -4.5975  0.7452 -6.1691 <0.0001
## bs2(trans=2)                   -3.3147  0.5569 -5.9517 <0.0001
## bs3(trans=2)                   -2.9635  0.7585 -3.9070  0.0001
## bs4(trans=2)                   -1.1017  0.7477 -1.4734  0.1406
## bs5(trans=2)                   -0.0010  0.7215 -0.0014  0.9989
## bs1(trans=3)                   -3.9838  4.6234 -0.8617  0.3889
## bs2(trans=3)                   -2.1982  1.3070 -1.6818  0.0926
## bs3(trans=3)                   -3.0823  1.2546 -2.4567  0.0140
## bs4(trans=3)                    0.4384  1.0536  0.4161  0.6773
## bs5(trans=3)                   -0.4419  1.0717 -0.4124  0.6801
##
## Integration:
## method: (pseudo) adaptive Gauss-Hermite
## quadrature points: 9
##
## Optimization:
## Convergence: 0
```

To use the multi-step pseudo-adaptive Gauss-Hermite rule, we have to source two functions inspired by JM:

```
source("modified.log.posterior.b2.R")
source("modified.ranef.jointModel.R")
```

Same joint multi-state model with:

- 9 and 9 Gauss-Hermite quadrature points in the two-step pseudo-adaptative numerical integration to approximate the integral over random effects. We can choose the posterior mode (true definition) or the posterior mean (faster) of the random effects of the fitted joint model (defined in 'init') to update the quadrature points. Here the mode is used.

```
jointFit_2step_GHk9_9 <-
  JMstateModel(lmeObject = lmeFit,
```

```
                survObject = coxFit,
                timeVar = "times",
                parameterization = "both",
                method = "spline-PH-aGH",
                interFact = list(value = ~ strata(trans) - 1,
                                 slope = ~ strata(trans) - 1,
                                 data = data_mstate),
                derivForm = dForm,
                Mstate = TRUE,
                data.Mstate = data_mstate,
                ID.Mstate = "id",
                control = list(GHk = 9, lng.in.kn = 1),
                init = jointFit_1step_GHk9,
                init.type.ranef = "mode",
                verbose = TRUE)
summary(jointFit_2step_GHk9_9)
```

```
##
## Call:
## JMstateModel(lmeObject = lmeFit, survObject = coxFit, timeVar = "times",
##     parameterization = "both", method = "spline-PH-aGH", interFact = list(value = ~strata(trans) -
##         1, slope = ~strata(trans) - 1, data = data_mstate), derivForm = dForm,
##     init = jointFit_1step_GHk9, control = list(GHk = 9, lng.in.kn = 1),
##     Mstate = TRUE, data.Mstate = data_mstate, ID.Mstate = "id",
##     init.type.ranef = "mode", verbose = TRUE)
##
## Data Descriptives:
## Longitudinal Process     Event Process
## Number of Observations: 10065    Number of Events: 420 (84%)
## Number of Groups: 500
##
## Joint Model Summary:
## Longitudinal Process: Linear mixed-effects model
## Event Process: Stratified relative risk model with spline-approximated
##      baseline risk function
## Parameterization: Time-dependent + time-dependent slope
##
##    log.Lik      AIC      BIC
##  -5205.224 10484.45 10640.39
##
## Variance Components:
##                              StdDev    Corr
## (Intercept)                  0.6335  (Intr)   times
## times                        0.4100  0.0677
## I((1 + times)^(-1.2) - 1)  1.3481  0.4642  0.5436
## Residual                     0.2750
##
## Coefficients:
## Longitudinal Process
##                                Value Std.Err z-value p-value
## (Intercept)                  -0.2578  0.0910 -2.8326  0.0046
## times                        -0.1933  0.0596 -3.2447  0.0012
## I((1 + times)^(-1.2) - 1)    0.6466  0.2002  3.2292  0.0012
## X                             0.7936  0.0413 19.1969 <0.0001
```

```
## times:X                       0.2685  0.0273  9.8250 <0.0001
## I((1 + times)^(-1.2) - 1):X  1.0680  0.0916 11.6578 <0.0001
##
## Event Process
##                                 Value Std.Err z-value p-value
## X.1                            0.1026  0.1267  0.8099  0.4180
## X.2                           -0.0459  0.1299 -0.3536  0.7237
## X.3                           -0.3098  0.1494 -2.0740  0.0381
## Assoct:strata(trans)trans=1    0.3979  0.0937  4.2462 <0.0001
## Assoct:strata(trans)trans=2   -0.0047  0.0487 -0.0965  0.9231
## Assoct:strata(trans)trans=3    0.1001  0.0857  1.1684  0.2426
## Assoct.s:strata(trans)trans=1  3.0096  0.4211  7.1475 <0.0001
## Assoct.s:strata(trans)trans=2  0.7069  0.3884  1.8199  0.0688
## Assoct.s:strata(trans)trans=3 -0.1260  0.8693 -0.1449  0.8848
## bs1(trans=1)                  -5.6680  0.8090 -7.0058 <0.0001
## bs2(trans=1)                  -4.1498  0.6200 -6.6932 <0.0001
## bs3(trans=1)                  -4.8575  0.9423 -5.1546 <0.0001
## bs4(trans=1)                  -6.5758  1.2768 -5.1502 <0.0001
## bs5(trans=1)                  -2.1303  1.5957 -1.3350  0.1819
## bs1(trans=2)                  -4.5946  0.7459 -6.1600 <0.0001
## bs2(trans=2)                  -3.3358  0.5571 -5.9872 <0.0001
## bs3(trans=2)                  -2.9304  0.7577 -3.8675  0.0001
## bs4(trans=2)                  -1.1270  0.7478 -1.5072  0.1318
## bs5(trans=2)                  -0.0078  0.7219 -0.0107  0.9914
## bs1(trans=3)                  -4.3569  4.7907 -0.9094  0.3631
## bs2(trans=3)                  -2.2500  1.2974 -1.7342  0.0829
## bs3(trans=3)                  -2.9001  1.2416 -2.3357  0.0195
## bs4(trans=3)                  -0.0771  1.0349 -0.0745  0.9406
## bs5(trans=3)                  -0.1699  0.9932 -0.1711  0.8641
##
## Integration:
## method: (pseudo) adaptive Gauss-Hermite
## quadrature points: 9
##
## Optimization:
## Convergence: 0
```

Score test for the need of a Gaussian frailty term in the joint multi-state model

Load the required functions:

```
source("score_test_frailty.R")
source("deriva_forward_reduced.R")
```

Apply the score test:

```
score_test_jointFit_2step_GHk9_9 <- score_test_frailty(jointFit_2step_GHk9_9)
```

```
score_test_jointFit_2step_GHk9_9
```

```
## $U_i
##   [1] -0.0766926864  0.3290214916 -0.0654603218 -0.1236376816 -0.0967030085
##   [6]  0.0249811782 -0.1756648052 -0.4899895894 -0.0623875936 -0.2455738226
```

```
##  [11] -0.0239151749 -0.0856969436 -0.0047852012 -0.1161554205 -0.0140258206
##  [16] -0.3516704844 -0.1165976113 -0.0286392787 10.3959630082 -0.1397654797
##  [21]  1.0332497396 -0.0142339620  0.0047345888 -0.0712429353 -0.3122657588
##  [26] -0.8154066252  0.2450557609  0.4750234736  0.3585267809 -0.7235499798
##  [31]  0.1173270165 -0.0534774621 -0.2038831047 -0.9956114878 -0.5384534582
##  [36]  0.3583691332  0.3873239226 -0.3018932715  1.0382973970 -0.0168621557
##  [41] -0.0339095730 -0.3330188369 -0.5819110151  0.4643681510  0.7985044371
##  [46] -0.3683887086 -0.8655421448 -0.4575779894  0.4769995079 -0.0342924434
##  [51] -0.0872698309  0.3042202336 -0.0722535362 -0.9008811033 -0.0325710049
##  [56] -1.0895877069 -0.0111507419 -0.0231234059  0.4646944035 -0.0139555587
##  [61] -0.0660236968 -0.0687917119 -0.9487667145 -0.1680851412 -0.1104121158
##  [66] -0.6038274813 -0.0250686752 -0.0033858229  0.1166574881  0.3330464093
##  [71]  0.8194351712 -0.9592718165 -0.2275592590 -0.6100228063 -0.5589204868
##  [76] -0.1719091978 -0.4607818421  0.4138007719 -0.0758431498 -0.0214098448
##  [81] -0.4572111328  0.0922823907 -0.5809002377  0.4711562473 -0.0940385094
##  [86] -0.0999320424 -0.0979327700 -0.0741300115 -0.1167419514 -0.1226074545
##  [91]  0.6873339954 -0.0071850770 -0.2794765362 -0.0076616816 -0.1223104982
##  [96] -0.0272998941  0.1884038875  0.4958290766 -0.5707429585 -0.0778842763
## [101] -0.2980894003 -0.1229073849 -0.9301232861 -0.0704710749 -0.0247306890
## [106] -0.8772285768  0.5973836160 -0.0690352897 -0.1794674464  0.1883435665
## [111] -0.6228659582 -0.0212737799 -0.0065048466  0.2478053837  0.2426076680
## [116] -0.4283584956 -0.0566592672  0.0465243481 -0.1763810338 -0.5864671003
## [121] -0.1222147967  0.4279565249 -0.5636274453 -0.1103295727  0.4676515764
## [126] -0.5439885454 -0.3505916751 -0.5648814882 -1.0092733752 -0.5929361566
## [131]  0.3013183502  0.4654458261  0.3452053590 -0.0911785029  0.0192374547
## [136] -0.0407663272 -0.5854547645  0.0229839217  1.2499354820  0.1024830315
## [141] -0.0237183348 -0.1088120359  0.1708396206 -0.3758593177 -0.1764470953
## [146]  0.1566615353  0.7697264005 -0.4181041582 -0.4452317512  0.4201470706
## [151] -0.0304715364 -0.5302610414 -0.1437095219 -0.5872210683  0.7314078383
## [156] -0.5070628225  0.0420568917 -0.0371282225 -0.0658083986 -0.1239272154
## [161]  0.5963946232  0.1003834041 -0.8691979789 -0.0193434769 -0.0793118195
## [166] -0.0039011022 -0.4958398844 -0.0435819792  0.3804947245  0.4825999812
## [171] -0.1218236796  0.2518553325 -0.0256989042 -0.2775094592 -0.0416653311
## [176] -0.0555302714 -0.1525067209 -0.0096383606 -0.5666944958 -0.0662134144
## [181] -0.0249193281  1.0354848211  2.9107433634 -0.0998342957 -0.1094450631
## [186] -1.1227220978  0.3913181038 -0.3543601753  0.0053036934  0.4275756538
## [191]  0.2290006380 -1.1146090972 -0.1466590217 -0.1249365137 -0.9370538109
## [196]  0.4424274589  0.5592766945  1.0303229051 -0.4102467540  1.4856520685
## [201] -0.1399870923 -0.6082819443  0.3316050272 -0.5728630618 -0.6204972794
## [206] -0.0773202199 -0.1238013541  0.4236333327 -0.0092227885 -0.0109924073
## [211]  0.0114215764  0.4569508136 -0.5921224032 -0.5634888734  0.5082259473
## [216] -0.1203587281 -0.1263966932 -0.0836656072 -0.3549575049 -0.0898125569
## [221] -0.1236191886  0.4824658775 -0.1014974945  0.1004037672 -0.0363218396
## [226] -0.4662979856  0.3427530606 -0.1197821220  1.7705844162 -0.0902296739
## [231]  0.4360504080 -0.0977047921 -0.5955240222 -0.0643964119 -0.1226295083
## [236] -0.3846713283 -0.5820091993 -0.0908567170  0.2080308076 -0.2971281874
## [241] -0.2060979748  0.4215431672 -0.0057648700 -0.0153061335 -0.7707764098
## [246] -0.0378543348 -0.3066472651  0.0917379672  0.5678798156 -0.1898563736
## [251]  0.4902287566 -0.0606010310  0.2357996446 -0.0153645822 -0.0120405093
## [256] -0.0103057414 -0.0213999304 -0.1049672962  0.4425644695  0.0871710160
## [261] -0.2159261693 -1.0792302675 -0.3322457414 -0.0589341720 -0.1043704244
## [266]  1.3980734852  0.6407058134 -0.1143783322 -0.9515831668 -0.0107813628
## [271] -0.3067039997  0.3406136973 -0.0629086613 -0.4043049297 -0.1668118031
## [276] -0.0007758921 -0.2822903337 -0.5878596018 -0.5714230318 -0.0609320495
```

```
## [281] -0.0908353340 -0.5882606460 -0.0090429666  0.0184538800  0.4943455643
## [286]  0.1214269034  0.1457648943  0.0913087930 -0.0479595879  0.3768988654
## [291]  0.1991785098  0.3543608608 -1.0761739126 -1.0111855751 -0.4101604096
## [296] -0.3230088632 -0.1235173479 -0.9735961540  0.2171706360 -0.4965450300
## [301] -0.4078627582 -0.0396964202  0.3851482046 -0.6156898035 -0.0748391645
## [306] -0.9031231101 -0.0157779571 -0.1154455894 -0.1014576920  0.5531145668
## [311] -0.0466894022 -0.0578405551  0.2649350503 -0.2461870539  0.7794168938
## [316]  3.2056629310  0.3474328952 -0.0651195789 -0.6092929255 -0.0865347538
## [321]  0.1662476602 -0.0152552969 -0.0933369422 -0.5991801711  0.4517395677
## [326] -0.0399614435 -0.0736127686 -0.2036352881 -0.0449524440  0.3440916690
## [331] -0.0803033761  0.2160630283 -0.3170776379 -0.1230008592 -0.1860665558
## [336] -0.0228035277 -0.1107997024 -0.5809949405 -0.0218256276 -0.0705433581
## [341] -0.7055490423 -0.5317014642 -0.0438266981  0.0202474084 -0.0554157144
## [346] -0.4764582452 -0.4955371552  0.5184879244 -0.0958260157 -0.1006411239
## [351] -0.1477146541 -0.0813042570  0.1764301964 -0.1995340746 -0.2842889008
## [356] -0.6238003212 -0.0429625399 -0.0481485272  1.4835108272 -0.6139766043
## [361] -0.4877913984 -0.5070240340  0.1615714270 -0.0970270945 -0.2057009256
## [366]  0.0681038201 -0.4759646193 -0.0209623780 -0.5837770256 -0.3110317252
## [371] -0.0801148171 -0.0477363817 -0.0918385083 -0.0875419958 -0.4147559641
## [376]  0.2029095493 -0.0072021089  0.1388637658 -0.0333930711 -0.0402983158
## [381]  0.4666059266 -0.3849109227  0.0296210469 -0.1122798852 -0.5096114594
## [386] -1.1163922951 -0.2796604080 -0.0868643265 -0.9977419262  0.0119049682
## [391]  0.6938417538 -0.2191198117 -0.2473621018 -0.0351293862  0.7741206199
## [396] -0.2274657449 -0.0091104839 -0.0243771009  0.1342550164 -0.0124111218
## [401] -0.5539261659 -0.1029735943 -0.6003742433  0.3689707235 -0.1203101141
## [406] -0.0516148078 -0.5432421021  1.5065948442  0.5286688105  0.3037021693
## [411] -0.1048013494 -0.0963740969 -0.0983431486 -0.5483996147 -0.1180960484
## [416]  0.2147786438  0.0466761093  0.2489350060 -0.1529226970  6.3467587922
## [421] -0.3381522097 -0.0672329283  1.2324893518  0.3527311367 -0.0704785772
## [426] -0.0862046317 -0.0274479011  0.0647489382 -0.3152607916 -0.1051964457
## [431] -0.4184261528 -0.1217859937  0.0837477965  0.8681966785 -0.3344500887
## [436]  0.2448793180 -0.1195402352 -0.1166303281 -0.0947346648 -0.5498601552
## [441] -0.0036077123  0.4590031884 -1.0472191624 -0.3974112711 -0.1488332746
## [446] -0.2404604645 -0.4806427043 -0.4411899111 -1.0953495663  0.0975781791
## [451]  0.8259773422  0.3795709782 -0.7565866212 -0.5936878221 -0.9555908690
## [456] -0.0542445686  2.1239578329 -0.1246014558 -0.9665286909 -0.0593827220
## [461]  1.6856983400 -0.0269720416  0.1690230514 -0.1001131498 -0.6557805831
## [466]  0.2652788332 -0.0208544152 -0.4039975647  0.3158115761  0.4691310047
## [471] 14.4470321960 -0.2968705594 -0.0776719869 -0.0852799889 -0.0152921488
## [476] -0.0613891635 -0.2960364538  1.5659042318  1.2272048078  0.4062346502
## [481] -0.0475453369 -0.0294850650 -0.1227519624 -0.3502487177  0.0553574422
## [486]  1.1611893574 -0.0543906061  0.0456721620 -0.0294673004 -0.1197306991
## [491] -0.2780366842 -0.1037769411 -0.0924556810 -0.2512532257  0.0982698235
## [496] -0.5649846226  0.3894123660 -0.1249123223 -0.2819075688  1.8986530004
##
## $U
## [1] 7.791381
##
## $var_U
## [1] 125.5215
##
## $stat
## [1] 0.4836275
##
```

```
## $pval
## [1] 0.2433919
##
## $conv
## [1] 0
```

```
# U_i: Individual contributions to the score statistic
# U: Score statistic
# var_U: Asymptotic variance of the score statistic corrected for the nuisance parameters
# stat: Test statistic
# pval: P-value of the test (H0: absence of frailty, H1: presence of frailty)
# conv: convergence of the model (0:TRUE, 1:FALSE)
```

Joint multi-state model with transformation of the true current level of the marker

In this section we propose to estimate a joint model with shared random effects where the association between the marker's evolution and each transition intensity is explained through the true current slope of the marker and a parametric transformation of the true current level of the marker.

Here we depict an example where the transformation of the true current level, its gradient and hessian functions:

```
transform.value <- function(y) { # transformation function
  1 / (1 + exp(-(y - 0.71) / 0.44))
}

gr.transform.value <- function(x, y) { # gradient of the transformation function
  ((x/0.44) * exp((y - 0.71) / 0.44)) / (1 + exp((y - 0.71) / 0.44))^2
}

H.transform.value <- function(x1, x2, y) { # hessian of the transformation function
  ((x1 * x2) / 0.44^2 * exp((y - 0.71) / 0.44) * (1 - exp((y - 0.71) / 0.44))) /
    (1 + exp((y - 0.71) / 0.44))^3
}
```

Load the required functions to estimate the joint multi-state model:

```
# Modified functions (extensions) from JM
source("JMstateModel.R")
source("LogLik.splineGH.R")
source("Score.splineGH.R")
source("gr.longSplinePH.R")
source("gr.survSplinePH.R")
source("H.longSplinePH.R")
source("initial.surv.R")
source("opt.longSplinePH.R")
source("opt.survSplinePH.R")
source("splinePHGH.fit.R")
source("modified.log.posterior.b2.R")
source("modified.ranef.jointModel.R")

# Functions from JM
source("dropAttr.R")
```

```
source("gauher.R")
source("dmvnorm.R")
source("gaussKronrod.R")
source("nearPD.R")
source("chol.transf.R")
source("deriv.D.R")
source("jacobian2.R")
source("fd.vec.R")
```

Estimate the joint multi-state model:

```
jointFit_transfo_1step_GHk3 <-
  JMstateModel(lmeObject = lmeFit,
               survObject = coxFit,
               timeVar = "times",
               parameterization = "both",
               method = "spline-PH-aGH",
               interFact = list(value = ~ strata(trans) - 1,
                                slope = ~ strata(trans) - 1,
                                data = data_mstate),
               derivForm = dForm,
               Mstate = TRUE,
               data.Mstate = data_mstate,
               ID.Mstate = "id",
               transform.value = transform.value,
               gr.transform.value = gr.transform.value,
               H.transform.value = H.transform.value,
               control = list(GHk = 3, lng.in.kn = 1),
               verbose = TRUE)
summary(jointFit_transfo_1step_GHk3)
```

```
jointFit_transfo_2step_GHk3_9 <-
  JMstateModel(lmeObject = lmeFit,
               survObject = coxFit,
               timeVar = "times",
               parameterization = "both",
               method = "spline-PH-aGH",
               interFact = list(value = ~ strata(trans) - 1,
                                slope = ~ strata(trans) - 1,
                                data = data_mstate),
               derivForm = dForm,
               Mstate = TRUE,
               data.Mstate = data_mstate,
               ID.Mstate = "id",
               transform.value = transform.value,
               gr.transform.value = gr.transform.value,
               H.transform.value = H.transform.value,
               control = list(GHk = 9, lng.in.kn = 1),
               init = jointFit_transfo_1step_GHk3,
               init.type.ranef = "mode",
               verbose = TRUE)
summary(jointFit_transfo_2step_GHk3_9)
```

```r
summary(jointFit_transfo_2step_GHk3_9)
```

```
##
## Call:
## JMstateModel(lmeObject = lmeFit, survObject = coxFit, timeVar = "times",
##     parameterization = "both", method = "spline-PH-aGH", interFact = list(value = ~strata(trans) -
##         1, slope = ~strata(trans) - 1, data = data_mstate), derivForm = dForm,
##     init = jointFit_transfo_1step_GHk3, control = list(GHk = 9,
##         lng.in.kn = 1), Mstate = TRUE, data.Mstate = data_mstate,
##     ID.Mstate = "id", init.type.ranef = "mode", transform.value = transform.value,
##     gr.transform.value = gr.transform.value, H.transform.value = H.transform.value,
##     verbose = TRUE)
##
## Data Descriptives:
## Longitudinal Process     Event Process
## Number of Observations: 10065    Number of Events: 420 (84%)
## Number of Groups: 500
##
## Joint Model Summary:
## Longitudinal Process: Linear mixed-effects model
## Event Process: Stratified relative risk model with spline-approximated
##      baseline risk function
## Parameterization: Time-dependent + time-dependent slope
##
##    log.Lik      AIC      BIC
##  -5211.266 10496.53 10652.47
##
## Variance Components:
##                             StdDev    Corr
## (Intercept)                 0.6332  (Intr)   times
## times                       0.4104  0.0655
## I((1 + times)^(-1.2) - 1)  1.3444  0.4629  0.5421
## Residual                    0.2750
##
## Coefficients:
## Longitudinal Process
##                                Value Std.Err z-value p-value
## (Intercept)                  -0.2553  0.0907 -2.8154  0.0049
## times                        -0.1866  0.0490 -3.8081  0.0001
## I((1 + times)^(-1.2) - 1)    0.6531  0.1948  3.3532  0.0008
## X                             0.7925  0.0411 19.2677 <0.0001
## times:X                       0.2647  0.0190 13.9641 <0.0001
## I((1 + times)^(-1.2) - 1):X  1.0649  0.0875 12.1646 <0.0001
##
## Event Process
##                                  Value Std.Err z-value p-value
## X.1                             0.1357  0.1275  1.0639  0.2874
## X.2                            -0.0173  0.1299 -0.1328  0.8944
## X.3                            -0.2667  0.1461 -1.8254  0.0679
## Assoct:strata(trans)trans=1     1.0968  0.4253  2.5790  0.0099
## Assoct:strata(trans)trans=2    -0.3464  0.3215 -1.0773  0.2814
## Assoct:strata(trans)trans=3     0.0767  0.8529  0.0899  0.9284
## Assoct.s:strata(trans)trans=1  3.5863  0.4206  8.5273 <0.0001
## Assoct.s:strata(trans)trans=2  0.9551  0.3709  2.5751  0.0100
```

```
## Assoct.s:strata(trans)trans=3  0.7723  0.4462  1.7307  0.0835
## bs1(trans=1)                  -5.9209  0.7963 -7.4355 <0.0001
## bs2(trans=1)                  -5.2222  0.6002 -8.7006 <0.0001
## bs3(trans=1)                  -4.6213  0.9271 -4.9846 <0.0001
## bs4(trans=1)                  -6.3090  1.2152 -5.1917 <0.0001
## bs5(trans=1)                  -1.0345  1.3220 -0.7825  0.4339
## bs1(trans=2)                  -4.3642  0.7513 -5.8085 <0.0001
## bs2(trans=2)                  -3.4273  0.5207 -6.5823 <0.0001
## bs3(trans=2)                  -2.7292  0.7796 -3.5006  0.0005
## bs4(trans=2)                  -1.0782  0.7441 -1.4490  0.1474
## bs5(trans=2)                   0.0392  0.7003  0.0560  0.9553
## bs1(trans=3)                  -6.1132  5.7200 -1.0687  0.2852
## bs2(trans=3)                  -2.9901  1.2765 -2.3424  0.0192
## bs3(trans=3)                  -3.2723  1.4567 -2.2463  0.0247
## bs4(trans=3)                   0.0948  1.1747  0.0807  0.9357
## bs5(trans=3)                  -0.0833  1.2495 -0.0667  0.9468
##
## Integration:
## method: (pseudo) adaptive Gauss-Hermite
## quadrature points: 9
##
## Optimization:
## Convergence: 0
```

Apply the score test to this new model:

```
score_test_jointFit_transfo_2step_GHk3_9 <- score_test_frailty(jointFit_transfo_2step_GHk3_9)
score_test_jointFit_transfo_2step_GHk3_9
```