Examples of focused model comparison: multi-state models

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Abstract

This vignette illustrates focused model comparison with the **fic** package for covariate selection in multi-state models fitted with the **msm** package. A challenge of this example is that a single model involves several regression models fitted simultaneously, so that the set of parameters has a non-standard structure. Additionally, the focus is a complicated function of the model parameters.

Keywords: models,survival.

1. Multi-state models for panel data

The **msm** package (Jackson 2011) fits continuous-time Markov multi-state models to "panel-observed" longitudinal data. That is, data in which a categorical outcome, or *state*, is observed at a series of times for a set of individuals. A typical application is to states of disease recorded at clinic visits. The actual times of transition between states are not observed, and we only know the state of the process at the visit times. The likelihood for this class of models was orginally described by Kalbfleisch and Lawless (1985).

The example dataset `psor` in the package records the progression of joint damage for 305 patients with psoriatic arthritis (from Gladman and Farewell 1999) Each of the 806 rows represents a clinic visit. The outcome is the variable `state`, where 1, 2, 3, and 4 represent 0, 1–4, 5–9 and 10 or more damaged joints, respectively.

A four-state continuous-time Markov model is fitted with the structure illustrated in Figure 1, where the (unobserved) instantaneous transitions in continuous time are assumed to only occur between adjacent states, from state 1 to state 2, from state 2 to state 3, and from state 3 to state 4. There are two binary covariates, `hieffusn` (presence of five or more effusions) and `ollwsdrt` (low erythrocyte sedimentation rate), that are assumed to affect the intensity parameters governing all three of the transitions. The covariates are constant through time and measured at baseline. The transition intensity from state r to state s for person i with covariates $\mathbf{x}_i$ is then

$$q_{irs}(x) = q_{rs}^{(0)} \exp(\boldsymbol{\beta}_{rs}\mathbf{x}_i)$$

where $\boldsymbol{\beta}_{rs} = (\beta_{rs}^{(1)}, \beta_{rs}^{(2)})$ is the vector of log hazard ratios on the r–s transition for the two covariates.
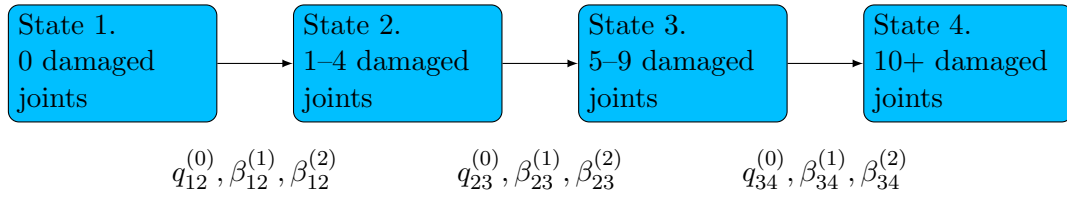
Figure 1: Multi-state transition structure and parameters for the psoriatic arthritis example

To fit the model in **msm**, a matrix `Qind` is defined that indicates which instantaneous transitions are permitted, from the state indicated in the rows to the state indicated in the columns. The **msm** function fits the model with the given covariates, which by default affect all transitions.

```
if (!require("msm"))
    stop("The `msm` package should be installed
to run code in this vignette")

## Loading required package:  msm

Qind <- rbind(c(0, 1, 0, 0),
              c(0, 0, 1, 0),
              c(0, 0, 0, 1),
              c(0, 0, 0, 0))
psor.wide.msm <- msm(state ~ months, subject=ptnum, data=psor,
                     qmatrix = Qind,  gen.inits=TRUE,
                     covariates = ~ollwsdrt+hieffusn)

## Warning in seq.default(length = nip):  partial argument match of 'length' to
'length.out'
## Warning in seq.default(length = nipc):  partial argument match of 'length' to
'length.out'
## Warning in seq.default(length = nshortpars):  partial argument match of 'length'
to 'length.out'
## Warning in seq.default(length = x$qmodel$npars + x$qcmodel$npars):  partial
argument match of 'length' to 'length.out'
## Warning in seq.default(length = ni):  partial argument match of 'length' to
'length.out'
## Warning in seq.default(length = ni + ni * nc):  partial argument match of 'length'
to 'length.out'
## Warning in seq.default(length = x$qmodel$npars + x$qcmodel$npars):  partial
argument match of 'length' to 'length.out'
## Warning in seq.default(length = ni):  partial argument match of 'length' to
'length.out'
## Warning in seq.default(length = ni + ni * nc):  partial argument match of 'length'
to 'length.out'
```

```
psor.wide.msm


##
## Call:
## msm(formula = state ~ months, subject = ptnum, data = psor, qmatrix = Qind,    gen.ini
##
## Maximum likelihood estimates
## Baselines are with covariates set to their means
```

Warning in seq.default(length = x$qmodel$npars + x$qcmodel$npars): partial argument match of 'length' to 'length.out'

Warning in seq.default(length = ni): partial argument match of 'length' to 'length.out'

Warning in seq.default(length = ni + ni * nc): partial argument match of 'length' to 'length.out'

Warning in seq.default(length = x$qcmodel$ncovs): partial argument match of 'length' to 'length.out'

```
##
## Transition intensities with hazard ratios for each covariate
##                   Baseline                      ollwsdrt
## State 1 - State 1 -0.1004 (-0.12750,-0.07898)
## State 1 - State 2  0.1004 ( 0.07898, 0.12750) 0.7320 (0.4258,1.2585)
## State 2 - State 2 -0.1623 (-0.20601,-0.12789)
## State 2 - State 3  0.1623 ( 0.12789, 0.20601) 0.4579 (0.2643,0.7932)
## State 3 - State 3 -0.2607 (-0.34952,-0.19453)
## State 3 - State 4  0.2607 ( 0.19453, 0.34952) 1.5757 (0.7776,3.1928)
##                   hieffusn
## State 1 - State 1
## State 1 - State 2 2.338 (1.0937,4.997)
## State 2 - State 2
## State 2 - State 3 1.681 (0.9500,2.975)
## State 3 - State 3
## State 3 - State 4 1.394 (0.7738,2.511)
##
## -2 * log-likelihood:  1113
## [Note, to obtain old print format, use "printold.msm"]
```

The hazard ratios $exp(\boldsymbol{\beta}_{rs})$ for the two covariates are presented in the model output. The confidence intervals are wide, which suggests that a smaller model might give more precise estimates.

2. Focused comparison of multi-state models fitted with "msm"

Focused model comparison is performed to assess whether removing the covariate effects for

particular transitions lead to more precise estimates of a focus quantity, defined below. The unusual feature of this example, compared to a standard covariate selection problem, is that the model involves three regressions fitted simultaneously, one for each transition.

We compare the wide model and six further submodels with covariates on different transitions, as defined in the table below. Model 7 is the wide model where both covariates affect all transitions, and models 1–6 are defined by fixing particular β_{rs} to 0 in the wide model.

Model	ollwsdrt	hieffusn
	affects transition from state:	
1	none	none
2	none	3
3	none	2,3
4	none	1,2,3
5	3	1,2,3
6	2,3	1,2,3
7	1,2,3	1,2,3

Table 1: Specification of multi-state regression models being compared

The seven models correspond to the rows of the following indicator matrix that can be supplied to `fic` to compare the models. The columns indicate the parameters, in the order $(q_{12}^{(0)}, q_{23}^{(0)}, q_{34}^{(0)}, \beta_{12}^{(1)}, \beta_{23}^{(1)}, \beta_{34}^{(1)}, \beta_{12}^{(2)}, \beta_{23}^{(2)}, \beta_{34}^{(2)})$. This is the order understood by the `updatepars.msm` function below in the **msm** package, which we will need to define the focus function.

```
inds <- rbind(
    c(1,1,1,0,0,0,0,0,0),
    c(1,1,1,0,0,0,0,0,1),
    c(1,1,1,0,0,0,0,1,1),
    c(1,1,1,0,0,0,1,1,1),
    c(1,1,1,0,0,1,1,1,1),
    c(1,1,1,0,1,1,1,1,1),
    c(1,1,1,1,1,1,1,1,1)
)
```

The focus function in this example is taken as the expected total time spent in state 4 over 10 years for people currently in state 1 without `ollwsdrt` or `hieffusn`. This is defined as

$$\int_0^{10} p_{14}(t|\mathbf{x}=0)$$

where $p_{rs}(t|\mathbf{x})$ is the probability of being in state s at time t for a person in state r at time 0 with covariates $\mathbf{x}$. This is the r, s entry of the *transition probability matrix* $P(t|\mathbf{x})$, defined for a time-homogeneous continuous-time Markov model with intensity matrix $Q(\mathbf{x})$ as the matrix exponential of $tQ(\mathbf{x})$.

The **msm** package has the function `totlos.msm` to calculate the expected total time in each state, for a given model, covariate values and time interval. For the wide model, in this example, this is

```
totlos.msm(psor.wide.msm, covariates=0, tot=10)
```

```
## State 1 State 2 State 3 State 4
##   6.431   1.995   0.935   0.639
```

However, for `fic`, the focus needs to be defined as a function of the *vector of parameters* `pars` that define $Q(\mathbf{x})$, rather than a function of the *fitted model object*. To accomplish this, **msm** provides the function `updatepars.msm`. This alters a fitted model object (supplied in its first argument) by changing the point estimates to the values supplied in the second argument. This allows the focus function for `fic` to be defined as

```
focus_tlos <- function(pars){
    x.new <- updatepars.msm(psor.wide.msm, pars)
    totlos.msm(x.new, covariates=0, tot=10)["State 4"]
}
```

The same technique can be used for various other multi-state model outputs in **msm** which are complex functions of the model parameters.

Note that `updatepars.msm` is only available in **msm** version 1.6.6 or later, available from CRAN since 3 Feb 2017.

Finally, the focused model comparison is performed.

```
library(fic)
fic(wide=psor.wide.msm, inds=inds, focus=focus_tlos)
```

```
##   vals mods  rmse rmse.adj      bias     se  FIC
## 1    A    1 0.1137    0.114  5.87e-02 0.0974 1.55
## 2    A    2 0.0826    0.105  0.00e+00 0.1054 1.67
## 3    A    3 0.0903    0.109  0.00e+00 0.1086 2.27
## 4    A    4 0.1171    0.117 -3.84e-02 0.1107 4.77
## 5    A    5 0.1582    0.158 -1.07e-01 0.1169 9.85
## 6    A    6 0.1214    0.121 -2.05e-02 0.1197 5.24
## 7    A    7 0.1260    0.126  1.79e-17 0.1260 5.74
```

The estimated biases in the focus (estimated as 0.64 years under the wide model, see the output from `totlos.msm` above) range from 0 to -0.1. The standard error of the focus increases as covariates are added to the model.

Compare models 4, 5, 6 and 7, which include `hieffusn` for all transitions. The bias and MSE for model 5 are worse than that for models 6 and 7, since the association of `ollwsdrt` with transition 2 was omitted from model 5. Further omitting the effect of `ollwsdrt` for transition 1 does not increase the estimated bias, since the association is not strong for this transition.

However models 1-3, where `ollwsdrt` is removed from the model altogether, have lower MSEs than models 4-7 that include `ollwsdrt`. The biases in the focus estimate from omitting this covariate are estimated to be negligible for models 2 and 3. Model 2, which includes the potentially-large effect of `ollwsdrt` on the third transition, has the lowest MSE.

References

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