msmtools

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Contents

T	Introduction						
	1.1	Longitudinal Dataset	-				
	1.2	Enhancing the Longitudinal Structure with augment()	2				
	1.3	What if a more complex status structure is needed?	4				
2	Graphical Assessment of a Multi-state Model						
	2.1	Comparing fitted and empirical survival with survplot()	-				
	2.2	Comparing expected and observed prevalences with prevplot()	13				

1 Introduction

Package **msmtools** is an R package whose main goal is to facilitate the workflow with longitudinal datasets which need to be analyzed in the context of multi-state models. In particular, msmtools acts as the msm package companion.

1.1 Longitudinal Dataset

Everytime we observe a given subject multiple times, we come up with a longitudinal dataset. This means that measures are repeated n times in a sequence which, in general, may not be equal for all the subjects. Moreover, a longitudinal dataset could be viewed as a multilevel dataset: a first level is given by the subject, and a second level is given by the single observation carried out on that subject. A very common case of longitudinal dataset deals with hospital admissions. A patient, our subject, can have a series of entries which correspond to hospital admissions. Each hospital admission is recorded in a single row of the dataset. Let's consider a simplified version of the hosp dataset which comes with msmtools package and represents synthetic hospital admissions for 10 patients. For a detailed description of the dataset, please run ?hosp. For demonstration purposes, we extract only the first 2 patients, reducing the hosp dataset to a test sample of 17 rows per 8 variables as you can see below.

```
data( hosp )
hosp[1:17, .( subj, adm number, gender, age, label 2,
                dateIN, dateOUT, dateCENS ) ]
##
       subj adm number gender age label 2
                                                            dateOUT
                                                                      dateCENS
                                                 dateIN
##
                             F
                                 83
                                       dead 2008-11-30 2008-12-12 2011-04-28
    1:
                      1
##
    2:
          1
                      2
                             F
                                 83
                                       dead 2009-01-26 2009-02-16 2011-04-28
##
    3:
          1
                      3
                             F
                                 83
                                       dead 2009-05-13 2009-05-15 2011-04-28
##
    4:
          1
                      4
                             F
                                 83
                                       dead 2009-05-20 2009-05-25 2011-04-28
                      5
##
    5:
                             F
                                 83
                                       dead 2009-06-12 2009-06-16 2011-04-28
          1
                             F
##
    6:
          1
                      6
                                 83
                                       dead 2009-06-20 2009-06-25 2011-04-28
##
    7:
          1
                      7
                             F
                                 83
                                       dead 2009-07-17 2009-07-22 2011-04-28
                             F
                                       dead 2010-04-15 2010-04-20 2011-04-28
##
    8:
          1
                      8
                                 84
##
    9:
          1
                      9
                             F
                                 84
                                       dead 2010-10-11 2010-10-14 2011-04-28
## 10:
          1
                     10
                             F
                                 85
                                       dead 2011-01-14 2011-01-17 2011-04-28
## 11:
                             F
                                       dead 2011-04-27 2011-04-28 2011-04-28
          1
                     11
                                 85
## 12:
          2
                      1
                             F
                                 99
                                      alive 2007-09-17 2007-09-27 2012-12-31
          2
                      2
## 13:
                             F 100
                                      alive 2009-04-09 2009-04-17 2012-12-31
          2
## 14:
                      3
                             F 103
                                      alive 2012-04-16 2012-04-20 2012-12-31
## 15:
          2
                      4
                             F 103
                                      alive 2012-04-24 2012-05-19 2012-12-31
## 16:
          2
                      5
                             F 103
                                      alive 2012-05-20 2012-05-25 2012-12-31
          2
                             F 103
                                      alive 2012-08-19 2012-08-21 2012-12-31
## 17:
                      6
```

So, these two patients are 'observed' 11 and 6 times through years, respectively.

These data format are very common when dealing with observational studies, or with chronic disease monitoring and with hospital admissions recording. In general, they are a well stabilized system to collect information.

1.2 Enhancing the Longitudinal Structure with augment()

Why the standard longitudinal structure is not enough if a multi-state model has to be run? A first observation could be that we are not able to infer anything about the state in which a given subject (i.e. patient) is at a particular point in time (i.e. hospital admission). The function augment() comes into play for this reason: to take advantage of the longitudinal structure in order to extract usable information to fuel a multi-state model. augment() takes a longitudinal dataset with exact starting and ending times and reshape it to produce an augmented version. For instance, if you apply augment() to the dataset above, you get what follows:

no t death has been passed. Assuming that dateCENS contains both censoring ## and death time hosp augmented[1:35, .(subj, adm number, gender, age, label 2, augmented, status, n status)] ## subj adm number gender age label 2 augmented status n status F 83 dead 2008-11-30 ## 1: 1 IN 1 IN 2: 1 83 OUT ## 1 F dead 2008-12-12 1 OUT 2 3: 1 F 83 dead 2009-01-26 IN ## 2 IN 2 F OUT ## 4: 1 83 dead 2009-02-16 2 OUT 3 F ## 5: 1 83 dead 2009-05-13 IN 3 IN ## 6: 1 3 F 83 dead 2009-05-15 OUT 3 OUT 7: 4 F 83 ## 1 dead 2009-05-20 IN 4 IN ## 8: 4 F 83 dead 2009-05-25 OUT 4 OUT 1 9: 5 F 83 dead 2009-06-12 ## 1 IN 5 IN ## 10: 1 5 F 83 dead 2009-06-16 OUT 5 OUT F ## 11: 1 6 83 dead 2009-06-20 IN 6 IN ## 12: 1 6 F 83 dead 2009-06-25 OUT 6 OUT ## 13: 1 7 F 83 dead 2009-07-17 IN 7 IN 7 ## 14: 1 F 83 dead 2009-07-22 OUT 7 OUT ## 15: 1 8 F 84 dead 2010-04-15 IN 8 IN ## 16: 1 8 F 84 dead 2010-04-20 OUT 8 OUT ## 17: 9 F 84 dead 2010-10-11 IN 1 9 IN ## 18: 1 9 F 84 dead 2010-10-14 OUT 9 OUT ## 19: 1 10 F 85 dead 2011-01-14 IN 10 IN ## 20: 1 10 F 85 dead 2011-01-17 OUT 10 OUT ## 21: 1 11 F 85 dead 2011-04-27 IN 11 IN F ## 22: 1 11 85 dead 2011-04-28 DEAD DEAD ## 23: 2 F 1 99 alive 2007-09-17 IN 1 IN ## 24: 2 F alive 2007-09-27 1 99 OUT 1 OUT ## 25: 2 2 F 100 alive 2009-04-09 IN 2 IN ## 26: 2 2 F 100 alive 2009-04-17 OUT 2 OUT ## 27: 2 3 F 103 alive 2012-04-16 IN 3 IN ## 28: 3 2 F 103 alive 2012-04-20 OUT 3 OUT ## 29: 2 4 F 103 alive 2012-04-24 IN 4 IN 2 F 103 OUT ## 30: 4 alive 2012-05-19 4 OUT ## 31: 2 5 F 103 alive 2012-05-20 IN 5 IN ## 32: 2 5 F 103 OUT 5 OUT alive 2012-05-25 2 ## 33: 6 F 103 alive 2012-08-19 IN 6 IN ## 34: 2 6 F 103 alive 2012-08-21 OUT 6 OUT 2 6 F 103 ## 35: alive 2012-08-21 OUT 6 OUT ## subj adm number gender age label 2 augmented status n status

Despite the fact that not the same variables have been reported because of layout concerns,

two things come up at first sight. In the first place, the number of rows is more than doubled. We now have 35 observations against the initial 17. In the second place, new variables have been created. We will describe them in a minute.

Given the complexity of the data, which can be very high, building a subject specific status flag which marks a its condition at given time steps, could be tricky and computationally intensive. At the end of the study, so at the censoring time, a subject, in general, can be alive, dead inside a given transition if death occurs within t_start and t_end , or outside a given transition if death occurs otherwise. After n events, the corresponding flag sequence is given by 2n+1 for subjects alive and dead outside the transition, while it is just 2n for subjects who died inside of it. Let us consider an individual with 3 events. His/her status combinations will be as follows:

- ALIVE: IN-OUT | IN-OUT | IN-OUT | OUT
- DEAD OUT: IN-OUT | IN-OUT | IN-OUT | DEAD
- **DEAD IN**: IN-OUT | IN-OUT | IN-DEAD.

This operation produces a dataset in the augmented long format which allows to neatly model transitions between the given states.

From now on, we refer to each row as a transition for which we define a state in which the subject lies. augment() automatically creates 4 new variables (if argument more_status is missing):

- augmented: the new timing variable for the process when looking at transitions. If t_augmented is missing, then augment() creates augmented by default. The function looks directly to t start and t end to build it and thus it inherits their class;
- status: a status flag which looks at state. augment() automatically checks whether argument pattern has 2 or 3 unique values and computes the correct structure of a given subject. The variable is cast as character;
- status_num: the corresponding integer version of status;
- n_status: a mix of status and status_num cast as character. status_num comes into play when a model on the progression of the process is intended.

1.3 What if a more complex status structure is needed?

augment() by default takes a very simple status structure given by 3 different values. In general, this is enough to define a multi-state model. But what if we need a more complex structure. Let's consider again the dataset hosp for the 3rd, 4th, 5th, and 6th patient with the following variables:

```
##
           3
                             0
                                 0
                                         df 2012-09-18 2012-09-27 2012-12-31
    1:
                       2
                                 1
    2:
           3
                             0
                                         it 2012-11-28 2012-12-15 2012-12-31
##
                       3
                                 0
##
    3:
           3
                             1
                                      rehab 2012-12-18 2012-12-28 2012-12-31
    4:
           4
                       1
                             0
                                 0
                                         df 2008-08-13 2008-09-20 2012-12-31
##
##
    5:
           4
                       2
                             0
                                 0
                                         df 2012-03-18 2012-03-19 2012-12-31
##
    6:
           4
                       3
                             0
                                 1
                                         it 2012-07-02 2012-07-20 2012-12-31
    7:
           5
                       1
                             0
                                 0
                                         df 2006-02-09 2006-02-25 2008-04-16
##
                                 0
                                         df 2009-03-05 2009-03-16 2010-12-19
##
    8:
           6
                       1
                             0
    9:
           6
                       2
##
                             0
                                 0
                                         df 2009-07-06 2009-07-20 2010-12-19
           6
                       3
                                 0
                                         df 2010-11-17 2010-11-23 2010-12-19
## 10:
                             0
           6
                                         df 2010-12-05 2010-12-19 2010-12-19
## 11:
                             0
                                 0
```

As you can see, we have two variables which take into account the type of hospital admission. rehab marks a rehabilitation admission while it marks an intensive therapy one. They are both binary and integer variables, so one can compose them to get something which is informative and, at the same time, usable in the context of 'making a status'. We then created the variable rehab_it which marks all the information in one place and it is a character. You can pass rehab_it to the argument more_status to tell augment() to add these information into a new structure. Now, it is important to remember that augment() introduces some rules when you require to compute a more complex status structure. As you can see from the dataset, many values of rehab_it are set to df. This stands for 'default' and when augment() finds it, it just compute the default status you already passed to argument state (i.e. in this case, it can be 'IN', 'OUT', or 'DEAD'). The argument more_status always looks for the value df, hence whenever you need to specify a default transition make sure to label it with this value. So, if we run augment() on this sample, we obtain the following:

```
hosp augmented = augment( data = hosp, data key = subj,
                           n events = adm number, pattern = label 2,
                           t_start = dateIN, t_end = dateOUT,
                           t cens = dateCENS, more_status = rehab_it,
                           verbose = FALSE )
## Warning in augment(data = hosp, data_key = subj, n_events = adm_number, :
## no t death has been passed. Assuming that dateCENS contains both censoring
## and death time
hosp augmented [ 36:60, . ( subj, adm number, rehab it,
                           augmented, status, status_exp, n_status_exp ) ]
                                   augmented status status exp n status exp
##
       subj adm number rehab it
          3
##
    1:
                              df 2012-09-18
                                                  IN
                                                          df IN
                                                                      1 df IN
##
    2:
          3
                      1
                              df 2012-09-27
                                                OUT
                                                         df OUT
                                                                     1 df OUT
          3
                      2
##
    3:
                              it 2012-11-28
                                                 IN
                                                          it IN
                                                                      2 it IN
##
    4:
          3
                      2
                               it 2012-12-15
                                                OUT
                                                         it OUT
                                                                     2 it OUT
          3
                      3
                           rehab 2012-12-18
##
    5:
                                                 IN
                                                       rehab IN
                                                                  3 rehab IN
                                                      rehab OUT
##
    6:
          3
                      3
                           rehab 2012-12-28
                                                OUT
                                                                 3 rehab OUT
```

##	7:	3	3	rohah	2012-12-28	OUT	rehab OUT	3 rehab_OUT
		_	3				-	-
##	8:	4	1		2008-08-13	IN	df_IN	1 df_IN
##	9:	4	1	df	2008-09-20	OUT	df_OUT	1 df_OUT
##	10:	4	2	df	2012-03-18	IN	df_IN	2 df_IN
##	11:	4	2	df	2012-03-19	OUT	df_OUT	2 df_OUT
##	12:	4	3	it	2012-07-02	IN	it_IN	3 it_IN
##	13:	4	3	it	2012-07-20	OUT	it_OUT	3 it_OUT
##	14:	4	3	it	2012-07-20	OUT	it_OUT	3 it_OUT
##	15:	5	1	df	2006-02-09	IN	df_IN	1 df_IN
##	16:	5	1	df	2006-02-25	OUT	df_OUT	1 df_OUT
##	17:	5	1	df	2008-04-16	DEAD	DEAD	DEAD
##	18:	6	1	df	2009-03-05	IN	df_IN	1 df_IN
##	19:	6	1	df	2009-03-16	OUT	df_OUT	1 df_OUT
##	20:	6	2	df	2009-07-06	IN	df_IN	2 df_IN
##	21:	6	2	df	2009-07-20	OUT	df_OUT	2 df_OUT
##	22:	6	3	df	2010-11-17	IN	df_IN	3 df_IN
##	23:	6	3	df	2010-11-23	OUT	df_OUT	3 df_OUT
##	24:	6	4	df	2010-12-05	IN	df_IN	4 df_IN
##	25:	6	4	df	2010-12-19	DEAD	DEAD	DEAD
##		subj	${\tt adm_number}$	rehab_it	augmented	status	status_exp	n_status_exp

Beside the usual status variables, of which we reported only status, augment() computed two more:

- status_exp: is the direct expansion of status and the variable you passed to more_status, which in this case is rehab_it. The function composes them by pasting a '_' in between. This is the main reason why it is worth to build a character variable if you know you need to fuel it in as an indicator of a more complex status structure;
- n_status_exp: similar to what has been done before, augment() mixes information coming from the current expandend status and the number of admission to give you the time evolution of the process.

2 Graphical Assessment of a Multi-state Model

msmtools has been mainly developed to easily manage and work with longitudinal datasets which need to be restructured in order to get msm to work properly.

However, **msmtools** comes with two more functions which try to address graphically and in a very efficient way the problem of the Goodness-of-Fit (Gof) for a multi-state model. When dealing with this type of models, GoF is always a tough quest. Furthermore, up to now, no formal statistical tests are defined when a multi-state model is computed within an exact time framework.

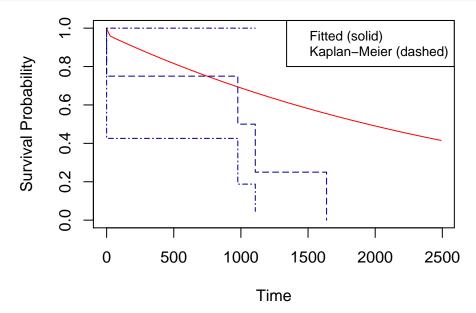
2.1 Comparing fitted and empirical survival with survplot()

One of the most common graphical method to assess whether a multi-state model is behaving the way we expect, is to compare the empirical survival with the fitted one. survplot() helps out doing this and few more things. The function is a wrapper of the already known plot.survfit.msm() from the package msm.

Suppose we ran a multi-state model on dataset hosp with the following code:

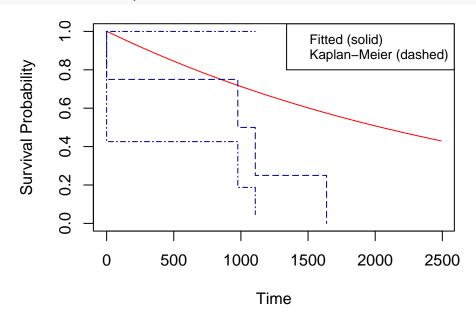
```
hosp augmented = augment( data = hosp, data key = subj,
                          n_events = adm_number, pattern = label_2,
                          t_start = dateIN, t_end = dateOUT,
                          t cens = dateCENS, verbose = FALSE )
## Warning in augment(data = hosp, data key = subj, n events = adm number, :
## no t death has been passed. Assuming that dateCENS contains both censoring
## and death time
# let's define the initial transition matrix for our model
Qmat = matrix( data = 0, nrow = 3, ncol = 3, byrow = TRUE )
Qmat[1, 1:3] = 1
Qmat[2, 1:3] = 1
colnames( Qmat ) = c( 'IN', 'OUT', 'DEAD' )
rownames( Qmat ) = c( 'IN', 'OUT', 'DEAD' )
Qmat
        IN OUT DEAD
##
             1
## IN
## OUT
            1
                  1
        1
## DEAD O
             0
                  0
# attaching the msm package and running the model using
# gender and age as covariates
library( msm )
msm_model = msm( status_num ~ augmented_int,
                 subject = subj, data = hosp_augmented,
                 covariates = ~ gender + age,
                 exacttimes = TRUE, gen.inits = TRUE,
                 qmatrix = Qmat, method = 'BFGS',
                 control = list( fnscale = 6e+05, trace = 0,
                                 REPORT = 1, maxit = 10000)
```

We now have a multi-state model for which we can carry out some graphical inspections. So, we want a simple comparison between the fitted survival curve and the empirical one, computed using the Kaplan-Meier estimator. The code is as follows:



With no surprises, the plot is not so satisfying due to the really small dataset we provided.

Now, survplot() takes several parameters, many of them come with a default value. For instance, the figureabove has been computed for a transition (IN - DEAD). We can pass to argument from any starting state we want. If to is missing, survplot() will check what is the higher value in the corresponding msm object and grabs it. Of course, you are free to compute any survival you want, given the transition is allowed in the initial transition matrix Qmat. Let's plot the survival comparison for the transition (OUT - DEAD):

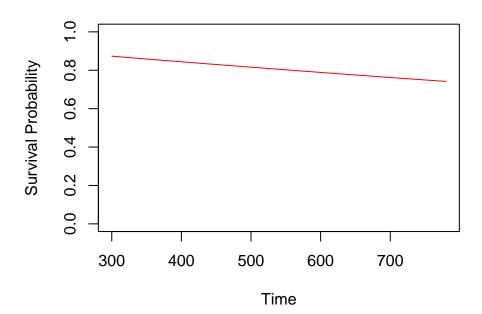


If we do not want to show the Kaplan-Meier, we can pass km = FALSE, which is the default.

2.1.1 Setting a custom time sequence

By default survplot() computes the fitted survival on a given grid. The number of grid points is given by grid. In some cases, one would like to pass a custom time sequence. This can be achieved by passing the argument times a numeric vector. Now grid is ignored.

Consider our dataset and suppose we want to compute a fitted survival only fo specific points in time. The following code addresses this request.



2.1.2 Obtaining the dataset for the Kaplan-Meier

It is possible to tell survplot() to return the associated Kaplan-Meier dataset by setting return.km = TRUE. This fastly computes the data through data.table. Passing only km = TRUE won't return any data, even if they must be computed anyway to plot results.

```
survplot( msm_model, ci = 'none', return.km = TRUE,
          verbose = FALSE, do.plot = FALSE )
##
      subject mintime mintime exact anystate
## 1:
             1
                 15092
                                  1107
                                               1
## 2:
             5
                                     0
                 13985
                                               1
## 3:
             6
                                               1
                 14962
                                   977
## 4:
             7
                 15623
                                 1638
```

A preview of the dataset is printed out only if no assignment is done. If you want to store the information in the current environmen, you must assign survplot() to an object as follows:

```
# running survplot() and assigning it to an object
km data = survplot( msm model, ci = 'none', return.km = TRUE,
                     verbose = FALSE, do.plot = FALSE )
# let's see the dataset
km data
##
      subject mintime mintime exact anystate
## 1:
                15092
                                1107
                                             1
## 2:
            5
                                             1
                13985
                                   0
## 3:
            6
                 14962
                                  977
                                             1
## 4:
                15623
                                             1
                                 1638
```

The structure of the data is consistent. survplot() always computes a dataset in wide format, as requested by survfit with 3 columns:

- *subject*: the ordered subject ID as passed to msm function;
- *mintime*: the time at which the event occurred;
- anystate: tansition indicator to compute the Kaplan-Meier.

The only modification you might encounter really depends on argument exacttimes. This is inherited from msm function whose aim was to tell the model that transitions occurred at exact and known times, including deaths. This is the main reason why this argument should always be set the same way you set it in msm. In our case, we do have a multi-state model in which transitions are well known and exact as you can see from the msm call above. survplot() puts exacttimes = TRUE by default so we don't have to worry about it. As you can see from the results, km_data has another column named mintime_exact. This is the relative time for each subject.

2.1.3 Obtaining the dataset for the fitted survival

Similarly to what done for the Kaplan-Meier, it is possible to obtain the data used to compute the fitted survival as well. This can be achieve by setting return.p = TRUE. If times is passed, then the resulting dataset will have as many rows as the elements in times. If times is missing, then survplot() uses grid to know how many time points are requested. Below there is the snippet that addresses what described.

```
## 2: 26.14 0.9596

## 3: 51.28 0.9503

## 4: 76.42 0.9422

## 5: 101.56 0.9341

## 6: 126.70 0.9262
```

As before, only the first 6 rows are printed. Saving the data in the current environment follows the same procedure as seen before:

```
# running survplot() and assigning it to an object
fitted data = survplot( msm_model, ci = 'none', return.p = TRUE,
                        verbose = FALSE, do.plot = FALSE )
# let's see the dataset
fitted data
##
       time probs
       1.00 0.9957
## 1:
## 2:
      26.14 0.9596
      51.28 0.9503
## 3:
## 4:
      76.42 0.9422
## 5: 101.56 0.9341
## 6: 126.70 0.9262
```

The structure of the data is consistent here too. survplot() always computes a dataset in wide format with 2 columns:

- *time*: time at which to compute the fitted survival. It can be obtained either by **grid** or by **times** so that the cardinality of the data depends on them;
- probs: the corresponding value of the fitted survival.

Of course, you can request survplot() to return both the datasets by passing all the parameters. Below you can see the code and the output when no assignment is done and when you save the data into a new object.

```
# just running survplot()
survplot( msm_model, ci = 'none',
                      return.km = TRUE, return.p = TRUE,
                      verbose = FALSE, do.plot = FALSE )
## $km
      subject mintime mintime exact anystate
##
## 1:
                 15092
            1
                                 1107
                                              1
## 2:
            5
                 13985
                                    0
                                              1
                                  977
## 3:
            6
                 14962
                                              1
```

```
## 4:
                15623
                                1638
            7
##
## $fitted
##
        time probs
## 1:
        1.00 0.9957
## 2:
       26.14 0.9596
## 3:
       51.28 0.9503
## 4: 76.42 0.9422
## 5: 101.56 0.9341
## 6: 126.70 0.9262
# running survplot() and assigning it to an object
all data = survplot( msm model, ci = 'none',
                     return.km = TRUE, return.p = TRUE,
                     verbose = FALSE, do.plot = FALSE )
# let's see the dataset
all data
## $km
##
      subject mintime mintime exact anystate
                15092
                                1107
## 1:
            1
                                            1
## 2:
            5
                13985
                                   0
                                            1
## 3:
            6
                14962
                                 977
                                            1
            7
## 4:
                15623
                                1638
                                            1
##
## $fitted
##
        time probs
## 1:
        1.00 0.9957
## 2:
       26.14 0.9596
## 3:
       51.28 0.9503
## 4:
       76.42 0.9422
## 5: 101.56 0.9341
## 6: 126.70 0.9262
```

all_data is a list of two elements. If you want to split up the datasets, just use common syntax:

```
# do not extract data using just one [].
# This keeps the class, so it returns a list
km_data_wrong = all_data[ 1 ]
# extracting data using the list way so be careful to use double []
km_data_1 = all_data[[ 1 ]]
# extracting data using the '$' access operator
km_data_2 = all_data$km
```

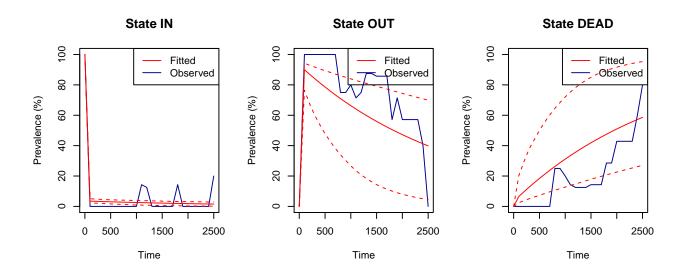
```
identical( km data wrong, km data 1 )
## [1] FALSE
identical( km_data_1, km_data_2 )
## [1] TRUE
km data 1
      subject mintime mintime exact anystate
## 1:
            1
                15092
                                1107
                                             1
## 2:
            5
                13985
                                   0
                                            1
## 3:
            6
                14962
                                 977
                                            1
## 4:
            7
                15623
                                            1
                                1638
fitted data 1 = all data[[ 2 ]]
fitted data 2 = all data$fitted
identical( fitted_data_1, fitted data 2 )
## [1] TRUE
fitted data 1
##
        time probs
## 1:
        1.00 0.9957
## 2:
       26.14 0.9596
## 3: 51.28 0.9503
## 4: 76.42 0.9422
## 5: 101.56 0.9341
## 6: 126.70 0.9262
```

2.2 Comparing expected and observed prevalences with prevplot()

A second graphical tool which helps us in the attempt to understand the goodness of the model is given by comparing the expected and observed prevalences. prevplot() is a wrapper of the plot.prevalence.msm() function inside the msm package but, again, it does more things.

Consider the multi-state model we have built above. We can compute the prevalences using prevalence.msm() function. This produces a named list which will be used inside prevplot(). For instance, running the following code produces a plot of prevalences for each state of the model.

```
# and plotting them using prevplot()
prevplot( msm_model, prev, ci = TRUE, devnew = F )
```



It is mandatory for prevplot() to work that a msm object and a list compute by prevalence.msm are passed.

It is also possibile to plot the following statistic:

$$M^2 = \frac{(O_{is} - E_{is})^2}{E_{is}}$$

which gives an idea of the deviance from the Markov model. This is computed according to Titman and Sharples (2008). The following code addresses this request.

```
prevplot( msm_model, prev, M = TRUE, ci = TRUE, devnew = F )
```

