Multi-state modelling with R: the msm package

Version 0.3.2

Christopher Jackson
Department of Epidemiology and Public Health
Imperial College, London

chris.jackson@imperial.ac.uk

Abstract

The multi-state Markov model is a useful way of describing a process in which an individual moves through a series of stages in continuous time. The msm package for R allows a general multi-state model to be fitted to longitudinal data. Data consist of observations of the process at arbitrary times, so that the exact times when the state changes are unobserved. For example, the progression of chronic diseases is often described by stages of severity, and the state of the patient may only be known at doctor or hospital visits. Features of msm include the ability to model transition rates between stages in terms of covariates. A form of hidden Markov model can also be fitted in which the states are misclassified. This manual introduces the theory behind multi-state models and gives a tutorial in the typical use of the msm package. Multi-state models with misclassification are covered in the final section.

Contents

1 Multi-state models

1.1 Introduction

Figure 1.1 illustrates a multi-state model in continuous time. Its four states are labelled **1, 2, 3, 4**. At a time t the individual is in state $S(t)$. The arrows show which transitions are possible between states. The next state to which the individual moves, and the time of the change, are governed by a set of *transition intensities* $q_{rs}(t, z(t))$ for each pair of states r and s. The intensities may also depend on the time of the process t, and a set of individual-specific or time-varying explanatory variables $z(t)$. The intensity represents the instantaneous risk of moving from state r to state s:

$$q_{rs}(t, z(t)) = \lim_{\delta t \to 0} P(S(t + \delta t) = s | S(t) = r)/\delta t \tag{1}$$

The intensities form a matrix Q whose rows sum to zero, so that the diagonal entries are defined by $q_{rr} = -\sum_{s \neq r} q_{rs}$. To fit a multi-state model to data, we estimate this transition intensity matrix. We concentrate on *Markov* models here. The Markov assumption is that future evolution only depends on the current state. That is, $q_{rs}(t, z(t), \mathcal{F}_t)$ is independent of $\mathcal{F}_t$, the observation history $\mathcal{F}_t$ of the process up to the time preceding t. See, for example, Cox and Miller[1] for a thorough introduction to the theory of continuous-time Markov chains.

1.2 Disease progression models

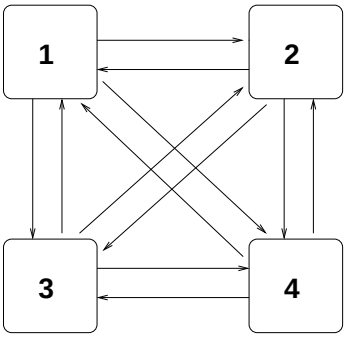
Many chronic diseases have a natural interpretation in terms of staged progression. Multi-state Markov models in continuous time are often used to model the course of diseases. A commonly-used model is illustrated in figure 2. This represents a series of successively more severe disease stages, and an 'absorbing' state, often death. The patient may advance into or recover from adjacent disease stages, or die at any disease stage. Observations of the stage $S_i(t)$ are made on a number of individuals i at arbitrary times t, which may vary between individuals. The stages of disease may be modelled as a homogeneous continuous-time Markov process, with a transition matrix Q, pictured below figure 2.

A commonly-used model is the *illness-death* model, with three states representing health, illness and death (figure 3). Transitions are permitted from health to illness, illness to death and health to death. Recovery from illness to health is sometimes also considered.

A wide range of medical situations have been modelled using multi-state methods, for example, screening for abdominal aortic aneurysms (Jackson *et al.*[2]), problems following lung transplantation (Jackson and Sharples[3]), problems following heart transplantation (Sharples[4], Klotz and Sharples[5]), hepatic cancer (Kay[6]), HIV infection and AIDS (Longini *et al.*[7], Satten and Longini[8], Guihenneuc-Jouyaux *et al.*[9], Gentleman *et al.*[10]), diabetic complications (Marshall and Jones[11], Andersen[12]), breast cancer screening (Duffy and Chen[13], Chen *et al.*[14]), cervical cancer screening (Kirby and Spiegelhalter[15]) and liver cirrhosis (Andersen *et al.*[16]). Many of these references also describe the mathematical theory, which will be reviewed in the following sections.

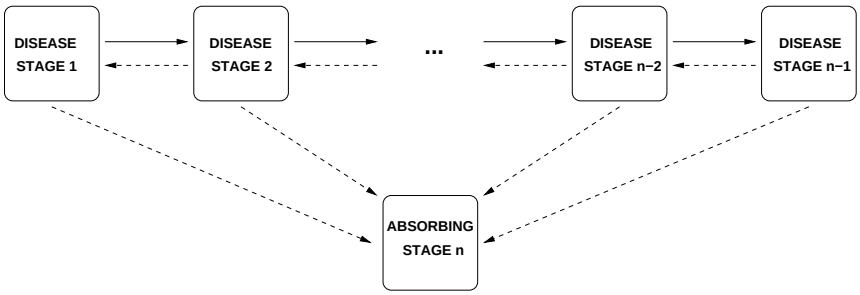
1.3 Arbitrary observation times

Longitudinal data from monitoring disease progression are often incomplete in some way. Usually patients are seen at intermittent follow-up visits, at which monitoring information is collected, but



$$Q = \begin{pmatrix} q_{11} & q_{12} & q_{13} & q_{14} \\ q_{21} & q_{22} & q_{23} & q_{24} \\ q_{31} & q_{32} & q_{33} & q_{34} \\ q_{41} & q_{42} & q_{43} & q_{44} \end{pmatrix}$$

Figure 1: General multi-state model



$$Q = \begin{pmatrix} q_{11} & q_{12} & 0 & 0 & \dots & q_{1n} \\ q_{21} & q_{22} & q_{23} & 0 & \dots & q_{2n} \\ 0 & q_{32} & q_{33} & q_{34} & \ddots & q_{3n} \\ 0 & 0 & q_{43} & q_{44} & \ddots & q_{4n} \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \dots & 0 \end{pmatrix}$$

Figure 2: General model for disease progression

information from the periods between visits is not available. Often the exact time of disease onset is unknown. Thus, the changes of state in a multi-state model usually occur at unknown times. Also a subject may only be followed up for a portion of their disease history. A fixed observation schedule may be specified in advance, but in practice times of visits may vary due to patient and hospital pressures. The states of disease progression models often include death. Death times are commonly recorded to within a day.

A typical sampling situation is illustrated in figure 4. The individual is observed at four occasions through 10 months. The final occasion is the death date which is recorded to within a day. The only other information available is the occupation of stages 2, 2, and 1 at respective times 1.5, 3.5 and 5. The times of movement between stages and the stage occupancy in between the observation times are unknown. Although the patient was in stage 3 between 7 and 9 months this was not observed at all.

Informative sampling times To fit a model to longitudinal data with arbitrary sampling times we must consider the reasons why observations were made at the given times. This is analogous to the problem of missing data, where the fact that a particular observation is missing may implicitly give information about the value of that observation. Possible observation schemes include:

- *fixed*. Each patient is observed at fixed intervals specified in advance.
- *random*. The sampling times vary randomly, independently of the current stage of the disease.
- *doctor's care*. More severely ill patients are monitored more closely. The next sampling time is chosen on the basis of the current disease state.
- patient *self-selection*. A patient may decide to visit the doctor on occasions when they are in a poor condition.

Grüger *et al.* [17] discussed conditions under which sampling times are *informative*. If a multi-state model is fitted, ignoring the information available in the sampling times, then inference may be biased. Mathematically, because the sampling times are often themselves random, they should be modelled along with the observation process X_t. However the ideal situation is where the joint likelihood for the times and the process is proportional to the likelihood obtained if the sampling times were fixed in advance. Then the parameters of the process can be estimated independently of the parameters of the sampling scheme.

In particular, they showed that fixed, random and doctor's care observation policies are not informative, whereas patient self-selection is informative.

1.4 Likelihood for the multi-state model

Kay [6] described a general method for evaluating the likelihood for a general multi-state model in continuous time, applicable to any form of transition matrix. The only available information is the observed state at a set of times, as in figure 4. The sampling times are assumed to be non-informative.

The likelihood is calculated from the transition probability matrix $P(t)$. For a time-homogeneous process, the (r, s) entry of $P(t)$ is the probability of being in state s at a time $t+u$ in the future, given the state at time u is r. It does not say anything about the time of transition from r to s, indeed the process may have entered other states between times u and $t + u$. $P(t)$ can be calculated by taking the matrix exponential of the transition intensity matrix (see, for example, Cox and Miller [1]).

$$P(t) = \exp(tQ) \tag{2}$$

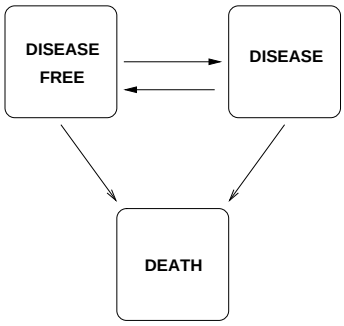


Figure 3: Illness-death model

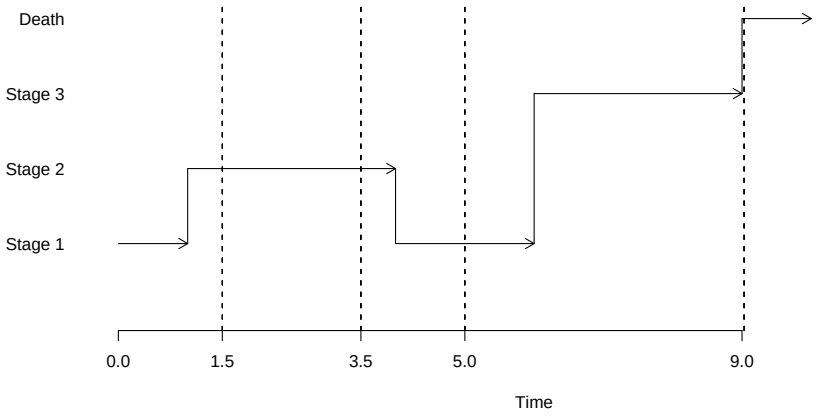


Figure 4: Evolution of a multi-state model. The process is observed on four occasions

Suppose i indexes M individuals. The data for individual i consist of a series of times $(t_{i1}, \ldots, t_{in_i})$ and corresponding states $(S(t_{i1}), \ldots, S(t_{in_i}))$. Consider a general multi state model, with a pair of successive observed disease states $S(t_j), S(t_{j+1})$ at times t_j, t_{j+1}. The contribution to the likelihood from this pair of states is

$$L_{i,j} = p_{S(t_j)S(t_{j+1})}(t_{j+1} - t_j) \tag{3}$$

This is the entry of the transition matrix $P(t)$ at the $S(t_j)$th row and $S(t_{j+1})$th column, evaluated at $t = t_{j+1} - t_j$.

The full likelihood $L(Q)$ is the product of all such terms $L_{i,j}$ over all individuals and all transitions. It depends on the unknown transition matrix Q, which was used to determine $P(t)$.

Death states In observational studies of chronic diseases, it is common that the time of death is known, but the state on the previous instant before death is unknown. If $S(t_{j+1}) = D$ is such a death state, then the contribution to the likelihood is summed over the unknown state m on the day before death:

$$L_{i,j} = \sum_{m \neq D} p_{S(t_j),m}(t_{j+1} - t_j) q_{m,D} \tag{4}$$

assuming a time unit of days. The sum is taken over all possible states m which can be visited between $S(t_j)$ and D.

Exactly observed transition times If the times $(t_{i1}, \ldots, t_{in_i})$ had been the *exact* transition times between the states, with no transitions between the observation times, then the contributions would be of the form

$$L_{i,j} = p_{S(t_j)S(t_j)}(t_{j+1} - t_j) q_{S(t_j)S(t_{j+1})} \tag{5}$$

since the state is assumed to be $S(t_j)$ throughout the interval between t_j and t_{j+1} with a known transition to state $S(t_{j+1})$ at t_{j+1}.

1.5 Covariates

The relation of constant or time-varying characteristics of individuals to their transition rates is often of interest in a multi-state model. Explanatory variables for a particular transition intensity can be investigated by modelling the intensity as a function of these variables. Marshall and Jones [11] described a form of a *proportional hazards* model, where the transition intensity matrix elements q_{rs} which are of interest can be replaced by

$$q_{rs}(z(t)) = q_{rs}^{(0)} \exp(\beta_{rs}^T z(t))$$

The new Q is then used to determine the likelihood. If the covariates $z(t)$ are time dependent, the contributions to the likelihood of the form $p_{rs}(t-u)$ are replaced by

$$p_{rs}(t - u, z(u))$$

although this requires that the value of the covariate is known at every observation time u. Sometimes covariates are observed at different times to the main response, for example recurrent disease events

or other biological markers. In some of these cases it could be assumed that the covariate is a step function which remains constant between its observation times. Marshall and Jones [11] described likelihood ratio and Wald tests for covariate selection and testing hypotheses, for example whether the effect of a covariate is the same for all forward transitions in a disease progression model.

1.6 Multi-state models with misclassification

Hidden Markov models In a *hidden Markov model* (HMM) the states of the Markov chain are not observed. The observed data are governed by some probability distribution conditionally on the unobserved state. The evolution of the underlying Markov chain is still governed by a transition intensity matrix Q (figure 5). This class of model is commonly used in areas such as speech and signal processing [18] and the analysis of biological sequence data [19]. In engineering and biological sequencing applications, the Markov process usually evolves over an equally-spaced, discrete 'time' space. Therefore most of the theory of HMM estimation was developed for discrete-time models. HMMs have less frequently been used in medicine, where continuous time processes are often more suitable. A disease process evolves in continuous time, and patients are often monitored at irregular and differing intervals.

The `msm` package can fit continuous-time multi-state models with misclassification, which are a special case of HMM. In these models the observed data are states, assumed to be misclassifications of the true, underlying states.

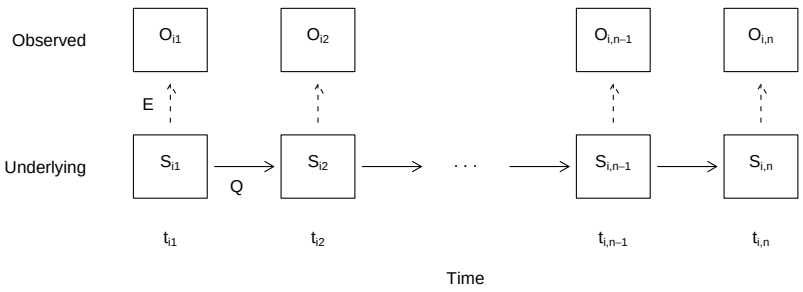


Figure 5: A hidden Markov model in continuous time. Observed states are generated conditionally on an underlying Markov process.

Screening tests with misclassification Consider a Markov model with at least a disease-free and a disease state. When screening for the presence of the disease, the screening process can sometimes be subject to error. Then the Markov disease process $S_i(t)$ for individual i is not observed directly,

but through realisations $O_i(t)$. The quality of a diagnostic test is often measured by the probabilities that the true and observed states are equal, $Pr(O_i(t) = r|S_i(t) = r)$. Where r represents a 'positive' disease stage, this is the *sensitivity*, or the probability that a true positive is detected by the test. Where r represents a 'negative' or disease-free stage, this represents the *specificity*, or the probability that, given the condition of interest is absent, the test produces a negative result.

General misclassification model As an extension to the simple multi-state model described in section 1, we describe a general multi-state model with misclassification. For patient i, observation time t_{ij}, observed states O_{ij} are generated conditionally on true states S_{ij} according to a *misclassification matrix* E. This is a $n \times n$ matrix, whose (r, s) entry is

$$e_{rs} = Pr(O(t_{ij}) = s|S(t_{ij}) = r), \tag{6}$$

which we first assume to be independent of time t. Analogously to the entries of Q, some of the e_{rs} may be fixed to reflect knowledge of the diagnosis process. For example, the probability of misclassification may be negligibly small for non-adjacent states of disease. Thus the progression through underlying states is governed by the transition intensity matrix Q, while the observation process of the underlying states is governed by the misclassification matrix E.

To investigate explanatory variables $w(t)$ for the probability of misclassification e_{rs} for each pair of stages r and s, a logistic model can be used,

$$\log \frac{e_{rs}(t)}{1 - e_{rs}(t)} = \gamma_{rs}^T w(t). \tag{7}$$

Maximum likelihood estimation A type of EM algorithm known as the *Baum-Welch* or *forward-backward* algorithm [20, 21], is commonly used for hidden Markov model estimation in discrete-time applications. See, for example, Durbin *et al.* [19], Albert [22]. A generalisation of this algorithm to continuous time was described by Bureau *et al.* [23].

The `msm` package uses a direct method of calculating likelihoods in discrete or continuous time based on matrix products. This type of method has been described by Macdonald and Zucchini [24, pp. 77–79], Lindsey [25, p.73] and Guttorp [26]. Satten and Longini [8] used this method to calculate likelihoods for a hidden Markov model in continuous time with observations of a continuous marker generated conditionally on underlying discrete states. The matrix-product method is now illustrated for the misclassification model. However it can be generalised to any form of data generated conditionally on states of a hidden Markov process.

Patient i's contribution to the likelihood is

$$\begin{aligned} L_i &= Pr(O_{i1}, \ldots, O_{im_i}) \\ &= \sum Pr(O_{i1}, \ldots, O_{im_i}|S_{i1}, \ldots, S_{im_i}) Pr(S_{i1}, \ldots, S_{im_i}) \end{aligned} \tag{8}$$

where the sum is taken over all possible paths of underlying states $S_{i1}, \ldots, S_{im_i}$. Assume that the observed states are conditionally independent given the values of the underlying states. Also assume the Markov property, $Pr(S_{ij}|S_{i,j-1}, \ldots, S_{i1}) = Pr(S_{ij}|S_{i,j-1})$. Then the contribution L_i can be written as a product of matrices, as follows. To derive this matrix product, decompose the overall sum in equation 9 into sums over each underlying stage. The sum is accumulated over the unknown

first state, the unknown second state, and so on until the unknown final state:

$$L_i = \sum_{S_{i1}} Pr(O_{i1}|S_{i1})Pr(S_{i1}) \sum_{S_{i2}} Pr(O_{i2}|S_{i2})Pr(S_{i2}|S_{i1}) \sum_{S_{i3}} Pr(O_{i3}|S_{i3})Pr(S_{i3}|S_{i2}) \\ \ldots \sum_{S_{im_i}} Pr(O_{im_i}|S_{im_i})Pr(S_{im_i}|S_{in_{i-1}}) \quad (9)$$

where $Pr(O_{ij}|S_{ij})$ is the misclassification probability $e_{S_{ij}O_{ij}}$. $Pr(S_{i,j+1}|S_{ij})$ is the $(S_{ij}, S_{i,j+1})$ entry of the Markov chain transition matrix $P(t)$ evaluated at $t = t_{i,j+1} - t_{ij}$. Let f be the vector of initial stage occupation probabilities $Pr(S_{i1})$, and let $\mathbf{1}$ be a column vector consisting of ones. For $j = 2, \ldots, m_i$ let T_{ij} be the $n \times n$ matrix with (r, s) entry

$$e_{sO_{ij}} p_{rs}(t_{ij} - t_{i,j-1})$$

Then subject i's likelihood contribution is

$$L_i = f T_{i2} T_{i3}, \ldots T_{im_i} \mathbf{1} \quad (10)$$

If $S(t_j) = D$ is an absorbing state such as death, measured without error, whose entry time is known exactly, then the contribution to the likelihood is summed over the unknown state at the previous instant before death. the day before entry. The (r, s) entry of T_{ij} is then

$$p_{rs}(t_j - t_{j-1}) q_{s,D}$$

2 Fitting multi-state models with msm

msm is a package of functions for multi-state modelling using the R statistical software. The msm function itself implements maximum-likelihood estimation for general multi-state models with optional covariates or misclassification. We illustrate its use with a set of data from monitoring heart transplant patients. Throughout this section ">" indicates the R command prompt, *slanted typewriter* text indicates R commands, and typewriter text R output.

2.1 Installing msm

The easiest way to install the msm package on a computer connected to the Internet is to run the R command:

```
> install.packages(msm)
```

This downloads msm from the CRAN archive of contributed R packages (cran.r-project.org or one of its mirrors) and installs it to the default R system library. To install to a different location, for example if you are a normal user with no administrative privileges, create a directory in which R packages are to be stored, say, /your/library/dir, and run

```
> install.packages(msm, library = "/your/library/dir")
```

After msm has been installed, its functions can be made visible in an R session by

```
> library(msm)
```

or, if it has been installed in a location outside the default library path,

```
> library(msm, lib.loc = "/your/library/dir")
```

2.2 Getting the data in

The data can be specified as a series of observations, grouped by patient. At minimum it should be a data frame with variables indicating

- the subject identification number,
- the time of the observation,
- the observed state of the process.

The subject ID does not need to be numeric, but data must be grouped by subject, and observations must be ordered by time within subjects. An example data set, taken from monitoring a set of heart transplant recipients, is provided with msm. This data set can be made available to the current R session by issuing the command

```
> data(heart)
```

The first three patient histories are shown below. There are 622 patients in all. `PTNUM` is the subject identifier. Approximately each year after transplant, each patient has an angiogram, which detects coronary allograft vasculopathy (CAV), a deterioration of the arterial walls. The result of the test is in the variable `state`, with possible values 1, 2, 3 representing CAV-free, mild CAV and moderate or severe CAV respectively. A value of 4 is recorded at the date of death. `years` gives the time of the test in years since the heart transplant. Other variables include `age` (age at screen), `dage` (donor age), `sex` (0=male, 1=female), `pdiag` (primary diagnosis, or reason for transplant - IHD represents ischaemic heart disease, IDC represents idiopathic dilated cardiomyopathy), and `cumrej` (cumulative number of rejection episodes).

```
> heart[1:21, ]
```

	PTNUM	age	years	dage	sex	pdiag	cumrej	state
1	100002	52.49589	0.000000	21	0	IHD	0	1
2	100002	53.49863	1.002740	21	0	IHD	2	1
3	100002	54.49863	2.002740	21	0	IHD	2	2
4	100002	55.58904	3.093151	21	0	IHD	2	2
5	100002	56.49589	4.000000	21	0	IHD	3	2
6	100002	57.49315	4.997260	21	0	IHD	3	3
7	100002	58.35068	5.854795	21	0	IHD	3	4
8	100003	29.50685	0.000000	17	0	IHD	0	1
9	100003	30.69589	1.189041	17	0	IHD	1	1
10	100003	31.51507	2.008219	17	0	IHD	1	3
11	100003	32.49863	2.991781	17	0	IHD	2	4
12	100004	35.89589	0.000000	16	0	IDC	0	1
13	100004	36.89863	1.002740	16	0	IDC	2	1
14	100004	37.90685	2.010959	16	0	IDC	2	1
15	100004	38.90685	3.010959	16	0	IDC	2	1
16	100004	39.90411	4.008219	16	0	IDC	2	1
17	100004	40.88767	4.991781	16	0	IDC	2	1
18	100004	41.91781	6.021918	16	0	IDC	2	2
19	100004	42.91507	7.019178	16	0	IDC	2	3
20	100004	43.91233	8.016438	16	0	IDC	2	3
21	100004	44.79726	8.901370	16	0	IDC	2	4

The data can also be specified as a list of *transitions*, rather than observations. See, for, example, the aneurysm screening data set `aneur` supplied with the `msm` package. Each row of the data file then represents a pair of observations. Columns indicate the starting state, the finishing state, and the time difference between the two observations. Additional variables may be given, representing the covariate value which is assumed to be constant within this time interval. However, this form of data can not be used for multi-state models with misclassification (section 1.6), which do not assume successive transitions within the same individual are independent. It also discards potentially useful information about individual histories. Therefore we recommend storing data as lists of observations, rather than transitions.

A useful way to summarise multi-state data is as a frequency table of pairs of consecutive states. This counts over all individuals, for each state r and s, the number of times an individual had an

observation of state r followed by an observation of state s. The function `statetable.msm` can be used to produce such a table, as follows,

```
> statetable.msm(state, PTNUM, data = heart)
```

```
    to
from 1    2    3    4
   1 1367  204   44  148
   2   46  134   54   48
   3    4   13  107   55
```

Thus there were 148 CAV-free deaths, 48 deaths from state 2, and 55 deaths from state 3. On only four occasions was there an observation of severe CAV followed by an observation of no CAV.

2.3 Specifying a model

We now specify the multi-state model to be fitted to the data. A model is governed by a transition intensity matrix Q. For the heart transplant example, there are four possible states through which the patient can move, corresponding to CAV-free, mild/moderate CAV, severe CAV and death. We assume that the patient can advance or recover from consecutive states while alive, and die from any state. Thus the model is illustrated by figure 2 with four states, and we have

$$Q = \begin{pmatrix} -(q_{12}+q_{14}) & q_{12} & 0 & q_{14} \\ q_{21} & -(q_{21}+q_{23}+q_{24}) & q_{23} & q_{24} \\ 0 & q_{32} & -(q_{32}+q_{34}) & q_{34} \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

It is important to remember that this defines which *instantaneous* transitions can occur in the Markov process, and that the data are *snapshots* of the process (see section 1.3). Although there were 44 occasions on which a patient was observed in state 1 followed by state 3, the underlying model specifies that the patient must have passed through state 2 in between. If your data represent the exact and complete transition times of the process, then you must specify `exacttimes=TRUE` in the call to `msm`.

To tell `msm` what the allowed transitions of our model are, we define a matrix of the same size as Q, containing ones in the positions where the entries of Q are non-zero. The diagonal entries of this matrix do not matter, as the diagonal entries of Q are defined as minus the sum of all the other entries in the row. This matrix will eventually be used as an argument to the `msm` function.

```
> twoway4.q <- rbind(c(0, 1, 0, 1), c(1, 0, 1, 1),
+     c(0, 1, 0, 1), c(0, 0, 0, 0))
```

Fitting the model is a process of finding values of the seven unknown transition intensities: q_{12}, q_{14}, q_{21}, q_{23}, q_{24}, q_{32}, q_{34}, which maximise the likelihood.

2.4 Specifying initial values

The likelihood is maximised by numerical methods, which need a set of initial values to start the search for the maximum. For reassurance that the true maximum likelihood estimates have been

found, models should be run repeatedly starting from different initial values. However a sensible choice of initial values can be important for unstable models with flat or multi-modal likelihoods. For example, the transition rates for a model with misclassification could be initialised at the corresponding estimates for an approximating model without misclassification. Initial values for a model without misclassification could be set by supposing that transitions between stages take place only at the observation times. If we observe n_{rs} transitions from state r to state s, and a total of n_r transitions from state r, then q_{rs}/q_{rr} can be estimated by n_{rs}/n_r. Then, given a total of T_r years spent in state r, the mean sojourn time $1/q_{rr}$ can be estimated as T_r/n_r. Thus, n_{rs}/T_r is a crude estimate of q_{rs}. The `msm` package provides a function `crudeinits.msm` for calculating initial values in this way.

```
> crudeinits.msm(state, years, PTNUM, data = heart,
+     qmatrix = twoway4.q)

       1-2        1-4        2-1        2-3        2-4
0.06798932 0.04932559 0.11681788 0.13713403 0.12189692
       3-2        3-4
0.04908401 0.20766310
```

However, if there are are many changes of state in between the observation times, then this crude approach may fail to give sensible initial values. For the heart transplant example we could also guess that the mean period in each state before moving to the next is about 2 years, and there is an equal probability of progression, recovery or death. This gives $q_{rr} = -0.5$ for $r = 1, 2, 3$, and $q_{12} = q_{14} = 0.25$, $q_{21} = q_{23} = q_{24} = 0.166$, $q_{32} = q_{34} = 0.25$.

```
> inits1 <- c(0.25, 0.25, 0.166, 0.166, 0.166, 0.25,
+     0.25)
```

2.5 Running `msm`

To fit the model, call the `msm` function with the appropriate arguments. For our running example, we have defined a data set `heart`, a matrix `twoway4.q` indicating the allowed transitions, and a vector of initial values `inits1`. We are ready to run `msm`.

Model 1: simple bidirectional model

```
> heart.msm <- msm(state ~ years, subject = PTNUM,
+     data = heart, qmatrix = twoway4.q, inits = inits1,
+     death = 4, control = list(trace = 2, REPORT = 1))
```

In this example the day of death is assumed to be recorded exactly, as is usual in studies of chronic diseases. At the previous instant before death the state of the patient is unknown. Thus we specify `death = 4`, to indicate to `msm` that state 4 is a "death" state. In terms of the multi-state model, a "death" state is assumed to have a known entry time, but the individual is in an unknown transient state at the previous instant. If the model had five states and states 4 and 5 were two competing causes of death with death times recorded exactly, then we would specify `death = c(4,5)`.

While the `msm` function runs, it searches for the maximum of the likelihood of the unknown parameters. Internally, it uses the R function `optim` to minimise the minus log-likelihood. When

the data set, the model, or both, are large, then this may take a long time. It is then useful to see the progress of the optimisation algorithm. To do this, we specify a `control` argument, which is passed internally to the `optim` function. See the help page for `optim`,

```
> help(optim)
```

for more options to control the optimisation. When completed, the `msm` function returns a value. This value is a list of the important results of the model fitting, including the parameter estimates and their covariances. To keep these results for post-processing, we store them in an R object, here called `heart.msm`. When running several similar `msm` models, it is recommended to store the respective results in informatively-named objects.

2.6 Showing results

To show the maximum likelihood estimates and their standard errors, type the name of the fitted model object at the R command prompt. [1]

```
> heart.msm

 Multi-state Markov models in continuous time

 Maximum likelihood estimates:

  * Matrix of transition intensities

           Stage 1    Stage 2    Stage 3    Stage 4
Stage 1 -0.1702183  0.1276873  0.0000000 0.04253093
Stage 2  0.2244044 -0.6061764  0.3405681 0.04120391
Stage 3  0.0000000  0.1312478 -0.4361194 0.30487158
Stage 4  0.0000000  0.0000000  0.0000000 0.00000000

    corresponding standard errors

            Stage 1     Stage 2    Stage 3     Stage 4
Stage 1 0.009591235 0.009011503 0.00000000 0.004766354
Stage 2 0.033839353 0.047507655 0.03943857 0.026048798
Stage 3 0.000000000 0.033126540 0.05232290 0.039311099
Stage 4 0.000000000 0.000000000 0.00000000 0.000000000

  * No covariates on transition intensities

  * Mean sojourn times in transient states

$estimate
```

[1] This is equivalent to typing `print.msm(heart.msm)`. The function `print.msm` formats the important information in the model object for printing on the screen.

```
 Stage 1  Stage 2  Stage 3
5.874810 1.649685 2.292950

$SE
  Stage 1   Stage 2   Stage 3
0.3310261 0.1292902 0.2750939


 -2 * log-likelihood:  3968.803
```

From the estimated intensity matrix, we see patients are three times as likely to develop symptoms than die without symptoms (first row). After disease onset (stage 2), progression to severe symptoms (stage 3) is 50% more likely than recovery, and death from the severe disease stage is rapid (mean of 2.32 years in stage 3).

Section 2.9 describes various functions that can be used to obtain summary information from the fitted model.

2.7 Covariates on the transition rates

We now model the effect of explanatory variables on the rates of transition, using a proportional intensities model. Now we have an intensity matrix $Q(z)$ which depends on a covariate vector z. For each entry of $Q(z)$, the transition intensity for patient i at observation time j is $q_{rs}(z_{ij}) = q_{rs}^{(0)} \exp(\beta_{rs}^T z_{ij})$. The covariates z are specified through the `covariates` argument to `msm`. If z_{ij} is time-dependent, we assume it is constant in between the observation times of the Markov process. By default `msm` calculates the probability for a state transition from times $t_{i,j-1}$ to t_{ij} using the covariate value at time $t_{i,j-1}$, but this can be changed to $t_{i,j}$ by specifying an argument `covmatch="next"` to `msm`.

We consider a model with just one covariate, female sex. Out of the 622 transplant recipients, 535 are male and 87 are female. We give an extra seven initial values of zero, one for the linear effect of sex on each intensity on the log scale.

Model 2: sex as a covariate

```
> inits2 <- c(0.25, 0.25, 0.166, 0.166, 0.166, 0.25,
+     0.25, 0, 0, 0, 0, 0, 0, 0)
> heartsex.msm <- msm(state ~ years, subject = PTNUM,
+     data = heart, qmatrix = twoway4.q, inits = inits2,
+     death = 4, covariates = ~sex)
```

The `msm` object will now include the estimated covariate effects and their standard errors.

```
> heartsex.msm

 Multi-state Markov models in continuous time

 Maximum likelihood estimates:
```

```
  * Matrix of transition intensities with covariates set to their means

           Stage 1    Stage 2    Stage 3    Stage 4
Stage 1 -0.1725700  0.1308243  0.0000000 0.04174566
Stage 2  0.2429489 -0.6811473  0.3794389 0.05875954
Stage 3  0.0000000  0.1748329 -0.4813113 0.30647840
Stage 4  0.0000000  0.0000000  0.0000000 0.00000000

    corresponding standard errors

            Stage 1     Stage 2    Stage 3     Stage 4
Stage 1 0.009861878 0.009330237 0.00000000 0.004796208
Stage 2 0.036009814 0.055421172 0.04446338 0.025496156
Stage 3 0.000000000 0.047381133 0.06043816 0.039572377
Stage 4 0.000000000 0.000000000 0.00000000 0.000000000

  * Linear effects on log transition intensities of sex
           Stage 1    Stage 2   Stage 3   Stage 4
Stage 1  0.00000000 -0.6276312 0.0000000 0.2141289
Stage 2 -0.01686394  0.0000000 0.4473718 0.5854001
Stage 3  0.00000000  0.7750932 0.0000000 0.6701311
Stage 4  0.00000000  0.0000000 0.0000000 0.0000000

    corresponding standard errors

          Stage 1   Stage 2   Stage 3   Stage 4
Stage 1 0.0000000 0.2596304 0.0000000 0.2940437
Stage 2 0.5264277 0.0000000 0.4808718 0.9448464
Stage 3 0.0000000 1.3722379 0.0000000 0.4245680
Stage 4 0.0000000 0.0000000 0.0000000 0.0000000

  * Mean sojourn times in transient states with covariates set to their means

$estimate
 Stage 1  Stage 2  Stage 3
5.794751 1.468111 2.077657

$SE
  Stage 1   Stage 2   Stage 3
0.3311533 0.1194521 0.2608910


 -2 * log-likelihood:  3961.345
```

Comparing the estimated log-linear effects of age and their standard errors, we see that the disease onset rate is smaller for females, whereas none of the other effects are large with respect to their standard

errors. The first matrix shown in the output of printing `heartsex.msm` is the estimated transition intensity matrix $q_{rs}(z) = q_{rs}^{(0)} \exp(\beta_{rs}^T z)$ with the covariate z set to its mean value in the data. This represents an average intensity matrix for the population of 535 male and 87 female patients. To extract separate intensity matrices for male and female patients ($z = 0$ and 1 respectively), use the function `qmatrix.msm`, as shown below. This and similar summary functions will be described in more detail in section 2.9.

```
> qmatrix.msm(heartsex.msm, covariates = list(sex = 0))

$estimates
           Stage 1    Stage 2    Stage 3    Stage 4
Stage 1 -0.1817581  0.1410729  0.0000000 0.04068518
Stage 2  0.2434417 -0.6577886  0.3595788 0.05476804
Stage 3  0.0000000  0.1592840 -0.4420497 0.28276567
Stage 4  0.0000000  0.0000000  0.0000000 0.00000000

$SE
           Stage 1    Stage 2    Stage 3    Stage 4
Stage 1 0.01090040 0.01038033 0.00000000 0.00510312
Stage 2 0.03743910 0.05314155 0.04205737 0.02631547
Stage 3 0.00000000 0.03930374 0.05532671 0.03848095
Stage 4 0.00000000 0.00000000 0.00000000 0.00000000

> qmatrix.msm(heartsex.msm, covariates = list(sex = 1))

$estimates
           Stage 1     Stage 2    Stage 3    Stage 4
Stage 1 -0.1257126  0.07531247  0.0000000 0.05040009
Stage 2  0.2393708 -0.90016988  0.5624516 0.09834748
Stage 3  0.0000000  0.34577278 -0.8984365 0.55266369
Stage 4  0.0000000  0.00000000  0.0000000 0.00000000

$SE
           Stage 1    Stage 2   Stage 3    Stage 4
Stage 1 0.02112043 0.01875171 0.0000000 0.01340388
Stage 2 0.12051421 0.31215974 0.2623446 0.08001062
Stage 3 0.00000000 0.46674836 0.4691708 0.22226296
Stage 4 0.00000000 0.00000000 0.0000000 0.00000000
```

We may also want to constrain the effect of age to be equal for certain transition rates, to reduce the number of parameters in the model, or to investigate hypotheses on the covariate effects. A `constraint` argument can be used to indicate which of the transition rates have common covariate effects.

Model 3: constrained covariate effects

```
> inits3 <- c(0.25, 0.25, 0.166, 0.166, 0.166, 0.25,
+     0.25, 0, 0, 0)
> heart3.msm <- msm(state ~ years, subject = PTNUM,
+     data = heart, qmatrix = twoway4.q, inits = inits3,
+     death = 4, covariates = ~sex, constraint = list(sex = c(1,
+         2, 3, 1, 2, 3, 2)))
```

This constrains the effect of age to be equal for the progression rates q_{12}, q_{23}, equal for the death rates q_{14}, q_{24}, q_{34}, and equal for the recovery rates q_{21}, q_{32}. The intensity parameters are assumed to be ordered by reading across the rows of the transition matrix, starting at the first row: $(q_{12}, q_{14}, q_{21}, q_{23}, q_{24}, q_{32}, q_{34})$, giving constraint indicators `(1,2,3,1,2,3,2)`. Any vector of increasing numbers can be used for the indicators. Notice we have four fewer parameters in the model, therefore we give four fewer initial values.

In a similar manner, we can constrain some of the baseline transition intensities to be equal to one another, using the `qconstraint` argument. For example, to constrain the rates q_{12} and q_{23} to be equal, and q_{24} and q_{34} to be equal, specify `qconstraint = c(1,2,3,1,4,5,4)`.

2.8 Fixing parameters at their initial values

For exploratory purposes we may want to fit a model assuming that some parameters are fixed, and estimate the remaining parameters. This may be necessary in cases where there is not enough information in the data to be able to estimate a proposed model, and we have strong prior information about a certain transition rate. To do this, use the `fixedpars` argument to `msm`. For model 1, the following statement fixes the parameters numbered 2, 5, 7, that is, q_{14}, q_{24}, q_{34}, to their initial values (0.25, 0.166 and 0.25, respectively).

Model 4: fixed parameters

```
> inits4 <- c(0.25, 0.25, 0.166, 0.166, 0.166, 0.25,
+     0.25)
> heart4.msm <- msm(state ~ years, subject = PTNUM,
+     data = heart, qmatrix = twoway4.q, inits = inits4,
+     death = 4, control = list(trace = 2, REPORT = 1),
+     fixedpars = c(2, 5, 7))
```

A `fixedpars` statement can also be useful for fixing covariate effect parameters to zero, that is to assume no effect of a covariate on a certain transition rate.

2.9 Extractor functions

We may want to extract some of the information from the `msm` model fit for post-processing, for example for plotting graphs or generating summary tables. A set of functions is provided for extracting interesting features of the fitted model.

Intensity matrices The function `qmatrix.msm` extracts a transition intensity matrix and the corresponding standard errors for a given set of covariate values, as shown in section 2.7. Standard errors are obtained by the delta method. The `msm` package provides a general-purpose function

`deltamethod` for estimating the variance of a function of a random variable X given the expectation and variance of X. See `help(deltamethod)` for further details.

Transition probability matrices The function `pmatrix.msm` extracts the estimated transition probability matrix $P(t)$ within a given time. For example, for model 1, the 10 year transition probabilities are given by:

```
> pmatrix.msm(heart.msm, t = 10)

           Stage 1    Stage 2    Stage 3   Stage 4
Stage 1 0.30959690 0.09780067 0.08775948 0.5048430
Stage 2 0.17187999 0.06588634 0.07810046 0.6841332
Stage 3 0.05943821 0.03009829 0.04705873 0.8634048
Stage 4 0.00000000 0.00000000 0.00000000 1.0000000
```

Thus, a typical person in stage 1, disease-free, has a probability of 0.5 of being dead ten years from now, a probability of 0.3 being still disease-free, and probabilities of 0.1 of being alive with mild/moderate or severe disease, respectively.

This assumes Q is constant within the desired time interval. For non-homogeneous processes, where Q varies with time-dependent covariates but can be approximated as piecewise constant, there is an equivalent function `pmatrix.piecewise.msm`. Consult its help page for further details.

Mean sojourn times The function `sojourn.msm` extracts the estimated mean sojourn times in each transient state, for a given set of covariate values.

```
> sojourn.msm(heart.msm)

$estimate
 Stage 1  Stage 2  Stage 3
5.874810 1.649685 2.292950

$SE
  Stage 1   Stage 2   Stage 3
0.3310261 0.1292902 0.2750939
```

Total length of stay Mean sojourn times describe the average period in a single stay in a state. For processes with successive periods of recovery and relapse, we may want to forecast the total time spent healthy or diseased, before death. The function `totlos.msm` estimates the forecasted total length of time spent in each transient state s between two future time points t_1 and t_2, for a given set of covariate values. This defaults to the expected amount of time spent in each state between the start of the process (time 0, the present time) and death or a specified future time. This is obtained as

$$L_s = \int_{t_1}^{t_2} P(t)_{r,s} dt$$

where r is the state at the start of the process, which defaults to 1. This is calculated using numerical integration. For model 1, each patient is forecasted to spend 9 years disease free, 2.2

years with mild or moderate disease and 1.8 years with severe disease. Notice that there are currently no estimates of error available from `totlos.msm`, however bootstrap methods may be feasible for simpler models.

```
> totlos.msm(heart.msm)

 Stage 1  Stage 2  Stage 3
8.823770 2.236885 1.746796
```

Ratio of transition intensities The function `qratio.msm` estimates a ratio of two entries of the transition intensity matrix at a given set of covariate values, together with a standard error estimated using the delta method. For example, we may want to estimate the ratio of the progression rate q_{12} into the first stage of disease to the corresponding recovery rate q_{21}. For example in model 1, recovery is 1.8 times as likely as progression.

```
> qratio.msm(heart.msm, ind1 = c(2, 1), ind2 = c(1,
+     2))

$estimate
[1] 1.757452

$se
[1] 0.2455929
```

Hazard ratios for transition The function `hazard.msm` gives the estimated hazard ratios corresponding to each covariate effect on the transition intensities. 95% confidence limits are computed by assuming normality of the log-effect. For example, for model 2 with female sex as a covariate, the following hazard ratios show more clearly that the only transition on which the effect of sex is significant at the 5% level is the 1-2 transition.

```
> hazard.msm(heartsex.msm)

$sex
                          HR       L95        U95
Stage 2 - Stage 1 0.9832775 0.3504128  2.7591300
Stage 1 - Stage 2 0.5338549 0.3209412  0.8880165
Stage 3 - Stage 2 2.1707943 0.1474238 31.9646322
Stage 2 - Stage 3 1.5641957 0.6094980  4.0143008
Stage 1 - Stage 4 1.2387824 0.6961528  2.2043748
Stage 2 - Stage 4 1.7957093 0.2818262 11.4417045
Stage 3 - Stage 4 1.9544936 0.8504353  4.4918704
```

Setting covariate values All of these extractor functions take an argument called `covariates`. If this argument is omitted, for example,

```
> qmatrix.msm(heart.msm)
```

then the intensity matrix is evaluated as $Q(\bar{x})$ with all covariates set to their mean values $\bar{x}$ in the data. Alternatively, set `covariates` to 0 to return the result $Q(0)$ with covariates set to zero. This will usually be preferable for categorical covariates, where we wish to see the result for the baseline category.

```
> qmatrix.msm(heartsex.msm, covariates = 0)
```

Alternatively, the desired covariate values can be specified explicitly as a list,

```
> qmatrix.msm(heartsex.msm, covariates = list(sex = 1))
```

If a covariate is categorical, that is, an R *factor* with k levels, then we use its internal representation as a set of $k - 1$ 0/1 indicator functions. For example, consider a covariate `cov`, with three levels, `VAL1, VAL2, VAL3`, where the baseline level is `VAL1`. To set the value of `cov` to be `VAL1`, `VAL2` or `VAL3`, respectively, use statements such as

```
> qmatrix.msm(example.msm, covariates = list(age = 60,
+     covVAL2 = 0, covVAL3 = 0))
> qmatrix.msm(example.msm, covariates = list(age = 60,
+     covVAL2 = 1, covVAL3 = 0))
> qmatrix.msm(example.msm, covariates = list(age = 60,
+     covVAL2 = 0, covVAL3 = 1))
```

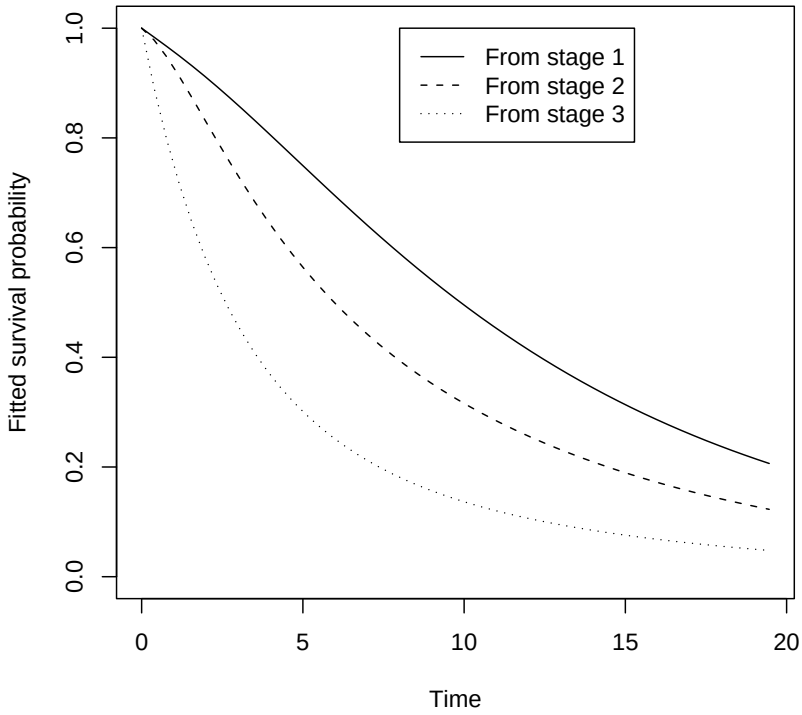
respectively. (This procedure is likely to be simplified in future versions of the package.)

2.10 Survival plots

In studies of chronic disease, an important use of multi-state models is in predicting the probability of survival for patients in increasingly severe stages of disease, for some time t in the future. This can be obtained directly from the transition probability matrix $P(t)$.

The function `plot.msm` produces a plot of the expected probability of survival against time, from each transient state. Survival is defined as not entering the final absorbing state.

```
> plot.msm(heart.msm, legend.pos = c(8, 1))
```



This shows that the 10-year survival probability with severe CAV is approximately 0.1, as opposed to 0.3 with mild CAV and 0.5 without CAV. With severe CAV the survival probability diminishes very quickly to around 0.3 in the first five years after transplant.

A more sophisticated analysis of these data might explore competing causes of death from causes related or unrelated to the disease under study.

2.11 Convergence failure

Inevitably if over-complex models are applied with insufficient data then the parameters of the model will not be identifiable. This will result in the optimisation algorithm failing to find the maximum of the log-likelihood, or even failing to evaluate the likelihood. For example, it will commonly be inadvisable to include several covariates in a model simultaneously.

Initial values Make sure that a sensible set of initial values have been chosen. The optimisation may only converge within a limited range of 'informative' initial values.

Scaling It is often necessary to apply a scaling factor to normalise the likelihood (`fnscale`), or certain individual parameters (`parscale`). This may prevent overflow or underflow problems within the optimisation. For example, if the value of the -2 $\times$ log-likelihood is around 5000,

then the following option leads to an minimisation of the -2 $\times$ log-likelihood on an approximate unit scale: `options = list(fnscale = 5000)`

Convergence criteria Sometimes the optimisation may report convergence, but fail to calculate any standard errors. In these cases, the Hessian of the log-likelihood at the converged solution is not positive definite. Thus the reported solution is probably close to the maximum, but not the maximum. This type of problem can sometimes be solved by tightening the criteria (`reltol`, defaults to `1e-08`) for reporting convergence of the optimisation. For example, `options = list(reltol = 1e-16)`.

Alternatively consider using smaller step sizes for the numerical approximation to the gradient, used in calculating the Hessian. This is given by the control parameter `ndeps`. For example, for a model with 5 parameters, `options = list(ndeps = rep(1e-6, 5))`

Model simplification If none of these numerical adjustments lead to convergence, then the model is probably over-complicated. There may not be enough information in the data on a certain transition rate. It is always recommended to count all the pairs of transitions between states in successive observation times, making a frequency table of previous state against current state (function `statetable.msm`). Although the data are a series of snapshots of a continuous-time process, and the actual transitions take place in between the observation times, this type of table may still be helpful. If there are not many observed 'transitions' from state 2 to state 4, for example, then the data may be insufficient to estimate q_{24}.

For a staged disease model (figure 2), the number of disease states should be low enough that all transition rates can be estimated. Consecutive stages of disease severity should be merged if necessary. If it is realistic, consider applying constraints on the intensities or the covariate effects so that the parameters are equal for certain transitions, or zero for certain transitions.

2.12 Model assessment

Observed and expected prevalence To compare the relative fit of two nested models, it is easy to compare their likelihoods. However it is not always easy to determine how well a fitted multi-state model describes an irregularly-observed process. Ideally we would like to compare observed data with fitted or expected data under the model. If there were times at which all individuals were observed then the fit of the expected numbers in each state or *prevalences* can be assessed directly at those times. Otherwise, some approximations are necessary. We could assume that an individual's state at an arbitrary time t was the same as the state at their previous observation time. This might be fairly accurate if observation times are close together. This approach is taken by the function `prevalence.msm`, which constructs a table of observed and expected numbers and percentages of individuals in each state at a set of times.

A set of expected counts can be produced if the process begins at a common time for all individuals. Suppose at this time, each individual is in state 0. Then given $n(t)$ individuals are under observation at time t, the expected number of individuals in state r at time t is $n(t)P(t)_{0,r}$.

For example, we calculate the observed expected numbers and percentages at two-yearly intervals up to 20 years after transplant, for the heart transplant model `heart.msm`. The number of individuals still alive and under observation decreases from 622 to 251 at year 20.

```
> options(digits = 3)
> prevalence.msm(heart.msm, times = seq(0, 20, 2))
```

```
Calculating approximate observed state prevalences...
Forecasting expected state prevalences...
$Observed
   Stage 1 Stage 2 Stage 3 Stage 4 Total
0      622       0       0       0   622
2      507      20       7      54   588
4      330      37      24      90   481
6      195      43      28     129   395
8      117      44      21     161   343
10      60      25      22     189   296
12      26      11      12     221   270
14      11       3       6     238   258
16       4       0       3     245   252
18       0       0       2     249   251
20       0       0       0     251   251

$Expected
   Stage 1 Stage 2 Stage 3 Stage 4 Total
0    622.0    0.00    0.00     0.0   622
2    437.0   74.51   23.70    52.8   588
4    279.8   68.66   38.66    93.9   481
6    184.2   52.07   37.95   120.8   395
8    129.9   39.41   32.84   140.9   343
10    91.6   28.95   25.98   149.4   296
12    68.7   22.21   20.80   158.3   270
14    54.0   17.73   17.02   169.2   258
16    43.5   14.41   14.05   180.0   252
18    35.8   11.92   11.72   191.6   251
20    29.6    9.88    9.77   201.8   251

$"Observed percentages"
   Stage 1 Stage 2 Stage 3 Stage 4
0   100.00    0.00   0.000    0.00
2    86.22    3.40   1.190    9.18
4    68.61    7.69   4.990   18.71
6    49.37   10.89   7.089   32.66
8    34.11   12.83   6.122   46.94
10   20.27    8.45   7.432   63.85
12    9.63    4.07   4.444   81.85
14    4.26    1.16   2.326   92.25
16    1.59    0.00   1.190   97.22
18    0.00    0.00   0.797   99.20
20    0.00    0.00   0.000  100.00

$"Expected percentages"
   Stage 1 Stage 2 Stage 3 Stage 4
```

```
0    100.0    0.00    0.00    0.00
2     74.3   12.67    4.03    8.97
4     58.2   14.27    8.04   19.51
6     46.6   13.18    9.61   30.57
8     37.9   11.49    9.57   41.07
10    31.0    9.78    8.78   50.48
12    25.4    8.23    7.70   58.64
14    20.9    6.87    6.60   65.59
16    17.3    5.72    5.57   71.43
18    14.3    4.75    4.67   76.32
20    11.8    3.94    3.89   80.38
```

Comparing the observed and expected percentages in stages 1, 2 and 3, we see that the predicted number of individuals who die is under-estimated by the model from year 8 onwards. Similarly the number of individuals sill alive and free of CAV (Stage 1) is over-estimated by the model for year 10 onwards.

Such discrepancies could have many causes. One possibility is that the transition rates vary with the time since the beginning of the process, the age of the patient, or some other omitted covariate, so that the Markov model is *non-homogeneous*. This could be accounted for by modelling the intensity as a function of age, for example, such as a piecewise-constant function. In this example, it is likely that the hazard of death increases with age, so the model underestimates the number of deaths when forecasting far into the future.

Another cause of poor model fit may sometimes be the failure of the Markov assumption. That is, the transition intensities may depend on the time spent in the current state (a semi-Markov process) or other characteristics of the process history. Accounting for the process history is difficult as the process is only observed through a series of snapshots. For a multi-state model with one-way progression through states, and frequent observations, we may be able to estimate the time spent in each state by each individual.

2.13 Fitting misclassification models with `msm`

In fact, in the heart transplant example from section 2.2, it is not medically realistic for patients to recover from a diseased state to a healthy state. Progression of coronary artery vasculopathy is thought to be an irreversible process. The angiography scan for CAV is actually subject to error, which leads to some false measurements of CAV states and apparent recoveries. Thus we account for misclassification by fitting a *hidden Markov model* using `msm`. Firstly we replace the two-way multi-state model by a one-way model with transition intensity matrix

$$Q = \begin{pmatrix} -(q_{12}+q_{14}) & q_{12} & 0 & q_{14} \\ 0 & -(q_{23}+q_{24}) & q_{23} & q_{24} \\ 0 & 0 & -q_{34} & q_{34} \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

We also assume that true state 1 (CAV-free) can be classified as state 1 or 2, state 2 (mild/moderate CAV) can be classified as state 1, 2 or 3, while state 3 (severe CAV) can be classified as state 2 or 3.

Recall that state 4 represents death. Thus our matrix of misclassification probabilities is

$$E = \begin{pmatrix} 1-e_{12} & e_{12} & 0 & 0 \\ e_{21} & 1-e_{21}-e_{23} & e_{23} & 0 \\ 0 & e_{32} & 1-e_{32} & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

with underlying states as rows, and observed states as columns.

To model observed states with misclassification, we define an indicator matrix `ematrix` for the states that can be misclassified. We then call `msm` as before, but set `misc=TRUE` and specify the `ematrix`. We also need initial values for five unknown transition intensities (given in the order $q_{12}, q_{14}, q_{23}, q_{24}, q_{34}$) and four unknown misclassification probabilities (given in the order $e_{12}, e_{21}, e_{23}, e_{32}$). The indicator matrix `qmatrix` for the permitted transition intensities also changes to correspond to the new Q representing the progression-only model for the underlying states.

We use an alternative quasi-Newton optimisation algorithm (`method="BFGS"`) which can often be faster than the default Nelder-Mead simplex-based algorithm. An optional argument `initprobs` could also have been given here, representing a vector f of the probabilities of occupying each true state at the initial observation. If not given, all individuals are assumed to be in true state 1 at their initial observation.

Model 5: multi-state model with misclassification

```
> oneway4.q <- rbind(c(0, 1, 0, 1), c(0, 0, 1, 1),
+     c(0, 0, 0, 1), c(0, 0, 0, 0))
> ematrix <- rbind(c(0, 1, 0, 0), c(1, 0, 1, 0),
+     c(0, 1, 0, 0), c(0, 0, 0, 0))
> miscinits <- c(0.148, 0.0171, 0.202, 0.081, 0.126,
+     0.1, 0.1, 0.1, 0.1)
> heartmisc.msm <- msm(state ~ years, misc = TRUE,
+     subject = PTNUM, data = heart, inits = miscinits,
+     qmatrix = oneway4.q, ematrix = ematrix, death = 4,
+     method = "BFGS")
> heartmisc.msm

 Multi-state Markov models in continuous time

 Maximum likelihood estimates:

  * Matrix of transition intensities

        Stage 1 Stage 2 Stage 3 Stage 4
Stage 1  -0.142   0.101   0.000  0.0407
Stage 2   0.000  -0.261   0.227  0.0339
Stage 3   0.000   0.000  -0.308  0.3085
Stage 4   0.000   0.000   0.000  0.0000

    corresponding standard errors
```

```
        Stage 1 Stage 2 Stage 3 Stage 4
Stage 1  0.0086 0.00812  0.0000 0.00464
Stage 2  0.0000 0.02567  0.0340 0.02378
Stage 3  0.0000 0.00000  0.0371 0.03714
Stage 4  0.0000 0.00000  0.0000 0.00000

  * No covariates on transition intensities

  * Matrix of misclassification probabilities

        Stage 1 Stage 2 Stage 3 Stage 4
Stage 1   0.992 0.00766   0.000       0
Stage 2   0.245 0.70393   0.051       0
Stage 3   0.000 0.12438   0.876       0
Stage 4   0.000 0.00000   0.000       1

    corresponding standard errors

        Stage 1 Stage 2 Stage 3 Stage 4
Stage 1 0.00334 0.00334  0.0000       0
Stage 2 0.03835 0.03619  0.0140       0
Stage 3 0.00000 0.04200  0.0420       0
Stage 4 0.00000 0.00000  0.0000       0

  * No covariates on misclassification probabilities

  * Mean sojourn times in transient states

$estimate
Stage 1 Stage 2 Stage 3
   7.04    3.84    3.24

$SE
Stage 1 Stage 2 Stage 3
  0.426   0.378   0.390


 -2 * log-likelihood:  3952
```

Thus there is an estimated probability of 0.01 that mild/moderate CAV will be diagnosed erroneously, but a rather higher probability of 0.24 that underlying mild/moderate CAV will be diagnosed as CAV-free. Between the two CAV stages, the mild stage will be misdiagnosed as severe with a probability of 0.05, and the severe state will be misdiagnosed as mild with a probability of 0.12.

The model also estimates the progression rates through underlying stages. An average of 7 years is spent disease-free, an average of 3.8 years is spent with mild/moderate disease, and periods of

severe disease last 3.2 years on average before death.

2.14 Effects of covariates on misclassification rates

We can investigate how the probabilities of misclassification depend on covariates in a similar way to the transition intensities, using a `misccovariates` argument to `msm`. For example, we now include female sex as a covariate for the misclassification probabilities. This requires an extra four initial values for the linear effect for each of the logit-probabilities, which we set to zero.

Model 6: misclassification model with misclassification probabilities modelled on sex

```
> miscinits <- c(0.148, 0.0171, 0.202, 0.081, 0.126,
+     0.1, 0.1, 0.1, 0.1, 0, 0, 0, 0)

> heartmiscsex.msm <- msm(state ~ years, misc = TRUE,
+     subject = PTNUM, data = heart, inits = miscinits,
+     qmatrix = oneway4.q, ematrix = ematrix, death = 4,
+     misccovariates = ~sex, control = list(trace = 1,
+         REPORT = 1), method = "BFGS")

> heartmiscsex.msm

 Multi-state Markov models in continuous time

 Maximum likelihood estimates:

  * Matrix of transition intensities

        Stage 1 Stage 2 Stage 3 Stage 4
Stage 1  -0.144   0.104   0.000  0.0394
Stage 2   0.000  -0.281   0.229  0.0525
Stage 3   0.000   0.000  -0.303  0.3030
Stage 4   0.000   0.000   0.000  0.0000

    corresponding standard errors

        Stage 1 Stage 2 Stage 3 Stage 4
Stage 1   0.009 0.00862  0.0000 0.00458
Stage 2   0.000 0.02744  0.0303 0.01943
Stage 3   0.000 0.00000  0.0349 0.03486
Stage 4   0.000 0.00000  0.0000 0.00000

  * No covariates on transition intensities

  * Matrix of misclassification probabilities with covariates set to their me

        Stage 1 Stage 2 Stage 3 Stage 4
```

```
Stage 1   0.991  0.0092  0.0000       0
Stage 2   0.256  0.6945  0.0493       0
Stage 3   0.000  0.1443  0.8557       0
Stage 4   0.000  0.0000  0.0000       1

    corresponding standard errors

        Stage 1 Stage 2 Stage 3 Stage 4
Stage 1 0.00346 0.00346  0.0000       0
Stage 2 0.04661 0.04418  0.0140       0
Stage 3 0.00000 0.04589  0.0459       0
Stage 4 0.00000 0.00000  0.0000       0

  * Linear effects on logit misclassification probabilities of sex
        Stage 1 Stage 2 Stage 3 Stage 4
Stage 1    0.00  -0.796   0.000       0
Stage 2    1.19   0.000  -0.855       0
Stage 3    0.00   1.562   0.000       0
Stage 4    0.00   0.000   0.000       0

    corresponding standard errors

        Stage 1 Stage 2 Stage 3 Stage 4
Stage 1    0.00    1.14    0.00       0
Stage 2    1.02    0.00    1.19       0
Stage 3    0.00    1.35    0.00       0
Stage 4    0.00    0.00    0.00       0

  * Mean sojourn times in transient states

$estimate
Stage 1 Stage 2 Stage 3
   6.97    3.56    3.30

$SE
Stage 1 Stage 2 Stage 3
  0.437   0.347   0.380


 -2 * log-likelihood:  3948
```

Considering the large standard errors relative to their estimates, we do not see any significant effect of sex on the fitted misclassification probabilities, so that men a no more or less likely than women to have an inaccurate angiography scan.

2.15 Extractor functions

As well as the functions described in section 2.9 for extracting useful information from fitted models, there are a number of extractor functions specific to models with misclassification.

Misclassification matrix The function `ematrix.msm` gives the estimated misclassification probability matrix at the given covariate values. For illustration, the fitted misclassification probabilities for men and women in model 6 are given by

```
> ematrix.msm(heartmiscsex.msm, covariates = list(sex = 0))

$estimates
        Stage 1 Stage 2 Stage 3 Stage 4
Stage 1    0.99  0.0101  0.0000       0
Stage 2    0.23  0.7158  0.0543       0
Stage 3    0.00  0.1226  0.8774       0
Stage 4    0.00  0.0000  0.0000       1

$SE
        Stage 1 Stage 2 Stage 3 Stage 4
Stage 1 0.00405 0.00405  0.0000       0
Stage 2 0.03927 0.03704  0.0154       0
Stage 3 0.00000 0.03928  0.0393       0
Stage 4 0.00000 0.00000  0.0000       0

> ematrix.msm(heartmiscsex.msm, covariates = list(sex = 1))

$estimates
        Stage 1 Stage 2 Stage 3 Stage 4
Stage 1   0.995 0.00458  0.0000       0
Stage 2   0.495 0.48074  0.0238       0
Stage 3   0.000 0.39989  0.6001       0
Stage 4   0.000 0.00000  0.0000       1

$SE
        Stage 1 Stage 2 Stage 3 Stage 4
Stage 1 0.00489 0.00489  0.0000       0
Stage 2 0.25639 0.25361  0.0268       0
Stage 3 0.00000 0.32073  0.3207       0
Stage 4 0.00000 0.00000  0.0000       0
```

although these are not useful in this situation as there was no significant gender difference in angiography accuracy. The standard errors for the estimates for women are higher, since there are only 87 women in this set of 622 patients.

Odds ratios for misclassification The function `odds.msm` gives the estimated odds ratios corresponding to each covariate effect on the misclassification probabilities.

```
> odds.msm(heartmiscsex.msm)

$sex
                          OR    L95   U95
Obs Stage 1 | Stage 2 3.288 0.4459 24.25
Obs Stage 2 | Stage 1 0.451 0.0480  4.24
Obs Stage 2 | Stage 3 4.769 0.3357 67.75
Obs Stage 3 | Stage 2 0.425 0.0414  4.37
```

underlining the lack of any significant

Observed and expected prevalences The function `prevalence.msm` is intended to assess the goodness of fit of the hidden Markov model for the *observed* states to the data. Tables of observed prevalences of observed states are calculated as described in section 2.12, by assuming that observed states are retained between observation times.

The expected numbers of individuals in each observed state are calculated similarly. Suppose the process begins at a common time for all individuals, and at this time, the probability of occupying *true* state r is f_r. Then given $n(t)$ individuals under observation at time t, the expected number of individuals in true state r at time t is the rth element of the vector $n(t)fP(t)$. Thus the expected number of individuals in *observed* state r is the rth element of the vector $n(t)fP(t)E$, where E is the misclassification probability matrix.

The expecter prevalences (not shown) for this example are similar to those forecasted by the model without misclassification, with underestimates of the rates of death from 8 years onwards. To improve this model's long-term prediction ability, it is probably necessary to account for the natural increase in the hazard of death from any cause as people become older.

2.16 Recreating the path through underlying states

In speech recognition and signal processing, *decoding* is the procedure of determining the underlying states that are most likely to have given rise to the observations. The most common method of reconstructing the most likely state path is the *Viterbi* algorithm. Originally proposed by Viterbi [27], it is also described by Durbin *et al.* [19] and Macdonald and Zucchini [24] for discrete-time hidden Markov chains. For continuous-time models it proceeds as follows. Suppose that a hidden Markov model has been fitted and a Markov transition matrix $P(t)$ and misclassification matrix E are known. Let $v_i(k)$ be the probability of the most probable path ending in state k at time t_i.

1. Estimate $v_k(t_1)$ using known or estimated initial-state occupation probabilities.
2. For $i = 1 \ldots N$, calculate $v_l(t_i) = e_{l,O_{t_i}} \max_k v_k(t_{i-1}) P_{kl}(t_i - t_{i-1})$. Let $K_i(l)$ be the maximising value of k.
3. At the final time point N, the most likely underlying state S_N^* is the value of k which maximises $v_k(T_N)$.
4. Retrace back through the time points, setting $S_{i-1}^* = K_i(S_i^*)$.

The computations should be done in log space to prevent underflow. The `msm` package provides the function `viterbi.msm` to implement this method. For example, the following is an extract from a result of calling `viterbi.msm` to determine the most likely underlying states for all patients. The results for patient 100103 are shown, who appeared to 'recover' to a less severe stage of disease while in stage 3. We assume this is not biologically possible for the true states, so we expect that either the observation of state 3 at time 4.98 was an erroneous observation of state 2, or their apparent state 2 at time 5.94 was actually state 3. According to the expected path constructed using the Viterbi algorithm, it is the observation at time 5.94 which is most probably misclassified.

```
> vit <- viterbi.msm(heartmisc.msm)
> vit[vit$subject == 100103, ]
```

```
    subject time observed fitted
567  100103 0.00        1      1
568  100103 2.04        1      1
569  100103 4.08        2      2
570  100103 4.98        3      3
571  100103 5.94        2      3
572  100103 7.01        3      3
573  100103 8.05        3      3
574  100103 8.44        4      4
```

3 msm reference guide

The R help page for msm gives details of all the allowed arguments and options to the msm function. To view this online in R, type:

```
> help(msm)
```

Similarly all the other functions in the package have help pages, which should always be consulted in case of doubt about how to call them. The web-browser based help interface may often be convenient - type

```
> help.start()
```

and navigate to Packages ... msm, which brings up a list of all the functions in the package with links to their documentation, and a link to this manual in PDF format.

References

[1] D. R. Cox and H. D. Miller. *The Theory of Stochastic Processes*. Chapman and Hall, London, 1965.

[2] C. H. Jackson, L. D. Sharples, S. G. Thompson, S. W. Duffy, and E. Couto. Multistate Markov models for disease progression with classification error. *Journal of the Royal Statistical Society, Series D - The Statistician*, 52(2):193–209, July 2003.

[3] C. H. Jackson and L. D. Sharples. Hidden Markov models for the onset and progression of bronchiolitis obliterans syndrome in lung transplant recipients. *Statistics in Medicine*, 21:113–128, 2002.

[4] L. D. Sharples. Use of the Gibbs sampler to estimate transition rates between grades of coronary disease following cardiac transplantation. *Statistics in Medicine*, 12:1155–1169, 1993.

[5] J. H. Klotz and L. D. Sharples. Estimation for a Markov heart transplant model. *The Statistician*, 43(3):431–436, 1994.

[6] R. Kay. A Markov model for analysing cancer markers and disease states in survival studies. *Biometrics*, 42:855–865, 1986.

[7] I. M. Longini, W. S. Clark, R. H. Byers, J. W. Ward, W. W. Darrow, G. F. Lemp, and H. W. Hethcote. Statistical analysis of the stages of HIV infection using a Markov model. *Statistics in Medicine*, 8:851–843, 1989.

[8] G. A. Satten and I. M. Longini. Markov chains with measurement error: Estimating the 'true' course of a marker of the progression of human immunodeficiency virus disease. *Applied Statistics - Journal of the Royal Statistical Society Series C*, 45(3):275–295, 1996.

[9] C. Guihenneuc-Jouyaux, S. Richardson, and I. M. Longini. Modelling markers of disease progression by a hidden Markov process: Application to characterising CD4 cell decline. *Biometrics*, 56:733–741, 2000.

[10] R. C. Gentleman, J. F. Lawless, J. C. Lindsey, and P. Yan. Multi-state Markov models for analysing incomplete disease history data with illustrations for HIV disease. *Statistics in Medicine*, 13(3):805–821, 1994.

[11] G. Marshall and R. H. Jones. Multi-state Markov models and diabetic retinopathy. *Statistics in Medicine*, 14, 1995.

[12] P. K. Andersen. Multistate models in survival analysis: a study of nephropathy and mortality in diabetes. *Statistics in Medicine*, 7(6):661–670, 1988.

[13] S. W. Duffy and H. H. Chen. Estimation of mean sojourn time in breast cancer screening using a Markov chain model of entry to and exit from preclinical detectable phase. *Statistics in Medicine*, 14:1531–1543, 1995.

[14] H. H. Chen, S. W. Duffy, and L. Tabar. A Markov chain method to estimate the tumour progression rate from preclinical to clinical phase, sensitivity and positive predictive value for mammography in breast cancer screening. *The Statistician*, 45(3):307–317, 1996.

[15] A. J. Kirby and D. J. Spiegelhalter. Statistical modelling for the precursors of cervical cancer. In *Case Studies in Biometry*. Wiley, New York, 1994.

[16] P. K. Andersen, L. S. Hansen, and N. Keiding. Assessing the influence of reversible disease indicators on survival. *Statistics in Medicine*, 10:1061–1067, 1991.

[17] J. Grüger, R. Kay, and M. Schumacher. The validity of inferences based on incomplete observations in disease state models. *Biometrics*, 47:595–605, 1991.

[18] B. H. Juang and L. R. Rabiner. Hidden Markov models for speech recognition. *Technometrics*, 33:251–272, 1991.

[19] R. Durbin, S. Eddy, A. Krogh, and G. Mitchison. *Biological Sequence Analysis: Probabilistic Models of Proteins and Nucleic Acids*. Cambridge University Press, 1998.

[20] L. E. Baum and T. Petrie. Statistical inference for probabilistic functions of finite state Markov chains. *Annals of Mathematical Statistics*, 37:1554–1563, 1966.

[21] L. E. Baum, T. Petrie, G. Soules, and N. Weiss. A maximisation technique occurring in the statistical analysis of probabilistic functions of Markov chains. *Annals of Mathematical Statistics*, 41:164–171, 1970.

[22] P. S. Albert. A mover-stayer model for longitudinal marker data. *Biometrics*, 55(4):1252–1257, 1999.

[23] A. Bureau, J. P. Hughes, and S. C. Shiboski. An S-Plus implementation of hidden Markov models in continuous time. *Journal of Computational and Graphical Statistics*, 9:621–632, 2000.

[24] I. L. Macdonald and W. Zucchini. *Hidden Markov and Other Models for Discrete-Valued Time Series*. Chapman and Hall, London, 1997.

[25] J. K. Lindsey. *Models for Repeated Measurements*. Oxford Statistical Science Series. Oxford University Press, second edition, 1999.

[26] P. Guttorp. *Stochastic Modeling of Scientific Data*. Chapman and Hall, London, 1995.

[27] J. Viterbi. Error bounds for convolutional codes and an asymptotically optimal decoding algorithm. *IEEE Transactions on Information Theory*, 13:260–269, 1967.