Cohort discrete Markov model

Monday 22 March, 1-2pm UK Time.

Lecture 10 PDF version

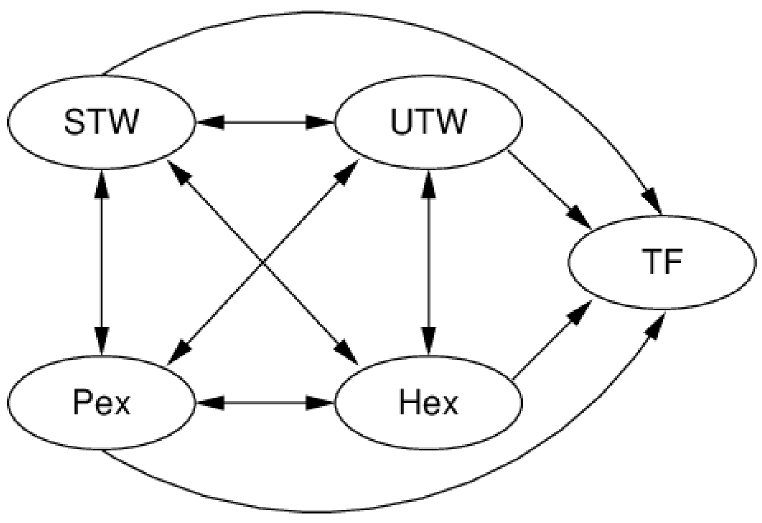
Instructions

The following exercise helps you run the Markov model and the underlying Bayesian model to estimate the transition probabilities in Rand BUGS. You should also look specifically at BMHE and actually run through the calculations to make sure you understand how the process works. In particular, look at the part relative to discounting and how you do that, which is very prevelent in real applied work.

1. Open the file `MarkovModel1.txt` and inspect the BUGS model code. Make sure you understand the assumptions encoded in the model.
2. Follow the script `MarkovModel1.R`, which will guide you through the necessary steps to create the data, run the MCMC model and then perform the relevant economic analysis from R.

Solutions

The R script guides you through the process of running the Markov model analysis for the asthma problem seen in the lecture.



The graphical representation of the Markov model for the 'asthma' problem discussed in section 5.4 of BMHE

The script first sets up the number of states $S = 5$ and the number of time points $J = 12$ weeks in the virtual follow up. Also, we load the data, given in the form of matrices with the observed transitions across the states, during the actual follow up in the trial. The code is relatively straightforward — we use the R command `matrix` to define the data. Notice that the numbers included in the matrix are read by row (as the command `byrow=TRUE` suggests).

```
S = 5
r.0 = (matrix(c(
66,32,0,0,2,
42,752,0,5,20,
0,4,0,1,0,
0,0,0,0,0,
0,0,0,0,156),c(S,S),byrow=TRUE))

r.0
```

```
     [,1] [,2] [,3] [,4] [,5]
[1,]   66   32    0    0    2
[2,]   42  752    0    5   20
[3,]    0    4    0    1    0
[4,]    0    0    0    0    0
[5,]    0    0    0    0  156
```

You can check that these tie up with the matrix presented in the lecture slides — notice that `r.0` indicates the data for the control arm.

Perhaps more interestingly, the script also defines the prior distribution for the parameters $\boldsymbol\lambda$ in terms of a Dirichlet distribution.

Click to view more details on the Dirichlet distribution

In this case, the “scale” parameter of the Dirichlet distribution is assumed to be $\alpha_0 = \alpha_1 = 10$. This assumption implies:

- We effectively assume the same prior distribution in both arms of the trial. α_0 governs the behaviour of the control arm, while α_1 is the parameter defining how the probabilities $\lambda_1, \ldots, \lambda_S$ act in the treatment arm.
- We define `alpha.0 = alpha.1 = rep(scale, S)`; this implies that

```
scale=10
alpha.0 = alpha.1 = rep(scale,S)
alpha.1
```

```
[1] 10 10 10 10 10
```

i.e. that *in the prior*, each of the $S = 5$ categories (STW, UTW, Pex, Hex, TF) is assumed to have the same probability `scale`/ $\sum_{s=1}^S$ `scale`. Intuitively, we specify our prior by imagining a “thought experiment” in which the sample size is $\sum_{s=1}^S$ `scale`=50, in this case. This sample size is assumed in our prior to be distributed equally across the $S = 5$ states, so that we think that there are `scale`=10 individuals in each of the states. This is a relatively strong prior. For example, a Dirichlet(0.1,0,1,0.1,0.1,0.1) would indicate the same thought experiment with a sample size of just $5 \times 0.1 = 0.5$ individuals, of which 0.1 is allocated to each of the states.

Of course, there’s nothing special about this construction — in fact simply convenience. We may have thought about this problem much more carefully and determined that in fact we would expect, in the prior, more individuals to be in the STW state, say twice as many as in UTW, three times as many as in Pex, four times as many as in Hex and 10 times as many as in TF. This could translate, for example, into a Dirichlet(10,5,3.3,2.5,1) prior. If we felt very confident about this, we may even express our prior into a Dirichlet(1000,500,330,250,100) prior — i.e. with the same proportionality but much larger numbers, to imply bigger precision.

The script also proceeds to define the initial values. This is also interesting. We use the mathematical results whereby we can simulate from a Dirichlet distribution by first constructing independent Gamma variables and then rescaling the simulated values by their sum. In R, we create the `inits` function, in which we first simulate a matrix of Gamma(scale, 1) values using the command `rgamma(4*S,scale,1)`; then we place the resulting vector of $4 \times S$ values into a matrix of dimension $4 \times S$, e.g. the object `temp.0`. Notice that because TF is assumed to be an *absorbing* state, by definition $\boldsymbol\lambda_S = (0, 0, 0, 0, 1)$. Thus, we do not need to initialise this row of the matrix of parameters $\boldsymbol\lambda$ and therefore, we only need a matrix of size $4 \times S$. Next, we create the variable `sum.temp.0` in which we record the row totals of `temp.0` and then construct the matrix `mat.0` by rescaling `temp.0` by these totals. Finally, we use the command `list` to store the named variables we want to output in the function `inits`, i.e. `lambda.0` and `lambda.1`.

```
inits <- function(){
    temp.0 <- matrix(rgamma(4*S,scale,1),4,S)
    sum.temp.0 <- apply(temp.0,1,sum)
    mat.0 <- temp.0/sum.temp.0
    temp.1 <- matrix(rgamma(4*S,scale,1),4,S)
    sum.temp.1 <- apply(temp.1,1,sum)
    mat.1 <- temp.1/sum.temp.1
    list(lambda.0=rbind(mat.0,rep(NA,S)),lambda.1=rbind(mat.1,rep(NA,S)))
}

inits()
```

```
$lambda.0
          [,1]      [,2]      [,3]       [,4]      [,5]
[1,] 0.1367148 0.2708367 0.1352461 0.21845825 0.2387441
[2,] 0.2394441 0.1511931 0.2422506 0.07746196 0.2896502
[3,] 0.2639766 0.1886723 0.2333637 0.12466572 0.1893216
[4,] 0.2030572 0.2130542 0.2078937 0.21050545 0.1654894
[5,]        NA        NA        NA         NA        NA

$lambda.1
          [,1]      [,2]      [,3]      [,4]      [,5]
[1,] 0.2816162 0.2599484 0.1552761 0.1044593 0.1987000
[2,] 0.1655711 0.1753585 0.1682811 0.2903701 0.2004192
[3,] 0.1537964 0.2466832 0.1723070 0.2117649 0.2154484
[4,] 0.2488889 0.2192683 0.2167701 0.1542114 0.1608613
[5,]        NA        NA        NA        NA        NA
```

Once the BUGS model has run, we have estimates for the transition probabilities $\boldsymbol\lambda$. Given these simulations, we can construct the Markov model "virtual" follow up, using the following code.

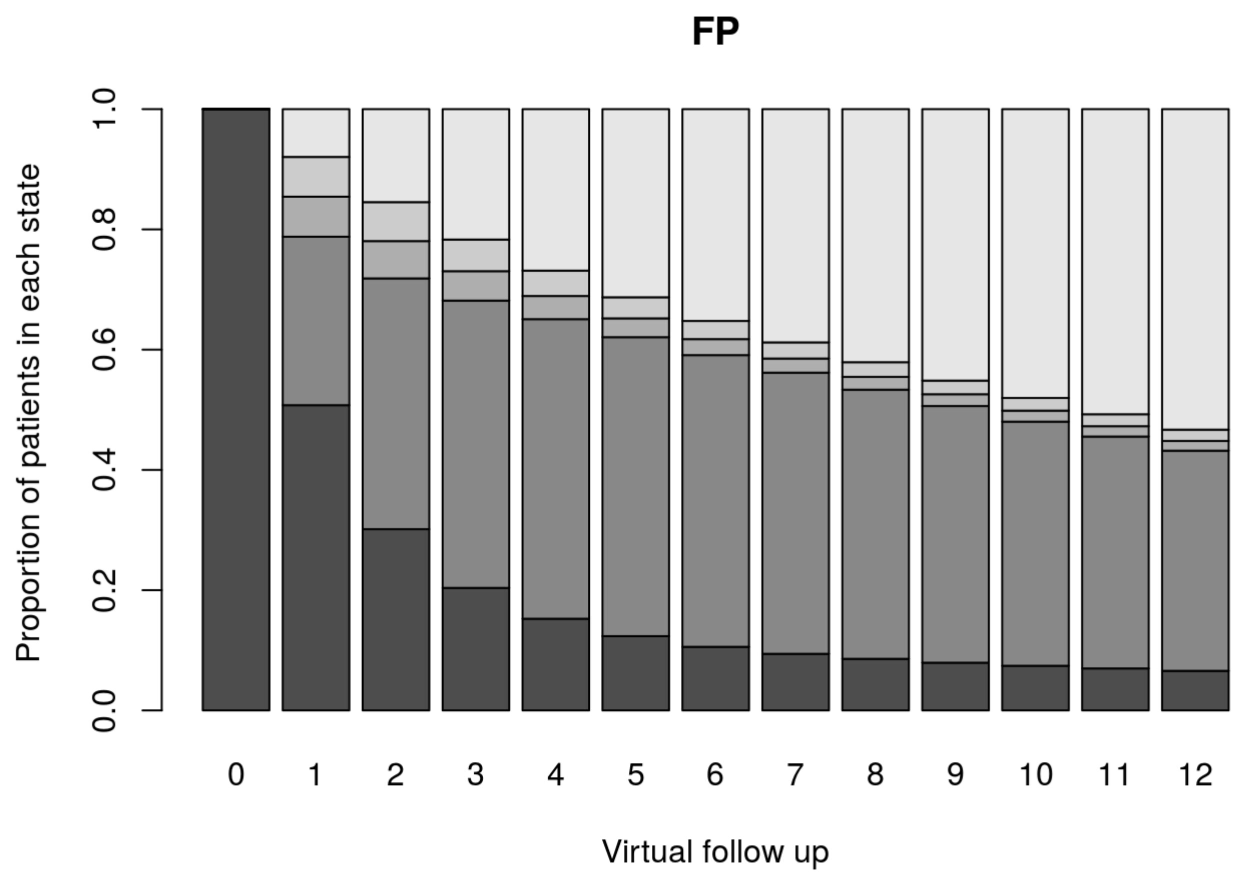
```r
# Now run the Markov model from R
start <- c(1,0,0,0,0)   # NB analysis for 1 single patient!
                        # (can create a "virtual" population of N individuals
                        #  and allocate them across the states at time j=0)
# Markov transitions
m.0 <- m.1 <- array(NA,c(n.sims,S,(J+1)))
for (s in 1:S){
    m.0[,s,1] <- start[s]
    m.1[,s,1] <- start[s]
}

lam0=lam1=array(NA,c(n.sims,S,S))
for (i in 1:n.sims) {
  lam0[i,,]=rbind(lambda.0[i,,],c(0,0,0,0,1))
  lam1[i,,]=rbind(lambda.1[i,,],c(0,0,0,0,1))
    for (j in 2:(J+1)){
        for (s in 1:S){
           # Use the new matrices lam0 and lam1 to do the matrix multiplication
            m.0[i,s,j] <- sum(m.0[i,,j-1]*lam0[i,,s])
            m.1[i,s,j] <- sum(m.1[i,,j-1]*lam1[i,,s])
        }
    }
}
```

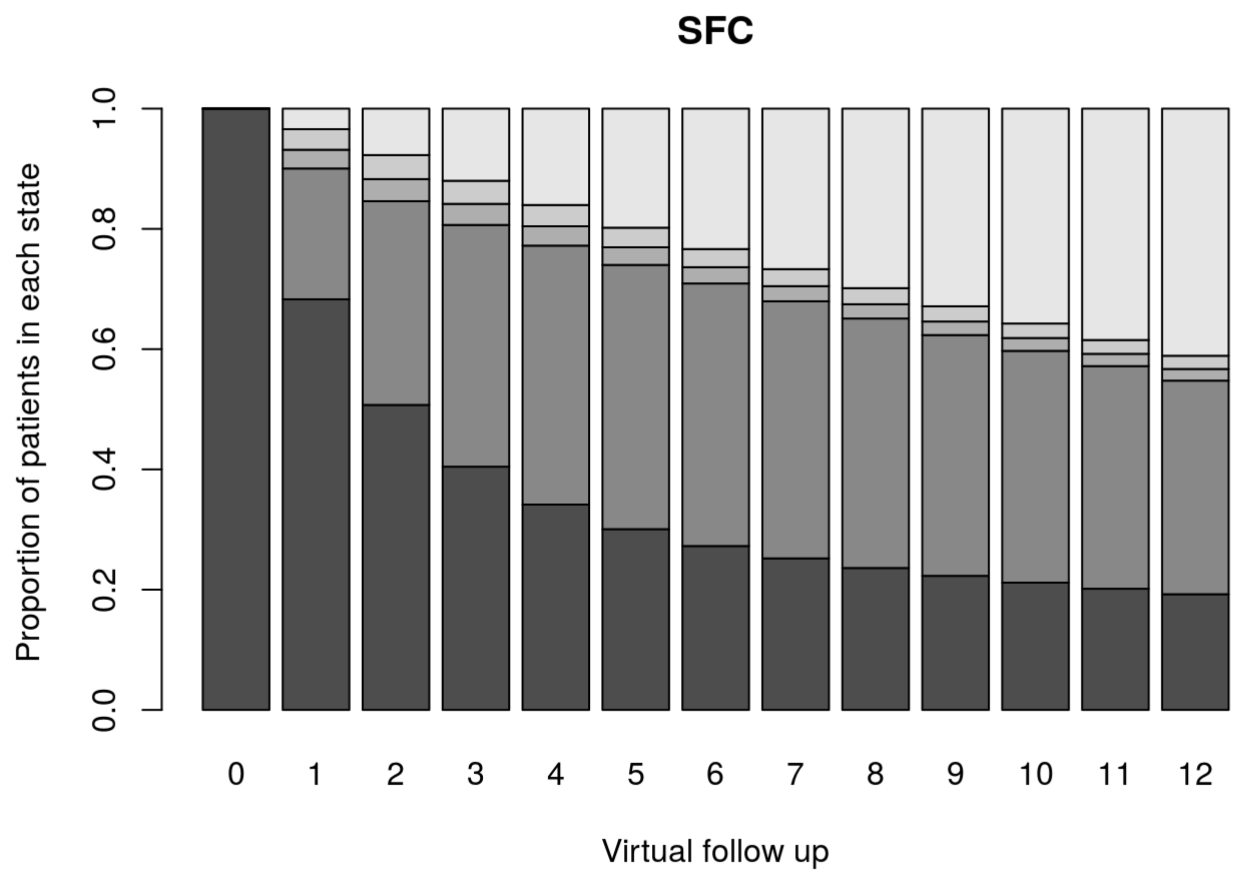
For simplicity, we run the MM for a single patient and we initialise the "cohort" so that the patient is in state $s=1$ (STW) at the beginning of the follow up ($j=0$). There's no special reason for this; we could have a larger size of the cohort (e.g. the sum of the vector `start`); or we may have a different initial distribution across the states.

Then we construct the arrays `m.0` and `m.1` in which we will store the total transitions in each state and for each time. We use the recursive relationship $\boldsymbol{m}_{j+1}=\boldsymbol{m}_j\boldsymbol{\Lambda}_j$, where $\boldsymbol\Lambda_j$ is the $S\times S$ matrix storing the transition probabilities for all the states, at time j. Notice that because the objects `lambda.0` and `lambda.1` are obtained as output from `bugs`, they are arrays where the first dimension is the number of simulations produced.

Notice that BUGS stores the simulations for the "random" part of the matrix $\boldsymbol\Lambda_j$. In fact, because the last row (containing the transition probabilities off the absorbing state TF) is deterministically defined, BUGS doesn't consider it a parameter. Thus, before we can apply the matrix multiplication, we need to construct a matrix, which we call `lam0` and `lam1` respectively for the control and active treatment arm, in the code above, in which we stack up the $i-$ MCMC simulated values for the first $(S-1)$ rows of the transition probability matrix (estimating the transitions off the states STW, UTW, Pex and Hex) and a row vector of values (00001), which indicates that for the state TF, the only possible movement is to remain in it.

The rest of the script post-process the output of the Bayesian model to create a “Markov trace”, i.e. a barplot displaying the number/proportion of patients transitioning in each state at each time point. This is a useful graph, as it allows us to try and make sense of the underlying population dynamics that is implied by the Markov model we have constructed. In real-life applications, we would want to produce this graph and validate it with the help of the wider research team (including clinicians and experts of the subject matter).





In the above barplots, the darker bar indicates the proportion of individuals in STW and increasingly lighter colours indicate, respectively, the proportion of people in UTW, Pex, Hex and TF. As is possible to see, the active treatment (SFC) seems to be associated with a population dynamics in which more people tend to remain in the most favourable outcome (STW).

Finally, we define and apply discounting to the resulting costs and effects and then use BCEA to produce the economic analysis. The code is fairly straighforward. Firstly, we define the discount rate, set at 3.5% for both benefits and costs. Notice that this is the “standard” *annual* discount rate suggested by NICE. In this particular example, the virtual follow up is set at $J = 12$ weeks, so technically we don’t really need to discount the output (as 12 weeks is barely 4 months, let alone more than one year!). Then we fill in the elements of the vectors `disc.b` and `disc.c` with the discounted series of values.

```r
## General formulation to apply discount
delta.b <- 0.035    # discount rate for benefits (3.5%)
delta.c <- 0.035    # discount rate for costs (3.5%)
# Defines the discount factors
disc.b <- numeric(); disc.c <- numeric()
disc.b[1] <- 1; disc.c[1] <- 1
for (j in 2:J) {
    disc.b[j] <- (1+delta.b)^(j-1)
    disc.c[j] <- (1+delta.c)^(j-1)
}

disc.b
```

```
 [1] 1.000000 1.035000 1.071225 1.108718 1.147523 1.187686 1.229255 1.272279
 [9] 1.316809 1.362897 1.410599 1.459970
```

Essentially, the discounted multiplier for time $j = 0$ is simply 1 (no discounting); at time $j = 1$ it is 1.035; and at the end of follow up is 1.45997.

Then, we actually apply these discounting multipliers to the estimated effects and costs.

```r
disc.cost0 <- disc.eff0 <- disc.cost1 <- disc.eff1 <- matrix(NA,mm1$n.sims,J)
for (j in 1:J) {
    disc.cost0[,j] <- cost0[,j]/disc.c[j]
    disc.cost1[,j] <- cost1[,j]/disc.c[j]
    disc.eff0[,j] <- m.0[,1,j]/disc.b[j]
    disc.eff1[,j] <- m.1[,1,j]/disc.b[j]
}

# Shows difference between raw and discounted costs (for 1st simulation)
cost0[1,]
```

```
 [1] 123.40552 128.13698 108.92009  90.09485  76.39604  67.38421  61.71168
 [8]  58.21596  56.08440  54.79163  54.00969  53.53732
```

```r
disc.cost0[1,]
```

```
 [1] 123.40552 123.80385 101.67807  81.26040  66.57474  56.73569  50.20249
 [8]  45.75722  42.59114  40.20231  38.28848  36.67016
```

As is possible to see, the raw costs are actually higher than the discounted counterparts (apart from the first element, for which the discounting multiplier is 1 and so, effectively, no discounting occurs).

At this point, we define the economic outcome as the sum of the discounted series of values for benefits and costs, over the $J = 12$ time points, using the following code.

```r
# Sums the values across all time points and creates matrix of costs
c <- matrix(NA,n.sims,2)
c[,1] <- apply(cost0,1,sum)
c[,2] <- apply(cost1,1,sum)

# Effectiveness
e <- matrix(NA,n.sims,2)
e[,1] <- apply(m.0[,1,],1,sum)
e[,2] <- apply(m.1[,1,],1,sum)
```

And to complete the analysis, we run BCEA

```
# Cost-effectiveness analysis
library(BCEA)
ints <- c("FP","SFC")
m <- bcea(e,c,ref=2,interventions=ints,Kmax=300)
```

which can be used to summarise the economic model.

```
summary(m)
```

```
NB: k (wtp) is defined in the interval [0 - 300]

Cost-effectiveness analysis summary

Reference intervention:  SFC
Comparator intervention: FP

Optimal decision: choose SFC for k <  and  for k >=


Analysis for willingness to pay parameter k = 300

    Expected utility
FP           -250.17
SFC           523.57

             EIB   CEAC   ICER
SFC vs FP 773.74 0.9995 -94.31

Optimal intervention (max expected utility) for k = 300: SFC

EVPI 386.89
```

PREVIOUS

Practical 7. Markov models --- SOLUTIONS