Elementary Markov Model (Chancellor 1997)

Monotherapy versus combination therapy for HIV

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Introduction

This vignette is an example of an elementary cohort Markov model using the `rdecision` package. It is based on the example given by Briggs *et al*[1] (Exercise 2.5) which itself is based on a Markov model described by Chancellor *et al*.[2] The model compares a combination therapy of Lamivudine/Zidovudine versus Zidovudine monotherapy in people with HIV infection.

Creating the model

The variables used in the model are all numerical constants, and are defined as follows. The original model was based on annual transition probabilities; these are converted to instantaneous hazard rates in units of events/year.

```
# transition rates calculated from annual transition probabilities
trAB <- -log(1-0.202)/1
trAC <- -log(1-0.067)/1
trAD <- -log(1-0.010)/1
trBC <- -log(1-0.407)/1
trBD <- -log(1-0.012)/1
trCD <- -log(1-0.250)/1
# Costs
dmca <- 1701 # direct medical costs associated with state A
dmcb <- 1774 # direct medical costs associated with state B
dmcc <- 6948 # direct medical costs associated with state C
ccca <- 1055 # Community care costs associated with state A
cccb <- 1278 # Community care costs associated with state B
cccc <- 2059 # Community care costs associated with state C
# Drug costs
cAZT <- 2278 # zidovudine drug cost
cLam <- 2086 # lamivudine drug cost
# Other parameters
RR <- 0.509 # treatment effect
cDR <- 6 # annual discount rate, costs (%)
oDR <- 6 # annual discount rate, benefits (%)
```

The monotherapy model is constructed by forming a graph, with each state as a node and each transition as an edge. Nodes (of class `MarkovState`) and edges (class `MarkovTransition`) have various properties whose values reflect the variables of the model (costs, rates etc.). The rate for one of the outgoing transitions from each non-absorbing state is set to NULL to allow the sum of probabilities leaving each state, per cycle, to be adjusted to 1. The usual case, as here, is to set the self-loop rates to NULL (i.e. the probability of remaining in a state is given by one minus the probability of leaving the state).

```
# create Markov states for monotherapy (zidovudine only)
s.mono.A <- MarkovState$new("A", cost=dmca+ccca+cAZT)
s.mono.B <- MarkovState$new("B", cost=dmcb+cccb+cAZT)
s.mono.C <- MarkovState$new("C", cost=dmcc+cccc+cAZT)
s.mono.D <- MarkovState$new("D", cost=0)
# create transitions
tAA <- MarkovTransition$new(s.mono.A, s.mono.A, r=NULL)
tAB <- MarkovTransition$new(s.mono.A, s.mono.B, r=trAB)
tAC <- MarkovTransition$new(s.mono.A, s.mono.C, r=trAC)
tAD <- MarkovTransition$new(s.mono.A, s.mono.D, r=trAD)
tBB <- MarkovTransition$new(s.mono.B, s.mono.B, r=NULL)
tBC <- MarkovTransition$new(s.mono.B, s.mono.C, r=trBC)
tBD <- MarkovTransition$new(s.mono.B, s.mono.D, r=trBD)
tCC <- MarkovTransition$new(s.mono.C, s.mono.C, r=NULL)
tCD <- MarkovTransition$new(s.mono.C, s.mono.D, r=trCD)
tDD <- MarkovTransition$new(s.mono.D, s.mono.D, r=NULL)
# construct the model
m.mono <- CohortMarkovModel$new(
  V = list(s.mono.A, s.mono.B, s.mono.C, s.mono.D),
  E = list(tAA, tAB, tAC, tAD, tBB, tBC, tBD, tCC, tCD, tDD),
  discount.cost = cDR/100,
  discount.utility = oDR/100
)
```

Checking the model

Diagram

A representation of the model in DOT format (Graphviz) can be created using the `as_DOT` function of `CohortMarkovModel`. The function returns a character vector which can be saved in a file (`.gv` extension) for visualization with the `dot` tool of Graphviz, or plotted directly in R via the `DiagrammeR` package. The Markov model for monotherapy is as follows:

Summary of model states

```
#model.states <- m.mono$stateSummary()
```

Summary of annual transition probabilities

```
#transition.matrix <- m.mono$transitionSummary()
```

Running the model

Single cycle

Model function `cycle` applies one cycle of a Markov model to a defined starting population in each state. It returns a table with one row per state, and each row containing several columns, including the population at the end of the state, and the cost of occupancy of states, normalized by the number of patients in the cohort, with discounting applied. For example, the first cycle of the model is as follows:

```
# create starting populations
#populations <- c('A'=1000, 'B'=0, 'C'=0, 'D'=0)
```

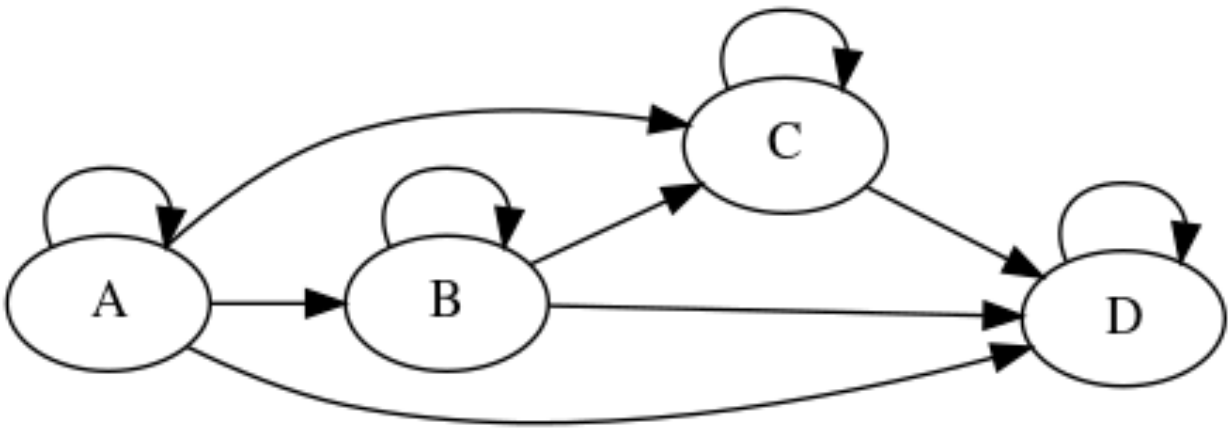

Figure 1: Markov model for monotherapy

```
#m.mono$setPopulations(populations)
# run the model
#DF <- m.mono$cycle()
```

which returns the following result:

Multiple cycles

Multiple cycles are run by feeding the state populations at the end of one cycle into the next. Function `cycles` returns a data frame with one row per cycle, and each row containing the state populations and the aggregated cost of occupancy for all states, with discounting applied. If costs per state, per cycle, are needed, use the lower level function `cycle` to extract state values. Below, this is done for the first 20 cycles of the model. In addition, the proportion of patients alive at each cycle is added to the table.

```
# create starting populations
#N <- 1000
#populations <- c('A'=N, 'B'=0, 'C'=0, 'D'=0)
#m.mono$setPopulations(populations)
# run 20 cycles
#DF.mono <- m.mono$cycles(nCycles=20+1)
# calculate the proportion alive at each cycle
#DF.mono$Alive <- (DF.mono$A + DF.mono$B + DF.mono$C)/N
```

This yields the following summary table for monotherapy:

Model results

Expected survival

The estimated life years is given by summing the proportions of patients left alive at each cycle.[1, Exercise 2.5] This is proved as follows. If patients are assumed to die at the start of the cycle, then the expected life years is equal to the probability of death in one cycle multiplied by the survival time. If p_i is the proportion of patients alive at the start of cycle i, then the expected life years is given by

$$\begin{aligned} E[LY] &= (p_0 - p_1) \times 0 + (p_2 - p_1) \times 1 + \quad \ldots \quad + (p_{n-1} - p_n) \times (n-1) \\ &= \sum_1^N (p_{i-1} - p_i) \times (i-1) \\ &= \sum_1^N (ip_{i-1} - ip_i - p_{i-1} + p_i) \\ &= \sum_1^N (i-1)p_{i-1} - \sum_1^N ip_i + \sum_1^N p_i \\ &= -Np_n + \sum_1^N p_i \end{aligned}$$

If $p_N = 0$ (*i.e.* all patients have died by cycle N), then $E[LY] = \sum_1^N p_i$.

Combination therapy

For combination therapy, the model is constructed as follows:

```
# create Markov states for combination therapy (zidovudine and lamivudine)
#state.comb.A <- MarkovState$new("A", dmca+ccca+cAZT+cLam)
```

```
#state.comb.B <- MarkovState$new("B", dmcb+cccb+cAZT+cLam)
#state.comb.C <- MarkovState$new("C", dmcc+cccc+cAZT+cLam)
#state.comb.D <- MarkovState$new("D", 0)
## transition matrix for combination therapy
#I.comb <- matrix(
#  data = c(0.858, 0.103, 0.034, 0.005,
#           0.000, 0.787, 0.207, 0.006,
#           0.000, 0.000, 0.873, 0.127,
#           0.000, 0.000, 0.000, 1.000),
#  nrow = 4,
#  ncol = 4,
#  byrow = T,
#  dimnames = list(c('A', 'B', 'C', 'D'), c('A', 'B', 'C', 'D'))
#)
## construct the model
#m.comb <- MarkovModel$new(
#  states = list(state.comb.A, state.comb.B, state.comb.C, state.comb.D),
#  Ip = I.comb,
#  discount = 6.0
#)
```

In this model, lamivudine is given for the first 2 years, with the treatment effect assumed to persist for the same period. The state populations and cycle numbers are retained by the model between calls to `cycle` or `cycles` making it easy to change probabilities or costs during a simulation. Helper functions `setAnnualCost`, `setEntryCost` (for a `MarkovState` object) and `setTransitions` (for a `MarkovModel` object) are provided for that purpose.

```
# run combination therapy model for 2 years
#N <- 1000
#populations <- c('A'=N, 'B'=0, 'C'=0, 'D'=0)
#m.comb$setPopulations(populations)
#DF.comb <- m.comb$cycles(nCycles=2+1)
## revise costs and transitions, and run model for next 18 years
#state.comb.A$setAnnualCost(1701+1055+2278)
#state.comb.B$setAnnualCost(1774+1278+2278)
#state.comb.C$setAnnualCost(6948+2059+2278)
#m.comb$setTransitions(I.mono)
#DF.comb <- rbind(DF.comb, m.comb$cycles(nCycles=18))
## calculate the proportion alive at end of each cycle
#DF.comb$Alive <- (DF.comb$A + DF.comb$B + DF.comb$C)/N
```

The cycle history for combination therapy is as follows:

Comparison of treatments

The ICER is calculated by running both models and calculating the incremental cost per life year gained.

References

1 Briggs A, Claxton K, Sculpher M. *Decision modelling for health economic evaluation.* Oxford, UK: Oxford University Press; 2006.

2 Chancellor JV, Hill AM, Sabin CA, Simpson KN, Youle M. Modelling the cost effectiveness of Lamivudine/Zidovudine combination therapy in HIV infection. *Pharmacoeconomics* 1997;**12**:54–66.