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 <- 0 # 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 within the package. The usual case, as here, is to set the self-loop rates to NULL and the package will compute the probability of remaining in a state as one minus the probability of leaving the state. Because the model is intended to evaluate survival, the utility of states A, B and C are set to 1 (by default) and state D to zero. Thus the incremental quality adjusted life years gained per cycle is equivalent to the survival function.

```
# 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, utility=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),
  hcc = FALSE,
  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 shown in Figure 1.

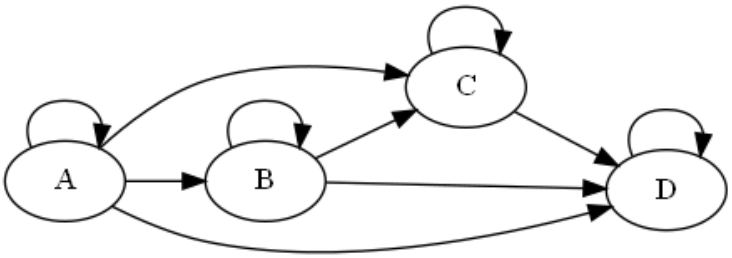

Figure 1: Markov model for monotherapy. A: 200 < cd4 < 500, B: cd4 < 200, C: AIDS, D: Death.

Model states

The states in the model can be tabulated with the function `tabulate_states`. For the monotherapy model, the states are tabulated below. The cost of each state includes the annual cost of AZT (Zidovudine).

Name	Cost
A	5034
B	5330
C	11285
D	0

Per-cycle transition probabilities

The per-cycle transition probabilities, which are the cells of the Markov transition matrix, can be extracted from the model via the function `transition_probability`. For the monotherapy model, the transition matrix is shown below. This is consistent with the Table 1 of Chancellor *et al.*[2]

	A	B	C	D
A	0.721	0.202	0.067	0.01
B	0	0.581	0.407	0.012
C	0	0	0.75	0.25
D	0	0	0	1

Running the model

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.

Multiple cycles are run by feeding the state populations at the end of one cycle into the next. Function `cycles` does this and 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. This is done below for the first 20 cycles of the model, without half cycle correction, with discount. In addition, the proportion of patients alive at each cycle (the Markov trace) is added to the table. The populations and discounted costs are consistent with Briggs *et al*, Table 2.3,[1] and the QALY column is consistent with Table 2.4 (without half cycle correction). No discount was applied to the utilities.

```
# create starting populations
N <- 1000
populations <- c(A = N, B = 0, C = 0, D = 0)
m.mono$set_populations(populations)
# run 20 cycles
DF.mono <- m.mono$cycles(ncycles=20)
```

Years	A	B	C	D	Cost	QALY
0	1000	0	0	0	0	0
1	721	202	67	10	5153	0.99
2	520	263	181	36	5392	0.964
3	375	258	277	90	5367	0.91

Years	A	B	C	D	Cost	QALY
4	270	226	338	166	5052	0.834
5	195	186	363	256	4537	0.744
6	140	147	361	351	3925	0.649
7	101	114	340	445	3296	0.555
8	73	87	308	532	2703	0.468
9	53	65	271	611	2175	0.389
10	38	48	234	680	1723	0.32
11	27	36	197	739	1347	0.261
12	20	26	164	789	1042	0.211
13	14	19	135	831	798	0.169
14	10	14	110	865	607	0.135
15	7	10	89	893	458	0.107
16	5	7	72	916	344	0.084
17	4	5	57	934	257	0.066
18	3	4	45	948	191	0.052
19	2	3	36	959	142	0.041
20	1	2	28	968	104	0.032

Model results

Monotherapy

The estimated life years is approximated by summing the proportions of patients left alive at each cycle (Briggs *et al*[1], Exercise 2.5). This is an approximation because it ignores the population who remain alive after 21 years, and assumes all deaths occurred at the start of each cycle. For monotherapy the expected life gained is 7.979 years at a cost of 4.461385×10^4 GBP.

Combination therapy

For combination therapy, a similar model is constructed. The annual cost of

```
# create Markov states for combination therapy (zidovudine and lamivudine)
s.comb.A <- MarkovState$new("A", dmca+ccca+cAZT+cLam)
s.comb.B <- MarkovState$new("B", dmcb+cccb+cAZT+cLam)
s.comb.C <- MarkovState$new("C", dmcc+cccc+cAZT+cLam)
s.comb.D <- MarkovState$new("D", 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.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.