Combination versus monotherapy for HIV

Chancellor et al, 1997

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Introduction

This vignette is an example of a simple Markov model using the `rdecision` package. It is based on the example given by Briggs (2006, Exercise 2.5) which itself is based on a Markov model which compared a combination therapy of Lamivudine/Zidovudine versus Zidovudine monotherapy in people with HIV infection (Chancellor et al. 1997).

Creating the model

The monotherapy model is created as follows:

```
# create Markov states for monotherapy (zidovudine only)
state.mono.A <- MarkovState$new("A", 1701+1055+2278)
state.mono.B <- MarkovState$new("B", 1774+1278+2278)
state.mono.C <- MarkovState$new("C", 6948+2059+2278)
state.mono.D <- MarkovState$new("D", 0)
# transition matrix for monotherapy
I.mono <- matrix(
  data = c(0.721, 0.202, 0.067, 0.010,
           0.000, 0.581, 0.407, 0.012,
           0.000, 0.000, 0.750, 0.250,
           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.mono <- MarkovModel$new(
  states=list(state.mono.A, state.mono.B, state.mono.C, state.mono.D),
  Ip=I.mono,
  discount=6.0
)
```

Checking the model

Although several checks are made on the model when it is created, such as transition probabilities from a state being less than unity, not all errors can be detected automatically. A summary of the model, suitable for printing with markdown or similar, may be created using the helper functions in class 'MarkovModel'.

Summary of model states

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

Name	hasCycleLimit	cycleLimit	Entry.Cost	Annual.Cost
A	FALSE	NA	0	5034
B	FALSE	NA	0	5330
C	FALSE	NA	0	11285
D	FALSE	NA	0	0

Summary of annual transition probabilities

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

	A	B	C	D
A	0.721	0.202	0.067	0.010
B	0.000	0.581	0.407	0.012
C	0.000	0.000	0.750	0.250
D	0.000	0.000	0.000	1.000

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

which returns the following result:

	Cycle	Population	Normalized.Cycle.Cost
A	0	1000	0
B	0	0	0
C	0	0	0
D	0	0	0

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:

Cycle	Cost	A	B	C	D	Alive
0	0.0000	1000.000000	0.000000	0.00000	0.00000	1.0000000
1	5153.0840	721.000000	202.000000	67.00000	10.00000	0.9900000
2	5392.2140	519.841000	263.004000	180.77100	36.38400	0.9636160
3	5366.7964	374.805361	257.813206	277.45022	89.93121	0.9100688
4	5052.0286	270.234665	225.500156	338.12960	166.13558	0.8338644
5	4537.3315	194.839194	185.602993	363.48149	256.07633	0.7439237
6	3925.1614	140.479059	147.192856	361.20576	351.12233	0.6488777
7	3296.2640	101.285401	113.895819	340.22391	444.59487	0.5554051
8	2703.2976	73.026774	86.633122	308.30965	532.03045	0.4679695
9	2174.9502	52.652304	65.085252	271.38471	610.87773	0.3891223
10	1722.6597	37.962311	48.450297	233.55594	680.03145	0.3199685
11	1346.8318	27.370826	35.818010	197.42970	739.38147	0.2606185
12	1041.6145	19.734366	26.339171	164.48405	789.44241	0.2105576
13	798.1925	14.228478	19.289400	135.40528	831.07684	0.1689232
14	606.8751	10.258733	14.081294	110.35806	865.30192	0.1346981
15	458.3073	7.396546	10.253496	89.18696	893.16300	0.1068370
16	344.0880	5.332910	7.451383	71.55896	915.65674	0.0843433
17	257.0161	3.845028	5.406502	57.05924	933.68923	0.0663108
18	191.1168	2.772265	3.917873	45.25249	948.05737	0.0519426
19	141.5508	1.998803	2.836282	35.71969	959.44523	0.0405548
20	104.4704	1.441137	2.051638	28.07805	968.42917	0.0315708

Model results

Expected survival

The estimated life years is given by summing the proportions of patients left alive at each cycle (Briggs, Claxton, and Sculpher 2006, 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

$$E[LY] = (p_0 - p_1) \times 0 + (p_2 - p_1) \times 1 + \quad ... \quad + (p_{n-1} - p_n) \times (n-1)$$

$$= \sum_1^N (p_{i-1} - p_i) \times (i-1)$$

$$= \sum_1^N (ip_{i-1} - ip_i - p_{i-1} + p_i)$$

$$= \sum_1^N (i-1)p_{i-1} - \sum_1^N ip_i + \sum_1^N p_i$$

$$= -Np_n + \sum_1^N p_i$$

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$new("A", 1701+1055+2278+2086)
state.comb.B <- MarkovState$new("B", 1774+1278+2278+2086)
state.comb.C <- MarkovState$new("C", 6948+2059+2278+2086)
state.comb.D <- MarkovState$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:

Cycle	Cost	A	B	C	D	Alive
0	0.0000	1000.000000	0.000000	0.00000	0.00000	1.0000000
1	6912.6623	858.000000	103.000000	34.00000	5.00000	0.9950000
2	6737.3065	736.164000	169.435000	80.17500	14.22600	0.9857740
3	5039.9117	530.774244	247.146863	178.41428	43.66461	0.9563354
4	4997.9344	382.688230	250.808725	269.96136	96.54169	0.9034583
5	4710.6271	275.918214	223.022891	330.19028	170.86861	0.8291314
6	4241.5870	198.937032	185.311779	356.89955	258.85164	0.7411484
7	3679.3306	143.433600	147.851424	356.42534	352.28964	0.6477104
8	3097.6005	103.415626	114.875265	337.10458	444.60453	0.5553955
9	2545.9992	74.562666	87.632485	306.51152	531.29333	0.4687067
10	2052.3174	53.759682	65.976132	270.54576	609.71843	0.3902816
11	1628.2053	38.760731	49.191589	233.36350	678.68418	0.3213158
12	1274.7869	27.946487	36.409981	197.64057	738.00296	0.2619970
13	987.1004	20.149417	26.799389	164.92171	788.12949	0.2118705
14	757.2182	14.527730	19.640627	135.94864	829.88300	0.1701170
15	576.2517	10.474493	14.345806	110.92857	864.25113	0.1357489
16	435.5308	7.552110	10.450761	89.73697	892.26016	0.1077398
17	327.2190	5.445071	7.597418	72.06217	914.89534	0.0851047
18	244.5683	3.925896	5.514004	57.50360	933.05650	0.0669435
19	181.9612	2.830571	3.996668	45.63493	947.53783	0.0524622
20	134.8360	2.040842	2.893839	36.04249	959.02283	0.0409772

Comparison of treatments

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

Over the 20 year time horizon, the expected life years for monotherapy was 8.979 years at a total cost per patient of 44,614 GBP. The expected life years with combination therapy was 9.927 at a total cost per patient of 50,563 GBP. The incremental change in life years was 0.948 years at an incremental cost of 5,949 GBP, giving an ICER of 6275.12 GBP.

References

Briggs, Andrew, Karl Claxton, and Mark Sculpher. 2006. *Decision Modelling for Health Economic Evaluation.* Oxford, UK: Oxford University Press.

Chancellor, Jeremy V., Andrew M. Hill, Caroline A. Sabin, Kit N. Simpson, and Mike Youle. 1997. "Modelling the Cost Effectiveness of Lamivudine/Zidovudine Combination Therapy in HIV Infection." *Pharmacoeconomics.*