

Illustrative healthy-sick-dead 3-state model

Appendix of ‘Krijkamp EM, Alarid-Escudero F, Enns EA, Hunink MGM, Pechlivanoglou P, Jalal HJ.’ **A multidimensional array representation of state-transition model dynamics.** (submitted, June 2019)

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Illustrative 3-state cohort model

In this illustrative example, we follow a cohort of healthy 70-year-old individuals over their remaining lifetime, using 30 annual cycles. The healthy individuals can get sick, they can die or stay healthy. Sick individuals can fully recover, transitioning back to healthy, remain sick or die. The state-transition diagram is shown in Figure 1. Remaining in each of these health states is associated with some utilities and costs (the state rewards). In addition to these state rewards, transition dis-utilities and costs apply. Getting sick is associated with a sudden decrease of quality of life of 0.1. In addition, transitioning to dead incurs a one-time cost of \$4,000. Both the state and transition rewards are constant over time. All parameters of this model are fictitious, not based on a specific disease and described in the table below. We use some prefixed to name our variables and we try to use a `<x>.<y>.<varName>` structure as consistent as possible, with x being the data type prefix, e.g. `a.` for arrays, `m.` for matrix, `df.` for data frames etc. and y being the variable type prefix, e.g. `c.` for costs, `p.` for probabilities, `u.` for utilities etc.

Parameter	R name	Value
Time horizon (n_t)	<code>n.t</code>	30 years
Names of health states (n)	<code>v.n</code>	H, S, D
Annual transition probabilities		
- Disease onset (H to S)	<code>p.HS</code>	0.30
- Recovery (S to H)	<code>p.SH</code>	0.15
Annual mortality		
- All-cause (H to D)	<code>p.HD</code>	0.05
- Disease specific (S to D)	<code>p.SD</code>	0.20
Annual costs		
- Healthy individuals	<code>c.H</code>	\$1,000
- Sick individuals	<code>c.S</code>	\$3,000
- Dead individuals	<code>c.D</code>	\$0
Utility weights		
- Healthy individuals	<code>u.H</code>	1.00
- Sick individuals	<code>u.S</code>	0.60
- Dead individuals	<code>u.D</code>	0.00
Transition rewards		
- Utility decrement of healthy individuals when transitioning to S	<code>du.HS</code>	0.10
- Cost of dying	<code>ic.D</code>	\$4,000

01 Initial setup

We start by loading the packages and functions needed.

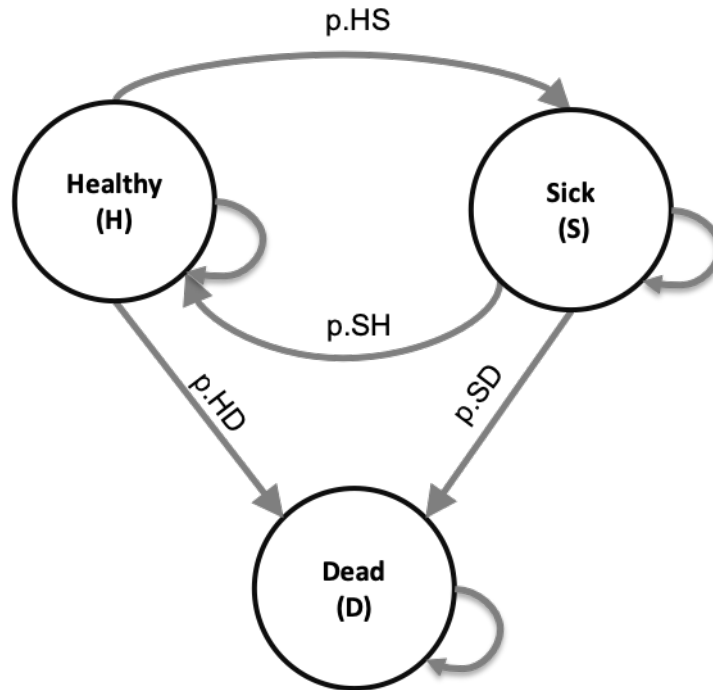


Figure 1: State-transition diagram of the 3-state model

```
#### 01.1 Load packages and functions ####
library(reshape2) # load reshape2 to transform data
library(ggplot2)  # load ggplot2 for nice looking plots
```

01.2 External parameters

In this section, we specify the starting age of the cohort, the number of cycles, the names of the health states and model parameters.

```
#### 01.2.1 General setup ####
age      <- 70 # age of starting cohort
n.t      <- 30 # time horizon, number of cycles
v.age.names <- age:(age + n.t - 1) # vector with age names
v.n      <- c("H", "S", "D") # vector with the 3 health states of the model:
# Healthy (H), Sick (S), Dead (D)
n.states <- length(v.n) # number of health states
```

Next we store the base-case parameters.

```
#### 01.2.3 Generate initial set of base-case external parameters ####
# Costs
c.H <- 1000 # cost of remaining one cycle healthy
c.S <- 3000 # cost of remaining one cycle sick
c.D <- 0    # cost of being dead (per cycle)
# State utilities
u.H <- 1    # utility when healthy
u.S <- 0.60 # utility when sick
```

```

u.D   <- 0      # utility when healthy
# Transition probabilities (per cycle)
p.HS  <- 0.30   # probability to become sick when healthy
p.HD  <- 0.05   # probability to die when healthy
p.SH  <- 0.15   # probability to become healthy when sick
p.SD  <- 0.20   # probability to die when sick
# Transition rewards
du.HS <- 0.10   # one-time utility decrement when becoming sick
ic.D  <- 4000   # one-time cost of dying

```

02 Define and initialize matrices and vectors

In this section, we initialize the matrices and vectors used for storing the data. The transition probability matrix, `m.P`, is initialized. The next step is to initialize the state vector `v.m0`. All individuals start healthy. This state vector is used to inform the first row of the cohort trace matrix `m.M`.

Equation 1-2

```

#### 02.1 Initial state vector ####
# the cohort start in the Healthy health state
v.m0 <- c(H = 1, S = 0, D = 0)
v.m0

```

```

## H S D
## 1 0 0

```

```

#### 02.2 Cohort trace
## Create the Markov cohort trace matrix m.M capturing the proportion of the cohort
# in each state at each cycle

m.M <- matrix(0, # initialize cohort trace
             nrow = (n.t + 1), ncol = n.states,
             dimnames = list(0:n.t, v.n))

m.M[1, ] <- v.m0 # store the initial state vector

```

```

#### 02.3 Transition probability matrix ####
# matrix m.P at the first cycle
m.P <- matrix(NA,
             nrow = n.states, ncol = n.states,
             dimnames = list(v.n, v.n))

# Fill in matrix
# From Healthy
m.P["H", "H"] <- 1 - (p.HS + p.HD)
m.P["H", "S"] <- p.HS
m.P["H", "D"] <- p.HD
# From Sick
m.P["S", "H"] <- p.SH
m.P["S", "S"] <- 1 - (p.SH + p.SD)
m.P["S", "D"] <- p.SD

```

```

# From Death
m.P["D", "H"] <- 0
m.P["D", "S"] <- 0
m.P["D", "D"] <- 1

m.P # print the transition probability matrix

##      H      S      D
## H 0.65 0.30 0.05
## S 0.15 0.65 0.20
## D 0.00 0.00 1.00

```

We have determined all parameters for the general set up, we specified our input parameters, initialized all structures and filled the transition probability matrix `m.P` and the first row of our cohort trace `m.M`. The next step is running the Markov model.

03 Traditional cohort trace approach

In this section, we run the Markov model for the entire time horizon. The calculation shown in Equation 3 needs to be performed for all cycles. Therefore, we create a loop starting at $t = 1$ until $t = n.t$. The transition probability matrix, `m.P` is multiplied with the cohort trace `m.M[t,]`, using matrix multiplication, specified in R with `%*%`, to fill the next row of the `m.M[t + 1,]`.

Equation 3

```

for(t in 1:n.t){ # loop through the number of cycles
  # estimate the state vector for the next cycle (t + 1)
  m.M[t + 1, ] <- m.M[t, ] %*% m.P
}

```

Equation 4

When printing the first six rows of `m.M` we see that everyone starts healthy and over time the cohort transitions towards sick and dead.

```

head(round(m.M, 3)) # show the first six lines of the cohort trace

##      H      S      D
## 0 1.000 0.000 0.000
## 1 0.650 0.300 0.050
## 2 0.468 0.390 0.143
## 3 0.362 0.394 0.244
## 4 0.295 0.365 0.341
## 5 0.246 0.325 0.428

```

Running the model using equation 3, results in the traditional cohort trace. This gives information about state occupation at each cycle and allows us to apply state rewards (e.g. `c.H`, `u.H`, etc.), but it is not possible to include the transition rewards (e.g. `du.HS` and `ic.D`). In order to include these rewards, we need to know when individuals made the transition. The dynamics array approach facilitates this and will be explained in the next section.

04 Dynamics array approach

The dynamics array approach starts similar as the traditional cohort trace approach, meaning that the first two sections are identical for the two approaches. The biggest difference is the additional array structure of dimensions `n.states x n.states x n.t` to store the transition dynamics. In R indexing start at 1, therefore, we initialize the array `a.A` using `n.state + 1`. This allows us to store the results from cycle 0 until cycle `n.t`. The initial state vectors `v.m0` is used to inform the initial cycle of the array. ##### Equation 5

```
a.A <- array(0, dim = c(n.states, n.states, n.t + 1),
             dimnames = list(v.n, v.n, 0:n.t)) # initialize array
diag(a.A[, , 1]) <- v.m0 # store the initial state vector in the diagonal of A
a.A[, , 1] # print the first cycle
```

```
##   H S D
## H 1 0 0
## S 0 0 0
## D 0 0 0
```

Equation 6

Now we run the model using the dynamics array approach. In this approach, iteratively over time, we multiply the transition probability matrix `m.P` with array `a.A` using element-wise multiplication, indicated with the `*` in R. The information about all transitions is stored in the `t + 1`-th “slice” of `a.A`.

```
# run the model
for(t in 1:n.t){                                # loop through the number of cycles
  a.A[, , t + 1] <- colSums(a.A[, , t]) * m.P # estimate the transition dynamics at t + 1
}
```

Equation 7 and 8

Printing the first three cycles of the dynamics array `a.A` gives an impression of the results. Like in the transition probability matrix `m.P`, the rows specify in which health state the individual started at the beginning of the cycle, while the columns inform you about where individuals transitioned to. In cycle 0 everyone started in the healthy states. At cycle 1 we can see that the values look very similar to the transition probabilities. From cycle 2 and onwards the information in `a.A` becomes more interesting. In cycle 2, we see that 0.65 of the cohort stayed healthy, 0.3 transitioned from healthy towards sick and 0.05 of the population died. In addition, we see that 0 of the cohort recovered, 0 stayed Sick and 0.05 died from Sick. All these values sum to 1 since we are still describing what happens to the full cohort over time.

```
a.A[, , 1:3] # shown for two cycles
```

```
## , , 0
##
##   H S D
## H 1 0 0
## S 0 0 0
## D 0 0 0
##
## , , 1
##
##      H      S      D
```

```
## H 0.65 0.3 0.05
## S 0.00 0.0 0.00
## D 0.00 0.0 0.00
##
## , , 2
##
##      H      S      D
## H 0.4225 0.195 0.0325
## S 0.0450 0.195 0.0600
## D 0.0000 0.000 0.0500
```

```
sum(a.A[, , 3]) # sum for t = 3
```

```
## [1] 1
```

When you sum the values in each column of `a.A`, the health states towards which the individuals transition to, you get which proportion of the cohort was in each health state for that cycle. The code below shows this for the health state sick.

```
sum(a.A[, "S", 3]) # sum the column of S at t = 3
```

```
## [1] 0.39
```

Equation 9

We can obtain `m.M` from `a.A` by summing the values in each column of `a.A` for all points in time. By transposing this in turn, we get the traditional cohort trace `m.M`. In order to compare this matrix with the directly generated `m.M` via equation 3 we name it, `m.M_A`.

```
# recovering M from A
m.MViaA <- t(colSums(a.A)) # sum over the columns of a.A and transpose
```

Since a Markov model is stochastic, the cohort trace obtained from `a.A` should be identical to `m.M`. We check this using the `==` function. We use rounding on 10 decimals, to avoid wrong `FALSE` results that have to do with floating point comparison issues.

05 Apply state and transition rewards

By now you know how to run a state-transition cohort model using the dynamics array approach and how to interpret or summarize the results. In this section, we demonstrate how to apply state and transition rewards. We start by initiating and filling two matrices for both costs and effects. On the diagonal are the costs for staying one cycle in that state (state rewards), while the costs off the diagonal are the costs for staying one cycle in that state plus the transition cost associated with that transition (transition rewards).

Equation 10

```
#### 05.1 Create reward matrices for both costs and effects ####
m.R.costs <- m.R.effects <- matrix(NA,
                                   nrow = n.states, ncol = n.states,
                                   dimnames = list(v.n, v.n))
```

```

# Fill in matrix for costs
# From Healthy
m.R.costs["H", "H"] <- c.H
m.R.costs["H", "S"] <- c.H
m.R.costs["H", "D"] <- c.H + ic.D
# From Sick
m.R.costs["S", "H"] <- c.S
m.R.costs["S", "S"] <- c.S
m.R.costs["S", "D"] <- c.S + ic.D
# From Death
m.R.costs["D", "H"] <- c.D
m.R.costs["D", "S"] <- c.D
m.R.costs["D", "D"] <- c.D

# Fill in matrix for effects
# From Healthy
m.R.effects["H", "H"] <- u.H
m.R.effects["H", "S"] <- u.H - du.HS
m.R.effects["H", "D"] <- u.H
# From Sick
m.R.effects["S", "H"] <- u.S
m.R.effects["S", "S"] <- u.S
m.R.effects["S", "D"] <- u.S
# From Death
m.R.effects["D", "H"] <- u.D
m.R.effects["D", "S"] <- u.D
m.R.effects["D", "D"] <- u.D

```

These rewards matrices look as follow. We see that staying healthy costs \$1000, while someone that transitions from healthy towards dead makes costs of \$5000. In the effects matrix we see that an individual gets a utility of 1 assign for staying healthy, while when the individual transitions towards Sick the decrement of $ic.HS$ is included, resulting in a utility of 0.90.

```
m.R.costs    # show the reward matrix for costs
```

```
##      H      S      D
## H 1000 1000 5000
## S 3000 3000 7000
## D      0      0      0
```

```
m.R.effects  # show the reward matrix for effects
```

```
##      H      S      D
## H 1.0 0.9 1.0
## S 0.6 0.6 0.6
## D 0.0 0.0 0.0
```

Equation 12

In this section we create outcome arrays, **a.Y**, one for costs, **a.Y_costs**, and one for effects, **a.Y_effects**. These arrays show the costs and QALYs generated with each transition at each cycle. By iteratively element-wise multiplication of the reward matrices, **m.R_costs** and **m.R_effects**, with array **a.A** we can fill the outcome arrays.

```
#### 05.2 Expected QALYs and Costs per cycle for each strategy ####
a.Y.costs <- a.Y.effects <- array(0, dim = c(n.states, n.states, n.t + 1),
    dimnames = list(v.n, v.n, 0:n.t))
# initialize arrays
a.Y.costs[, , 1] <- a.A[, , 1] * m.R.costs
a.Y.effects[, , 1] <- a.A[, , 1] * m.R.effects

for(t in 1:n.t){
  # element-wise-multiplication of array A with the rewards matrices
  a.Y.costs[, , t + 1] <- a.A[, , t + 1] * m.R.costs
  a.Y.effects[, , t + 1] <- a.A[, , t + 1] * m.R.effects
}
```

Please note that we are now showing all these calculations in a step-wise approach, resulting in having a couple of loops for time. All iterative process, creating `m.M`, `a.A` and the `m.R` and `a.Y`, can be combined within the same loop for time.

Equation 12

The final step is to calculate the total costs and QALYs. We first calculate the expected cost and QALYs per cycle and store them in the vectors `v.Costs` and `v.QALYs`. Then, we sum the values within each vector to compute the total expected cost (TC) and QALYs (TE).

```
# calculate the expected costs per cycle
v.costs <- rowSums(t(colSums(a.Y.costs)))
# calculate the expected QALYs per cycle
v.QALYs <- rowSums(t(colSums(a.Y.effects)))

TC <- sum(v.costs) # calculate the total expected costs
TE <- sum(v.QALYs) # calculate the total expected QALYS

v.results <- c(TC, TE) # combine the total expected costs and QALYs
names(v.results) <- c("Costs", "Effect") # name the vector
v.results # print the results
```

```
##      Costs      Effect
## 20850.708  1006.626
```

06 Plot cohort trace

The results of a cohort trace are much easier to interpret via a graph. Using the function `ggplot` we show the proportion of the cohort in each state (y-axis) at each cycle (x-axis) in Figure 2.

At the end of the model we save the important objects so they can be used without the need to run the model again.

```
save(m.M, file = "../output/cohort_trace.RData") # save the object
save(a.A, file = "../output/array.RData") # save the object
```

07 Estimation of epidemiological measures

As mentioned in the brief report, full exposition of computing epidemiological measures from array `A` is case-specific and is beyond the scope of this brief report. We do however, like to illustrate the concept using

Cohort trace of the stylistic 3-state model

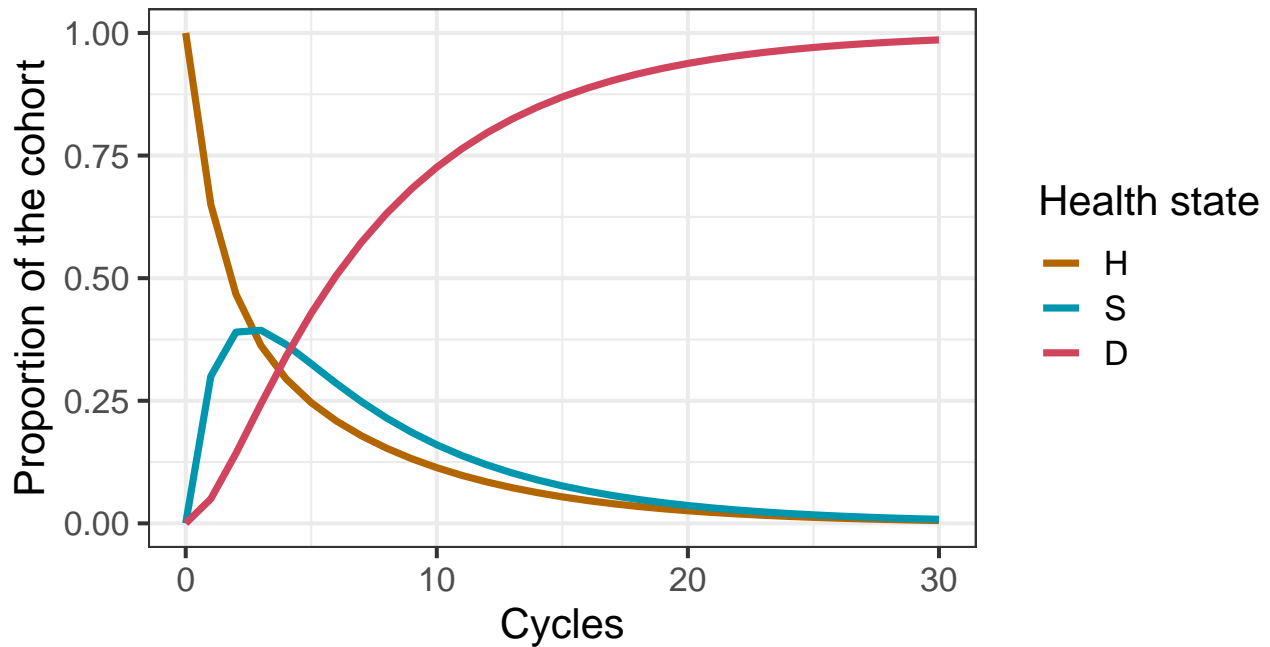


Figure 2: Cohort trace of the model

a very simple example. For our illustrative 3-state model we can calculate the ratio of those than transitioned from sick to dead at each cycle to those that transitioned to dead from healthy and sick. To calculate this, we initiate a vector of length $n.t$ to store the data and since all individuals start out healthy the initial value of this vector is 0. Next, we iteratively calculate the ratio.

```
v.e <- numeric(n.t + 1) # create the vector v.e
v.e[1] <- 0             # initiate the vector
# calculate the ratio across all cycles starting in cycle 2
v.e[-1] <- a.A["S", "D", -1] / (a.A["H", "D", -1] + a.A["S", "D", -1])
```

Next, we prepare the data to get a nice plot.

```
df.e <- as.data.frame(cbind(0:n.t, v.e)) # create a dataframe with cycles and proportion that dies each
colnames(df.e) <- c("cycle", "proportion") # name the columns of the dataframe
```

Our final step is to save the figure in the figs folder.

```
ggsave("../figs/Proportion_death_from_sick.png", width = 8, height = 6) # save the plot
```

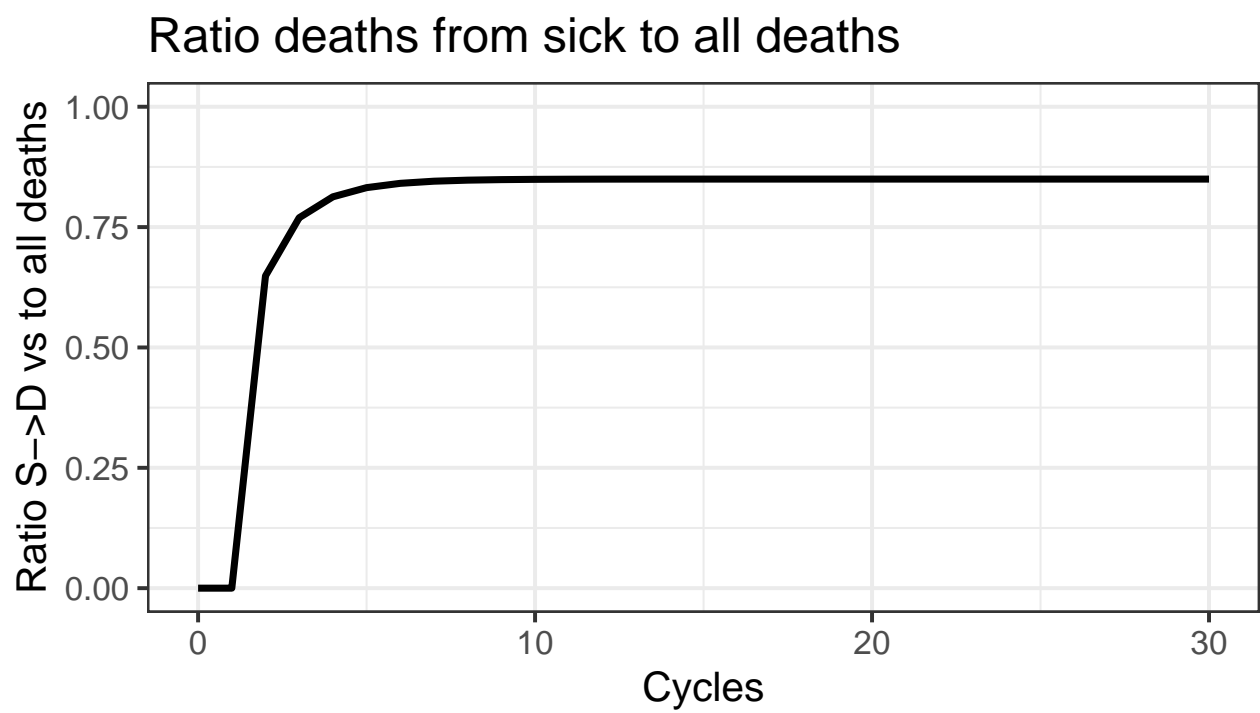


Figure 3: Ratio of those dying from sick to those dying from both healthy and sick