Cost-Effectiveness and Decision Modeling in R
Markov Model Variants Exercise

The DARTH workgroup

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Exercise I: Variations on the Sick-Sicker Markov Model

Previously, you built a Markov of the Sick-Sicker model where transition probabilities were assumed to be constant over time. In this exercise, you will expand on that model to incorporate age-dependence (time-varying probabilities) and history-dependence.

History-dependence

It has been recently discovered that the risk of progression from Sick to Sicker increases the longer a person has been sick. This increase follows a Weibull growth curve, calculated as

$$p_{S1S2(t)} = \lambda_\gamma t^{(\gamma-1)}$$

where t is the t-th cycle (year) that a person has been in the Sick state. $\lambda = 0.08$ and $\gamma = 1.1$ are the scale and shape parameters of the Weibull function, respectively.

We will now expand the age-dependent model to include this history dependence by adding tunnel states for S1, as shown in Figure 2.
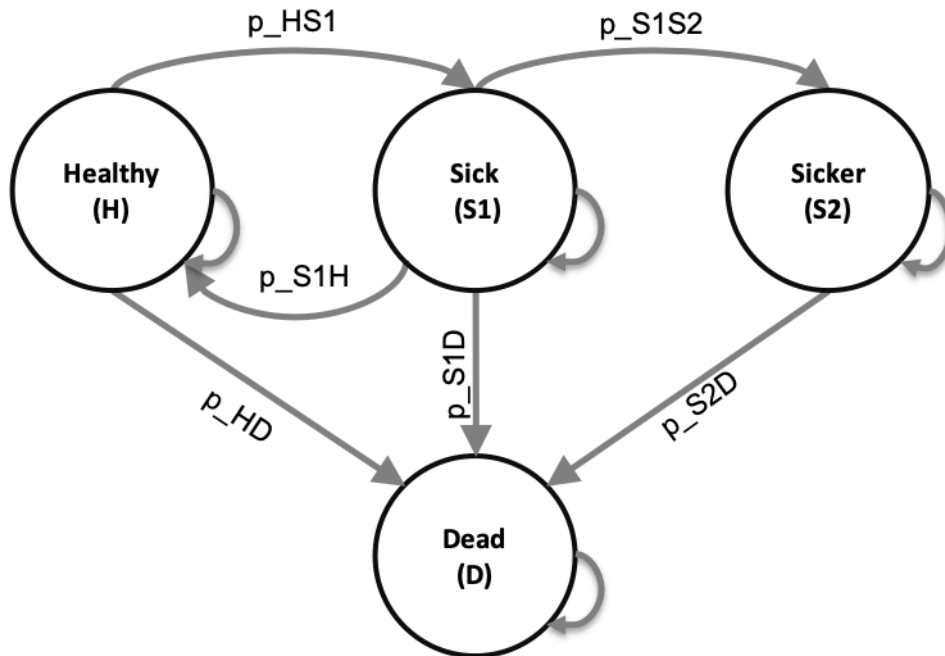

Figure 1: Schematic representation of the Sick-Sicker model

Tasks

1. Starting from the age-dependent Markov model in the R function "Markov_Sick-Sicker_time.R", expand the 3D transition probability array to account for tunnels.
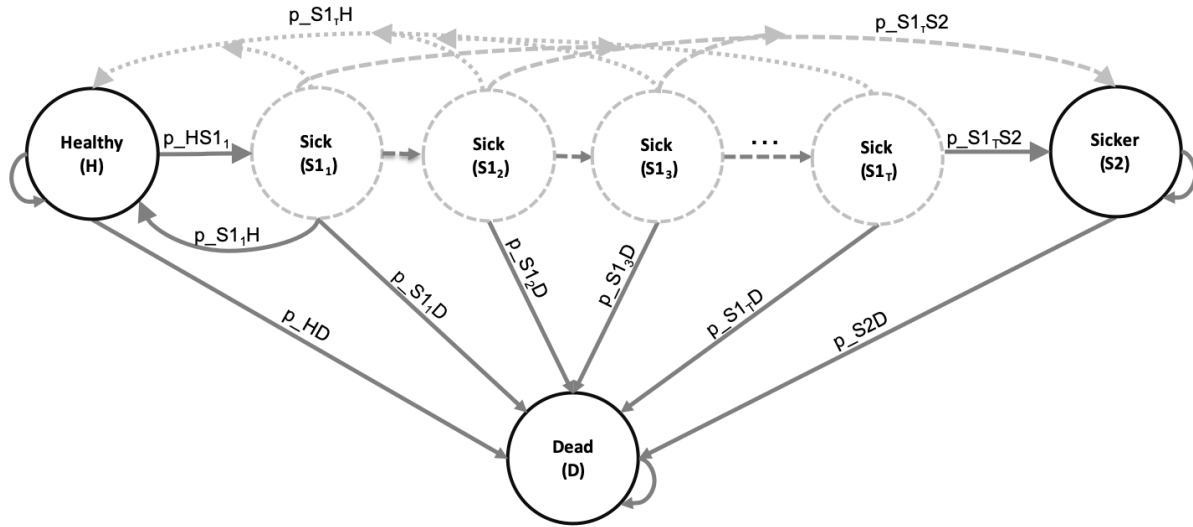
Figure 2: Schematic representation of the Sick-Sicker model with tunnels states for S1

2. Create the parameter `p_S1S2` as a Weibull function as follows:

- `p_S1S2 <- l*g*(1:tunnel_size)^{g-1}`, where
- `l <- 0.08` (scale)
- `g <- 1.1` (shape)

3. Fill in the 3D transition probability array accounting for the tunnel states for S1

4. Plot the survival curve for the cohort under no treatment. Extra challenge: plot the survival curves for all three Markov model versions (time-homogenous, age-dependent, and history-dependent) in one graph so you can compare.

Parameter	R name	Value
Time horizon	n_t	30 years
Cycle length		1 year
Names of health states	v_n	H, S1, S2, D
Annual discount rate (costs/QALYs)	d_r	3%
Annual transition probabilities		
- Disease onset (H to S1)	p_HS1	0.15
- Recovery (S1 to H)	p_S1H	0.5
- Disease progression (S1 to S2)	p_S1S2	Weibull function
Annual mortality		
- All-cause mortality (H to D)	p_HD	1 - exp(-v_r_HD)
- Hazard ratio of death in S1 vs H	hr_S1	3
- Hazard ratio of death in S2 vs H	hr_S2	10
Annual costs		
- Healthy individuals	c_H	$2,000
- Sick individuals in S1	c_S1	$4,000
- Sick individuals in S2	c_S2	$15,000
- Dead individuals	c_D	$0
- Additional costs of sick individuals treated in S1 or S2	c_trt	$12,000

Parameter	R name	Value
Utility weights		
- Healthy individuals	u_H	1.00
- Sick individuals in S1	u_S1	0.75
- Sick individuals in S2	u_S2	0.50
- Dead individuals	u_D	0.00
Intervention effect		
- Utility for treated individuals in S1	u_trt	0.95

*Note: To calculate the probability of dying from S1 and S2, use the hazard ratios provided. To do so, first convert the probability of dying from healthy, p_HD, to a rate; then multiply this rate by the appropriate hazard ratio; finally, convert this rate back to a probability. Recall that you can convert between rates and probabilities using the following formulas: $r = -log(1 - p)$ and $p = 1 - e^{(-rt)}$

Exercise II: Probabilistic sensitivity analysis of the Sick-Sicker Markov model

This exercise continues based on the age-and-history-dependent deterministic Markov model of the Sick-Sicker model from Exercise I. In this exercise, you will do a probabilistic sensitivity analysis (PSA) with 1000 simulations (n_sim). The Table describes the distributions for the variables you used in the previous exercise.

Table II: Input parameters for probabilistic analysis

Parameter	Distribution	Distribution values
Number of simulation	n_sim	1000
Annual transition probabilities		
- Disease onset (H to S1)	Beta	$\alpha = 30,\ \beta = 170$
- Recovery (S1 to H)	Beta	$\alpha = 60,\ \beta = 60$
- Disease progression (S1 to S2) in the time-homogeneous model	Beta	$\alpha = 84,\ \beta = 716$
Annual mortality		
- All-cause mortality (H to D)	Beta	$\alpha = 10,\ \beta = 1990$
- Hazard ratio of death in S1 vs H	Lognormal	$\mu = log(3),\ \sigma = 0.01$
- Hazard ratio of death in S2 vs H	Lognormal	$\mu = log(10),\ \sigma = 0.02$
Annual costs		
- Healthy individuals	Gamma	shape $= 100.0$, scale $= 20.0$
- Sick individuals in S1	Gamma	shape $= 177.8$, scale $= 22.5$
- Sick individuals in S2	Gamma	shape $= 225.0$, scale $= 66.7$
- Additional costs of sick individuals treated in S1 or S2	Gamma	shape $= 73.5$, scale $= 163.3$
Utility weights		
- Healthy individuals	Tr. Normal	$\mu = 1.00,\ \sigma = 0.01,\ b = 1$
- Sick individuals in S1	Tr. Normal	$\mu = 0.75,\ \sigma = 0.02,\ b = 1$
- Sick individuals in S2	Tr. Normal	$\mu = 0.50,\ \sigma = 0.03,\ b = 1$
Intervention effect		
- Utility for treated individuals in S1	Tr. Normal	$\mu = 0.95,\ \sigma = 0.02,\ b = 1$

Tasks

5. Create the `calculate_ce_out` R function of the Sick-Sicker Markov model in the file "Functions_markov_sick-sicker_tunnels.R".

6. Create a function called `gen_psa` to sample values for the uncertain parameters using the appropriate distributions. Hint: package `truncnorm` deals with truncated normal distributions.

7. Open the file "markov_sick-sicker_tunnels_SA_template.R" and conduct a probabilistic Cost-Effectiveness analysis of treatment vs no-treatment.

8. Create histograms of model inputs.

9. Create a cost-effectiveness plane to present discounted costs and QALYs.

10. Create the cost-effectiveness acceptability curves (CEAC) and frontier (CEAF) for the treatment comparison assuming WTP thresholds of $0 to $200,000.

11. Create the expected loss curves (ELCs) plot

12. Create an expected value of perfect information (EVPI) plot.