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

The DARTH workgroup

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Please cite our publications when using this code:

- Jalal H, Pechlivanoglou P, Krijkamp E, Alarid-Escudero F, Enns E, Hunink MG. An Overview of R in Health Decision Sciences. Med Decis Making. 2017; 37(3): 735-746. https://journals.sagepub.com/doi/abs/10.1177/0272989X16686559

- Krijkamp EM, Alarid-Escudero F, Enns EA, Jalal HJ, Hunink MGM, Pechlivanoglou P. Microsimulation modeling for health decision sciences using R: A tutorial. Med Decis Making. 2018;38(3):400–22. https://journals.sagepub.com/doi/abs/10.1177/0272989X18754513

- Krijkamp EM, Alarid-Escudero F, Enns E, Pechlivanoglou P, Hunink MM, Jalal H. A Multidimensional Array Representation of State-Transition Model Dynamics. Med Decis Making. 2020 Online first. https://doi.org/10.1177/0272989X19893973

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.
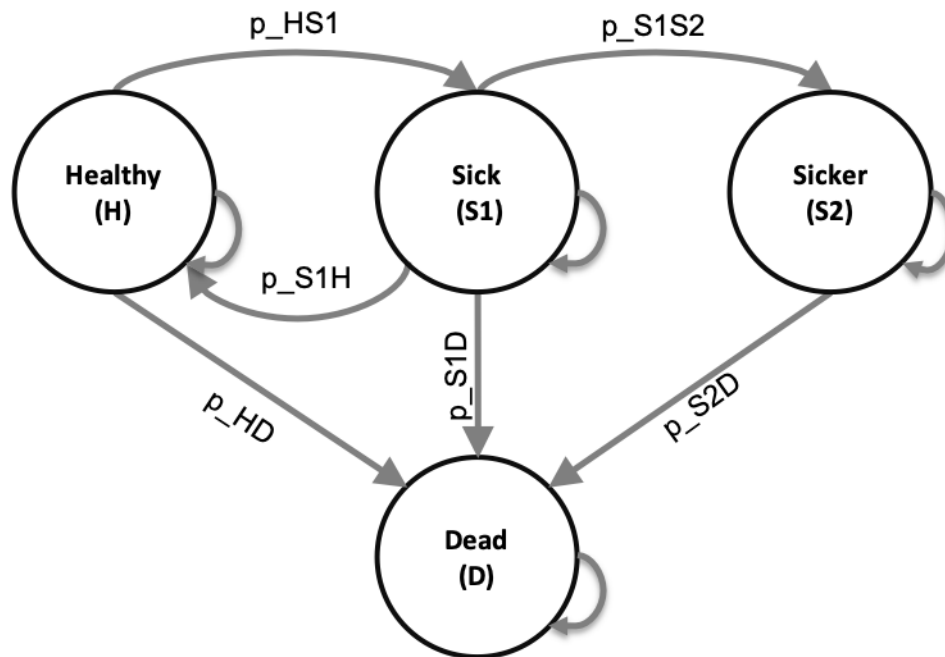

Figure 1: Schematic representation of the Sick-Sicker model

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.

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
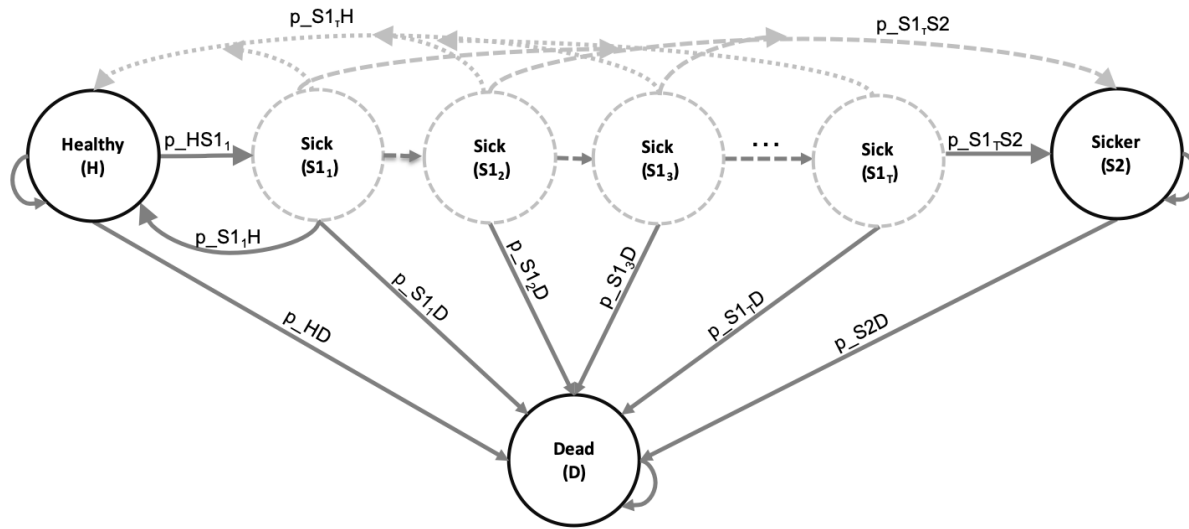
Figure 2: Schematic representation of the Sick-Sicker model with tunnels states for S1

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
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

Parameter	Distribution	Distribution values
- 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.