

# A Tutorial on Time-Dependent Cohort State-Transition Models in R

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2021-06-18

## Abstract

This tutorial shows how to implement time-dependent cohort state-transition models (cSTMs) to conduct cost-effectiveness analyses (CEA) in R, where transition probabilities and rewards vary by time. We account for two types of time dependency: time since the start of the simulation (simulation-time dependency) and time spent in a health state (state residence dependency). This tutorial is based on an accompanying tutorial that introduces how to implement time-independent cSTMs. We illustrate how to conduct a CEA of multiple strategies based on a time-dependent cSTM using a previously published cSTM, including probabilistic sensitivity analyses. We also demonstrate how to compute various epidemiological outcomes of interest, such as survival probability and prevalence. To illustrate the concepts, we provide both the mathematical notation and the R code to execute the calculations. Finally, similar to the introductory tutorial, we provide a public repository with the R code for broader implementation.

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## 1 Introduction

Cohort state-transition models (cSTMs) are a type of decision model used to evaluate different health policy and clinical strategies, such as screening and surveillance programs,<sup>1,2</sup> diagnostic procedures,<sup>3</sup> disease management programs,<sup>4</sup> and interventions.<sup>5,6</sup> cSTMs can be either time-independent or time-dependent. In an accompanying tutorial,<sup>7</sup> we describe the components of a time-independent cSTM, illustrate the implementation of these cSTMs and conduct a cost-effectiveness analysis (CEA) in R, a statistical software with increasing use in health decision sciences.<sup>8</sup> Time dependence could be either on time since the start of the simulation (simulation-time dependency) or time spent in a health state (state residence dependency). In this tutorial, we cover the implementation of a cSTM with one or both types of time dependencies. We first expand the Sick-Sicker example described in the accompanying tutorial<sup>7</sup> to have simulation time-dependency and state residence dependency, as well as state and transition rewards. We then describe each of the components of time-dependent cSTMs, illustrate the implementation of these components by expanding the example described in the accompanying tutorial and conduct a CEA comparing four strategies, including a probabilistic sensitivity analysis. We also demonstrate how to compute various epidemiological outcomes of interest, such as survival probability and prevalence. Readers can find the most up-to-date model code and code to create the tutorial graphs in the accompanying GitHub repository (<https://github.com/DARTH-git/cohort-modeling-tutorial-timedep>). We assume that the reader is familiar with the basics of decision modeling and the basics of developing time-independent cSTMs in R, as described in the accompanying tutorial.

## 2 Time-dependent cSTMs

Time-dependency in cSTMs means that transition probabilities or rewards are not fixed over time. Time dependency in cSTMs is desirable to represent disease processes over relatively long periods accurately where the transition probabilities may change. In this tutorial, we describe two types of time dependency: (1) *simulation-time dependency* that refers to the dependence on time since simulation starts, with age-specific background mortality being a common important example,<sup>9</sup> and (2) *state residence dependency*, which means that transition probabilities or rewards depend on the duration of time the cohort spends in a given state. We first describe how to implement simulation-time dependent cSTMs and then add state residence dependency to account for both time dependencies.

## 2.1 Simulation-time dependency

Simulation-time dependency can be accounted for by defining the transition probability matrix as a function of time,  $P_t$ . The elements of  $P_t$  are the transition probabilities of moving from state  $i$  to state  $j$  as a function of time  $t$ ,  $p_{[i,j,t]}$ , where  $\{i, j\} = 1, \dots, n_S$  and  $t = 0, \dots, n_T$ , with  $n_S$  being the number of health states of the model and  $n_T$  the number of cycles that represent total simulation time.

$$P_t = \begin{bmatrix} p_{[1,1,t]} & p_{[1,2,t]} & \cdots & p_{[1,n_S,t]} \\ p_{[2,1,t]} & p_{[2,2,t]} & \cdots & p_{[2,n_S,t]} \\ \vdots & \vdots & \ddots & \vdots \\ p_{[n_S,1,t]} & p_{[n_S,2,t]} & \cdots & p_{[n_S,n_S,t]} \end{bmatrix}.$$

Note that all rows of the transition probability matrix in each cycle  $t$  must sum to one,  $\sum_{j=1}^{n_S} p_{[i,j,t]} = 1$  for all  $i = 1, \dots, n_S$  and  $t = 0, \dots, n_T$ .

After defining the transition probability matrix, we need to specify the initial distribution of the cohort at  $t = 0$ . These two components will allow us to simulate the transitions of the cohort across health states over time. Therefore, we define  $\mathbf{m}_0$  as the vector that captures the distribution of the cohort among the states at  $t = 0$  (i.e., the initial state vector). The state vector at cycle  $t + 1$  ( $\mathbf{m}_{t+1}$ ) is then calculated as the matrix product of the state vector at cycle  $t$ ,  $\mathbf{m}_t$ , and the transition probability matrix that the cohort faces in cycle  $t$ ,  $P_t$ ,

$$\mathbf{m}_{t+1} = \mathbf{m}_t P_t \quad \text{for} \quad t = 0, \dots, (n_T - 1). \quad (1)$$

Equation (1) is iteratively evaluated until  $t = n_T$ .

The cohort trace matrix,  $M$ , is a matrix of dimensions  $(n_T + 1) \times n_S$  where each row is a state vector  $(-\mathbf{m}_t-)$ , such that

$$M = \begin{bmatrix} -\mathbf{m}_0- \\ -\mathbf{m}_1- \\ \vdots \\ -\mathbf{m}_{n_T}- \end{bmatrix}.$$

$M$  stores the output of the cSTM, which we can use to compute various epidemiological outcomes, such as prevalence and survival probability over time, and economic outcomes, such as cumulative resource use and costs.

## 2.2 Time dependency on state residence

The implementation of state residence dependency is slightly more involved than simulation-time dependency. As described above, dependence on state residence time occurs when transition probabilities or rewards depend on the time spent in a given state. To account for state residence dependency, we expand the number of states with as many transient states as the number of cycles for which state residency is required. These transient states are often referred to as *tunnel* states where the cohort stays for only one cycle and either transition to the next tunnel state or completely exit the tunnel.

In a scenario where state-residence in one state lasts  $n_{\text{tunnels}}$  cycles, this state needs to be expanded into  $n_{\text{tunnels}}$  states, and the transition probability matrix also needs to be expanded to incorporate these additional transient states. This will result in a transition probability matrix of dimensions  $n_{S_{\text{tunnels}}} \times n_{S_{\text{tunnels}}}$ , where  $n_{S_{\text{tunnels}}}$  is the total number of health states ( $n_{S_{\text{tunnels}}} = n_S + n_{\text{tunnels}} - 1$ ). If the transition probabilities are also dependent on simulation time, we add a third dimension such that the dimensions will become  $n_{S_{\text{tunnels}}} \times n_{S_{\text{tunnels}}} \times n_T$ . As state residence dependency extends in more health states, the total number of health states will increase, causing what has been referred to as “state explosion”. Table 1 describes the core components of time-dependent cSTMs and their suggested R code names.

Table 1: Core components of time-dependent cSTMs with their R name.

| Element                        | Description   | R name                        |
|--------------------------------|---|-------------------------------|
| $n_S$                          | Number of states                                      | <code>n_states</code>         |
| $\mathbf{m}_0$                 | Initial state vector                                  | <code>v_s_init</code>         |
| $\mathbf{m}_t$                 | State vector in cycle $t$                             | <code>v_mt</code>             |
| $M$                            | Cohort trace matrix                                   | <code>m_M</code>              |
| $\mathbf{P}$                   | Time-dependent transition probability array           | <code>a_P</code>              |
| $\mathbf{A}$                   | Transition-dynamics array                             | <code>a_A</code>              |
| $n_{\text{tunnels}}$           | Number of tunnel states                               | <code>n_tunnel_size</code>    |
| $n_{S_{\text{tunnels}}}$       | Number of states including tunnel states              | <code>n_states_tunnels</code> |
| $\mathbf{m}_{\text{tunnels}0}$ | Initial state vector for the model with tunnel states | <code>v_s_init_tunnels</code> |

For a more detailed description of these components with their variable types, data structure, and R name, please see the Supplementary Material.

### 3 Case study: Time-dependent Sick-Sicker model

Similar to the introductory tutorial, we will demonstrate how to implement time-dependent cSTMs in R using the 4-state “Sick-Sicker” model<sup>7</sup> to account for time dependency. We will use this cSTM to conduct a CEA of different treatment strategies accounting for transition rewards. The state-transition diagram of the Sick-Sicker model is presented in Figure 1. We first adapt the cSTM to account for simulation-time dependency by allowing age-dependent background mortality and then expand it to account for state-residence dependency.

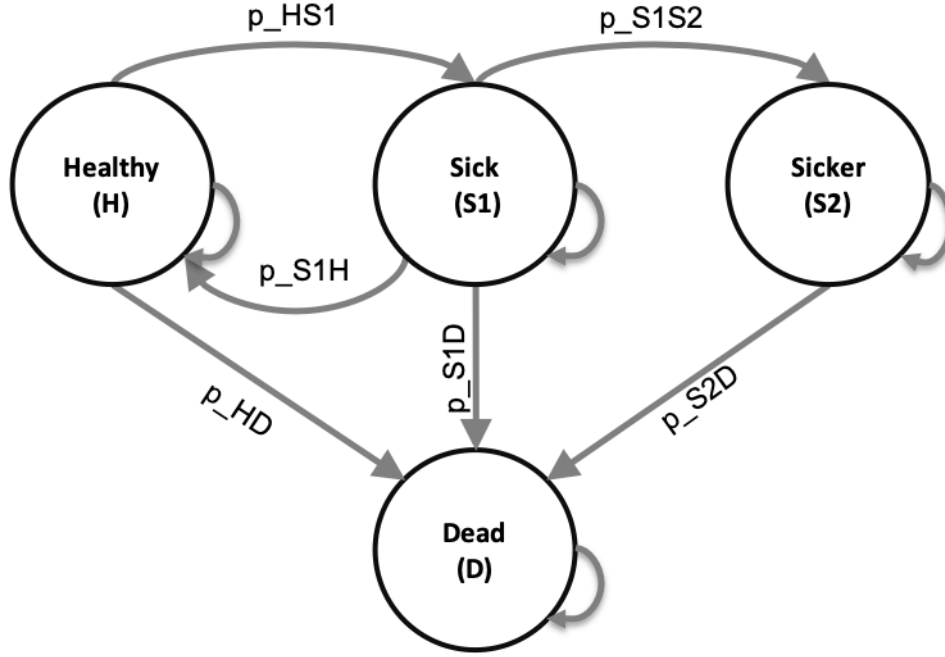


Figure 1: State-transition diagram of the Sick-Sicker cohort state-transition model with the name of the health states and possible transitions with their corresponding transition probability names.

The model simulates the health care costs and quality-adjusted life-years (QALYs) of a cohort of 25-year-old individuals at risk of developing a hypothetical disease that has two stages: “Sick” and “Sicker”.<sup>10</sup> We simulate the cohort of individuals who all start in the “Healthy” state (denoted by “H”) over their lifetime, which means that we will simulate the cohort for 75 cycles. The total number of cycles is denoted as  $n_T$  and defined in R as `n_cycles`. Healthy individuals face age-specific background mortality and those who become ill over time transition to the “Sick” state (denoted by “S1”). Once healthy individuals get sick, they incur a one-time utility decrement of 0.01 (`du_HS1`, a disutility of transitioning from H to S1) and a transition cost of \$1,000 (`ic_HS1`) that reflects the acute impacts of developing the illness. The S1 state is associated with higher mortality, higher health care costs, and lower quality of life than the H state. Once in the S1 state, individuals may recover (returning to the H state), die (move to the D state), or progress further to the “Sicker” state (denoted by “S2”), with further increases in mortality risk and health care costs and reduced quality of life. We assume that it is not possible to distinguish between individuals in S1 and S2. In the state-residence time-dependent model, the risk of progressing from S1 to S2 is a function of the duration of time spent in S1. Individuals in S1 and S2 face an increased hazard of death, compared to healthy individuals, in the form of a hazard ratio (HR) of 3 and 10, respectively, relative to the background age-specific mortality hazard rate. Once simulated individuals die, they transition to the absorbing D state, where they remain, and incur a one-time cost of \$2,000 (`ic_D`) that reflects the expected acute care preceding death. All transitions between non-death states are assumed to be conditional on surviving each cycle. We simulated the evolution of the cohort in one-year discrete-time cycles.

We use this cSTM to evaluate the cost-effectiveness of four strategies: Strategy A, strategy B, a combination of A and B (strategy AB), and the standard of care (strategy SoC). Strategy A involves administering treatment A to individuals in S1 and S2 but only increases the QoL of individuals in S1 from 0.75 (utility

without treatment,  $u_{S1}$ ) to 0.95 (utility with treatment A,  $u_{trtA}$ ) and costs \$12,000 per year ( $c_{trtA}$ ).<sup>11</sup> This strategy does not impact the QoL of individuals in S2, nor does it change the risk of becoming sick or progressing through the sick states. Strategy B uses treatment B to reduce only the rate of Sick individuals progressing to the S2 state with a hazard ratio (HR) of 0.6 ( $hr_{S1S2\_trtB}$ ) and costs \$13,000 per year ( $c_{trtB}$ ) and does not affect QoL. Strategy AB involves administering both treatments A and B. We discount both costs and QALYs at an annual rate of 3%. Model parameters and the corresponding R variable names are presented in Table 2 and follow the notation described in the DARTH coding framework.<sup>12</sup>

Note that for strategy A, the model has the same structure and identical transition probabilities to SoC. The only difference is the added cost of the treatment for S1 or S2, and QoL increases for S1. After comparing the four strategies in terms of expected QALYs and costs, we calculate the incremental cost per QALY gained between non-dominated strategies.

Table 2: Description of parameters, their R variable name, base-case values and distribution.

| Parameter  | R name                        | Base-case    | Distribution               |
|--|-------------------------------|--------------|----------------------------|
| Number of cycles ( $n_T$ )                               | <code>n_cycles</code>         | 75 years     | constant                   |
| Names of health states                                   | <code>v_names_states</code>   | H, S1, S2, D | constant                   |
| Annual discount rate for costs                           | <code>d_c</code>              | 3%           | constant                   |
| Annual discount rate for QALYs                           | <code>d_e</code>              | 3%           | constant                   |
| Number of PSA samples ( $K$ )                            | <code>n_sim</code>            | 1,000        | constant                   |
| Annual transition probabilities conditional on surviving |                               |              |                            |
| - Disease onset (H to S1)                                | <code>p_HS1</code>            | 0.15         | beta(30, 170)              |
| - Recovery (S1 to H)                                     | <code>p_S1H</code>            | 0.5          | beta(60, 60)               |
| - Time-independent disease progression (S1 to S2)        | <code>p_S1S2</code>           | 0.105        | beta(84, 716)              |
| - Time-dependent disease progression (S1 to S2)          | <code>v_p_S1S2_tunnels</code> |              |                            |
| Weibull parameters                                       |                               |              |                            |
| Scale ( $\lambda$ )                                      | <code>p_S1S2_scale</code>     | 0.08         | lognormal(log(0.08), 0.02) |
| Shape ( $\gamma$ )                                       | <code>p_S1S2_shape</code>     | 1.10         | lognormal(log(1.10), 0.05) |
| Annual mortality   |                               |              |                            |
| - Age-dependent background mortality rate (H to D)       | <code>v_r_HDage</code>        | age-specific | constant                   |
| - Hazard ratio of death in S1 vs H                       | <code>hr_S1</code>            | 3.0          | lognormal(log(3.0), 0.01)  |
| - Hazard ratio of death in S2 vs H                       | <code>hr_S2</code>            | 10.0         | lognormal(log(10.0), 0.02) |
| Annual costs   |                               |              |                            |
| - Healthy individuals                                    | <code>c_H</code>              | \$2,000      | gamma(100.0, 20.0)         |

| Parameter   | R name       | Base-case | Distribution             |
|---|--------------|-----------|--------------------------|
| - Sick individuals in S1  | c_S1         | \$4,000   | gamma(177.8, 22.5)       |
| - Sick individuals in S2  | c_S2         | \$15,000  | gamma(225.0, 66.7)       |
| - Dead individuals  | c_D          | \$0       | -                        |
| - Cost of treatment A as an additional costs on individuals treated in S1 or S2 | c_trtA       | \$12,000  | gamma(576.0, 20.8)       |
| - Cost of treatment B as an additional costs on individuals treated in S1 or S2 | c_trtB       | \$13,000  | gamma(676.0, 19.2)       |
| Utility weights   |              |           |                          |
| - Healthy individuals   | u_H          | 1.00      | beta(200, 3)             |
| - Sick individuals in S1  | u_S1         | 0.75      | beta(130, 45)            |
| - Sick individuals in S2  | u_S2         | 0.50      | beta(230, 230)           |
| - Dead individuals  | u_D          | 0.00      | constant                 |
| Treatment A effectiveness   |              |           |                          |
| - Utility for treated individuals in S1   | u_trtA       | 0.95      | beta(300, 15)            |
| Treatment B effectiveness   |              |           |                          |
| - Reduction in rate of disease progression (S1 to S2) as hazard ratio (HR)      | hr_S1S2_trtB | log(0.6)  | lognormal(log(0.6), 0.1) |
| Transition rewards  |              |           |                          |
| - Utility decrement of healthy individuals when transitioning to S1             | du_HS1       | 0.01      | beta(11,1088)            |
| - Cost of healthy individuals when transitioning to S1                          | ic_HS1       | \$1,000   | gamma(25, 40)            |
| - Cost of dying when transitioning to D   | ic_D         | \$2,000   | gamma(100, 20)           |

The R code below describes the initialization of the input parameters.

```
## General setup
cycle_length <- 1 # cycle length equal one year
n_age_init <- 25 # age at baseline
n_age_max <- 100 # maximum age of follow up
n_cycles <- n_age_max - n_age_init # number of cycles
# The 4 health states of the model:
v_names_states <- c("H", # Healthy (H)
                    "S1", # Sick (S1)
                    "S2", # Sicker (S2)
                    "D") # Dead (D)
n_states <- length(v_names_states) # number of health states
d_e <- 0.03 # discount rate for QALYs of 3% per cycle
d_c <- 0.03 # discount rate for costs of 3% per cycle
v_names_str <- c("Standard of care", # store the strategy names
                 "Strategy A",
                 "Strategy B",
```

```

"Strategy AB")

## Transition probabilities (per cycle), hazard ratios and odds ratio (OR)
p_HS1 <- 0.15 # probability of becoming Sick when Healthy
p_S1H <- 0.5  # probability of becoming Healthy when Sick
p_S1S2 <- 0.105 # probability of becoming Sicker when Sick
hr_S1 <- 3    # hazard ratio of death in Sick vs Healthy
hr_S2 <- 10   # hazard ratio of death in Sicker vs Healthy

# Effectiveness of treatment B
hr_S1S2_trtB <- 0.6 # hazard ratio of becoming Sicker when Sick under treatment B

## State rewards
## Costs
c_H <- 2000 # cost of being Healthy for one cycle
c_S1 <- 4000 # cost of being Sick for one cycle
c_S2 <- 15000 # cost of being Sicker for one cycle
c_D <- 0 # cost of being dead for one cycle
c_trtA <- 12000 # cost of receiving treatment A for one cycle
c_trtB <- 13000 # cost of receiving treatment B for one cycle
# Utilities
u_H <- 1 # utility of being Healthy for one cycle
u_S1 <- 0.75 # utility of being Sick for one cycle
u_S2 <- 0.5 # utility of being Sicker for one cycle
u_D <- 0 # utility of being dead for one cycle
u_trtA <- 0.95 # utility when receiving treatment A for one cycle

## Transition rewards
du_HS1 <- 0.01 # one-time utility decrement when transitioning from Healthy to Sick
ic_HS1 <- 1000 # one-time cost when transitioning from Healthy to Sick
ic_D <- 2000 # one-time cost when dying

```

### 3.1 Simulation-time dependency

To illustrate the implementation of simulation-time dependency in the Sick-Sicker cSTM, we model all-cause mortality as a function of age. We obtain all-cause mortality from life tables in the form of age-specific mortality hazard rates,  $\mu(a)$ , where  $a$  refers to age. For this example, we create a vector `v_r_mort_by_age` with age-specific background mortality hazard rates for 0 to 100 year-olds obtained from the 2015 US life-tables.<sup>13</sup> To compute the transition probability from state H to state D, corresponding to cohort's age at each cycle, we transform the rate  $\mu(a)$  to a transition probability assuming a constant exponential hazard rate within each year of age

$$p_{[H,D,t]} = 1 - \exp\{-\mu(a_0 + t)\},$$



where  $a_0 = 25$  is the starting age of the cohort. Instead of iterating through the mortality hazard rates, we obtain a vector of background mortality hazard rates for the ages of interest between 25 through 100 by subsetting  $\mu(a)$  (R variable name `v_r_mort_by_age`) for these ages. We transform the resulting R variable, `v_r_HDage`, to a probability.

```
# Age-specific mortality rate in the Healthy state (background mortality)
v_r_HDage <- v_r_mort_by_age[(n_age_init + 1) + 0:(n_cycles - 1)]
# Transform to age-specific background mortality risk
v_p_HDage <- 1 - exp(-v_r_HDage)
```

Because mortality in S1 and S2 are relative to background mortality, adding age dependency to background mortality results in age-dependent mortality in S1 and S2 as well as in H. To generate the age-specific mortality in S1 and S2, we multiply the age-specific background mortality rate, `v_r_HDage`, by the constant hazard ratios `hr_S1` and `hr_S2`, respectively. We then convert the resulting age-specific mortality rates to probabilities.

```
## Age-specific mortality rates in the Sick and Sicker states
v_r_S1Dage <- v_r_HDage * hr_S1 # when Sick
v_r_S2Dage <- v_r_HDage * hr_S2 # when Sicker
## Age-specific probabilities of dying in the Sick and Sicker states
v_p_S1Dage <- 1 - exp(-v_r_S1Dage) # when Sick
v_p_S2Dage <- 1 - exp(-v_r_S2Dage) # when Sicker
```

To incorporate simulation-time dependency into the transition probability matrix, we expand the dimensions of the matrix and create a 3-dimensional transition probability array,  $\mathbf{P}$  and  $\mathbf{a\_P}$  in R, of dimensions  $n_S \times n_S \times n_T$ . The first two dimensions of this array correspond to transitions between states and the third dimension to time. The  $t$ -th element in the third dimension corresponds to the transition probability matrix at cycle  $t$ . A visual representation of  $\mathbf{a\_P}$  is shown in Figure 2.

$$\mathbf{a\_P} = \begin{matrix} & \begin{matrix} \nearrow n_t \\ \nearrow n_s \end{matrix} & \begin{bmatrix} p_{[H,H,n_t]} & p_{[H,S1,n_t]} & p_{[H,S2,n_t]} & p_{[H,D,n_t]} \\ p_{[H,H,2]} & p_{[H,S1,2]} & p_{[H,S2,2]} & p_{[H,D,2]} \\ p_{[S1,H,1]} & p_{[S1,S1,1]} & p_{[S1,S2,1]} & p_{[S1,D,1]} & p_{[S1,D,2]} & p_{[S1,D,n_t]} \\ p_{[S2,H,1]} & p_{[S2,S1,1]} & p_{[S2,S2,1]} & p_{[S2,D,1]} & p_{[S2,D,2]} & p_{[S2,D,n_t]} \\ p_{[D,H,1]} & p_{[D,S1,1]} & p_{[D,S2,1]} & p_{[D,D,1]} & p_{[D,D,2]} & p_{[D,D,n_t]} \end{bmatrix} \end{matrix}$$

Figure 2: A 3-dimensional representation of the transition probability array of the Sick-Sicker model with simulation-time dependency.

First, we initialize  $\mathbf{a\_P}$  with a default value of zero for all transition probabilities.

```
# Initialize the transition probability array
a_P <- array(0, dim = c(n_states, n_states, n_cycles),
             dimnames = list(v_names_states, v_names_states, 0:(n_cycles - 1)))
```

Filling `a_P` with the corresponding transition probabilities of the cohort under the SoC strategy is comparable with filling `m_P` for a time-independent cSTM, accounting for the time dimension, which is represented by the third dimension of the array. However, this requires a slight modification of the code from the time-independent cSTM. The code below illustrates how to assign age-dependent transition probabilities in the third dimension of the array. For constant transitions over time, we only need to provide one value for the transition probability. R replicates the value of such transitions as many times as the number of cycles ( $n_T + 1$  times in our example).

```
### Fill in array
## From H
a_P["H", "H", ] <- (1 - v_p_HDage) * (1 - p_HS1)
a_P["H", "S1", ] <- (1 - v_p_HDage) * p_HS1
a_P["H", "D", ] <- v_p_HDage
## From S1
a_P["S1", "H", ] <- (1 - v_p_S1Dage) * p_S1H
a_P["S1", "S1", ] <- (1 - v_p_S1Dage) * (1 - (p_S1H + p_S1S2))
a_P["S1", "S2", ] <- (1 - v_p_S1Dage) * p_S1S2
a_P["S1", "D", ] <- v_p_S1Dage
## From S2
a_P["S2", "S2", ] <- 1 - v_p_S2Dage
a_P["S2", "D", ] <- v_p_S2Dage
## From D
a_P["D", "D", ] <- 1
```

As mentioned above, each slice along the third dimension of `a_P` corresponds to a transition probability matrix. For example, the transition matrix for 25-year-olds in the Sick-Sicker model under the SoC strategy can be retrieved using:

```
a_P[, , 1]
```

```
##           H           S1           S2           D
## H  0.8491385 0.1498480 0.0000000 0.001013486
## S1 0.4984813 0.3938002 0.1046811 0.003037378
## S2 0.0000000 0.0000000 0.9899112 0.010088764
## D  0.0000000 0.0000000 0.0000000 1.000000000
```

Similar to the time-independent cSTM, treatment A does not change the transition probabilities. For treatment B, we first initialize the three-dimensional array of transition probabilities, `a_P_trtB` as a copy of `a_P` and update only the probability of remaining in S1 and the transition probability from S1 to S2 (i.e., `p_S1S2` is replaced with `p_S1S2_trtB`).

```

## Initialize transition probability array for treatment B
a_P_trtB <- a_P
## Update only transition probabilities from S1 involving p_S1S2
a_P_trtB["S1", "S1", ] <- (1 - v_p_S1Dage) * (1 - (p_S1H + p_S1S2_trtB))
a_P_trtB["S1", "S2", ] <- (1 - v_p_S1Dage) * p_S1S2_trtB

```

Once we create the transition probability arrays, we check they are valid (i.e., ensuring transition probabilities are between 0 and 1, and transition probabilities from each state sum to 1) using the functions `check_sum_of_transition_array` and `check_transition_probability`, provided in the `darthtools` package (<https://github.com/DARTH-git/darthtools>).

```

### Check if transition probability matrices are valid
## Check that transition probabilities are [0, 1]
check_transition_probability(a_P)
check_transition_probability(a_P_trtB)
## Check that all rows sum to 1
check_sum_of_transition_array(a_P,      n_states = n_states, n_cycles = n_cycles)
check_sum_of_transition_array(a_P_trtB, n_states = n_states, n_cycles = n_cycles)

```

In the Sick-Sicker model, the entire cohort starts in the Healthy state. Therefore, we create the  $1 \times n_S$  initial state vector `v_s_init` with all of the cohort assigned to the H state:

```

v_s_init <- c(H = 1, S1 = 0, S2 = 0, D = 0) # initial state vector
v_s_init
# H S1 S2 D
# 1 0 0 0

```

We use the variable `v_s_init` to initialize  $M$  represented by `m_M` for the cohorts under SoC strategy and strategy A because the transition probabilities are the same under both strategies, and by `m_M_trtB` for the cohorts under strategies B and AB because both transition probabilities under both strategies are affected by treatment B. Note that the initial state vector, `v_s_init`, can be modified to account for the distribution of the cohort across the states at the start of the simulation and might vary by strategy. To simulate the cohort over the  $n_T$  cycles for the simulation-time-dependent cSTM, we initialize two new cohort trace matrices `m_M_ad` and `m_M_ad_trtB`.

```

## Initialize cohort trace for age-dependent (ad) cSTM under SoC
m_M_ad <- matrix(NA,
                 nrow = (n_cycles + 1), ncol = n_states,
                 dimnames = list(0:n_cycles, v_names_states))
# Store the initial state vector in the first row of the cohort trace
m_M_ad[1, ] <- v_s_init
## Initialize cohort trace under treatment B
m_M_ad_trtB <- m_M_ad # structure and initial states remain the same.

```

We then use the matrix product to get the state vector at cycle  $t$ . This equation is similar to the one described for the time-independent model. The only modification required is to index the transition probability arrays

$a_P$  and  $a_{P\_trtB}$  by  $t$  to obtain the cycle-specific transition probability matrices.

```
# Iterative solution of age-dependent cSTM
for(t in 1:n_cycles){
  # For SoC
  m_M_ad[t + 1, ] <- m_M_ad[t, ] %*% a_P[, , t]
  # For treatment B
  m_M_ad_trtB[t + 1, ] <- m_M_ad_trtB[t, ] %*% a_P_trtB[, , t]
}
```

A graphical representation of the cohort trace for all cycles of the age-dependent cSTM under strategies SoC and A is shown in Figure 3.

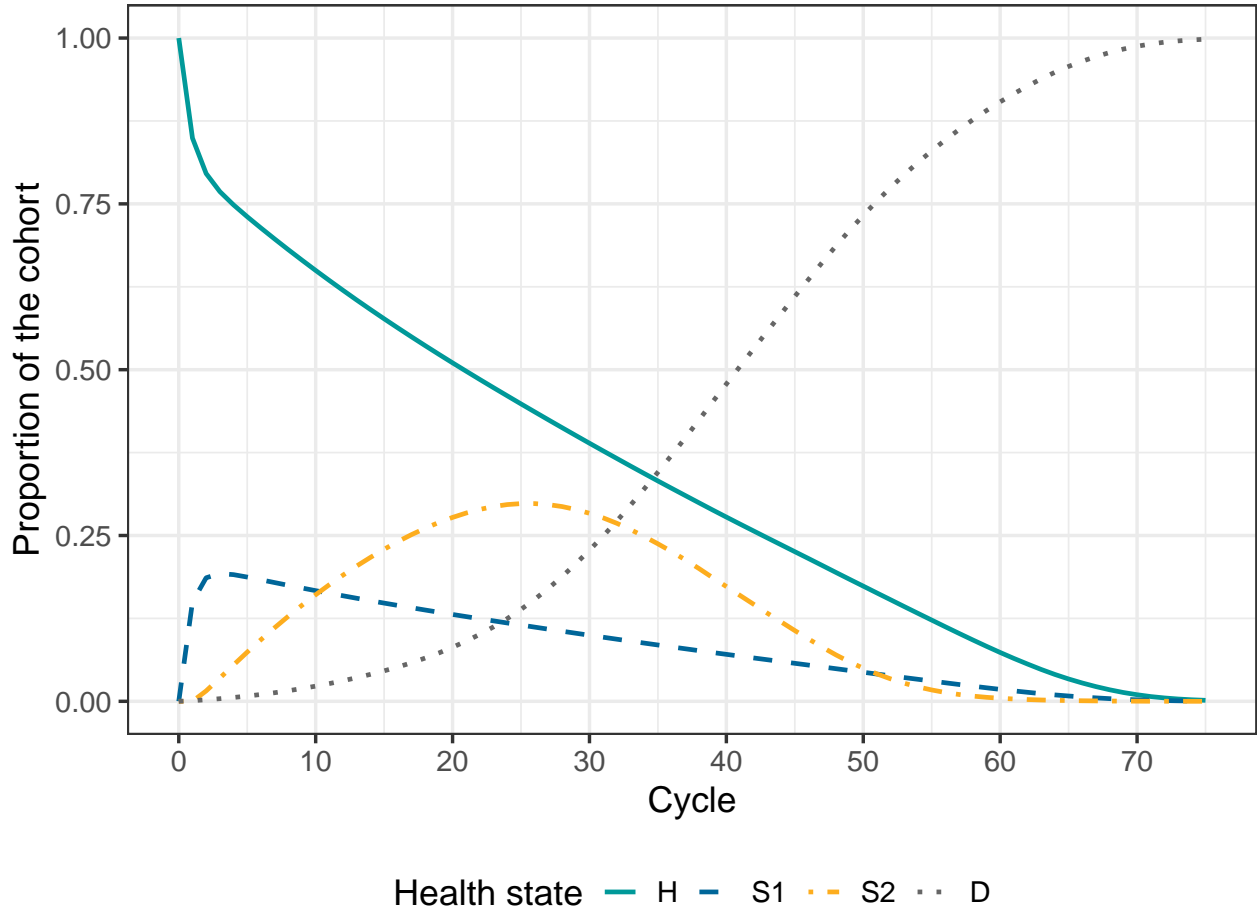


Figure 3: Cohort trace of the age-dependent cSTM under strategies SoC and A.

### 3.2 Time dependency on state residence

To add a state-residence dependency to the simulation-time-dependent Sick-Sicker model defined above, we assume the risk of progression from S1 to S2 increases the longer the cohort remains in the S1 state. This increase follows a Weibull hazard function, defined as

$$p_{[S1\tau, S2, \tau]} = \lambda \gamma \tau^{(\lambda-1)},$$

where  $\tau = 1, \dots, n_{\text{tunnels}}$  represents the duration that the cohort has been in S1, and  $\lambda$  and  $\gamma$  are the scale and shape parameters of the Weibull function, respectively. We assume that state-residence dependency affects the cohort in the S1 state throughout the whole simulation (i.e.,  $n_{\text{tunnels}} = n_T$ ) and create a new variable called `n_tunnel_size` with the length of the tunnel equal to `n_cycles`. Thus, there will be 75 S1 tunnel states plus 3 more states (H, S2, D) resulting in a total of  $n_{S_{\text{tunnels}}} = 78$ .

Figure 4 shows the Sick-Sicker model's state-transition diagram with state-residence dependency with  $n_{\text{tunnels}}$  tunnel states for S1.

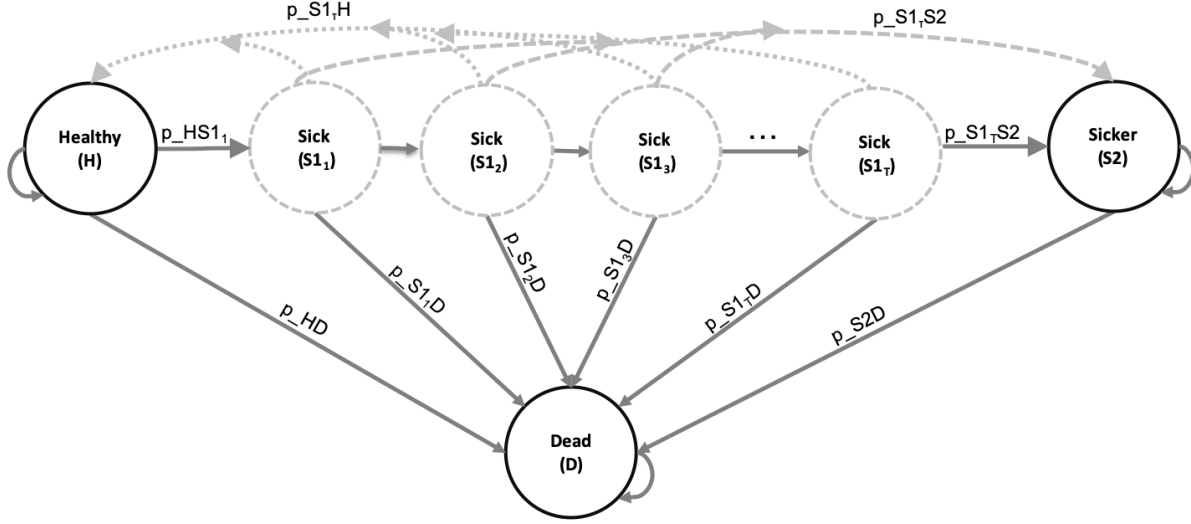


Figure 4: State-transition diagram of the Sick-Sicker model with tunnel states expanding the Sick state ( $S1_1, S1_2, \dots, S1_{n_{\text{exttunnels}}}$ ).

To implement state-residence dependency in the Sick-Sicker, we create the vector variables `v_Sick_tunnel` and `v_names_states_tunnels` with the names of the Sick tunnel states' and all the states of the cSTM, including tunnels, respectively, and use the parameters listed in Table 1.

```
## Number of tunnels
n_tunnel_size <- n_cycles
## Name for tunnel states of Sick state
v_Sick_tunnel <- paste("S1_", seq(1, n_tunnel_size), "Yr", sep = "")
## Create variables for model with tunnels
v_names_states_tunnels <- c("H", v_Sick_tunnel, "S2", "D") # state names
n_states_tunnels <- length(v_names_states_tunnels)          # number of states
## Initialize first cycle of Markov trace accounting for the tunnels
v_s_init_tunnels <- c(1, rep(0, n_tunnel_size), 0, 0)
```

Based on the updated parameters, the state-residence-dependent transition probability from Sick to Sicker based on a Weibull function, `v_p_S1S2_tunnels`, is:

```

# Weibull parameters
p_S1S2_scale <- 0.08 # scale
p_S1S2_shape <- 1.1 # shape
# Weibull function
v_p_S1S2_tunnels <- p_S1S2_scale * p_S1S2_shape *
  (1:n_tunnel_size)^(p_S1S2_shape-1)

```

To adapt the 3-dimensional transition probability array to incorporate both age and state-residence dependence in the Sick-Sicker model under SoC, we first create an expanded 3-dimensional array accounting for tunnels, `a_P_tunnels`. The dimensions of this array are  $n_{S_{\text{tunnels}}} \times n_{S_{\text{tunnels}}} \times n_T$ . A visual representation of `a_P_tunnels` of the Sick-Sicker model with tunnel states expanding the Sick state is shown in Figure 5.

```

# Initialize array
a_P_tunnels <- array(0, dim = c(n_states_tunnels, n_states_tunnels, n_cycles),
  dimnames = list(v_names_states_tunnels,
    v_names_states_tunnels,
    0:(n_cycles - 1)))

```

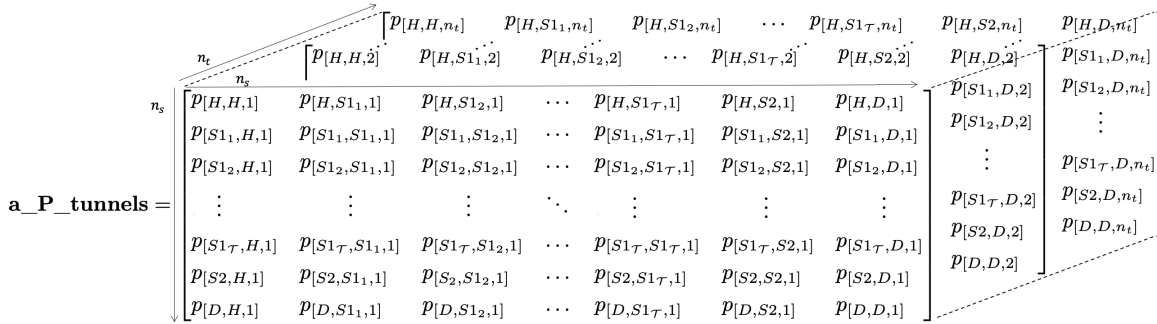


Figure 5: The 3-dimensional transition probability array of the Sick-Sicker model expanded to account for age-dependence and S1 state-residence using tunnel states.

Filling `a_P_tunnels` with the corresponding transition probabilities is similar to how it's done with `a_P` above, with the difference being that we now fill the transition probabilities from all the tunnel states by iterating through all the tunnel states and assigning the corresponding disease progression transition probabilities.

```

### Fill in array
## From H
a_P_tunnels["H", "H", ] <- (1 - v_p_HDage) * (1 - p_HS1)
a_P_tunnels["H", v_Sick_tunnel[1], ] <- (1 - v_p_HDage) * p_HS1
a_P_tunnels["H", "D", ] <- v_p_HDage
## From S1
for(i in 1:(n_tunnel_size - 1)){
  a_P_tunnels[v_Sick_tunnel[i], "H", ] <- (1 - v_p_S1Dage) * p_S1H
  a_P_tunnels[v_Sick_tunnel[i],
    v_Sick_tunnel[i + 1], ] <- (1 - v_p_S1Dage) *

```

```

                                (1 - (p_S1H + v_p_S1S2_tunnels[i]))
a_P_tunnels[v_Sick_tunnel[i], "S2", ] <- (1 - v_p_S1Dage) * v_p_S1S2_tunnels[i]
a_P_tunnels[v_Sick_tunnel[i], "D", ] <- v_p_S1Dage
}
# Repeat code for the last cycle to force the cohort stay in the last tunnel state of Sick
a_P_tunnels[v_Sick_tunnel[n_tunnel_size], "H", ] <- (1 - v_p_S1Dage) * p_S1H
a_P_tunnels[v_Sick_tunnel[n_tunnel_size],
            v_Sick_tunnel[n_tunnel_size], ] <- (1 - v_p_S1Dage) *
            (1 - (p_S1H + v_p_S1S2_tunnels[n_tunnel_size]))
a_P_tunnels[v_Sick_tunnel[n_tunnel_size], "S2", ] <- (1 - v_p_S1Dage) *
            v_p_S1S2_tunnels[n_tunnel_size]
a_P_tunnels[v_Sick_tunnel[n_tunnel_size], "D", ] <- v_p_S1Dage
### From S2
a_P_tunnels["S2", "S2", ] <- 1 - v_p_S2Dage
a_P_tunnels["S2", "D", ] <- v_p_S2Dage
# From D
a_P_tunnels["D", "D", ] <- 1

```

Accounting for the effectiveness of treatment B is done similarly to the simulation-time-dependent approach above. We first transform `v_p_S1S2_tunnels` to a vector of rates, `v_r_S1S2_tunnels`, assuming exponentially distributed transitions across the tunnel states, and multiply it by the hazard ratio of treatment B. Then, we transform back to probabilities to produce `v_p_S1S2_tunnels_trtB`, a vector of transition probabilities that account for the duration of S1 state-residence under treatment B.

```

## Transform risk of progression from Sick to Sicker to a rate
# vector of rates of becoming Sicker when Sick
v_r_S1S2_tunnels <- -log(1-v_p_S1S2_tunnels)/cycle_length
# apply hazard ratio to rate to obtain transition rate of becoming Sicker when
# Sick for treatment B
r_S1S2_tunnels_trtB <- v_r_S1S2_tunnels * hr_S1S2_trtB
# transform rate to probability to become Sicker when Sick under treatment B
# conditional on surviving
v_p_S1S2_tunnels_trtB <- 1-exp(-r_S1S2_tunnels_trtB*cycle_length)

```

Then, we initialize the three-dimensional transition probability array for treatment B, `a_P_tunnels_trtB`, based on `a_P_tunnels`. The only difference is that we update the transition probabilities from S1 involving `v_p_S1S2_tunnels` to using `v_p_S1S2_tunnels_trtB` instead.

```

## Initialize transition probability array for treatment B
a_P_tunnels_trtB <- a_P_tunnels
## Update only transition probabilities from S1 involving v_p_S1S2_tunnels
for(i in 1:(n_tunnel_size - 1)){
  a_P_tunnels_trtB[v_Sick_tunnel[i], "H", ] <- (1 - v_p_S1Dage) * p_S1H
  a_P_tunnels_trtB[v_Sick_tunnel[i],
                  v_Sick_tunnel[i + 1], ] <- (1 - v_p_S1Dage) *

```

```

                                (1 - (p_S1H + v_p_S1S2_tunnels_trtB[i]))
a_P_tunnels_trtB[v_Sick_tunnel[i], "S2", ] <- (1 - v_p_S1Dage) * v_p_S1S2_tunnels_trtB[i]
a_P_tunnels_trtB[v_Sick_tunnel[i], "D", ] <- v_p_S1Dage
}
# repeat code for the last cycle to force the cohort stay in the last tunnel state of Sick
a_P_tunnels_trtB[v_Sick_tunnel[n_tunnel_size], "H", ] <- (1 - v_p_S1Dage) * p_S1H
a_P_tunnels_trtB[v_Sick_tunnel[n_tunnel_size],
                v_Sick_tunnel[n_tunnel_size], ] <- (1 - v_p_S1Dage) *
                (1 - (p_S1H + v_p_S1S2_tunnels_trtB[n_tunnel_size]))
a_P_tunnels_trtB[v_Sick_tunnel[n_tunnel_size], "S2", ] <- (1 - v_p_S1Dage) *
                v_p_S1S2_tunnels_trtB[n_tunnel_size]
a_P_tunnels_trtB[v_Sick_tunnel[n_tunnel_size], "D", ] <- v_p_S1Dage

```

Once we have created both three-dimensional transition probability arrays with tunnels, we check they are valid (i.e., between 0 and 1 and transition probabilities from each state sum to 1).

```

### Check if transition probability matrices are valid
## Check that transition probabilities are [0, 1]
check_transition_probability(a_P_tunnels)
check_transition_probability(a_P_tunnels_trtB)
## Check that all rows sum to 1
check_sum_of_transition_array(a_P_tunnels,      n_states = n_states_tunnels,
                             n_cycles = n_cycles)
check_sum_of_transition_array(a_P_tunnels_trtB, n_states = n_states_tunnels,
                             n_cycles = n_cycles)

```

To simulate the cohort over the  $n_T$  cycles for the cSTM accounting for state-residence dependency, we initialize two new cohort trace matrices for the SoC and treatment B, `m_M_tunnels` and `m_M_tunnels_trtB`, respectively. The dimensions of both matrices are  $(n_T + 1) \times n_{S_{\text{tunnels}}}$ .

```

# Initialize cohort for state-residence cSTM under SoC
m_M_tunnels <- matrix(0,
                    nrow = (n_cycles + 1), ncol = n_states_tunnels,
                    dimnames = list(0:n_cycles, v_names_states_tunnels))
# Store the initial state vector in the first row of the cohort trace
m_M_tunnels[1, ] <- v_s_init_tunnels
## Initialize cohort trace under treatment B
m_M_tunnels_trtB <- m_M_tunnels

```

We then use the matrix product, similar to the simulation-time-dependent cSTM, to generate the full cohort trace.

```

# Iterative solution of state-residence-dependent cSTM
for(t in 1:n_cycles){
  # For SoC
  m_M_tunnels[t + 1, ] <- m_M_tunnels[t, ] %*% a_P_tunnels[, , t]

```



```

# Under treatment B
m_M_tunnels_trtB[t + 1,] <- m_M_tunnels_trtB[t, ] %*% a_P_tunnels_trtB[, , t]
}

```

To compute a summarized cohort trace to capture occupancy in the H, S1, S2, D states under SoC, we aggregate over the tunnel states in each cycle (Figure 6).

```

# Create aggregated trace
m_M_tunnels_sum <- cbind(H = m_M_tunnels[, "H"],
                        S1 = rowSums(m_M_tunnels[, which(v_names_states=="S1"):
                                      (n_tunnel_size + 1)]),
                        S2 = m_M_tunnels[, "S2"],
                        D = m_M_tunnels[, "D"])

```

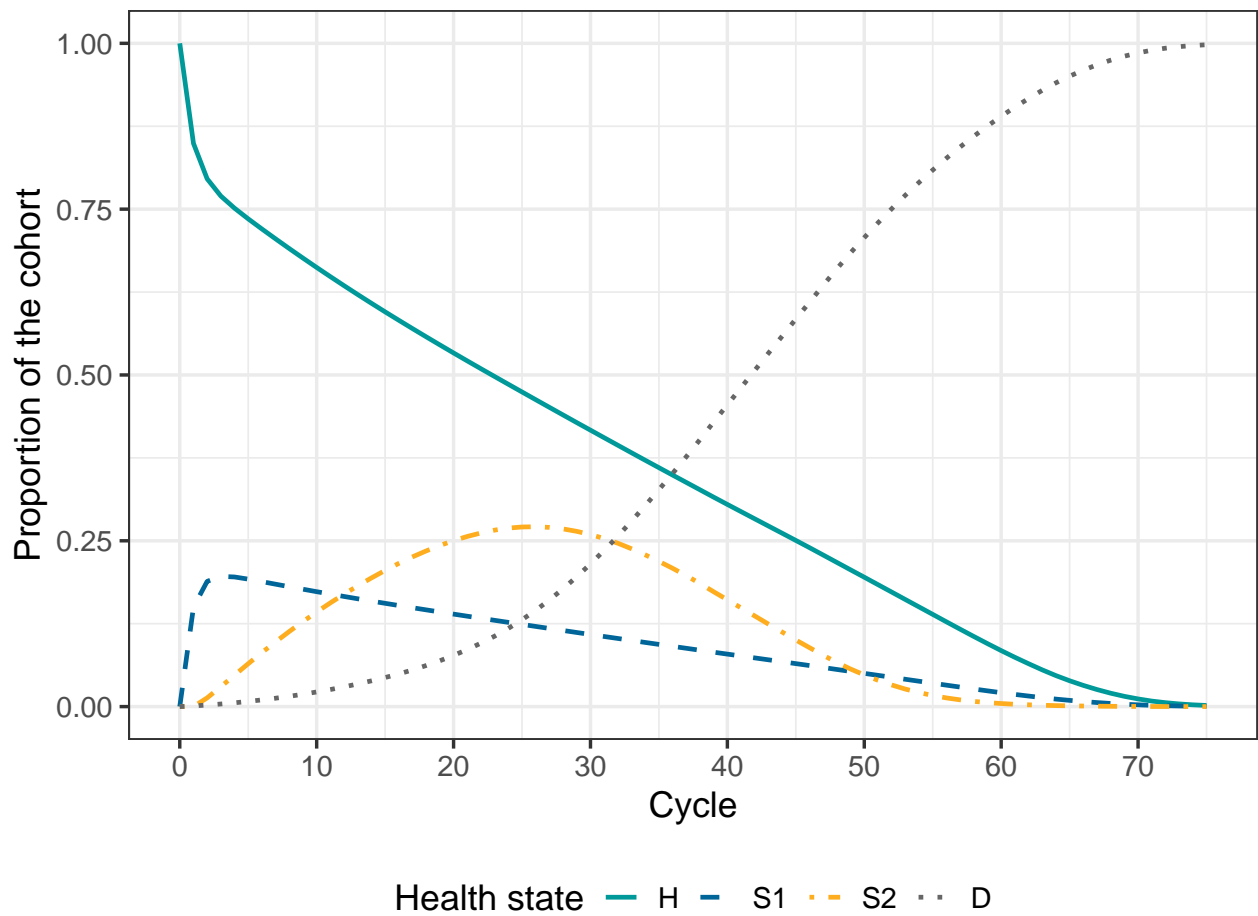


Figure 6: Cohort trace of the age-dependent cSTM accounting for state-residence dependency under strategies SoC and A.

## 4 Epidemiological and economic outputs

cSTMs can be used to generate different epidemiological and economic outputs. In a CEA, the main outcomes are typically the total discounted expected QALYs and total costs accrued by the cohort over the

predefined time horizon. However, epidemiological outcomes can be helpful for complementary analyses, such as calibration and validation. Some common epidemiological outcomes include survival, prevalence, incidence, the average number of events, and lifetime risk of events.<sup>14</sup> We show how to obtain some of these outcomes from the trace and transition probability objects.

## 4.1 Epidemiological measures

Here we provide the epidemiological definition of some of these outcomes and how they can be generated from a cSTM using the simulation-time-dependent Sick-Sicker cSTM under SoC. In the GitHub repository, we provide the code to generate these outcomes from the state-residence-dependent cSTM.

### 4.1.1 Survival probability

The survival probability,  $S(t)$ , captures the proportion of the cohort remaining alive by cycle  $t$ . To estimate  $S(t)$  from the simulated cohort of the simulation-time-dependent Sick-Sicker model, shown in Figure 7, we sum the proportions of the non-death states for all  $n_T$  cycles in `m_M_ad`.

```
v_S_ad <- rowSums(m_M_ad[, -which(v_names_states == "D")]) # vector with survival curve
```

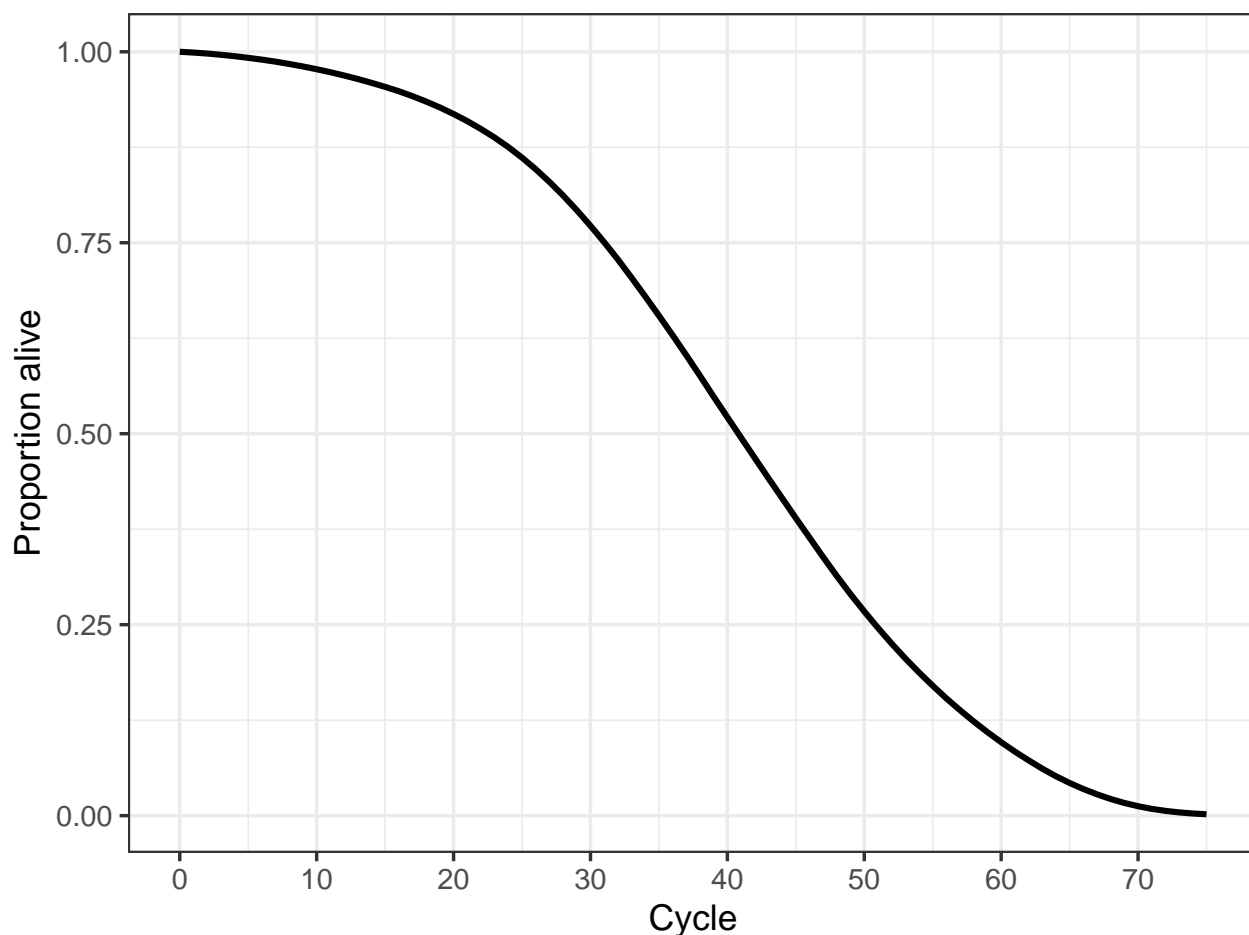


Figure 7: Survival curve of the age-dependent cSTM

### 4.1.2 Life expectancy

Life expectancy (LE) refers to the expected number of time units remaining to be alive.<sup>15</sup> In continuous-time, LE is the area under the entire survival curve.<sup>16</sup>

$$LE = \int_{t=0}^{\infty} S(t)dt.$$

In discrete-time using cSTMs, we often calculate restricted LE over a fixed time horizon (e.g.,  $n_T$ ) at which most of the cohort has transitioned to the Dead state and is defined as

$$LE = \sum_{t=0}^{n_T} S(t).$$

In the simulation-time-dependent Sick-Sicker model, where we simulated a cohort over  $n_T=75$  cycles, life expectancy `le_ad` is 41.2 cycles, which is calculated as

```
le_ad <- sum(v_S_ad) # life expectancy
```

Note that this equation expresses LE in the units of  $t$ . We use an annual cycle length; thus, the resulting LE will be in years. Analysts can also use other cycle lengths (e.g., monthly or daily), but the LE must be correctly converted to the desired unit if different than the cycle length units.

### 4.1.3 Prevalence

Prevalence is defined as the proportion of the population or cohort with a specific condition (or being in a particular health state) among those alive.<sup>17</sup> To calculate the prevalence of S1 at cycle  $t$ ,  $\text{prev}(t)_i$ , we compute the ratio between the proportion of the cohort in S1 and the proportion alive at that cycle.<sup>18</sup> The proportion of the cohort alive is given by the survival probability  $S(t)$  defined above. The individual prevalence of the S1 and S2 health states and the overall prevalence of sick individuals (i.e., S1 + S2) of the age-dependent Sick-Sicker cSTM at each cycle  $t$  is computed as follows and are shown in Figure 8.

```
v_prev_S1    <- m_M_ad[, "S1"] / v_S_ad          # vector with prevalence of Sick
v_prev_S2    <- m_M_ad[, "S2"] / v_S_ad          # vector with prevalence of Sicker
v_prev_S1S2  <- rowSums(m_M_ad[, c("S1", "S2")]) / v_S_ad # prevalence of Sick and Sicker
```

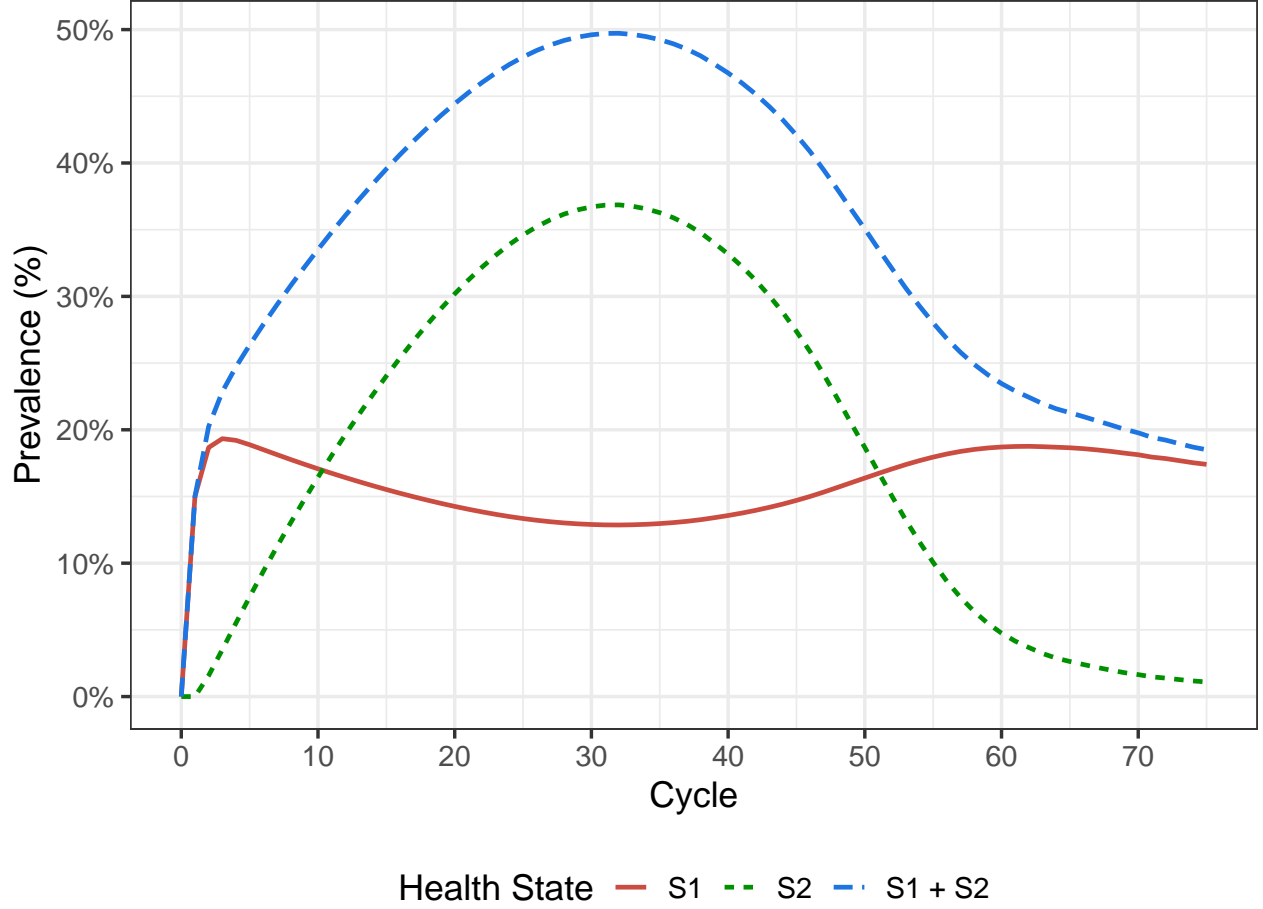


Figure 8: Prevalence of sick states in age-dependent cSTM

## 4.2 Economic outcomes

In CEA, we can calculate economic outcomes by using either state or transition rewards. A “state reward” refers to a value assigned to individuals for being in a given state. In a cost-utility context, these could be either utilities or costs associated with remaining in a specific health state for one cycle. In the accompanying tutorial, we describe how to incorporate state rewards in CEA.<sup>7</sup> A “transition reward” refers to the increase or decrease in either costs or utilities of transitioning from one state to another, which may be associated with a one-time cost or utility impact.

### 4.2.1 State rewards

For the Sick-Sicker model, we create a vector of utilities and costs for each of the four strategies considered. The vectors of utilities and costs,  $v\_u\_SoC$  and  $v\_c\_SoC$ , respectively, contain the utilities and costs corresponding with being in each of the four health states under SoC which are shown in Table 2.

```
# Vector of state utilities under SOC
v_u_SoC <- c(H = u_H, S1 = u_S1, S2 = u_S2, D = u_D)
# Vector of state costs under SoC
v_c_SoC <- c(H = c_H, S1 = c_S1, S2 = c_S2, D = c_D)
```

We account for the benefits and costs of both treatments individually and their combination to create the state-reward vectors under treatments A and B (strategies A and B, respectively) and when applied jointly (strategy AB). Only treatment A affects QoL, so we create a vector of utilities for strategy A,  $v\_u\_strA$ , where we substitute the utility of being in S1 under SoC,  $u\_S1$ , with the utility associated with the benefit of treatment A in being in that state,  $u\_trtA$ . Treatment B does not affect QoL, so the vector of utilities for strategy B,  $v\_u\_strB$ , is the same as for SoC. However, when both treatments A and B are applied jointly (strategy AB), the resulting vector of utilities  $v\_u\_strAB$  equals that of strategy A.

```
# Vector of state utilities for strategy A
v_u_strA <- c(H = u_H, S1 = u_trtA, S2 = u_S2, D = u_D)
# Vector of state utilities for strategy B
v_u_strB <- v_u_SoC
# Vector of state utilities for strategy AB
v_u_strAB <- v_u_strA
```

Both treatments A and B incur a cost. To create the vector of state costs for strategy A,  $v\_c\_strA$ , we add the cost of treatment A,  $c\_trtA$ , to the state costs of S1 and S2. Similarly, when constructing the vector of state costs for strategy B,  $v\_c\_strB$ , we add the cost of treatment B,  $c\_trtB$ , to the state costs of S1 and S2. Finally, for the vector of state costs for strategy AB,  $v\_c\_strAB$ , we add both treatment costs to the state costs of S1 and S2.

```
# Vector of state costs for strategy A
v_c_strA <- c(H = c_H,
             S1 = c_S1 + c_trtA,
             S2 = c_S2 + c_trtA,
             D = c_D)
# Vector of state costs for strategy B
v_c_strB <- c(H = c_H,
             S1 = c_S1 + c_trtB,
             S2 = c_S2 + c_trtB,
             D = c_D)
# Vector of state costs for strategy AB
v_c_strAB <- c(H = c_H,
              S1 = c_S1 + (c_trtA + c_trtB),
              S2 = c_S2 + (c_trtA + c_trtB),
              D = c_D)
```

#### 4.2.2 Transition rewards

In the Sick-Sicker model, we previously mentioned that dying (i.e., transitioning to the Dead state) incurs a one-time cost of \$2,000 that reflects the acute care that might be received immediately preceding death. This one-time cost could include emergency services, hospitalization, or other healthcare utilization to address the ultimately fatal health complication. We also have a utility decrement and a cost increment on the transition from H to S1. Whereas the cost and utility of S1 reflect the cost and utility of being chronically sick, respectively, transition rewards capture the short-term impact of the acute events of becoming sick, such

as hospitalization, stabilization, and so on.

Incorporating transition rewards requires keeping track of the proportion of the cohort that transitions between health states in each cycle while capturing what the states of origin and destination are. The cohort trace,  $M$ , does not capture this information. However, recovering this information is relatively straightforward and has been described in detail by Krijkamp et al. (2020).<sup>19</sup> Briefly, this approach involves changing the core computation in a traditional cSTM, from  $m_t P_t$  to  $\text{diag}(m_t) P_t$ . This simple change allows us to compute the proportion of the cohort that transitions between the states of origin and destination in cycle  $t$ . The result is no longer a cohort trace matrix, but rather a three-dimensional array that we refer to as a transition-dynamics array ( $\mathbf{A}$ ) with dimensions  $n_S \times n_S \times [n_T + 1]$ . The  $t$ -th slice of  $\mathbf{A}$ ,  $A_t$ , is a matrix that stores the proportion of the population that transition between states of origin and destination between cycles  $t - 1$  and  $t$ . Similarly, we define the transition rewards by the states of origin and destination.

To account for both state and transition rewards, create a *matrix* of rewards  $R_t$  of dimensions  $n_S \times n_S$ . The off-diagonal entries of  $R_t$  store the transition rewards, and the diagonal of  $R_t$  stores the state rewards for cycle  $t$  and assumes that rewards occur at the beginning of the cycle.<sup>22</sup> Finally, we multiply this matrix by  $A_t$ , the  $t$ -th slice of  $A$ , apply discounting, within-cycle correction, and compute the overall reward for each strategy outcome. Below, we illustrate these concepts in R.

To compute  $\mathbf{A}$  for the age-dependent Sick-Sicker model under SOC, we initialize a three-dimensional array `a_A` of dimensions  $n_S \times n_S \times [n_T + 1]$  and set the diagonal of the first slice to the initial state vector `v_s_init`. We create a three-dimensional array for the cohort under treatment B, `a_A_trtB`, as a copy of the array under SoC.

```
# Initialize transition-dynamics array under SoC
a_A <- array(0,
             dim = c(n_states, n_states, (n_cycles + 1)),
             dimnames = list(v_names_states, v_names_states, 0:n_cycles))
# Set first slice to the initial state vector in its diagonal
diag(a_A[, , 1]) <- v_s_init
# Initialize transition-dynamics array under treatment B
a_A_trtB <- a_A
```

We then compute a matrix multiplication between a diagonal matrix of each of the  $t$ -th rows of the cohort trace matrix under SoC and treatment B, denoted as `diag(m_M_ad[t, ])` and `diag(m_M_ad_trtB[t, ])`, by the  $t$ -th matrix of the array of transition matrices, `a_P[, , t]` and `a_P_trtB[, , t]`, respectively, over all  $n_T$  cycles.

```
# Iterative solution to produce the transition-dynamics array
for (t in 1:n_cycles){
  # For SoC
  a_A[, , t + 1] <- diag(m_M_ad[t, ]) %*% a_P[, , t]
  # For treatment B
  a_A_trtB[, , t + 1] <- m_M_ad_trtB[t, ] * a_P_trtB[, , t]
}
```

To create the arrays of rewards for costs and utilities for the age-dependent Sick-Sicker cSTM, we create

strategy-specific three-dimensional arrays of rewards and fill each of their rows across the third dimension with the vector of state rewards.

```
# Arrays of state and transition rewards
# Utilities under SoC
a_R_u_SoC <- array(matrix(v_u_SoC, nrow = n_states, ncol = n_states, byrow = T),
                    dim = c(n_states, n_states, n_cycles + 1),
                    dimnames = list(v_names_states, v_names_states, 0:n_cycles))
# Costs under SoC
a_R_c_SoC <- array(matrix(v_c_SoC, nrow = n_states, ncol = n_states, byrow = T),
                    dim = c(n_states, n_states, n_cycles + 1),
                    dimnames = list(v_names_states, v_names_states, 0:n_cycles))
# Utilities under Strategy A
a_R_u_strA <- array(matrix(v_u_strA, nrow = n_states, ncol = n_states, byrow = T),
                    dim = c(n_states, n_states, n_cycles + 1),
                    dimnames = list(v_names_states, v_names_states, 0:n_cycles))
# Costs under Strategy A
a_R_c_strA <- array(matrix(v_c_strA, nrow = n_states, ncol = n_states, byrow = T),
                    dim = c(n_states, n_states, n_cycles + 1),
                    dimnames = list(v_names_states, v_names_states, 0:n_cycles))
# Utilities under Strategy B
a_R_u_strB <- array(matrix(v_u_strB, nrow = n_states, ncol = n_states, byrow = T),
                    dim = c(n_states, n_states, n_cycles + 1),
                    dimnames = list(v_names_states, v_names_states, 0:n_cycles))
# Costs under Strategy B
a_R_c_strB <- array(matrix(v_c_strB, nrow = n_states, ncol = n_states, byrow = T),
                    dim = c(n_states, n_states, n_cycles + 1),
                    dimnames = list(v_names_states, v_names_states, 0:n_cycles))
# Utilities under Strategy AB
a_R_u_strAB <- array(matrix(v_u_strAB, nrow = n_states, ncol = n_states, byrow = T),
                     dim = c(n_states, n_states, n_cycles + 1),
                     dimnames = list(v_names_states, v_names_states, 0:n_cycles))
# Costs under Strategy AB
a_R_c_strAB <- array(matrix(v_c_strAB, nrow = n_states, ncol = n_states, byrow = T),
                     dim = c(n_states, n_states, n_cycles + 1),
                     dimnames = list(v_names_states, v_names_states, 0:n_cycles))
```

To account for the transition rewards, we either add or subtract them in the corresponding location of the reward matrix representing the transitions of interest. For example, to account for the disutility of transitioning from H to S1 for strategy A, we subtract the disutility to the entry of the array of rewards corresponding to the transition from H to S1 across all cycles.

```
# Add disutility due to transition from Healthy to Sick
a_R_u_strA["H", "S1", ] <- a_R_u_strA["H", "S1", ] - du_HS1
```

In a similar approach, we add the costs of transitioning from H to S1 and the cost of dying for strategy A.

```
# Add transition cost due to transition from Healthy to Sick
a_R_c_strA["H", "S1", ] <- a_R_c_strA["H", "S1", ] + ic_HS1
# Add transition cost of dying from all non-dead states
a_R_c_strA[-n_states, "D", ] <- a_R_c_strA[-n_states, "D", ] + ic_D
a_R_c_strA[, , 1]
```

```
##      H      S1      S2      D
## H  2000 17000 27000 2000
## S1 2000 16000 27000 2000
## S2 2000 16000 27000 2000
## D  2000 16000 27000    0
```

Below, we show how to add the transition rewards to the reward matrices corresponding to SoC and strategies B and AB.

```
## SoC
# Add disutility due to transition from H to S1
a_R_u_SoC["H", "S1", ] <- a_R_u_SoC["H", "S1", ] - du_HS1
# Add transition cost due to transition from H to S1
a_R_c_SoC["H", "S1", ] <- a_R_c_SoC["H", "S1", ] + ic_HS1
# Add transition cost of dying from all non-dead states
a_R_c_SoC[-n_states, "D", ] <- a_R_c_SoC[-n_states, "D", ] + ic_D

## Strategy B
# Add disutility due to transition from Healthy to Sick
a_R_u_strB["H", "S1", ] <- a_R_u_strB["H", "S1", ] - du_HS1
# Add transition cost due to transition from Healthy to Sick
a_R_c_strB["H", "S1", ] <- a_R_c_strB["H", "S1", ] + ic_HS1
# Add transition cost of dying from all non-dead states
a_R_c_strB[-n_states, "D", ] <- a_R_c_strB[-n_states, "D", ] + ic_D

## Strategy AB
# Add disutility due to transition from Healthy to Sick
a_R_u_strAB["H", "S1", ] <- a_R_u_strAB["H", "S1", ] - du_HS1
# Add transition cost due to transition from Healthy to Sick
a_R_c_strAB["H", "S1", ] <- a_R_c_strAB["H", "S1", ] + ic_HS1
# Add transition cost of dying from all non-dead states
a_R_c_strAB[-n_states, "D", ] <- a_R_c_strAB[-n_states, "D", ] + ic_D
```

The state and transition rewards are applied to the model dynamics by element-wise multiplication between **A** and **R**, indicated by the  $\odot$  sign, which produces the array of outputs for all  $n_T$  cycles, **Y**. Formally,

$$\mathbf{Y} = \mathbf{A} \odot \mathbf{R} \quad (2)$$



To obtain  $\mathbf{Y}$  for QALYs and costs for all four strategies, we apply Equation (2) by the element-wise multiplication of the transition array  $\mathbf{a}_A$  by the corresponding array of rewards.

```
# For SoC
a_Y_c_SoC <- a_A * a_R_c_SoC
a_Y_u_SoC <- a_A * a_R_u_SoC
# For Strategy A
a_Y_c_strA <- a_A * a_R_c_strA
a_Y_u_strA <- a_A * a_R_u_strA
# For Strategy B
a_Y_c_strB <- a_A_trtB * a_R_c_strB
a_Y_u_strB <- a_A_trtB * a_R_u_strB
# For Strategy AB
a_Y_c_strAB <- a_A_trtB * a_R_c_strAB
a_Y_u_strAB <- a_A_trtB * a_R_u_strAB
```

The total rewards for each health state at cycle  $t$ ,  $\mathbf{y}_t$ , is obtained by summing the rewards across all  $j = 1, \dots, n_S$  health states for all  $n_T$  cycles.

$$\mathbf{y}_t = \mathbf{1}^T \mathbf{Y}_t = \left[ \sum_{i=1}^{n_S} Y_{[i,1,t]}, \sum_{i=1}^{n_S} Y_{[i,2,t]}, \dots, \sum_{i=1}^{n_S} Y_{[i,n_S,t]} \right]. \quad (3)$$

To obtain the expected costs and QALYs per cycle for each strategy,  $\mathbf{y}$ , we apply Equation (3) again across all the matrices of the third dimension of  $\mathbf{Y}$  for all the outcomes.

```
# Vectors of rewards
# QALYs under SoC
v_qaly_SoC <- rowSums(t(colSums(a_Y_u_SoC)))
# Costs under SoC
v_cost_SoC <- rowSums(t(colSums(a_Y_c_SoC)))
# QALYs under Strategy A
v_qaly_strA <- rowSums(t(colSums(a_Y_u_strA)))
# Costs under Strategy A
v_cost_strA <- rowSums(t(colSums(a_Y_c_strA)))
# QALYs under Strategy B
v_qaly_strB <- rowSums(t(colSums(a_Y_u_strB)))
# Costs under Strategy B
v_cost_strB <- rowSums(t(colSums(a_Y_c_strB)))
# QALYs under Strategy AB
v_qaly_strAB <- rowSums(t(colSums(a_Y_u_strAB)))
# Costs under Strategy AB
v_cost_strAB <- rowSums(t(colSums(a_Y_c_strAB)))
```

### 4.2.3 Within-cycle correction and discounting future rewards

Following the accompanying tutorial,<sup>7</sup> here we use Simpson's 1/3rd rule as a WCC,<sup>21</sup> and use exponential discounting for costs and QALYs. The within-cycle correction vector, **wcc**, is the same for both costs and QALYs; thus, only one vector, **v\_wcc**, is required.

```
## Vector with cycles
v_cycles <- seq(1, n_cycles+1)
## Generate 2/3 and 4/3 multipliers for even and odd entries, respectively
v_wcc <- ((v_cycles %% 2)==0)*(2/3) + ((v_cycles %% 2)!=0)*(4/3)
## Substitute 1/3 in first and last entries
v_wcc[1] <- v_wcc[n_cycles + 1] <- 1/3
```

The discount vectors, **d**, for costs and QALYs for the Sick-Sicker model, **v\_dwc** and **v\_dwe**, respectively, are

```
# Discount weight for effects
v_dwe <- 1 / ((1 + d_e) ^ (0:(n_cycles)))
# Discount weight for costs
v_dwc <- 1 / ((1 + d_c) ^ (0:(n_cycles)))
```

To account for both discounting and within-cycle correction, we incorporate **wcc** in equation (4) using an element-wise multiplication with **d**, indicated by the  $\odot$  sign.

$$y = \mathbf{y}' (\mathbf{d} \odot \mathbf{wcc}). \quad (4)$$

The total expected discounted costs and QALYs under all four strategies accounting for within-cycle correction, **y**, is obtained by applying Equation (4) to the expected outcomes accounting for transition rewards.

```
### For SoC
## QALYs
n_tot_qaly_SoC <- t(v_qaly_SoC) %*% (v_dwe * v_wcc)
## Costs
n_tot_cost_SoC <- t(v_cost_SoC) %*% (v_dwc * v_wcc)
### For Strategy A
## QALYs
n_tot_qaly_strA <- t(v_qaly_strA) %*% (v_dwe * v_wcc)
## Costs
n_tot_cost_strA <- t(v_cost_strA) %*% (v_dwc * v_wcc)
### For Strategy B
## QALYs
n_tot_qaly_strB <- t(v_qaly_strB) %*% (v_dwe * v_wcc)
## Costs
n_tot_cost_strB <- t(v_cost_strB) %*% (v_dwc * v_wcc)
### For Strategy AB
## QALYs
n_tot_qaly_strAB <- t(v_qaly_strAB) %*% (v_dwe * v_wcc)
```

### ## Costs

```
n_tot_cost_strAB <- t(v_cost_strAB) %*% (v_dwc * v_wcc)
```

The total expected discounted QALYs and costs for the age-dependent Sick-Sicker model under the four strategies accounting for within-cycle correction are shown in Table 3.

Table 3: Total expected discounted QALYs and costs per average individual in the cohort of the age-dependent Sick-Sicker model by strategy accounting for within-cycle correction .

|                  | Costs     | QALYs  |
|------------------|-----------|--------|
| Standard of care | \$114,560 | 19.142 |
| Strategy A       | \$211,911 | 19.840 |
| Strategy B       | \$194,481 | 20.480 |
| Strategy AB      | \$282,370 | 21.302 |

## 5 Cost-effectiveness analysis and incremental cost-effectiveness ratios (ICERs)

To conduct the cost-effectiveness analysis, we follow the coding approach described in the accompanying tutorial.<sup>7</sup> We combine the total expected discounted costs and QALYs for all four strategies into outcome-specific vectors, `v_cost_str` for costs and `v_qaly_str` for QALYs. We use the R package `dampack` (<https://cran.r-project.org/web/packages/dampack/>)<sup>22</sup> to calculate the incremental costs and effectiveness and the incremental cost-effectiveness ratio (ICER) between non-dominated strategies and create the data frame `df_cea` with this information.

### ### Vector of costs

```
v_cost_str <- c(n_tot_cost_SoC, n_tot_cost_strA, n_tot_cost_strB, n_tot_cost_strAB)
```

### ### Vector of effectiveness

```
v_qaly_str <- c(n_tot_qaly_SoC, n_tot_qaly_strA, n_tot_qaly_strB, n_tot_qaly_strAB)
```

### ### Calculate incremental cost-effectiveness ratios (ICERs)

```
df_cea <- dampack::calculate_icers(cost = v_cost_str,  
                                  effect = v_qaly_str,  
                                  strategies = v_names_str)
```

In terms of their costs and effectiveness, SoC is the least costly and effective strategy, followed by Strategy B producing an expected benefit of 1.338 QALYs per individual for an additional expected cost of \$79,920 with an ICER of \$59,726/QALY followed by Strategy AB with an ICER \$106,927/QALY. Strategy A is a dominated strategy. The results of the CEA of the age-dependent Sick-Sicker model are presented in Table 4. The non-dominated strategies, SoC, B, and AB, form the cost-effectiveness efficient frontier of the CEA based on the age-dependent Sick-Sicker model (Figure 9).

Table 4: Cost-effectiveness analysis results for the age-dependent Sick-Sicker model. ND: Non-dominated strategy; D: Dominated strategy.

| Strategy         | Costs (\$) | QALYs  | Incremental Costs (\$) | Incremental QALYs | ICER (\$/QALY) | Status |
|------------------|------------|--------|------------------------|-------------------|----------------|--------|
| Standard of care | 114,560    | 19.142 | NA                     | NA                | NA             | ND     |
| Strategy B       | 194,481    | 20.480 | 79,920                 | 1.338             | 59,726         | ND     |
| Strategy AB      | 282,370    | 21.302 | 87,890                 | 0.822             | 106,927        | ND     |
| Strategy A       | 211,911    | 19.840 | NA                     | NA                | NA             | D      |

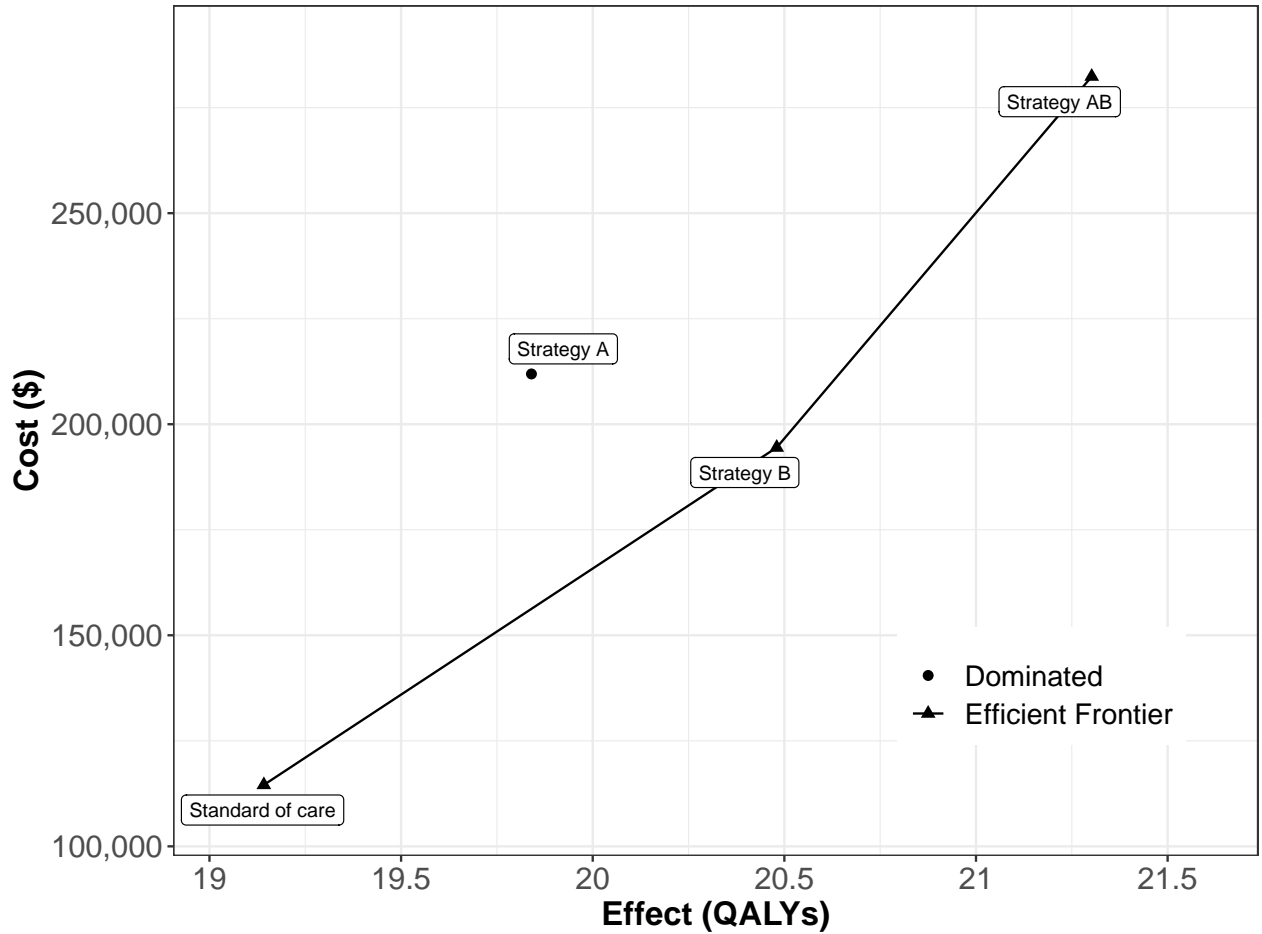


Figure 9: Cost-effectiveness efficient frontier of all four strategies for the age-dependent Sick-Sicker model.

## 6 Probabilistic sensitivity analysis

To quantify the effect of model parameter uncertainty on cost-effectiveness outcomes, we conducted a probabilistic sensitivity analysis (PSA).<sup>23</sup> In a PSA, we randomly draw parameter sets from distributions that reflect the current uncertainty in model parameter estimates. The distribution for all the parameters and their values is described in Table 2 and more detailed in the Supplementary Material. For each sampled set of parameter values, we compute model outcomes (e.g., total discounted cost and QALYs) for each strategy.

In a previously published manuscript, we describe the implementation of these steps in R.<sup>12</sup>

To conduct the PSA of the CEA using the time-independent Sick-Sicker cSTM, we sampled 1,000 parameter sets for all the parameters from the distributions defined in Table 2. For each sampled parameter set, we simulated each strategy. Results from a PSA can be represented in various ways. For example, the joint distribution, 95% confidence ellipse, and the expected values of the total discounted costs and QALYs for each strategy can be plotted in a cost-effectiveness (CE) scatter plot ( Figure 10),<sup>24</sup> where each of the 1,000 simulations are plotted as a point in the graph. The CE scatter plot for CEA using the time-independent model shows that strategy AB has the highest expected costs and QALYs. Standard of care has the lowest expected cost and QALYs. Strategy B is more effective and least costly than Strategy A. Strategy A is a strongly dominated strategy.

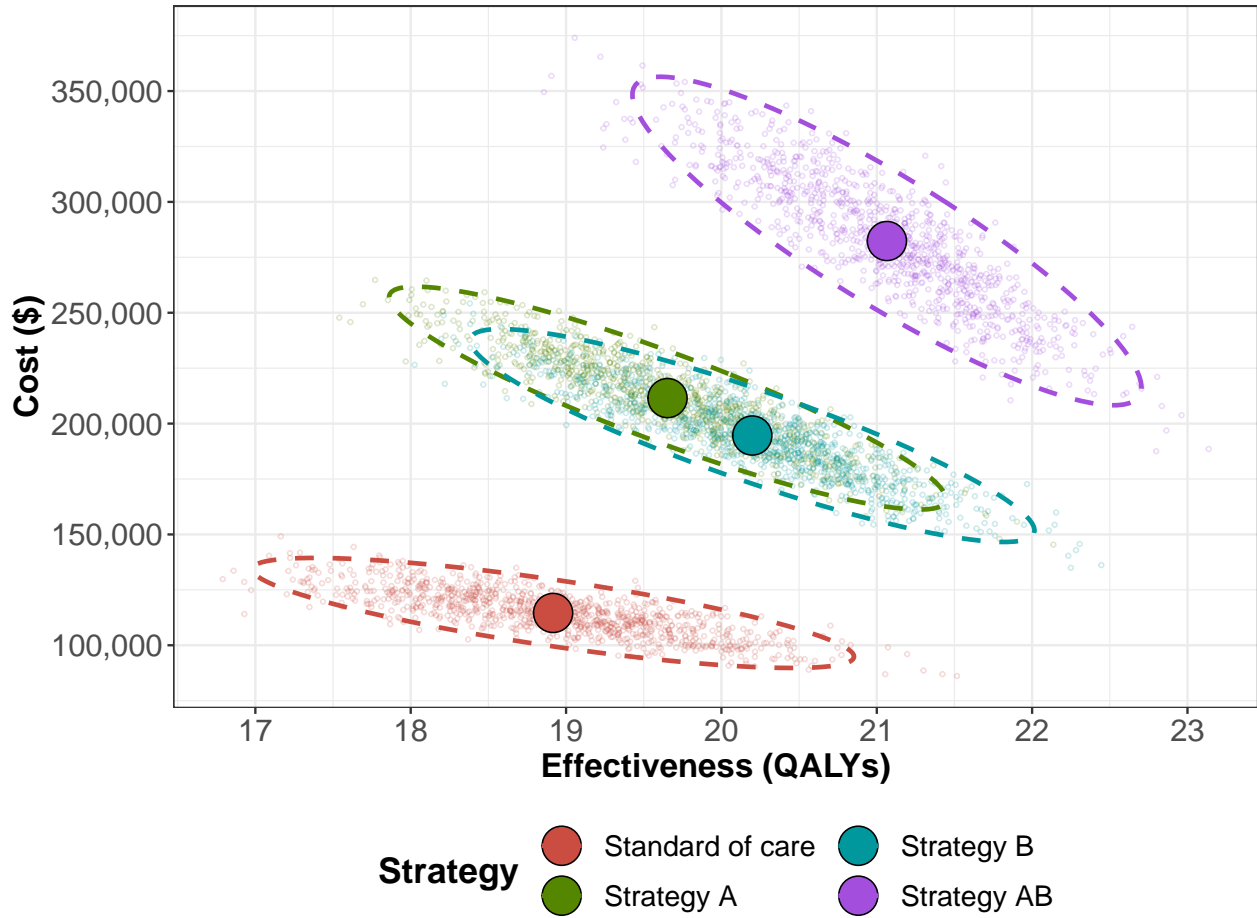


Figure 10: Cost-effectiveness scatter plot.

In Figure 11, we present the cost-effectiveness acceptability curves (CEACs) showing the probability that each strategy is cost-effective, and the cost-effectiveness frontier (CEAF), which shows the strategy with the highest expected net monetary benefit (NMB), over a range of willingness-to-pay (WTP) thresholds. The NMB for each strategy is defined as the product of total discounted QALYs and the WTP threshold minus the total discounted costs,<sup>25</sup> calculated for each PSA parameter set sample. At WTP thresholds less than \$65,000 per QALY, SoC is the strategy with the highest probability of being cost-effective and the highest

expected NMB. Strategy B has the highest probability of being cost-effective and the highest expected NMB for WTP thresholds greater than \$65,000 and smaller than \$105,000 per QALY. Strategy AB, has the highest expected NMB for WTP thresholds greater than or equal to \$105,000 and is the strategy with the highest probability of being cost-effective.

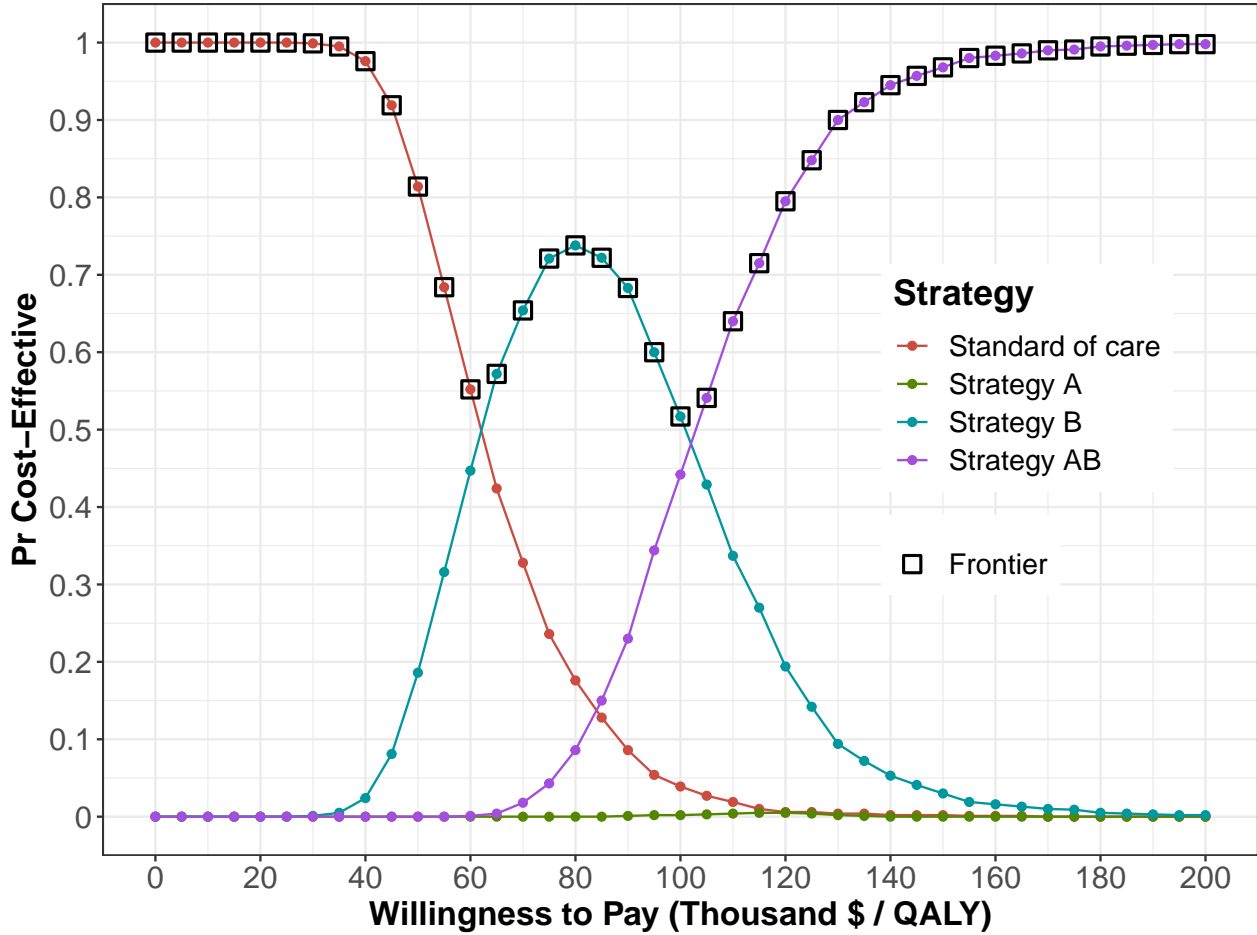


Figure 11: Cost-effectiveness acceptability curves (CEACs) and frontier (CEAF).

We quantify expected loss from each strategy over a range of WTP thresholds with the expected loss curves (ELCs). (Figure 12). The expected loss considers both the probability of making the wrong decision and the magnitude of the loss due to this decision, representing the foregone benefits of choosing a suboptimal strategy. The expected loss of the optimal strategy represents the lowest envelope of the ELCs because, given current information, the loss cannot be minimized further. The lower envelope also represents the expected value of perfect information (EVPI), which quantifies the value of eliminating parameter uncertainty. The strategy SoC has the lowest expected loss for WTP thresholds less than \$60,000 per QALY, strategy B has the lowest expected loss for WTP threshold greater than or equal to \$65,000 and less than \$105,000. Strategy AB has the lowest expected loss for WTP threshold greater than or equal to \$105,000 per QALY. At a WTP threshold of \$65,000 per QALY, the EVPI is highest at \$6,953. For a more detailed description of these outputs and the R code to generate them, we refer the reader to a previous publication by our group.<sup>26</sup>

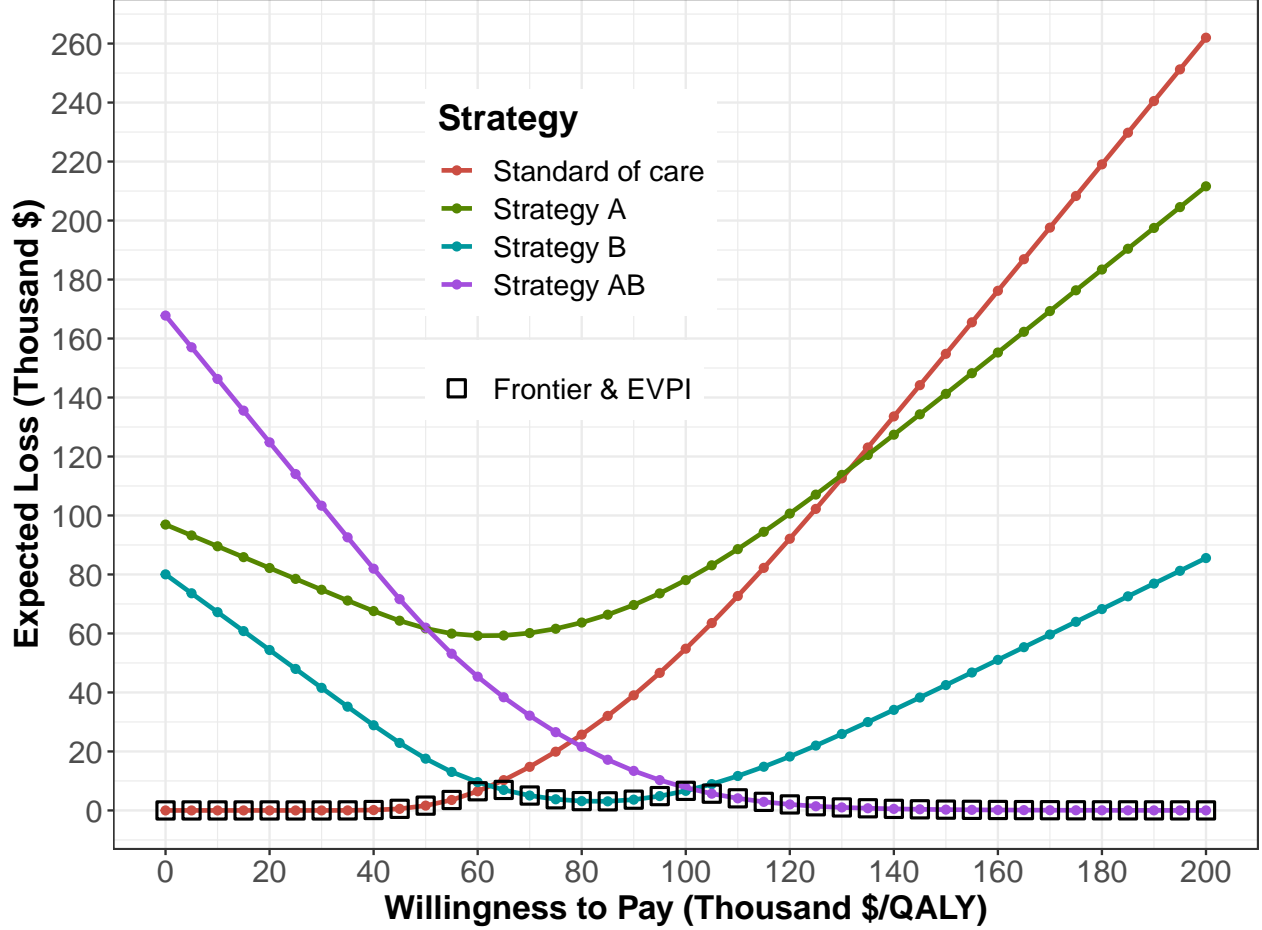


Figure 12: Expected loss curves (ELCs) and expected value of perfect information (EVPI).

## 7 Discussion

In this tutorial, we provided a conceptualization of time-dependent cSTMs with their mathematical description and a walk-through of their implementation for CEA in R using a previously published example. We used R as the programming language of choice to show these models' implementation with accompanying code throughout the tutorial. We describe time-dependency based on the time since the start of the simulation (simulation time-dependency) or on time spent in a health state (state residence). We showed how to generate various epidemiological outputs and how to incorporate transition rewards in CEAs.

There are several alternative approaches to incorporate time-dependency in cSTMs in R and various programming languages. For example, another approach to accomodate age-dependency involves updating the time-varying elements of the transition probability matrix  $P_t$  at each time point  $t$ . That would alleviate the need for the construction of the array `a_P`. Updating the transition matrix at each cycle can reduce computer memory requirements but at the expense of increasing the number of operations in the update of  $P_t$  at every cycle. Another approach to account for history dependence is to use a 3-dimensional transition probability matrix with dimensions for the current state, future state, and time in the current state.<sup>27</sup> However, this multidimensional matrix will have to be expanded by another dimension to incorporate age dependence

by replicating the states for as many age groups are considered in the model. In this tutorial, we used the third dimension as the cohort’s age. We incorporated state-residence time dependency by expanding the corresponding health states on the second dimension of the 3-dimensional array to account for time spent in the current state. This approach’s benefit is that we can still use the transition dynamics array to capture all states’ transitions for all cycles.

The parameterization of our example model assumes all parameters are known, or at least, the characterization of their uncertainty is known (i.e., we know their distributions). However, to construct a real-world cSTM, modelers must conduct a thorough synthesis of current evidence to determine these models’ appropriate structure and inform all parameters. For example, determining whether transitions between non-death health states are estimated conditional on being alive or as competing risks.<sup>23</sup> Similarly, our PSA analysis simplifies reality where all model parameters are assumed to be independent of each other. However, parameters could be correlated with each other or have a rank order, and appropriate statistical methods that simulate these correlations or rank order might be needed.<sup>28</sup> We encourage modelers to use appropriate statistical methods to synthesize and quantify model parameters uncertainty accurately. Also, modelers should correctly specify all model parameters for the cycle length of the model. For example, adjusting an annual mortality rate to a weekly probability requires some probability revision.<sup>29</sup>

As described in the accompanying tutorial, cSTMs are recommended when the number of states is considered “not too large”.<sup>14</sup> This recommendation arises because as the number of states increases, it becomes more difficult to keep track of their construction. It is possible to build fairly complex cSTMs in R as long as the size of the transition probability matrix and outputs of interest can be stored in the RAM memory of the computer running the analysis. For example, a typical PC with 8GB of RAM can handle a transition probability array of about 1000 states and 600 time slices. However, these matrices can grow quickly, and if the required number of states gets too large and difficult to manage its coding, it becomes preferable to use a stochastic (Monte Carlo) version of the state-transition model – often called individual-based state-transition models (iSTM) or microsimulation models – rather than a cohort simulation model.<sup>14</sup> In an iSTM, the risks and rewards of simulated individuals need not depend only on a current health state; it may also depend on their characteristics and attributes. In addition, modelers can store health state history and other events over time for each individual to determine the risk of new events and corresponding costs and effects. Thus, we recommend thinking about the required model structure before implementing it some model structures might remain the same. An iSTM will also require additional functions to describe the dependency of transition probabilities and rewards on individuals’ history. In a previous tutorial, we showed how to construct these functions for an iSTM using the Sick-Sicker example.<sup>11</sup>

In summary, this tutorial provides a conceptualization of time-dependent cSTMs and a step-by-step guide to implement them in R. We aim to add to the current body of literature and material on building this type of decision models, so health decision scientists and health economists can develop cSTMs in a more flexible, efficient, open-source manner, and encouraging increased transparency and reproducibility.

## 8 Acknowledgements

Dr Alarid-Escudero was supported by a grant from the National Cancer Institute (U01-CA-199335) as part of the Cancer Intervention and Surveillance Modeling Network (CISNET), and the Gordon and Betty Moore Foundation. Miss Krijkamp was supported by the Society for Medical Decision Making (SMDM) fellowship



through a grant by the Gordon and Betty Moore Foundation (GBMF7853). Dr Enns was supported by a grant from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under award no. K25AI118476. Dr Hunink receives Royalties from Cambridge University Press for a textbook on Medical Decision Making, reimbursement of expenses from the European Society of Radiology (ESR) for work on the ESR guidelines for imaging referrals, reimbursement of expenses from the European Institute for Biomedical Imaging Research (EIBIR) for membership of the Scientific Advisory Board, and research funding from the American Diabetes Association, the Netherlands Organization for Health Research and Development, the German Innovation Fund, Netherlands Educational Grant (“Studie Voorschot Middelen”), and the Gordon and Betty Moore Foundation. Dr Jalal was supported by a grant from the National Institute on Drug Abuse of the National Institute of Health under award no. K01DA048985. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The funding agencies had no role in the design of the study, interpretation of results, or writing of the manuscript. The funding agreement ensured the authors’ independence in designing the study, interpreting the data, writing, and publishing the report. We also want to thank the anonymous reviewers of *Medical Decision Making* for their valuable suggestions and the students who have taken our classes and provided invaluable feedback to improve the clarity and usability of our materials.

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