Cohort State-Transition Models (cSTMs)

Day 2

A Challenge for Public Policy

- Complete course of public policies might never be directly observed.

- Randomized controlled trials of *every* potential preventive and treatment policy is not feasible.

- Even the best available data will rely on surrogate markers and intermediate endpoints.

- The information required to develop policies will require synthesis of data from many sources.

Elements of a Decision Analysis

- Identify and bound the decision problem
- **Structure the elements of the problem into a logical framework over time (i.e., build a model)**
- Identify, retrieve, and characterize the information needed
- Conduct a base case analysis
- Evaluate uncertainty

Problems

- Critical details make the decision problem complex
- Events occur at different times and repeatedly
- Risk of infection decreases with time, risk of negative consequences increase with time
- Fixed time horizon does not consider long term consequences, such as life expectancy and quality-adjusted life expectancy
- Limited ability to evaluate a broader set of questions or to consider alternative strategies

Markov models are most useful when....

- decision problem involves <u>risk over time</u>
- <u>timing of events</u> is important
  - early risk, late benefit
- events may happen <u>more than once</u>
- <u>states change</u> over time
  - progression from mild to severe status

Time-homogeneous

Markov Property: Markovian Assumption

- Specifies that the behavior of the process subsequent to any cycle depends only on its description in that cycle. The process has no memory for earlier cycles.

- A separate state must be created for each subset of the cohort that has a prognosis (or utility or cost).

Markov Process

- Modeling technique, derived from matrix algebra, that helps get around some of the "limitations" of a simple decision tree with a fixed time horizon
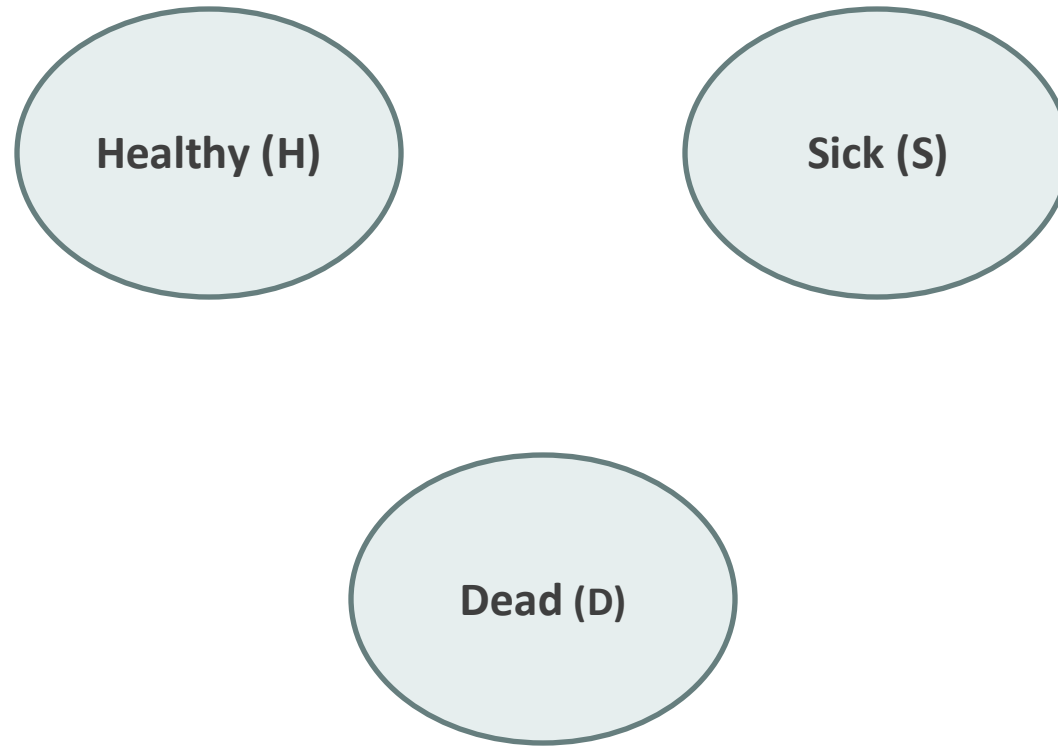
Implicit Assumptions

- States are mutually exclusive
- States are collectively exhaustive
- Memorylessness

Building a Markov Model

- *Determine health states*
- Determine transitions
- Choose cycle length
- Estimate transition probabilities
- Estimate state utilities and costs per cycle
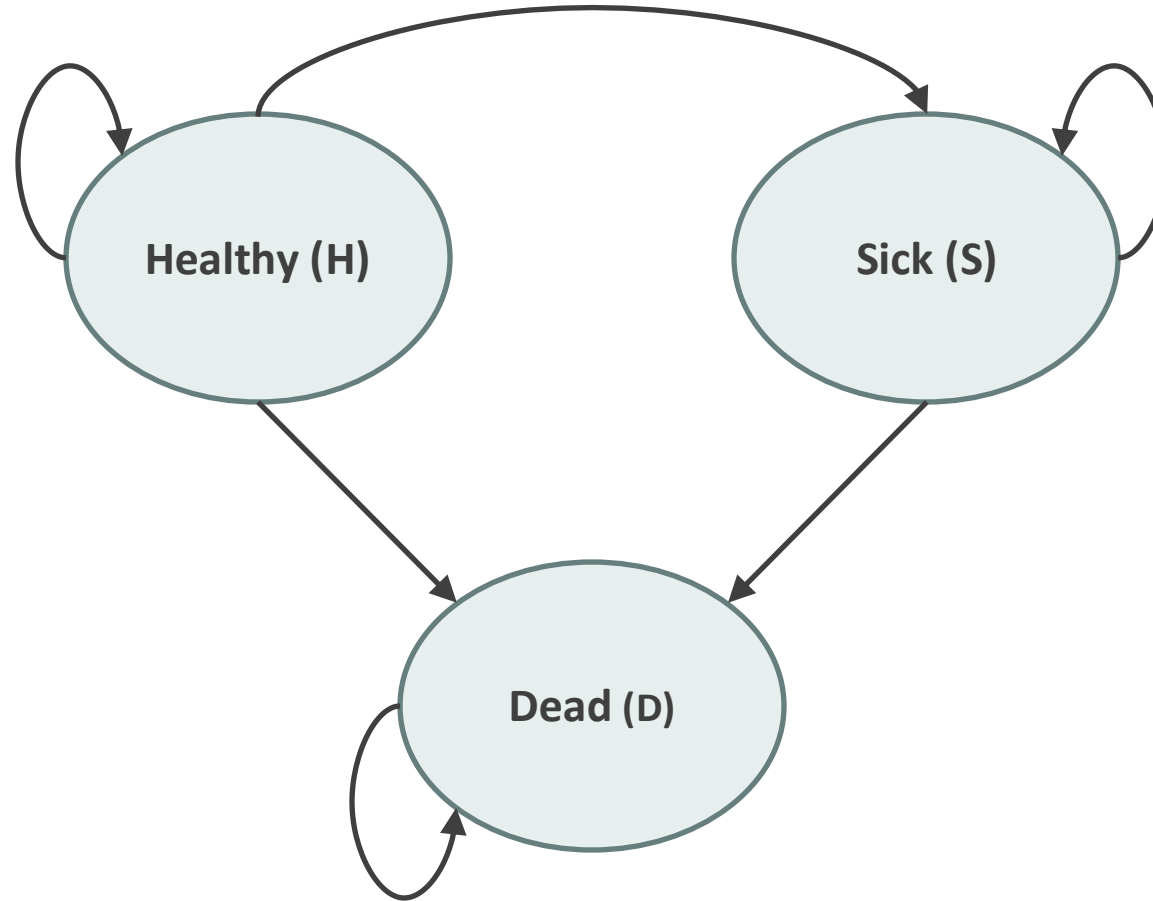- Calculate
- (Sensitivity analysis)

Markov Health States

Building a Markov Model

- Determine health states
- *Determine transitions*
- Choose cycle length
- Estimate transition probabilities
- Estimate state utilities and costs per cycle
- Calculate
- (Sensitivity analysis)

State Transition Diagram (STD)

Building a Markov Model

- Determine health states
- Determine transitions
- *Choose cycle length*
- Estimate transition probabilities
- Estimate state utilities and costs per cycle
- Calculate
- (Sensitivity analysis)

Cycle

A brief time interval during which individuals within a cohort may make a transition into another health state or remain in the current health state.
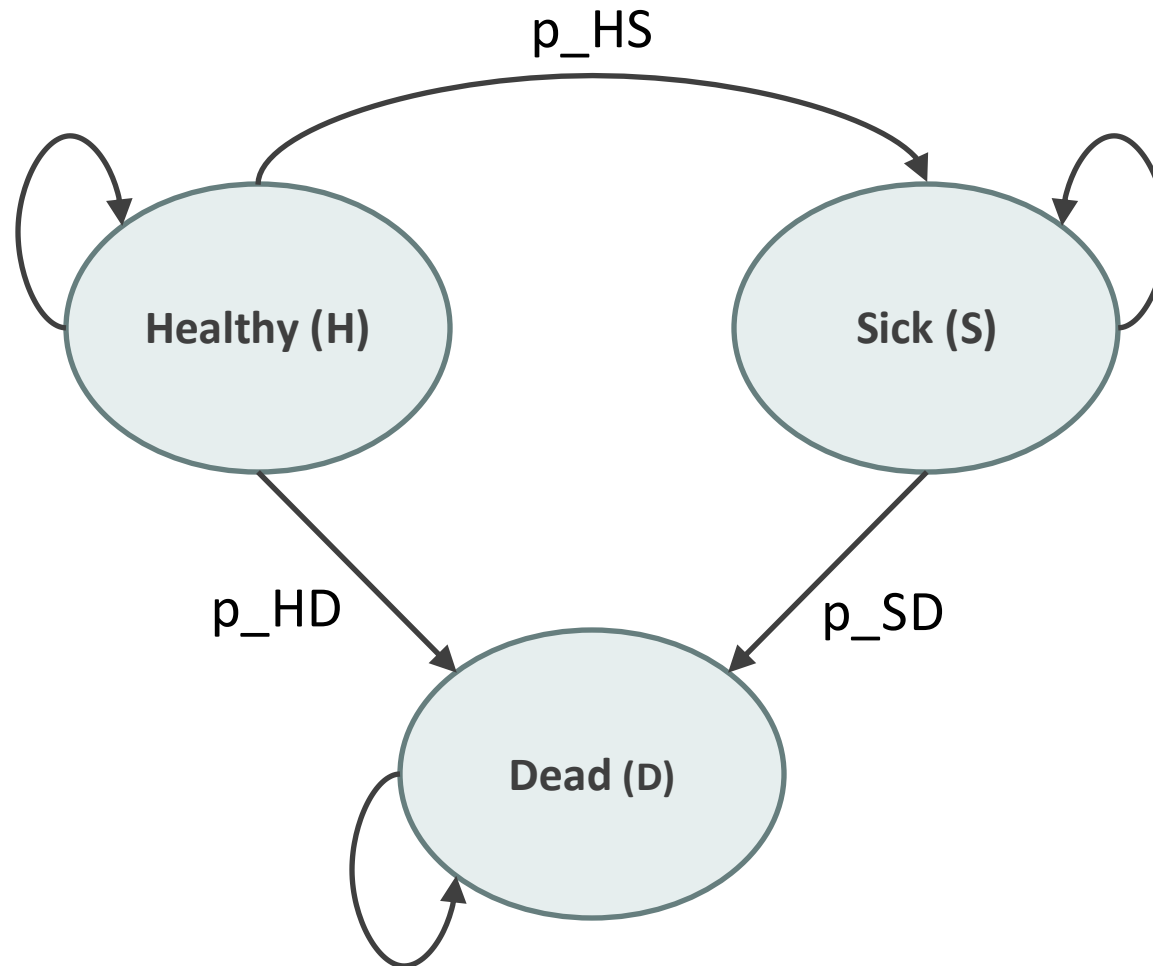
Building a Markov Model

- Determine health states

- Determine transitions

- Choose cycle length

- *Estimate transition probabilities*

- Estimate state utilities and costs per cycle

- Calculate

- (Sensitivity analysis)

Transition Probability

The chance that patients in a particular state will transition to another state *during* the course of a cycle.
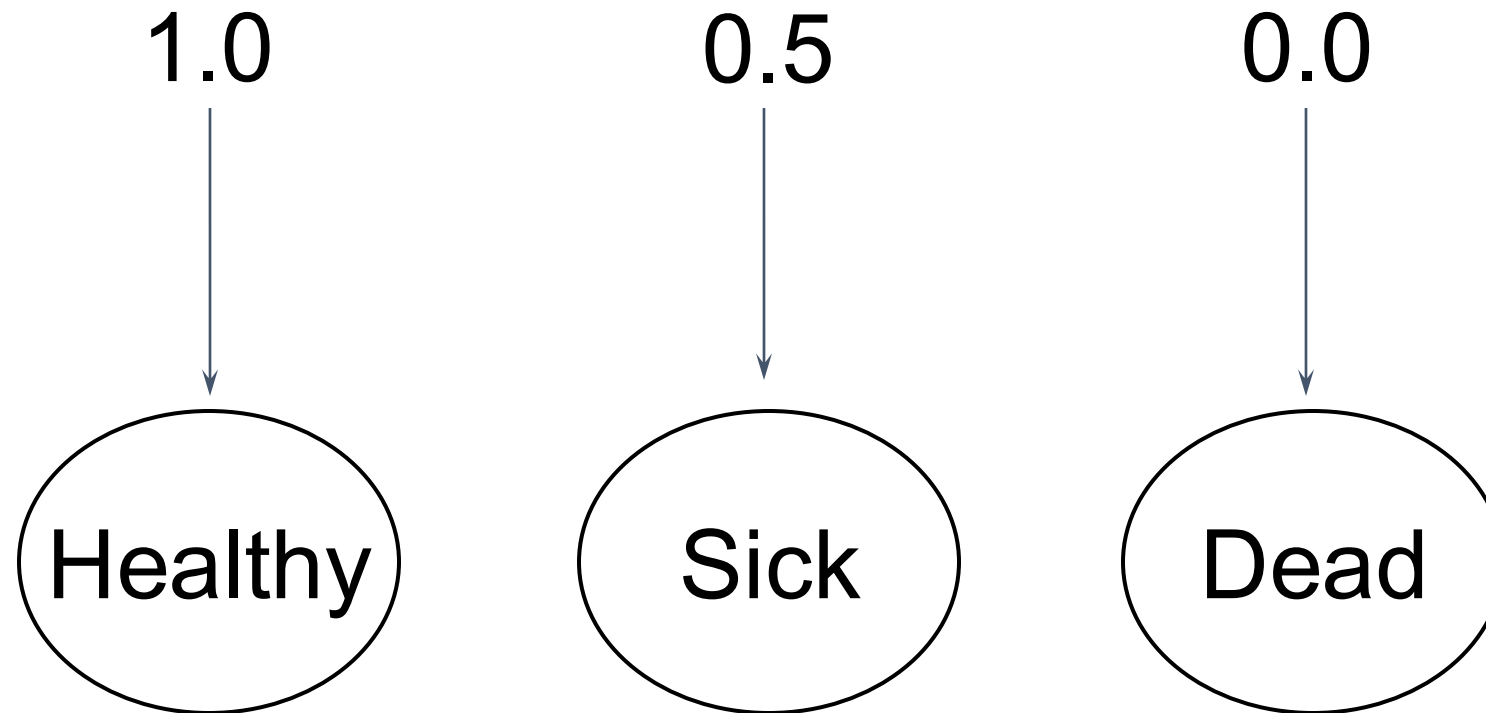
State Transition Diagram (STD)
p_ij= transition probability from state *i* to state *j*

Building a Markov Model

- Determine health states

- Determine transitions

- Choose cycle length

- Estimate transition probabilities

- *Estimate state utilities and costs per cycle*

- Calculate

- (Sensitivity analysis)

Quality-of-Life Adjustment

Building a Markov Model

- Determine health states
- Determine transitions
- Choose cycle length
- Estimate transition probabilities
- Estimate state utilities and costs per cycle
- *Calculate*
- (Sensitivity analysis)

Methods of Evaluation

- Closed-form fundamental matrix solution
- Cohort simulation
  - » hypothetical cohort of patients transition through the model simultaneously
- Monte Carlo simulation
  - » first order simulation randomly selects an individual from the hypothetical cohort and they transition through the model one at a time

Methods of Evaluation

- Closed-form fundamental matrix solution
- **Cohort simulation**
  - » **hypothetical cohort of patients transition through the model simultaneously**
- Monte Carlo simulation
  - » first order simulation randomly selects an individual from the hypothetical cohort and they transition through the model one at a time

Cohort Simulation

- A cSTM consists of three core components:

1. A state vector $\boldsymbol{m}_t$ that stores the distribution of the cohort across all n_S health states in cycle t, where $t = [0, 1, ..., n_T]$

2. A cohort trace matrix M that stacks $\boldsymbol{m}_t$ for all t and represents the distribution of the cohort in the various states over time

3. A transition probability P

State vector (m_t with n_S health states):

- Each i-th element of m_t represents the distribution of the i-th health state in cycle t, referred to as $m_{[t,i]}$

$$\boldsymbol{m}_t = \begin{bmatrix} m_{[t,1]} & m_{[t,2]} & \cdots & m_{[t,n_S]} \end{bmatrix}$$

Transition Matrix (n_S health states):

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

- Where $p_{[i,j]}$ represents the transition probability of transitioning <u>from</u> state i <u>to</u> state j, and $\{i,j\} = 1, \dots, n_S$.
- $0 < p_{[i,j]} < 1$ and $\sum_{j=1}^{n_S} p_{[i,j]} = 1$ for all $i = 1, \dots, n_S$

Cohort at next cycle using matrix multiplication

- Cohort distribution at next time step calculated through matrix multiplication

$$m_{t+1} = m_t\, P \text{ for } t = 0, \dots, (n_T - 1)$$

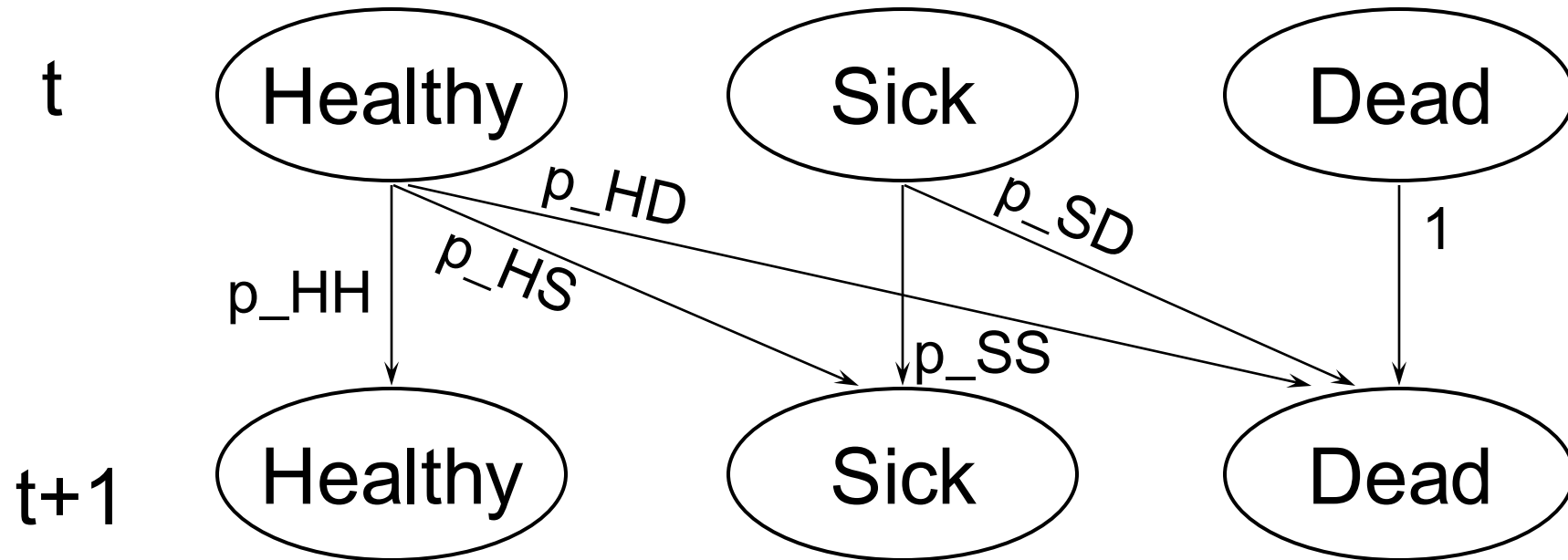$$\left[m_{[t+1,1]}\; m_{[t+1,2]} \cdots m_{[t+1,n_S]}\right] = \left[m_{[t,1]}\; m_{[t,2]} \cdots m_{[t,n_S]}\right]\begin{bmatrix} & P & \end{bmatrix}$$

Cohort trace M

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

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

Three-State Markov Model

Types of Markov Models

- <u>Absorbing models</u> (e.g., includes death)

  Goal: Calculate *residence times* in transient states

  » means (e.g., life expectancy)

  » weighted means (e.g., QALE, discounted LE)

- <u>Non-absorbing models</u> (e.g., nonfatal states)

  Goal: Calculate long-run proportions of time spent in each state

  » equilibrium distribution across states

Outputs of Absorbing Models

- Life expectancy: average number of cycles in "live" states

- Weighted life expectancy: average number of cycles in "live" states, each weighted by a state utility or cost

- Discounted life expectancy: average number of cycles in "live" states, each cycle weighted by $(1+r)^{-t}$

Back to the Simple Example

Transition Matrix

$$
M = \quad \begin{array}{c} \\ \text{From} \end{array} \quad \begin{array}{c} \\ H \\ S \\ D \end{array} \quad \overset{\displaystyle \text{To}}{\overset{\displaystyle H \qquad S \qquad D}{\begin{bmatrix} p_{HH} & p_{HS} & p_{HD} \\ 0 & p_{SS} & p_{SD} \\ 0 & 0 & 1 \end{bmatrix}}}
$$

Initial State Vector

$$
m_0 = \overset{\displaystyle H \qquad S \qquad D}{\begin{bmatrix} m_{[0,1]} & m_{[0,2]} & m_{[0,3]} \end{bmatrix}}
$$

Back to the Simple Example

Transition Matrix

$$M = \quad \text{From} \quad \begin{array}{c} \\ H \\ S \\ D \end{array} \begin{array}{ccc} & \text{To} & \\ H & S & D \\ \begin{bmatrix} 0.75 & 0.20 & 0.05 \\ 0 & 0.85 & 0.15 \\ 0 & 0 & 1 \end{bmatrix} \end{array}$$

Initial State Vector

$$m_0 = \begin{array}{ccc} H & S & D \\ [1 & 0 & 0] \end{array}$$

Cohort at next cycle using matrix multiplication

- Cohort distribution at next time step calculated through matrix multiplication

$$m_{t+1} = m_t\, P$$

$$\left[m_{[t+1,1]}\ m_{[t+1,2]}\ m_{[t+1,3]}\right] = \left[m_{[t+1,1]}\ m_{[t+1,2]}\ m_{[t+1,3]}\right]\left[\quad P \quad\right]$$

Cohort at next cycle using matrix multiplication

- Cohort distribution at next time step calculated through matrix multiplication

$$\begin{bmatrix} & & \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix} \begin{bmatrix} 0.75 & 0.20 & 0.05 \\ 0 & 0.85 & 0.15 \\ 0 & 0 & 1 \end{bmatrix}$$

Cohort at next cycle using matrix multiplication

- Cohort distribution at next time step calculated through matrix multiplication

$$[\qquad\qquad\qquad] = [1 \quad 0 \quad 0]\begin{bmatrix} 0.75 & 0.20 & 0.05 \\ 0 & 0.85 & 0.15 \\ 0 & 0 & 1 \end{bmatrix}$$

$$\text{P(H at } t = 1) = (1)(0.75) + (0)(0) + (0)(0) = 0.75$$

Cohort at next cycle using matrix multiplication

- Cohort distribution at next time step calculated through matrix multiplication

$$[0.75 \quad\quad\quad] = [1 \quad 0 \quad 0]\begin{bmatrix} 0.75 & 0.20 & 0.05 \\ 0 & 0.85 & 0.15 \\ 0 & 0 & 1 \end{bmatrix}$$

$$P(H \text{ at } t = 1) = (1)(0.75) + (0)(0) + (0)(0) = 0.75$$

Cohort at next cycle using matrix multiplication

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Cohort at next cycle using matrix multiplication

- Cohort distribution at next time step calculated through matrix multiplication

$$[0.75 \quad\quad\quad] = [1 \quad 0 \quad 0]\begin{bmatrix} 0.75 & 0.20 & 0.05 \\ 0 & 0.85 & 0.15 \\ 0 & 0 & 1 \end{bmatrix}$$

$$\text{P(S at } t = 1) = (1)(0.20) + (0)(0.85) + (0)(0) = 0.20$$

Cohort at next cycle using matrix multiplication

- Cohort distribution at next time step calculated through matrix multiplication

$$[0.75 \ 0.20 \qquad] = [1 \quad 0 \quad 0] \begin{bmatrix} 0.75 & 0.20 & 0.05 \\ 0 & 0.85 & 0.15 \\ 0 & 0 & 1 \end{bmatrix}$$

$$P(S \ \text{at} \ t = 1) = (1)(0.20) + (0)(0.85) + (0)(0) = 0.20$$

Cohort at next cycle using matrix multiplication

- Cohort distribution at next time step calculated through matrix multiplication

$$[0.75 \ 0.20 \quad] = [1 \quad 0 \quad 0] \begin{bmatrix} 0.75 & 0.20 & 0.05 \\ 0 & 0.85 & 0.15 \\ 0 & 0 & 1 \end{bmatrix}$$

Cohort at next cycle using matrix multiplication

- Cohort distribution at next time step calculated through matrix multiplication

$$[0.75 \quad 0.20 \qquad] = [1 \quad 0 \quad 0] \begin{bmatrix} 0.75 & 0.20 & 0.05 \\ 0 & 0.85 & 0.15 \\ 0 & 0 & 1 \end{bmatrix}$$

$$P(D \text{ at } t = 1) = (1)(0.05) + (0)(0.15) + (0)(1) = 0.05$$

Cohort at next cycle using matrix multiplication

- Cohort distribution at next time step calculated through matrix multiplication

$$[0.75\ 0.20\ 0.05] = [1\quad 0\quad 0]\begin{bmatrix} 0.75 & 0.20 & 0.05 \\ 0 & 0.85 & 0.15 \\ 0 & 0 & 1 \end{bmatrix}$$

$$P(D \text{ at } t = 1) = (1)(0.05) + (0)(0.15) + (0)(1) = 0.05$$

Two-cycle state vector

$P(\text{H at } t = 2) = (0.75)(0.75) + (0.20)(0) + (0.05)(0) = 0.56$

$P(\text{S at } t = 2) = (0.75)(0.20) + (0.20)(0.85) + (0.05)(0) = 0.32$

$P(\text{D at } t = 2) = (0.75)(0.05) + (0.20)(0.15) + (0.05)(1) = 0.05$

$$[0.56 \ 0.32 \ 0.12] = [0.75 \ 0.20 \ 0.05] \begin{bmatrix} 0.75 & 0.20 & 0.05 \\ 0 & 0.85 & 0.15 \\ 0 & 0 & 1 \end{bmatrix}$$

$$m_2 = m_1 \, P = (m_0 P)P = m_0 P^2$$

Year 2 vector

Matrix squared

Estimating Mean Residence Times in States from the Transition Matrix

$$P = \begin{bmatrix} 0.75 & 0.20 & 0.05 \\ 0 & 0.85 & 0.15 \\ 0 & 0 & 1 \end{bmatrix} \quad Q = \begin{bmatrix} 0.75 & 0.20 \\ 0 & 0.85 \end{bmatrix} \quad R = \begin{bmatrix} 0.05 \\ 0.15 \end{bmatrix} \quad I = [1]$$

$I =$ Identity matrix (1's in right diagonal, 0 otherwise)

Let $n_{ij} =$ expected residence time in state j, given start in state i at time 0 and define N as

$$N = \begin{bmatrix} n_{11} & n_{12} \\ n_{21} & n_{22} \end{bmatrix}$$

Key model result

Closed-Form Solution

$$\begin{bmatrix} n_{11} & n_{12} \\ n_{21} & n_{22} \end{bmatrix} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} + \begin{bmatrix} 0.75 & 0.20 \\ 0 & 0.85 \end{bmatrix} \begin{bmatrix} n_{11} & n_{12} \\ n_{21} & n_{22} \end{bmatrix}$$

$$N = I + QN$$

$$N - QN = I$$

$$N(I - Q) = I$$

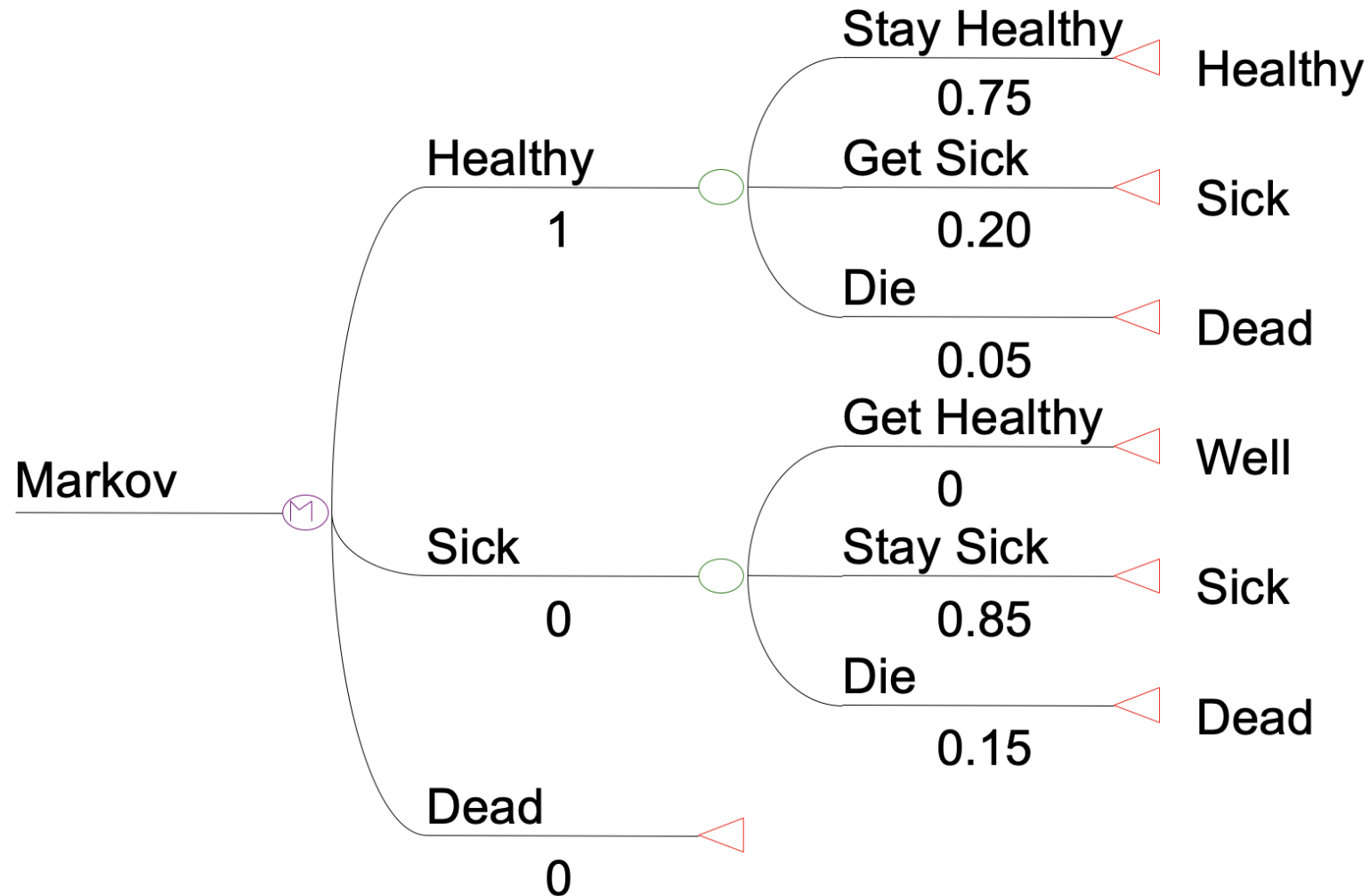$$N = (I - Q)^{-1} \quad \text{Fundamental matrix solution}$$

In the example...

$$(I - Q) = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} - \begin{bmatrix} 0.75 & 0.20 \\ 0 & 0.85 \end{bmatrix} = \begin{bmatrix} 0.25 & -0.80 \\ 0 & 0.15 \end{bmatrix}$$

$$(I - Q)^{-1} = \begin{bmatrix} 4.0 & 21.3 \\ 0 & 6.7 \end{bmatrix}$$ LE = 25.3 (start Healthy)
LE = 6.70 (start Sick)

With discounting:

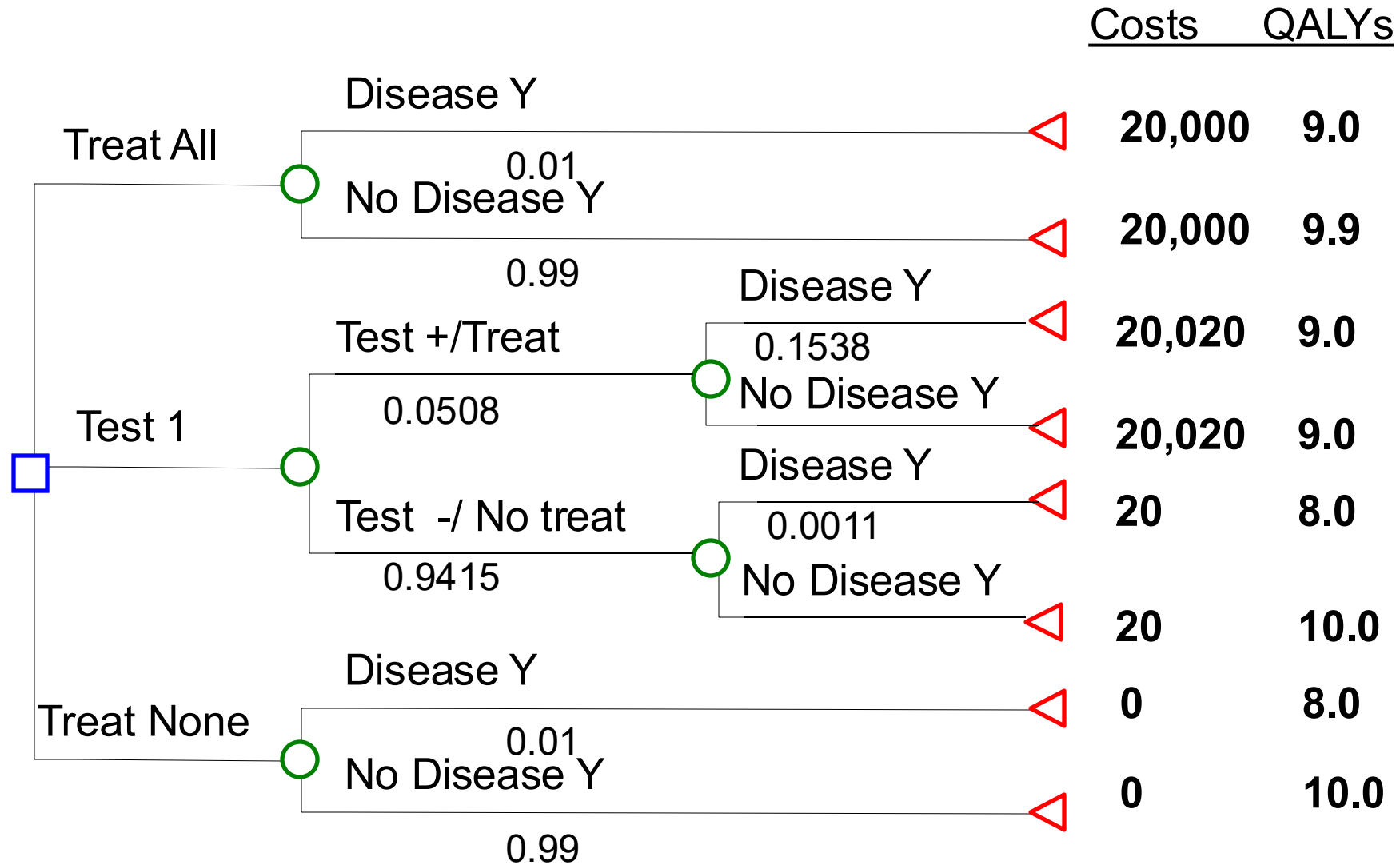$$N = \left(I - \frac{Q}{1 + r}\right)^{-1}$$

Matrix Form in a Tree Form

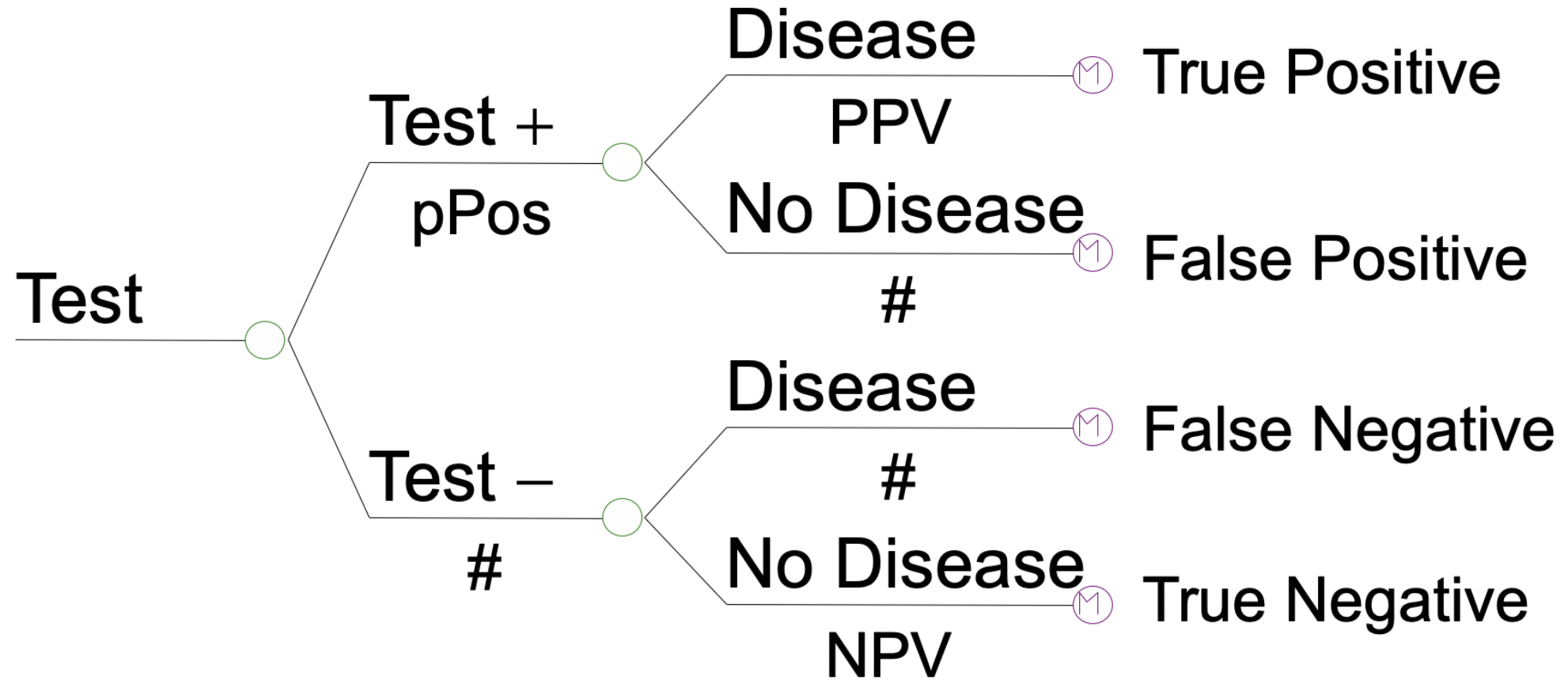# A more common structure...
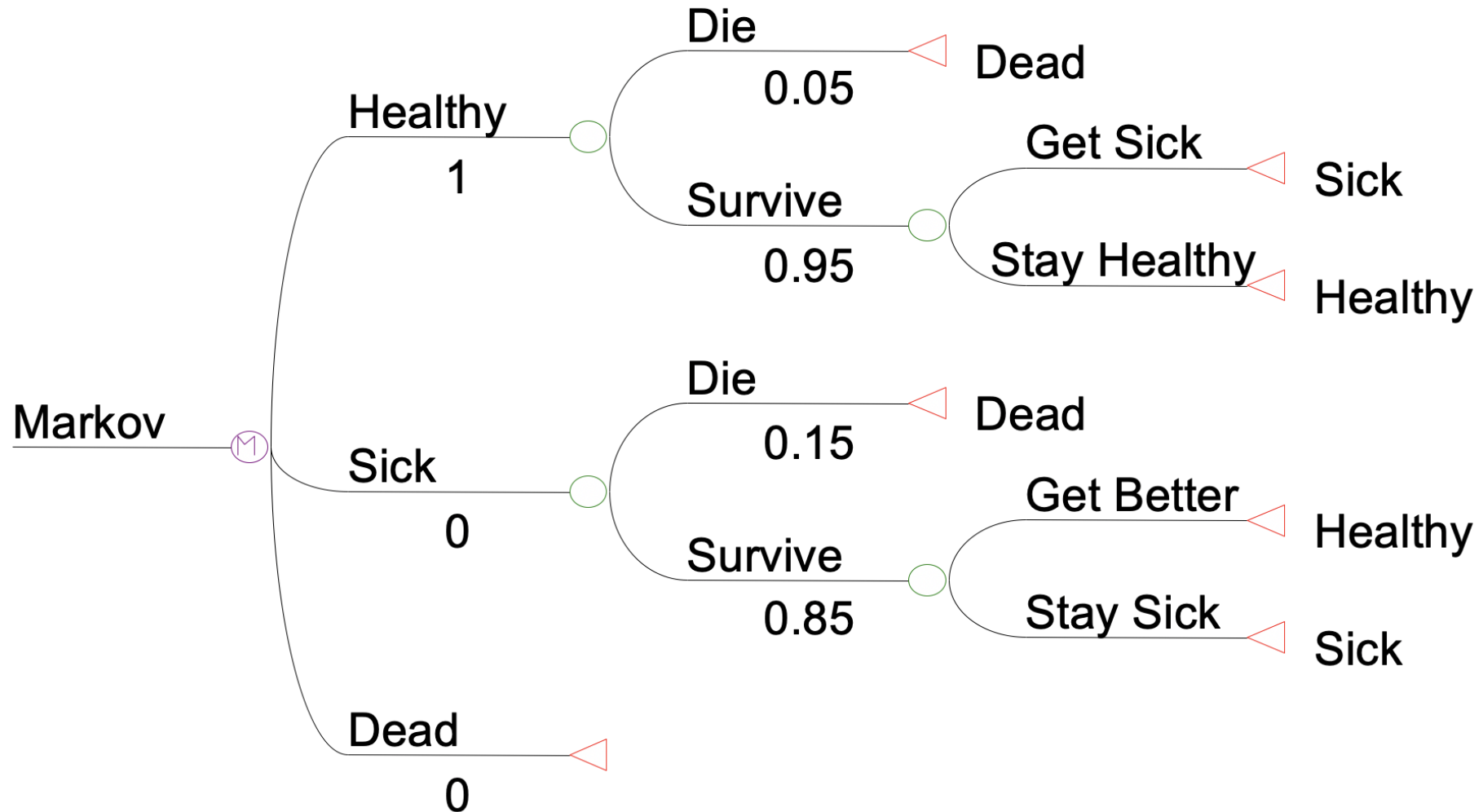
Markov Cycle Trees

- Markov models can be "grafted" onto decision trees at terminal nodes (i.e., Markov nodes)

- The averaged-out value at a Markov node is the desired summary value of the Markov process (e.g., QALE)

CEA of Test 1

	Costs	QALYs
Treat All — Disease Y (0.01)	20,000	9.0
Treat All — No Disease Y (0.99)	20,000	9.9
Test 1 — Test +/Treat (0.0508) — Disease Y (0.1538)	20,020	9.0
Test 1 — Test +/Treat — No Disease Y	20,020	9.0
Test 1 — Test -/No treat (0.9415) — Disease Y (0.0011)	20	8.0
Test 1 — Test -/No treat — No Disease Y	20	10.0
Treat None — Disease Y (0.01)	0	8.0
Treat None — No Disease Y (0.99)	0	10.0

Typical Diagnostic Test Strategy

Markov Cohort Method

- Provides Markov trace (which shows the distribution of the population in each cycle)

- Gives an *approximation* to residence times

- Allows for half-cycle correction

- Calculates average number of cycles in each state (can weight cycles by utility or discount factor)
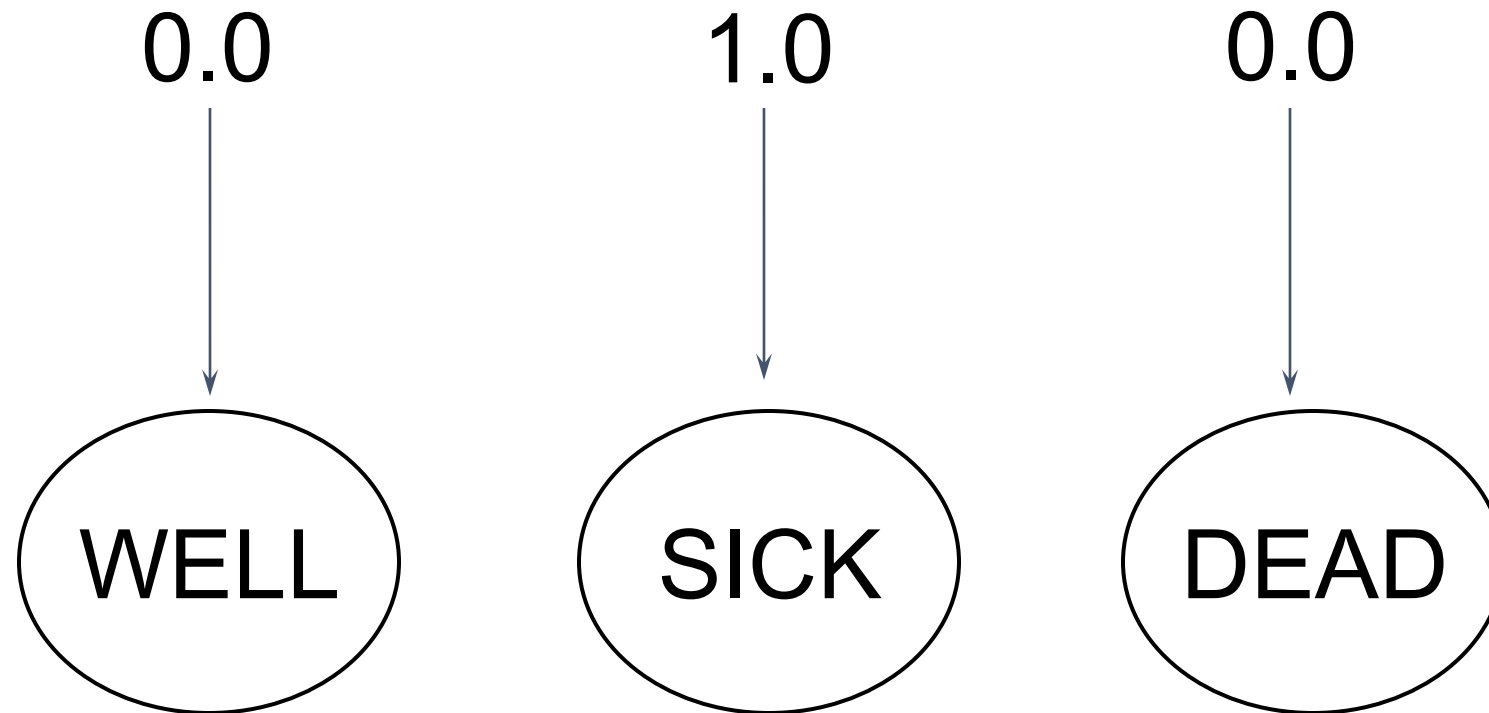
Life Expectancy
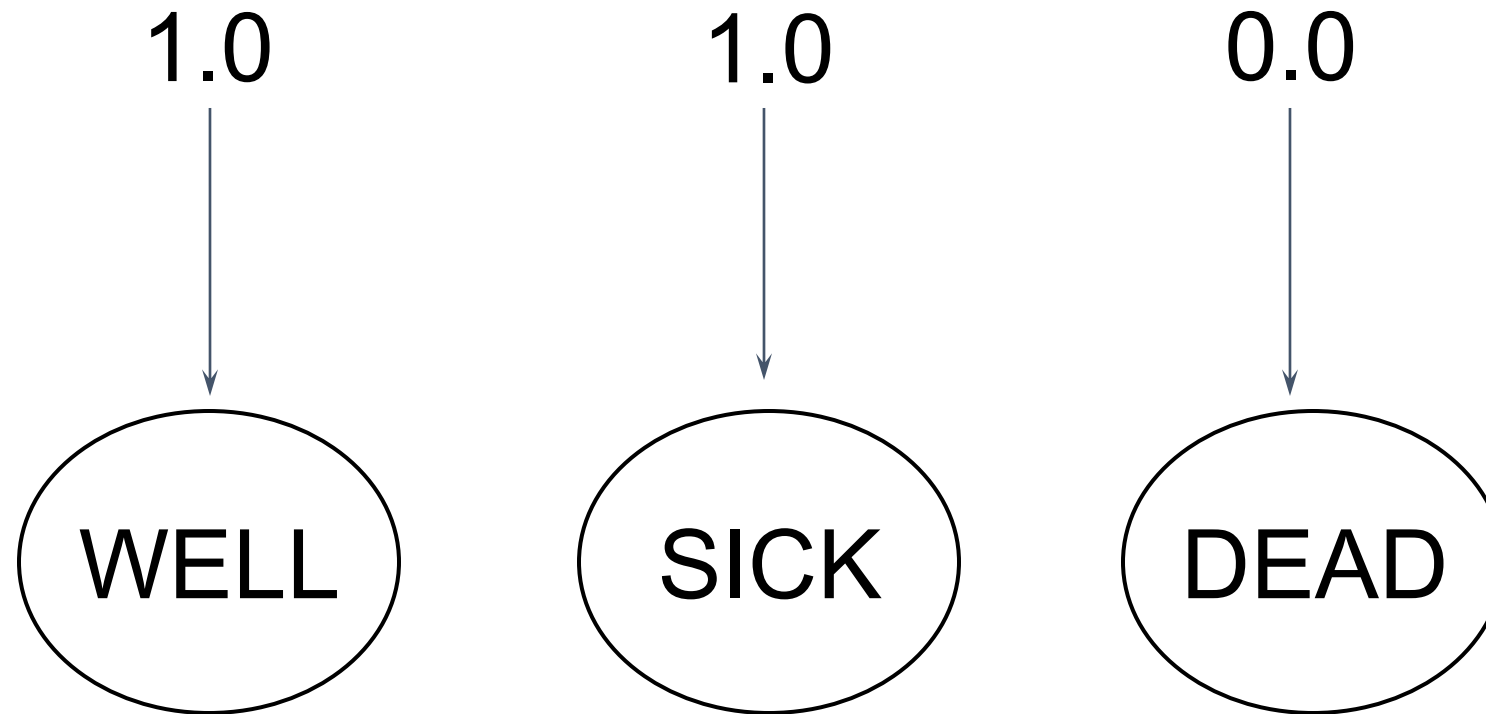
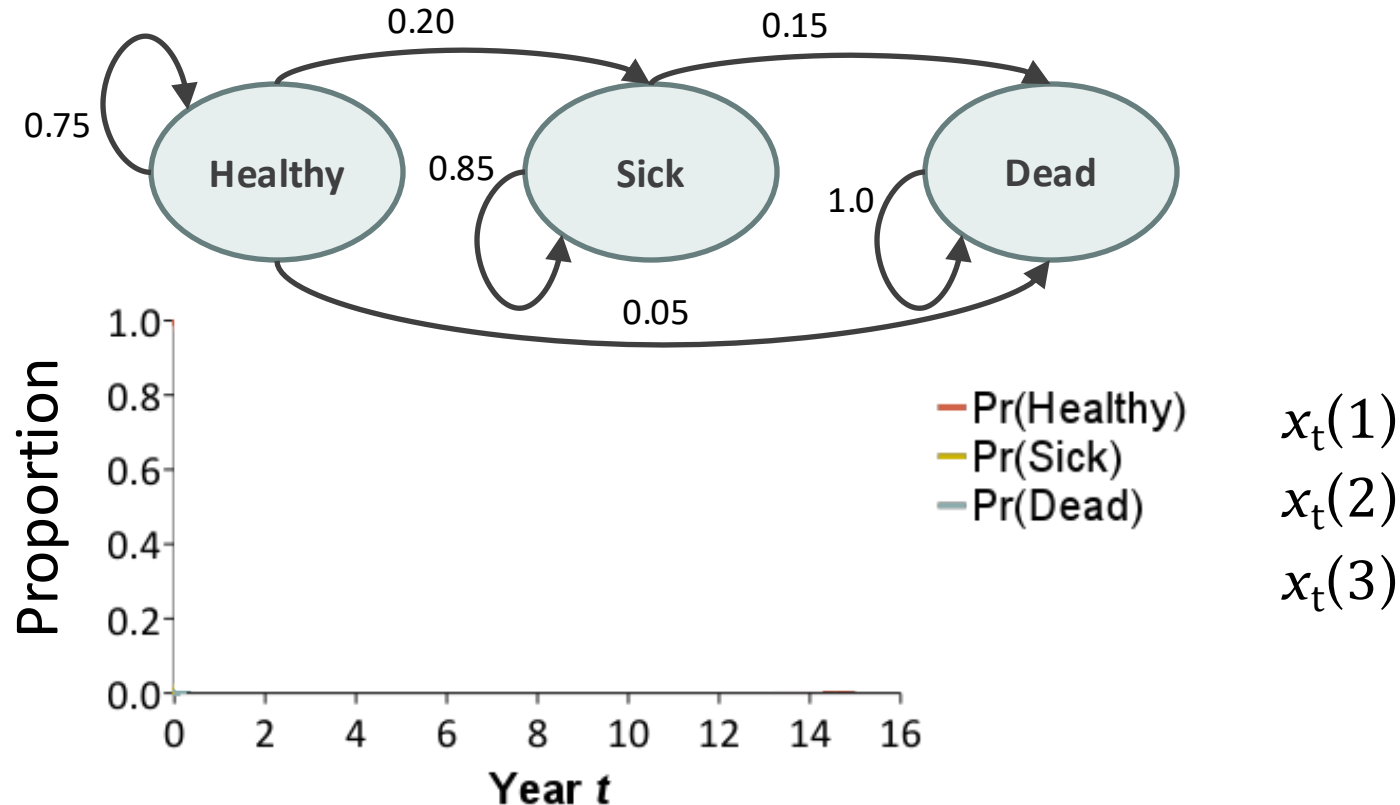# Discounted Life Expectancy
(r = discount rate, t = _stage)

$$\frac{1.0}{(1+r)^t}$$

$$\frac{1.0}{(1+r)^t}$$

0.0

WELL

SICK

DEAD

Model Outcome ?

Markov cohort trace

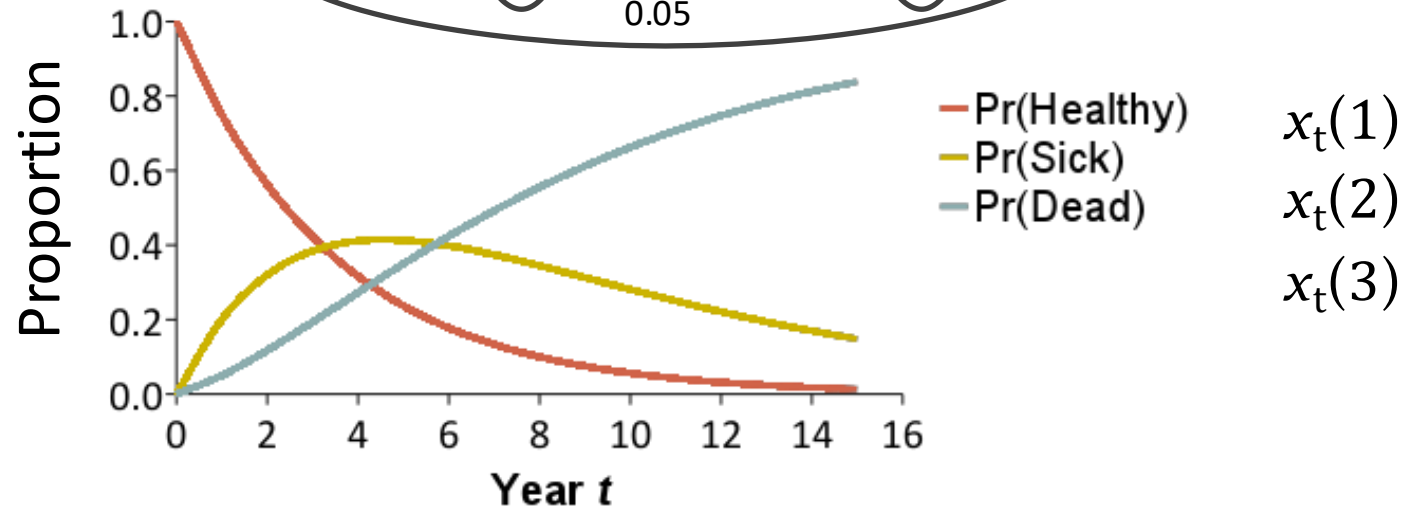- Reflects the distribution of a cohort of patients over a set of states over time
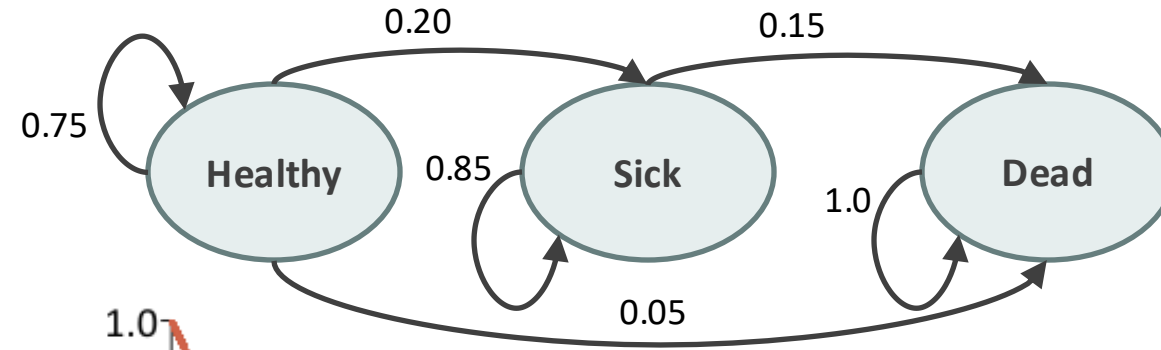

$$x_{10} = [0.06 \qquad 0.28 \qquad 0.66]$$

Markov cohort trace

- Reflects the distribution of a cohort of patients over a set of states over time

$x_{15} = [0.01 \qquad 0.15 \qquad 0.84]$

Markov cohort trace

- In R, let's define the cohort trace as `m_M` and the transition matrix as `m_P`

- To compute the trace, iterate the matrix multiplication between the state vector at time t and the transition matrix

```r
for(t in 1:n_t){
  m_M[t + 1, ] <- m_M[t, ] %*% m_P
}
```

Markov Trace (Life-Years)

- Calculate expected remaining LE, QALE, costs
  - Multiply cohort distribution by state-specific values to calculate expected value at each time
  - Sum expected values over time (discount if desired)

Life-Years: 1.0   1.0   0.0

Time	Healthy	Sick	Dead	E[LYs]
0	1.0	0.0	0.0	--
1	0.75	0.20	0.05	
2	0.56	0.32	0.12	
3	0.42	0.38	0.19	
	…	…	…	

Sum

$* 1/(1+r)$

$* 1/(1+r)^2$

$* 1/(1+r)^3$

Total life years: 6.77 years
(Remaining life expectancy)

Markov Trace (Costs)

- Calculate expected remaining LE, QALE, costs
  - Multiply cohort distribution by state-specific values to calculate expected value at each time
  - Sum expected values over time (discount if desired)

Costs:	$500	$2,500	$0	
Time	Healthy	Sick	Dead	E[Costs]
0	1.0	0.0	0.0	--
1	0.75	0.20	0.05	
2	0.56	0.32	0.12	
3	0.42	0.38	0.19	
	…	…	…	

Sum

* 1/(1+r)

* 1/(1+r)^2

* 1/(1+r)^3

Total costs: $11,557

(Total remaining lifetime costs)   69

Transition Probabilities

- Pr(Healthy → Dead) may not be conceptualized as one number
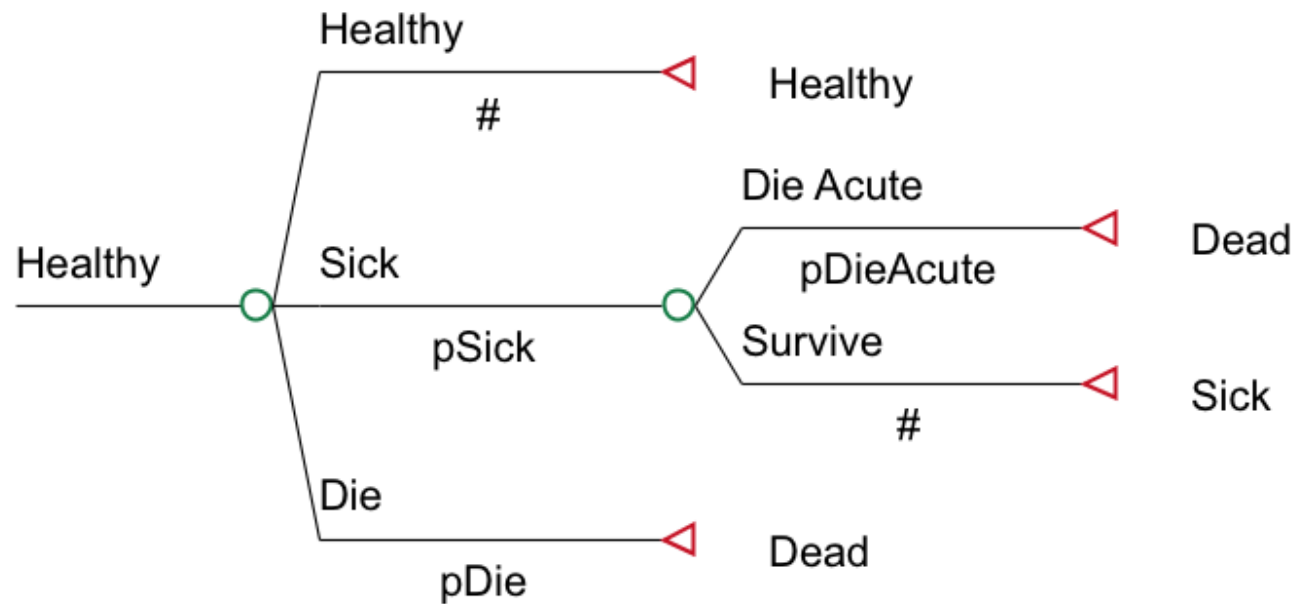
- p_HD = p_Die + p_Sick * p_DieAcute

Monte Carlo Simulation

1. Determine initial state at random, using the distribution of m_0

2. Simulate individual history, using random numbers to determine actual transitions from transition probabilities

3. Record # of cycles in each state

4. Repeat 1-3 many times (N)

5. Calculate mean # of cycles from sample of N

6. Calculate sampling error of estimates from sample of N, to check that precision is adequate
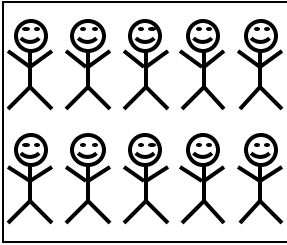
Monte Carlo Simulation
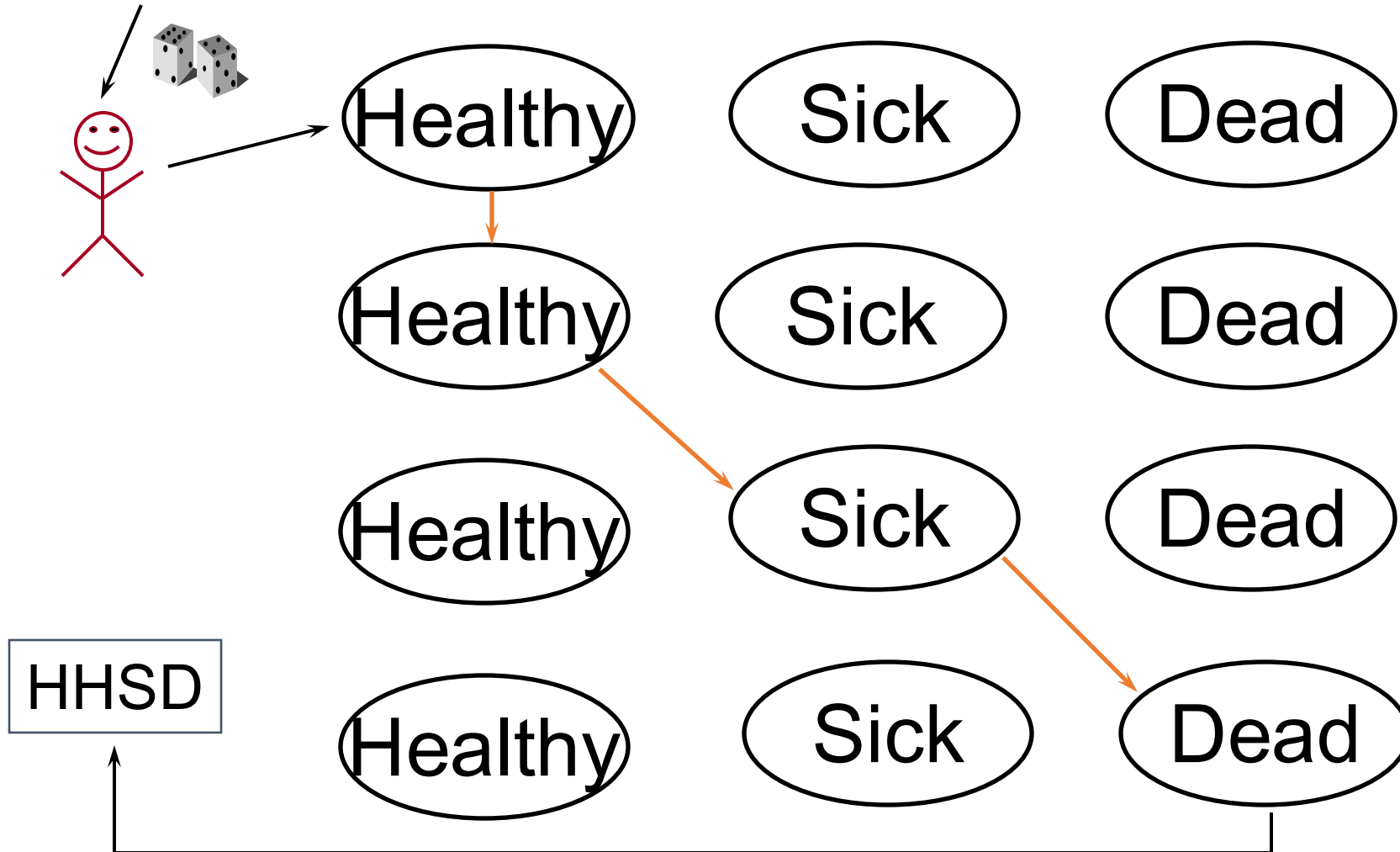
Comparison of Methods

- Cohort Method
  - short computing time
  - no sampling error in estimates
  - relatively easy to debug (with trace)
  - models can get large
- Monte Carlo Simulation
  - works well if there are a large # of variables
  - takes considerable computing time
  - potential for sampling error
  - more trouble debugging

Benefits of Markov Models

- Extrapolate benefits and costs beyond time horizon of existing data

- Consider all relevant policy strategies

- Incorporate data from multiple sources

- Evaluates "what if" scenarios

Extend Beyond Time Horizon

- Can "translate" an intermediate endpoint (e.g., increase in CD4 count, decrease of employment) into policy endpoints such as life years saved, quality-adjusted life years gained or economic returns

- Incorporates important long-term effects of policies

Data from Multiple Sources

- Data from primary sources

- Existing databases

- Studies reported in the literature

- Expert opinion

"What If" Scenarios

- How great would the increase in school attendance of a conditional cash transfer (CCT) program has to be to justify its implementation at a national level?

- How effective does a policy need to be, and at what duration of treatment effect, to replace current practices?

- Identifies important gaps in our knowledge

Typical Problems in Markov Modeling

- Population heterogeneity (e.g., risk factors)
  - » decompose states

- Transition probabilities depend on prior history
  - » expand state descriptions to reflect prior states
  - » special case (tunnel states): transition probabilities depend on duration in current state

R session

Time-dependent

Time-dependency

- **Since start of the simulation**
- Transition probabilities often depend on <u>age</u>
  - Background mortality
  - Risk of developing disease or experiencing an event
- **Depending on state residency**
- Some transition probabilities depend on time since an event, not age
  - e.g., The risk of developing recurrence among newly diagnosed cancer patients declines with time

Time-dependency since simulation start

- Transition probabilities often depend on time since model start
  - Background mortality
  - Risk of developing disease or experiencing an event

- In other words, matrix P is not the same every cycle

- Replace matrix P with matrices P_t, where t is time since model start

The Sick-Sicker model

- Four health states
- All individuals start in the Healthy state
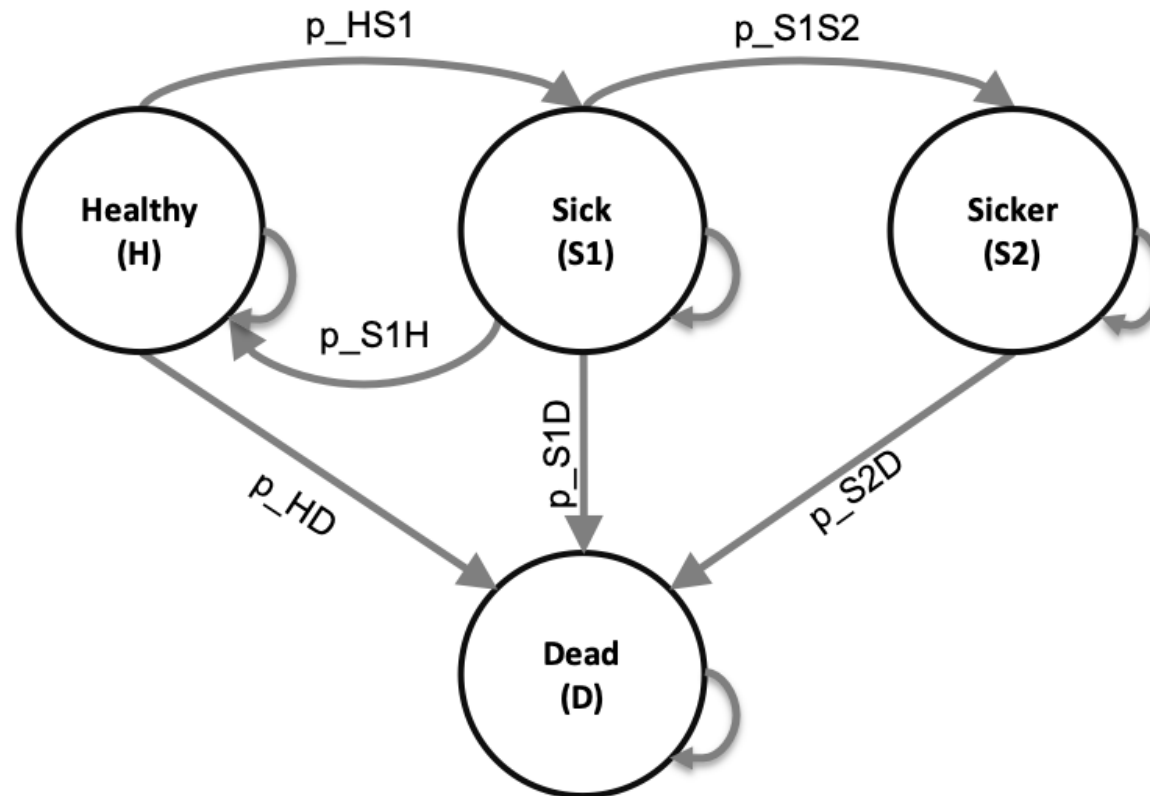
Time-dependency since simulation start

- We create a 3D <u>array,</u> `a_P`, that stores a collection of time-varying transition matrices, P_t, in the third dimension

- For the Sick-Sicker Markov model:

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

Time-dependency since simulation start

- Iterate over the third dimension of `a_P`

```
for(t in 1:n_t){
  m_M_ad[t + 1, ] <- m_M_ad[t, ] %*% a_P[, , t]
}
```

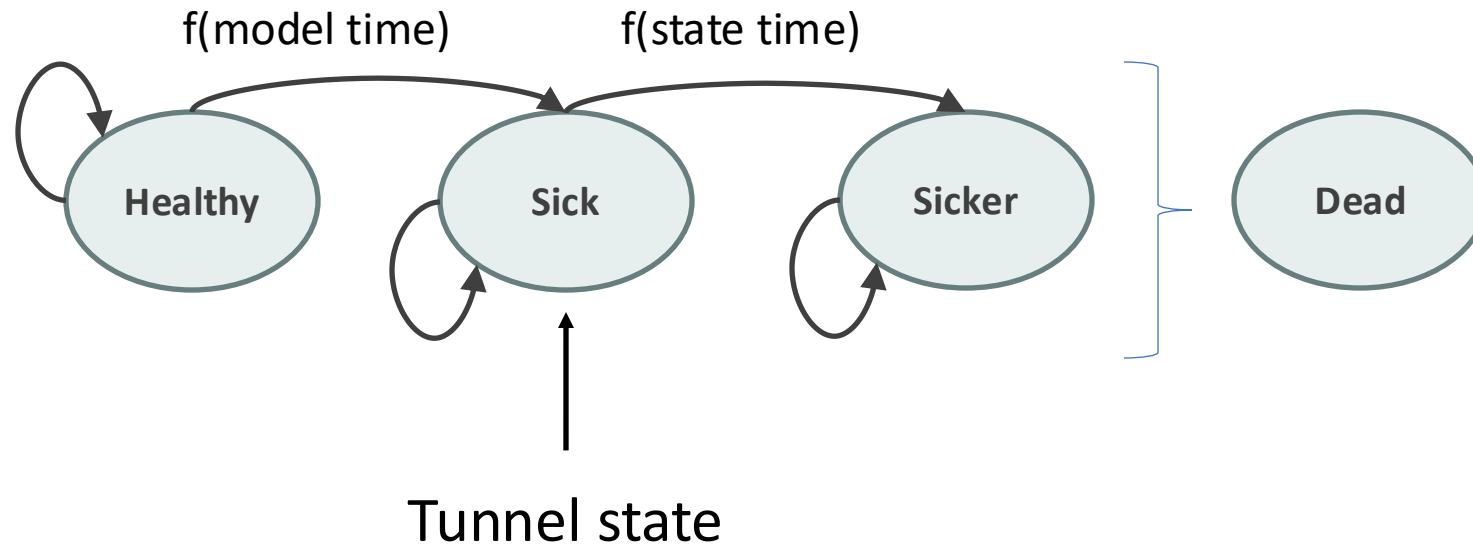# Time-dependency based on state-residence

- "Memoryless" property of Markov models is a BIG assumption
  - Transition probabilities only depend on the current state and not on past states

- Many transition probabilities depend on model history, not time since model start
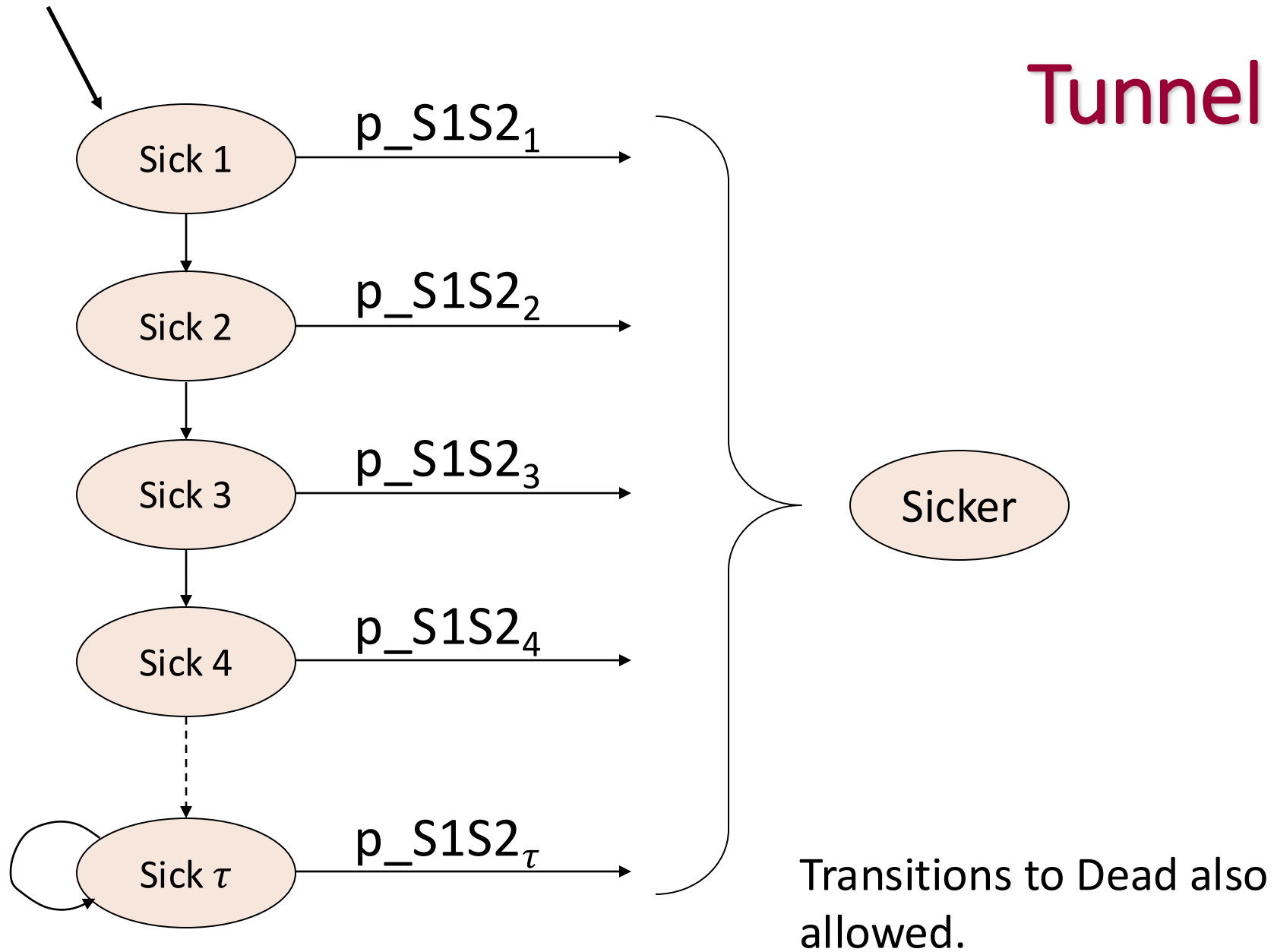 - Risk of myocardial infarction (MI) greater for persons with prior MI

Tunnel states

- If transition probabilities do not depend on the time since model start, replacing P with P_t does not work
  - E.g., Cohort of healthy patients at risk for cancer, but once cancer is diagnosed the risk of recurrence depends on time since diagnosis
- Solution?
  - Create "tunnel" states

Model with double time dependency

Tunnel states

p_S1S2$_1$

p_S1S2$_2$

p_S1S2$_3$

p_S1S2$_4$

p_S1S2$_\tau$

Sick 1

Sick 2

Sick 3

Sick 4

Sick τ

Sicker

Transitions to Dead also allowed.
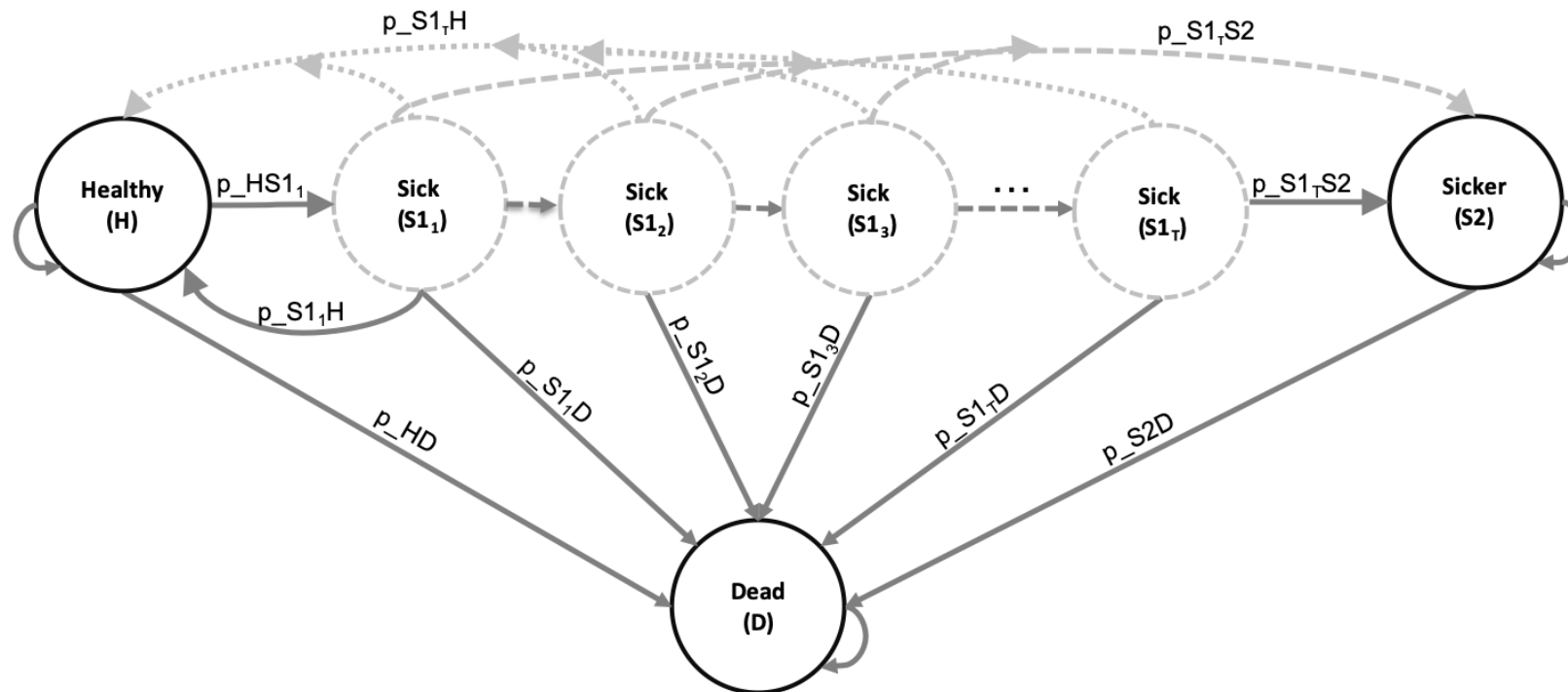
Time-dependent probabilities

- Progression from Sick to Sicker increases the longer a person has been sick

- This increase follows a Weibull hazard:

$$p_{S1S2}(\tau) = \lambda \gamma \tau^{(\gamma - 1)}$$

- τ represents the time since getting Sick

Time-dependent probabilities

- Expand the states of the 3D <u>array</u> by the number of cycles considered in the time-dependency variable(s)

- For the Sick-Sicker Markov model:

Time-dependent probabilities

- Expand the states of the 3D <u>array</u> by the number of cycles considered in the time-dependency variable(s)
- The transition array for the Sick-Sicker Markov model:

$$
\mathbf{a\_P\_tunnels} =
\begin{bmatrix}
p_{[H,H,1]} & p_{[H,S1_1,1]} & p_{[H,S1_2,1]} & \cdots & p_{[H,S1_T,1]} & p_{[H,S2,1]} & p_{[H,D,1]} \\
p_{[S1_1,H,1]} & p_{[S1_1,S1_1,1]} & p_{[S1_1,S1_2,1]} & \cdots & p_{[S1_1,S1_T,1]} & p_{[S1_1,S2,1]} & p_{[S1_1,D,1]} \\
p_{[S1_2,H,1]} & p_{[S1_2,S1_1,1]} & p_{[S1_2,S1_2,1]} & \cdots & p_{[S1_2,S1_T,1]} & p_{[S1_2,S2,1]} & p_{[S1_2,D,1]} \\
\vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\
p_{[S1_T,H,1]} & p_{[S1_T,S1_1,1]} & p_{[S1_T,S1_2,1]} & \cdots & p_{[S1_T,S1_T,1]} & p_{[S1_T,S2,1]} & p_{[S1_T,D,1]} \\
p_{[S2,H,1]} & p_{[S2,S1_1,1]} & p_{[S_2,S1_2,1]} & \cdots & p_{[S2,S1_T,1]} & p_{[S2,S2,1]} & p_{[S2,D,1]} \\
p_{[D,H,1]} & p_{[D,S1_1,1]} & p_{[D,S1_2,1]} & \cdots & p_{[D,S1_T,1]} & p_{[D,S2,1]} & p_{[D,D,1]}
\end{bmatrix}
$$

n_t n_s n_s

$p_{[H,H,2]}$ $p_{[H,S1_1,2]}$ $p_{[H,S1_2,2]}$ $\cdots$ $p_{[H,S1_T,2]}$ $p_{[H,S2,2]}$ $p_{[H,D,2]}$

$p_{[H,H,n_t]}$ $p_{[H,S1_1,n_t]}$ $p_{[H,S1_2,n_t]}$ $\cdots$ $p_{[H,S1_T,n_t]}$ $p_{[H,S2,n_t]}$ $p_{[H,D,n_t]}$

$p_{[S1_1,D,2]}$ $p_{[S1_2,D,2]}$ $p_{[S1_T,D,2]}$ $p_{[S2,D,2]}$ $p_{[D,D,2]}$

$p_{[S1_1,D,n_t]}$ $p_{[S1_2,D,n_t]}$ $p_{[S1_T,D,n_t]}$ $p_{[S2,D,n_t]}$ $p_{[D,D,n_t]}$

R session