

# 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

# cSTMs (aka Markov models) are most useful when...

- the decision problem involves risk over time
- timing of events is important
  - early risk, late benefit
- events may happen more than once
- states change 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

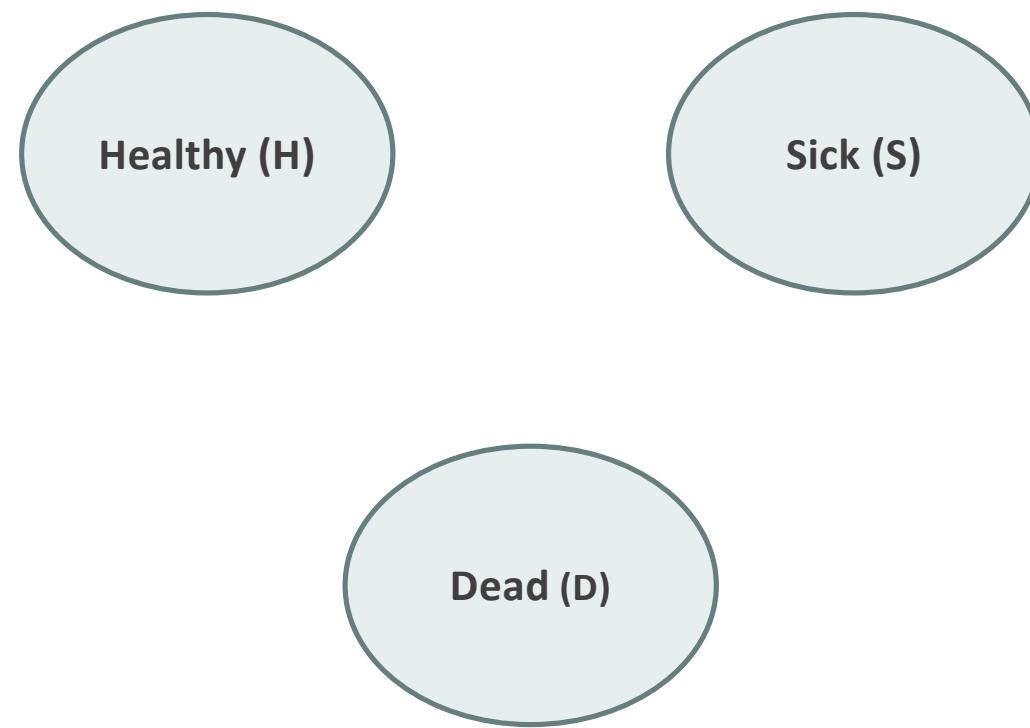
# Implicit Assumptions

- 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)

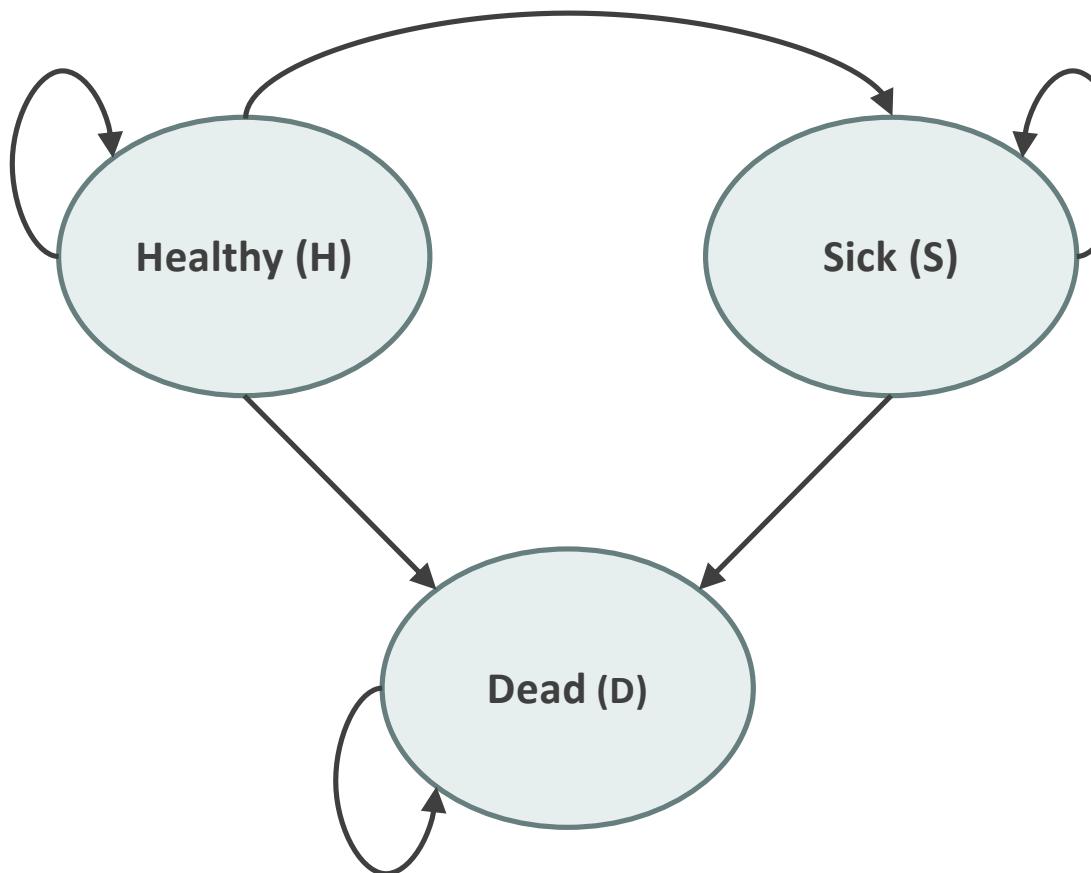
# Markov Health States



# Building a Markov Model

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# State Transition Diagram (STD)



# Building a Markov Model

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- Determine transitions
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# 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
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# Transition Probability

The chance that patients in a state will transition to another state *during* a cycle

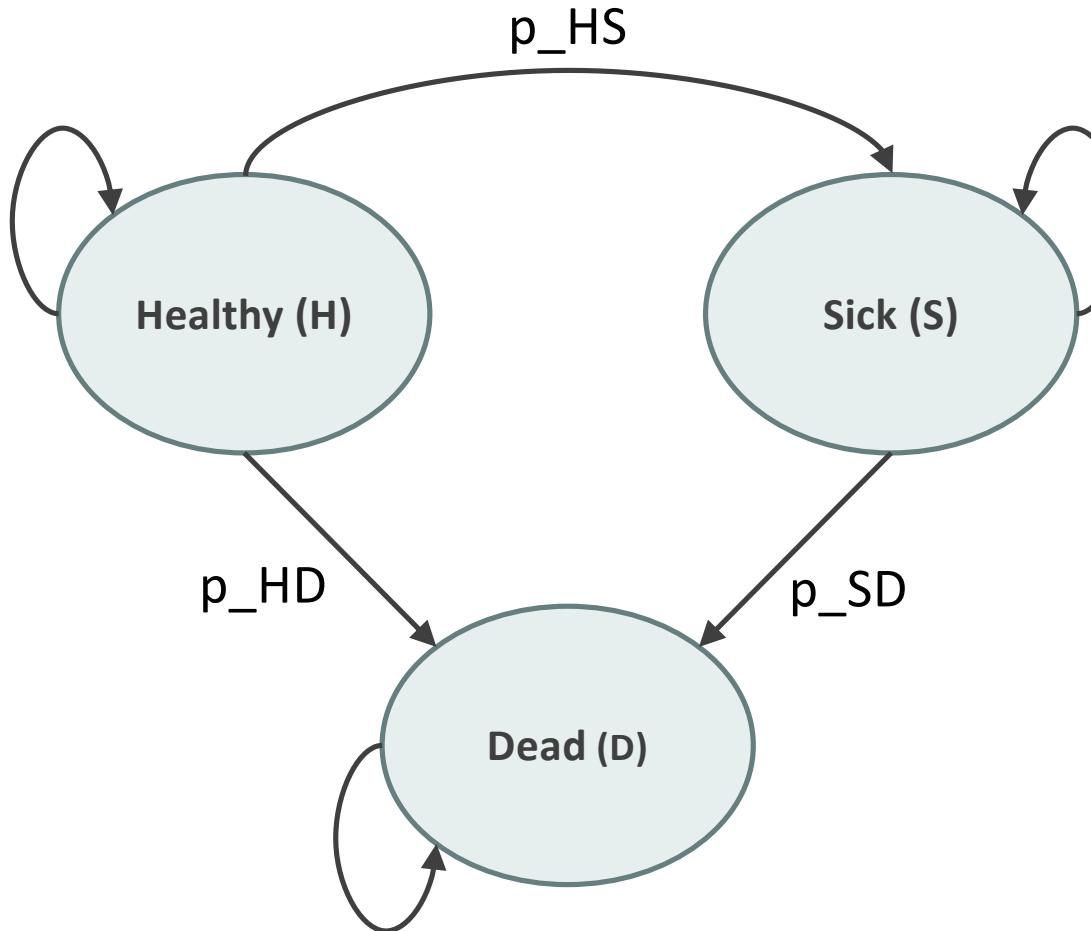
If individuals face a constant rate of,  $\lambda_{i,j}$ , of transitioning from health state  $i$  to health state  $j$ , the transition probability  $p_{i,j}$  is calculated as

$$p_{i,j} = 1 - \exp(-\lambda_{i,j})$$

This assumes events (i.e., transition between states) follow an exponential distribution

# State Transition Diagram (STD)

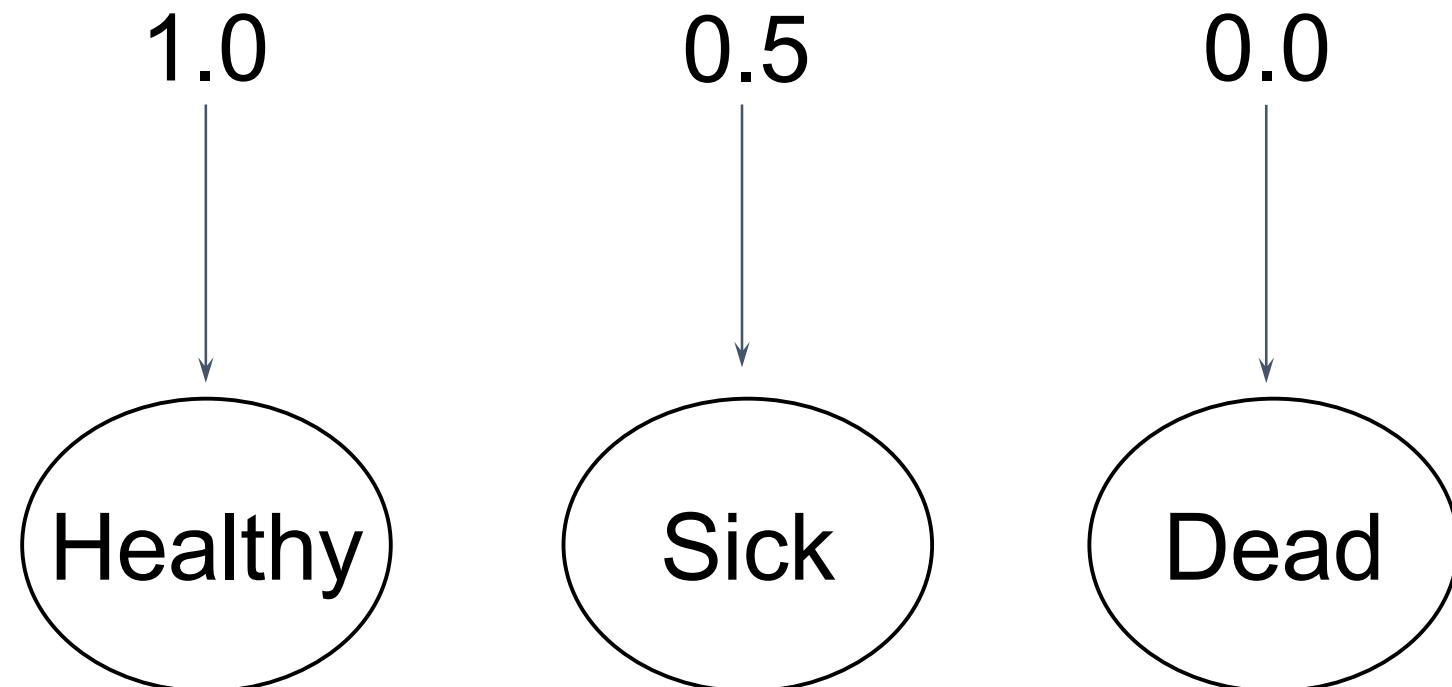
$p_{i,j}$ = transition probability from state  $i$  to state  $j$



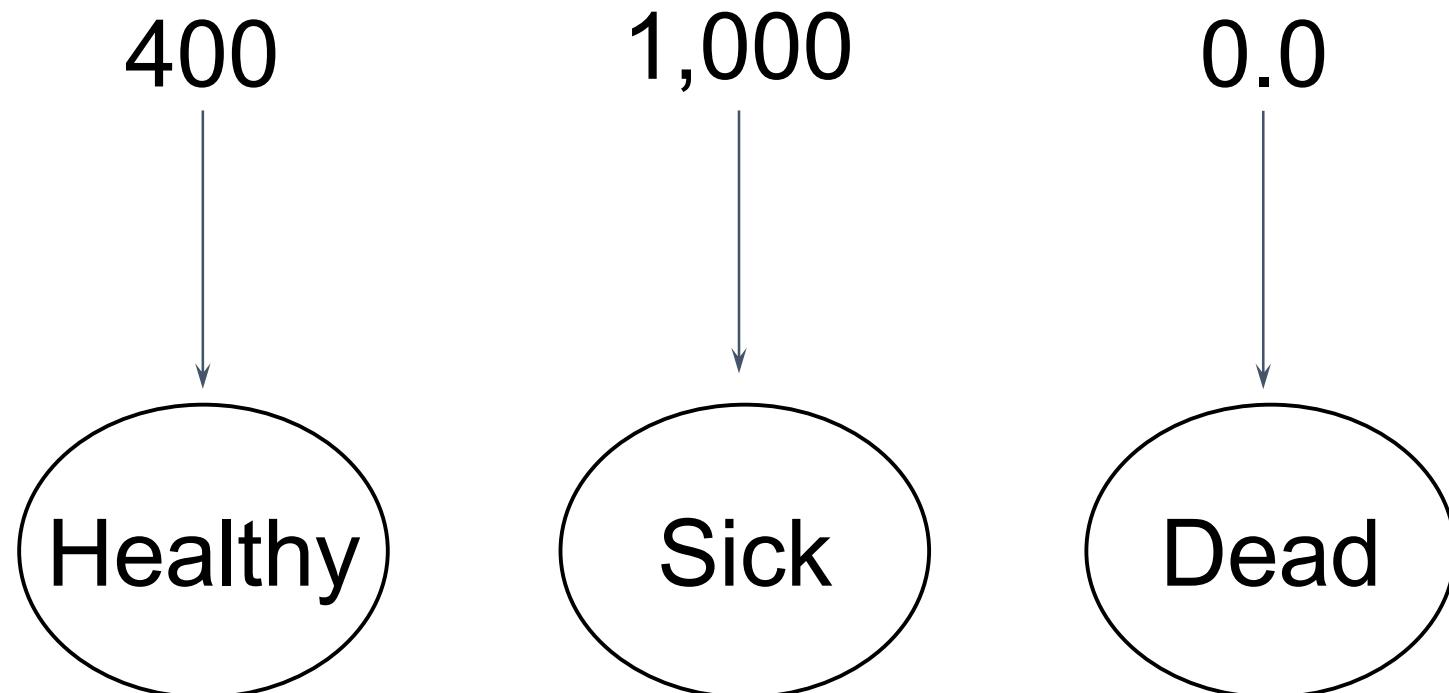
# Building a Markov Model

- 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 (utilities)



# Costs (\$)



# 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

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# Cohort Simulation

- A cSTM consists of three core components:
  1. A state vector  $\mathbf{m}_t$  that stores the distribution of the cohort across all  $n_S$  health states in cycle  $t$ , where  $t = [0, 1, \dots, n_T]$
  2. A cohort trace matrix  $M$  that stacks  $\mathbf{m}_t$  for all  $t$  and represents the distribution of the cohort in the various states over time
  3. A transition probability matrix  $P$

## State vector ( $m_t$ with $n_S$ health states):

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

$$\mathbf{m}_t = [m_{[t,1]} \ m_{[t,2]} \ \cdots \ m_{[t,n_S]}]$$

## 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 from state  $i$  to 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

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

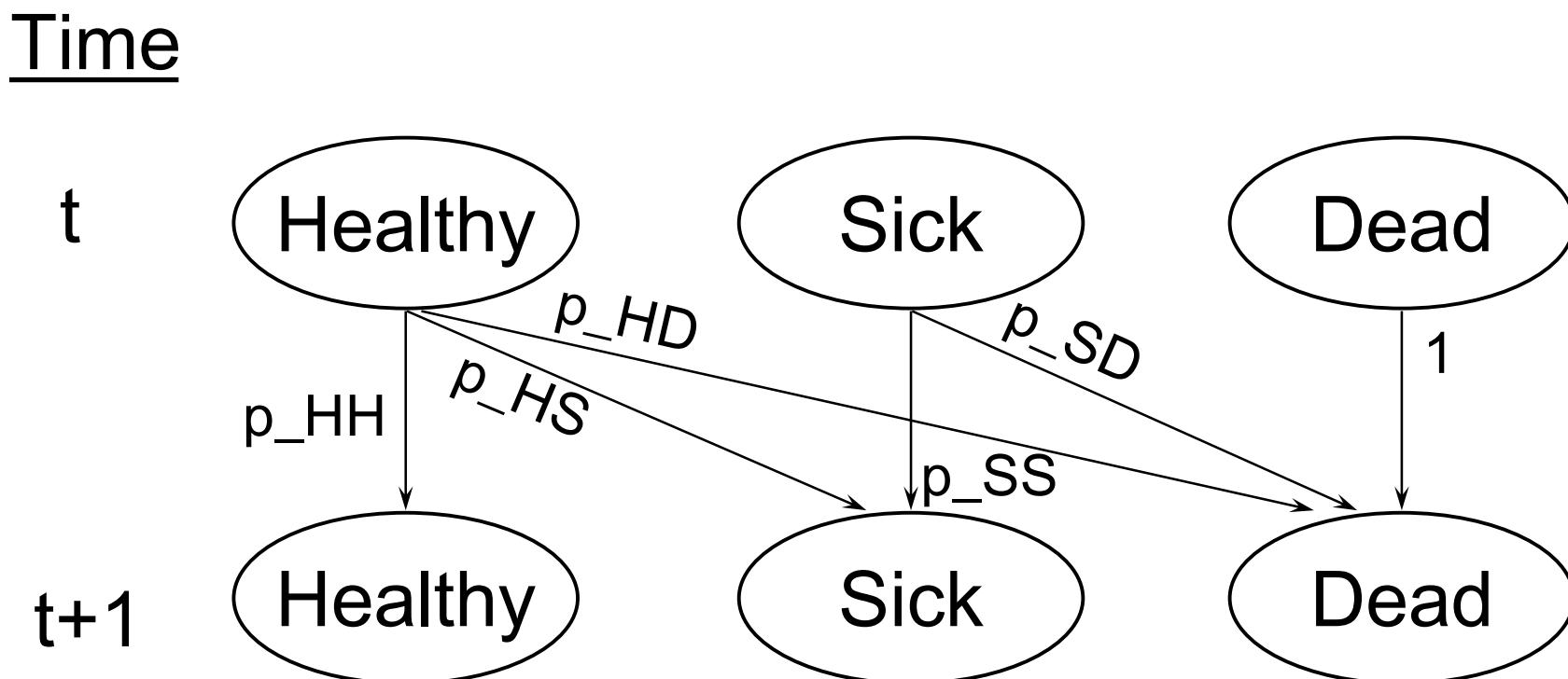
$$[m_{[t+1,1]} \ m_{[t+1,2]} \cdots m_{[t+1,n_S]}] = [m_{[t,1]} \ m_{[t,2]} \cdots m_{[t,n_S]}] \begin{bmatrix} & & P \\ & & \\ & & \end{bmatrix}$$

## 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

- Absorbing models (e.g., includes death)
  - Goal: Calculate *residence times* in transient states
    - » means (e.g., life expectancy)
    - » weighted means (e.g., QALE, discounted LE)
- Non-absorbing models (e.g., nonfatal states)
  - Goal: Calculate long-run proportions of time spent in each state
    - » equilibrium distribution across states

# Types of Markov Models

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- Non-absorbing models (e.g., nonfatal states)

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» equilibrium distribution across states

# Outputs of Absorbing Models

- Life expectancy: average number of cycles in “non-dead” states
- Weighted life expectancy: average number of cycles in “non-dead” 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

$$M = \begin{array}{ccccc} & & & \text{To} & \\ & & H & S & D \\ \text{From} & H & \left[ \begin{array}{ccc} p_{HH} & p_{HS} & p_{HD} \\ 0 & p_{SS} & p_{SD} \\ 0 & 0 & 1 \end{array} \right] \\ S & & & & \\ D & & & & \end{array}$$

## Initial State Vector

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

# Back to the Simple Example

## Transition Matrix

$$M = \begin{array}{ccccc} & & & \text{To} & \\ & & H & H & S & D \\ \text{From} & S & \left[ \begin{array}{ccc} 0.75 & 0.20 & 0.05 \\ 0 & 0.85 & 0.15 \\ 0 & 0 & 1 \end{array} \right] \\ D & & & & \end{array}$$

## Initial State Vector

$$m_0 = \begin{bmatrix} H \\ S \\ D \end{bmatrix} = [1 \quad 0 \quad 0]$$

# Cohort at next cycle using matrix multiplication

- Cohort distribution at next time step calculated through matrix multiplication

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

$$[m_{[t+1,1]} \ m_{[t+1,2]} \ m_{[t+1,3]}] = [m_{[t+1,1]} \ m_{[t+1,2]} \ m_{[t+1,3]}] \begin{bmatrix} & & \\ & & \\ & & P \end{bmatrix}$$

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

# Cohort at next cycle using matrix multiplication

- Cohort distribution at next time step calculated through matrix multiplication

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

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

# Cohort at next cycle using matrix multiplication

- Cohort distribution at next time step calculated through matrix multiplication

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

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

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

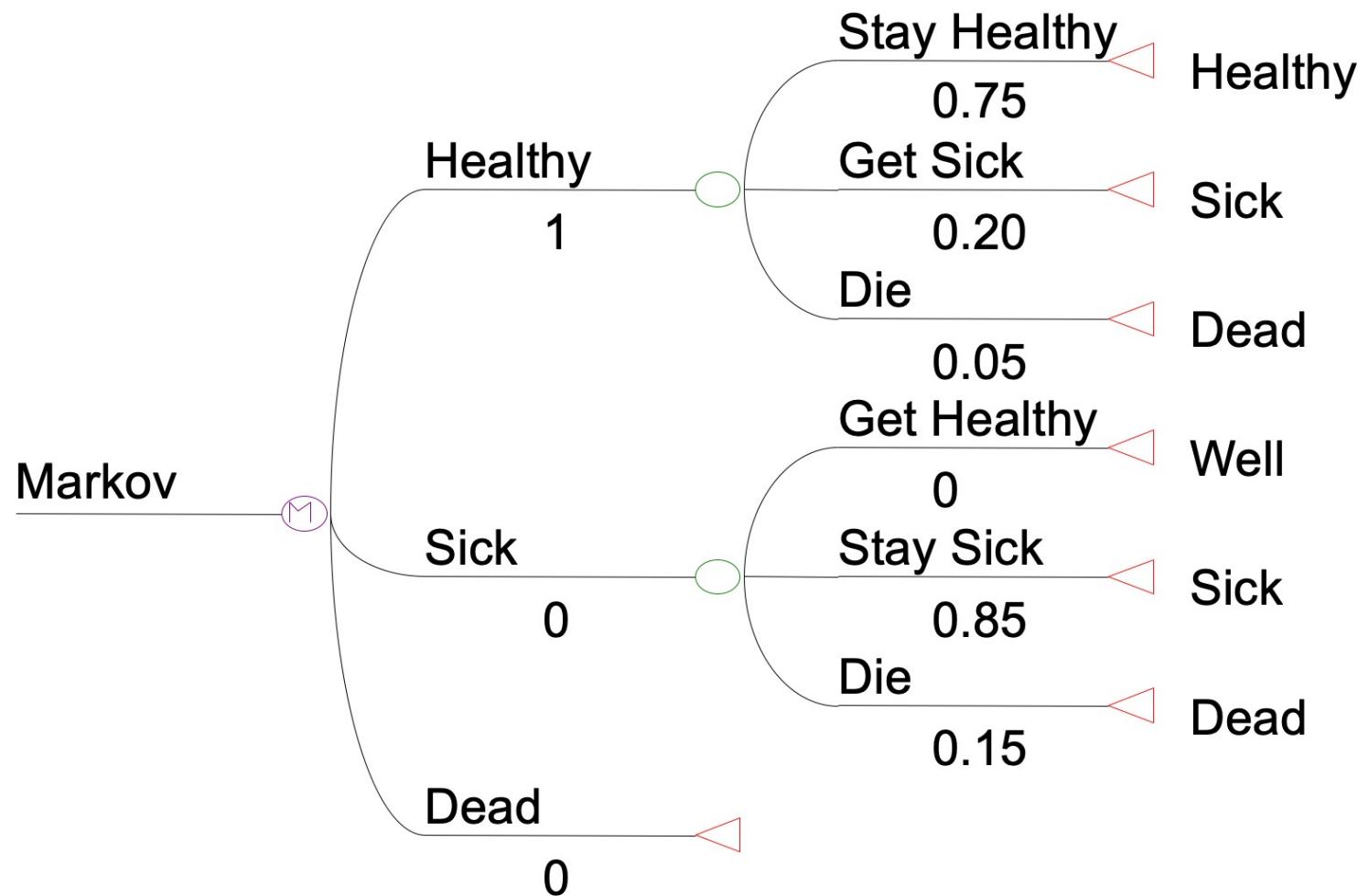
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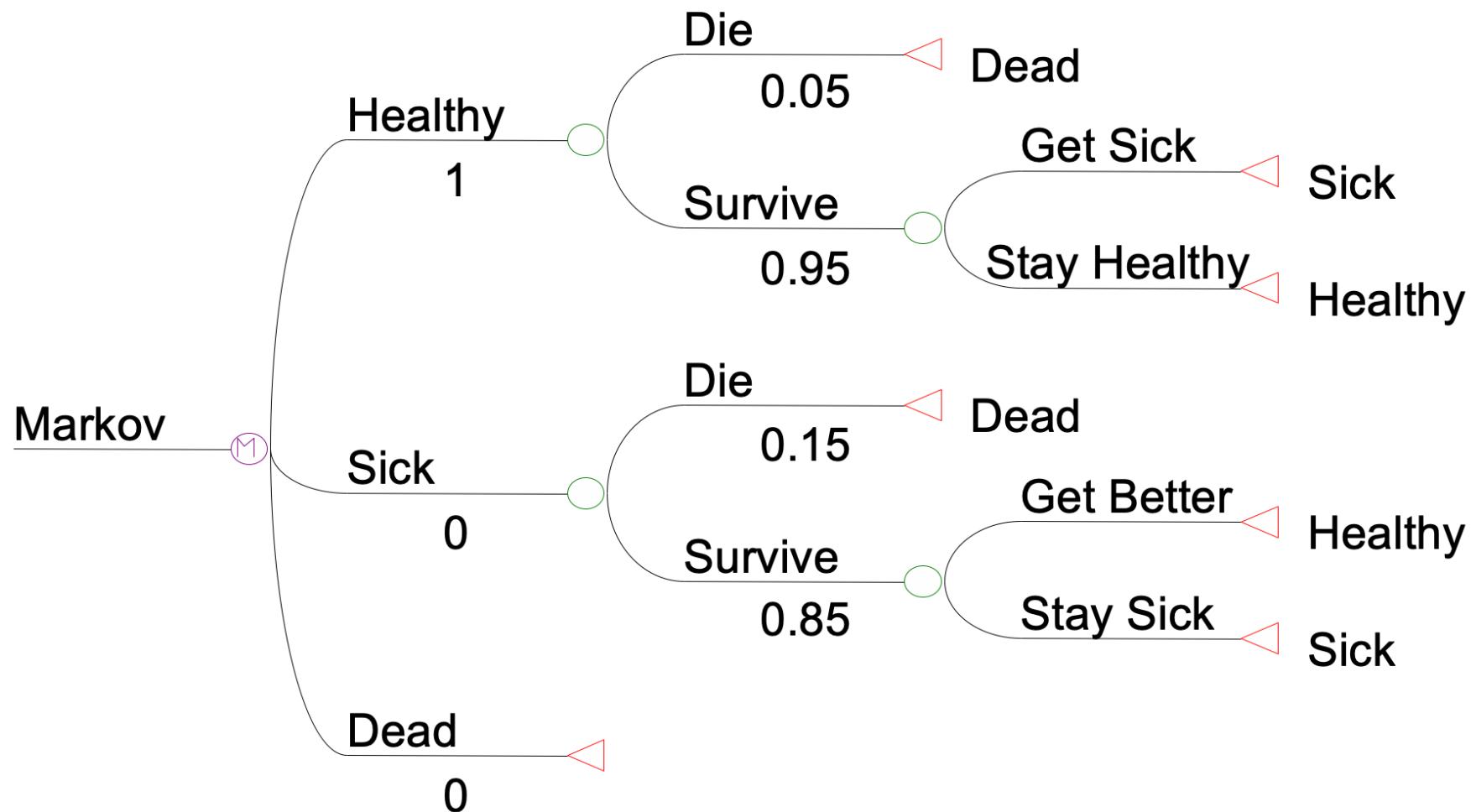
$$[0.75 \ 0.20 \ 0.05] = [1 \ 0 \ 0] \begin{bmatrix} 0.75 & 0.20 & 0.05 \\ 0 & 0.85 & 0.15 \\ 0 & 0 & 1 \end{bmatrix}$$

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

# Matrix Form in a Tree Form



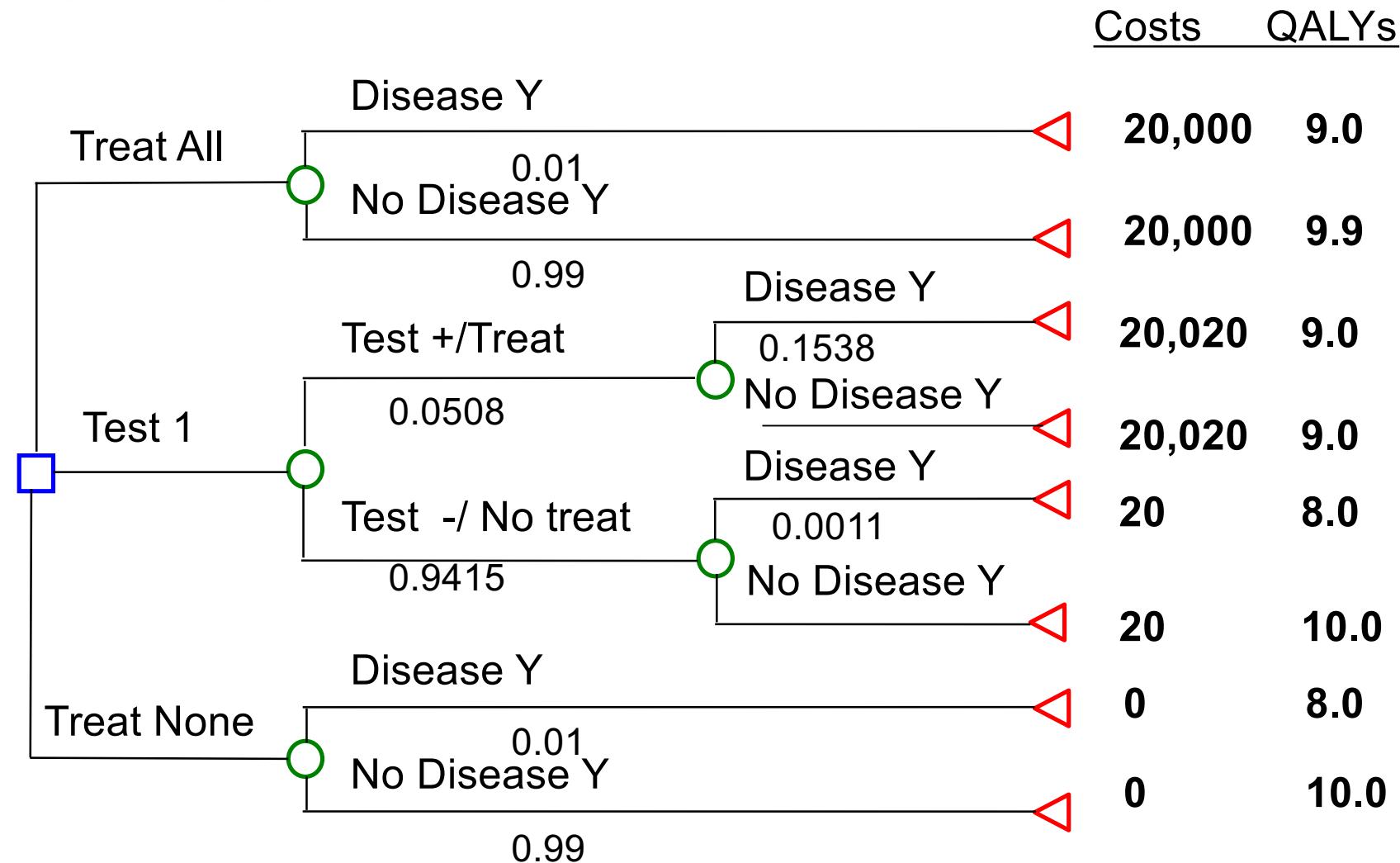
## A more common structure...



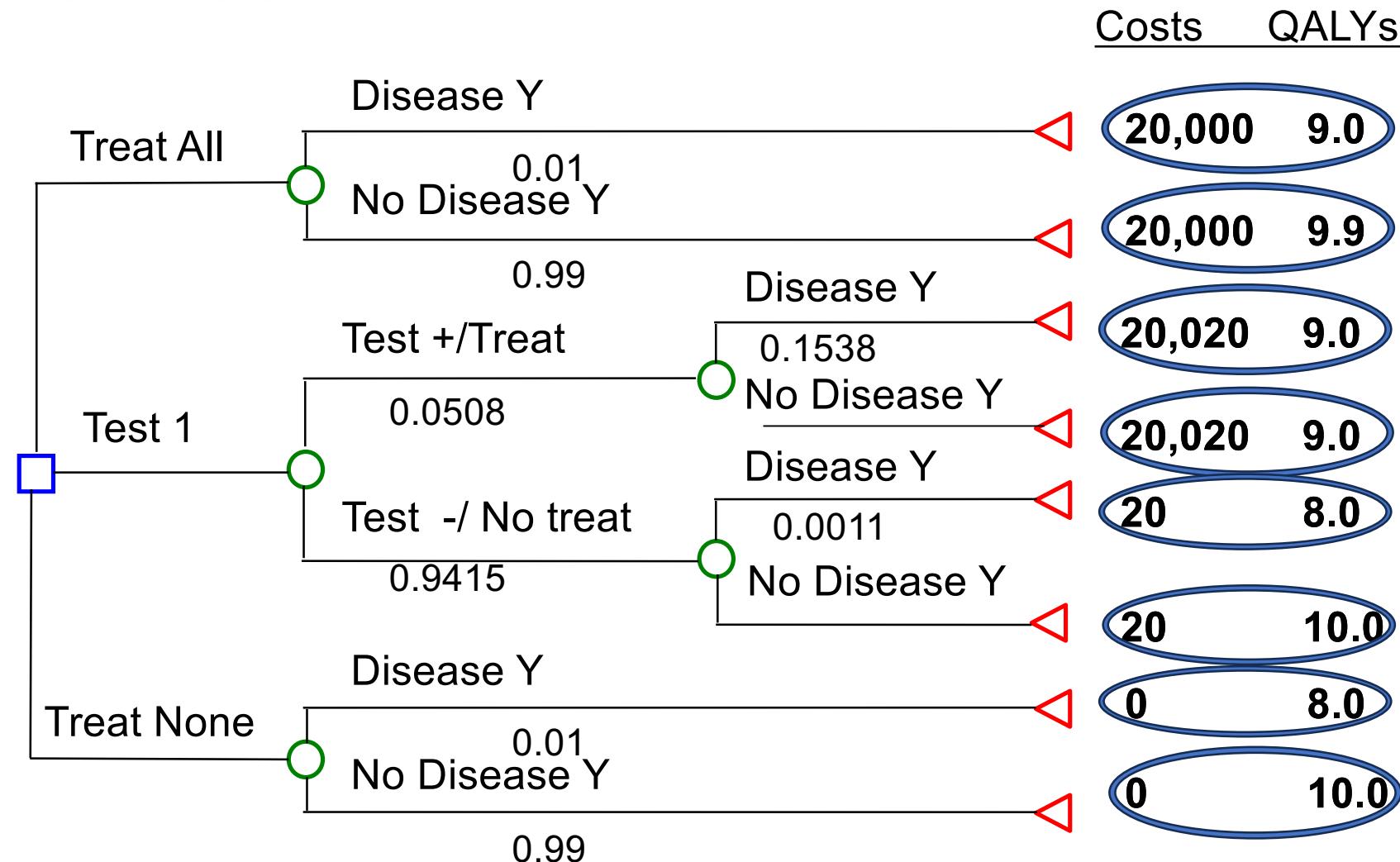
# Markov Cycle Trees

- 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

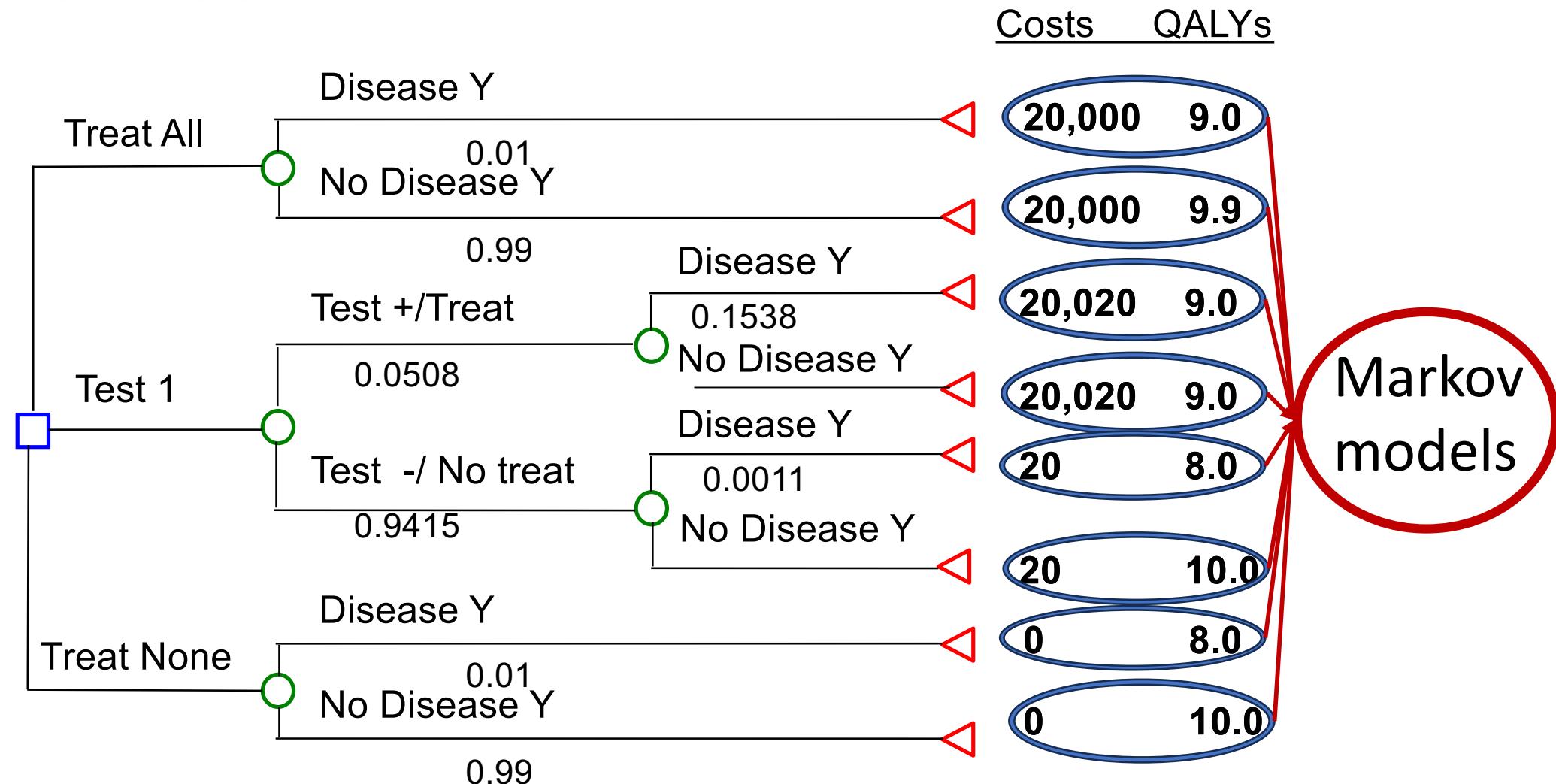


# CEA of Test 1

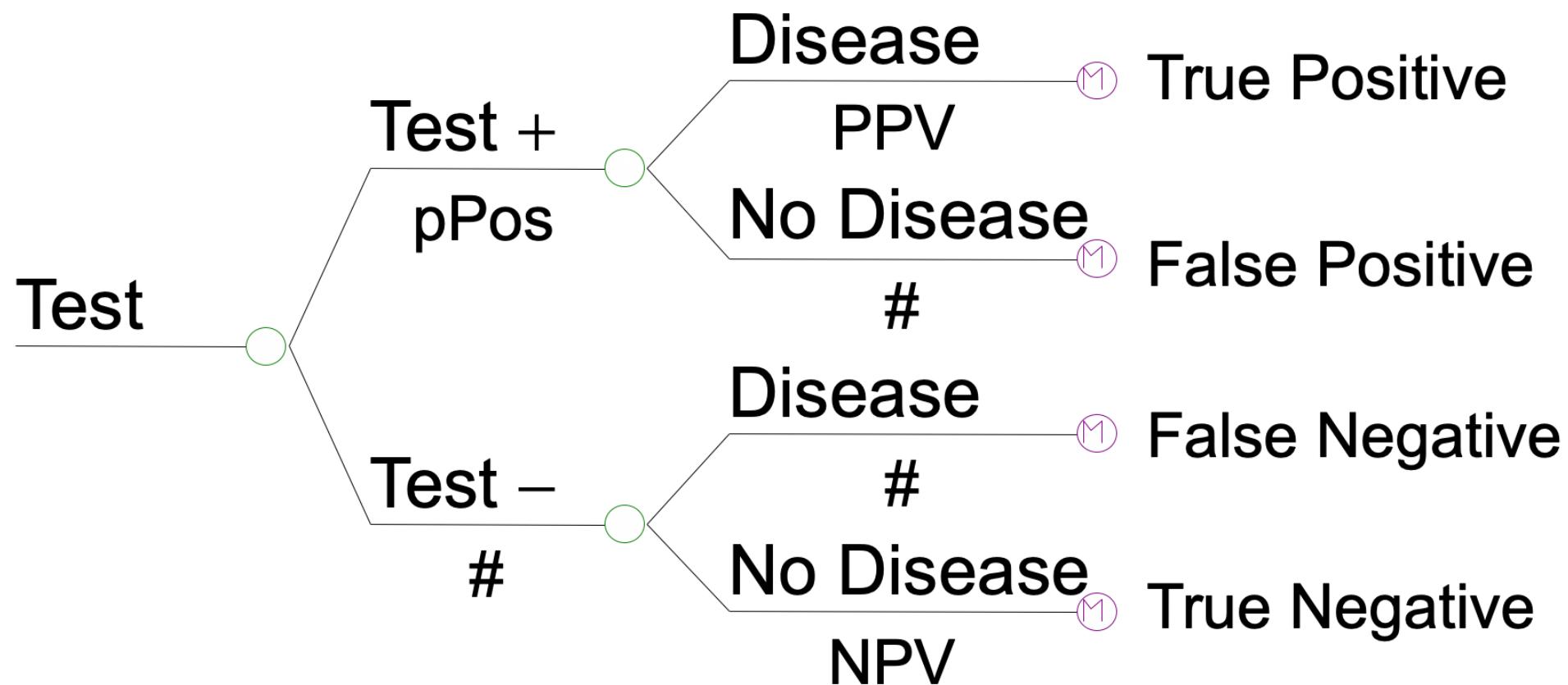


Where  
do these  
numbers  
come  
from?

# CEA of Test 1



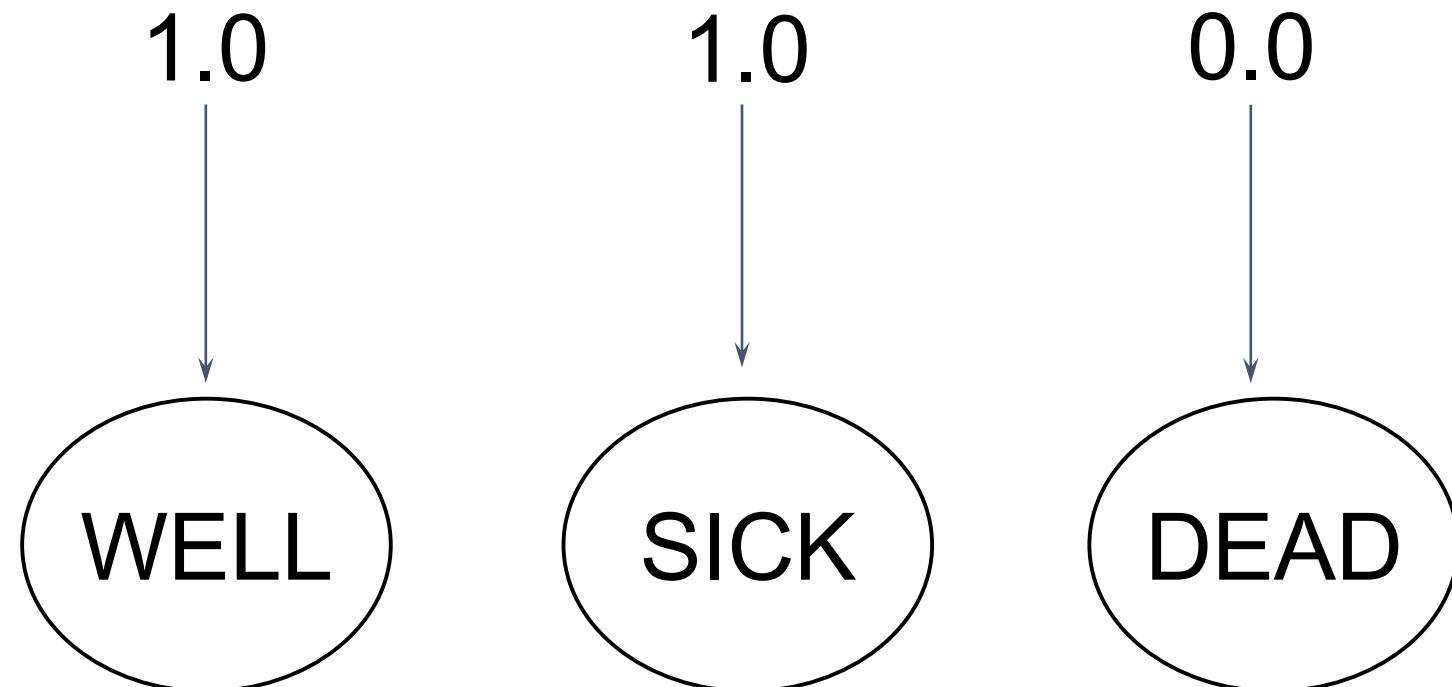
# Typical Diagnostic Test Strategy



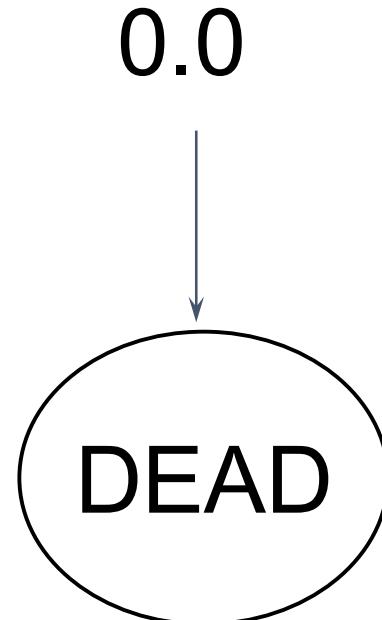
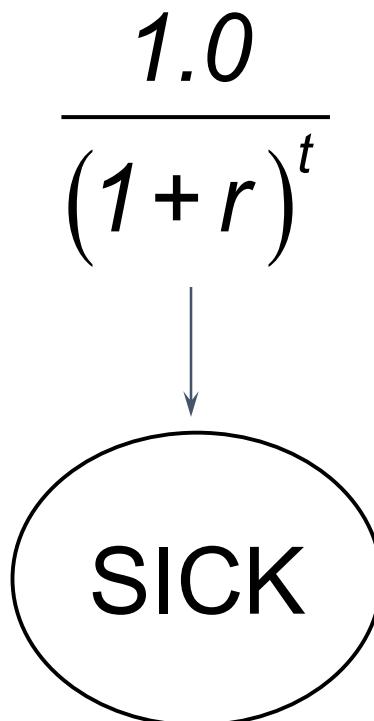
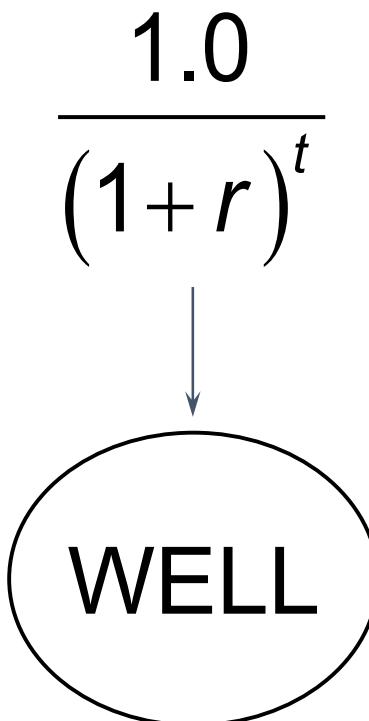
# Markov Cohort Method

- Generates a cohort trace (with 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)

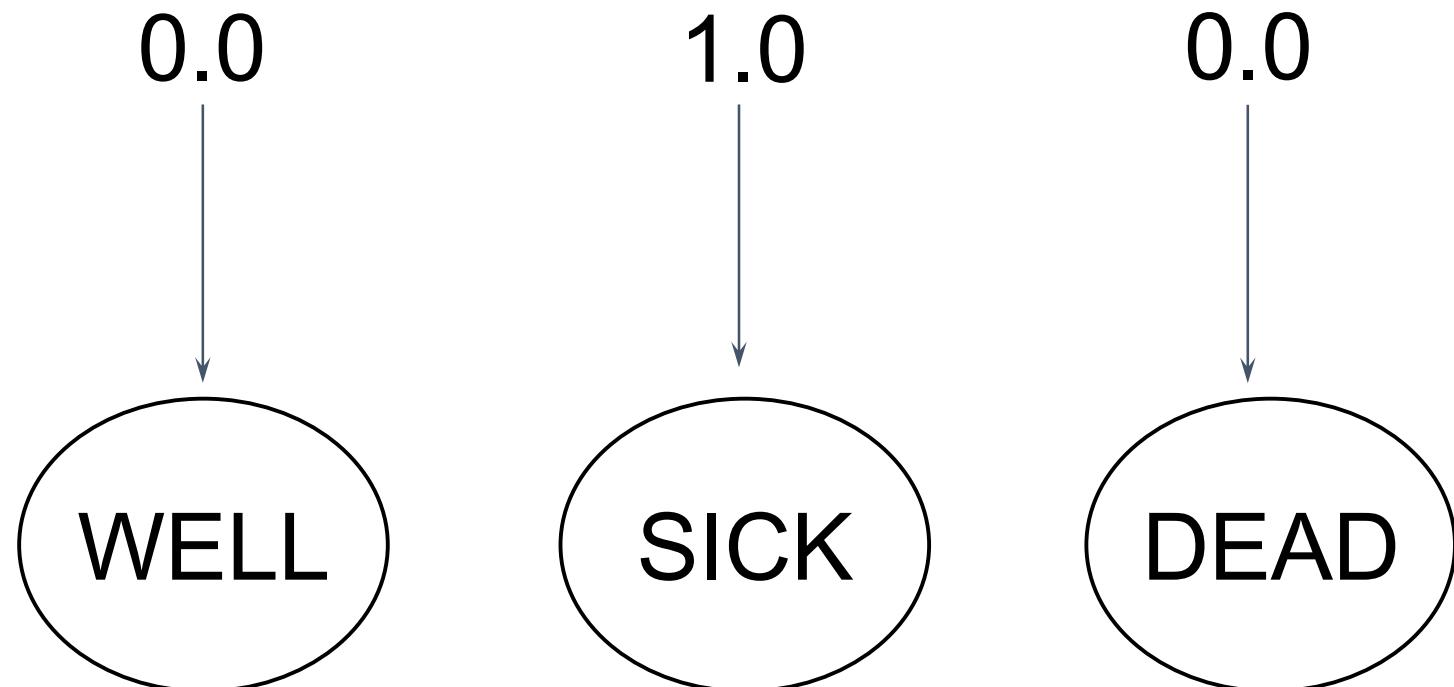
# Life Expectancy



# Discounted Life Expectancy (r = discount rate, t = \_stage)

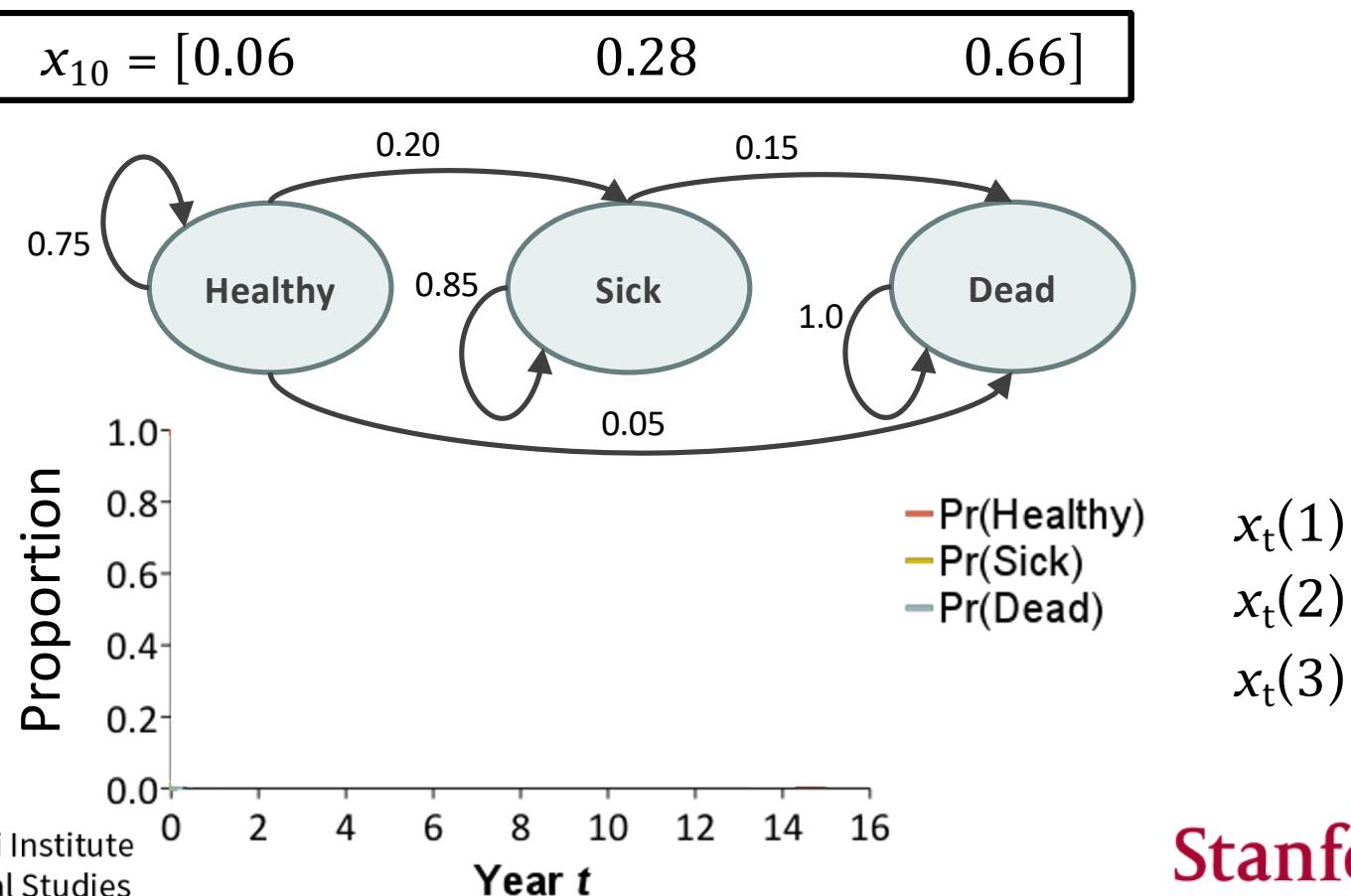


# Model Outcome ?



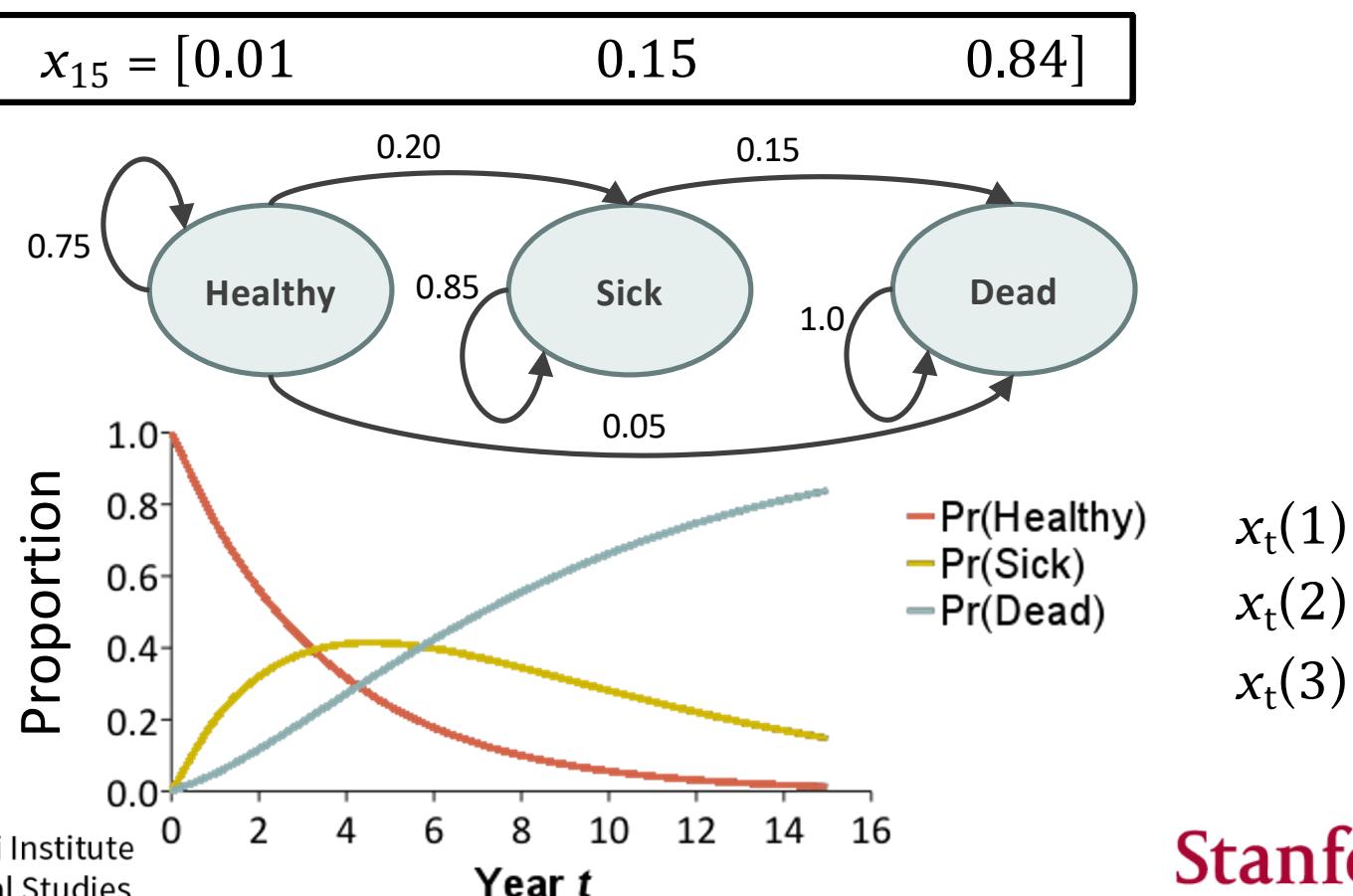
# Markov cohort trace

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



# Markov cohort trace

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



# 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

```
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

$$* \frac{1}{(1+r)}$$

$$* \frac{1}{(1+r)^2}$$

$$* \frac{1}{(1+r)^3}$$

Total life years: 6.67 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:	\$400	\$1,000	\$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	
	...	...	...	

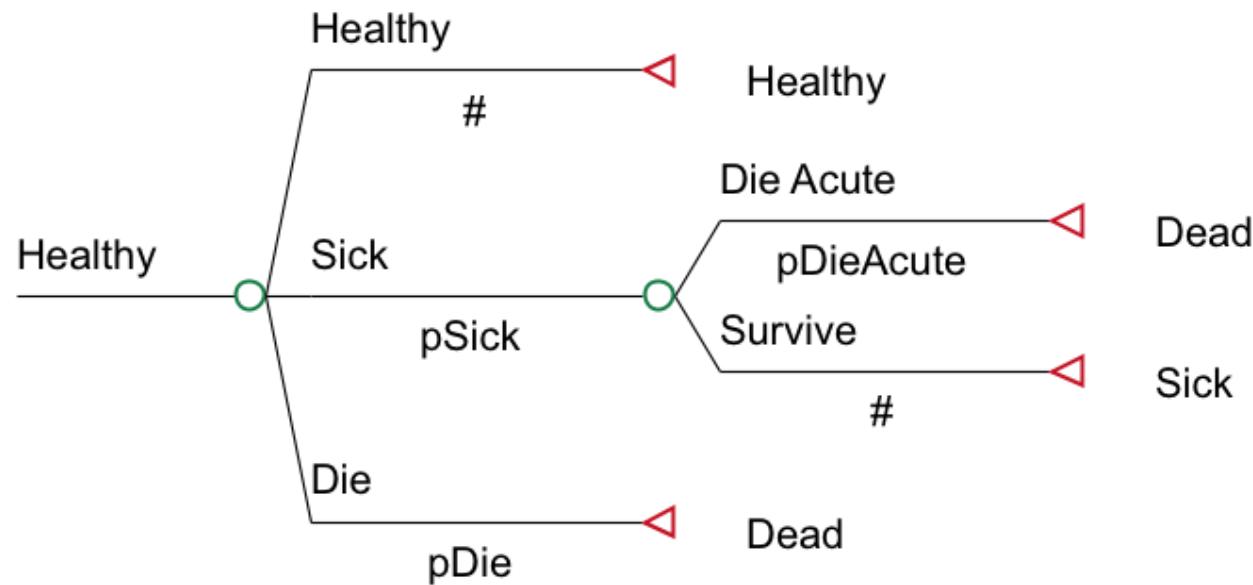
Total costs: \$6,933

Sum  
↓

$$\begin{aligned} & * \frac{1}{(1+r)} \\ & * \frac{1}{(1+r)^2} \\ & * \frac{1}{(1+r)^3} \end{aligned}$$

# Transition Probabilities

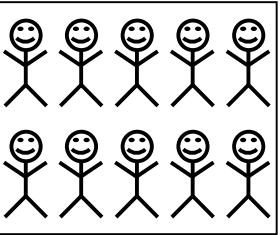
- $\Pr(\text{Healthy} \rightarrow \text{Dead})$  may not be conceptualized as one number



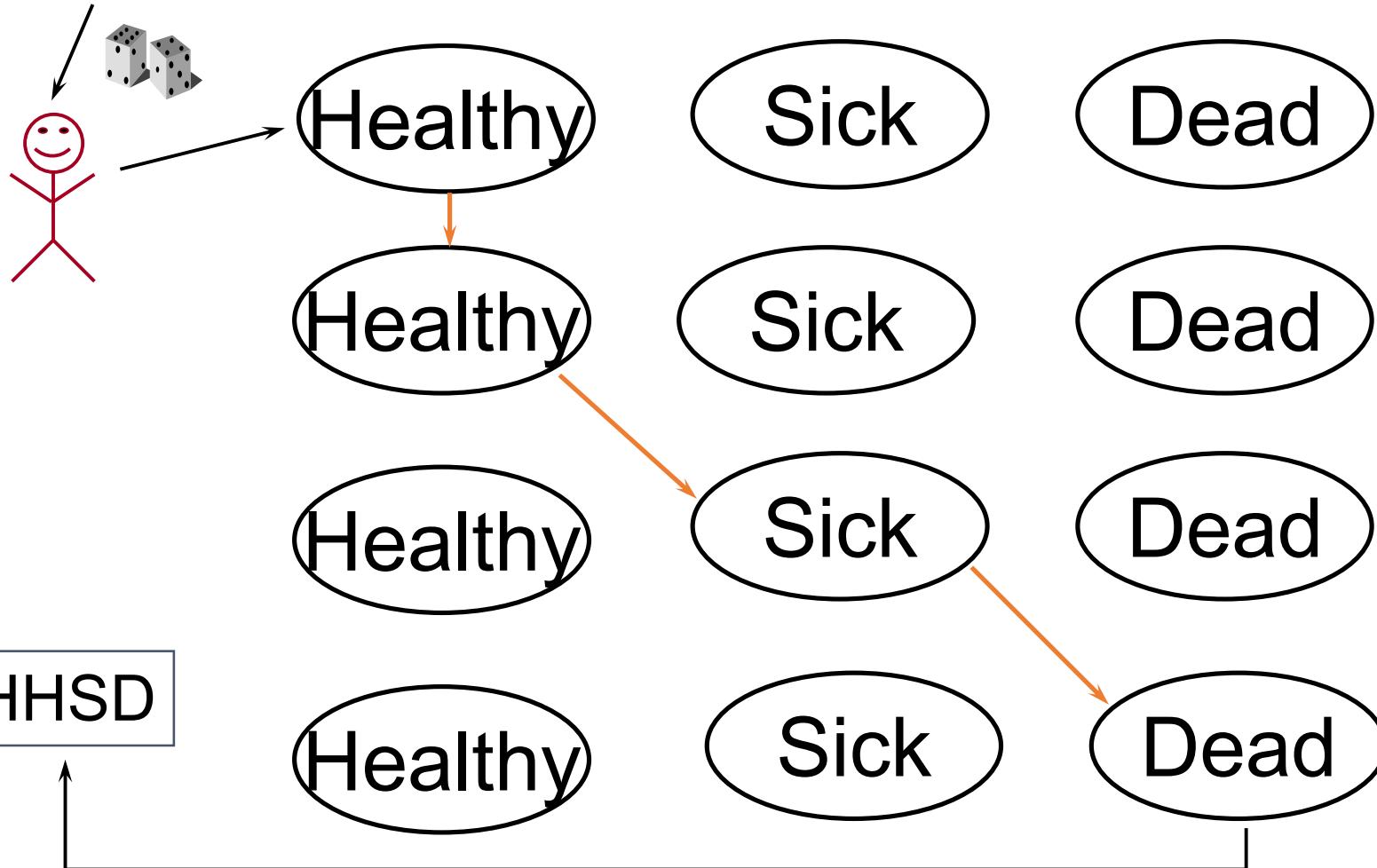
- $p_{HD} = p_{\text{Die}} + p_{\text{Sick}} * p_{\text{DieAcute}}$

# 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



# A tutorial on microsimulation modeling in R

Medical Decision Making



Impact Factor: 2.3 / 5-Year Impact Factor: 3.6

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## Microsimulation Modeling for Health Decision Sciences Using R: A Tutorial

[Eline M. Krijkamp](#), [Fernando Alarid-Escudero](#), [...], and [Petros Pechlivanoglou](#)   [View all authors and affiliations](#)

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<https://pubmed.ncbi.nlm.nih.gov/29587047/>

<https://journals.sagepub.com/doi/10.1177/0272989X18754513>

# 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 have 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 age
  - Create age-specific transition matrices
- 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 cSTMs

# Time-dependence

- **Since start of the simulation**
- Transition probabilities often depend on age
  - Background mortality
  - Risk of developing disease or experiencing an event
- **Depending on state residence**
- 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-dependence 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 from the start of the simulation

# Transition Matrix (time-homogeneous):

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

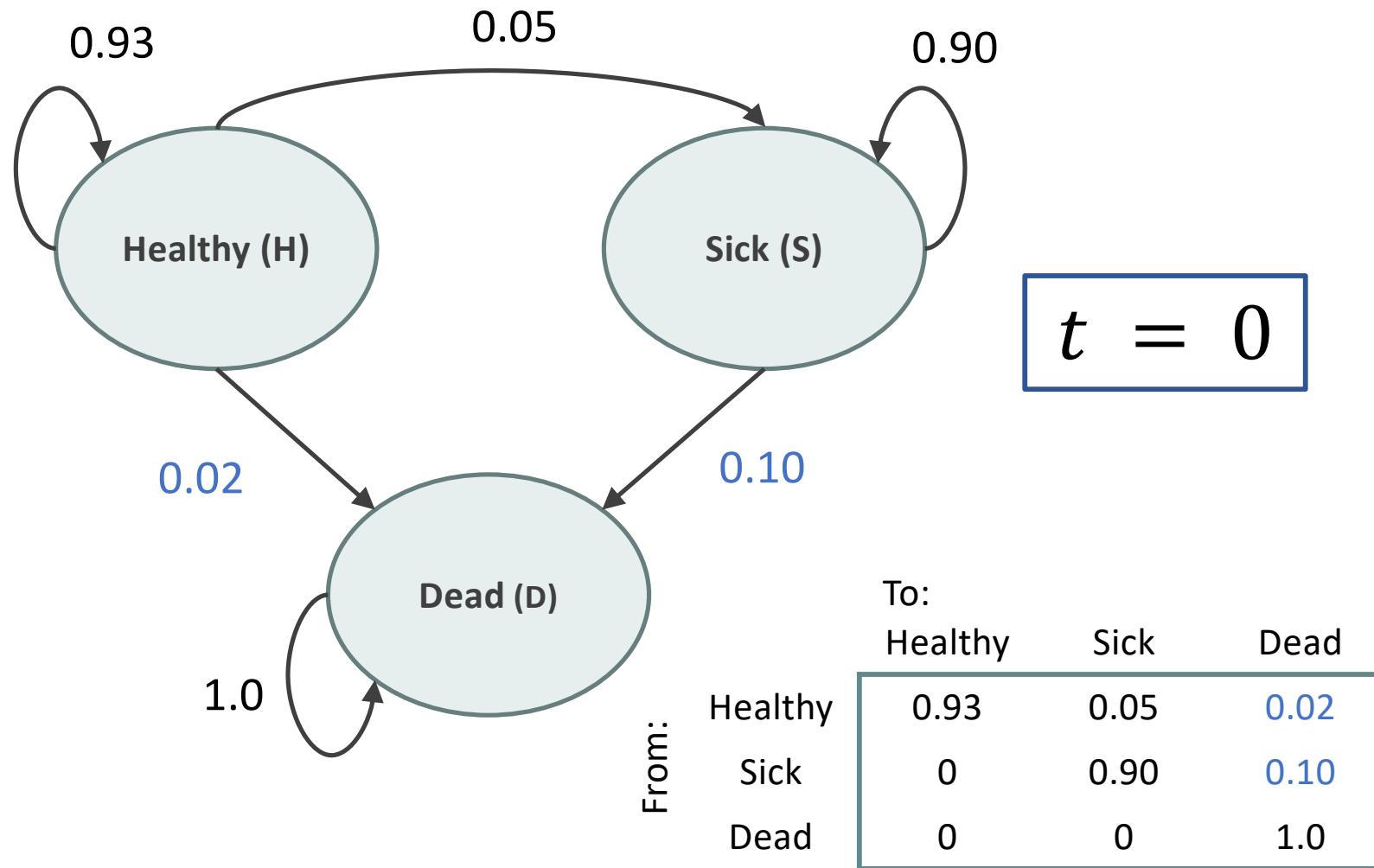
- Where  $p_{[i,j]}$  represents the transition probability of transitioning from state  $i$  to state  $j$ , and  $\{i, j\} = 1, \dots, n_S$ .
- $0 < p_{[i,j]} < 1$  and  $\sum_{j=1}^{n_S} p_{[i,j]} = 1$  for all  $i = 1, \dots, n_S$

## Transition Matrix (time-dependent):

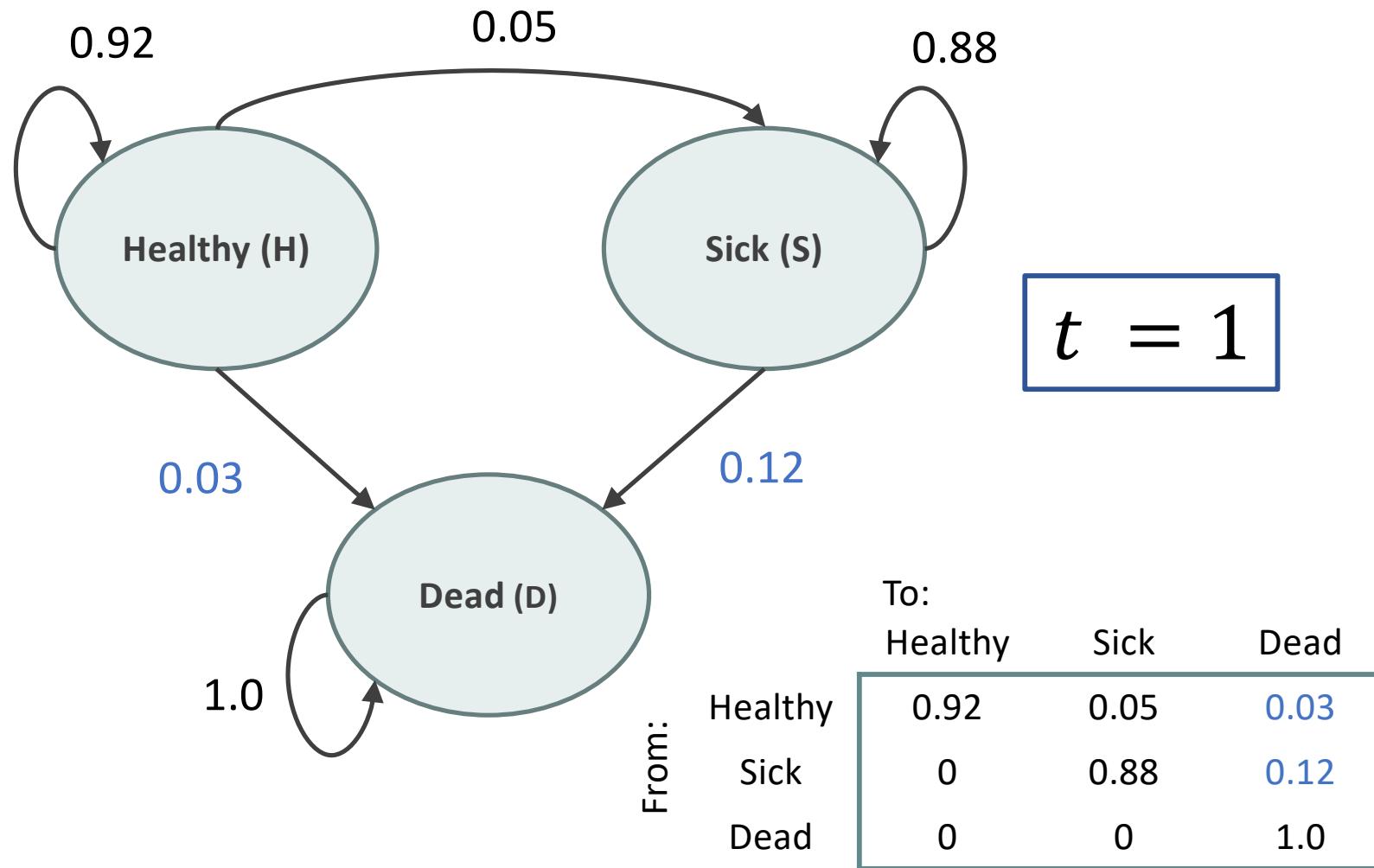
$$P_t = \begin{bmatrix} p_{[1,1,t]} & p_{[1,2,t]} & \cdots & p_{[1,n_S,t]} \\ p_{[2,1,t]} & p_{[2,2,t]} & \cdots & p_{[2,n_S,t]} \\ \vdots & \vdots & \ddots & \vdots \\ p_{[n_S,1,t]} & p_{[n_S,2,t]} & \cdots & p_{[n_S,n_S,t]} \end{bmatrix}$$

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

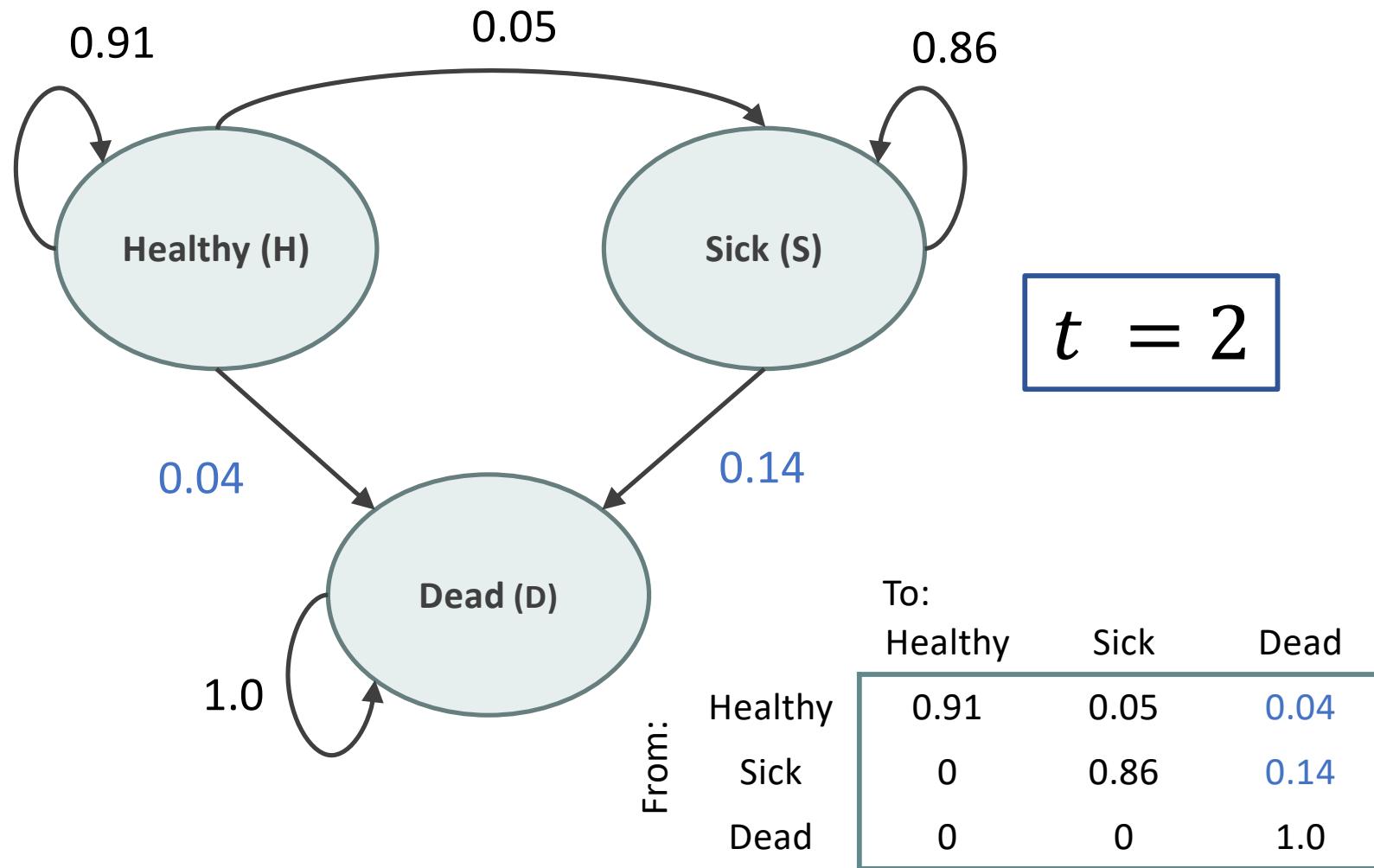
# Three-State Model



# Three-State Model



# Three-State Model



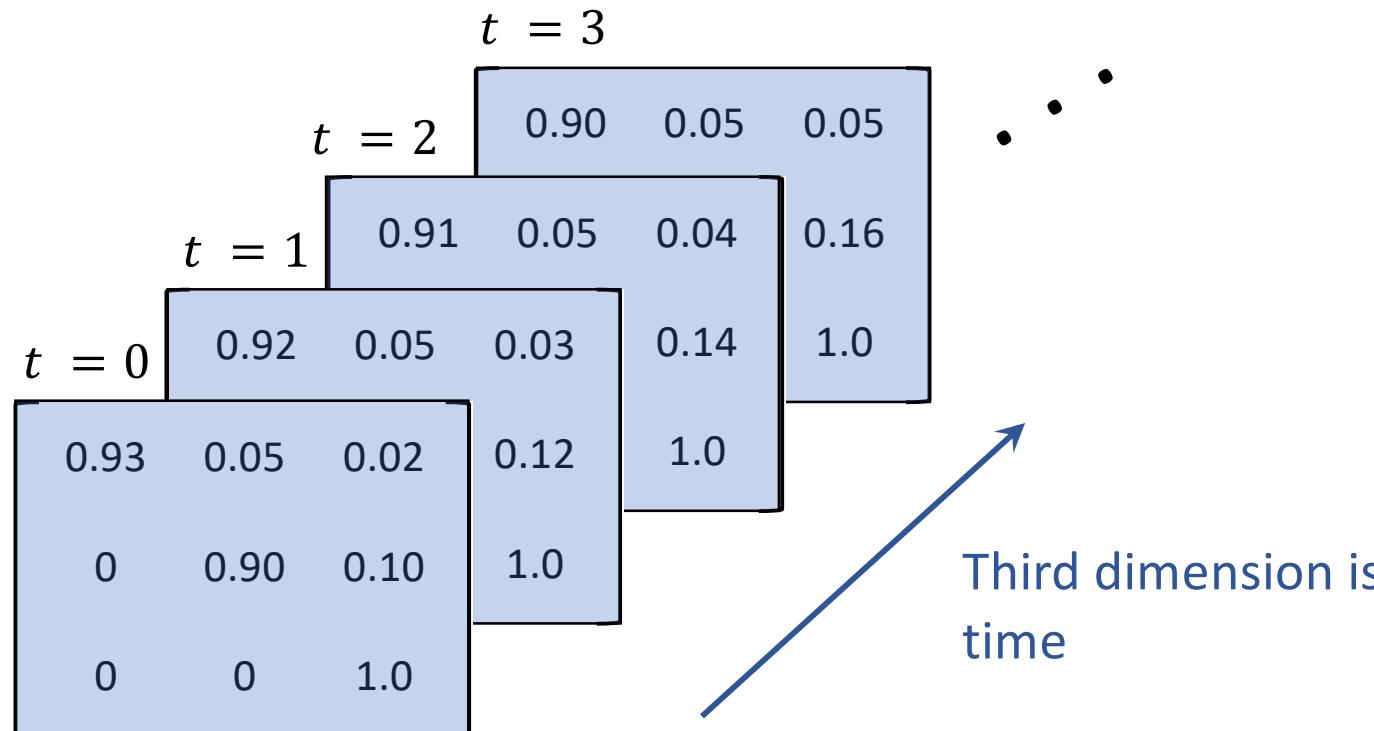
# Simulating Cohort with Time-Varying Probabilities

Cohort distribution at next time step is still calculated through matrix multiplication, but ***matrix changes over time***

$$\begin{bmatrix} \cdots & x_{t+1} & \cdots \end{bmatrix} = \begin{bmatrix} \cdots & x & \cdots \\ & t & \end{bmatrix} \begin{bmatrix} \text{Transition} \\ \text{Probability} \\ \text{Matrix} \\ P_t \end{bmatrix}$$

# Transition Probability Array

Stack cycle-specific transition probability matrices together to form a *transition probability array*



# Not on time-dependent probabilities

- Let  $h_{i,j}(\tau)$  be the time-dependent hazard for a transition from state  $i$  to state  $j$
- Then,  $H_{i,j}(\tau) = \int_0^\tau h_{i,j}(u)du$  is the cumulative hazard
- The rate of transition from S1 to S2 in cycle  $\tau$  is defined as the difference in cumulative hazards between consecutive cycles

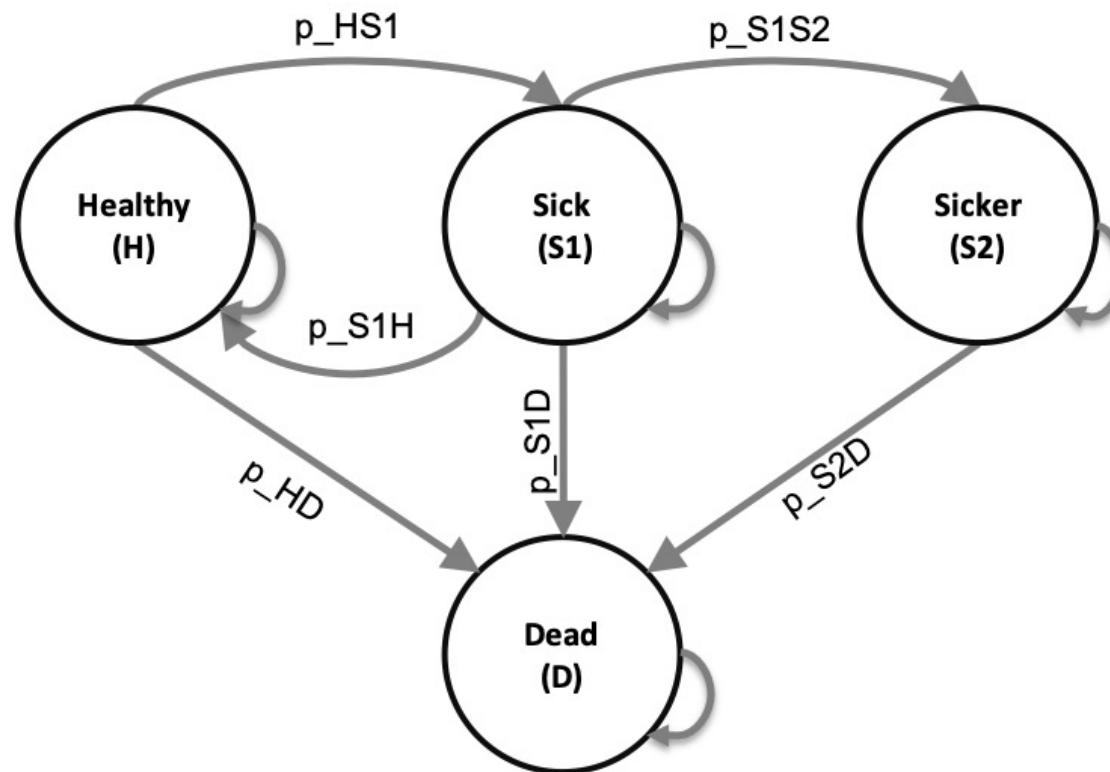
$$\mu_{[i,j,\tau]} = H_{i,j}(\tau) - H_{i,j}(\tau - 1)$$

- And the cycle-specific transition probability is

$$p_{[i,j,\tau]} = 1 - \exp(-\mu_{[i,j,\tau]})$$

# The Sick-Sicker model

- Four health states
- All individuals start in the Healthy state



# Time-dependence since simulation start

- We create a 3D array,  $a\_P$ , that stores a collection of time-varying transition matrices,  $P_t$ , in the third dimension
- For the Sick-Sicker Markov model:

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

# Time-dependence 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-dependence based on state-residence

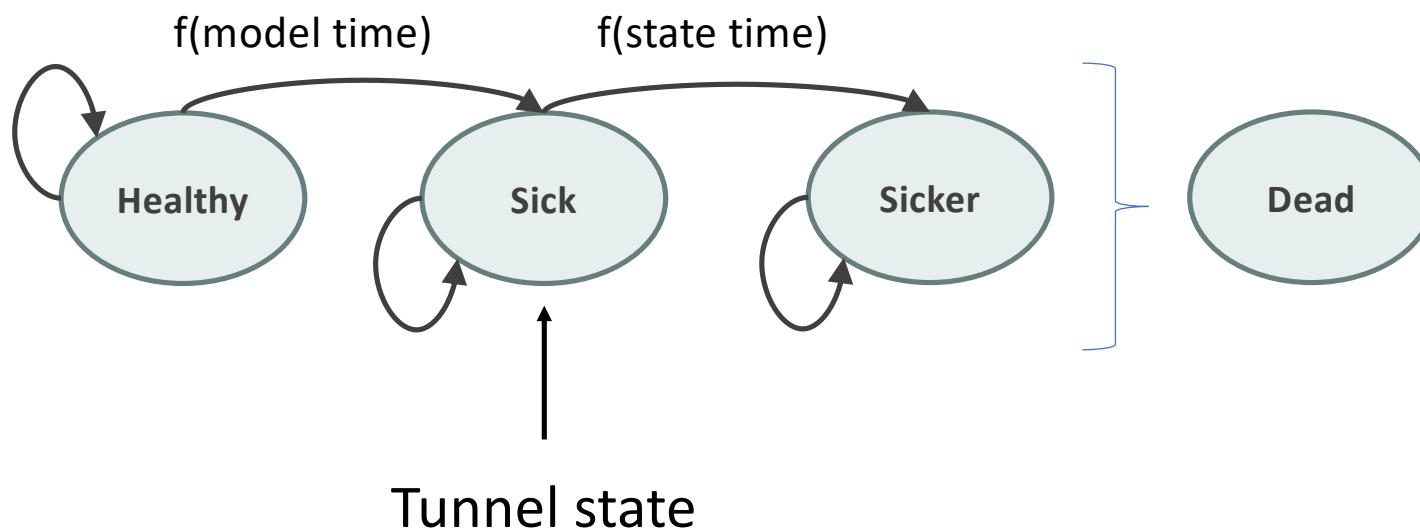
- “Memoryless” property of Markov models is a BIG assumption
  - Transition probabilities only depend on the current state and not on past states
- Many transition probabilities depend on model history, not time since model start
  - Risk of myocardial infarction (MI) greater for persons with prior MI

# Tunnel states

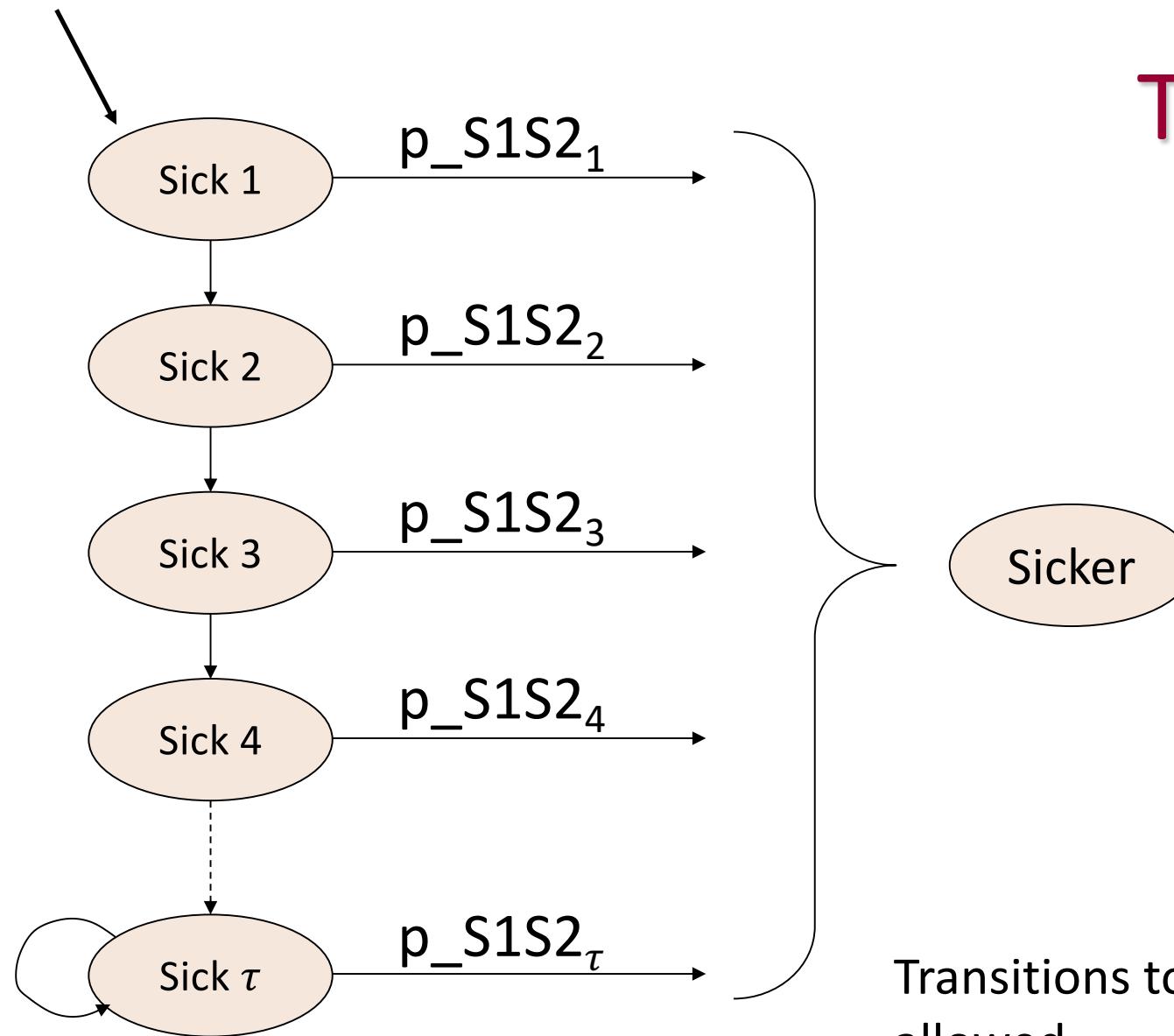
- Sometimes, transition probabilities depend on the time since an event in the model
  - E.g., Cohort of healthy patients at risk for cancer, but once cancer is diagnosed the risk of recurrence depends on time since diagnosis
- If transition probabilities do not depend on the time since model start, 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



Transitions to Dead also allowed.

# Time-dependent probabilities

- Progression from Sick to Sicker increases the longer a person has been sick, where  $\tau$  represents the time since getting Sick
- This increase follows a Weibull hazard:

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

- With a cumulative hazard

$$H_{S1S2}(\tau) = (\lambda\tau)^{(\gamma)}$$

# Time-dependent probabilities

- The rate of transition from S1 to S2 in cycle  $\tau$  is defined as the difference in cumulative hazards between consecutive cycles

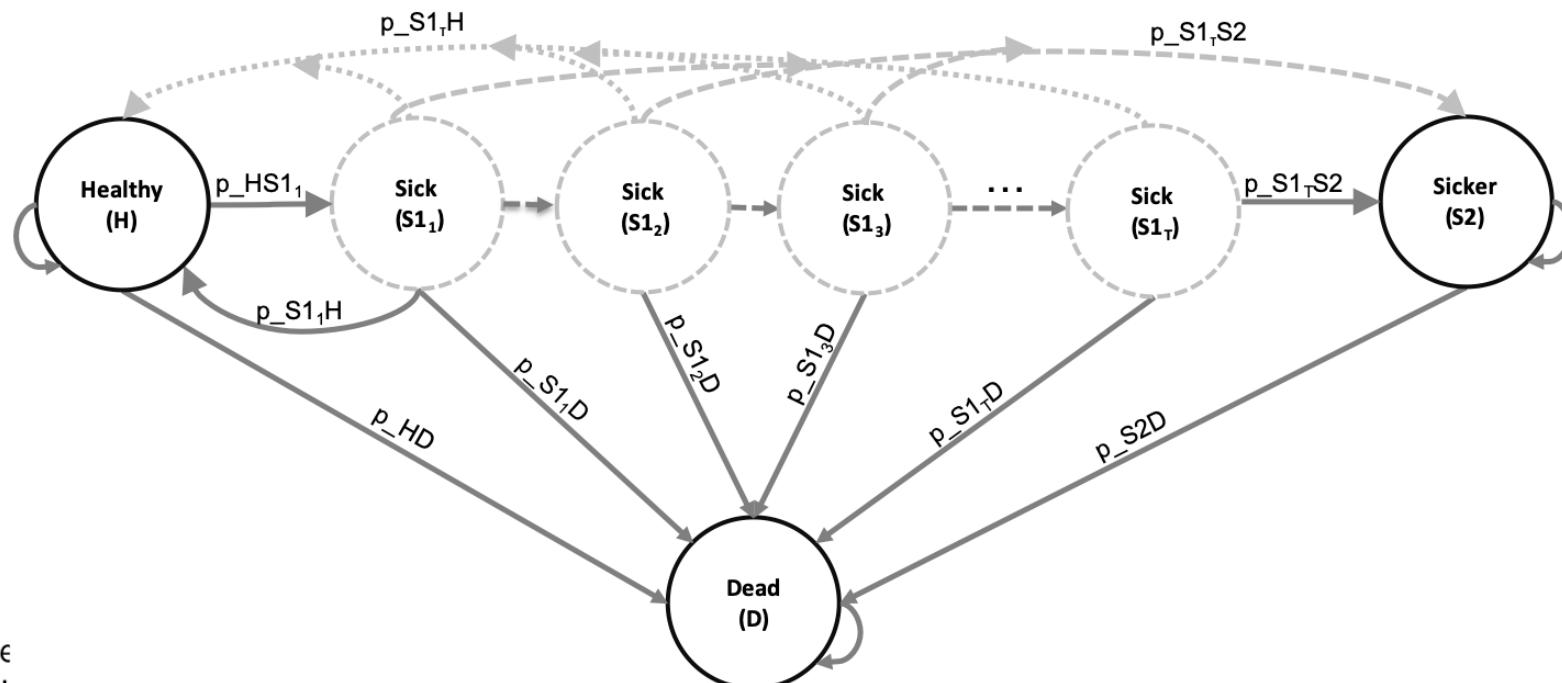
$$\mu_{[S1,S2,\tau]} = H_{S1S2}(\tau) - H_{S1S2}(\tau - 1) = (\lambda\tau)^{(\gamma)} - (\lambda(\tau - 1))^{(\gamma)}$$

- And the cycle-specific transition probability is

$$p_{[S1,S2,\tau]} = 1 - \exp(-\mu_{[S1,S2,\tau]})$$

# Time-dependent probabilities

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

$$\mathbf{a\_P\_tunnels} = \begin{bmatrix} & & p_{[H,H,n_t]} & p_{[H,S1_1,n_t]} & p_{[H,S1_2,n_t]} & \cdots & p_{[H,S1_\tau,n_t]} & p_{[H,S2,n_t]} & p_{[H,D,n_t]} \\ & & p_{[H,H,2]} & p_{[H,S1_1,2]} & p_{[H,S1_2,2]} & \cdots & p_{[H,S1_\tau,2]} & p_{[H,S2,2]} & p_{[H,D,2]} & p_{[S1_1,D,n_t]} \\ n_s & p_{[H,H,1]} & p_{[H,S1_1,1]} & p_{[H,S1_2,1]} & \cdots & p_{[H,S1_\tau,1]} & p_{[H,S2,1]} & p_{[H,D,1]} & p_{[S1_1,D,2]} & p_{[S1_2,D,n_t]} \\ p_{[S1_1,H,1]} & p_{[S1_1,S1_1,1]} & p_{[S1_1,S1_2,1]} & \cdots & p_{[S1_1,S1_\tau,1]} & p_{[S1_1,S2,1]} & p_{[S1_1,D,1]} & p_{[S1_2,D,2]} & \vdots & \\ p_{[S1_2,H,1]} & p_{[S1_2,S1_1,1]} & p_{[S1_2,S1_2,1]} & \cdots & p_{[S1_2,S1_\tau,1]} & p_{[S1_2,S2,1]} & p_{[S1_2,D,1]} & \vdots & & p_{[S1_\tau,D,n_t]} \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & p_{[S1_\tau,D,2]} & p_{[S2,D,n_t]} \\ p_{[S1_\tau,H,1]} & p_{[S1_\tau,S1_1,1]} & p_{[S1_\tau,S1_2,1]} & \cdots & p_{[S1_\tau,S1_\tau,1]} & p_{[S1_\tau,S2,1]} & p_{[S1_\tau,D,1]} & p_{[S2,D,2]} & & p_{[D,D,n_t]} \\ p_{[S2,H,1]} & p_{[S2,S1_1,1]} & p_{[S2,S1_2,1]} & \cdots & p_{[S2,S1_\tau,1]} & p_{[S2,S2,1]} & p_{[S2,D,1]} & p_{[D,D,2]} & & \\ p_{[D,H,1]} & p_{[D,S1_1,1]} & p_{[D,S1_2,1]} & \cdots & p_{[D,S1_\tau,1]} & p_{[D,S2,1]} & p_{[D,D,1]} & & & \end{bmatrix}$$

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# R session



Thank you!

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