Cohort State-Transition Models

Cohort State-Transition Modeling Overview

Cohort State-Transition Models

- Model that describes how a cohort is distributed across health states over time

  - e.g., healthy, sick, stable, progressed, dead

- Allow transitions between states with some probability

- Transitions are modeled in discrete time steps (e.g. weekly, monthly, yearly)

Cohort Model Assumptions

- Health states are mutually exclusive, collectively exhaustive

- Within a given health state, population is homogeneous

- Markovian assumption: transition probabilities depends only on current health state ("memoryless")

Simple State-Transition Model of HIV Progression

Transition probability matrix
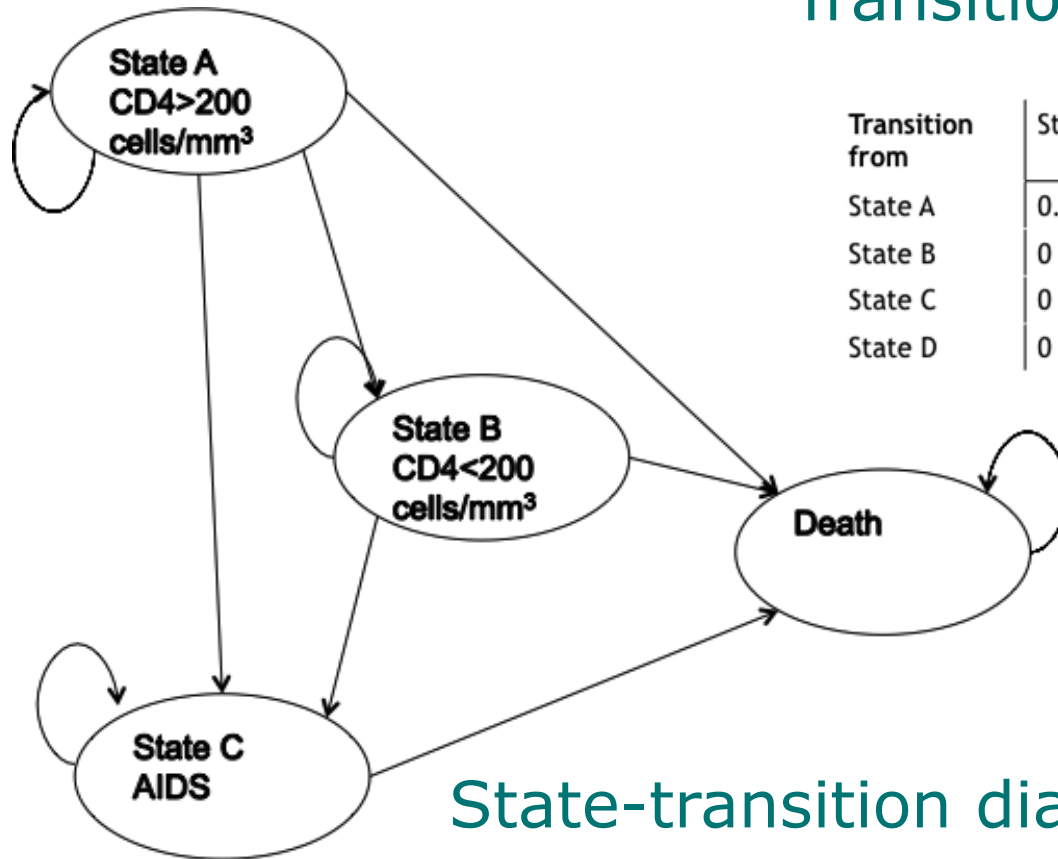
Transition from	State A	State B	State C	State D
State A	0.721	0.202	0.067	0.01
State B	0	0.581	0.407	0.012
State C	0	0	0.75	0.25
State D	0	0	0	1

State-transition diagram

Drummond, Michael F. *Methods for the economic evaluation of health care programmes*. Oxford university press, 2005.

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Cohort "Trace"

Number or proportion of individuals at each time step

Cycle	State A	State B	State C	State D	Total
0	1000	0	0	0	1000
	1000×0.721	1000×0.202	1000×0.067	1000×0.01	
1	721	202	67	10	1000
2	520	263	181	36	1000
3	375	258	277	90	1000
4	270	226	338	166	1000
5	195	186	363	256	1000
6	140	147	361	351	1000
7	101	114	340	445	1000
8	73	87	308	532	1000
9	53	65	271	611	1000
10	38	48	234	680	1000
11	27	36	197	739	1000
12	20	26	164	789	1000
13	14	19	135	831	1000
14	10	14	110	865	1000
15	7	10	89	893	1000
16	5	7	72	916	1000
17	4	5	57	934	1000
18	3	4	45	948	1000
19	2	3	36	959	1000
20	1	2	28	968	1000

Simple 3-State Example

Three-State Model

	To: Healthy	Sick	Dead
Healthy	p_HH	p_HS	p_HD
Sick	0	p_SS	p_SD
Dead	0	0	p_DD

From:
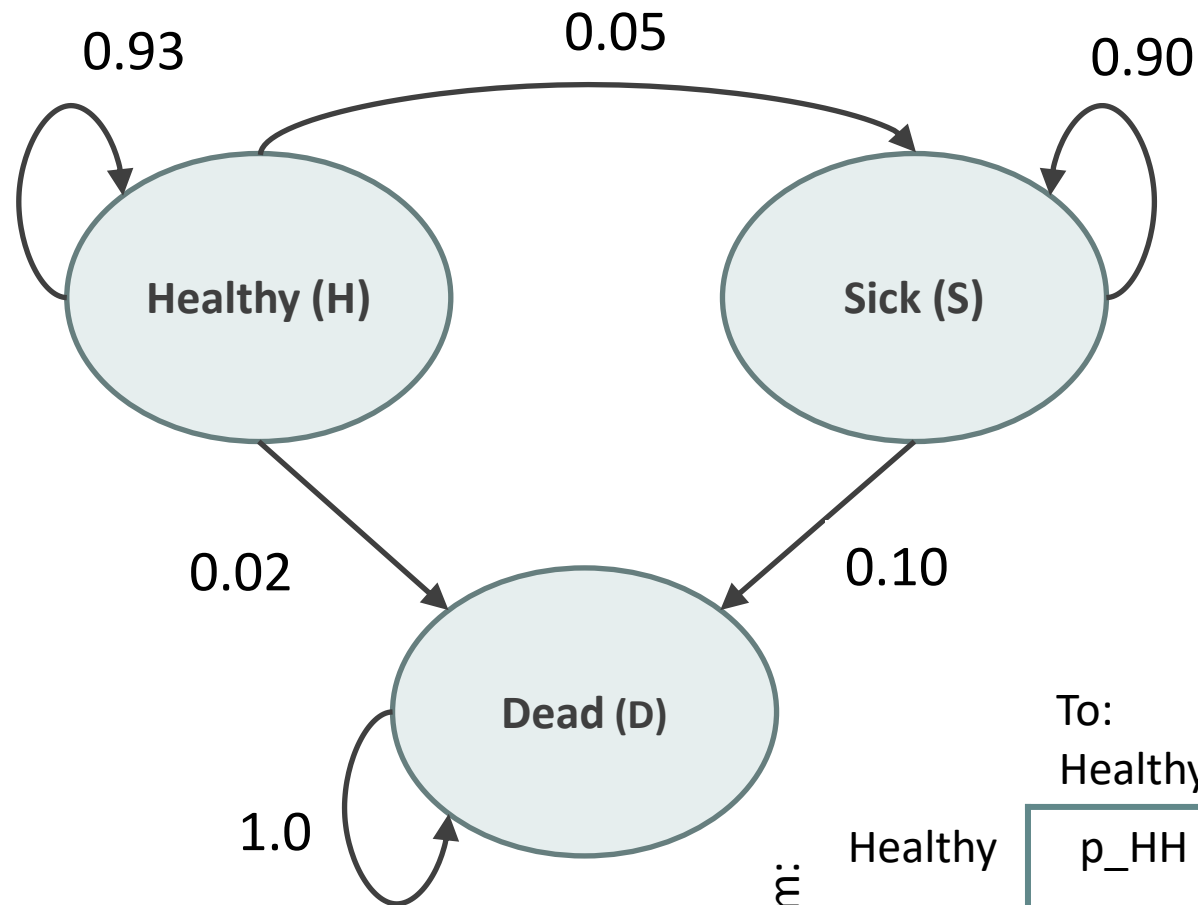
Three-State Model

	To: Healthy	Sick	Dead
Healthy	p_HH	p_HS	p_HD
Sick	0	p_SS	p_SD
Dead	0	0	p_DD

From:

Three-State Model

To:			
From:	Healthy	Sick	Dead
Healthy	0.93	0.05	0.02
Sick	0	0.90	0.10
Dead	0	0	1.0

Simulate the Cohort over Time

- Initial cohort distribution:

$$x_0 = \begin{bmatrix} 1.0 & 0.0 & 0.0 \end{bmatrix}$$ (everyone starts healthy)

- Cohort distribution at next time step is calculated through matrix multiplication

$$\begin{bmatrix} \rule{2em}{0.4pt} \ x_{t+1} \ \rule{2em}{0.4pt} \end{bmatrix} = \begin{bmatrix} \rule{2em}{0.4pt} \ x_t \ \rule{2em}{0.4pt} \end{bmatrix} \begin{bmatrix} \text{Transition} \\ \text{Probability} \\ \text{Matrix} \\ P \end{bmatrix}$$

Simulate the Cohort over Time

- Initial cohort distribution:

$$x_0 = \begin{bmatrix} 1.0 & 0.0 & 0.0 \end{bmatrix}$$

(everyone starts healthy)

- Cohort distribution at next time step is calculated through matrix multiplication

$$\begin{bmatrix} x_1 \\ \\ \end{bmatrix} = \begin{bmatrix} x_0 \\ 1.0 \cdot 0.0 \cdot 0.0 \end{bmatrix} \begin{bmatrix} 0.93 & 0.05 & 0.02 \\ 0 & 0.90 & 0.10 \\ 0 & 0 & 1.0 \end{bmatrix}$$

Simulate the Cohort over Time

- Initial cohort distribution:

$$x_0 = \begin{bmatrix} 1.0 & 0.0 & 0.0 \end{bmatrix}$$

(everyone starts healthy)

- Cohort distribution at next time step is calculated through matrix multiplication

$$\begin{bmatrix} x_1 \\ 0.93 \\ \end{bmatrix} = \begin{bmatrix} x_0 \\ 1.0 & 0.0 & 0.0 \end{bmatrix} \begin{bmatrix} 0.93 & 0.05 & 0.02 \\ 0 & 0.90 & 0.10 \\ 0 & 0 & 1.0 \end{bmatrix}$$
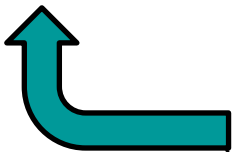
$(0.93)(1.0) + (0.0)(0.0) + (0.0)(0.0)$

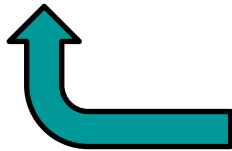$(p_{Healthy,Healthy})*\Pr(healthy) + (p_{Sick,Healthy})*\Pr(sick) + (p_{Dead,Healthy})*\Pr(dead)$

Simulate the Cohort over Time

- Initial cohort distribution:

$$x_0 = \begin{bmatrix} 1.0 & 0.0 & 0.0 \end{bmatrix}$$

(everyone starts healthy)

- Cohort distribution at next time step is calculated through matrix multiplication

$$\begin{bmatrix} x_1 \\ 0.93 & 0.05 \end{bmatrix} = \begin{bmatrix} x_0 \\ 1.0 \cdot 0.0 \cdot 0.0 \end{bmatrix} \begin{bmatrix} 0.93 & 0.05 & 0.02 \\ 0 & 0.90 & 0.10 \\ 0 & 0 & 1.0 \end{bmatrix}$$

$(0.05)(1.0) + (0.90)(0.0) + (0.0)(0.0)$

Simulate the Cohort over Time

- Initial cohort distribution:

$$x_0 = \begin{bmatrix} 1.0 & 0.0 & 0.0 \end{bmatrix}$$

(everyone starts healthy)

- Cohort distribution at next time step is calculated through matrix multiplication

$$
\overset{x_1}{\begin{bmatrix} 0.93 & 0.05 & 0.02 \end{bmatrix}} = \overset{x_0}{\begin{bmatrix} 1.0 & \cdot & 0.0 & \cdot & 0.0 \end{bmatrix}} \begin{bmatrix} 0.93 & 0.05 & 0.02 \\ 0 & 0.90 & 0.10 \\ 0 & 0 & 1.0 \end{bmatrix}
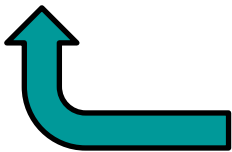$$

Simulate the Cohort over Time

- Initial cohort distribution:

$$x_0 = \begin{bmatrix} 1.0 & 0.0 & 0.0 \end{bmatrix}$$ (everyone starts healthy)

- Cohort distribution at next time step is calculated through matrix multiplication

$$
\underset{x_2}{\begin{bmatrix} 0.87 \end{bmatrix}} = \underset{x_1}{\begin{bmatrix} 0.93 & 0.05 & 0.02 \end{bmatrix}} \begin{bmatrix} 0.93 & 0.05 & 0.02 \\ 0 & 0.90 & 0.10 \\ 0 & 0 & 1.0 \end{bmatrix}
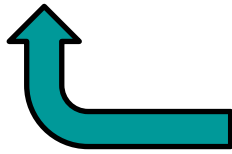$$

$(0.93)(0.93) + (0.0)(0.05) + (0.0)(0.02)$

Simulate the Cohort over Time

- Initial cohort distribution:

$$x_0 = \begin{bmatrix} 1.0 & 0.0 & 0.0 \end{bmatrix}$$ (everyone starts healthy)

- Cohort distribution at next time step is calculated through matrix multiplication

$$\overset{x_2}{\begin{bmatrix} 0.87 & 0.09 & \end{bmatrix}} = \overset{x_1}{\begin{bmatrix} 0.93 & 0.05 & 0.02 \end{bmatrix}} \begin{bmatrix} 0.93 & 0.05 & 0.02 \\ 0 & 0.90 & 0.10 \\ 0 & 0 & 1.0 \end{bmatrix}$$

$(0.05)(0.93) + (0.90)(0.05) + (0.0)(0.02)$

Simulate the Cohort over Time

- Initial cohort distribution:

$$x_0 = \begin{bmatrix} 1.0 & 0.0 & 0.0 \end{bmatrix}$$

(everyone starts healthy)

- Cohort distribution at next time step is calculated through matrix multiplication

$$
\underset{x_2}{\begin{bmatrix} 0.87 & 0.09 & 0.04 \end{bmatrix}} = \underset{x_1}{\begin{bmatrix} 0.93 & 0.05 & 0.02 \end{bmatrix}} \begin{bmatrix} 0.93 & 0.05 & 0.02 \\ 0 & 0.90 & 0.10 \\ 0 & 0 & 1.0 \end{bmatrix}
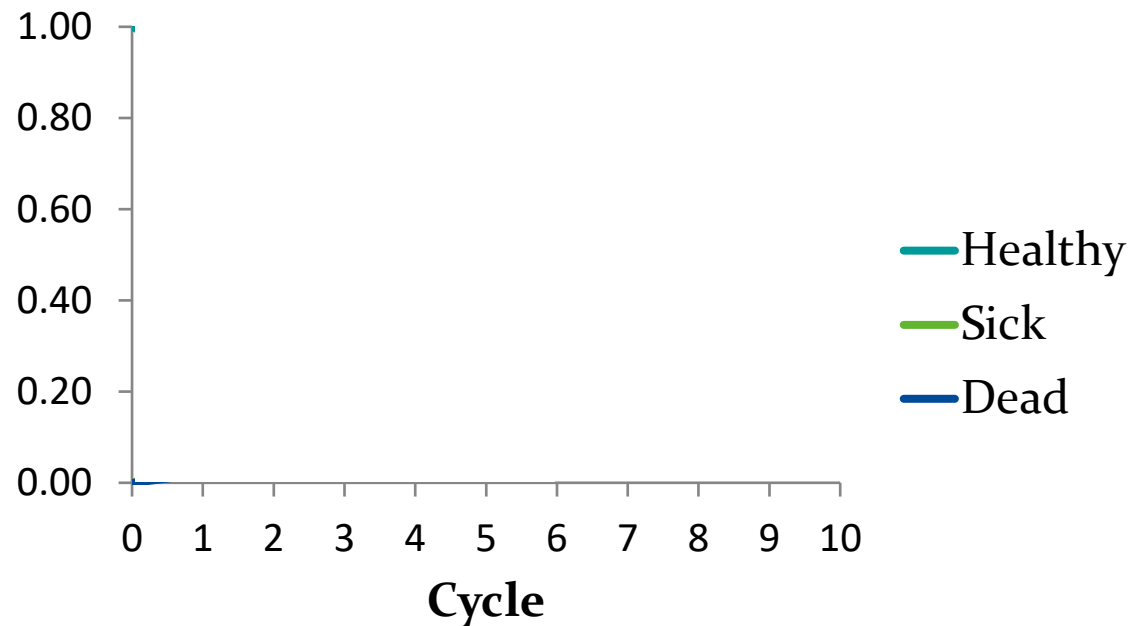$$

(0.02)(0.93) + (0.10)(0.05) + (1.0)(0.02)

Simulate the Cohort over Time

- Cohort distribution over time:

$$x_4 = \begin{bmatrix} 0.75 & 0.15 & 0.10 \end{bmatrix}$$

- Cohort trace:

Calculating Model Outcomes

Expected outcomes

- Expected remaining life-years, quality-adjusted life-years (QALYs), costs
  - Generally calculated over lifetime

- Multiply cohort distribution by state-specific values to calculate expected value at each cycle

- Sum expected values over time
  - discount if desired

Remaining Life-Expectancy

- State-specific values: 1 if alive, 0 if dead

State values: 1.0   1.0   0.0

Time	Healthy	Sick	Dead	E[LYs]
0	1.0	0.0	0.0	--
1	0.93	0.05	0.02	
2	0.87	0.09	0.04	
3	0.80	0.13	0.07	
	…	…	…	

Total life years: 21.0 years

Remaining QALE

- Remaining quality-adjusted life-expectancy (QALE)
- State-specific values: utility of that state

State values: 0.8   0.5   0.0

Time	Healthy	Sick	Dead	E[QALYs]
0	1.0	0.0	0.0	--
1	0.93	0.05	0.02	
2	0.87	0.09	0.04	
3	0.80	0.13	0.07	
	…	…	…	

Total QALYs: 14.7 QALYs

Remaining costs

- Remaining lifetime health care costs
- State-specific values: cost of spending one cycle in that health state

State values: $400 $1,000 $0

Time	Healthy	Sick	Dead	E[costs]
0	1.0	0.0	0.0	--
1	0.93	0.05	0.02	
2	0.87	0.09	0.04	
3	0.80	0.13	0.07	
	…	…	…	

Total health care costs: $12,531

Discounting

- In cost-effectiveness analysis, costs and QALYs are discounted at some rate, r

- At each cycle t, multiply expected outcome by the discount factor: $\frac{1}{(1+r)^t}$

State values: 0.8   0.5   0.0

Time	Healthy	Sick	Dead	E[QALYs]
0	1.0	0.0	0.0	--
1	0.93	0.05	0.02	0.77
2	0.87	0.09	0.04	0.74
3	0.80	0.13	0.07	0.71
	…	…	…	

Sum

* 1/(1+r)

* 1/(1+r)²

* 1/(1+r)³

Total QALYs: 14.7 QALYs

Total *discounted* (3% per year) QALYs: 10.2 QALYs

Time-Varying State-Transition Models

Time-Varying Probabilities

- Often transition probabilities change over time as the cohort ages
  - Background mortality
  - Risk of developing disease or experiencing an event

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

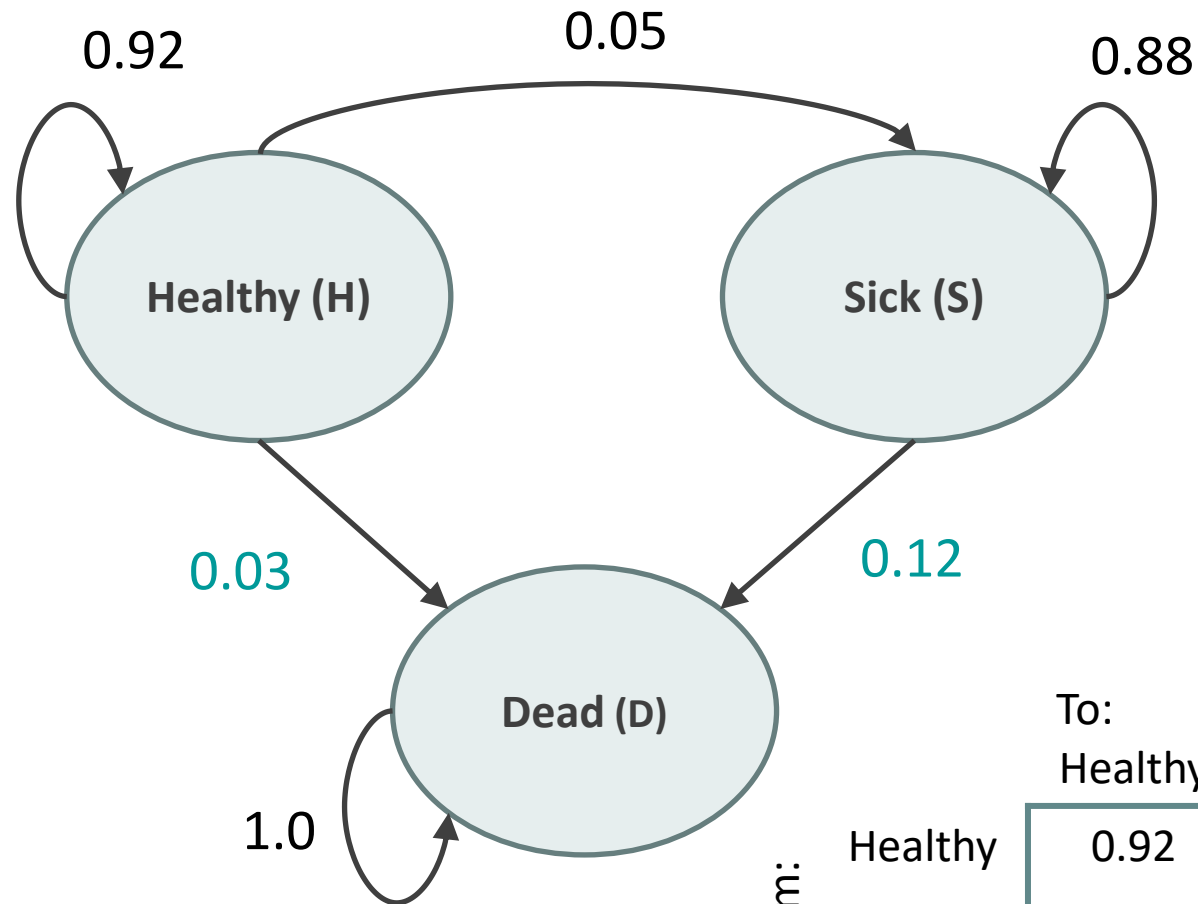- Replace matrix P with matrices P_t, where t is time from the start of the simulation

Three-State Model

0.93

0.05

0.90

Healthy (H)

Sick (S)

$t = 0$

0.02

0.10

Dead (D)
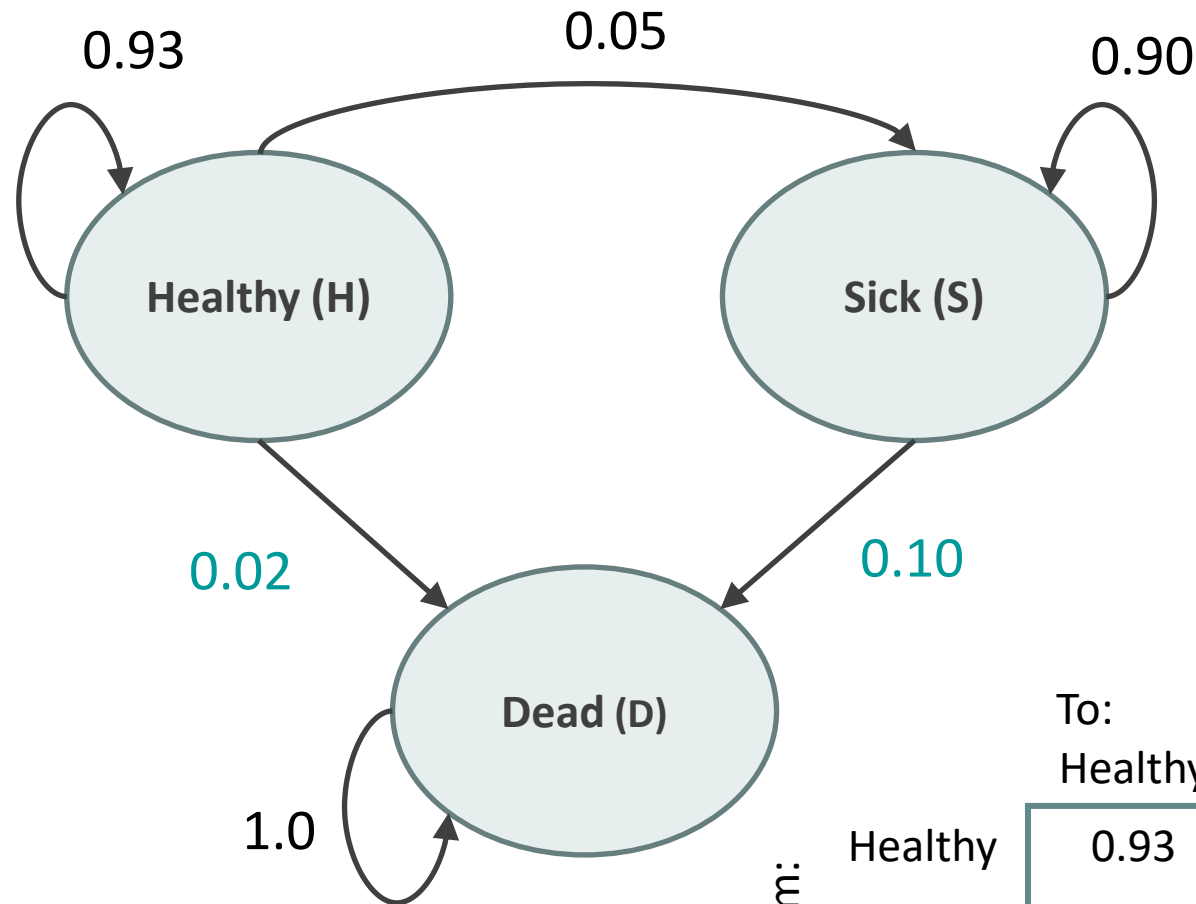
1.0

From:	To: Healthy	Sick	Dead
Healthy	0.93	0.05	0.02
Sick	0	0.90	0.10
Dead	0	0	1.0

Three-State Model

0.92   0.05   0.88

Healthy (H)   **Sick (S)**

$$t = 1$$

0.03   0.12

Dead (D)

1.0

	To: Healthy	Sick	Dead
Healthy	0.92	0.05	0.03
Sick	0	0.88	0.12
Dead	0	0	1.0

From:

Three-State Model

0.91

0.05

0.86

Healthy (H)

Sick (S)

$$t \ = \ 2$$

0.04

0.14

Dead (D)

1.0
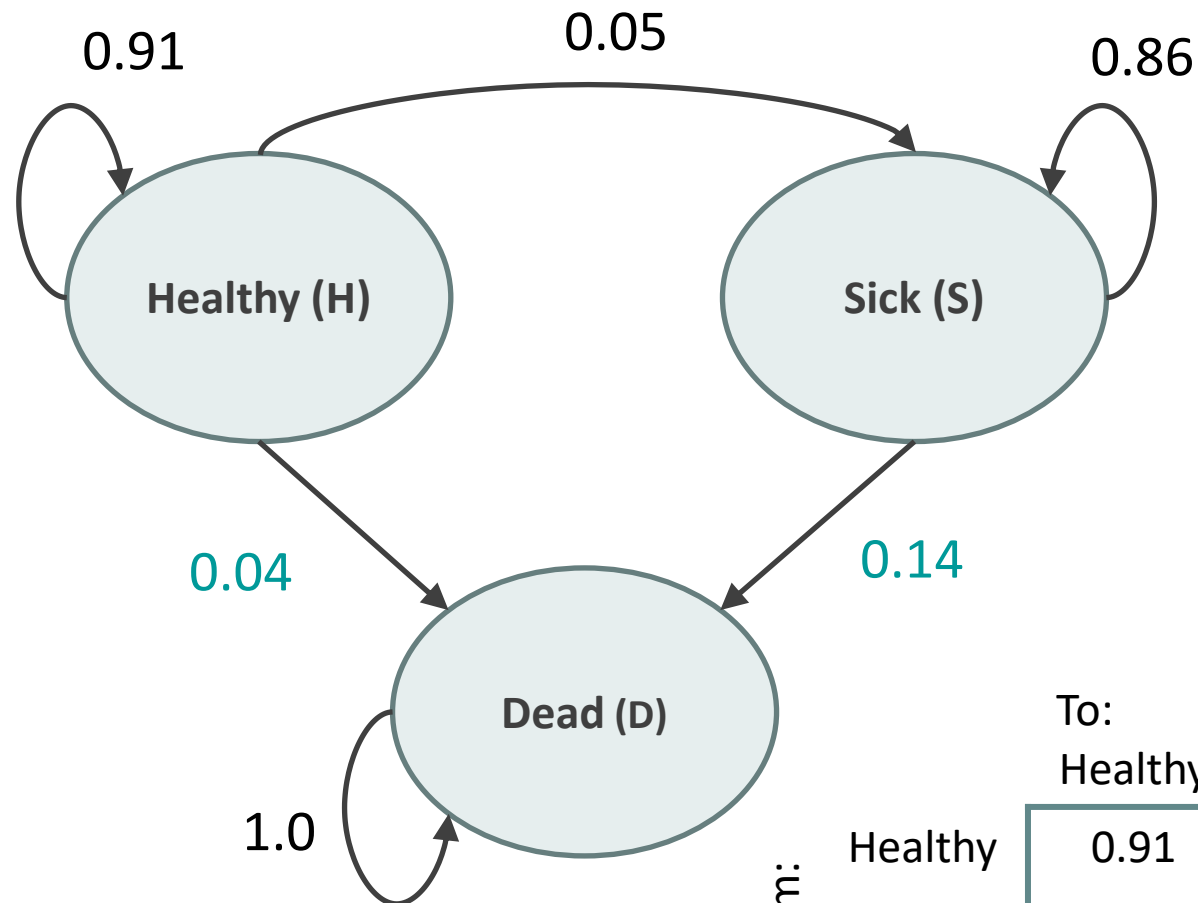
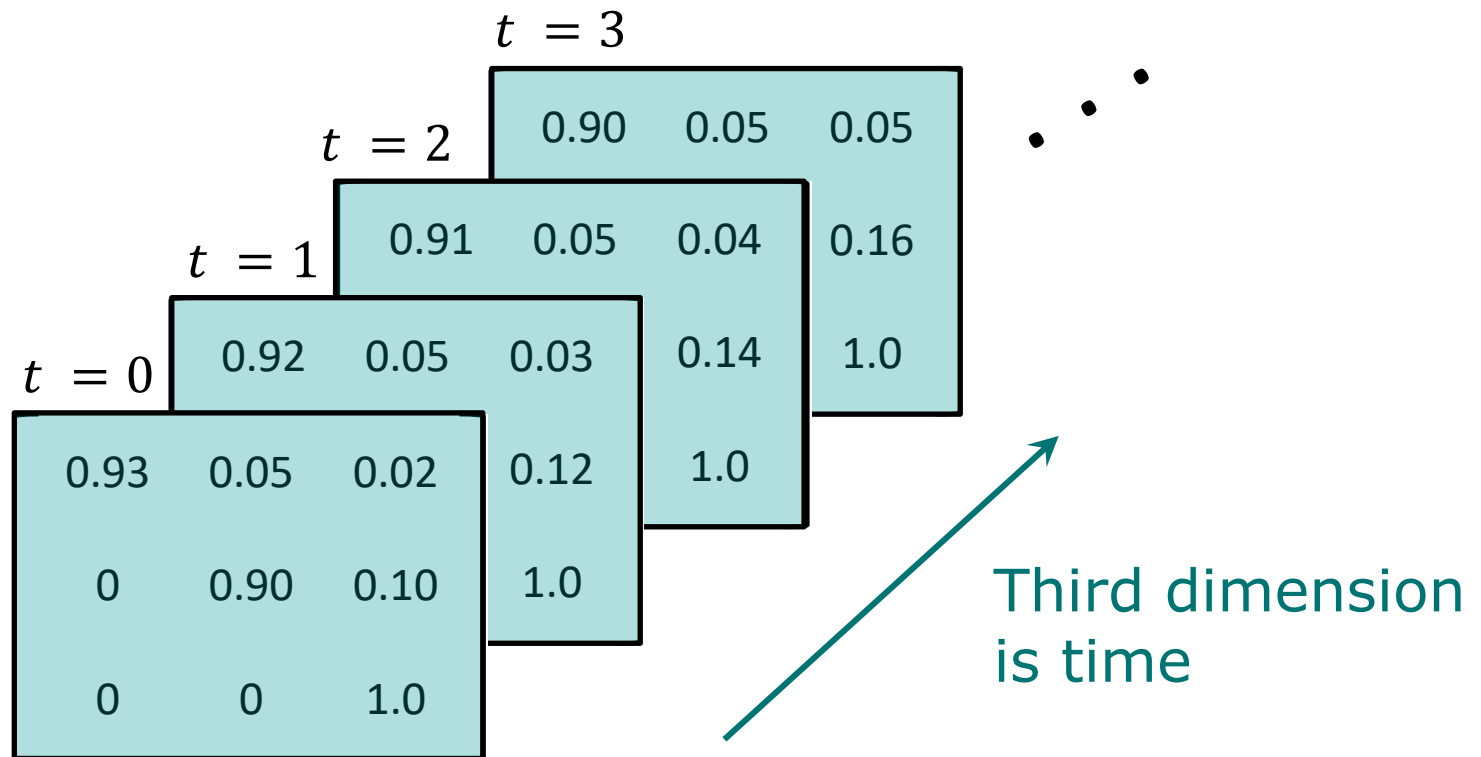|	To:		
From:	Healthy	Sick	Dead
Healthy	0.91	0.05	0.04
Sick	0	0.86	0.14
Dead	0	0	1.0

Simulating Cohort with Time-Varying Probabilities

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

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

Transition Probability Array

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

$t = 3$

0.90	0.05	0.05

$t = 2$

0.91	0.05	0.04	0.16

$t = 1$

0.92	0.05	0.03	0.14	1.0

$t = 0$

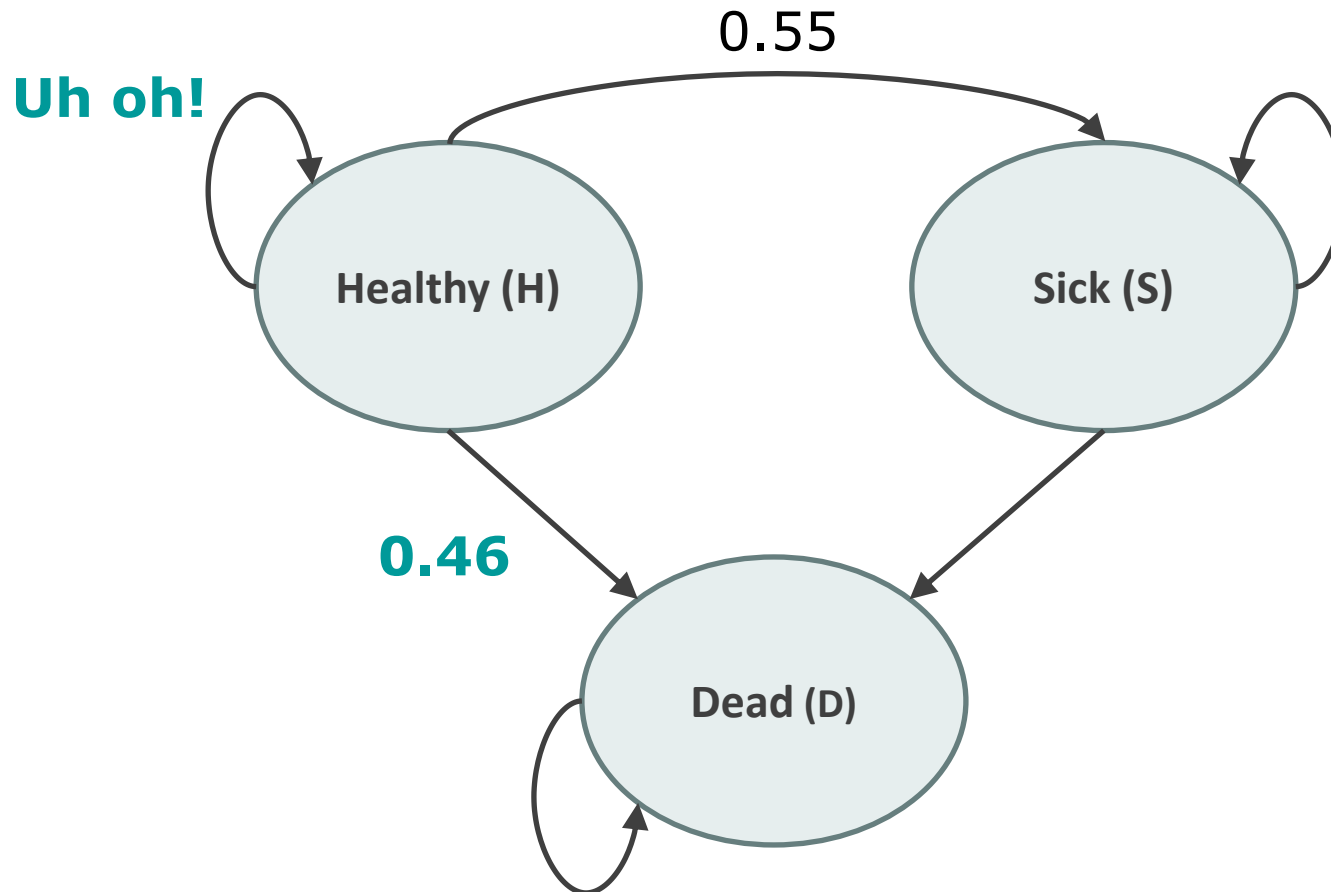| 0.93	0.05	0.02	0.12	1.0
0	0.90	0.10	1.0	
0	0	1.0		

Third dimension is time

Conditional Transitions

- Always need to ensure that rows of the transition probability matrix sum to 1

- When modeling aging cohorts over a lifetime, oldest ages have high probabilities of mortality
  - The sum of age-specific mortality with other possible events, if defined as independent, can exceed 1

- Defining transitions as conditional is one approach to avoiding this problem
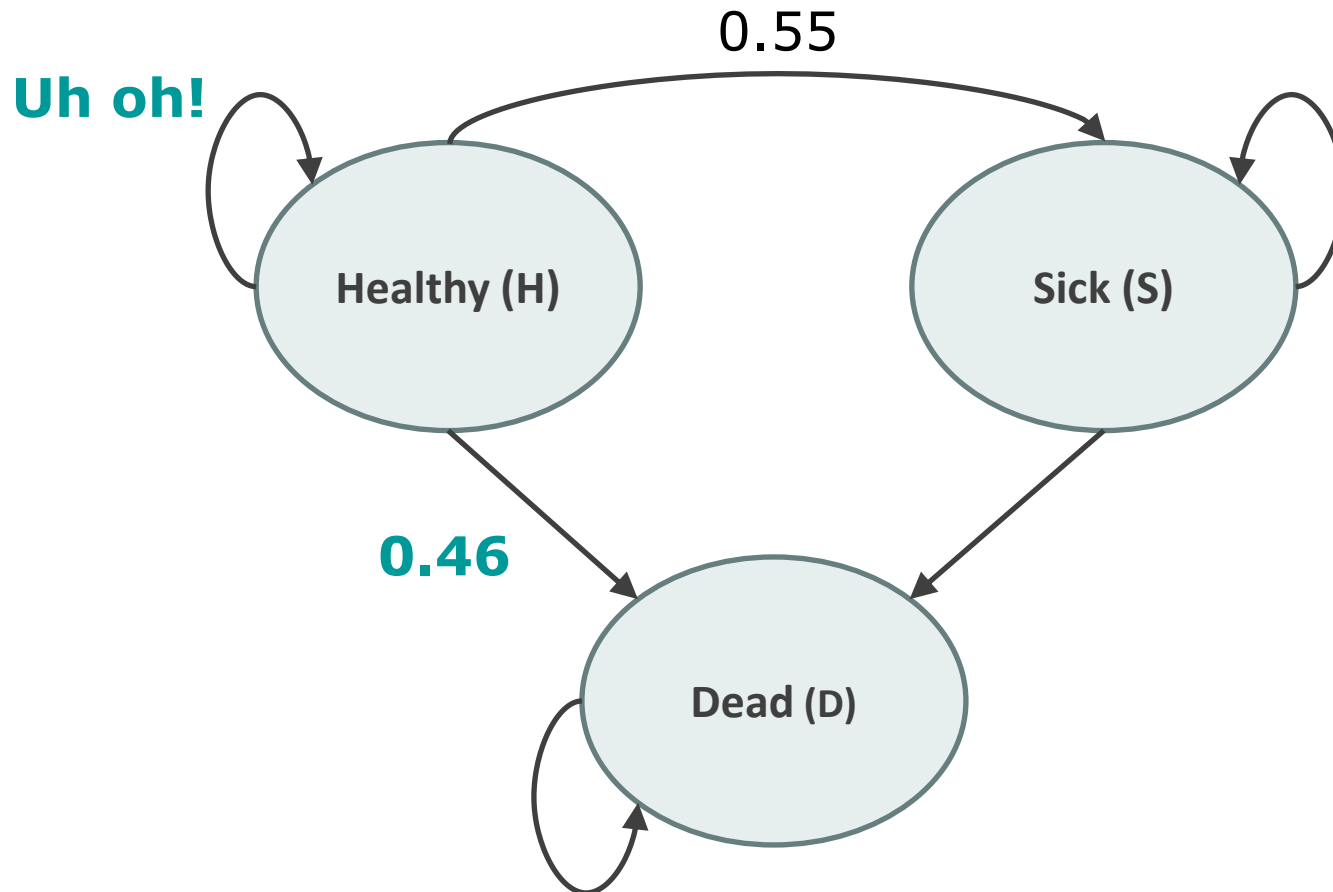
Conditional Transitions

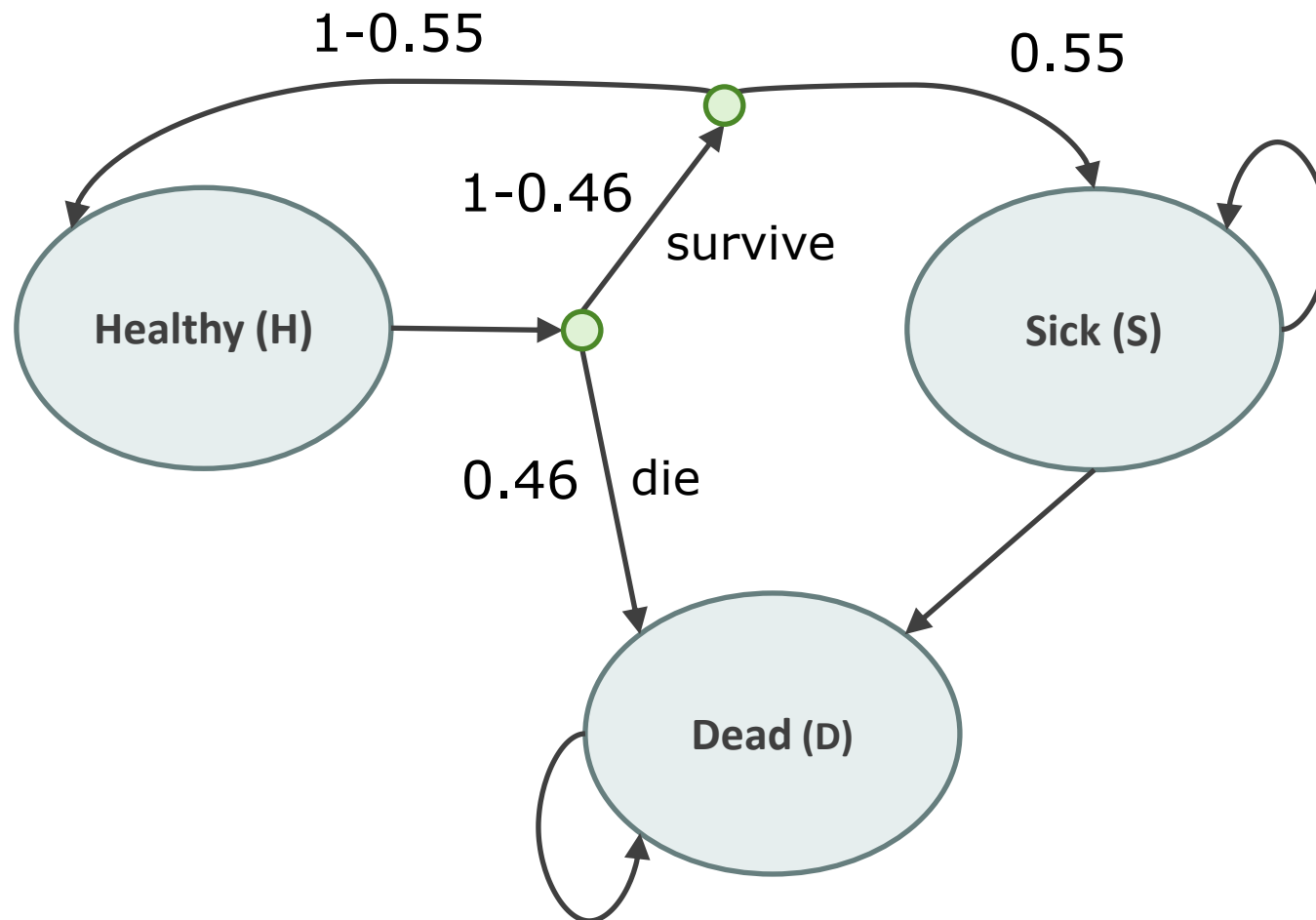- Problem: Sum of transition probabilities can exceed 1 over time

0.55

Uh oh!

Healthy (H)

Sick (S)

0.46

Dead (D)

Conditional Transitions

- Solution: Condition other events on survival

0.55
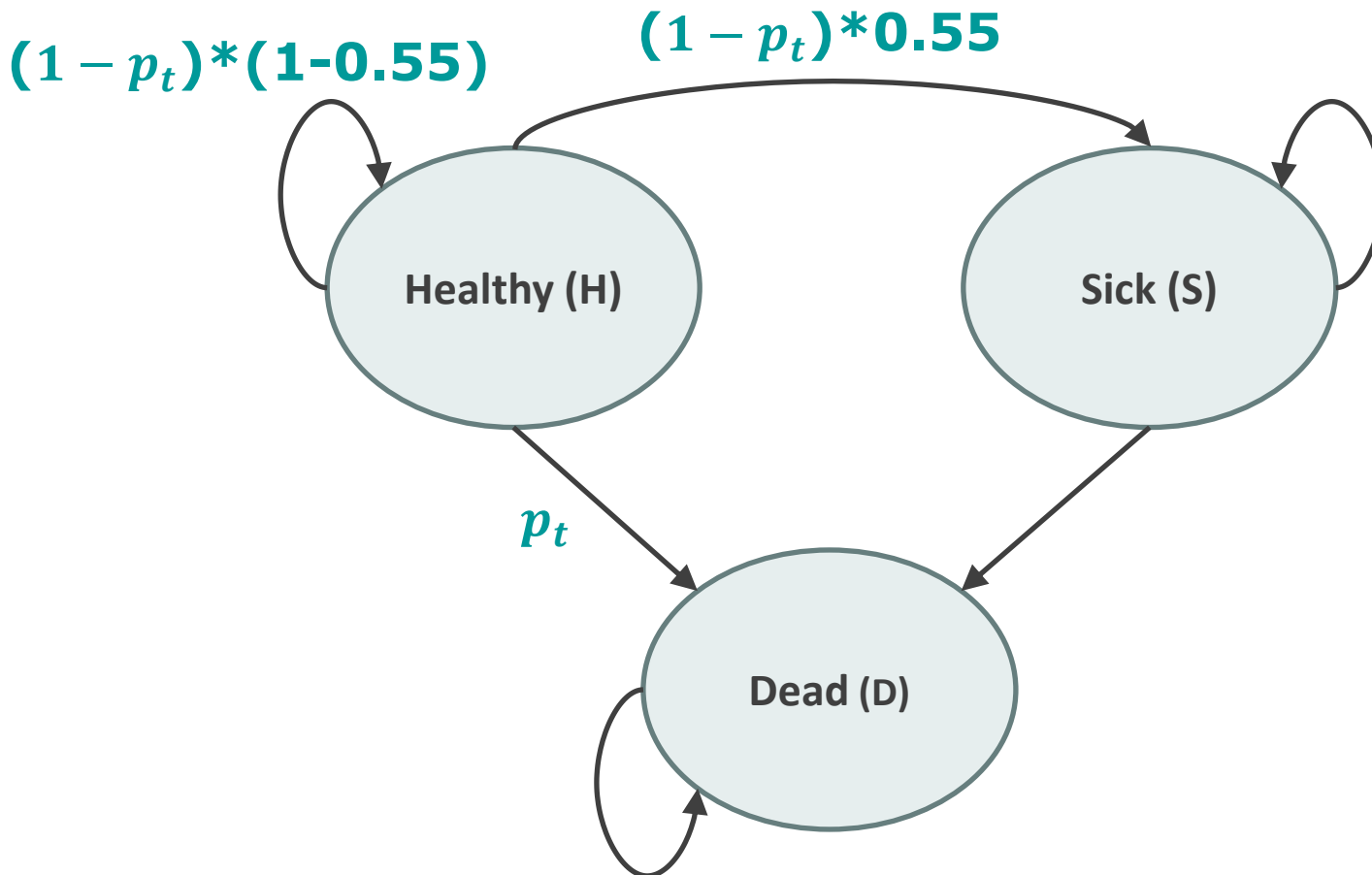
Uh oh!

Healthy (H)

Sick (S)

0.46

Dead (D)

Conditional Transitions

- Solution: Condition other events on survival

Conditional Transitions

- Solution: Condition other events on survival

$(1 - p_t)*$**(1-0.55)**

$(1 - p_t)*$**0.55**

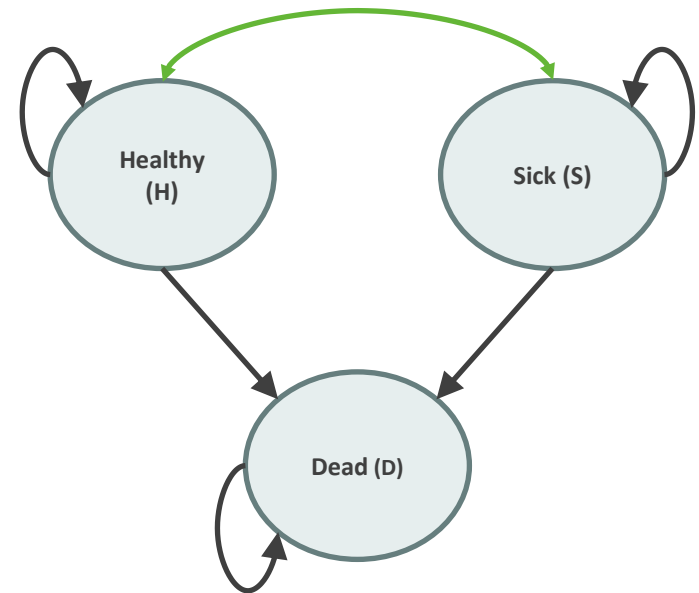Healthy (H)

Sick (S)

p_t

Dead (D)

# History Dependence

History Dependence

- "Memoryless" property of state transition 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 just time since model start

  - Risk of myocardial infarction (MI) greater for persons with prior MI

  - Effectiveness of a drug used as first-line therapy may be better than if used as second-line therapy

When history matters, create more states…

Healthy – Sick - Dead:

Once recovered, the risk of getting sick again or dying increases
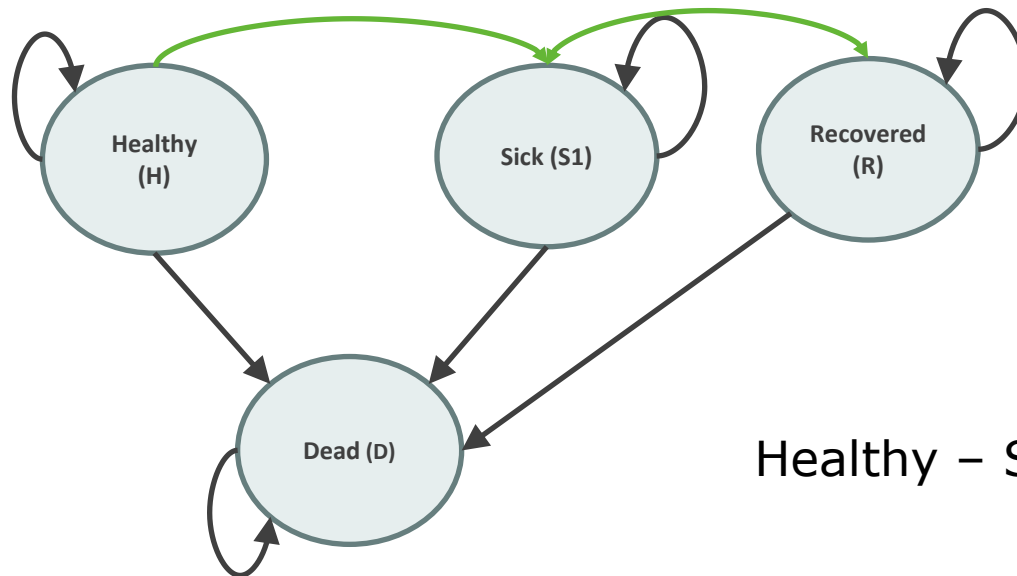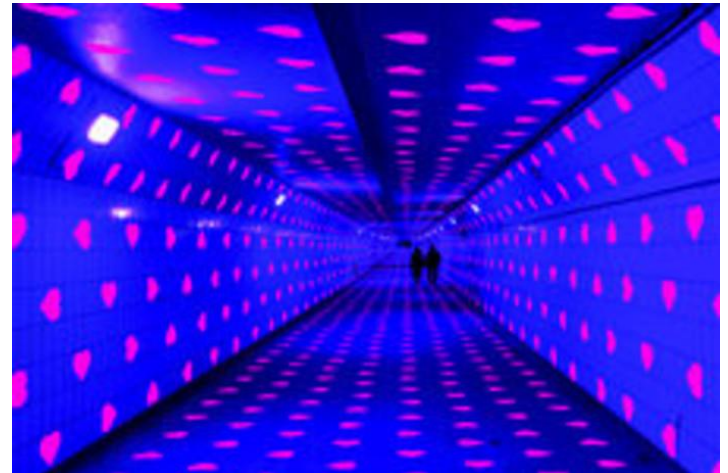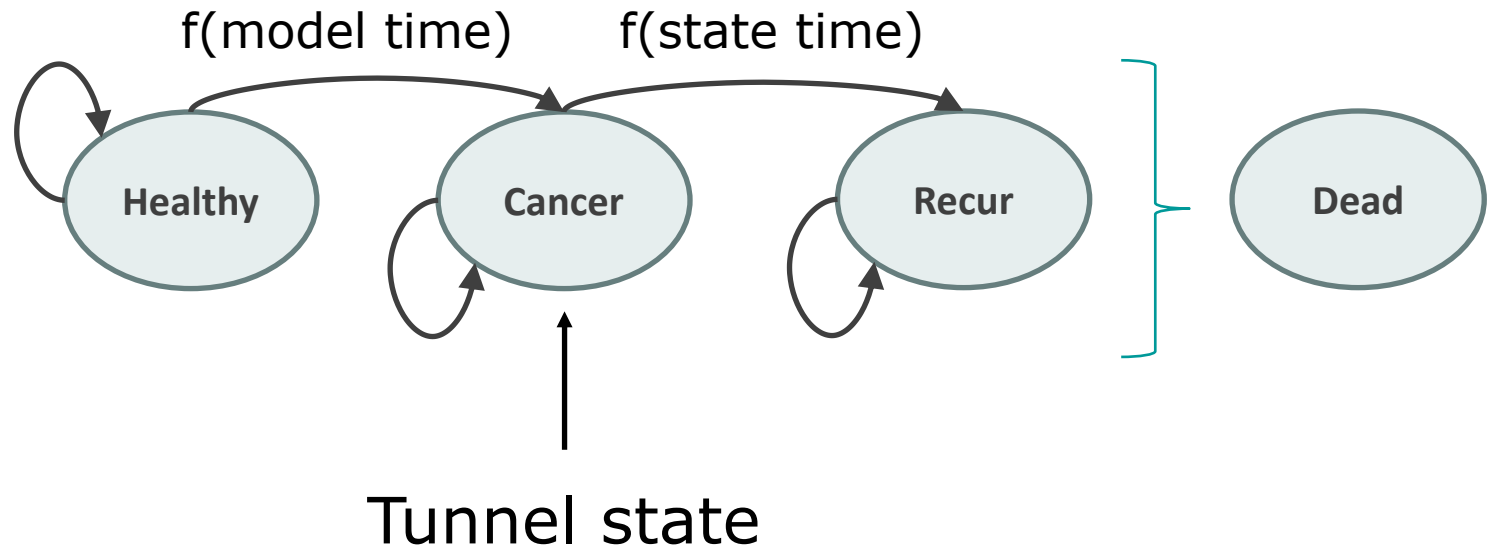

Healthy – Sick – Recovered - Dead

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

- Replacing P with P_t does not work, because it's not since model start

- Solution?

  - Create "tunnel" states

State Time

f(model time)   f(state time)

Healthy   Cancer   Recur   Dead

Tunnel state

Tunnel States

Cancer 1 — p_Recur_1 →

Cancer 2 — p_Recur_2 →

Cancer 3 — p_Recur_3 →

Cancer 4 — p_Recur_4 →

Cancer n — p_Recur_n →

Recur

Transitions to Dead also allowed.