Cohort state-transition Modeling in R

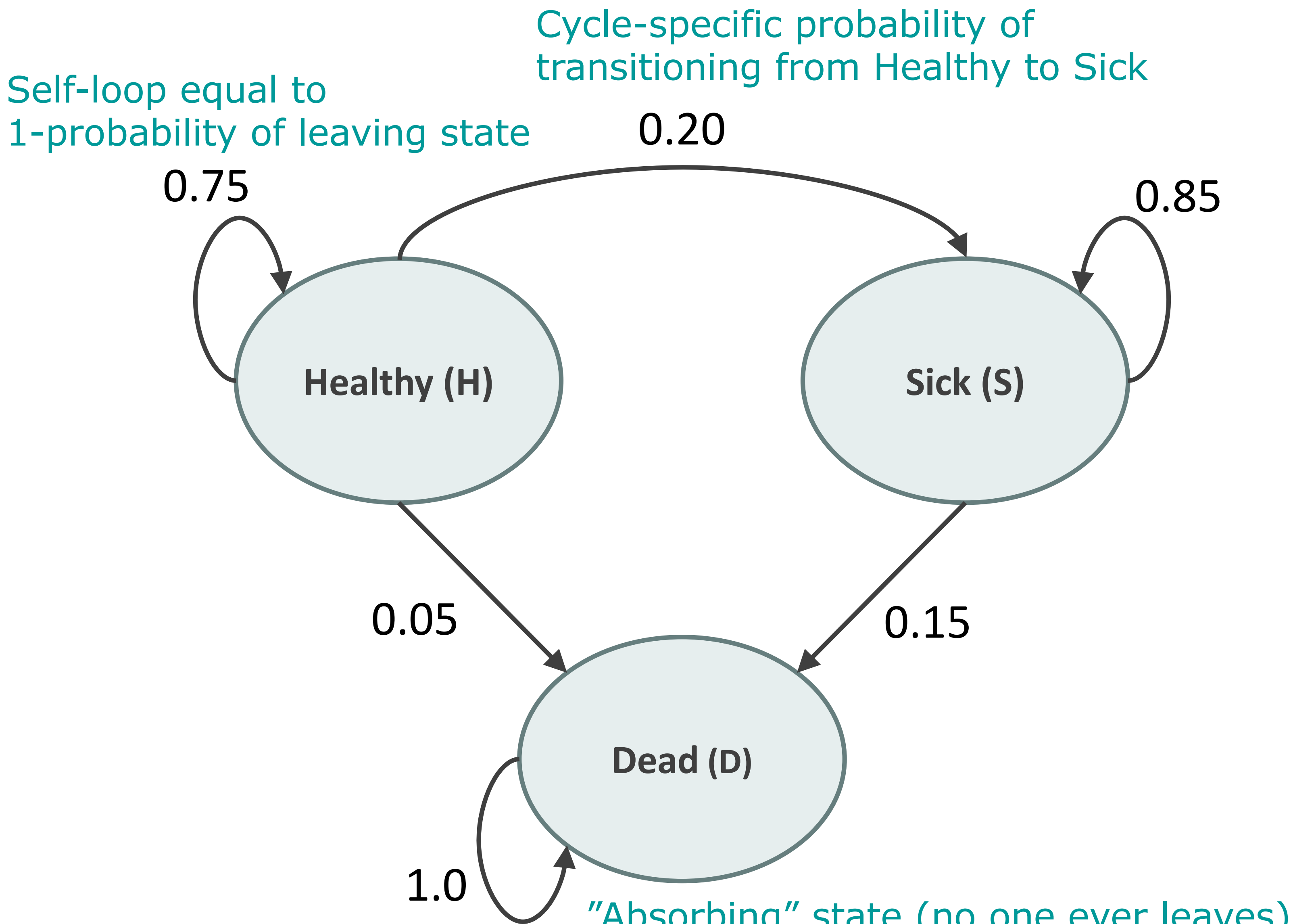
Decision Modeling for Public Health Workshop

November 15, 2022

Cohort State-Transition Models

- Describes a cohort of patients across a set of health states over time
  - Collectively exhaustive and mutually exclusive
- Transitions allowed between health states with some probability
- Transitions occur in discrete time cycles (months, years, etc.)

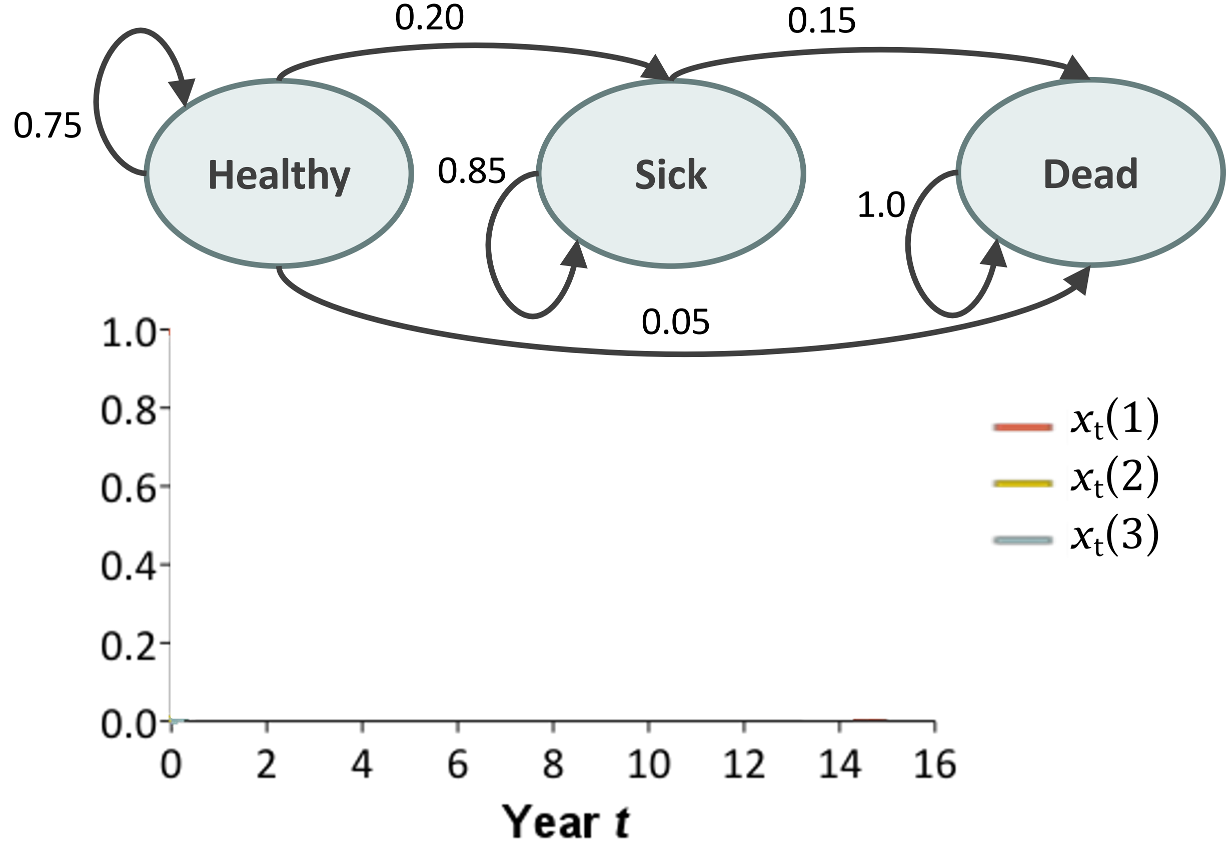
State-Transition Diagram



Simulate Cohort Over Time

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

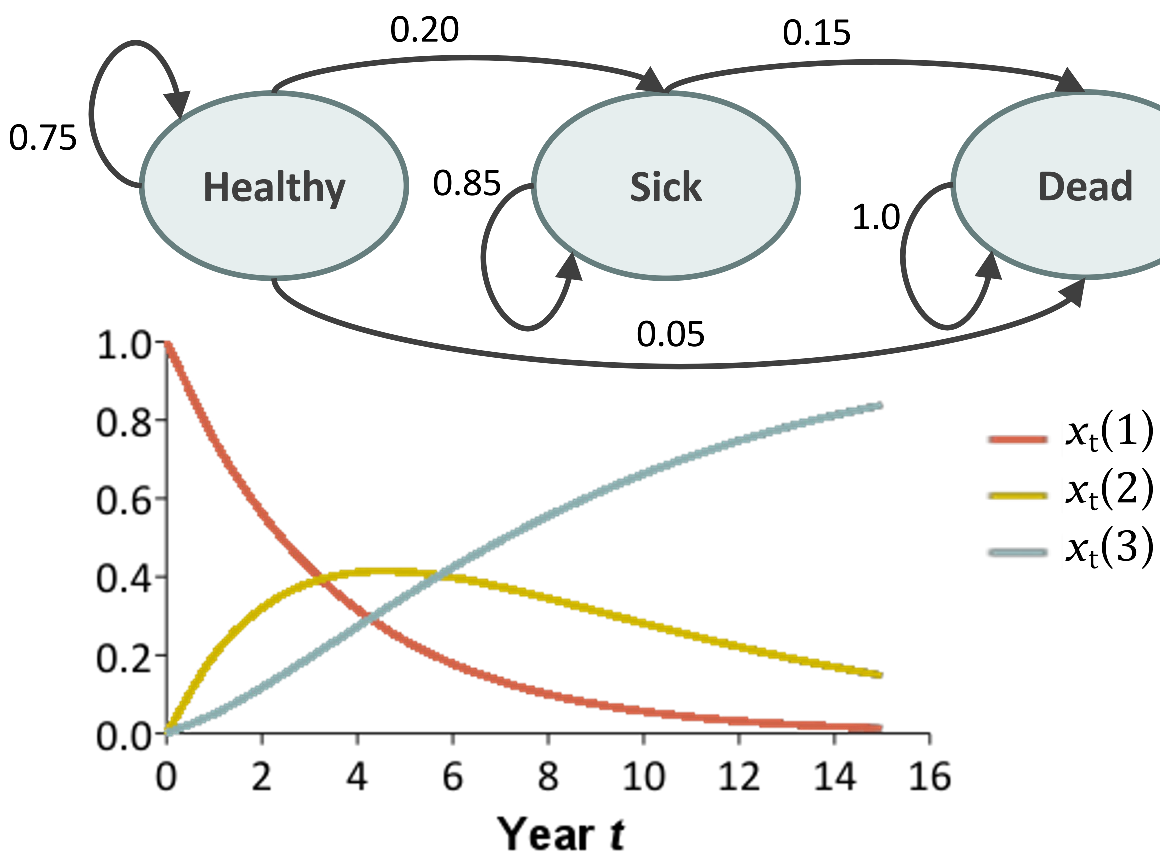
$$\boxed{x_{10} = [0.06 \quad\quad 0.28 \quad\quad 0.66]}$$



Simulate Cohort Over Time

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

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



Transition Matrix Calculations

- Summarize transition probabilities as a matrix

$$
\begin{array}{cc|ccc|}
 & & \text{To:} & & \\
 & & \text{Healthy} & \text{Sick} & \text{Dead} \\
\hline
\text{From:} & \text{Healthy} & 0.75 & 0.20 & 0.05 \\
 & \text{Sick} & 0 & 0.85 & 0.15 \\
 & \text{Dead} & 0 & 0 & 1.0 \\
\hline
\end{array} \quad = \quad A
$$

- Cohort distribution at next time step calculated through matrix multiplication

$$\begin{bmatrix} \text{——} & x_{\mathrm{t+1}} & \text{——} \end{bmatrix} = \begin{bmatrix} \text{——} & x_{\mathrm{t}} & \text{——} \end{bmatrix} \begin{bmatrix} & & \\ & A & \\ & & \end{bmatrix}$$

Transition Matrix Calculations

- Summarize transition probabilities as a matrix

From:	To: Healthy	Sick	Dead
Healthy	0.75	0.20	0.05
Sick	0	0.85	0.15
Dead	0	0	1.0

= A

- Cohort distribution at next time step calculated through matrix multiplication

$$\begin{bmatrix} \text{———} \; x_{t+1} \; \text{———} \end{bmatrix} = \begin{bmatrix} \text{———} \; x_{t} \; \text{———} \end{bmatrix} \underbrace{\begin{bmatrix} 0.75 & 0.20 & 0.05 \\ 0 & 0.85 & 0.15 \\ 0 & 0 & 1.0 \end{bmatrix}}_{A}$$

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\end{array}
= \quad \mathrm{A}
$$

- Cohort distribution at next time step calculated through matrix multiplication

$$
\underbrace{\begin{bmatrix} 0.75 & 0.20 & 0.05 \end{bmatrix}}_{x_1} = \underbrace{\begin{bmatrix} 1.0 & 0.0 & 0.0 \end{bmatrix}}_{x_0} \underbrace{\begin{bmatrix} 0.75 & 0.20 & 0.05 \\ 0 & 0.85 & 0.15 \\ 0 & 0 & 1.0 \end{bmatrix}}_{A}
$$

State-Transition Model Outcomes

- Outcomes (life-years, QALYs, costs, etc.) accrued by the cohort at each time step depend on the distribution across health states
- Each state assigned a value reflecting one cycle of residence
  - Cost per cycle
  - Utility
- At each cycle, multiply state-specific outcome by proportion of cohort in each state
- In CEA, outcomes are discounted to reflect time preferences
  - Prefer benefits now, costs later
  - Typical discount rate of 3% per year in US

Calculating Outcomes

- 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 r = 0.03

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 discounted life years: 6.77 years
(Remaining life expectancy)

Calculating Outcomes

- Multiply cohort distribution by state-specific values to calculate expected value at each time
  - Sum expected values over time (discount if desired)

r = 0.03

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 discounted costs: $11,557

(Total remaining lifetime costs)

Calculating Outcomes

- Multiply cohort distribution by state-specific values to calculate expected value at each time
  - Sum expected values over time (discount if desired)

r = 0.03

Utilities	1.0	0.8	0	
Time	Healthy	Sick	Dead	E[QALYs]
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 discounted QALYs: 5.95 QALYs
(Total remaining QALYs)

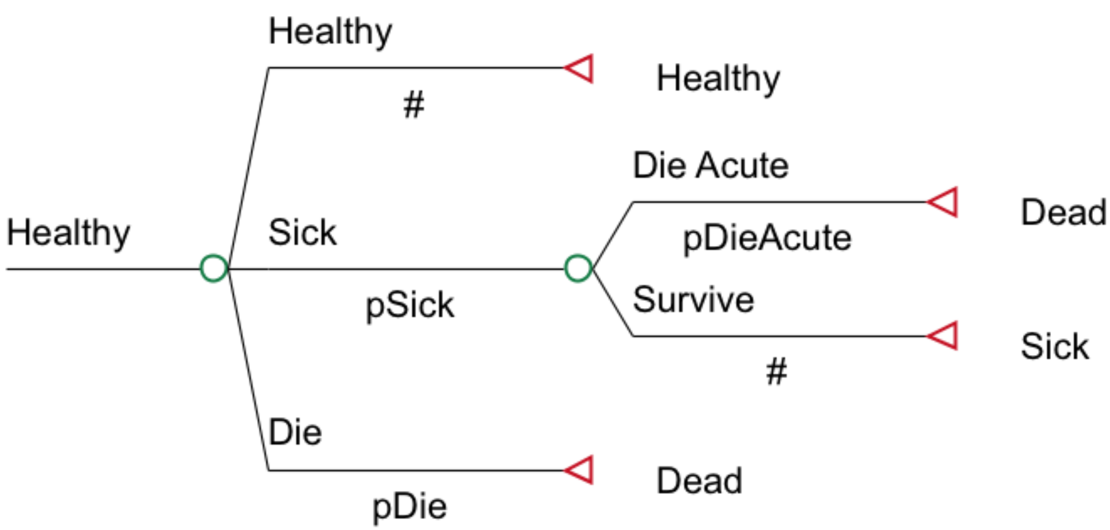
Designing a Cohort State-Transition Model

- Specify health states
- Define allowed transitions
- Choose cycle length
- Estimate transition probabilities
- Estimate state-specific values per cycle for outcomes of interests (costs, QALYs, etc.)

Additional Complexity in Cohort State-Transition Models

Within-Cycle Events

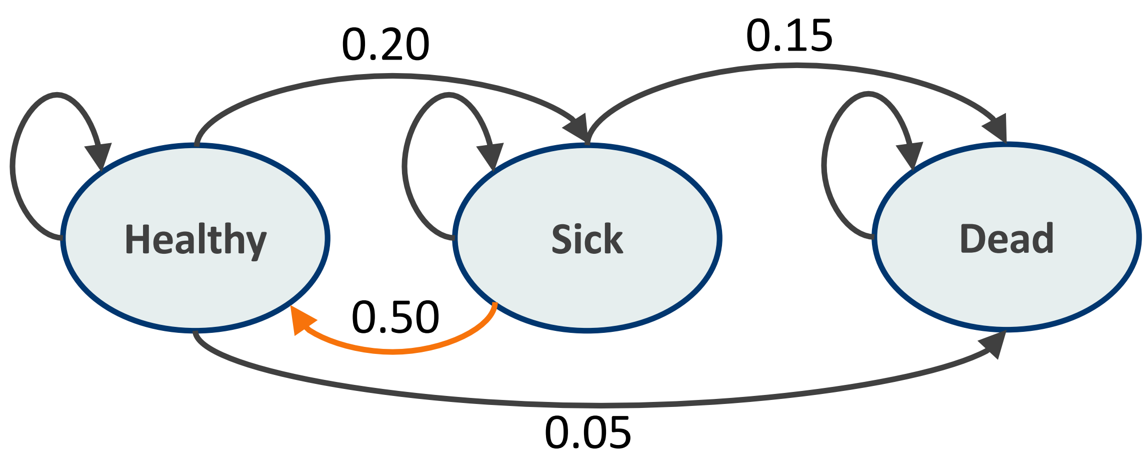
- Pr(Healthy → Dead) may conceptualized as a sequence of events within a cycle ("cycle tree")



- Pr(Healthy → Dead) = pDie + pSick * pDieAcute

Adding "Memory" Into States

- Same example as before, except can now recover from Sick and return to Healthy
  - Annual probability of recovery = 0.50
- But, for this illness, having been Sick in the past makes you more likely to get Sick in the future
  - Twice as likely to get Sick than those without history
- Track history of illness with additional Markov state



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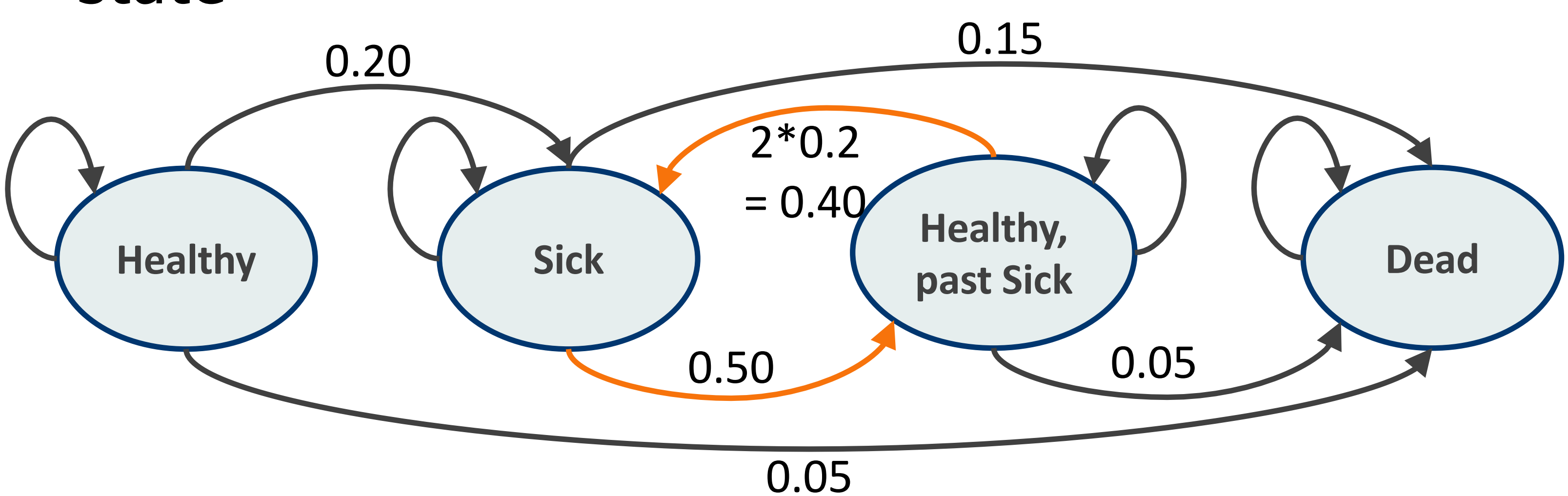


Time-dependency

Since start of the simulation

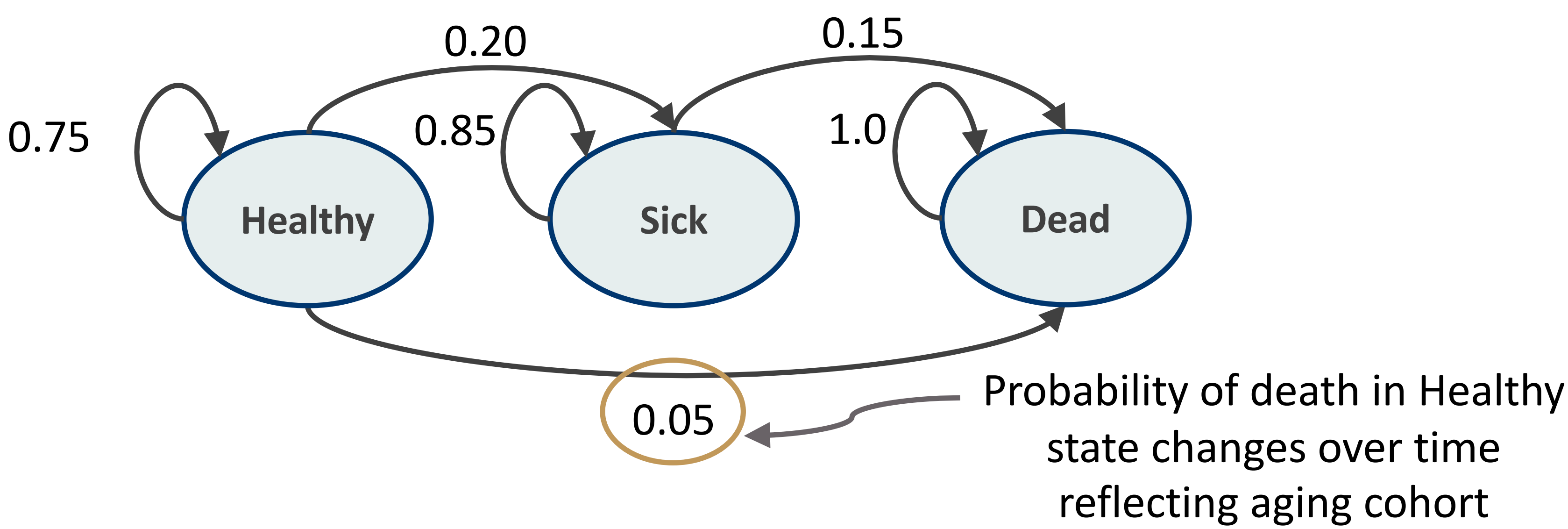
- Parameters vary by cycle
- Most often reflects probabilities that vary by <u>age</u>
  - Background mortality
  - Risk of disease onset

Depending on state residence time

- Some transition probabilities depend on time since an event
  - e.g., risk of developing recurrence among newly diagnosed cancer patients declines with time
- Cost or utility could vary over time spent in a health state

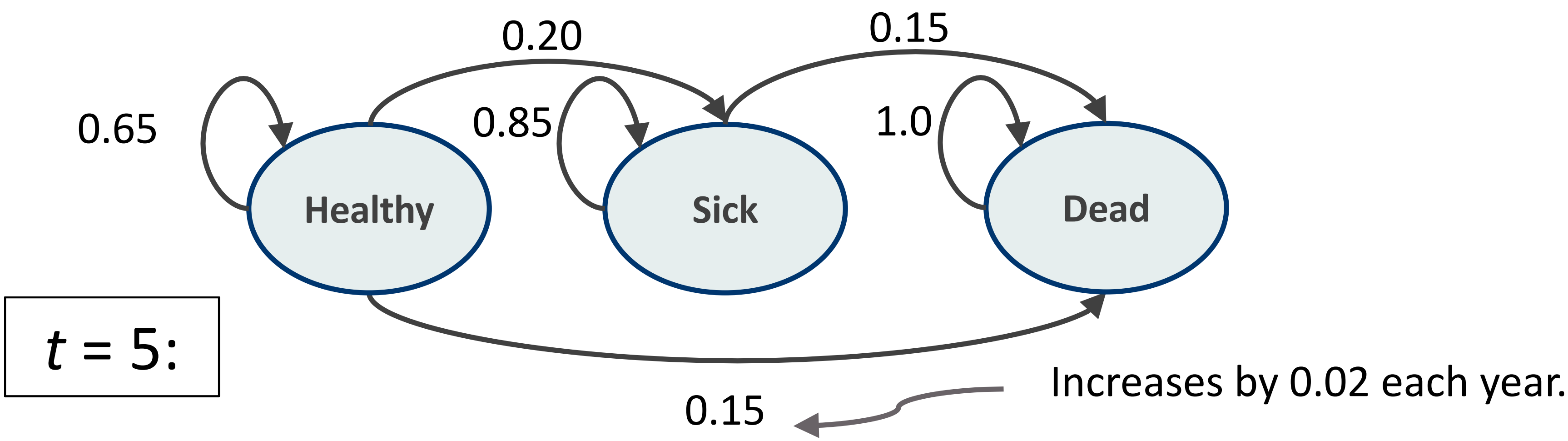
Simulation Time Dependency

- Some transition probabilities change every cycle
  - Transition matrix *A* is not constant over time



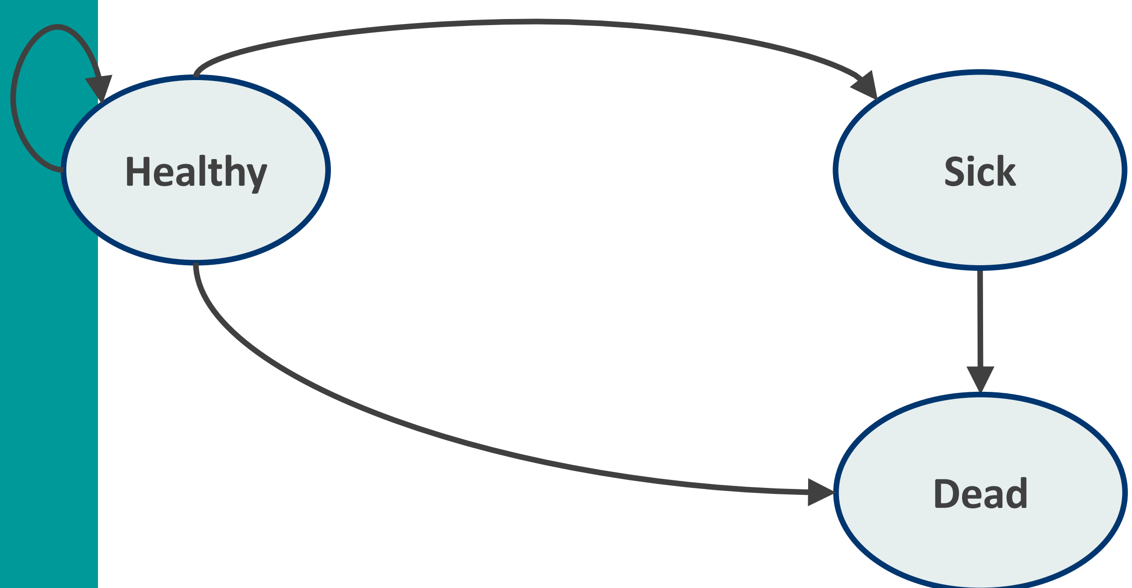
Simulation Time Dependency

- Some transition probabilities change every cycle
  - Transition matrix A is not constant over time
- Replace matrix A with matrices A_t, where t is time since simulation start



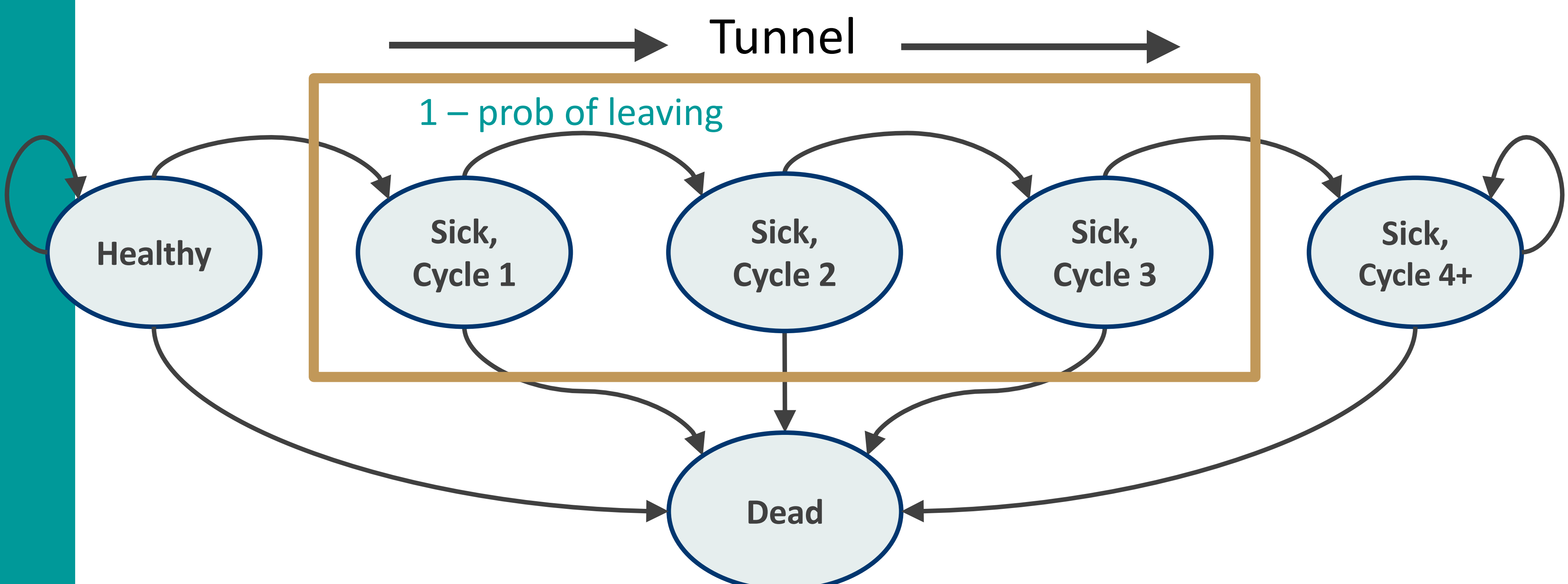
Residence Time Dependency

- Time spent in a state can be tracked using a series of "tunnel" states



Residence Time Dependency

- Time spent in a state can be tracked using a series of “tunnel” states
- Transition from one tunnel state to the next each time step (no self loops)

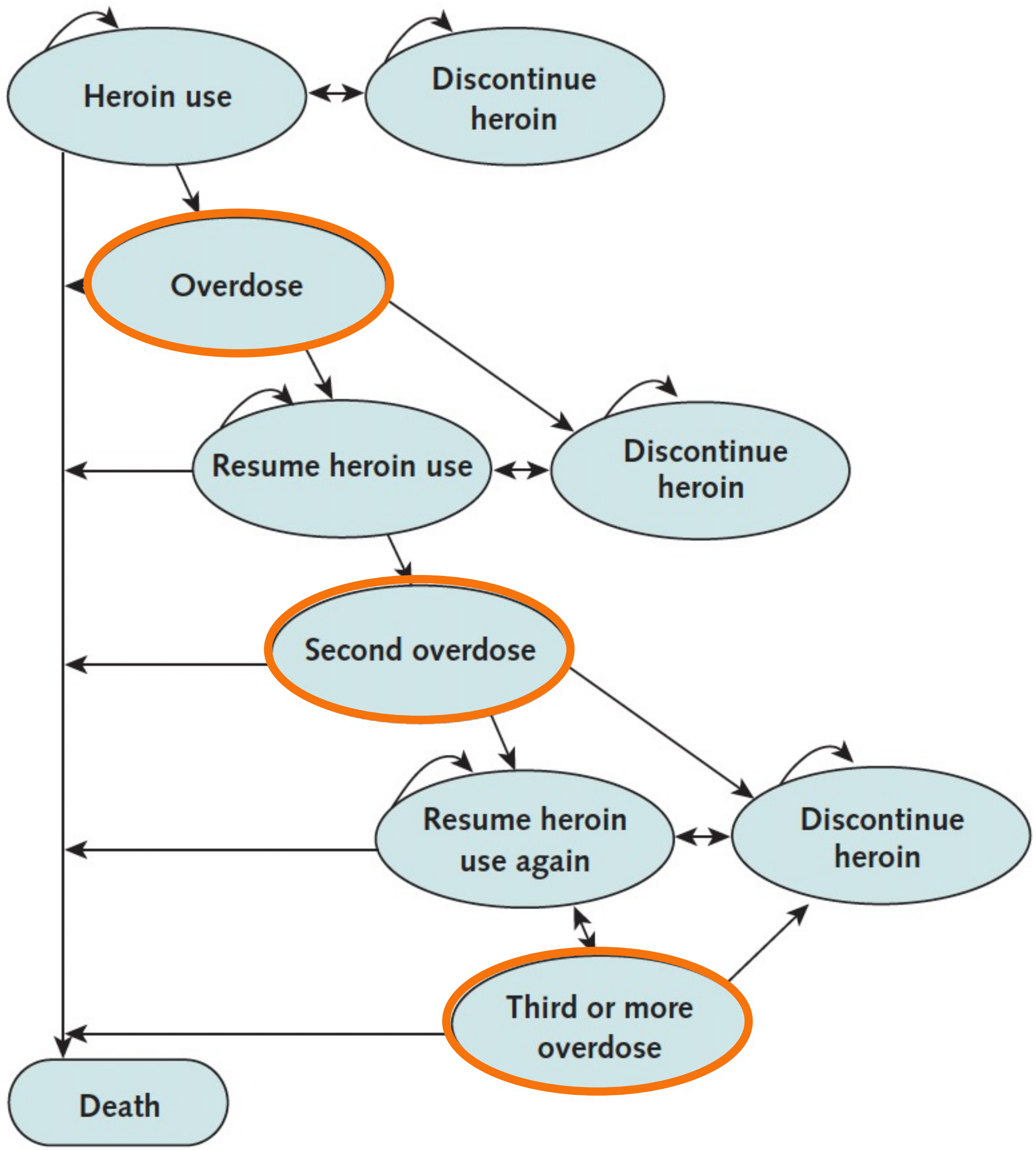


State-Transition Model CEA:
Naloxone Distribution for Overdose Prevention

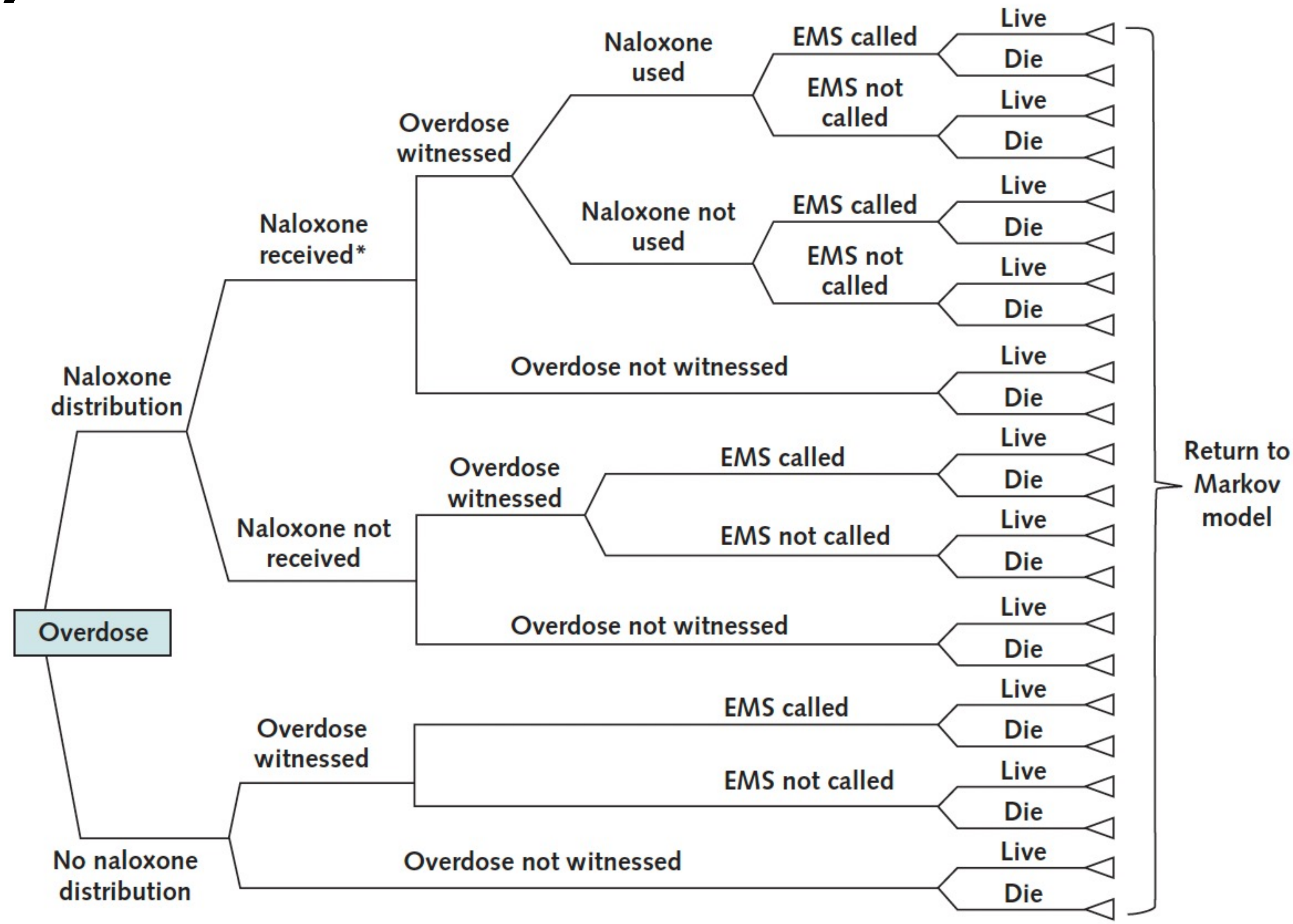
Study Context and Design

- Cost-effectiveness analysis of distributing naloxone in case of heroine overdose
  - Status quo: no distribution
  - Intervention: distribute naloxone to 20% of people who use heroine
- Population: Cohort of people who use heroine, starting at age 21
- Health outcomes: QALYs, overdose deaths averted
- Costs: naloxone kits, emergency transportation, emergency medical care
  - Sensitivity analysis including "costs to society"
- Time horizon: Lifetime

State-Transition Diagram



Cycle Tree



Overdose
Naloxone distribution
Naloxone received*
Overdose witnessed
Naloxone used
EMS called
Live
Die
EMS not called
Live
Die
Naloxone not used
EMS called
Live
Die
EMS not called
Live
Die
Overdose not witnessed
Live
Die
Naloxone not received
Overdose witnessed
EMS called
Live
Die
EMS not called
Live
Die
Overdose not witnessed
Live
Die
No naloxone distribution
Overdose witnessed
EMS called
Live
Die
EMS not called
Live
Die
Overdose not witnessed
Live
Die
Return to Markov model

Results

- Naloxone distribution ICER of $421 / QALy gained vs. no naloxone
- Highly cost-effective under many different assumptions, even worst case

Designing a model-based cost-effectiveness analysis

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Choosing your model type

Decision Trees

- Schematic representation of uncertain events/consequences of different alternatives
- Advantages:
  - Relatively simple; intuitive, clear visual representation
- Best for decisions made over a short time horizon
  - Clinical decisions (test, treat, etc.) for acute illness
  - Lifetime consequences can be quantified by using (pre-computed) life-expectancy as terminal value
- Not as appropriate in applications where there are repeated decisions or events
- Can be used to represent upfront strategy decisions, followed by a dynamic model for longer-term outcomes

Cohort State-Transition Models

- Dynamic model that reflects disease progression and other events in a cohort
- Advantages:
  - Represents dynamic processes
  - Still relatively simple and so computationally efficient
- Best for dynamic processes that
  - Can be represented with a reasonable number of states
  - Don’t dependent too much on individual heterogeneity (e.g., homogeneous cohort is a good approximation)
  - Minimal dependence on clinical history or time-in-state
- Usually deterministic (generate mean outcomes), but can be simulated stochastically

Quick Note: Compartmental Models

- Dynamic models similar to state-transition models, with key differences:
- Open population (not a cohort)
- Transition probabilities or rates can depend on population state → ***infectious processes***
  - e.g., risk of infection depends on prevalence of infection in the population

Microsimulation

- Stochastic dynamic model that simulates individuals, usually as a closed population
- Advantages:
  - Represents ***stochastic*** dynamic processes
  - Most flexible model type
  - Can capture ***complex dependencies*** on individual features, clinical history, time-since-event
  - Can capture interactions (agent-based model, network model)
- Best when a state-transition model is not sufficient
- Disadvantages
  - Computationally intensive, but can leverage parallel computing
  - Data intensive

Agent-Based Models

- Stochastic dynamic model that simulates individuals with interactions
  - Infectious processes
  - Behavioral influences
- Advantages:
  - Same advantages as microsimulation (flexible!)
- Disadvantages
  - Especially computationally intensive, requires simulating an entire population at once
  - Data intensive, including parameters governing interactions

Components of a Model-Based CEA

- Use the model to evaluate the costs and benefits of different strategies
- Strategy ← What you are choosing between
  - Clinical guidelines, treatment, new health technology, intervention, program, or policy
  - Consider combinations where relevant
- Costs ← What is included depends on perspective
  - Intervention costs, formal health care costs
  - Informal health care costs, societal costs
- Benefits ← Benefit depends on decision criteria
  - Infections averted, cases averted, disease-specific metrics
  - Life-years saved, quality-adjusted life-years saved

Decision criteria

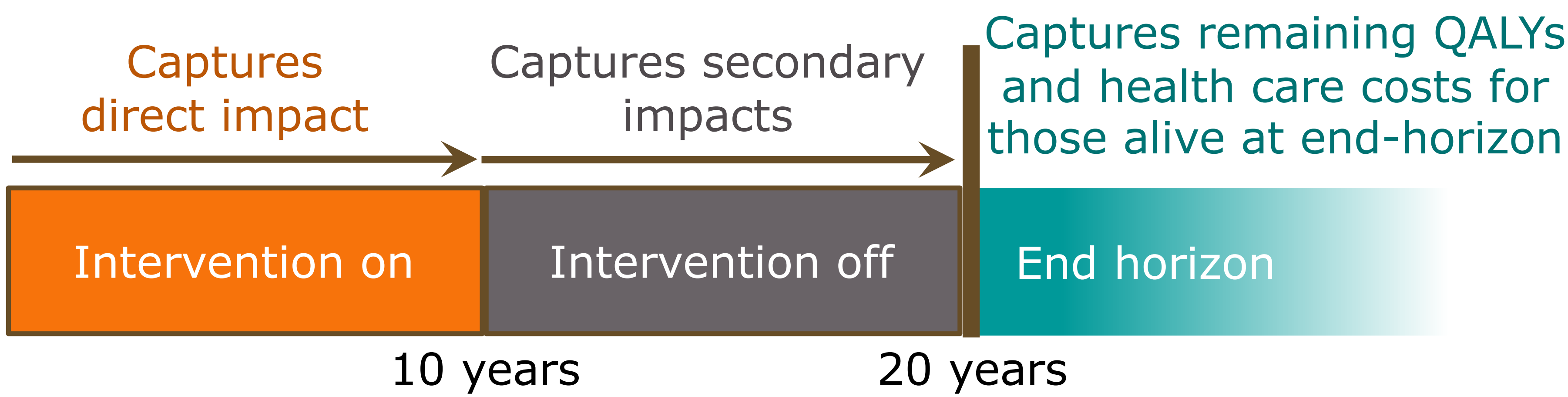
- How will you decide which strategy is optimal?
- Cost minimization
  - Strategy with lowest cost is optimal
  - Benefit is measured only in terms of averted costs (usually health care costs)
- Cost-effectiveness analysis
  - Strategy that maximizes health gains at a ”reasonable” cost is optimal
  - “Reasonable cost” means less than a cost-effectiveness threshold
  - Cost per QALY gained, cost per life-year gained, cost per infection/case averted

Cycle length

- For discrete-time, dynamic models, must select a cycle length
- Shorter cycle lengths better approximate continuous time and more accurately reflect event timing
- Longer cycle lengths reduce computational burden
- Timing of disease progression, screening, treatment, etc. influence appropriate cycle length

Time horizon

- Time frame over which costs and benefits will be aggregated
- Sufficiently long to capture strategy impacts
- Cohort / closed population: Generally, use lifetime
- Population models: need to define



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