Introduction to Markov models for cost-effectiveness analysis

14 February 2024

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The author has no relevant financial or nonfinancial relationships to disclose.

During the development, analysis, and preparation of this presentation, the author was an employee of the Veterans Health Administration, U.S. Department of Veterans Affairs.

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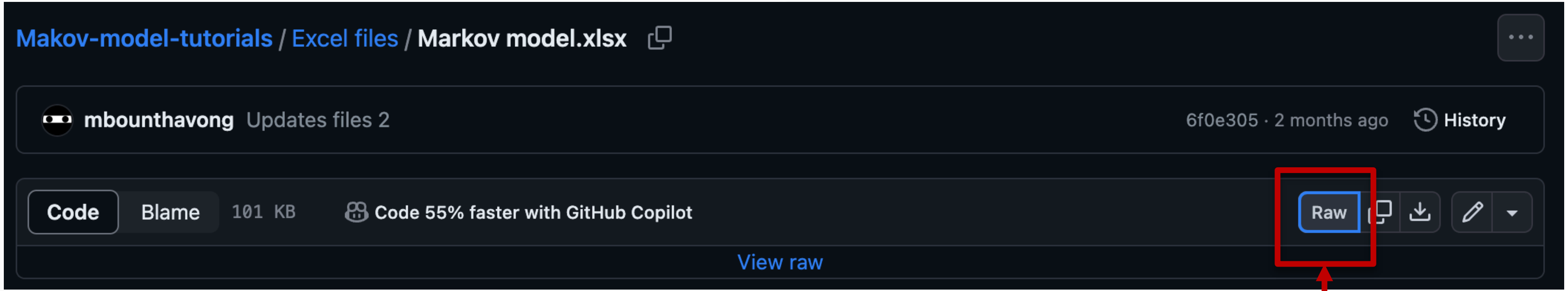

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Link to GitHub page

OUTLINE

Limitations of decision trees

Markov model description

Markov model features

Markov chain versus process

Discounting and Inflation

LIMITATIONS OF DECISION TREE (1)

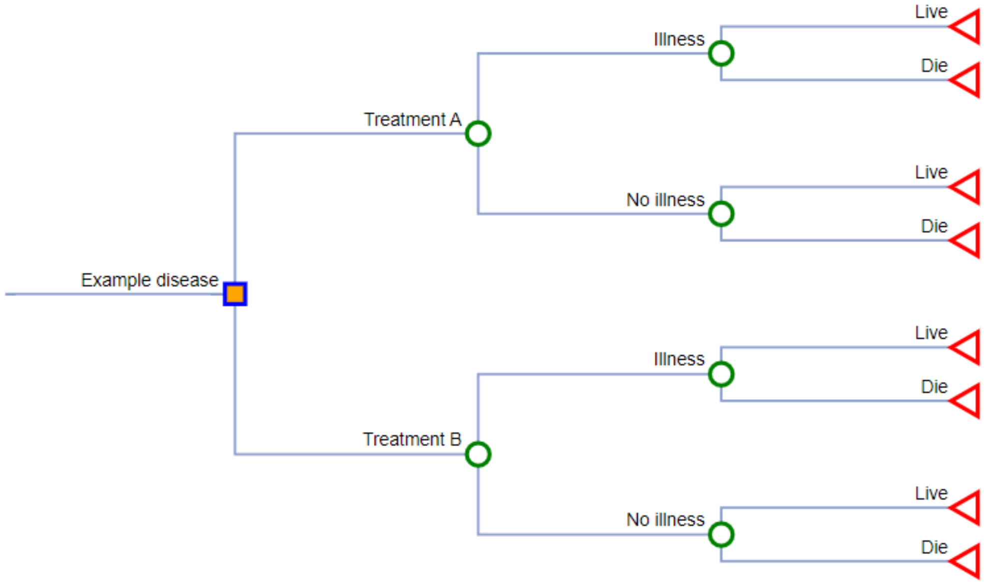
Chronic diseases have long time horizons

Can’t possibly capture all the re-entry points in a decision tree (becomes repetitive)

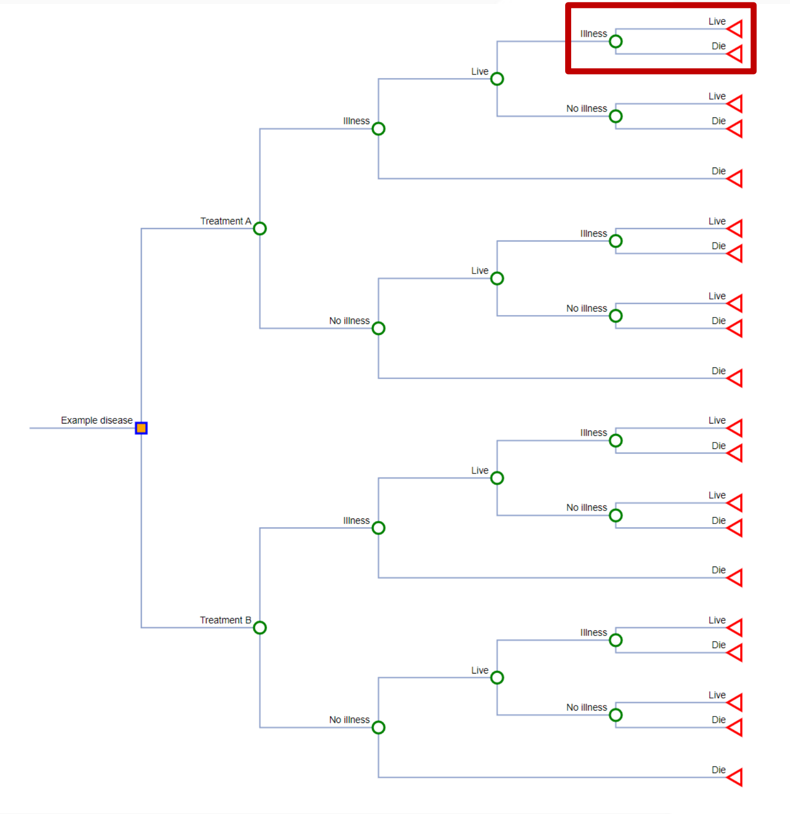
Markov re-entry nodes are convenient; decision branches are messy

Markov models are good alternatives to decision trees

LIMITATIONS OF DECISION TREE (2)



LIMITATIONS OF DECISION TREE (3)

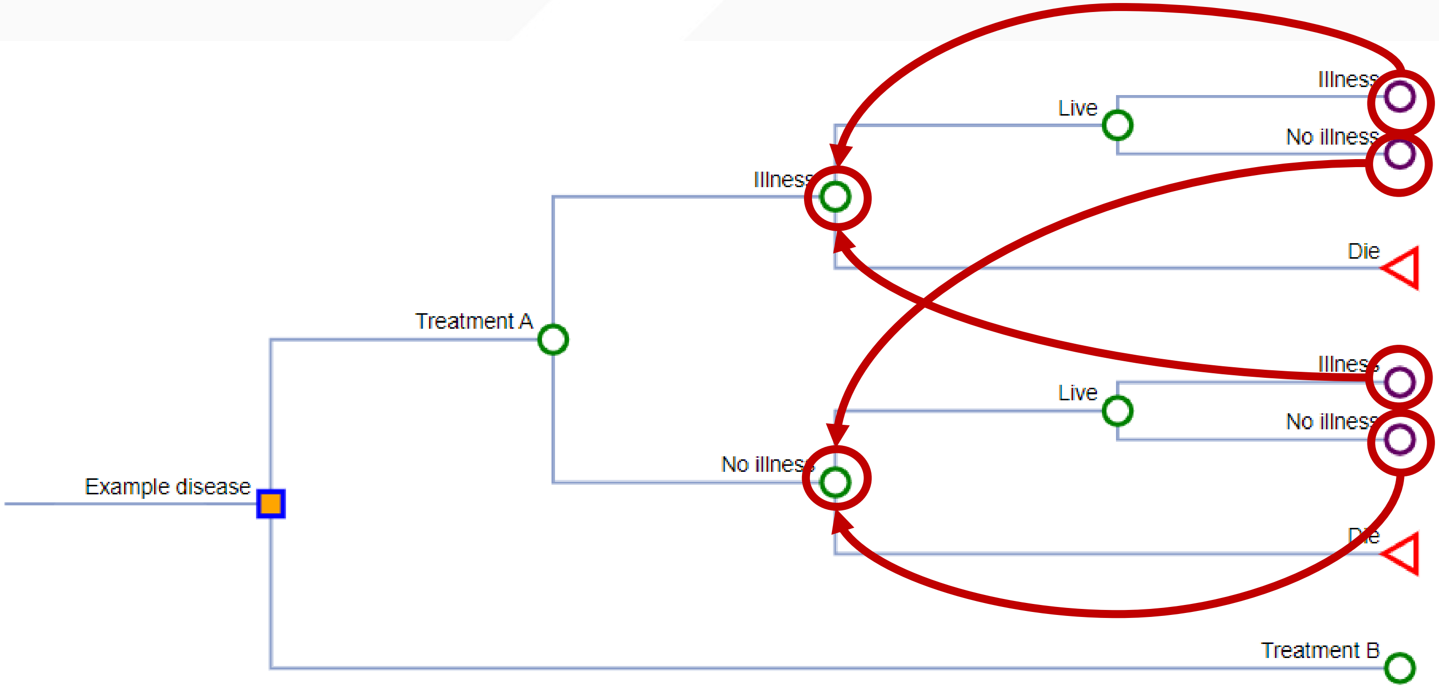


This part of the decision tree is a repeat of the Illness node.

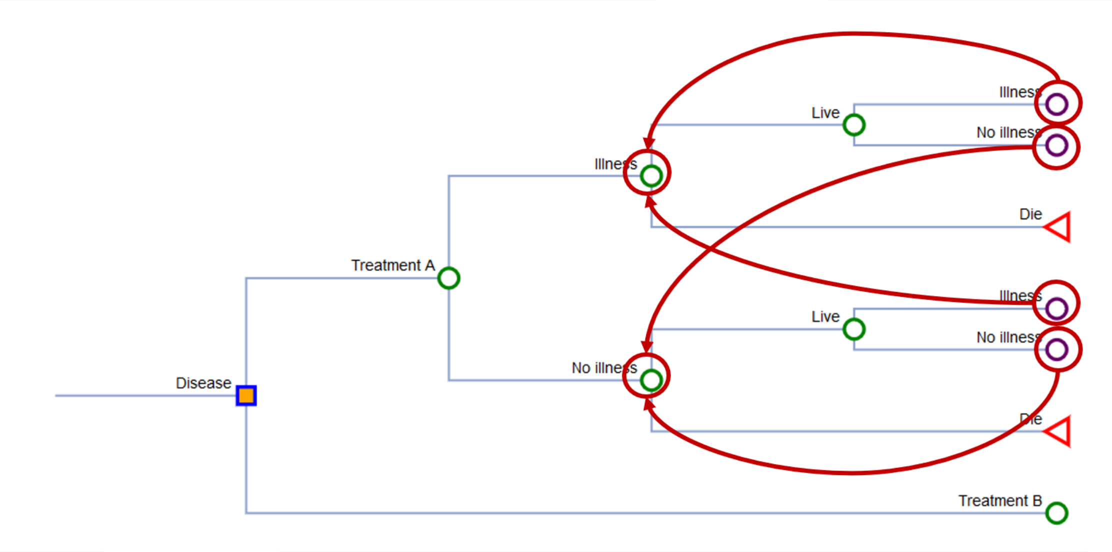
When a subject has an illness, they can live or die. If they live and have another illness, they can live or die once again.

This cycle repeats itself over and over.

LIMITATIONS OF DECISION TREE (4)



LIMITATIONS OF DECISION TREE (5)

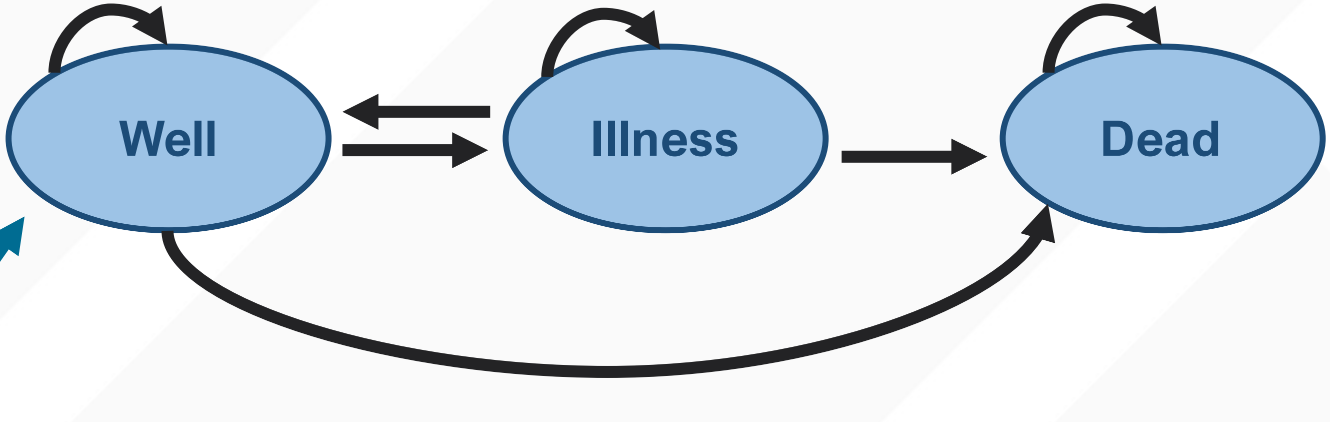


Well → Well
Well → Illness
Well → Death

Illness → Illness
Illness → Well
Illness → Death

Death → Death

MARKOV MODEL STRUCTURE



Costs
Benefits
} Assigned to the states

MARKOV MODEL - DESCRIPTION

Markov models are state-transition models

Useful when modeling chronic diseases

Each state represents a disease stage (or process)

Costs and benefits are assigned to each state

Can apply discounting

Individual subject can only be in one state at any cycle

MARKOV MODEL – DISEASE STATES

Asymptomatic state   Disease state   Absorbing state

MARKOV MODEL – TRANSITION PROBABILITIES (1)

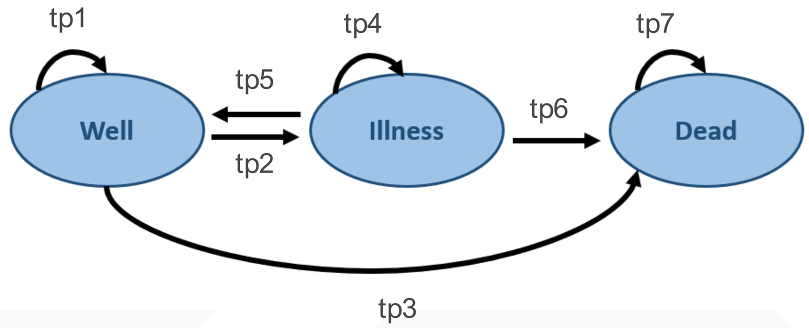
Well → Well tp1
Well → Illness tp2
Well → Death tp3

100%

Illness → Illness tp4
Illness → Well tp5
Illness → Death tp6

100%

Death → Death tp7



MARKOV MODEL – TRANSITION PROBABILITIES (2)

Well → Well tp1
Well → Illness tp2
Well → Death tp3

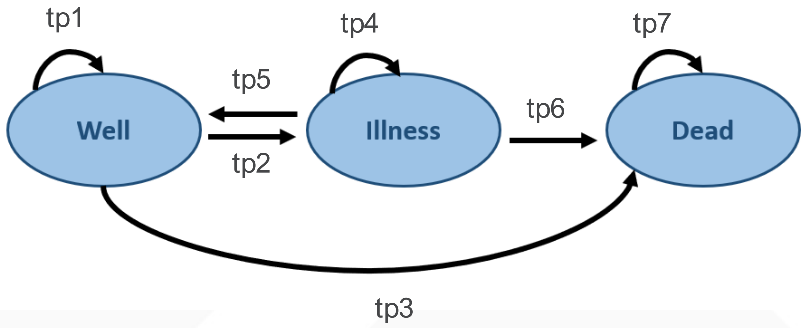
100%

Illness → Illness tp4
Illness → Well tp5
Illness → Death tp6

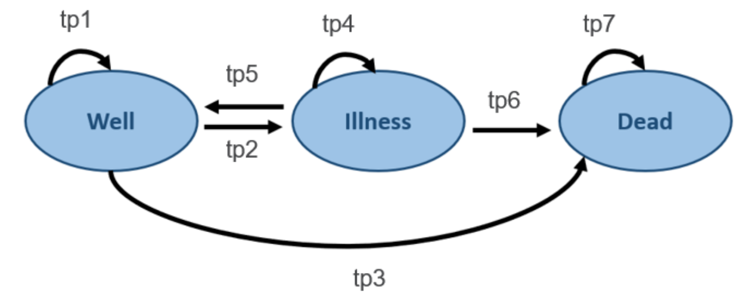
100%

Death → Death tp7

If you have tp2 and tp3, then
tp1 = 1 – tp2 – tp3

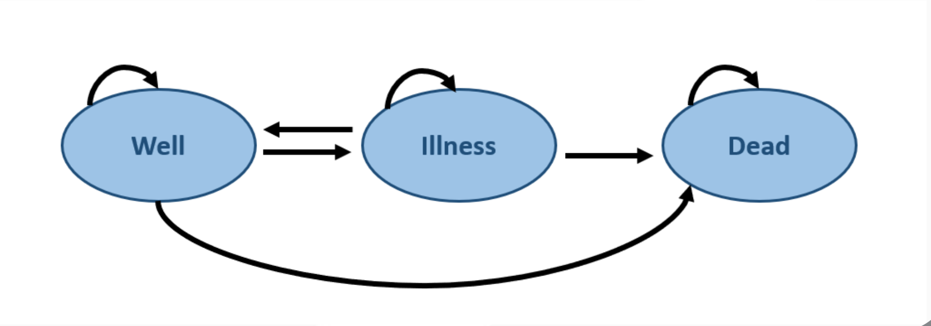


MARKOV MATRIX



From / To	Well	Illness	Dead
Well	tp1 (1 – tp2 – tp3)	tp2	tp3
Illness	tp5	tp4 (1 – tp5 – tp6)	tp6
Dead	0	0	tp7

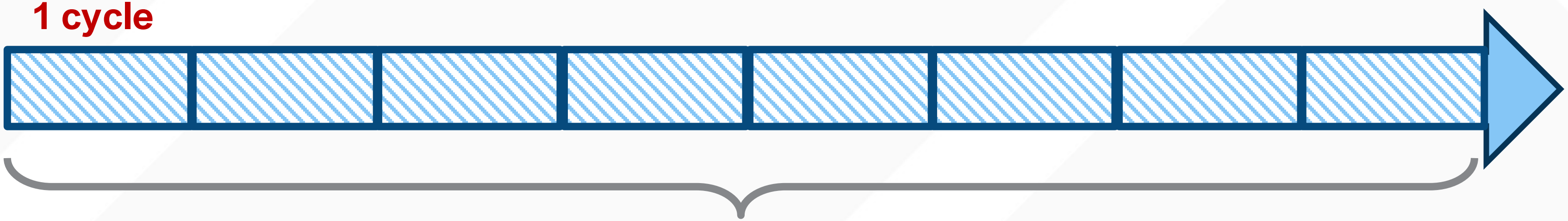
MARKOV MODEL – FEATURES



One iteration = Cycle

X-iterations = Time horizon

1 cycle

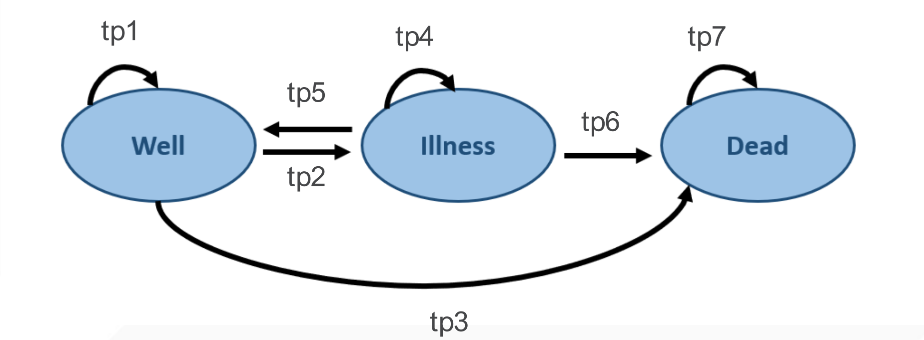


Time horizon

MARKOV CHAIN VERSUS PROCESS (1)

Markov chain – static transitions

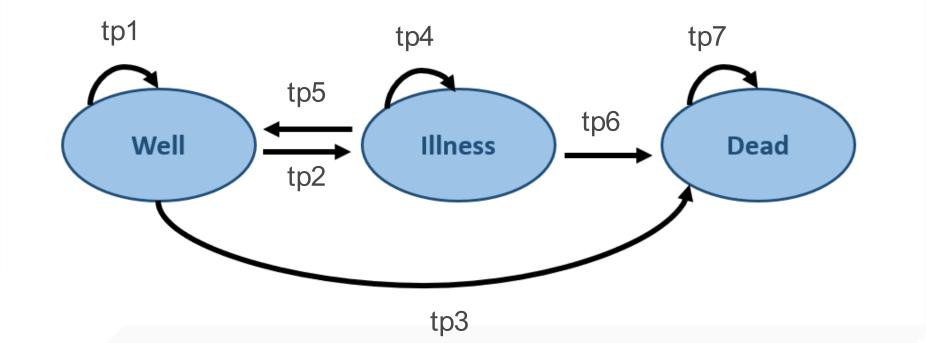
Markov process – dynamic transitions



MARKOV CHAIN VERSUS PROCESS (2)

Markov chain – static transitions

Markov process – dynamic transitions



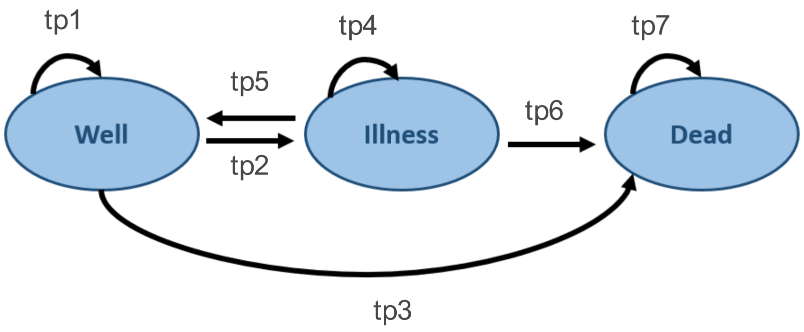
Transition probabilities remain static

If tp1 = 0.90 is cycle 1, then tp1 = 0.90 in cycle 2

MARKOV CHAIN VERSUS PROCESS (3)

Markov chain – static transitions

Markov process – dynamic transitions



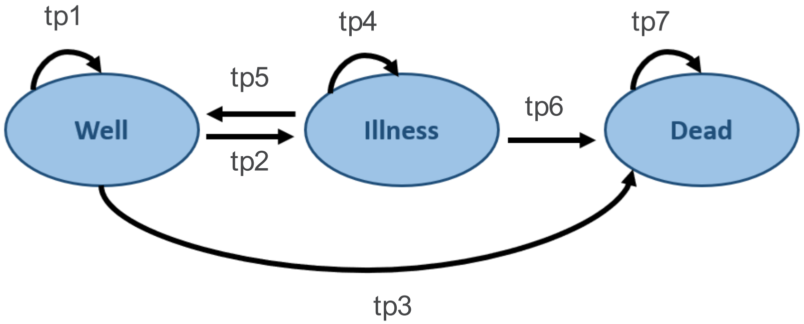
Transition probabilities change from cycle to cycle

Although tp1 = 0.90 is cycle 1, tp1 = 0.85 in cycle 2

MARKOV CHAIN VERSUS PROCESS (4)

Markov chain – static transitions

Markov process – dynamic transitions



This is useful when the cohort will have a lower survival over a long period of time

COHORT VERSUS MICROSIMULATIONS (1)

Cohort simulation

- Model a group of hypothetical patients at the same time
- Time horizon is fixed
- Computationally less intensive

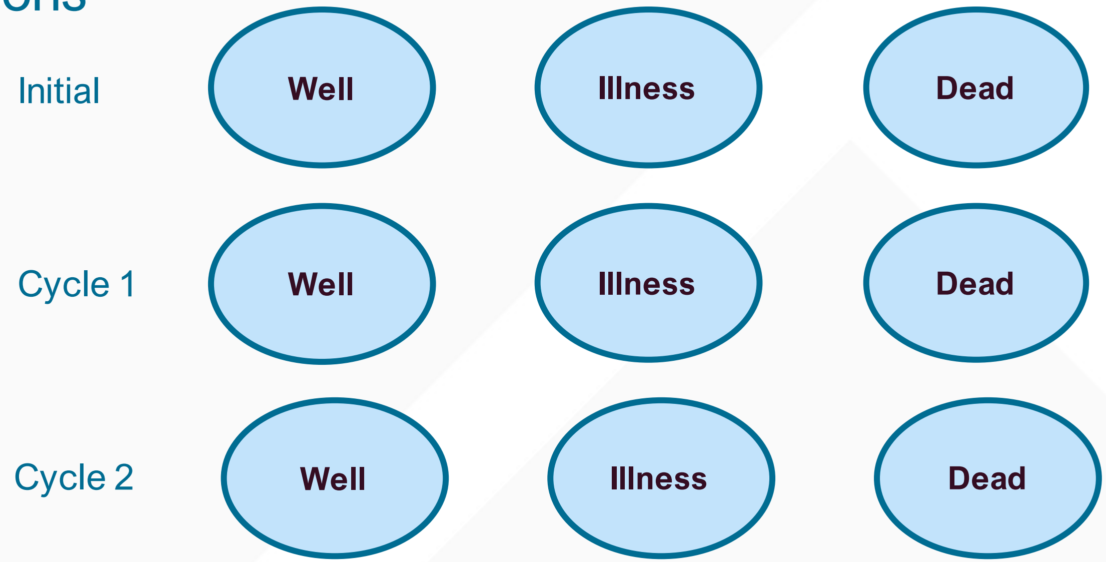
Individual or microsimulations (Monte Carlo)

- Individuals are modeled through the Markov models one at a time
- Time for each patient can be short or long
- Computationally intensive

COHORT VERSUS MICROSIMULATIONS (1)

Cohort simulation

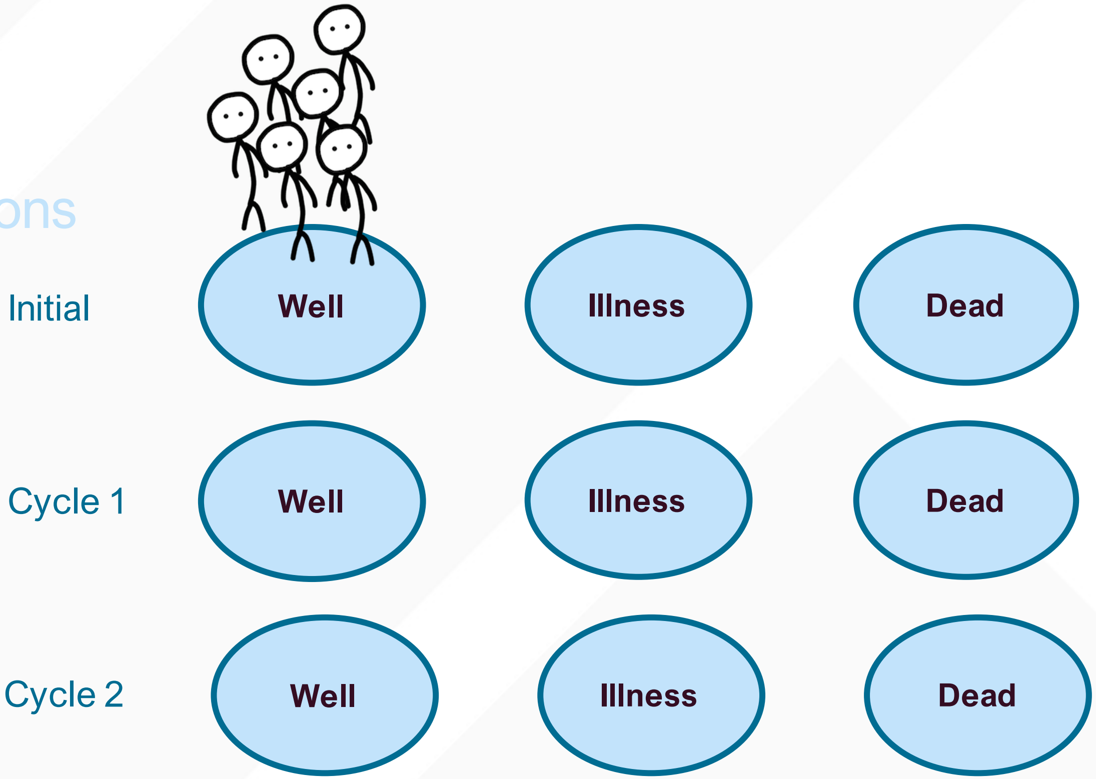
Individual or microsimulations



COHORT VERSUS MICROSIMULATIONS (2)

Cohort simulation

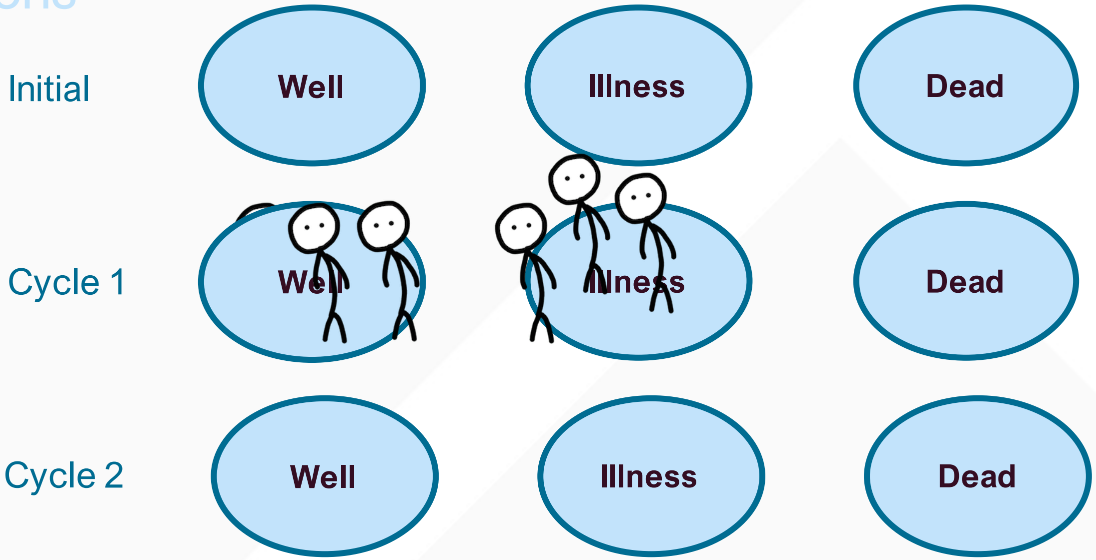
Individual or microsimulations



COHORT VERSUS MICROSIMULATIONS (3)

Cohort simulation

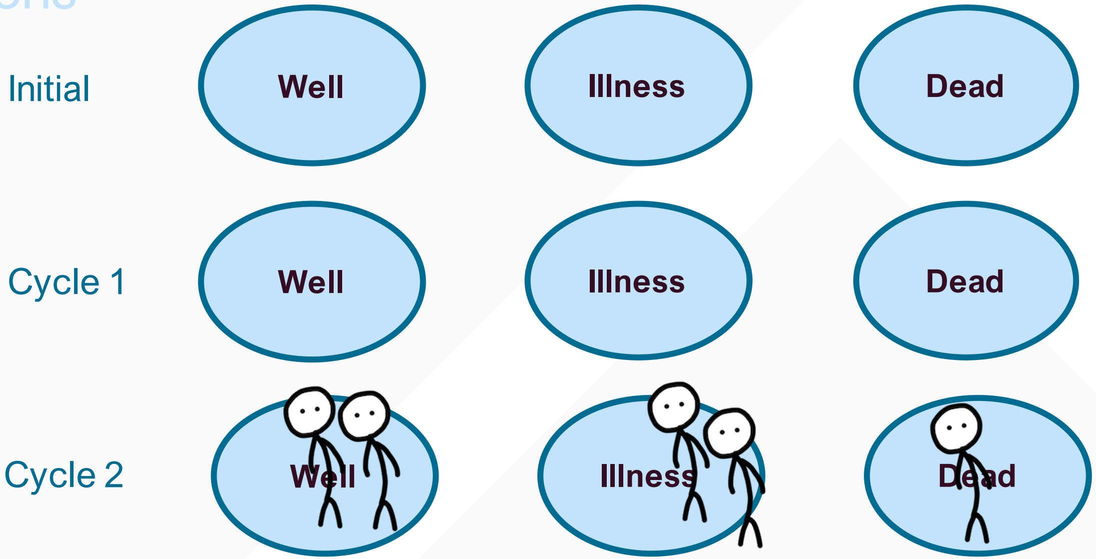
Individual or microsimulations



COHORT VERSUS MICROSIMULATIONS (4)

Cohort simulation

Individual or microsimulations

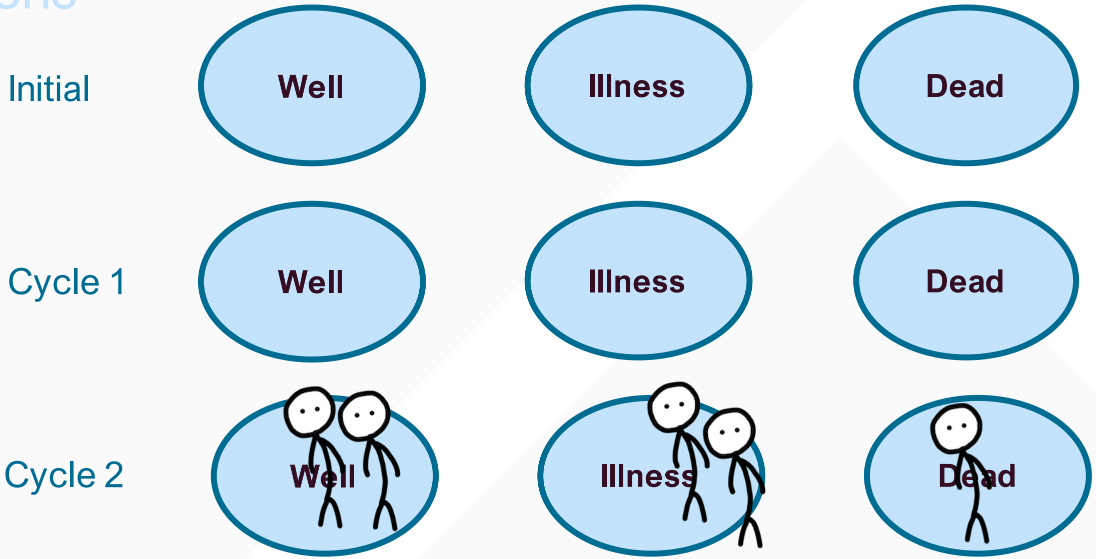


COHORT VERSUS MICROSIMULATIONS (5)

Cohort simulation

Individual or microsimulations

"Memoryless"
(Markovian Assumption)



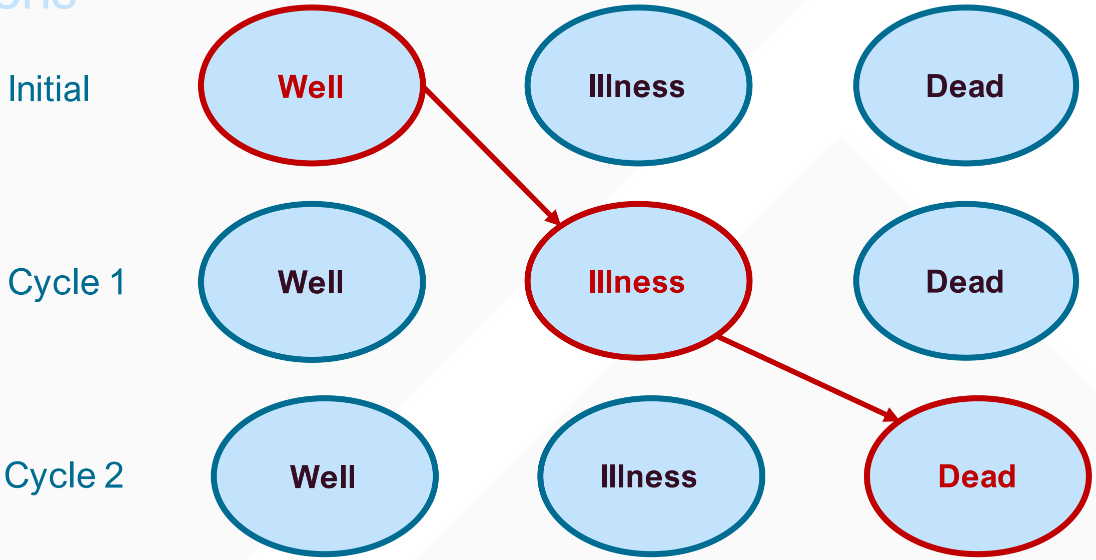
COHORT VERSUS MICROSIMULATIONS (6)

Cohort simulation

Individual or microsimulations

"Memoryless"
(Markovian Assumption)

Tunnel states are used to force the model to consider the previous state

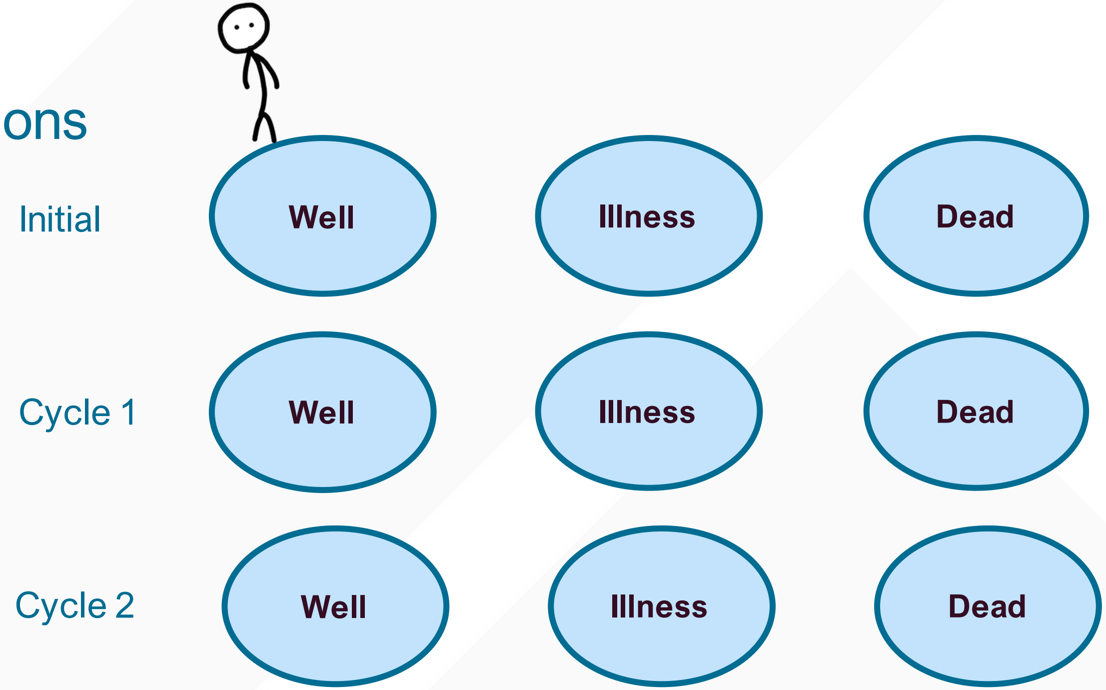


COHORT VERSUS MICROSIMULATIONS (7)

Cohort simulation

Individual or microsimulations

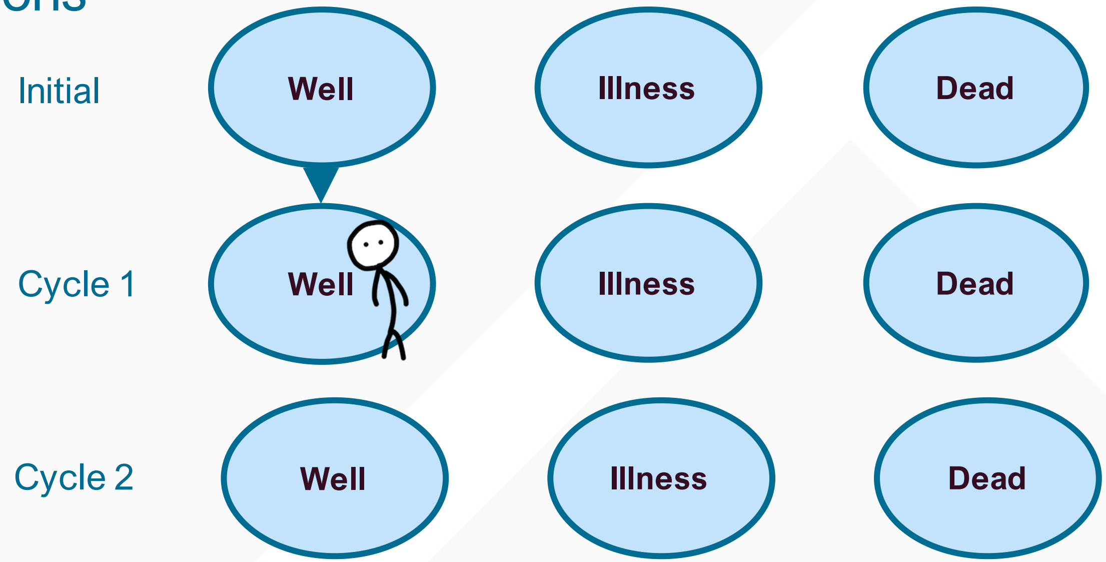
- “First order” Montel Carlo
- Generate variance around the cost and benefits



COHORT VERSUS MICROSIMULATIONS (8)

Cohort simulation

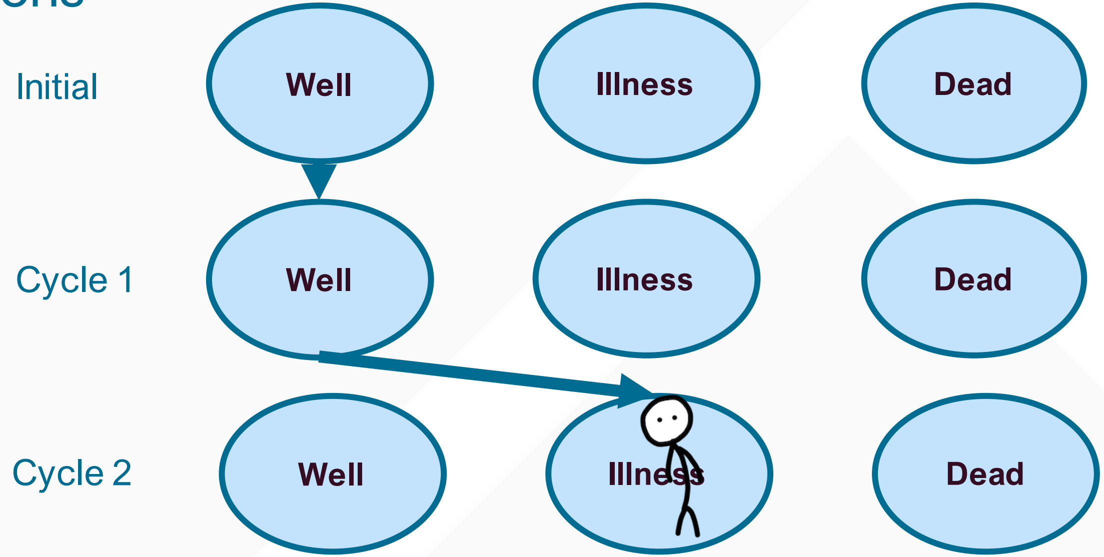
Individual or microsimulations



COHORT VERSUS MICROSIMULATIONS (9)

Cohort simulation

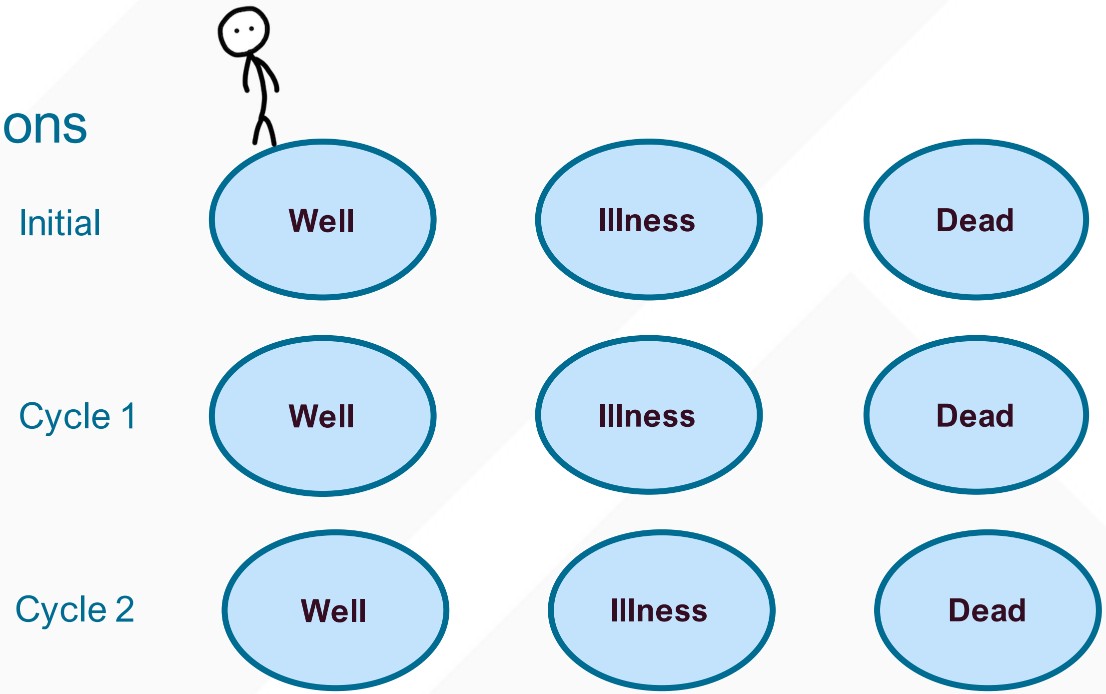
Individual or microsimulations



COHORT VERSUS MICROSIMULATIONS (10)

Cohort simulation

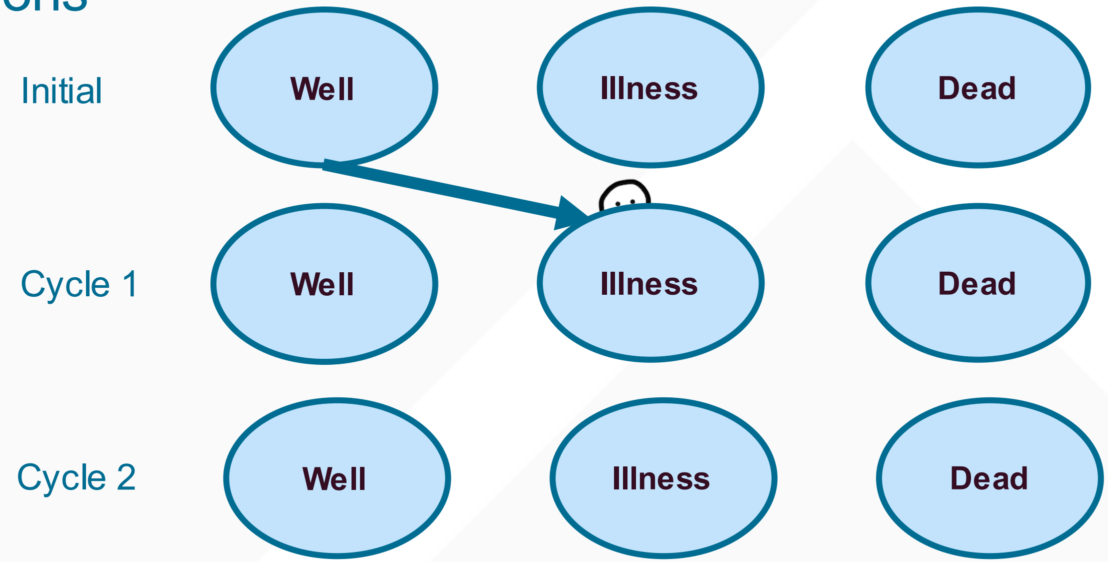
Individual or microsimulations



COHORT VERSUS MICROSIMULATIONS (11)

Cohort simulation

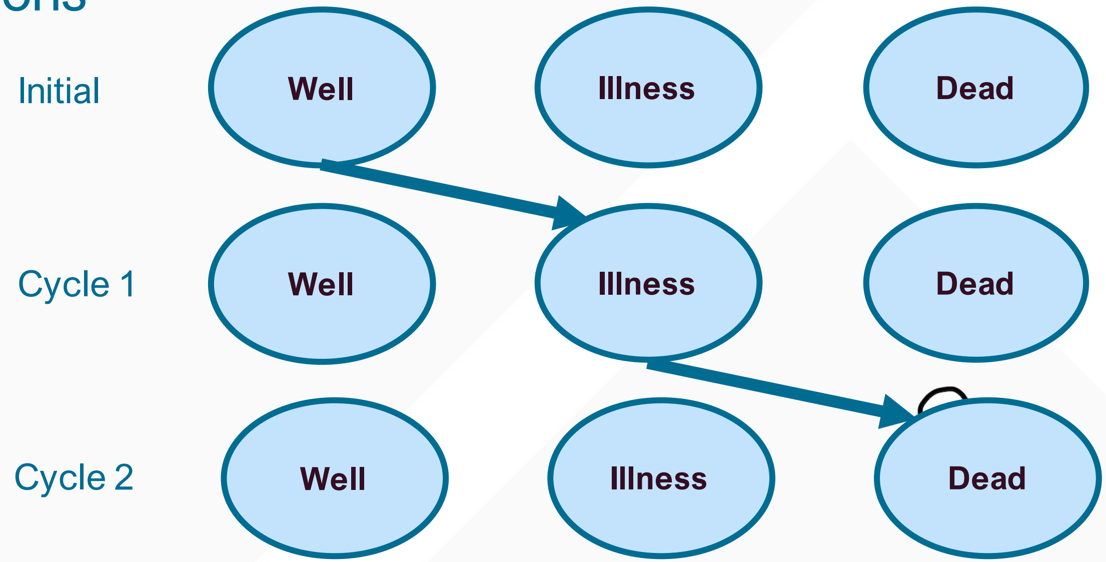
Individual or microsimulations



COHORT VERSUS MICROSIMULATIONS (12)

Cohort simulation

Individual or microsimulations



Estimating transition probabilities

Using existing studies to estimate probabilities for decision models

ESTIMATING TRANSITION PROBABILITIES (1)

Rate – Instantaneous likelihood of transition at any point in time (e.g., 5 events per 100 Person Years)

Probability – Proportion of a cohort that experiences the event over a specific period (e.g., 90% of patients had the event)

To get the transition probabilities in a Markov model using an existing study, estimate the rate, then estimate the probability for the time of interest using the rate

ESTIMATING TRANSITION PROBABILITIES (2)

Estimating the probability from a study:

Probability from study → Rate → Probability for model

$$Rate = \frac{-\ln(1-p)}{t}$$

$$Probability = 1 - e^{-rt}$$

p probability
t time
r rate

ESTIMATING TRANSITION PROBABILITIES (3)

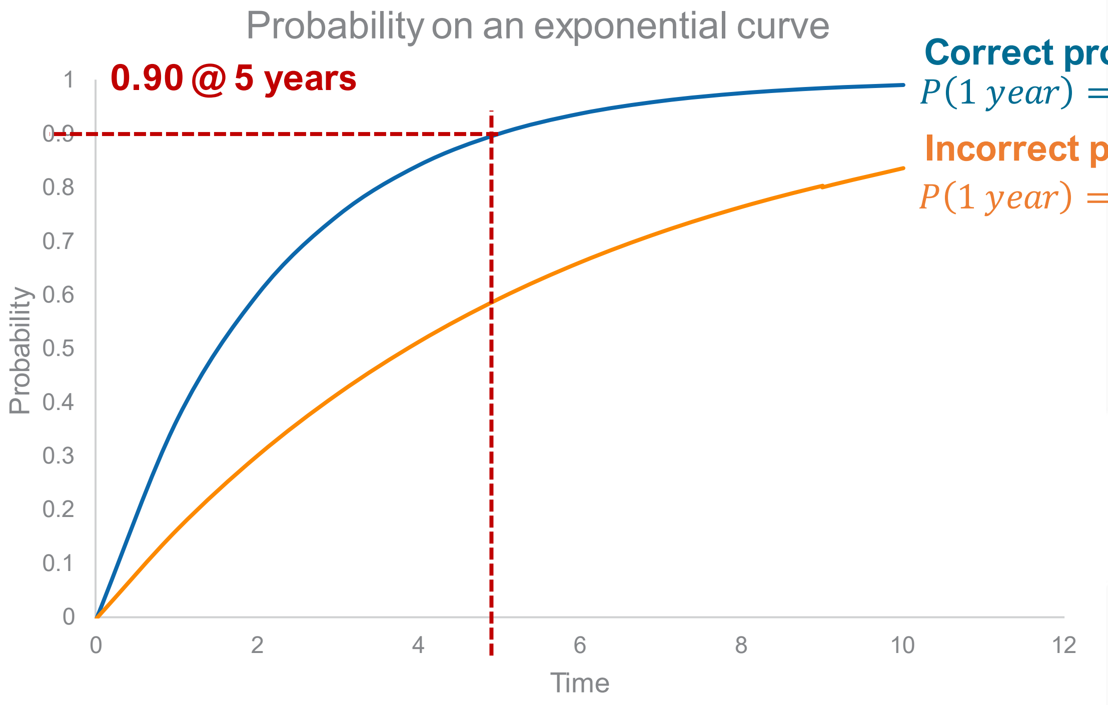
If the 5-year probability of achieving a cure is 90%, what is the 1-year probability?

You can't divide the 5-year probability by 5 (e.g., 90% / 5 = 18% to get the annual rate)

Probability from study → $Rate = \frac{-\ln(1-p)}{t}$ → $P(t) = 1 - e^{-rt}$

P(5 years) = 90% → $Rate = \frac{-\ln(1-0.90)}{5\ years} = 0.46$ → $P(1\ year) = 1 - e^{-(0.46)(1\ year)} = 0.37$

ESTIMATING TRANSITION PROBABILITIES (4)



Correct probability

$$P(1\ year) = 1 - e^{-(0.46)(1\ year)} = 0.37$$

Incorrect probability

$$P(1\ year) = 1 - e^{-(0.18)(1\ year)} = 0.16$$

ESTIMATING TRANSITION PROBABILITIES (5)

Suppose you had data from a meta-analysis where the relative risk of cure is 2.0 with a drug

What is the 1-year probability of cure using an annual rate of cure that is 0.47? (Hint: Is it not 2 x 0.47)

RR * rate → $P(t) = 1 - e^{-rt}$

2.0 X 0.47 = 0.94 → $P(1\ year) = 1 - e^{-(0.94)(1\ year)} = 0.61$

Discounting and inflation

Adjusting costs and outcomes for long time horizons

DISCOUNTING AND INFLATION

Net Present Value: Current purchasing power of currency

DISCOUNTING

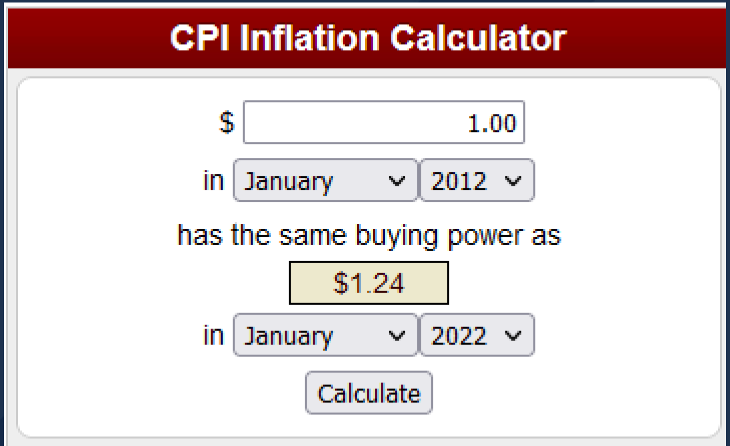
What is today's value of $1 10 years from now using a 3% discount rate?

$$V_0 = \frac{V_t}{(1+r)^t} \quad \Rightarrow \quad \$0.74 = \frac{\$1}{(1+0.03)^{10}}$$

V_0 = Value in today's term
V_t = Value at time t in the future
r = Discount rate
t = Time in the future

INFLATION

What is today's value of $1 from 10 years ago using the Consumer Price Index?



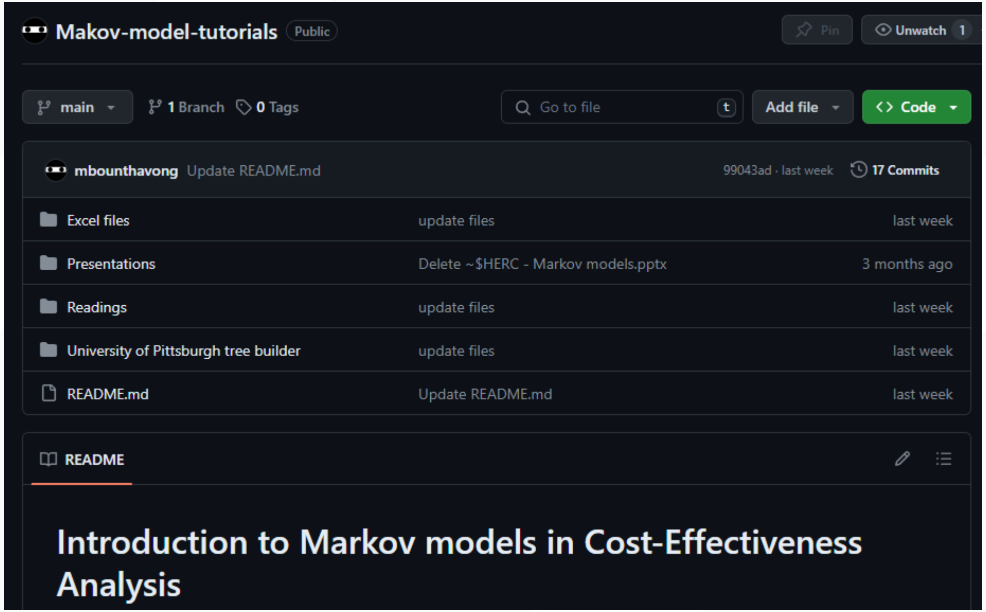
Use the CPI inflation calculator on the BLS website

Markov models using Excel

Tutorial on building Markov models in Excel

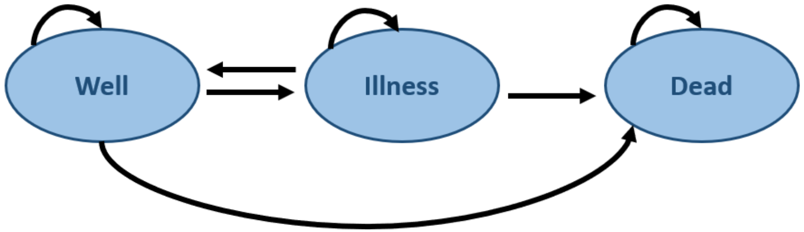
FILE LOCATION

You can download the Excel file from the workshop's GitHub site



SETTING UP THE MARKOV MODEL

List all the transitions



Transition states	Variable	Probability	Description
Well --> Well	1 - tp(well_illness) - tp(well_dead)	0.83	Remain in the Well state
Well --> Illness	tp(well_illness)	0.15	Transition from Well to Illness
Well --> Dead	tp(well_dead)	0.02	Transition from Well to Death
Illness --> Illness	1 - tp(illness_well) - tp(illness_dead)	0.65	Remain in the Illness state
Illness --> Well	tp(illness_well)	0.30	Transition from Illness to Well
Illness --> Dead	tp(illness_dead)	0.05	Transition from Illness to Death
Dead -- > Dead	tp(dead)	1.00	Remain in Death (Absorbing state)

MARKOV MATRIX

From / To	Well	Illness	Dead
Well	0.83	0.15	0.02
Illness	0.30	0.65	0.05
Dead	0	0	1.00

ASSIGN COSTS AND UTILITIES TO THE STATES

Since the costs and utilities are specific to each state you can list them in a table

Transition states	Costs	Utility	Description
Well	$500.00	1.00	These parameers are fictional
Illness	$2,000.00	0.50	These parameers are fictional
Dead	$0.00	0.00	These parameers are fictional

MODEL PROPERTIES

Each cycle is 1 year

Simulate for 100 years (or 100 cycles)

Apply an annual discount rate of 3% on costs and outcomes

MATHEMATICAL MODEL

Cohort size	1

We start at
cell E12

1 cycle = 1 year	Expected probabilities			
Cycle	Well	Illness	Dead	Total
0	1.0000	0.0000	0.0000	1
1	0.8300	0.1500	0.0200	1
2	0.7339	0.2220	0.0441	1
3	0.6757	0.2544	0.0699	1
4	0.6372	0.2667	0.0961	1
5	0.6089	0.2689	0.1222	1
6	0.5860	0.2661	0.1478	1
7	0.5663	0.2609	0.1728	1
8	0.5483	0.2545	0.1972	1
9	0.5314	0.2477	0.2209	1
10	0.5154	0.2407	0.2439	1

MATHEMATICAL MODEL

Cohort size	1

The size of the cohort.
We'll set this at 1.
The cell is G6.

At cycle 0, all subjects will start at the "Well" state.
In the cell, the formula is:
=$G$6 * 1
The "$" denotes that the column / row does not change.

1 cycle = 1 year	Expected probabilities			
Cycle	Well	Illness	Dead	Total
0	1.0000	0.0000	0.0000	1
1	0.8300	0.1500	0.0200	1
2	0.7339	0.2220	0.0441	1
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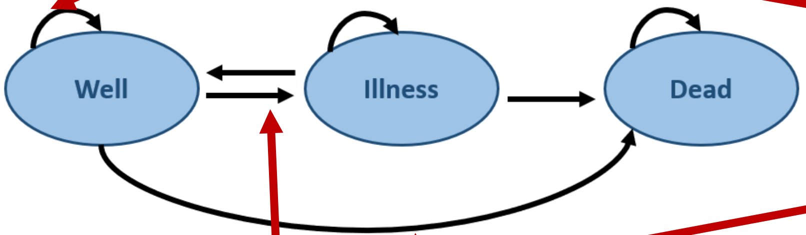
9	0.5314	0.2477	0.2209	1
10	0.5154	0.2407	0.2439	1

At cycle 0, zero subjects will start at the "Illness" and "Dead" states.
In these cells, the formulas are:
=$G$6 * 0

Based on probability theory the sum of the expected number of subjects should be equal to cell G6. In this case, that will be 1.

CALCULATING EXPECTED PROBABILITIES (1)

1 - tp(well_illness) - tp(well_dead)



tp(well_illness)

tp(well_dead)

1 cycle = 1 year	Expected probabilities			
Cycle	Well	Illness	Dead	Total
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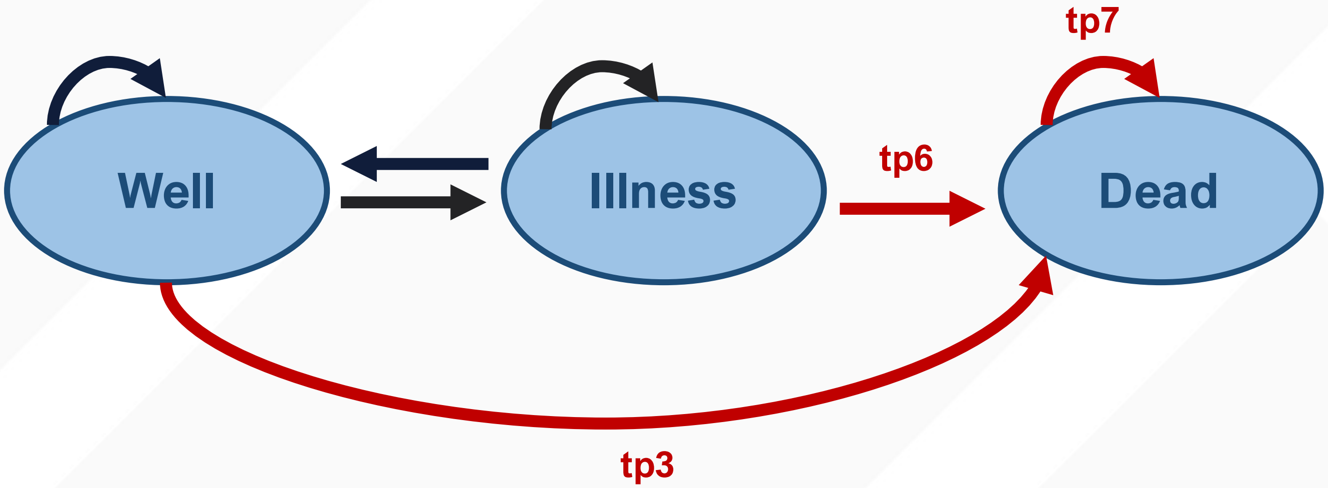
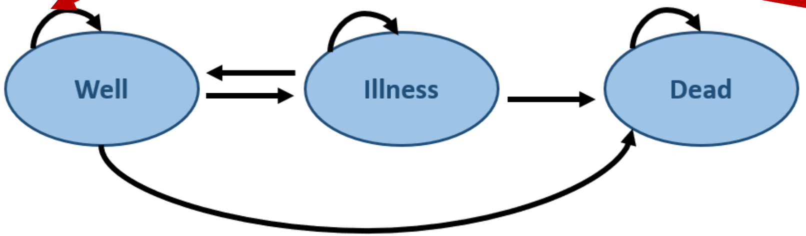
LIMITATIONS OF DECISION TREES (2)



CALCULATING EXPECTED PROBABILITIES (1)

1 - tp(well_illness) - tp(well_dead)



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8	0.5483	0.2545	0.1972	1
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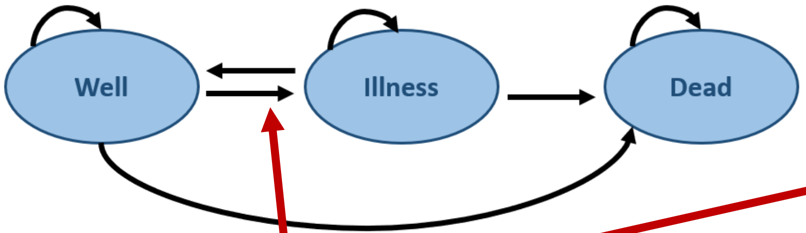
10	0.5154	0.2407	0.2439	1

CALCULATING EXPECTED PROBABILITIES (2)



tp(well_illness)

1 cycle = 1 year	Expected probabilities			
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1	0.8300	0.1500	0.0200	1
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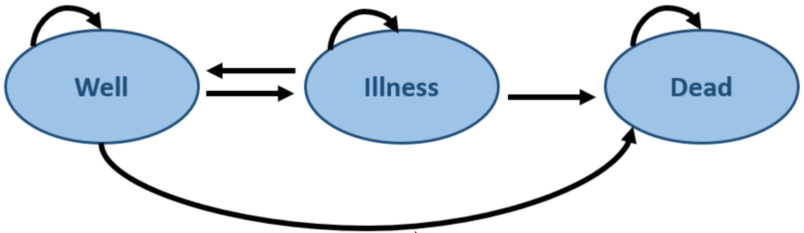
9	0.5314	0.2477	0.2209	1
10	0.5154	0.2407	0.2439	1

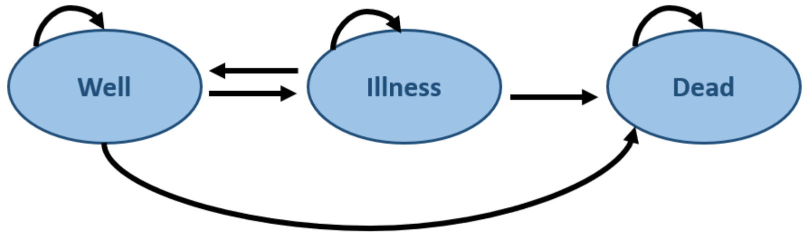
CALCULATING EXPECTED PROBABILITIES (3)



tp(well_dead)

1 cycle = 1 year	Expected probabilities			
Cycle	Well	Illness	Dead	Total
0	1.0000	0.0000	0.0000	1
1	0.8300	0.1500	0.0200	1
2	0.7339	0.2220	0.0441	1
3	0.6757	0.2544	0.0699	1
4	0.6372	0.2667	0.0961	1
5	0.6089	0.2689	0.1222	1
6	0.5860	0.2661	0.1478	1
7	0.5663	0.2609	0.1728	1
8	0.5483	0.2545	0.1972	1
9	0.5314	0.2477	0.2209	1
10	0.5154	0.2407	0.2439	1

CALCULATING EXPECTED PROBABILITIES (4)



1 cycle = 1 year	Expected probabilities			
Cycle	Well	Illness	Dead	Total
0	1.0000	0.0000	0.0000	1
1	0.8300	0.1500	0.0200	1
2	0.7339	0.2220	0.0441	1
3	0.6757	0.2544	0.0699	1
4	0.6372	0.2667	0.0961	1
5	0.6089	0.2689	0.1222	1
6	0.5860	0.2661	0.1478	1
7	0.5663	0.2609	0.1728	1
8	0.5483	0.2545	0.1972	1
9	0.5314	0.2477	0.2209	1
10	0.5154	0.2407	0.2439	1

Check to see that the probabilities sum to 1

CALCULATING EXPECTED COSTS AND UTILITIES (1)

1 cycle = 1 year	Expected probabilities			
Cycle	Well	Illness	Dead	Total
0	1.0000	0.0000	0.0000	1
1	0.8300	0.1500	0.0200	1
2	[illegible]	0.2220	0.0441	1
3	0.6757	0.2544	0.0699	1
4	0.6372	0.2667	0.0961	1
5	0.6089	0.2689	0.1222	1

Total Expected Costs		=	$31,128.64
Well	Illness	Dead	Total
$500.00	$0.00	$0.00	$500.00
$415.00	$300.00	$0.00	$715.00
[illegible]	$444.00	$0.00	$810.95
$337.87	$508.77	$0.00	$846.64
$318.59	$533.42	$0.00	$852.01
$304.44	$537.88	$0.00	$842.31

Total Expected QALYs		=	27.9098
Well	Illness	Dead	Total
1.0000	0.0000	0.0000	1.0000
0.8300	0.0750	0.0000	0.9050
0.7339	0.1110	0.0000	0.8449
0.6757	0.1272	0.0000	0.8029
0.6372	0.1334	0.0000	0.7705
0.6089	0.1345	0.0000	0.7433

Expected costs at cycle 1 is
0.83 * $500 = $415

CALCULATING EXPECTED COSTS AND UTILITIES (2)

1 cycle = 1 year	Expected probabilities			
Cycle	Well	Illness	Dead	Total
0	1.0000	0.0000	0.0000	1
1	0.8300	0.1500	0.0200	1
2	0.7339	0.2220	0.0441	1
3	0.6[illegible]57	0.2544	0.0699	1
4	0.6372	0.2667	0.0961	1
5	0.6089	0.2689	0.1222	1

Total Expected Costs		=	$31,128.64
Well	Illness	Dead	Total
$500.00	$0.00	$0.00	$500.00
$415.00	$300.00	$0.00	$715.00
$366.95	$444.00	$0.00	$810.95
$3[illegible]7.87	$508.77	$0.00	$846.64
$318.59	$533.42	$0.00	$852.01
$304.44	$537.88	$0.00	$842.31

Total Expected QALYs		=	27.9098
Well	Illness	Dead	Total
1.0000	0.0000	0.0000	1.0000
0.8300	0.0750	0.0000	0.9050
0.7339	0.1110	0.0000	0.8449
0.6757	0.1272	0.0000	0.8029
0.6372	0.1334	0.0000	0.7705
0.6089	0.1345	0.0000	0.7433

Expected costs at cycle 2 is
0.7339 * $500 = $366.95

CALCULATING EXPECTED COSTS AND UTILITIES (3)

1 cycle = 1 year

Expected probabilities

Cycle	Well	Illness	Dead	Total
0	1.0000	0.0000	0.0000	1
1	0.8300	0.1500	0.0200	1
2	0.7339	0.2220	0.0441	1
3	0.6757	0.2544	0.0699	1
4	0.6372	0.2667	0.0961	1
5	0.6089	0.2689	0.1222	1

Total Expected Costs = $31,128.64

Well	Illness	Dead	Total
$500.00	$0.00	$0.00	$500.00
$415.00	$300.00	$0.00	$715.00
$366.95	$444.00	$0.00	$810.95
$337.87	$508.77	$0.00	$846.64
$318.59	$533.42	$0.00	$852.01
$304.44	$537.88	$0.00	$842.31

Total Expected QALYs = 27.9098

Well	Illness	Dead	Total
1.0000	0.0000	0.0000	1.0000
0.8300	0.0750	0.0000	0.9050
0.7339	0.1110	0.0000	0.8449
0.6757	0.1272	0.0000	0.8029
0.6372	0.1334	0.0000	0.7705
0.6089	0.1345	0.0000	0.7433

Expected utility at cycle 1 is
0.83 * 1 = 0.83 QALYs

CALCULATING EXPECTED COSTS AND UTILITIES (4)

1 cycle = 1 year	Expected probabilities			
Cycle	Well	Illness	Dead	Total
0	1.0000	0.0000	0.0000	1
1	0.8300	0.1500	0.0200	1
2	0.7339	0.2220	0.0441	1
3	[illegible]	0.2544	0.0699	1
4	0.6372	0.2667	0.0961	1
5	0.6089	0.2689	0.1222	1

Total Expected Costs		=	$31,128.64
Well	Illness	Dead	Total
$500.00	$0.00	$0.00	$500.00
$415.00	$300.00	$0.00	$715.00
$366.95	$444.00	$0.00	$810.95
$337.87	$508.77	$0.00	$846.64
$318.59	$533.42	$0.00	$852.01
$304.44	$537.88	$0.00	$842.31

Total Expected QALYs		=	27.9098
Well	Illness	Dead	Total
1.0000	0.0000	0.0000	1.0000
0.8300	0.0750	0.0000	0.9050
0.7339	0.1110	0.0000	0.8449
0.6757	0.1272	0.0000	0.8029
0.6372	0.1334	0.0000	0.7705
0.6089	0.1345	0.0000	0.7433

Expected utility at cycle 2 is 0.7339 * 1 = 0.73 QALYs

CALCULATING EXPECTED COSTS AND UTILITIES (5)

Sum the costs to get the total expected costs

Sum the QALYs to get the total expected QALYs

1 cycle = 1 year	Expected probabilities			
Cycle	Well	Illness	Dead	Total
0	1.0000	0.0000	0.0000	1
1	0.8300	0.1500	0.0200	1
2	0.7339	0.2220	0.0441	1
3	0.6757	0.2544	0.0699	1
4	0.6372	0.2667	0.0961	1
5	0.6089	0.2689	0.1222	1

Total Expected Costs		=	$31,128.64
Well	Illness	Dead	Total
$500.00	$0.00	$0.00	$500.00
$415.00	$300.00	$0.00	$715.00
$366.95	$444.00	$0.00	$810.95
$337.87	$508.77	$0.00	$846.64
$318.59	$533.42	$0.00	$852.01
$304.44	$537.88	$0.00	$842.31

Total Expected QALYs		=	27.9098
Well	Illness	Dead	Total
1.0000	0.0000	0.0000	1.0000
0.8300	0.0750	0.0000	0.9050
0.7339	0.1110	0.0000	0.8449
0.6757	0.1272	0.0000	0.8029
0.6372	0.1334	0.0000	0.7705
0.6089	0.1345	0.0000	0.7433

APPLYING DISCOUNTING

1 cycle = 1 year	Expected probabilities			
Cycle	Well	Illness	Dead	Total
0	1.0000	0.0000	0.0000	1
1	0.8300	0.1500	0.0200	1
2	0.7339	0.2220	0.0441	1
3	0.6757	0.2544	0.0699	1
4	0.6372	0.2667	0.0961	1
5	0.6089	0.2689	0.1222	1

Transition states	Costs
Well	$500.00
Illness	$2,000.00
Dead	$0.00

$$V_0 = \frac{\boxed{V_t}}{(1+r)^{\boxed{t}}}$$

r is the annual discount rate at 3%

DISCOUNT EXPECTED COSTS AND UTILITIES (1)

1 cycle = 1 year	Expected probabilities			
Cycle	Well	Illness	Dead	Total
0	1.0000	0.0000	0.0000	1
1	0.8300	0.1500	0.0200	1
2	0.73[illegible]9	0.2220	0.0441	1
3	0.6757	0.2544	0.0699	1
4	0.6372	0.2667	0.0961	1
5	0.6089	0.2689	0.1222	1

Total Expected Costs		=	$16,238.55
Well	Illness	Dead	Total
$500.00	$0.00	$0.00	$500.00
$402.91	$291.26	$0.00	$694.17
$3[illegible]5.89	$418.51	$0.00	$764.40
$309.20	$465.60	$0.00	$774.79
$283.06	$473.94	$0.00	$757.00
$262.61	$463.98	$0.00	$726.59

Total Expected QALYs		=	15.0816
Well	Illness	Dead	Total
1.0000	0.0000	0.0000	1.0000
0.8058	0.0728	0.0000	0.8786
0.6918	0.1046	0.0000	0.7964
0.6184	0.1164	0.0000	0.7348
0.5661	0.1185	0.0000	0.6846
0.5252	0.1160	0.0000	0.6412

Expected costs at cycle 1 with discounting is

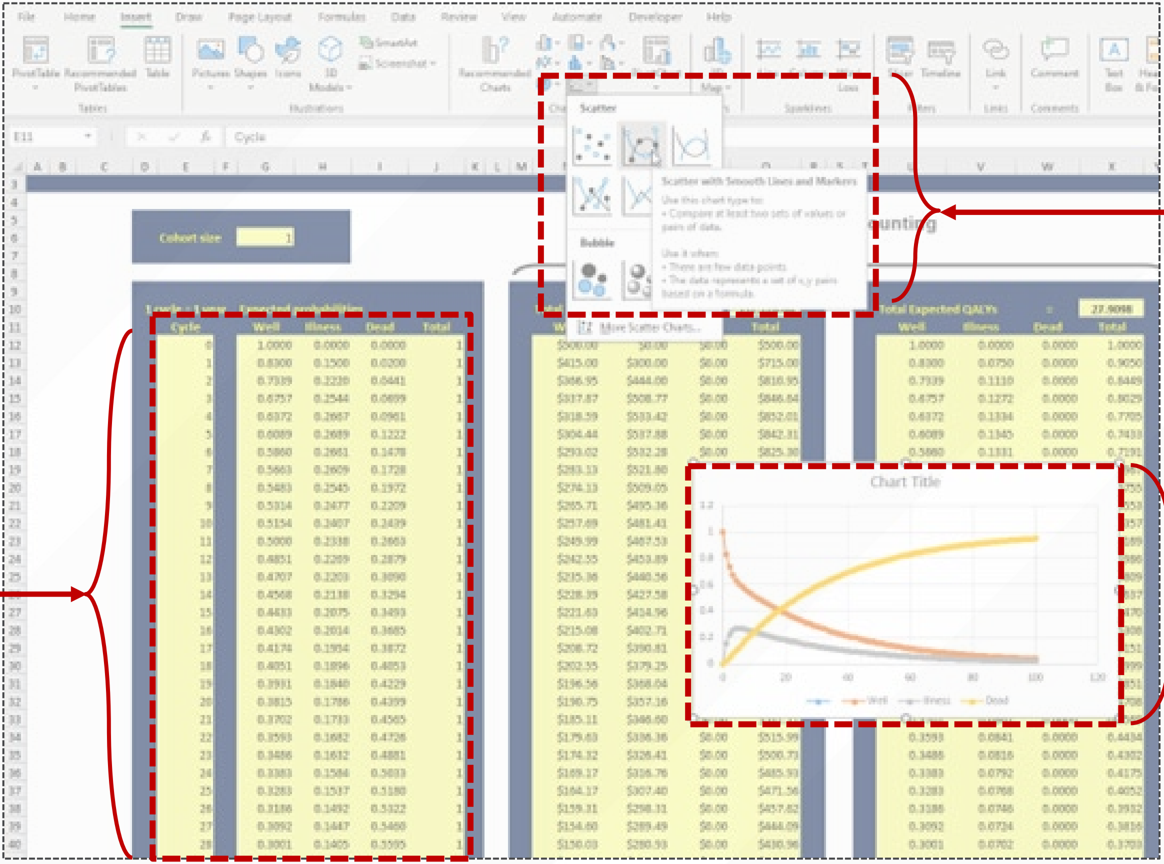
$$\$402.91 = \underbrace{(0.83 * \$500)}_{V_t} / \underbrace{(1 + 0.03)^1}_{(1+r)^t}$$

$$V_0 = \frac{V_t}{(1+r)^t}$$

MARKOV MODEL RESULTS (1)

Strategy	Total Cost	Total QALYs	Incremental Costs	Incremental QALYs	ICER
Without Discounting	$31,128.64	27.9098	$14,890.09	12.8282	$1,160.73
With Discounting	$16,238.55	15.0816			

MARKOV MODEL RESULTS (2)

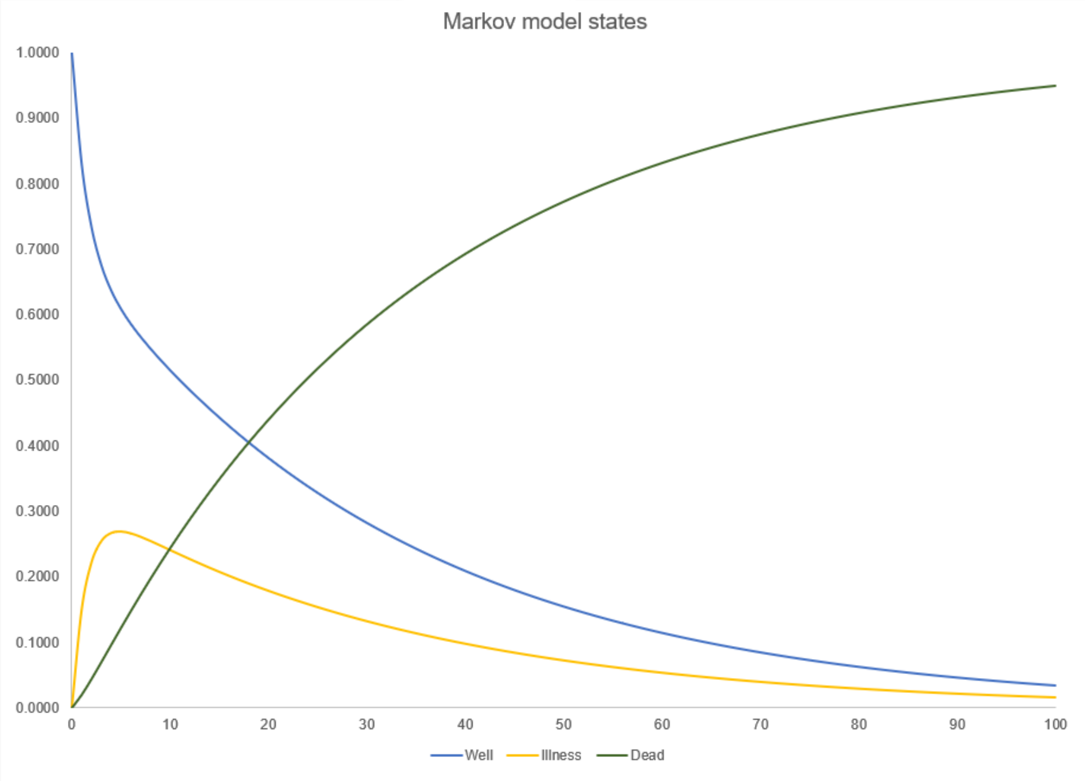


Step 1: Select the data from cycle 0 to 100

Step 2: Insert a chart using the X-Y scatter and the Scatter with Smooth Lines and Markers

Step 3: A chart will appear; make changes to match the figure

MARKOV MODEL RESULTS (2)



Questions

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REFERENCES

Briggs and Sculpher - Introduction to Markov Models

GitHub site for Markov model

Online Markov model tutorial (link)