

# **APPLIED COST-EFFECTIVENESS MODELING WITH R**

SMDM

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Devin Incerti

Jeroen Jansen

# Learning objectives

- Understand how R can be used to perform model-based cost-effectiveness analysis with existing packages;
- Develop own models in R by modifying existing code for commonly used model types;
- Understand how using R can improve reproducibility and transparency of model-based cost-effectiveness analysis

# Agenda

- Introduction
- Basic model taxonomy
- Simple Markov cohort model
- Semi-Markov multi-state model
- Cost-effectiveness analysis
- Summary

# Structure

- Presentation
- Exercises using R

# Online tutorial

The screenshot shows the GitHub repository page for `rcea`. The top navigation bar includes tabs for `rcea`, `0.0.1`, `Reference`, `Tutorials` (which is currently active), and a user icon. The main content area has a sidebar on the left with the repository name `rcea` and a description: "This is the repository for the rcea package. A range of models are covered including Markov cohort, semi-Markov individual patient and semi-Markov individual path sensitivity analysis can be used via the R package `hesim`." Below this, a note says "The course materials are available at <https://hesim-dev.github.io/rcea/>". The right side of the page displays the contents of the `Tutorials` dropdown menu, which includes links to "Simple Markov Cohort Model", "Incorporating Probabilistic Sensitivity Analysis", "Markov Cohort Model with hesim", "Semi-Markov Multi-state Model", "Partitioned Survival Model", and "Cost-effectiveness Analysis". To the right of the dropdown, there is a detailed description of the package: "node-based cost-effectiveness analysis (CEA) with R . A Markov cohort models, partitioned survival models, simulated costs and QALYs from a probabilistic framework. Analyses are conducted using both base R and". On the far right, there are sections for "Links", "Browse source code at <https://github.com/hesim-dev/rcea/>", "Report a bug at <https://github.com/hesim-dev/rcea/issues>", "License" (GPL-3), "Developers" (Devin Incerti, Author, maintainer; Jeroen P. Jansen, Author), and a footer note about the repository being a work in progress.

## Installation and setup

All required R packages and course materials can be installed with the following steps.

1. Open an R session. We recommend using [RStudio](#).
2. Install the `rcea` package from GitHub, which will also install all other required packages.

```
# install.packages("devtools") # You must install the "devtools" R package first.
devtools::install_github("hesim-dev/rcea")
```
3. Create a new project in your desired directory.

```
# Create a project named "rcea-exercises" within a directory named "Projects"
usethis::create_project("~/Projects/rcea-exercises")
```
4. Add the course materials (R scripts for the tutorials) to your new project.

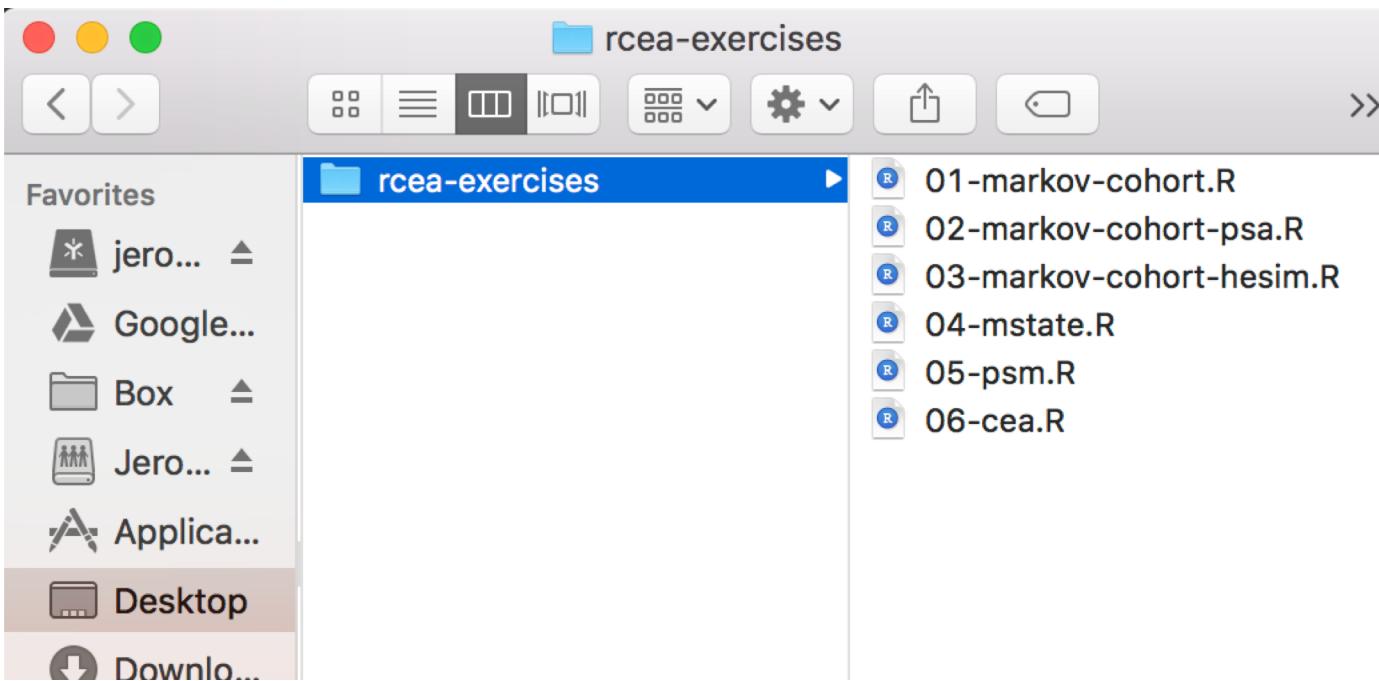
```
rcea::use_rcea("~/Projects/rcea-exercises")
```

## Tutorials

The course contains six tutorials:

1. **Markov Cohort Model:** A simple time-homogeneous Markov cohort model with fixed parameter values.
2. **Incorporating Probabilistic Sensitivity Analysis (PSA):** The Markov cohort model is re-analyzed using suitable probability

# R scripts for exercises



# RStudio Cloud

≡ Your Workspace / RCEA-SMDM2020

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File Edit Code View Plots Session Build Debug Profile Tools Help

Go to file/function Addins R 4.0.2

01-markov-cohort.R 02-markov-cohort-psa.R 03-markov-cohort-hesim.R 04-mstate.R 06-cea.R Run Source

```
1 #> ## ---- Overview ----
2 ## @knitr R-packages
3 library("rcea")
4 library("knitr")
5 library("kableExtra")
6 library("magrittr")
7 library("tibble")
8
9 ## ---- Model parameters ----
10 ## @knitr transition-probabilities
11 p_hd <- .002 # constant probability of dying when Healthy (all-cause mortality)
12 p_hs1 <- .15 # probability of becoming Sick when Healthy
13 p_s1h <- .05 # probability of becoming Healthy when Sick
14 p_s1s2 <- .105 # probability of becoming Sicker when Sick
15 p_s1d <- .006 # constant probability of dying when Sick
16 p_s2d <- .02 # constant probability of dying when Sicker
17
```

10:26 #> Model parameters R Script

Console Terminal Jobs

/cloud/project/ ↵

Environment History Connections Tuto

Import Dataset List

Global Environment

Data

ce_out	2000 obs. of 4 variables
ce_out_wi...	1000 obs. of 5 variables
ce_sim	List of 2
cea_pw_out	List of 4
data	2 obs. of 1 variable

Files Plots Packages Help Viewer

New Folder Upload Delete Rename

Cloud > project > rcea-exercises

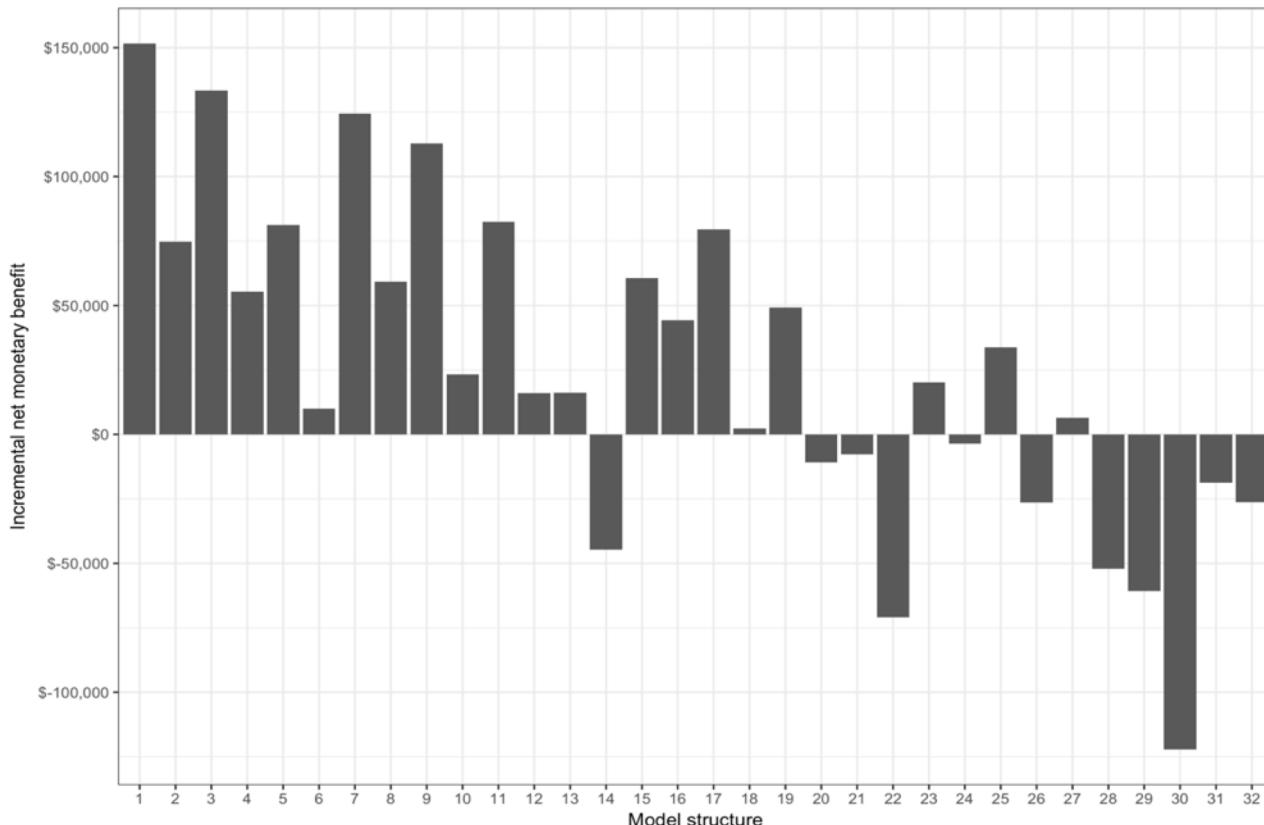
Name	Size
01-markov-cohort.R	4.1 KB
02-markov-cohort-psa.R	6.1 KB
03-markov-cohort-hesim.R	3.3 KB
04-mstate.R	4.3 KB
06-cea.R	3.4 KB

# **Introduction**

# **Criteria that economic models should strive to meet**

- Clinical realism
  - A model should reflect the state of evidence, the current understanding of the disease, and be accepted by clinical experts.
- Quantifying decision uncertainty
  - A model should be capable of quantifying decision uncertainty and informing prioritization of future research.
- Transparency and reproducibility
  - Resources should exist so that a model can be completely understood, reproduced, and pressure tested.
- Reusability and adaptability
  - It should be possible to easily update a model to reflect new clinical evidence or adapt it for a new market, indication, or intervention.

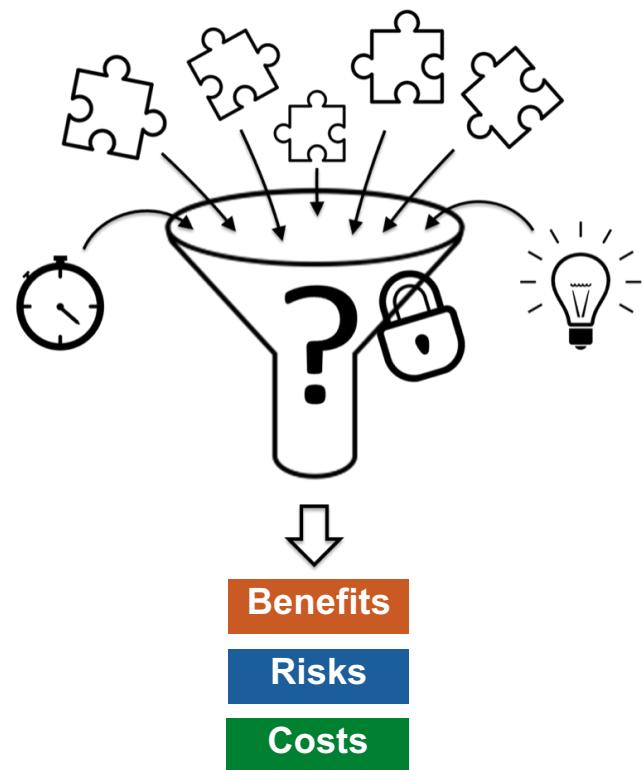
# Structural uncertainty



# Plugging in model input parameter estimates



# Transparency & reproducibility



# What do we mean with model transparency?

- Concept, math
- Face validity
- Implementation/programming
- Open-source, open-access
- *Familiarity with software?*

# Modeling in Excel

- Excel has been dominant software platform used by HE modelers, especially for HTA submissions
- Reasons are not surprising
  - Practically everyone with a computer has access to Excel
  - Does not require that you learn a new programming language
- Many consider its “transparency” to be an attribute
- With models in Excel, you can follow calculations that are being performed in every single cell of every single worksheet



Arial 9 A A

= = =

Wrap Text

Number

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Conditional Formatting

Format as Table

Cell Styles

Insert Delete Format

AutoSum Fill Clear Sort &amp; Filter

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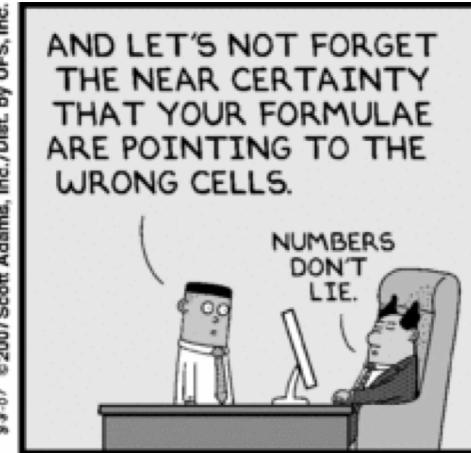
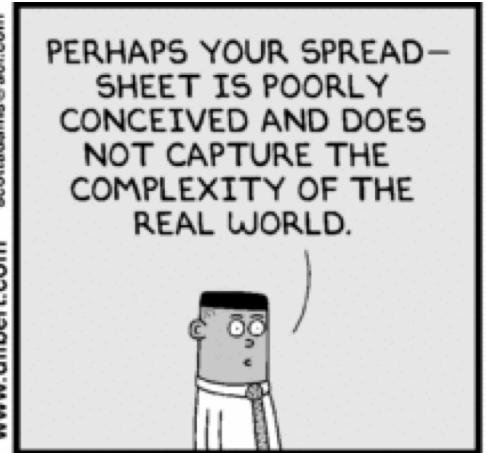
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V
1	PSA INPUTS																					
2																						
3																						
4	Efficacy and transitions between health states (other than death)		point estimate	SD(estimate)	low	high	distribution	alpha	beta	Source	sampled value from uncertainty distribution	value 'plugged in' model				One way sensitivity input low	One way sensitivity input high					
5	PROBABILITY Induction response Standard non-biologic treatment	0.355	0.017	0.322	0.390	beta	267.30	484.82			0.3562	0.3554				0.32	0.39					
6	OR Induction response Adalimumab 160/80/40 vs Standard non-biologic treatment	1.870		0.957	3.654	log-normal					1.9728	1.8700				0.96	3.65					
7	OR Induction response Golimumab 200/100/50(100) vs Standard non-biologic treatment	2.115		1.011	3.953	log-normal					1.9268	2.1150				1.01	3.95					
8	OR Induction response Infliximab 5mg/kg vs Standard non-biologic treatment	4.118		2.084	8.144	log-normal					2.4537	4.1180				2.08	8.14					
9																						
10	PROBABILITY Induction remission Standard non-biologic treatment	0.089	0.010	0.071	0.110	beta	71.65	729.91			0.0870	0.0894				0.07	0.11					
11	OR Induction remission Adalimumab 160/80/40 vs Standard non-biologic treatment	2.354		1.076	4.717	log-normal					2.8307	2.2540				1.08	4.72					
12	OR Induction remission Golimumab 200/100/50(100) vs Standard non-biologic treatment	2.989		1.324	6.277	log-normal					3.5223	2.9890				1.32	6.28					
13	OR Induction remission Infliximab 5mg/kg vs Standard non-biologic treatment	5.271		2.596	11.640	log-normal					5.2709	5.2710				2.60	11.64					
14																						
15	PROBABILITY sustained response Standard non-biologic treatment	0.829	0.016	0.797	0.858	beta	489.00	101.18			0.8459	0.8286				0.80	0.86					
16	OR sustained response Adalimumab 160/80/40	1.311		0.669	2.590	log-normal					1.9203	1.3110				0.67	2.59					
17	OR sustained response Golimumab 200/100/50(100)	1.623		1.067	2.502	log-normal					1.9808	1.6230				1.07	2.50					
18	OR sustained response Infliximab 5mg/kg	2.116		1.021	4.540	log-normal					2.8782	2.1160				1.02	4.54					
19																						
20	PROBABILITY sustained emission Standard non-biologic treatment	0.861	0.026	0.806	0.908	beta	151.60	24.49			0.9124	0.8609				0.81	0.91					
21	OR sustained emission Adalimumab 160/80/40	0.762		0.217	2.556	log-normal					0.3871	0.7624				0.22	2.56					
22	OR sustained emission Golimumab 200/100/50(100)	0.918		0.359	2.452	log-normal					1.1049	0.9180				0.36	2.45					
23	OR sustained emission Infliximab 5mg/kg	1.300		0.435	4.053	log-normal					1.7175	1.3000				0.44	4.05					
24																						
25	Proportion transition to release when losing emission status	0.000	0.000	#NUM!	#NUM!	beta	0.00	-1.00			0.0000	0.0000				0.00	0.00					
26																						
27	PROBABILITY maintenance discontinuation Standard non-biologic treatment	0.000	0.000	#NUM!	#NUM!	beta	0.00	-1.00			0.0000	0.0000				0.00	0.00					
28	OR maintenance discontinuation Adalimumab 160/80/40	0.000		0.000	0.000	log-normal					#NUM!	0.0000				0.00	0.00					
29	OR maintenance discontinuation Golimumab 200/100/50(100)	0.000		0.000	0.000	log-normal					#NUM!	0.0000				0.00	0.00					
30	OR maintenance discontinuation Infliximab 5mg/kg	0.000		0.000	0.000	log-normal					#NUM!	0.0000				0.00	0.00					
31																						
32	PROBABILITY success 1 round IV steroids	0.480	0.007	0.468	0.493	beta	2767.63	2993.46			0.4859	0.4804				0.47	0.49					
33	PROBABILITY success with 2nd round IV steroids given failure 1st round	0.480	0.007	0.468	0.493	beta	2767.63	2993.46			0.4799	0.4804				0.47	0.49					
34	PROBABILITY loss of response (relapse management)	0.171	0.016	0.142	0.203	beta	101.18	489.00			0.1751	0.1714				0.14	0.20					
35	PROBABILITY long term complications given remission (post-colectomy)	0.015	0.007	0.004	0.032	beta	4.41	290.51			0.0056	0.0149				0.00	0.03					
36	PROBABILITY successful recovery from long-term complications (post-colectomy)	1.000	0.000	#NUM!	#NUM!	beta	-1.00	0.00			1.0000	1.0000				1.00	1.00					
37																						
38	Safety (Induction treatment)																					
39																						
40	PROBABILITY serious infections Standard non-biologic treatment	0.016	0.003	0.011	0.021	beta	36.84	2283.37			0.0161	0.0159				0.01	0.02					
41	OR serious infections Adalimumab 160/80/40 vs Standard non-biologic treatment	1.100		0.830	1.460	log-normal					1.2132	1.1000				0.83	1.46					
42	OR serious infections Golimumab 200/100/50(100) vs Standard non-biologic treatment	1.100		0.830	1.460	log-normal					1.0408	1.1000				0.83	1.46					
43	OR serious infections Infliximab 5mg/kg vs Standard non-biologic treatment	1.100		0.830	1.460	log-normal					1.2286	1.1000				0.83	1.46					
44																						
45	PROBABILITY Adverse event 2 Standard non-biologic treatment	0.000	0.000	#NUM!	#NUM!	beta	0.00	-1.00			0.0000	0.0000				0.00	0.00					
46	OR Adverse event 2 Adalimumab 160/80/40 vs Standard non-biologic treatment	1.000		1.000	1.000	log-normal					1.0000	1.0000				1.00	1.00					
47	OR Adverse event 2 Golimumab 200/100/50(100) vs Standard non-biologic treatment	1.000		1.000	1.000	log-normal					1.0000	1.0000				1.00	1.00					
48	OR Adverse event 2 Infliximab 5mg/kg vs Standard non-biologic treatment	1.000		1.000	1.000	log-normal					1.0000	1.0000				1.00	1.00					
49																						
50	PROBABILITY Adverse event 3 Standard non-biologic treatment	0.000	0.000	#NUM!	#NUM!	beta	0.00	-1.00			0.0000	0.0000				0.00	0.00					
51	OR Adverse event 3 Adalimumab 160/80/40 vs Standard non-biologic treatment	1.000		1.000	1.000	log-normal					1.0000	1.0000				1.00	1.00					
52	OR Adverse event 3 Golimumab 200/100/50(100) vs Standard non-biologic treatment	1.000		1.000	1.000	log-normal					1.0000	1.0000				1.00	1.00					
53	OR Adverse event 3 Infliximab 5mg/kg vs Standard non-biologic treatment	1.000		1.000	1.000	log-normal					1.0000	1.0000				1.00	1.00					
54																						
55	PROBABILITY Adverse event 4 Standard non-biologic treatment	0.000	0.000	#NUM!	#NUM!	beta	0.00	-1.00			0.0000	0.0000				0.00	0.00					
56	OR Adverse event 4 Adalimumab 160/80/40 vs Standard non-biologic treatment	1.000		1.000	1.000	log-normal					1.0000	1.0000				1.00	1.00					
57	OR Adverse event 4 Golimumab 200/100/50(100) vs Standard non-biologic treatment	1.000		1.000	1.000	log-normal					1.0000	1.0000				1.00	1.00					
58	OR Adverse event 4 Infliximab 5mg/kg vs Standard non-biologic treatment	1.000		1.000	1.000	log-normal					1.0000	1.0000				1.00	1.00					

The screenshot shows the Microsoft Excel ribbon with the 'Home' tab selected. The ribbon includes sections for 'Clipboard' (Cut, Copy, Paste, Format), 'Font' (Font Style, Size, Alignment, Font Color, Font Style), 'Number' (Currency, Percentage, Decimal, Text, etc.), 'Cells' (Merge & Center, Conditional Formatting, Format as Table, Cell Styles), 'Table Tools' (Insert, Delete, Format), and 'Data' (AutoSum, Fill, Clear, Sort & Filter). The status bar at the bottom displays 'Page: 1 / 1'.

# Where is Waldo



# Time to change?



## Alternative



BCEA

heemod

hesim

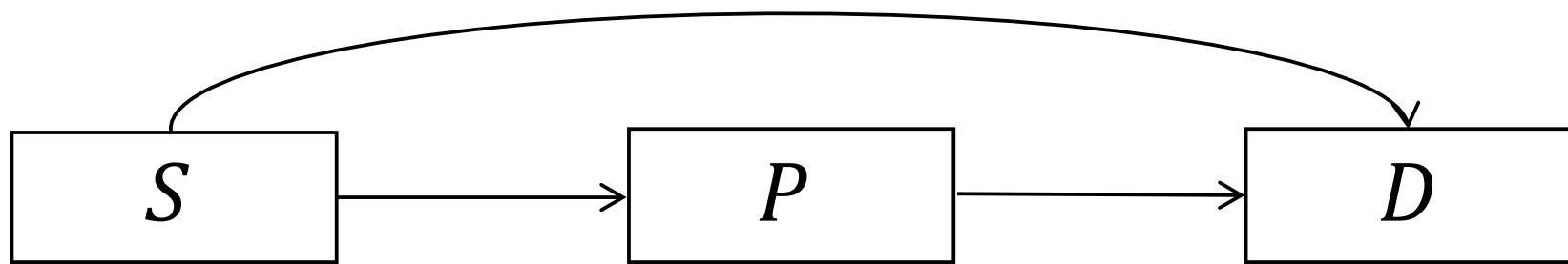
...

# What is R

- Statistical programming language and environment for statistical computing
- Free to use (open source, user developed packages that are transparent)
- Very good for data management, statistical analysis, and visualization
- Scripts contain all steps to perform an analysis
- CEA models can be coded from ‘scratch’ using base R or via convenient and improving packages

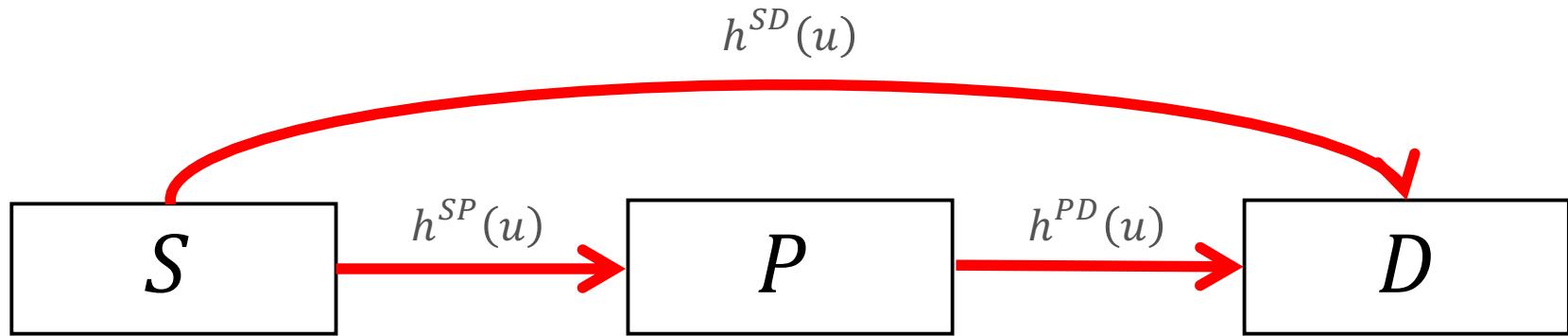
## **Basic model taxonomy**

# Health states describing course of disease over time



# Markov model

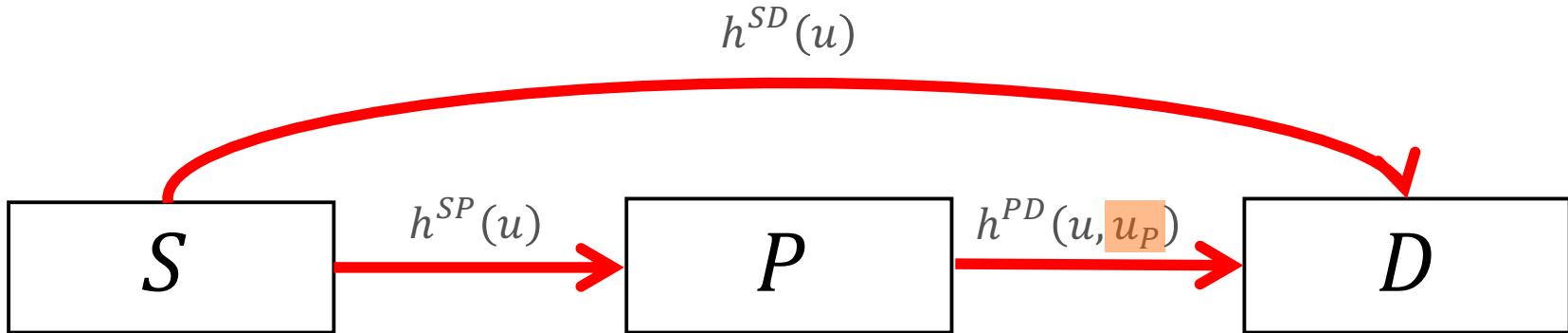
Clock forward



transition rates depend only on time in model

# Semi-Markov model

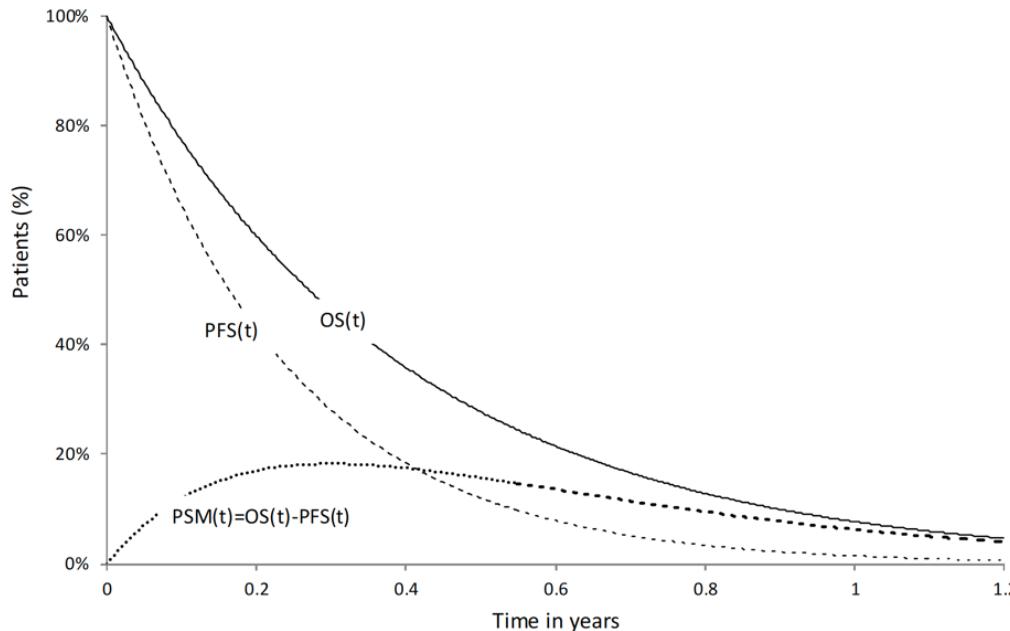
Clock reset



transition rates depend on time in model

some transitions depend on time in an intermediate health state

# Partitioned survival model



# Overview

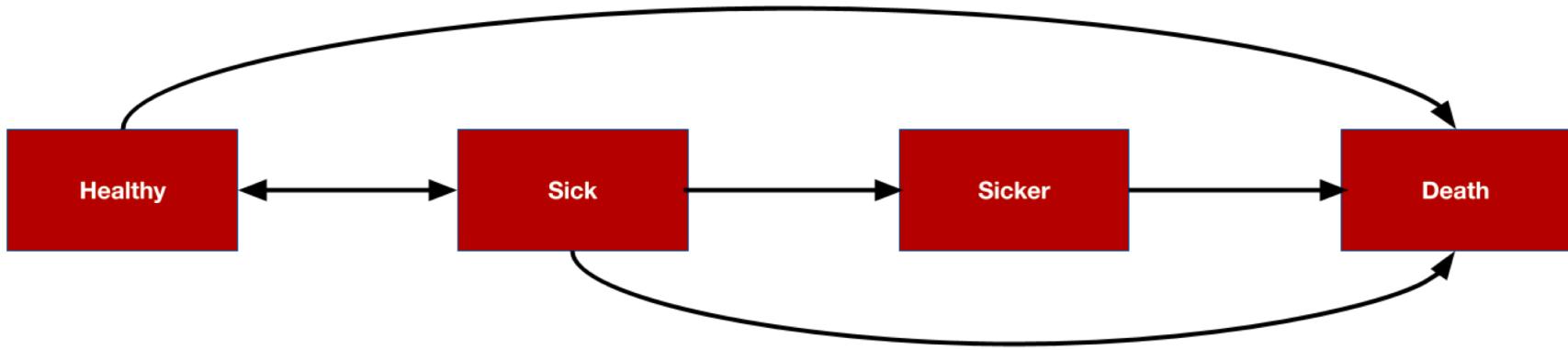
			discrete time	continuous time
state transition models	Markov ("Clock forward")	Cohort	cohort discrete time state transition models (cDTSTM) <ul style="list-style-type: none"><li>time-homogeneous Markov models</li><li>time-inhomogeneous Markov models</li></ul>	cohort continuous time state transition models
		Individual-level	individual-level discrete time state transition models (iDTSTM)	individual-level continuous time state transition models (iCTSTM)
	Semi-Markov ("Clock reset")*	Individual-level	iDTSTM	iCTSTM
n-state partitioned survival models**				

\*tunnel states can be used in a cohort model to approximate a semi-Markov process

\*\*Online tutorial provides instructions for partitioned survival models

## **Simple Markov cohort model**

# Model



# Model

- Annual transition probabilities with SOC

	Healthy	Sick	Sicker	Death
Healthy	0.848	0.15	0	0.002
Sick	0.5	0.389	0.105	0.006
Sicker	0	0	0.98	0.02
Death	0	0	0	1.000

- Relative risk of progression to a worse health state with new intervention is 0.8

- Drug costs

	New	SOC
Drug costs	12000	2000

- Other annual costs and utility

	Healthy	Sick	Sicker	Death
Direct medical	2000	4000	15000	0
Utility	1	0.75	0.5	0

- Annual discount rates of 3% for costs and 3% for QALYs

# SOC

	Healthy	Sick	Sicker	Death	Cycle	Healthy	Sick	Sicker	Death	discounted QALYs	discounted medical costs	discounted treatment costs	discounted total costs
Healthy	0.848	0.15	0	0.002	0	1.00000	0.00000	0.00000	0.00000	1.00000	2000.000	2000	
Sick	0.5	0.389	0.105	0.006	1	0.84800	0.15000	0.00000	0.00200	0.93252	2229.126	1937.864	
Sicker	0	0	0.98	0.02	2	0.79410	0.18555	0.01575	0.00460	0.88712	2419.321	1876.527	
Death	0	0	0	1	3	0.76618	0.19129	0.03492	0.00761	0.84843	2581.884	1816.350	
					4	0.74536	0.18934	0.05431	0.01099	0.81254	2721.140	1757.443	
					5	0.72674	0.18546	0.07310	0.01470	0.77840	2839.541	1699.850	
					6	0.70900	0.18115	0.09111	0.01873	0.74572	2938.972	1643.593	
	Healthy	Sick	Sicker	Death	80	0.11578	0.02960	0.29714	0.55748	0.02693	451.752	83.173	
Utility	1	0.75	0.5	0	81	0.11298	0.02888	0.29430	0.56384	0.02571	433.941	79.591	
Direct medical	2000	4000	15000	0	82	0.11025	0.02818	0.29145	0.57012	0.02455	416.778	76.159	
					83	0.10758	0.02750	0.28858	0.57634	0.02344	400.244	72.871	
Drug costs	2000				84	0.10498	0.02683	0.28570	0.58249	0.02237	384.317	69.722	
					85	0.10244	0.02619	0.28280	0.58858	0.02136	368.979	66.704	
					Sum					21.08			204,123

# Steps

- Define transition matrix SOC
- Define transition matrix New treatment
- Define utility and cost values by health state
- Calculate health state probabilities over time
- Calculate expected QALYs and costs
- Cost-effectiveness analysis

## Define transition matrix with standard of care

```
p_hd <- 0.002          # constant probability of dying when Healthy (all-cause mortality)
p_hs1 <- 0.15           # probability of becoming Sick when Healthy
p_s1h <- 0.5             # probability of becoming Healthy when Sick
p_s1s2 <- 0.105          # probability of becoming Sicker when Sick
p_s1d <- 0.006          # constant probability of dying when Sick
p_s2d <- 0.02            # constant probability of dying when Sicker

p_hh <- 1 - p_hs1 - p_hd
p_s1s1 <- 1 - p_s1h - p_s1s2 - p_s1d
p_s2s2 <- 1 - p_s2d
```

```
p_soc <- matrix(
  c(p_hh,  p_hs1,  0,      p_hd,
    p_s1h,  p_s1s1,  p_s1s2, p_s1d,
    0,      0,      p_s2s2, p_s2d,
    0,      0,      0,      1),
  byrow = TRUE,
  nrow = 4, ncol = 4
)
state_names <- c("H", "S1", "S2", "D")
rownames(p_soc) <- colnames(p_soc) <- state_names

print(p_soc)
```

	H	S1	S2	D
H	0.848	0.150	0.000	0.002
S1	0.500	0.389	0.105	0.006
S2	0.000	0.000	0.980	0.020
D	0.000	0.000	0.000	1.000

# Relative risk and transition matrix with New treatment

```
apply_rr <- function(p, rr = .8){  
  p["H", "S1"] <- p["H", "S1"] * rr  
  p["H", "S2"] <- p["H", "S2"] * rr  
  p["H", "D"] <- p["H", "S2"] * rr  
  p["H", "H"] <- 1 - sum(p["H", -1])  
  
  p["S1", "S2"] <- p["S1", "S2"] * rr  
  p["S1", "D"] <- p["S1", "D"] * rr  
  p["S1", "S1"] <- 1 - sum(p["S1", -2])  
  
  p["S2", "D"] <- p["S2", "D"] * rr  
  p["S2", "S2"] <- 1 - sum(p["S2", -3])  
  
  return(p)  
}  
  
p_new <- apply_rr(p_soc, rr = .8)
```

	H	S1	S2	D
H	0.8784	0.1200	0.000	0.0016
S1	0.5000	0.4112	0.084	0.0048
S2	0.0000	0.0000	0.984	0.0160
D	0.0000	0.0000	0.000	1.0000

# Utility and costs

```
utility <- c(1, .75, .5, 0)
costs_medical <- c(2000, 4000, 15000, 0)
costs_treat_soc <- c(rep(2000, 3), 0)
costs_treat_new <- c(rep(12000, 3), 0)
```

```
> utility
[1] 1.000 0.75 0.500 0.000
```

```
> costs_medical
[1] 2000 4000 15000 0
```

```
> costs_treat_soc
[1] 2000 2000 2000 0
```

```
> costs_treat_new
[1] 12000 12000 12000 0
```

# Simulation – health state probabilities

*Matrix multiplication*

```
x_init <- c(1, 0, 0, 0)  
x_init %*% p_soc
```

```
H      S1     S2      D  
[1,] 0.848  0.15    0  0.002
```

```
x_init %*% p_soc %*% p_soc
```

```
H      S1      S2      D  
[1,] 0.794104 0.18555 0.01575 0.004596
```

# Simulation – health state probabilities with a function

x0            The state vector at model cycle 0 (i.e., the initial state vector)  
p            The transition probability matrix  
n\_cycles    The number of model cycles. (Default is 85)

```
sim_markov_chain <- function(x0, p, n_cycles = 85){

  x <- matrix(NA, ncol = length(x0), nrow = n_cycles) # Initialize Markov trace
  x <- rbind(x0, x)                                     # Markov trace at cycle 0 is initial state vector
  colnames(x) <- colnames(p)                            # Columns are the health states
  rownames(x) <- 0:n_cycles                             # Rows are the model cycles

  for (t in 1:n_cycles){                                # Simulating state vectors at each cycle with for loop
    x[t + 1, ] <- x[t, ] %*% p
  }

  return(x)
}
```

# Simulation – health state probabilities with a function

```
x_soc <- sim_markov_chain(x_init, p_soc)
```

	H	S1	S2	D
0	1.0000000	0.0000000	0.0000000	0.000000000
1	0.8480000	0.1500000	0.0000000	0.002000000
2	0.7941040	0.18555000	0.01575000	0.004596000
3	0.7661752	0.19129455	0.03491775	0.007612508
4	0.7453638	0.18933986	0.05430532	0.010990981
5	0.7267385	0.18545778	0.07309990	0.014703854
6	0.7090031	0.18115385	0.09111097	0.018732076
7	0.6918116	0.17681931	0.10830990	0.023059224
8	0.6750659	0.17255445	0.12470973	0.027669961
9	0.6587331	0.16838356	0.14033376	0.032549614
---				
79	0.1186504	0.03032935	0.29995426	0.551065992
80	0.1157802	0.02959568	0.29713976	0.557484354
81	0.1129795	0.02887975	0.29430451	0.563836283
82	0.1102465	0.02818114	0.29145079	0.570121611
83	0.1075796	0.02749943	0.28858079	0.576340207
84	0.1049772	0.02683421	0.28569662	0.582491978
85	0.1024378	0.02618509	0.28280028	0.588576870

```
x_new <- sim_markov_chain(x_init, p_new)
```

	H	S1	S2	D
0	1.0000000	0.0000000	0.0000000	0.000000000
1	0.8784000	0.1200000	0.0000000	0.001600000
2	0.8315866	0.15475200	0.01008000	0.003581440
3	0.8078416	0.16342441	0.02291789	0.005816068
4	0.7913203	0.16414111	0.03627885	0.008259738
5	0.7771663	0.16245326	0.04948624	0.010894190
6	0.7638895	0.16006074	0.06234054	0.013709211
7	0.7510309	0.15748372	0.07478819	0.016697175
8	0.7384474	0.15488101	0.08682021	0.019851357
9	0.7260927	0.15230076	0.09844109	0.023165425
---				
79	0.2230518	0.04678750	0.31880122	0.411359506
80	0.2193224	0.04600523	0.31763055	0.417041788
81	0.2156554	0.04523604	0.31641290	0.422695618
82	0.2120498	0.04447971	0.31515012	0.428320406
83	0.2085044	0.04373603	0.31384402	0.433915590
84	0.2050182	0.04300478	0.31249634	0.439480634
85	0.2015904	0.04228575	0.31110880	0.445015028

# Computing a present value with a function

```
pv <- function(z, dr, t) {  
  z/(1 + dr)^t  
}  
  
z   A numeric quantity  
dr  Discount rate  
t   Vector of times to compute the present value
```

```
pv(1000, dr = .03, t = 0:4)
```

```
[1] 1000.0000 970.8738 942.5959 915.1417 888.4870
```

## QALYs after 1<sup>st</sup> cycle

```
x_soc[2, ] # State occupancy probabilities after 1st cycle
```

H	S1	S2	D
0.848	0.150	0.000	0.002

```
sum(x_soc[2, 1:3]) # Expected life-years after 1st cycle
```

```
[1] 0.998
```

```
sum(x_soc[2, ] * utility) # Expected utility after 1st cycle
```

```
[1] 0.9605
```

```
sum(pv(x_soc[2, ] * utility, .03, 1)) # Expected discounted utility after 1st cycle
```

```
[1] 0.9325
```

# Discounted QALYs for each cycle

```
compute_qalys <- function(x, utility, dr = .03){  
  n_cycles <- nrow(x) - 1  
  pv(x %*% utility, dr, 0:n_cycles)  
}
```

```
dqalys_soc <- compute_qalys(x_soc, utility = utility)  
dqalys_new <- compute_qalys(x_new, utility = utility)
```

```
head(dqalys_soc)
```

```
[,1]  
0 1.0000000  
1 0.9325243  
2 0.8871161  
3 0.8484324  
4 0.8125404  
5 0.7784024
```

```
head(dqalys_new)
```

```
[,1]  
0 1.0000000  
1 0.9401942  
2 0.8980022  
3 0.8619435  
4 0.8285724  
5 0.7968343
```

# Discounted cost for each cycle

```
compute_costs <- function(x, costs_medical, costs_treat, dr = .03){  
  
  n_cycles <- nrow(x) - 1  
  costs <- cbind(pv(x %*% costs_medical, dr, 0:n_cycles),  
                 pv(x %*% costs_treat, dr, 0:n_cycles))  
}  
  colnames(costs) <- c("medical", "treatment")  
  return(costs)  
}  
  
dcosts_soc <- compute_costs(x_soc, costs_medical, costs_treat_soc)  
dcosts_new <- compute_costs(x_new, costs_medical, costs_treat_new)
```

head(dcosts\_soc)

	medical	treatment
0	2000.000	2000.000
1	2229.126	1937.864
2	2419.321	1876.527
3	2581.884	1816.350
4	2721.140	1757.443
5	2839.541	1699.850

head(dcosts\_new)

	medical	treatment
0	2000.000	12000.00
1	2171.650	11631.84
2	2293.695	11270.64
3	2391.402	10917.83
4	2473.004	10573.78
5	2541.624	10238.54

# Cost-effectiveness

```
(sum(dcosts_new[-1, ]) - sum(dcosts_soc[-1, ])) /  
(sum(dqalys_new[-1, ]) - sum(dqalys_soc[-1, ]))
```

[1] 122946.8

```
format_costs <- function(x) formatc(x, format = "d", big.mark = ",")  
format_qalys <- function(x) formatc(x, format = "f", digits = 2)
```

```
make_icer_tb1 <- function(costs0, costs1, qalys0, qalys1){
```

```
# Computations  
total_costs0 <- sum(costs0)  
total_costs1 <- sum(costs1)  
total_qalys0 <- sum(qalys0)  
total_qalys1 <- sum(qalys1)  
incr_total_costs <- total_costs1 - total_costs0  
inc_total_qalys <- total_qalys1 - total_qalys0  
icer <- incr_total_costs/inc_total_qalys
```

```
# Make table  
tibble(  
  `Costs` = c(total_costs0, total_costs1) %>%  
  `Strategy` = c("SOC", "New"),  
  format_costs(),  
  `QALYS` = c(total_qalys0, total_qalys1) %>%  
  format_qalys(),  
  `Incremental costs` = c("--", incr_total_costs %>% format_costs()),  
  `Incremental QALYS` = c("--", inc_total_qalys %>% format_qalys()),  
  `ICER` = c("--", icer) %>% format_costs()  
) %>%  
kable() %>%  
kable_styling() %>%  
footnote(general = "Costs and QALYS are discounted at 3% per annum.", footnote_as_chunk = TRUE)  
}
```

# Cost-effectiveness

```
make_icer_tb1(costs0 = dcosts_soc[-1, ], costs1 = dcosts_new[-1, ],
               qalys0 = dqalys_soc[-1, ], qalys1 = dqalys_new[-1, ])
```

Strategy	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
SOC	204,123	21.08	--	--	--
New	464,390	23.19	260,266	2.12	122,946

Note: Costs and QALYs are discounted at 3% per annum.

# Steps

- Define transition matrix SOC
- Define transition matrix New treatment `apply_rr(p_soc, rr)`
- Define utility and cost values by health state
- Calculate health state probabilities over time `sim_markov_chain(x0, p, n_cycles)`
- Calculate expected QALYs and costs
  - `pv(z, dr, t)`
  - `compute_qalys(x, utility, dr)`
  - `compute_costs(x, costs_medical, costs_treat, dr)`
- Cost-effectiveness analysis `make_icer_tbl(costs0, costs1, qalys0, qalys1)`

# Complete R script

```
01-markov-cohort.R x
Source on Save | Run | Source | ...
1 ## ---- Overview -----
2 ## @knitr R-packages
3 library("rcea")
4 library("knitr")
5 library("kableExtra")
6 library("magrittr")
7 library("tibble")
8
9 ## ---- Model parameters -----
10 ## @knitr transition-probabilities
11 p_hd <- .0002 # constant probability of dying when Healthy (all-cause mortality)
12 p_hs1 <- .15 # probability of becoming Sick when Healthy
13 p_s1h <- .05 # probability of becoming Healthy when Sick
14 p_s1s2 <- .0105 # probability of becoming Sicker when Sick
15 p_s1d <- .006 # constant probability of dying when Sick
16 p_s2d <- .02 # constant probability of dying when Sicker
17
18 ## @knitr transition-probability-complements
19 p_hh <- 1 - p_hs1 - p_hd
20 p_s1s1 <- 1 - p_s1h - p_s1s2 - p_s1d
21 p_s2s2 <- 1 - p_s2d
22
23 ## @knitr tpmatrix
24 p_soc <- matrix(
25   c(p_hh, p_hs1, 0, p_hd,
26     p_s1h, p_s1s1, p_s1s2, p_s1d,
27     0, 0, p_s2s2, p_s2d,
28     0, 0, 0, 1),
29   byrow = TRUE,
30   nrow = 4, ncol = 4
31 )
32 state_names <- c("H", "S1", "S2", "D")
33 colnames(p_soc) <- rownames(p_soc) <- state_names
34 print(p_soc)
35
36 ## @knitr apply_rr
37 apply_rr <- function(p, rr = .8){
38   p["H", "S1"] <- p["H", "S1"] * rr
39   p["H", "S2"] <- p["H", "S2"] * rr
40   p["H", "D"] <- p["H", "D"] * rr
41   p["H", "H"] <- 1 - sum(p["H", -1])
42
43   p["S1", "S2"] <- p["S1", "S2"] * rr
44   p["S1", "D"] <- p["S1", "D"] * rr
45   p["S1", "S1"] <- 1 - sum(p["S1", -2])
```

# Tutorial

rcea 0.0.1

Reference

Tutorials ▾



## Simple Markov Cohort Model

2020-10-11

Source: vignettes/01-markov-cohort.Rmd

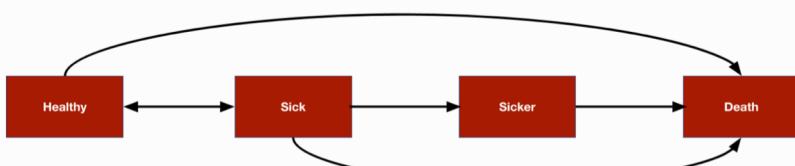
### 1 Overview

The most commonly used model for cost-effectiveness analysis (CEA) is the cohort discrete time state transition model (cDTSTM), commonly

<https://hesim-dev.github.io/rcea/articles/01-markov-cohort.html>

```
library("rcea")
library("knitr")
library("kableExtra")
library("magrittr")
library("tibble")
```

As an example, we will consider the 4-state sick-sicker model that has been described in more detail by [Alarid-Escudero et al.](#) The model will be used to compare two treatment strategies, a "New" treatment and the existing "standard of care (SOC)". The model consists 4 health states. Ordered from worst to best to worst, they are: Healthy (*H*), Sick (*S<sub>1</sub>*), Sicker (*S<sub>2</sub>*), and Death (*D*). Possible transitions from each state are displayed in the figure below.



### Contents

- 1 Overview
- 2 Theory
- 3 Model parameters
- 4 Simulation
- 5 Cost-effectiveness analysis

## Exercise 1: Simple Markov Cohort model

- *Modify R-script “01-markov-cohort-R”*

- *Change relative risk*
  - *Change drug costs*
  - *Change utilities*
  - *Change follow-up time (i.e. number of cycles)*

`sim_markov_chain(x0, p, n_cycles)`

- *Run modified script*

## **Simple Markov cohort model – Incorporating probabilistic sensitivity analysis**

# Probabilistic sensitivity analysis

- The standard methodology for quantifying the impact of parameter uncertainty is probabilistic sensitivity analysis (PSA)
- Propagating uncertainty in the input parameters throughout the model by randomly sampling sets of input values from suitable probability distributions
- Probability distributions are determined according to the distributional properties of the statistical estimates, which, in turn, depend on the statistical techniques used and the distributions of the underlying data
- R is a natural programming language for performing PSA
- Random samples can be drawn from almost any probability distribution

# Transition probabilities for SOC

- We assume that summary level data is available on transitions from the Healthy state ( $n = 1000$ ), Sick state ( $n = 1000$ ), and Sicker state ( $n = 800$ ).

```
transitions_soc <- matrix(  
  c(848, 150, 0, 2,  
    500, 389, 105, 6,  
    0, 0, 784, 16,  
    0, 0, 0, 23),  
  nrow = 4, byrow = TRUE)  
  
state_names <- c("H", "S1", "S2", "D")  
colnames(transitions_soc) <- rownames(transitions_soc) <- tolower(state_names)
```

	h	s1	s2	d
h	848	150	0	2
s1	500	389	105	6
s2	0	0	784	16
d	0	0	0	23

- The transitions from each state to the other 4 states can be modeled using a Dirichlet distribution

# Combining all model parameters

```
params <- list(
  alpha_soc = transitions_soc,
  lrr_mean = log(.8),
  lrr_lower = log(.71),
  lrr_upper = log(.9),
  c_medical = c(H = 2000, S1 = 4000, S2 = 15000, D = 0),
  c_soc = 2000,
  c_new = 12000,
  u_mean = c(H = 1, S1 = .75, S2 = 0.5, D = 0),
  u_se = c(H = 0, S1 = 0.03, S2 = 0.05, D = 0.0)
)
```

# Simulation

- The simulation proceeds by
  1. randomly sampling the parameters from the probability distributions specified
  2. running the Markov model for each draw of the parameters
- The result is a draw from the probability distribution of each of the model outputs of interest (i.e., state probabilities, QALYs, and costs).

# Sampling parameters

- While Base R can be used to draw samples of parameters, the functions `hesim::define_rng()` and `hesim::eval_rng()` simplify this process.
- Any random number generation function can be used inside the `define_rng()` block

```
rng_def <- define_rng({  
  
    lrr_se <- (lrr_upper - lrr_lower)/(2 * qnorm(.975))  
  
    list( # Parameters to return  
        p_soc = dirichlet_rng(alpha_soc),  
        rr_new = lognormal_rng(lrr_mean, lrr_se),  
        c_medical = gamma_rng(mean = c_medical, sd = c_medical),  
        c_soc = c_soc,  
        c_new = c_new,  
        u = beta_rng(mean = u_mean, sd = u_se)  
    )  
}, n = 1000)  
  
params_rng <- eval_rng(rng_def, params = params)  
  
attr(params_rng, "n") <- rng_def$n
```

# Sampling parameters

```
names(params_rng)
```

```
[1] "p_soc"      "rr_new"     "c_medical"  "c_soc"      "c_new"      "u"
```

```
head(as.matrix(params_rng$p_soc))
```

	h_h	h_s1	h_s2	h_d	s1_h	s1_s1	s1_s2	s1_d	s2_h	s2_s1
[1,]	0.8686001	0.1293872	0	0.002012649	0.5003043	0.3847703	0.10868135	0.006244105	0	0
[2,]	0.8474698	0.1499868	0	0.002543368	0.5146218	0.3964675	0.08375492	0.005155768	0	0
[3,]	0.8559237	0.1428611	0	0.001215126	0.5117574	0.3775261	0.10868021	0.002036291	0	0
[4,]	0.8550586	0.1429657	0	0.001975648	0.5139857	0.3777508	0.10303967	0.005223752	0	0
[5,]	0.8678962	0.1304462	0	0.001657694	0.5164343	0.3815376	0.09725638	0.004771722	0	0
[6,]	0.8530231	0.1459388	0	0.001038023	0.4991514	0.3750200	0.11846736	0.007361245	0	0
	s2_s2	s2_d	d_h	d_s1	d_s2	d_d				
[1,]	0.9786377	0.02136235	0	0	0	1				
[2,]	0.9871702	0.01282980	0	0	0	1				
[3,]	0.9786291	0.02137091	0	0	0	1				
[4,]	0.9809938	0.01900624	0	0	0	1				
[5,]	0.9793886	0.02061141	0	0	0	1				
[6,]	0.9750211	0.02497889	0	0	0	1				

# Simulating the Markov model

- One way that a Markov simulation can be generalized is to store “input data” in an object, i.e. data frame.
- Input data might consist of
  - treatment strategies
  - patients and subgroups
    - For instance, if we were simulating different subgroups we might store the age and sex associated with the subgroup which could, in turn, be used as covariates in a statistical model.

```
data <- data.frame(  
  strategy = c("New", "SOC")  
)
```

	strategy
1	New
2	SOC

## Simulating the Markov model – Create the function

- Set up a `sim_model()` function that runs the entire simulation.
  - Comprised of three smaller functions:
    - `sim_stateprobs()`
    - `compute_qalys()`
    - `compute_costs()`

# Simulating the Markov model – Create the function

```
sim_stateprobs <- function(p0, rr, strategy, n_cycles){  
  
  rr <- ifelse(strategy == "New", rr, 1)  
  
  p <- tpmatrix(  
    C,           p0$h_s1 * rr,  p0$h_s2 * rr,  p0$h_d * rr,  
    p0$s1_h,     C,           p0$s1_s2 * rr,  p0$s1_d * rr,  
    p0$s2_h,     p0$s2_s1,   C,           p0$s2_d * rr,  
    0,           0,           0,           1  
  )  
  
  x <- sim_markov_chain(x0 = c(1, 0, 0, 0),  
                         p = matrix(as.matrix(p), ncol = 4, byrow = TRUE),  
                         n_cycles = n_cycles)  
  
  return(x)  
}
```

`hesim::tpmatrix()` makes it easy to define a transition probability matrix.

`C` denotes that a given element is the complement of all other elements in that row, ensuring that the probabilities sum to 1.

`sim_markov_chain()` is the function we created previously

# Simulating the Markov model – Create the function

```
# QALYS
compute_qalys <- function(x, utility, dr = .03){

  n_cycles <- nrow(x) - 1
  pv(x %*% utility, dr, 0:n_cycles)
}
```

```
# Costs
compute_costs <- function(x, costs_medical, costs_treat, dr = .03){

  n_cycles <- nrow(x) - 1
  costs_treat <- c(rep(costs_treat, 3), 0)
  costs <- cbind(
    pv(x %*% costs_medical, dr, 0:n_cycles),
    pv(x %*% costs_treat, dr, 0:n_cycles)
  )
  colnames(costs) <- c("dcost_med", "dcost_treat")
  return(costs)
}
```

```

sim_model <- function(params_rng, data, n_cycles = 85, dr_qalys = .03, dr_costs = .03){
  PSA samples; tx strategy; no. cycles; discount rates
  # Initialize array of matrices
  n_samples <- attr(params_rng, "n")
  n_strategies <- nrow(data)
  out <- array(NA, dim = c(n_cycles + 1, 7, n_samples * n_strategies))
  dimnames(out) <- list(NULL, c("H", "S1", "S2", "D", "dqalys", "dcosts_med", "dcosts_treat"), NULL)

  # Run the simulation
  i <- 1
  for (s in 1:n_samples){ # Start PSA loop
    for (k in 1:n_strategies) { # Start treatment strategy loop
      x <- sim_stateprobs(p0 = params_rng$p_soc[s, ],
                           rr = params_rng$rr_new[s],
                           strategy = data$strategy[k],
                           n_cycles = n_cycles)
      dqalys <- compute_qalys(x, utility = unlist(params_rng$u[s]), dr = dr_qalys)
      dcosts <- compute_costs(x,
                               costs_medical = unlist(params_rng$c_medical[s]),
                               costs_treat = ifelse(data$strategy[k] == "SOC",
                                                    params_rng$c_soc,
                                                    params_rng$c_new), dr = dr_costs)
      out[, , i] <- cbind(x, dqalys, dcosts)
      i <- i + 1
    } # End treatment strategy loop
  } # End PSA loop

  # Store metadata and return
  attr(out, "n_samples") <- n_samples
  attr(out, "strategies") <- data$strategy
  return(out)
}

```

*An array to store the output.*  
*A series of matrices each with n\_cycles rows and columns for each output.*  
*There is one matrix for each parameter sample for the PSA and treatment strategy.*

*Simulates for each parameter sample and treatment strategy*

- state probabilities (with `sim_stateprobs()`)
- QALYs (with `compute_qalys()`)
- costs (with `compute_costs()`)

*The number of parameter samples and the names of the treatment strategies are saved as attributes (i.e., metadata) to the array.*

# Simulating the Markov model

```
sim_out <- sim_model(params_rng, data = data)

head(sim_out[, , 1])
```

	H	S1	S2	D	dqalys	dcosts_med	dcosts_treat
[1,]	1.0000000	0.0000000	0.000000000	0.000000000	1.0000000	639.2051	12000.00
[2,]	0.8927749	0.1055827	0.000000000	0.001642364	0.9440327	968.8714	11631.35
[3,]	0.8498706	0.1371191	0.009363733	0.003646603	0.9027066	1072.4091	11269.90
[4,]	0.8273444	0.1453902	0.021361082	0.005904295	0.8667374	1105.0422	10916.86
[5,]	0.8113717	0.1463692	0.033882825	0.008376274	0.8332591	1114.3372	10572.54
[6,]	0.7976015	0.1450801	0.046273111	0.011045289	0.8013670	1114.9710	10236.97

# Reorganize output

```
sim_out <- array_to_dt(sim_out)  
head(sim_out)
```

*Convert a 3D array (faster to store data) to a data.table so we can summarize outcomes for each parameter sample and treatment strategy very quickly.*

	cycle	strategy	sample	H	S1	S2	D	dqalys	dcosts_med	dcosts_treat
1:	0	New	1	1.0000000	0.0000000	0.000000000	0.000000000	1.0000000	639.2051	12000.00
2:	1	New	1	0.8927749	0.1055827	0.000000000	0.001642364	0.9440327	968.8714	11631.35
3:	2	New	1	0.8498706	0.1371191	0.009363733	0.003646603	0.9027066	1072.4091	11269.90
4:	3	New	1	0.8273444	0.1453902	0.021361082	0.005904295	0.8667374	1105.0422	10916.86
5:	4	New	1	0.8113717	0.1463692	0.033882825	0.008376274	0.8332591	1114.3372	10572.54
6:	5	New	1	0.7976015	0.1450801	0.046273111	0.011045289	0.8013670	1114.9710	10236.97

# Cost-effectiveness analysis

```
ce_out <- sim_out[cycle != 0,
                  .(dqalys = sum(dqalys),
                    dcots = sum(dcots_med) + sum(dcots_treat)),
                  by = c("sample", "strategy")]
ce_out
```

	sample	strategy	dqalys	dcots
1:	1	New	23.30567	372636.3
2:	1	SOC	21.36614	103030.7
3:	2	New	23.49382	380159.8
4:	2	SOC	22.71959	104017.1
5:	3	New	23.35243	463270.5
---				
1996:	998	SOC	20.63295	166641.1
1997:	999	New	21.82111	356686.6
1998:	999	SOC	19.58578	104643.0
1999:	1000	New	23.03594	559476.0
2000:	1000	SOC	21.79923	320811.6

# Cost-effectiveness analysis

```
ce_out_wider <- dcast(ce_out, sample ~ strategy,  
                      value.var = c("dqalys", "dcosts"))  
  
ce_out_wider
```

	sample	dqalys_New	dqalys_SOC	dcosts_New	dcosts_SOC
1:	1	23.30567	21.36614	372636.3	103030.72
2:	2	23.49382	22.71959	380159.8	104017.07
3:	3	23.35243	21.81066	463270.5	207518.50
4:	4	23.49622	21.45324	680491.2	474308.21
5:	5	24.11580	22.73777	492869.3	239480.34
---					
996:	996	23.05054	20.86090	578855.4	336586.31
997:	997	24.22340	22.48457	379255.5	93578.69
998:	998	22.22956	20.63295	452278.4	166641.12
999:	999	21.82111	19.58578	356686.6	104642.99
1000:	1000	23.03594	21.79923	559476.0	320811.62

# Cost-effectiveness analysis

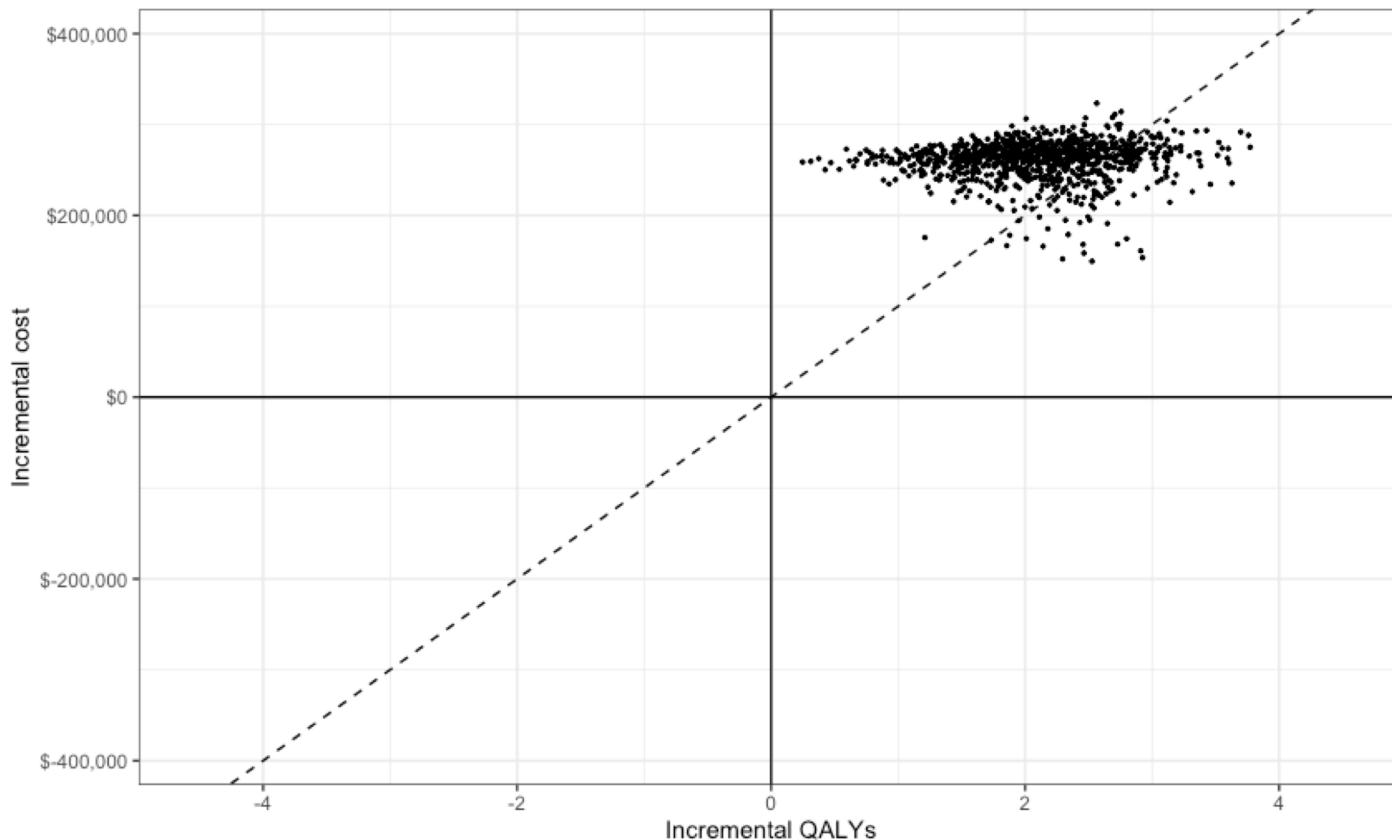
```
ce_out_wider[, idcosts := dcosts_New - dcosts_SOC]  
ce_out_wider[, idqalys := dqalys_New - dqalys_SOC]
```

	sample	dqalys_New	dqalys_SOC	dcosts_New	dcosts_SOC	idcosts	idqalys
1:	1	23.30567	21.36614	372636.3	103030.72	269605.6	1.9395308
2:	2	23.49382	22.71959	380159.8	104017.07	276142.7	0.7742344
3:	3	23.35243	21.81066	463270.5	207518.50	255752.0	1.5417635
4:	4	23.49622	21.45324	680491.2	474308.21	206183.0	2.0429732
5:	5	24.11580	22.73777	492869.3	239480.34	253388.9	1.3780308
---							
996:	996	23.05054	20.86090	578855.4	336586.31	242269.1	2.1896429
997:	997	24.22340	22.48457	379255.5	93578.69	285676.8	1.7388263
998:	998	22.22956	20.63295	452278.4	166641.12	285637.3	1.5966079
999:	999	21.82111	19.58578	356686.6	104642.99	252043.6	2.2353267
1000:	1000	23.03594	21.79923	559476.0	320811.62	238664.4	1.2367111

```
ce_out_wider[, .(icer = mean(idcosts)/mean(idqalys))]
```

	icer
1:	127000.5

# Cost-effectiveness plane



# Steps

- Define uncertainty for all model input parameters
- Sampling parameter values `hesim::define_rng()`, `hesim::eval_rng()`
- Define treatment strategies and population (data)
- Simulating the Markov model

```
sim_model(params_rng, data, n_cycles, dr_qalys, dr_costs)
sim_stateprobs(po, rr, strategy, n_cycles)
compute_qalys(x, utility, dr)
compute_costs(x, cost_medical, costs_treat, dr)
```

- Reorganize output `rbind_array()`, `array_to_dt()`
- Cost-effectiveness analysis

# Complete R script

```
02-markov-cohort-psa.R   
Source on Save | Run | Source |   
1 ## ---- Overview -----  
2 ## @knitr R-packages  
3 library("rcaea")  
4 library("hesim")  
5 library("data.table")  
6 library("magrittr")  
7 library("ggplot2")  
8  
9 ## ---- Model parameters -----  
10 ## @knitr tpmatrix  
11 transitions_soc <- matrix(  
12   c(848, 150, 0, 2,  
13     500, 389, 105, 6,  
14     0, 0, 784, 16,  
15     0, 0, 0, 23),  
16   nrow = 4, byrow = TRUE)  
17 state_names <- c("H", "S1", "S2", "D")  
18 colnames(transitions_soc) <- rownames(transitions_soc) <- tolower(state_names)  
19  
20 ## @knitr all-parameters  
21 params <- list(  
22   alpha_soc = transitions_soc,  
23   lrr_mean = log(.8),  
24   lrr_lower = log(.71),  
25   lrr_upper = log(.9),  
26   c_medical = c(H = 2000, S1 = 4000, S2 = 15000, D = 0),  
27   c_soc = 2000,  
28   c_new = 12000,  
29   u_mean = c(H = 1, S1 = .75, S2 = 0.5, D = 0),  
30   u_se = c(H = 0, S1 = 0.03, S2 = 0.05, D = 0.0)  
31 )  
32  
33 ## ---- Simulation -----  
34 ## @knitr sample-parameters  
35 rng_def <- define_rng({  
36   lrr_se <- (lrr_upper - lrr_lower)/(2 * qnorm(.975)) # Local object  
37   # not returned  
38   list( # Parameters to return  
39     p_soc = dirichlet_rng(alpha_soc),  
40     rr_new = lognormal_rng(lrr_mean, lrr_se),  
41     c_medical = gamma_rng(mean = c_medical, sd = c_medical),  
42     c_soc = c_soc,  
43     c_new = c_new,  
44     u = beta_rng(mean = u_mean, sd = u_se)  
45   )  
46 } sim_model(params_rng, data, n_cycles, dr_qalys, dr_costs) #
```

# Tutorial

rcea **0.0.1**

Reference

Tutorials ▾



## Incorporating Probabilistic Sensitivity Analysis

2020-10-11

Source: vignettes/02-markov-cohort-psa.Rmd

### 1 Overview

Probabilistic sensitivity analysis (PSA) is used to quantify the impact of parameter uncertainty on the uncertainty of model outputs. PSA is typically performed via a simulation approach whereby the model parameters are randomly sampled from suitable probability distributions and the entire model is simulated for each random draw of the parameters.

<https://hesim-dev.github.io/rcea/articles/02-markov-cohort-psa.html>

```
library("rcea")
library("hesim")
library("data.table")
library("magrittr")
library("ggplot2")
```

### 2 Model parameters

#### 2.1 Transition probabilities for SOC

The probability distribution used for transition probabilities will depend on the underlying data. In this case, we assume that summary level data is available on transitions from the Healthy state ( $n = 900$ ), Sick state ( $n = 900$ ), and Sicker state ( $n = 800$ ). The transitions from each state to the other 4 states can be modeled using a Dirichlet distribution (see Appendix).

```
transitions_soc <- matrix(
  c(848, 150, 0, 2,
    500, 389, 105, 6,
    0, 0, 784, 16,
    0, 0, 0, 23),
  nrow = 4, byrow = TRUE)
```

### Contents

- 1 Overview
- 2 Model parameters
- 3 Simulation
- 4 Cost-effectiveness analysis
- 5 Appendix

## Exercise 2: Incorporating probabilistic sensitivity analysis

- *Modify R-script “02-markov-cohort-psa.R”*
  - *Reduce sample size of data for transition matrix by 50%*
  - *Increase confidence interval for relative risk*
- *Run modified script*

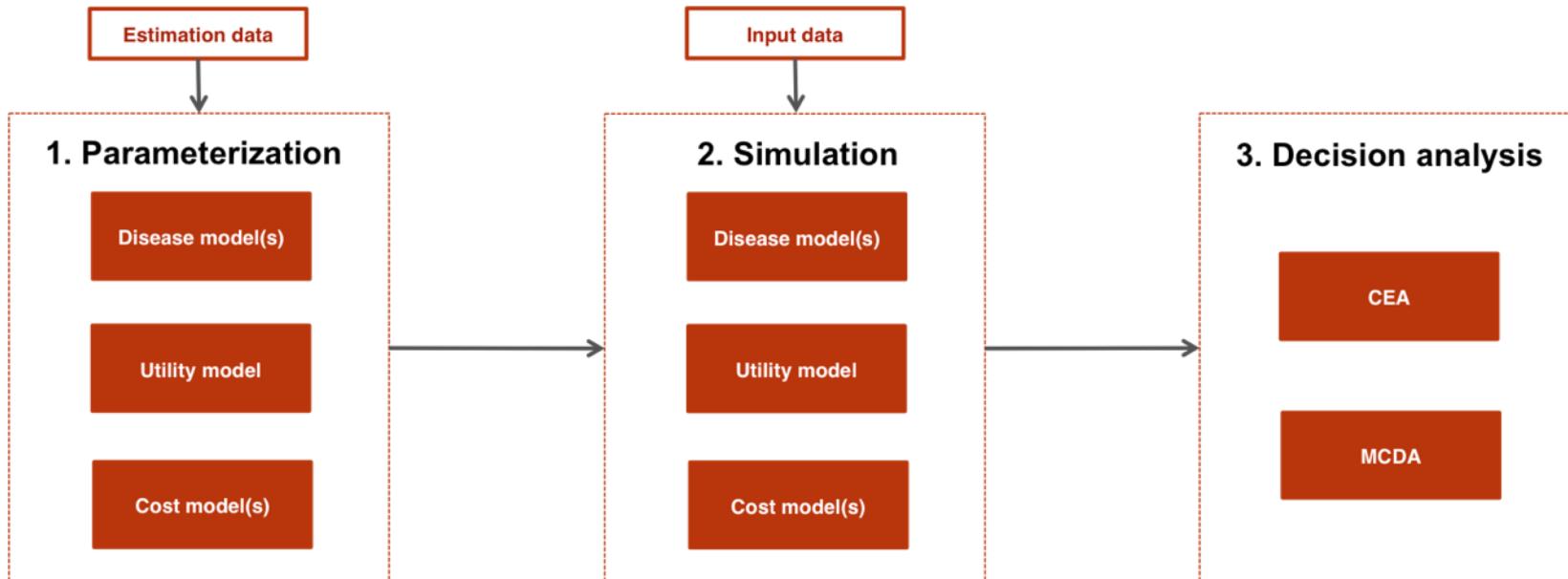
## **Simple Markov cohort model with hesim**



# What is hesim?

- A modular and computationally efficient R package for building simulation models for economic evaluation
- Supports both cohort and individual-level models, encompassing Markov (time-homogeneous and time-inhomogeneous) and semi-Markov processes
  - cohort discrete time state transition models (cDTSTM)
  - individual-level continuous time state transition models (iCTSTM)
  - n-state partitioned survival models (PSM)
- Parameterization by fitting a statistical model in R or by using estimates from external sources
- Nearly all simulation code written in C++ under the hood, but you don't need to know C++ to use it!

# hesim modeling process



# Economic models with **hesim**

1. Model set-up
2. Parameters
3. Simulation
  - a. Construction of model
  - b. Simulation of outcomes
4. Cost-effectiveness analysis

# Model setup

- Define target population and intervention strategies

```
strategies <- data.frame(  
  strategy_id = 1:2,  
  strategy_name = c("SOC", "New")  
)  
patients <- data.frame(  
  patient_id = 1,  
  age = 25  
)  
hesim_dat <- hesim_data(  
  strategies = strategies,  
  patients = patients  
)  
  
print(hesim_dat)
```

```
$strategies  
  strategy_id strategy_name  
1           1          SOC  
2           2          New  
  
$patients  
  patient_id age  
1           1    25  
  
attr(,"class")  
[1] "hesim_data"
```

# Model parameters

- Same list of parameters as used before

```
params <- list(  
  alpha_soc = transitions_soc,  
  lrr_mean = log(.8),  
  lrr_lower = log(.71),  
  lrr_upper = log(.9),  
  c_medical = c(H = 2000, S1 = 4000, S2 = 15000),  
  c_soc = 2000,  
  c_new = 12000,  
  u_mean = c(H = 1, S1 = .75, S2 = 0.5),  
  u_se = c(H = 0, S1 = 0.03, S2 = 0.05)  
)
```

## Model parameters – Random number generation (for PSA)

```
rng_def <- define_rng({  
  lrr_se <- (lrr_upper - lrr_lower)/(2 * qnorm(.975))  
  
  list( # Parameters to return  
    p_soc = dirichlet_rng(alpha_soc),  
    rr_new = lognormal_rng(lrr_mean, lrr_se),  
    c_medical = gamma_rng(mean = c_medical, sd = c_medical),  
    c_soc = c_soc,  
    c_new = c_new,  
    u = beta_rng(mean = u_mean, sd = u_se)  
  )  
}, n = 1000)
```

## Model parameters – Transformed parameters

- It is typically useful to "transform" underlying parameters (`params`) into transformed parameters (`tparams`) more relevant for the simulation
  - e.g., predicting an element of a transition probability matrix as a function of the treatment strategy
- We previously did this in the base R PSA example...

```

sim_model <- function(params_rng, data, n_cycles = 85, dr_qalys = .03, dr_costs = .03){

  # Initialize array of matrices
  n_samples <- attr(params_rng, "n")
  n_strategies <- nrow(data)
  out <- array(NA, dim = c(n_cycles + 1, 7, n_samples * n_strategies))
  dimnames(out) <- list(NULL, c("H", "S1", "S2", "D", "dqalys", "dcosts_med", "dcosts_treat"), NULL)

  # Run the simulation
  i <- 1
  for (s in 1:n_samples){ # Start PSA loop
    for (k in 1:n_strategies) { # Start treatment strategy loop
      x <- sim_stateprobs(p0 = params_rng$p_soc[s, ],
                           rr = params_rng$rr_new[s],
                           strategy = data$strategy[k],
                           n_cycles = n_cycles)
      dqalys <- compute_qalys(x, utility = unlist(params_rng$u[s]), dr = dr_qalys)
      dcosts <- compute_costs(x,
                               costs_medical = unlist(params_rng$c_medical[s]),
                               costs_treat = ifelse(data$strategy[k] == "SOC",
                                                    params_rng$c_soc,
                                                    params_rng$c_new), dr = dr_costs)
      out[, , i] <- cbind(x, dqalys, dcosts)
      i <- i + 1
    } # End treatment strategy loop
  } # End PSA loop

  # Store metadata and return
  attr(out, "n_samples") <- n_samples
  attr(out, "strategies") <- data$strategy
  return(out)
}

sim_out <- sim_model(params_rng, data = data)
sim_out <- array_to_dt(sim_out)

```

```
sim_stateprobs <- function(p0, rr, strategy, n_cycles){

  rr <- ifelse(strategy == "New", rr, 1)

  p <- tpmatrix(
    C,           p0$h_s1 * rr,  p0$h_s2 * rr,  p0$h_d * rr,
    p0$s1_h,     C,           p0$s1_s2 * rr,  p0$s1_d * rr,
    p0$s2_h,     p0$s2_s1,   C,           p0$s2_d * rr,
    0,           0,           0,           1
  )

  x <- sim_markov_chain(x0 = c(1, 0, 0, 0),
                        p = matrix(as.matrix(p), ncol = 4, byrow = TRUE),
                        n_cycles = n_cycles)

  return(x)
}
```

## Model parameters – Transformed parameters

- A `define_tparams()` block in `hesim` does the same thing, but most of the implementation is done for you (efficiently)
- A `define_tparams()` block returns:
  - `tpmatrix`: The transition probability matrix
  - `utility`: Utility assigned to each health state
  - `costs`: Costs assigned to each health state for each cost category
- All parameters are “transformed” using:
  1. Columns of input data
  2. Parameters returned by `define_rng()`

## Model parameters – Transformed parameters

- *Input data* (treatment strategies and patients) can be generated using `expand()`

```
input_data <- hesim::expand(hesim_dat, by = c("strategies", "patients"))

head(input_data)
```

```
  strategy_id patient_id strategy_name age
1:          1          1           SOC  25
2:          2          1           New  25
```

# Model parameters – Transformed parameters

- You write mathematical expressions
- Automatically loops over PSA iterations and input data rows

```
tparams_def <- define_tparams({  
  # The treatment effect (relative risk) varies by  
  # strategies (SOC is the reference strategy)  
  
  rr <- ifelse(strategy_name == "SOC", 1, rr_new)  
  
  list(  
    tpmatrix = tpmatrix(  
      C, p_soc$h_s1 * rr, p_soc$h_s2 * rr, p_soc$h_d * rr,  
      p_soc$s1_h, C, p_soc$s1_s2 * rr, p_soc$s1_d * rr,  
      p_soc$s2_h, p_soc$s2_s1, C, p_soc$s2_d * rr,  
      0, 0, 0, 1  
    ),  
    utility = u,  
    costs = list(  
      treatment = ifelse(strategy_name == "SOC", c_soc, c_new),  
      medical = c_medical  
    )  
  )  
})
```

Annotations:

- rr <- ifelse(strategy\_name == "SOC", 1, rr\_new)
  - rr: Parameter
  - strategy\_name: Input data
- list(
  - tpmatrix = tpmatrix(
    - C: Parameter
    - p\_soc\$h\_s1: Parameter (defined above)
    - rr: Parameter
    - p\_soc\$h\_d: Parameter (defined above)
    - p\_soc\$s1\_h: Input data
    - C: Parameter
    - p\_soc\$s1\_s2: Parameter (defined above)
    - p\_soc\$s1\_d: Parameter (defined above)
    - p\_soc\$s2\_h: Input data
    - p\_soc\$s2\_s1: Input data
    - C: Parameter
    - p\_soc\$s2\_d: Parameter (defined above)
    - 0: Input data
    - 0: Input data
    - 0: Input data
    - 1: Input data
  - utility = u: Parameter
  - costs = list(
    - treatment = ifelse(strategy\_name == "SOC", c\_soc, c\_new): Parameter
    - medical = c\_medical: Input data

# Simulation - Construct the model

- Combine the underlying parameters with the expressions for random number generation and parameter transformation

```
mod_def <- define_model(tparams_def = tparams_def,  
                        rng_def = rng_def,  
                        params = params)
```

- A economic model (of class CohortDtstm) can be created from a defined model (of class model\_def) and data using the generic function create\_CohortDtstm()

```
econmod <- create_CohortDtstm(mod_def, input_data)
```

- This object consists of a
  - transition model for simulating transition probabilities with \$sim\_stateprobs()
  - a utility model for simulating quality-adjusted life-years with \$sim\_qalys()
  - a set of cost models (for each cost category) for simulating costs with \$sim\_costs()

# Simulation – Simulating outcomes

## ■ Health state probabilities

```
econmod$sim_stateprobs(n_cycles = 85)
```

	sample	strategy_id	patient_id	grp_id	state_id	t	prob
1:	1		1	1		1 0	1.0000000
2:	1		1	1		1 1	0.8466964
3:	1		1	1		1 2	0.7929241
4:	1		1	1		1 3	0.7652357
5:	1		1	1		1 4	0.7446251
6:	1		1	1		1 5	0.7261680

## ■ QALYs

```
econmod$sim_qalys(  
  dr = 0.03, lys = TRUE,  
  integrate_method = "riemann_right"  
)
```

	sample	strategy_id	patient_id	grp_id	state_id	dr	qalys	lys
1:	1	1	1	1		1 0.03	14.604941	14.604941
2:	1	1	1	1		2 0.03	2.718281	3.660628
3:	1	1	1	1		3 0.03	2.595318	7.331531
4:	1	2	1	1		1 0.03	17.633196	17.633196
5:	1	2	1	1		2 0.03	2.632315	3.544860
6:	1	2	1	1		3 0.03	2.083739	5.886368

## ■ Costs

```
econmod$sim_costs(  
  dr = 0.03,  
  integrate_method = "riemann_right"  
)
```

	sample	strategy_id	patient_id	grp_id	state_id	dr	category	costs
1:	1	1	1	1		1 0.03	treatment	29209.882
2:	1	1	1	1		2 0.03	treatment	7321.257
3:	1	1	1	1		3 0.03	treatment	14663.061
4:	1	2	1	1		1 0.03	treatment	211598.347
5:	1	2	1	1		2 0.03	treatment	42538.323
6:	1	2	1	1		3 0.03	treatment	70636.410

# Cost-effectiveness analysis

- CEAs can be performed directly from the simulation output with **hesim**. Other R packages such as BCEA could also be considered
- First we need to aggregate (i.e., "summarize") costs and QALYs across health states

```
ce_sim <- econmod$summarize()
```

```
$costs
  category dr sample strategy_id      costs grp_id
1: treatment 0.03     1             1 51194.20    1
2: treatment 0.03     1             2 324773.08   1
3: treatment 0.03     2             1 48720.41    1
4: treatment 0.03     2             2 316828.55   1
5: treatment 0.03     3             1 51943.80    1
---
5996: total 0.03    998            2 402500.90   1
5997: total 0.03    999            1 197991.68   1
5998: total 0.03    999            2 461755.98   1
5999: total 0.03   1000            1 203541.38   1
6000: total 0.03   1000            2 461558.77   1

$qalys
  dr sample strategy_id      qalys grp_id
1: 0.03     1             1 19.91854    1
2: 0.03     1             2 22.34925    1
3: 0.03     2             1 19.87522    1
4: 0.03     2             2 22.71959    1
5: 0.03     3             1 21.39403    1
---
1996: 0.03    998            2 23.08819    1
1997: 0.03    999            1 21.25388    1
1998: 0.03    999            2 22.98019    1
1999: 0.03   1000            1 20.75811    1
2000: 0.03   1000            2 23.84501    1

attr(,"class")
[1] "ce"
```

# Cost-effectiveness analysis

- Here, we will consider a pairwise comparison between the new treatment and SOC with the `cea_pw()` function

```
cea_pw_out <- cea_pw(ce_sim, comparator = 1,  
                      dr_qalys = 0.03, dr_costs = 0.03)
```

- Although `cea_pw()` allows users to summarize output from a PSA we will just create an ICER table using means for now

```
icer_tbl(cea_pw_out, k = 50000, colnames = strategies$strategy_name)
```

SOC New	
Incremental QALYs	"-" "2.07 (0.98, 3.17)"
Incremental costs	"-" "257,766 (206,974, 289,881)"
Incremental NMB	"-" "-154,131 (-213,515, -79,172)"
ICER	"-" "124,362"
Conclusion	"-" "Not cost-effective" (at WTP threshold of \$50,000)

# Steps with `hesim`

## 1. Model set-up

- Specify the treatment strategies and target population(s)
  - `hesim_data()`

## 2. Parameters

- Estimate or define the parameters of the economic model
  - `define_rng()`, `define_tparams()`

## 3. Simulation

### a. Construction of model

- Create an economic model—consisting of separate statistical models for disease progression, costs, and utilities—that simulate outcomes as a function of *input data* (derived from Step 1) and *parameters* (from Step 2)
- `define_model()`, `create_CohortDtsim()`

### b. Simulation of outcomes

- Simulate outcomes (disease progression, costs, and quality-adjusted life-years (QALYs)) using the model constructed in Step 3
- `$sim_stateprobs()`, `$sim_qalys()`, `$sim_costs()`

## 4. Cost-effectiveness analysis

# Complete R script

The screenshot shows an RStudio interface with a code editor window titled "03-markov-cohort-hesim.R". The code is a script for performing a cost-effectiveness analysis using the hesim package. It includes sections for overview, model setup, parameters, and all-parameters, along with a define\_rng section. The code uses R's standard syntax with comments and variables like strategies, patients, and transitions\_soc.

```
## ---- Overview ----
## @knitr R-packages
library("hesim")
## ---- Model setup -----
## @knitr hesim-data
strategies <- data.frame(
  strategy_id = 1:2,
  strategy_name = c("SOC", "New")
)
patients <- data.frame(
  patient_id = 1,
  age = 25
)
hesim_dat <- hesim_data(
  strategies = strategies,
  patients = patients
)
print(hesim_dat)

## ---- Model parameters -----
## @knitr transitions
transitions_soc <- matrix(
  c(848, 150, 0, 2,
    500, 389, 105, 6,
    0, 0, 784, 16,
    0, 0, 0, 23),
  nrow = 4, byrow = TRUE)
state_names <- c("H", "S1", "S2", "D")
colnames(transitions_soc) <- rownames(transitions_soc) <- tolower(state_names)

## @knitr all-parameters
params <- list(
  alpha_soc = transitions_soc,
  lrr_mean = log(.8),
  lrr_lower = log(.71),
  lrr_upper = log(.9),
  c_medical = c(H = 2000, S1 = 4000, S2 = 15000),
  c_soc = 2000,
  c_new = 12000,
  u_mean = c(H = 1, S1 = .75, S2 = 0.5),
  u_se = c(H = 0, S1 = 0.03, S2 = 0.05)
)
## @knitr define_rng
```

115:59 # Cost-effectiveness analysis ↴

R Script ⇡

# Tutorial

rcea 0.0.1

Reference

Tutorials ▾



## Markov Cohort Model wth hesim

2020-10-11

Source: vignettes/03-markov-cohort-hesim.Rmd

### 1 Overview

This tutorial repeats the probabilistic sensitivity analysis (PSA) of the Markov cohort model simulation performed in the [previous tutorial](#) using `hesim`. We utilize the cohort discrete time state transition model (`cDTSTM`) class, which is another name for a (time-homogeneous or time-inhomogeneous) Markov cohort model.

<https://hesim-dev.github.io/rcea/articles/03-markov-cohort-hesim.html>

2. **Parameters:** Estimate or define the parameters of the economic model.
3. **Simulation:**
  - a. **Construction of model:** Create an economic model—consisting of separate statistical models for disease progression, costs, and utilities—that simulate outcomes as a function of *input data* (derived from Step 1) and *parameters* (from Step 2).
  - b. **Simulation of outcomes:** Simulate outcomes (disease progression, costs, and quality-adjusted life-years (QALYs)) using the model constructed in Step 3.

This analysis can be performed using the `hesim` package alone.

```
library("hesim")
```

### 2 Model setup

Before beginning an analysis, it is necessary to define the treatment strategies of interest and the target population of interest. We continue to run an analysis for two treatment strategies ("SOC" and the "New" treatment) and one representative 25-year old patient.

```
strategies <- data.frame(  
  strategy_id = 1:2,  
  strategy_name = c("SOC", "New")  
)  
patients <- data.frame(  
  ...)
```

### Contents

- 1 Overview
- 2 Model setup
- 3 Model parameters
- 4 Simulation
- 5 Cost-effectiveness analysis

## Exercise 3: Markov cohort model with hesim

### ■ Modify R-script “03-markov-cohort-hesim.R”

- Increase confidence interval for relative risk
- Modify the mean health state utility value
- Remove impact of the intervention on transitions from “healthy” to “sick”, “sicker”, and “death” (row 71)

### ■ Run modified script

```
tparams_def <- define_tparams({  
  ## The treatment effect (relative risk) is transformed so that it varies by  
  ## strategies (SOC is the reference strategy)  
  rr <- ifelse(strategy_name == "SOC", 1, rr_new)  
  
  list(  
    tpmatrix = tpmatrix(  
      C, p_soc$h_s1 * rr, p_soc$h_s2 * rr, p_soc$h_d * rr,  
      p_soc$s1_h, C, p_soc$s1_s2 * rr, p_soc$s1_d * rr,  
      p_soc$s2_h, p_soc$s2_s1, C, p_soc$s2_d * rr,  
      0, 0, 0, 1  
    ),  
    utility = u,  
    costs = list(  
      treatment = ifelse(strategy_name == "SOC", c_soc, c_new),  
      medical = c_medical  
    )  
  )  
})
```

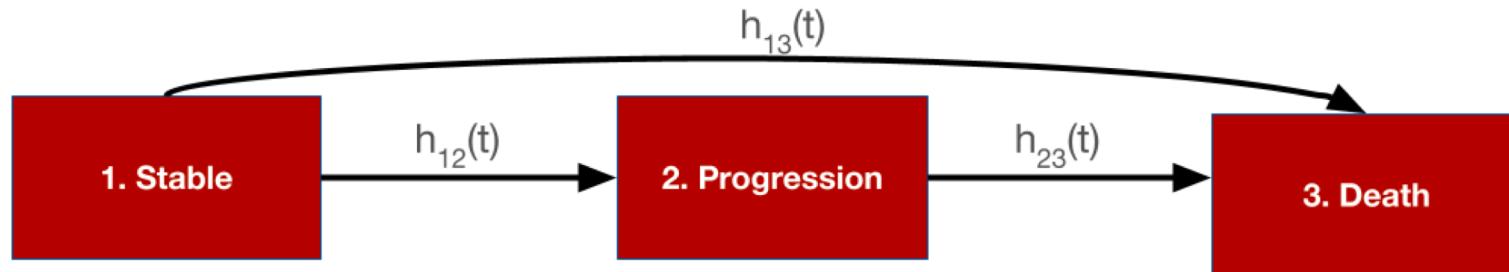
## **Semi-Markov multi-state model**

## Semi-Markov multi-state model

- Transition rates can depend on time in intermediate health states (unlike in a Markov model)
- Can only be simulated in a general manner using individual patient simulation (IPS)
- IPS is performed most efficiently using a **continuous time state transition model (CTSTM)**
- Ideally parameterizing by fitting a multi-state model

# Semi-Markov multi-state model

Clock reset



# Economic models with **hesim**

1. Model set-up
2. Parameters
3. Simulation
  - a. Construction of model
  - b. Simulation of outcomes
4. Cost-effectiveness analysis

## Model setup

- The transitions of a multi-state model in **hesim** must be characterized by a matrix where each element denotes a transition from a row to a column

```
tmat <- rbind(  
  c(NA, 1, 2),  
  c(NA, NA, 3),  
  c(NA, NA, NA)  
)  
colnames(tmat) <- rownames(tmat) <- c("Stable", "Progression", "Dead")  
  
print(tmat)
```

	Stable	Progression	Dead
Stable	NA	1	2
Progression	NA	NA	3
Dead	NA	NA	NA

# Model setup

```
n_patients <- 1000

patients <- data.table(
  patient_id = 1:n_patients,
  age = rnorm(n_patients, mean = 45, sd = 7),
  female = rbinom(n_patients, size = 1, prob = .51)
)

strategies <- data.frame(
  strategy_id = 1:2,
  strategy_name = c("SOC", "New")
)
n_strategies <- nrow(strategies)

states <- data.table(
  state_id = c(1, 2),
  state_name = c("Stable", "Progression")
)
n_states <- nrow(states)

hesim_dat <- hesim_data(
  strategies = strategies,
  patients = patients,
  states = states
)
```

*As in the cohort model, we must specify the target population and treatment strategies of interest*

*In an IPS we simulate many patients and then average outcomes across the simulated patients. 1,000 simulated patients should produce reasonably stable results*

*We also explicitly define the (non-death) health states, which we will use to model utility and costs*

*We always combine this information into one object*

# Model setup

```
print(hesim_dat)
```

```
$strategies
  strategy_id strategy_name
1              1             SOC
2              2            New

$patients
  patient_id     age female
1:          1 42.71774      0
2:          2 48.86723      0
3:          3 40.27539      1
4:          4 46.50052      1
5:          5 47.17538      1
---
996:        996 43.22279      0
997:        997 54.22166      0
998:        998 37.27172      0
999:        999 45.20616      0
1000:       1000 39.15981      1

$states
  state_id state_name
1:        1    Stable
2:        2 Progression

attr("class")
[1] "hesim_data"
```

## Parameter estimation

- In the cohort examples, we used parameter estimates from the literature
  - We will continue to do this for utility and costs
- However, in an ideal scenario, we would estimate parameters ourselves using patient-level data
  - We will fit a multi-state model in this manner by estimating transition specific hazards using the R package `flexsurv`

## Parameter estimation – Multi-state model

- Multi-state models can be fit by:
  - Estimating a joint survival model with interaction terms for different transition
  - Fitting separate survival models for each transition  
(Method used here)

# Parameter estimation – Multi-state model

## ■ Dataset

```
from to female      age patient_id final time_start time_stop status transition_id strategy_id
1:   1  2       1 54.37365        1     0  0.00000 11.66523    1         1      2
2:   1  3       1 54.37365        1     0  0.00000 11.66523    0         2      2
3:   2  3       1 54.37365        1     1 11.66523 15.00000    0         3      2
4:   1  2       1 58.93437        2     0  0.00000 15.00000    0         1      1
5:   1  3       1 58.93437        2     1  0.00000 15.00000    0         2      1
  strategy_name      time
1:      New 11.665231
2:      New 11.665231
3:      New  3.334769
4:      SOC 15.000000
5:      SOC 15.000000
```

## ■ Estimate parameters

```
wei_fits <- vector(length = 3, mode = "list")
for (i in 1:3){ # 3 possible transitions
  wei_fits[[i]] <- flexsurvreg(
    Surv(time, status) ~ strategy_name + female,
    data = data,
    subset = (transition_id == i) ,
    dist = "weibull")
}
wei_fits <- flexsurvreg_list(wei_fits)
```

# Parameter estimation – Multi-state model

Stable -> Progression

[[1]]

Call:

```
flexsurvreg(formula = Surv(time, status) ~ strategy_name + female,  
            data = data, subset = (transition_id == i), dist = "weibull")
```

Estimates:

	data	mean	est	L95%	U95%	se	exp(est)	L95%	U95%
shape		NA	1.9689	1.8843	2.0572	0.0441	NA	NA	NA
scale		NA	11.3409	10.8364	11.8688	0.2633	NA	NA	NA
strategy_nameNew	0.4930	-0.4609	-0.5147	-0.4072	0.0274	0.6307	0.5977	0.6655	
female	0.4990	0.3493	0.2958	0.4028	0.0273	1.4181	1.3442	1.4961	

N = 2000, Events: 1401, Censored: 599

Total time at risk: 16884.86

Log-likelihood = -4458.597, df = 4

AIC = 8925.194

New treatment increases  
time to progression

Shape parameter: whether the hazard is increasing ( $>1$ ), decreasing ( $<1$ ), or constant ( $=1$ )

Scale: whether the hazard is lower/higher at given time point

# Parameter estimation – Multi-state model

Stable -> Death

```
[[2]]  
call:  
flexsurvreg(formula = Surv(time, status) ~ strategy_name + female,  
    data = data, subset = (transition_id == i), dist = "weibull")
```

Estimates:

	data	mean	est	L95%	U95%	se	exp(est)	L95%	U95%
shape		NA	3.0233	2.7877	3.2788	0.1252	NA	NA	NA
scale		NA	18.3770	17.1128	19.7346	0.6683	NA	NA	NA
strategy_nameNew	0.4930	-0.5162	-0.5905	-0.4419	0.0379	0.5968	0.5541	0.6428	
female	0.4990	0.4104	0.3376	0.4833	0.0372	1.5074	1.4015	1.6214	

N = 2000, Events: 343, Censored: 1657

Total time at risk: 16884.86

Log-likelihood = -1407.966, df = 4

AIC = 2823.932

*Shape parameter: whether the hazard is increasing, decreasing, or constant*

*Scale: whether the hazard is lower/higher at given time point*

# Parameter estimation – Multi-state model

Progression -> Death

[[3]]

Call:

```
flexsurvreg(formula = Surv(time, status) ~ strategy_name + female,  
            data = data, subset = (transition_id == i), dist = "weibull")
```

Estimates:

	data	mean	est	L95%	U95%	se	exp(est)	L95%	U95%
shape		NA	3.6185	3.3423	3.9174	0.1466	NA	NA	NA
scale		NA	16.1803	14.8094	17.6781	0.7309	NA	NA	NA
strategy_nameNew	0.5360	-0.5450	-0.6376	-0.4523	0.0473	0.5799	0.5285	0.6361	
female	0.4675	0.3213	0.2547	0.3879	0.0340	1.3789	1.2901	1.4739	

N = 1401, Events: 377, Censored: 1024

Total time at risk: 9736.58

Log-likelihood = -1185.006, df = 4

AIC = 2378.012

*Shape parameter: whether the hazard is increasing, decreasing, or constant*

*Scale: whether the hazard is lower/higher at given time point*

## Parameters – Utility

```
utility_tb1 <- stateval_tb1(
  data.table(state_id = states$state_id,
            mean = c(.8, .6),
            se = c(0.02, .05)
  ),
  dist = "beta",
  hesim_data = hesim_dat)
```

```
state_id mean   se
1:       1  0.8 0.02
2:       2  0.6 0.05
```

## Parameters – Medical cost

```
medcost_tb1 <- stateval_tb1(  
  data.table(state_id = states$state_id,  
            mean = c(2000, 9500),  
            se = c(2000, 9500)  
,  
  dist = "gamma",  
  hesim_data = hesim_dat)
```

```
state_id mean    se  
1:          1 2000 2000  
2:          2 9500 9500
```

## Parameters – Drug cost

```
n_times <- 2

drugcost_tbl <- stateval_tbl(
  data.table(
    strategy_id = rep(strategies$strategy_id, each = n_states * n_times),
    state_id = rep(rep(states$state_id, each = n_strategies), n_times),
    time_start = rep(c(0, 3/12), n_states * n_strategies),
    est = c(rep(2000, 4), # Costs are always the same with SOC
           12000, 12000, 12000, 10000 # Costs with New drop after 3 months in progression state
    )
  ),
  dist = "fixed",
  hesim_data = hesim_dat)
```

When using an IPS, "state values" (like transition rates) can depend on time in an intermediate health state

We illustrate by assuming that costs for the new treatment are \$12,000 for the first 3 months in the progression state and then \$10,000 thereafter

(Would not be possible in a cohort model without creating tunnel states)

	strategy_id	state_id	time_id	time_start	time_stop	est
1:	1	1	1	0.00	0.25	2000
2:	1	1	2	0.25	Inf	2000
3:	1	2	1	0.00	0.25	2000
4:	1	2	2	0.25	Inf	2000
5:	2	1	1	0.00	0.25	12000
6:	2	1	2	0.25	Inf	12000
7:	2	2	1	0.00	0.25	12000
8:	2	2	2	0.25	Inf	10000
						105

# Simulation – Construct the model

## Disease model

- The transition model is constructed as a function of the fitted multi-state model and *input data* (treatment strategy and patients)

```
transmod_data <- expand(hesim_dat,
                         by = c("strategies", "patients"))
```

	strategy_id	patient_id	strategy_name	age	female
1:	1	1	SOC	42.71774	0
2:	1	2	SOC	48.86723	0
3:	1	3	SOC	40.27539	1
4:	1	4	SOC	46.50052	1
5:	1	5	SOC	47.17538	1
6:	1	6	SOC	53.21776	0

```
transmod <- create_IndivCtstmTrans(wei_fits, transmod_data,
                                    trans_mat = tmat, n = 500,
                                    clock = "reset",
                                    start_age = patients$age)
```

# Simulation – Construct the model

## Utility and cost models

```
# Utility
utilitymod <- create_Statevals(utility_tbl, n = 500)

# Costs
drugcostmod <- create_Statevals(drugcost_tbl, n = 500,
                                    time_reset = TRUE)
medcostmod <- create_Statevals(medcost_tbl, n = 500) So that costs depend on time in intermediate state

costmods <- list(Drug = drugcostmod,
                  Medical = medcostmod)
```

# Simulation – Construct the model

Combining the disease progression, cost, and utility models

```
econmod <- IndivCtstm$new(trans_model = transmod,  
                           utility_model = utilitymod,  
                           cost_models = costmods)
```

# Simulation - Simulating outcomes

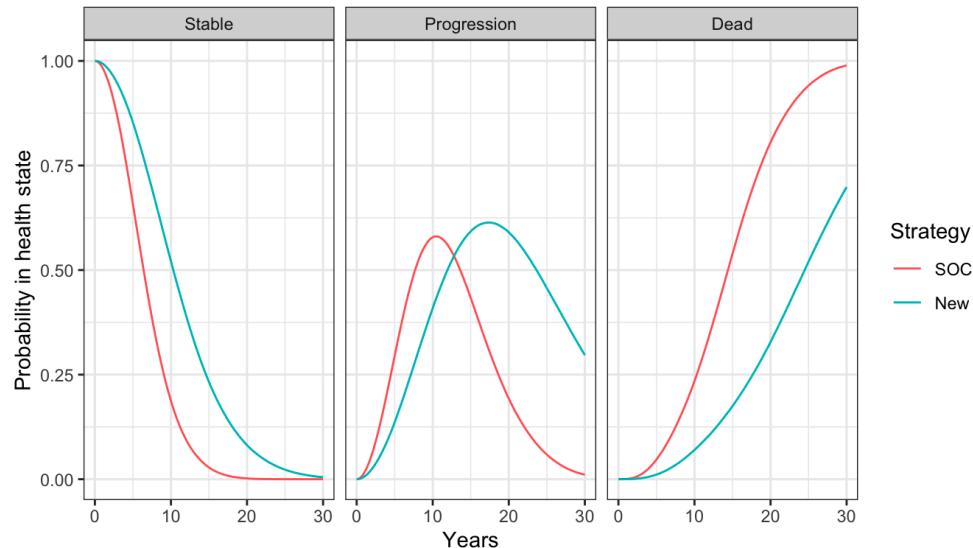
## Disease progression

```
econmod$sim_disease(max_age = 100)
```

```
head(econmod$disprog_)
```

	sample	strategy_id	patient_id	grp_id	from	to	final	time_start	time_stop
1:	1	1	1	1	1	2	0	0.000000	10.403221
2:	1	1	1	1	2	3	1	10.403221	20.171049
3:	1	1	2	1	1	2	0	0.000000	4.759907
4:	1	1	2	1	2	3	1	4.759907	19.568465
5:	1	1	3	1	1	2	0	0.000000	5.384254
6:	1	1	3	1	2	3	1	5.384254	19.427541

```
econmod$sim_stateprobs(t = seq(0, 30 , 1/12))
```



# Simulation - Simulating outcomes

## QALYs and costs

```
econmod$sim_qalys(dr = c(0,.03))
```

	sample	strategy_id	grp_id	state_id	dr	qalys	lys
1:	1		1	1	1	0 5.518113	6.778010
2:	1		1	1	2	0 5.596111	8.399302
3:	1		2	1	1	0 9.171519	11.265563
4:	1		2	1	2	0 9.377958	14.075543
5:	2		1	1	1	0 5.573405	6.806206
6:	2		1	1	2	0 4.870313	8.003933

```
econmod$sim_costs(dr = 0.03)
```

	sample	strategy_id	grp_id	state_id	dr	category	costs
1:	1		1	1	1	0.03	Drug 11968.06
2:	1		1	1	2	0.03	Drug 11710.68
3:	1		2	1	1	0.03	Drug 110002.04
4:	1		2	1	2	0.03	Drug 78500.50
5:	2		1	1	1	0.03	Drug 11998.25
6:	2		1	1	2	0.03	Drug 11226.46

# Cost-effectiveness analysis

```
ce_sim <- econmod$summarize()

cea_pw_out <- cea_pw(ce_sim, comparator = 1,
                      dr_qalys = .03, dr_costs = .03)

icer_tbl(cea_pw_out, colnames = strategies$strategy_name)
```

	SOC	New
Incremental QALYs	"-"	"3.79 (3.26, 4.38)"
Incremental costs	"-"	"191,540 (164,466, 251,826)"
Incremental NMB	"-"	"-2,280 (-60,588, 34,068)"
ICER	"-"	"50,602"
Conclusion	"-"	"Not cost-effective" <i>(default WTP in icer_tbl() is \$50,000)</i>

# Steps with `hesim`

## 1. Model set-up

- Specify the treatment strategies, target population(s), and model structure
  - `hesim_data()`

## 2. Parameters

- Estimate or define the parameters of the economic model
  - `flexsurvreg_list()`, `stateval_tb1()`

## 3. Simulation

### a. Construction of model

- Create an economic model—consisting of separate statistical models for disease progression, costs, and utilities—that simulate outcomes as a function of *input data* (derived from Step 1) and *parameters* (from Step 2)
- `create_IndivCtstmTrans()`, `create_Statevals()`, `IndivCtstm$new()`

### b. Simulation of outcomes

- Simulate outcomes (disease progression, costs, and quality-adjusted life-years (QALYs)) using the model constructed in Step 3
- `$sim_disease()`, `$sim_stateprobs()`, `$sim_qalys()`, `$sim_costs()`

## 4. Cost-effectiveness analysis

# Complete R script

The screenshot shows an RStudio interface with a code editor containing a script named '04-mstate.R'. The script is a complete R program for a survival analysis model, starting with library imports and ending with a 'hesim\_dat' object. The code is annotated with comments and uses various R packages like rcea, hesim, data.table, ggplot2, and flexsurv.

```
## ---- Overview -----
## @knitr R-setup
library("rcea")
library("hesim")
library("data.table")
library("ggplot2")
library("flexsurv")

set.seed(101) # Make random number generation reproducible

## ---- Model setup -----
tmat <- rbind(
  c(NA, 1, 2),
  c(NA, NA, 3),
  c(NA, NA, NA)
)
colnames(tmat) <- rownames(tmat) <- c("Stable", "Progression", "Dead")
print(tmat)

## @knitr hesim_data
n_patients <- 1000
patients <- data.table(
  patient_id = 1:n_patients,
  age = rnorm(n_patients, mean = 45, sd = 7),
  female = rbinom(n_patients, size = 1, prob = .51)
)

states <- data.table(
  state_id = c(1, 2),
  state_name = c("Stable", "Progression") # Non-death health states
)
n_states <- nrow(states)

strategies <- data.frame(
  strategy_id = 1:2,
  strategy_name = c("SOC", "New")
)
n_strategies <- nrow(strategies)

hesim_dat <- hesim_data(
  strategies = strategies,
  patients = patients,
  states = states
)
```

At the bottom of the screen, there is a status bar with the text '156:1 # Exercises ▾' and a 'R Script' tab.

# Tutorial

rcea **0.0.1**

Reference

Tutorials ▾



## Semi-Markov Multi-state Model

2020-10-10

Source: [vignettes/04-mstate.Rmd](#)

### 1 Overview

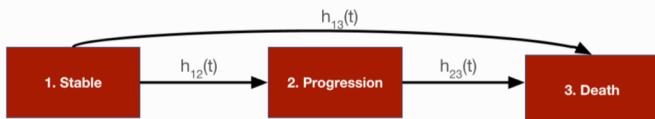
In this tutorial we use a continuous time state transition model (CTSTM) and relax many of the assumptions made in cohort discrete time state transition models (DTSTMs). First, since the model is in continuous time we do not require model cycles. Second, we estimate the

### Contents

- 1 Overview
- 2 Background
- 3 Model setup
- 4 Parameter estimation
- 5 Simulation
- 6 Cost-effectiveness analysis

<https://hesim-dev.github.io/rcea/articles/04-mstate.html>

To illustrate, we simplify the sick-sicker model so that it only contains three health states and modify the states—*Stable*, *Progression*, and *Dead*—to mimic an oncology application where patients transition from stable disease to progression to death. There are three transitions: (1) *Stable* to *Progression*, (2) *Stable* to *Dead*, and (3) *Progression* to *Dead*.



The following packages and settings will be used for the analysis. Note that while individual-level simulations can be computationally intensive, they run very quickly in `hesim` because they are implemented fully in C++ under the hood. You can learn more by looking at the `hesim` multi-state modeling vignette.

```
library("rcea")
library("hesim")
library("data.table")
library("ggplot2")
library("flexsurv")

set.seed(101) # Make random number generation reproducible
```

## Exercise 4: Semi-Markov multi-state model

- *Review and run the R-script “04-mstate.R”*

## **Cost-effectiveness analysis**

# Cost-effectiveness analysis

- The optimal treatment strategy is the one that maximizes the expected net monetary benefit (NMB)

$$NMB(j, \theta) = e_j(\theta) \cdot k - c_j(\theta)$$

Effectiveness  
(e.g., QALYs)      Willingness  
to pay                  Costs

*j* indexes a treatment strategy  
*θ* indexes a parameter set

$$j^* = \operatorname{argmax}_j E_\theta[NMB(j, \theta)]$$

*j\** is treatment with highest NMB  
averaged across all sets of *θ*

- Can also assess optimal strategy using incremental cost-effectiveness ratio (ICER). Treatment 1 is preferred to treatment 0 if<sup>1</sup>

$$k > \frac{E_\theta[c_1(\theta) - c_0(\theta)]}{E_\theta[e_1(\theta) - e_0(\theta)]} = ICER$$

<sup>1</sup>Only true if both incremental costs (numerator) and incremental effectiveness (denominator) are both positive. Treatment 1 dominates treatment 0 if it is more effective and less costly. Treatment 1 is dominated by treatment 0 if it is less effective and more costly. Treatment 1 is preferred to treatment 0 if it is less costly and less effective when  $k < ICER$ .

# Economic models with **hesim**

1. Model set-up
2. Parameters
3. Simulation
  - a. Construction of model
  - b. Simulation of outcomes
4. Cost-effectiveness analysis

# Cost-effectiveness analysis

- CEA functions from `hesim` to summarize decision uncertainty and `ggplot2` for visualization

```
library("hesim")
library("ggplot2")
theme_set(theme_minimal()) # Set ggplot2 theme
```

- CEA can be performed using the `cea()` and `cea_pw()` functions
  - `cea()` summarizes results by taking into account each treatment strategy in the analysis
  - `cea_pw()` summarizes “pairwise” results in which each treatment is compared to a comparator
- We will use these functions to analyze the distribution of costs and QALYs produced from the simulation of the semi-Markov CTSTM (a `hesim::ce` object)

# Cost-effectiveness analysis

```
ce_sim <- readRDS("ce_sim.rds")
```

\$costs

	category	dr	sample	strategy_id	costs	grp_id
1:	Drug	0.03	1		23678.74	1
2:	Drug	0.03	1		188502.54	1
3:	Drug	0.03	2		23224.71	1
4:	Drug	0.03	2		184885.23	1
5:	Drug	0.03	3		23011.36	1
---						
2996:	total	0.03	498		250188.10	1
2997:	total	0.03	499		63343.39	1
2998:	total	0.03	499		239276.32	1
2999:	total	0.03	500		50651.70	1
3000:	total	0.03	500		233785.48	1

\$qalys

	dr	sample	strategy_id	qalys	grp_id
1:	0.00	1		11.114224	1
2:	0.00	1		18.549477	1
3:	0.00	2		10.443717	1
4:	0.00	2		17.221927	1
5:	0.00	3		10.404786	1
---					
1996:	0.03	498		11.460201	1
1997:	0.03	499		8.406517	1
1998:	0.03	499		11.858450	1
1999:	0.03	500		8.063408	1
2000:	0.03	500		12.152292	1

# Cost-effectiveness analysis

```
wtp <- seq(0, 250000, 500) # willingness to pay per QALY

cea_pw_out <- cea_pw(ce_sim, comparator = 1, # Comparator is SOC (ID = 1)
                      dr_qalys = 0.03, dr_costs = 0.03,
                      wtp)

cea_out <- cea(ce_sim,
                dr_qalys = 0.03, dr_costs = 0.03,
                k = wtp)
```

# Cost-effectiveness plane

```
cea_pw_out$delta
```

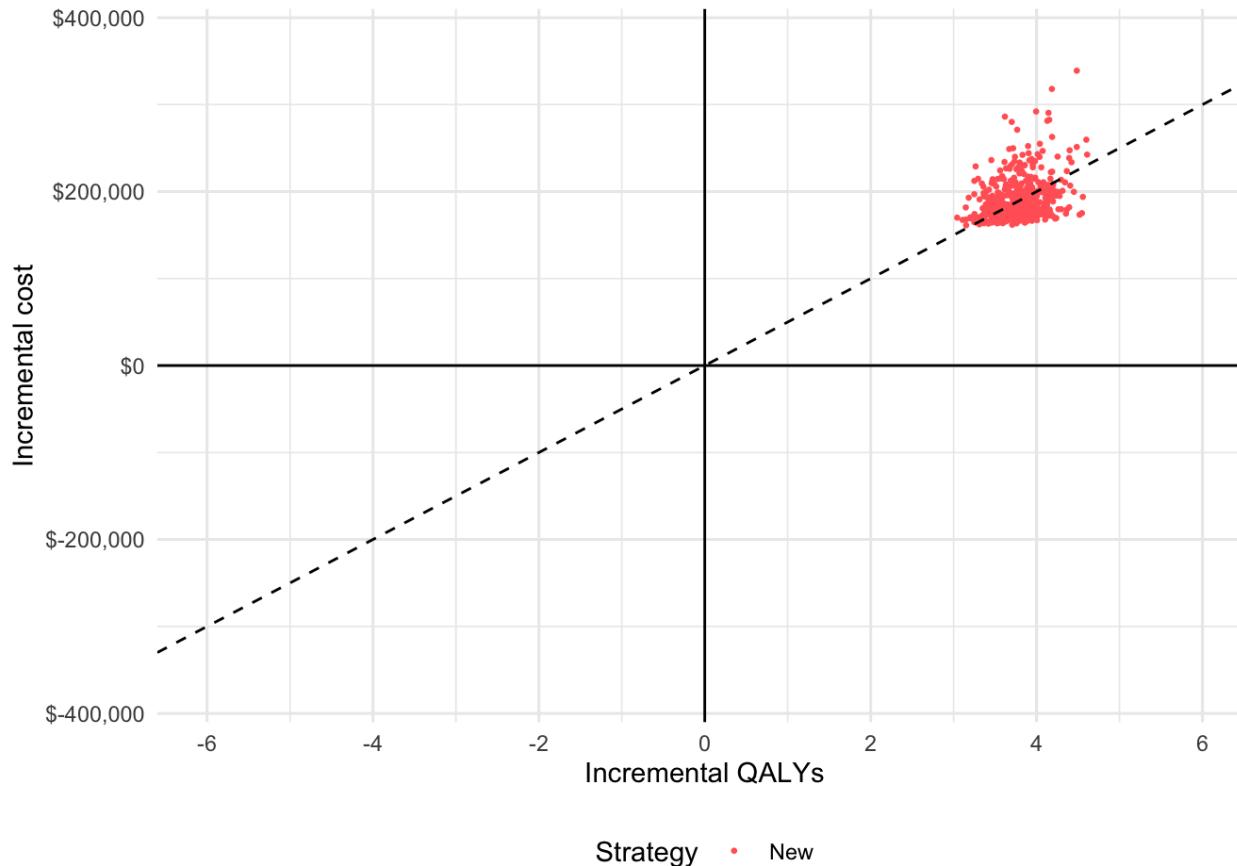
	sample	strategy_id	grp_id	ie	ic
1:	1		2	1 3.900703	173752.1
2:	2		2	1 3.700907	280151.1
3:	3		2	1 4.140923	207748.0
4:	4		2	1 3.765042	202362.6
5:	5		2	1 4.003303	188159.4
---					
496:	496		2	1 3.635187	178517.2
497:	497		2	1 3.903630	169764.4
498:	498		2	1 3.539451	180691.1
499:	499		2	1 3.451933	175932.9
500:	500		2	1 4.088884	183133.8

# Cost-effectiveness plane

```
strategy_factor <- function (x) {  
  factor(x, levels = 1:2, labels = c("soc", "New"))  
}  
format_dollar <- function(x) {  
  paste0("$", formatC(x, format = "d", big.mark =  
",",))  
}
```

```
ylim <- max(cea_pw_out$delta[, ic]) * 1.1  
xlim <- ceiling(max(cea_pw_out$delta[, ie]) * 1.1)  
  
ggplot(cea_pw_out$delta,  
       aes(x = ie, y = ic, col = strategy_factor(strategy_id))) +  
  geom_jitter(size = .5) +  
  xlab("Incremental QALYs") +  
  ylab("Incremental cost") +  
  scale_y_continuous(limits = c(-ylim, ylim),  
                     labels = format_dollar) +  
  scale_x_continuous(limits = c(-xlim, xlim), breaks = seq(-6, 6, 2)) +  
  theme(legend.position = "bottom") +  
  scale_colour_discrete(name = "Strategy") +  
  geom_abline(slope = 50000, linetype = "dashed") +  
  geom_hline(yintercept = 0) +  
  geom_vline(xintercept = 0)
```

# Cost-effectiveness plane



# Cost-effectiveness acceptability curve – Simultaneous comparison

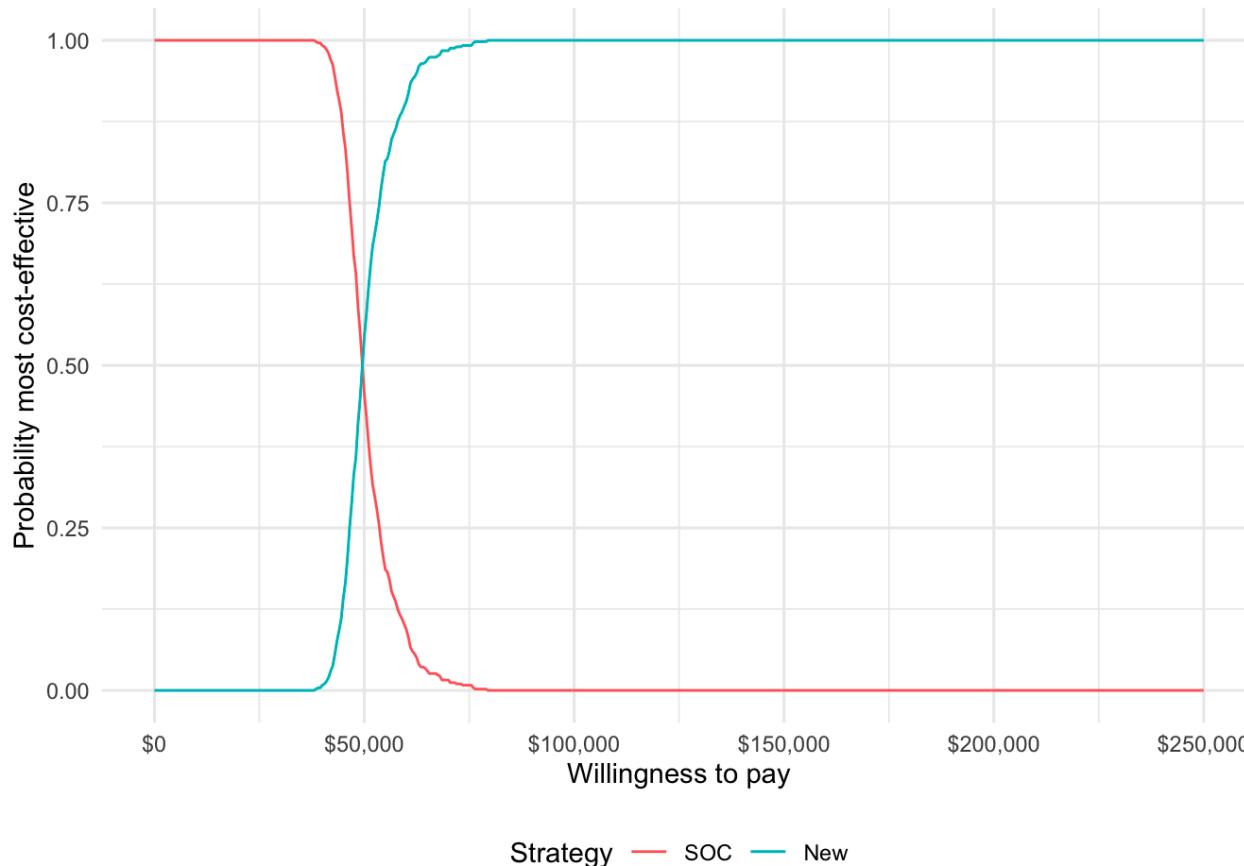
```
cea_out$mce
```

	k	strategy_id	grp_id	best	prob
1:	0	1	1	1	1
2:	0	2	1	0	0
3:	500	1	1	1	1
4:	500	2	1	0	0
5:	1000	1	1	1	1
---					
998:	249000	2	1	1	1
999:	249500	1	1	0	0
1000:	249500	2	1	1	1
1001:	250000	1	1	0	0
1002:	250000	2	1	1	1

# Cost-effectiveness acceptability curve – Simultaneous comparison

```
ggplot(cea_out$mce,
       aes(x = k, y = prob, col = strategy_factor(strategy_id))) +
  geom_line() +
  xlab("willingness to pay") +
  ylab("Probability most cost-effective") +
  scale_x_continuous(breaks = seq(0, max(wtp), length.out = 6),
                     label = format_dollar) +
  theme(legend.position = "bottom") +
  scale_colour_discrete(name = "Strategy")
```

## Cost-effectiveness acceptability curve – Simultaneous comparison



## Value of perfect information

- The expected value of perfect information (EVPI) combines the probability of being most effective with the *magnitude* of the expected NMB
- Intuitively, EVPI is the amount that a decision maker would be willing to pay to collect additional data and completely eliminate uncertainty
- Mathematically, the EVPI is defined as the difference between the maximum expected NMB given perfect information and the maximum expected NMB given current information

$$EVPI = E_{\theta} [\max_j NMB(j, \theta)] - \max_j E_{\theta} [NMB(j, \theta)]$$

*NMB for optimal treatment at each random draw of the parameters*

*NMB of treatment that is optimal when averaged across all parameter draws*

# Value of perfect information

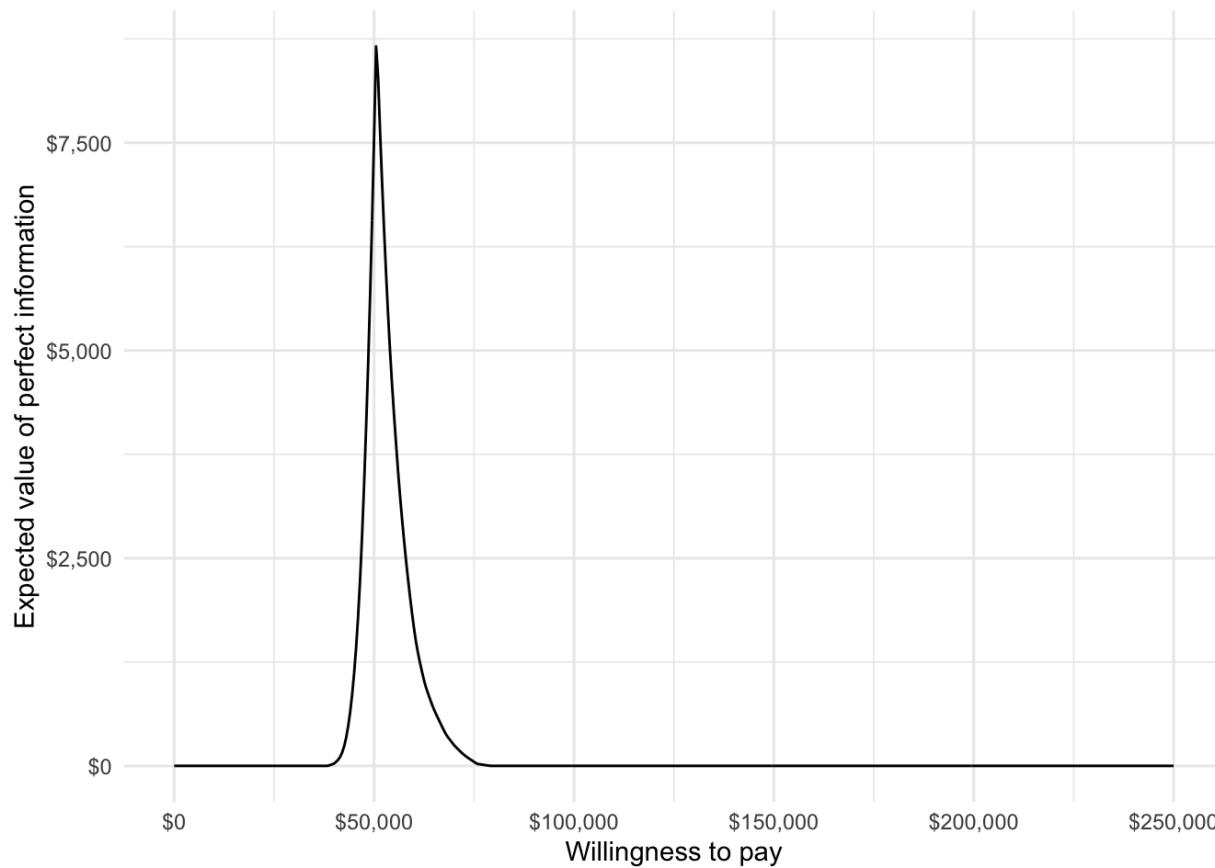
```
cea_out$evpi
```

```
  grp_id      k best    enmbci    enmbpi        evpi
1:     1      0   1 -115243.22 -115243.22 7.275958e-11
2:     1    500   1 -110620.84 -110620.84 -4.365575e-11
3:     1   1000   1 -105998.46 -105998.46 4.365575e-11
4:     1   1500   1 -101376.08 -101376.08 0.000000e+00
5:     1   2000   1 -96753.71 -96753.71 0.000000e+00
---
497:    1 248000   2 3297781.34 3297781.34 9.313226e-10
498:    1 248500   2 3305188.05 3305188.05 -4.656613e-10
499:    1 249000   2 3312594.76 3312594.76 0.000000e+00
500:    1 249500   2 3320001.46 3320001.46 -4.656613e-10
501:    1 250000   2 3327408.17 3327408.17 -9.313226e-10
```

# Value of perfect information

```
ggplot(cea_out$evpi, aes(x = k, y = evpi)) +  
  geom_line() +  
  xlab("willingness to pay") +  
  ylab("Expected value of perfect information") +  
  scale_x_continuous(breaks = seq(0, max(wtp), length.out = 6),  
                     label = format_dollar) +  
  scale_y_continuous(label = format_dollar) +  
  theme(legend.position = "bottom")
```

## Value of perfect information



# Complete R script

```
R 06-cea.R x
Source on Save Run Source
1 ## ---- Overview -----
2 ## @knitr R-setup
3 library("hesim")
4 library("ggplot2")
5 theme_set(theme_minimal()) # Set ggplot2 theme
6
7 ## ---- Application -----
8 ## @knitr conduct-cea
9 ce_sim <- readRDS("ce_sim.rds") # Load cost-effectiveness object
10 head(ce_sim)
11
12 wtp <- seq(0, 250000, 500) # Willingness to pay per QALY
13 cea_pw_out <- cea_pw(ce_sim, comparator = 1, # Comparator is SOC (ID = 1)
14                         dr_qalys = 0.03, dr_costs = 0.03,
15                         wtp)
16 cea_out <- cea(ce_sim,
17                  dr_qalys = 0.03, dr_costs = 0.03,
18                  k = wtp)
19
20 ## ---- Cost-effectiveness plane -----
21 ## @knitr helper-functions
22 strategy_factor <- function(x) {
23   factor(x, levels = 1:2, labels = c("SOC", "New"))
24 }
25
26 format_dollar <- function(x) {
27   paste0("$", formatC(x, format = "d", big.mark = ","))
28 }
29
30 ## @knitr ceplane-plot
31 ylim <- max(cea_pw_out$delta[, ic]) * 1.1
32 xlim <- ceiling(max(cea_pw_out$delta[, ie]) * 1.1)
33 ggplot(cea_pw_out$delta,
34        aes(x = ie, y = ic, col = strategy_factor(strategy_id))) +
35        geom_jitter(size = .5) +
36        xlab("Incremental QALYs") +
37        ylab("Incremental Costs") +
38        scale_color_manual(values = c("SOC" = "#31699b", "New" = "#e69138"))
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
59:1 # Application
```

# Tutorial

rcea **0.0.1**

Reference

Tutorials ▾



## Cost-effectiveness Analysis

2020-10-10

Source: vignettes/06-cea.Rmd

### Contents

1 Overview

2 Theory

3 Application

### 1 Overview

The prior tutorials have focused on constructing economic models to simulate disease progression, costs, and quality-adjusted life-years (QALYs). While incremental cost-effectiveness ratios (ICERs) have been computed and probabilistic sensitivity analysis (PSA) has been employed, we have not yet formalized cost-effectiveness analysis (CEA) or represented decision uncertainty.

<https://hesim-dev.github.io/rcea/articles/06-cea.html>

subgroups.

```
library("hesim")
library("ggplot2")
theme_set(theme_minimal()) # Set ggplot2 theme
```

### 2 Theory

CEA is based on estimating the net monetary benefit (NMB). For a given parameter set  $\theta$ , the NMB with treatment  $j$  is computed as the difference between the monetized health gains from an intervention less costs, or,

$$NMB(j, \theta) = e_j(\theta) \cdot k - c_j(\theta),$$

where  $e_j$  and  $c_j$  are measures of health outcomes (e.g. QALYs) and costs using treatment  $j$  respectively, and  $k$  is a decision makers willingness to pay (WTP) per unit of health outcomes. The optimal treatment is the one that maximizes the expected NMB,

$$j^* = \operatorname{argmax}_j E_\theta [NMB(j, \theta)].$$

For a pairwise comparison, treatment 1 is preferred to treatment 0 if the expected incremental net monetary benefit (INMB) is positive; that is, if  $E_\theta [INMB] > 0$  where the INMB is given by

$$INMB(\theta) = NMB(j=1, \theta) - NMB(j=0, \theta).$$

## Exercise 5: Cost-effectiveness analysis

- *Review and run the R-script “06-cea.R”*

# **Summary**

# So why R for CE modeling?

- One platform to do everything
  - parameter estimation
  - simulation
- More complex analysis and individual patient simulation
- Your problems are rarely unique
  - But even if they are, R facilitates development of custom models
- Easier to share and review
- Reproducible

# Cost-effectiveness analysis with R

- BCEA
- heemod
- hesim
- ...

## Why **hesim**?

- Focus on setting up and interpreting a model rather than implementation
  - Burdensome programming tasks have already been implemented and optimized
- Flexible enough to cover many problems
  - May need to write custom code for very complex or unique problems (beyond scope of course)
- Very fast!
  - IPS in **hesim** with 100 PSA iterations ran in .44 seconds; equivalent simulation in **mstate** package took 34 minutes (see [here](#))
  - Cohort model in **hesim** with 1,000 PSA iterations ran in 1 second (IPS in 9 seconds), while equivalent cohort model in **heemod** took 85 seconds (see [here](#))

# User interfaces with R Shiny

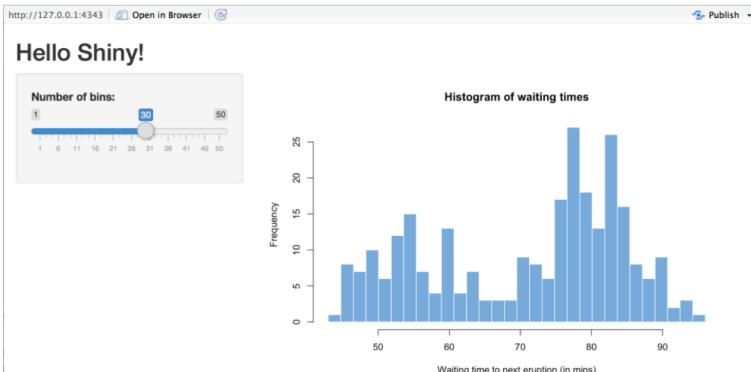
## LESSON 1

### Welcome to Shiny

Shiny is an R package that makes it easy to build interactive web applications (apps) straight from R. This lesson will get you started building Shiny apps right away.

```
install.packages("shiny")
```

### Examples



<https://shiny.rstudio.com/>

## Making Markov Models Shiny: A Tutorial

Robert Smith and Paul Schneider, SchHARR, University of Sheffield

### Sick Sicker Model in Shiny

Treatment Cost  
200

PSA runs  
1000

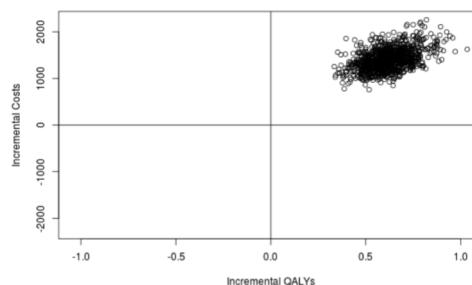
initial age  
10 25 80

Run / update model

### Results Table

Option	QALYs	Costs	Inc.QALYs	Inc.Costs	ICER
Treatment	18.59	100441.67	0.62	1406.24	2324.54
No Treatment	17.97	99035.43	NA	NA	NA

### Cost-effectiveness Plane



[https://r-hta.org/tutorial/markov\\_models\\_shiny/](https://r-hta.org/tutorial/markov_models_shiny/)

[Restore defaults](#)

Value of a QALY ⓘ \$ 150,000

[Save](#)[Run simulation](#)

## Treatment sequences ⓘ

[Show survival curves](#)

Line of therapy

Treatment regimen

Sequence number

I II III IV V

1L

gefitinib

erlotinib

afatinib

dacomitinib

osimertinib

T790M Status + - + - + -

2L

gefitinib

erlotinib

afatinib

dacomitinib

osimertinib

pbdc

pbdc + bevacizumab

pbdc

pbdc + nivolumab

pbdc + pembrolizumab

pbdc + atezolizumab

pbdc + bevacizumab

pbdc + bevacizumab + nivolumab

## Cost-effectiveness plane ⓘ

Sequence-comparator

I

II

III

IV

Expected outcomes

ICER

CE PLANE

CEAC

● Sequence II ● Sequence III ● Sequence IV — Value of a QALY

\$ 1,800,000

\$ 1,000,000

Incremental costs

\$ 0

- \$ 1,000,000

- \$ 1,800,000

-8.00 -6.00 -3.00 0.0 3.00 6.00 8.00

Incremental QALYs

Expected value of perfect information

 Restore defaults

Value of a QALY ⓘ \$ 150,000

 Save Run simulationR Code 

```
22 pats <- create_patients(n = 100)

23

24

25 txseq1 <- txseq(
26   first = c("gefitinib"),
27   second = c("osimertinib", "PBDC"),
28   second_plus = c("PBDC + atezolizumab", "PBDC + atezolizumab")
29 )

30

31 txseq2 <- txseq(
32   first = c("erlotinib"),
33   second = c("osimertinib", "PBDC"),
34   second_plus = c("PBDC + atezolizumab", "PBDC + atezolizumab")
35 )

36

37

38 txseq3 <- txseq(
39   first = c("afatinib"),
40   second = c("osimertinib", "PBDC"),
41   second_plus = c("PBDC + atezolizumab", "PBDC + atezolizumab")
42 )

43

44

45 txseq4 <- txseq(
46   first = c("osimertinib"),
47   second = c("PBDC", "PBDC"),
48   second_plus = c("PBDC + atezolizumab", "PBDC + atezolizumab")
```

pbdc + bevacizumab

pbdc + bevacizumab + nivolumab

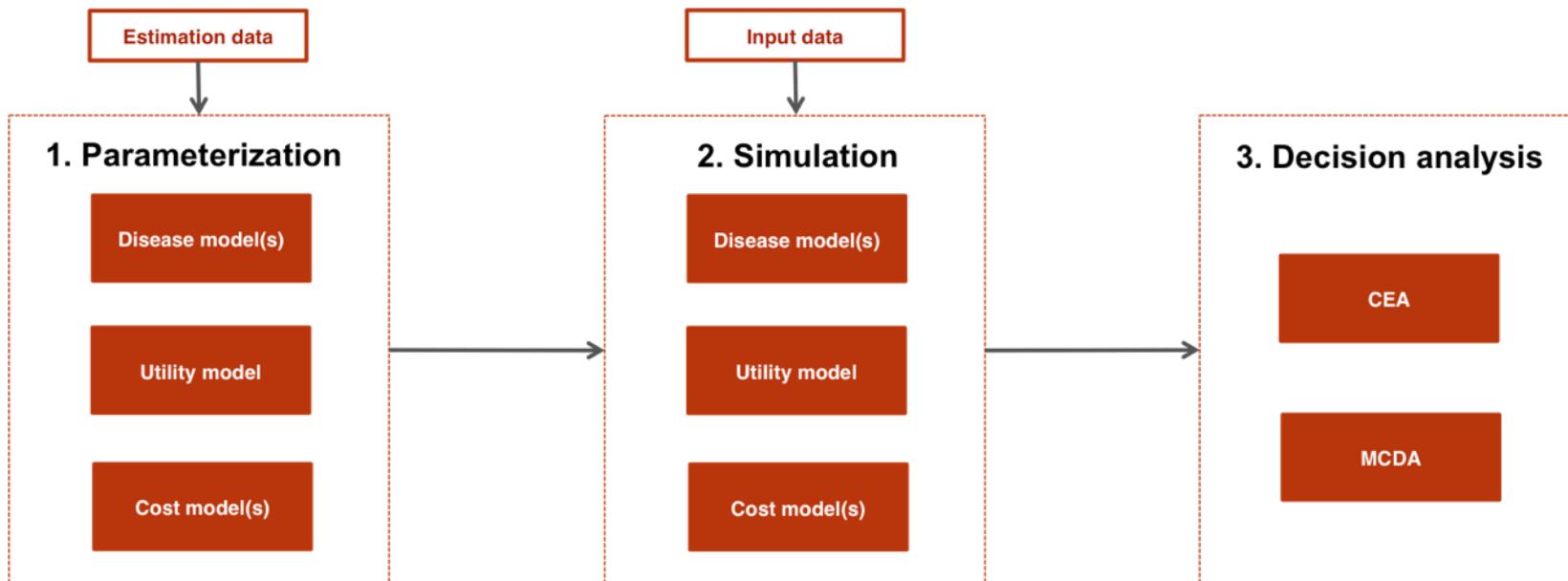


**Thank you**

[incerti.devin@gene.com](mailto:incerti.devin@gene.com)

[jeroen.jansen@ucsf.edu](mailto:jeroen.jansen@ucsf.edu)

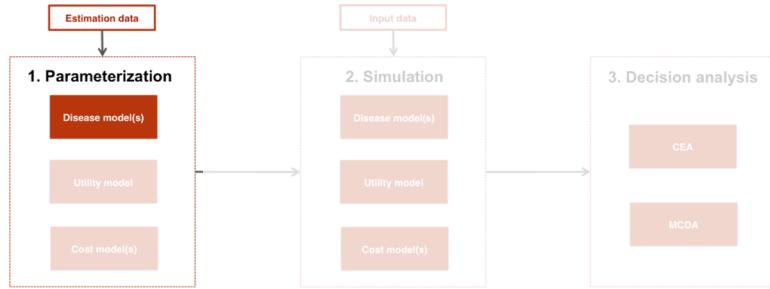
## Appendix – Building a model with **hesim**



# hesim overview

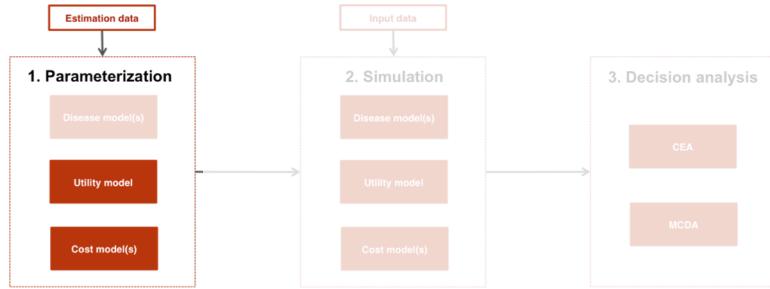
Economic model	<i>Object</i>	<i>Function</i>
Cohort discrete time state transition model (cDTSTM)	<code>CohortDtstm</code>	<code>create_CohortDtstm()</code> <code>CohortDtstm\$new()</code>
Individual-level continuous time state transition model (iCTSTM)	<code>IndivCtstm</code>	<code>IndivCtstm\$new()</code>
N-state partitioned survival model (PSM)	<code>Psm</code>	<code>Psm\$new()</code>

# hesim - Parameterization



Economic model		Disease progression		
		<i>Statistical model</i>	<i>Parameter Object</i>	<i>Model fit Function</i>
cDTSTM	<code>CohortDtstm</code>	Custom	<code>tparams_transprobs</code>	<code>define_model()</code>
		Multinomial logistic regression	<code>params_mlogit_list</code>	<code>multinom_list()</code>
iCTSTM	<code>IndivCtstm</code>	Multi-state model (joint likelihood)	<code>params_surv</code>	<code>flexsurv::flexsurvreg()</code>
		Multi-state model (transition-specific)	<code>params_surv_list</code>	<code>flexsurvreg_list()</code>
PSM	<code>Psm</code>	Independent survival models	<code>params_surv_list</code>	<code>flexsurvreg_list()</code>

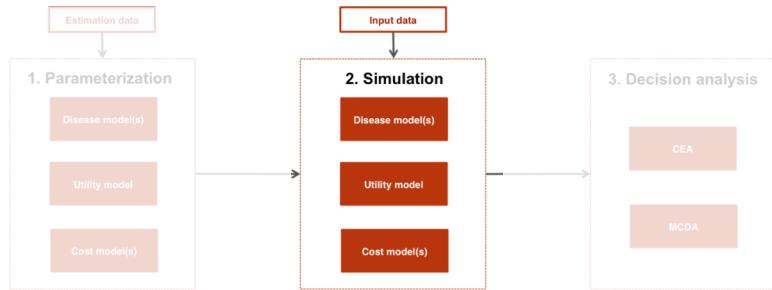
# hesim - Parameterization



Cost and utility		
<i>Statistical model</i>	<i>Parameter Object</i>	<i>Model fit Function</i>
Predicted means	<code>tparams_mean</code>	<code>stateval_tb1()</code>
	<code>tparams_mean</code>	<code>define_model()</code>
Linear model	<code>params_lm</code>	<code>Stats::lm()</code>

# hesim - Simulation

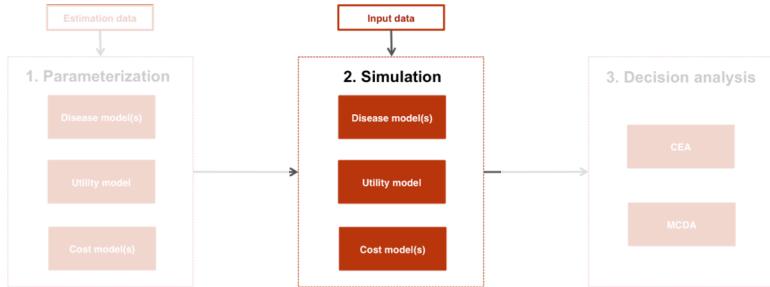
## Constructing an economic model



Economic model		Disease model	Utility model	Cost model(s)
cDTSTM	CohortDtstm	CohortDtstmTrans create_CohortDtstmTrans()	Statevals create_Statevals()	Statevals create_Statevals()
iCTSTM	IndivCtstm	IndivCtstmTrans create_IndivCtstmTrans()	Statevals create_Statevals()	Statevals create_Statevals()
PSM	Psm	PsmCurves create_PsmCurves()	Statevals create_Statevals()	Statevals create_Statevals()

# hesim - Simulation

## Simulating outcomes



Economic model		Disease progression	QALYs	Costs
cDTSTM	CohortDtstm	\$sim_stateprobs()	\$sim_qalys()	\$sim_costs()
iCTSTM	IndivCtstm	\$sim_disease() \$sim_stateprobs()	\$sim_qalys()	\$sim_costs()
PSM	Psm	\$sim_survival() \$sim_stateprobs()	\$sim_qalys()	\$sim_costs()