Discrete-time state transition models in R

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Class objectives

1. Review Markov cohort models

2. Learn how to implement a Markov cohort model in R
   - Basics in R
   - Briggs A et al model in R
3. Preview the assignment

Markov cohort model (review)

- Markov models in medical decision science simulate health transition over time (**discrete-** vs. continuous- time)

- Markov models are used to estimate **long-term** cost and health outcomes beyond the empirical study period, often attached to the end of a branch in decision trees

  e.g. For a cohort of patients who received treatment A and experienced post-treatment complication (with a probability of 0.2), what are their 5-year health and cost outcomes?

- Building blocks of Markov models include health states, transition probabilities, cycle, rewards or pay-offs
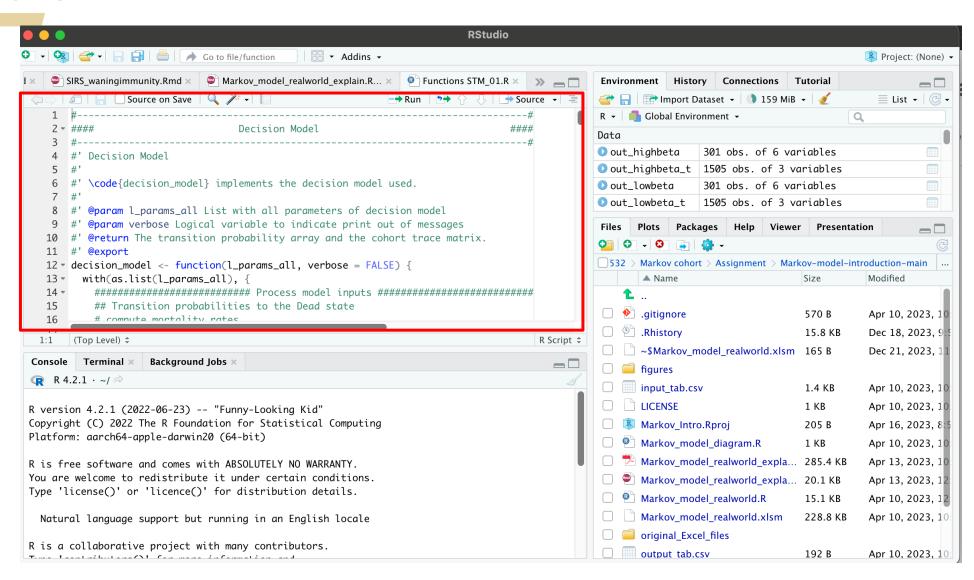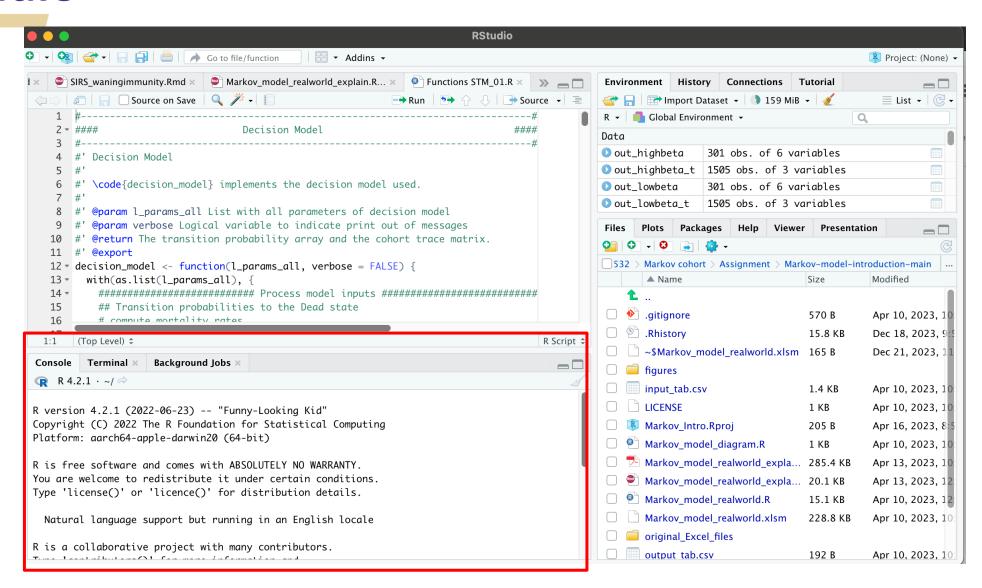
What is R?

- R is a free programming language and environment for statistical computing and graphics

- Users can add additional functionality such as mechanistic simulation modeling by using built-in functions, user-defined functions, and packages

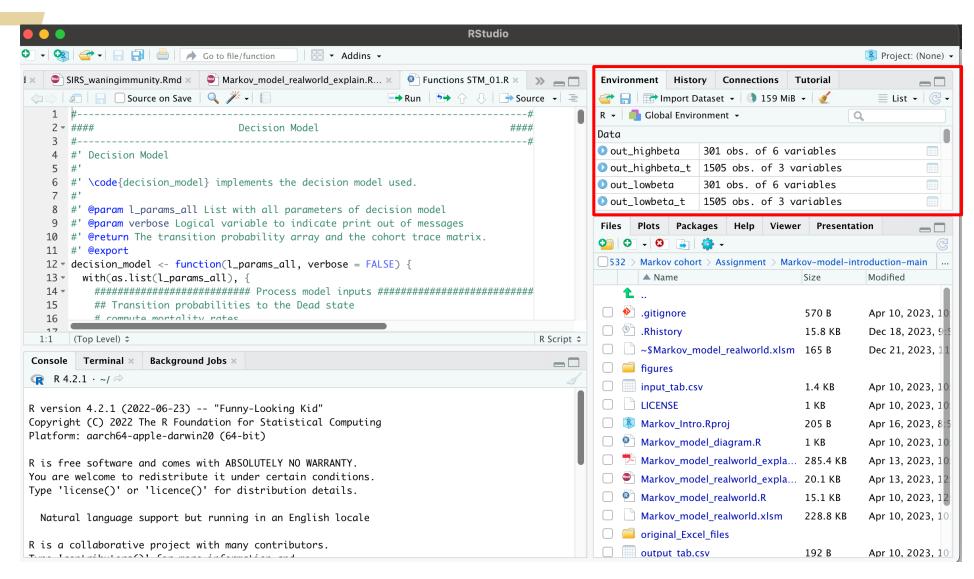- Any users can contribute to creating open-sourced R packages

R studio

- R studio is an IDE (Integrated Development Environment) for R where users can edit the code, import data, visualize graphics more easily compared to when writing the codes directly to R console.

R studio

R studio

R studio

R studio

Basics in R

- Creating variables of scalar, vector, and matrix: an operator '<-' assigns a value to a variable

Scalar

```
> age <- 65
> name <- 'Mary'
> print(age); print(name)
[1] 65
[1] "Mary"
```

Vector

```
> v_age <- c(25,34,65)
> v_name <- c('Tom','Kyu','Mary')
> print(v_age)
[1] 25 34 65
> print(v_name)
[1] "Tom"  "Kyu"  "Mary"
```

Matrix

```
> m_prob <- matrix(c(0.1,0.9,0,0.2,0.8,0,0.3,0.5,0.2),
+                  nrow = 3,
+                  dimnames = list(c("Healthy","Sick","Dead"),
+                                  c("Healthy","Sick","Dead")))
> m_prob
        Healthy Sick Dead
Healthy     0.1  0.2  0.3
Sick        0.9  0.8  0.5
Dead        0.0  0.0  0.2
```

Basics in R

```
> m1 <- m2 <- matrix(seq(1,9),nrow=3,byrow=FALSE)        > m3 <- m1 * m2
> m1                                                      > m4 <- m1 %*% m2
     [,1] [,2] [,3]
[1,]    1    4    7
[2,]    2    5    8
[3,]    3    6    9
```

- '*' operator implements element-wise multiplication between two matrices

```
> m3
     [,1] [,2] [,3]
[1,]    1   16   49
[2,]    4   25   64
[3,]    9   36   81
```

- '%*%' operator implements matrix multiplication between two matrices (dot product of each row vector (m1) and column vector (m2)

```
> m4
     [,1] [,2] [,3]              [,1] [,2] [,3]              [,1] [,2] [,3]
[1,]   30   66  102        [1,]    1    4    7        [1,]    1    4    7
[2,]   36   81  126   =    [2,]    2    5    8    X   [2,]    2    5    8
[3,]   42   96  150        [3,]    3    6    9        [3,]    3    6    9
```

Basics in R

- Array: a general data structure defined by a fixed number of dimensions; vectors (1D) and matrices (2D) are an example of array

```
pop<- array(data = rep(1,12),
            dim = c(2,3,2),
            dimnames = list(c("row1","row2"),
                            c("col1","col2","col3"),
                            c("Tx", "No Tx")))
> pop
, , Tx

     col1 col2 col3
row1    1    1    1
row2    1    1    1

, , No Tx

     col1 col2 col3
row1    1    1    1
row2    1    1    1
```

- List: a generic object consisting of an ordered collection of objects; can accommodate multiple data types

```
pop <- list( age = c(62,34,59),
             name = c("Mary","Kyu","Tom"),
             hometown = c("Seattle","Seoul","Rome"))
> print(pop)
$age
[1] 62 34 59

$name
[1] "Mary" "Kyu"  "Tom"

$hometown
[1] "Seattle" "Seoul"   "Rome"
> pop$name
[1] "Mary" "Kyu"  "Tom"
> pop$hometown[pop$name=='Kyu']
[1] "Seoul"
```
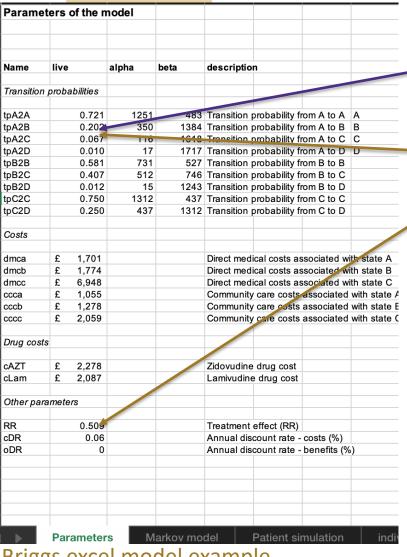
Basics in R

- A user-defined function

Name of the function   Arguments needed for the function

```r
f_simple <- function(n1, n2){

  sum <- n1 + n2          ←Operations
  prod <- n1 * n2

  return(c(sum,prod))  ← Return outputs
}
```

```r
> result <- f_simple(2,3)
> result
[1] 5 6
```

Translating an excel model in R

Category	Excel	R
Model organization	Define input parameters, run models, and compute outcomes in separate tabs	One code can streamline the works from defining input parameters, running models, to computing outcomes
Input parameters	Enter a value in a cell Link a cell to other cells	Assign a value to a variable Specify equations
Running Markov model	Repetitive calculation over rows	For-loop
Sensitivity analysis	Macro	For-loop

Translating an excel model in R

Parameters of the model

Name	live	alpha	beta	description	
Transition probabilities					
tpA2A	0.721	1251	483	Transition probability from A to A	A
tpA2B	0.202	350	1384	Transition probability from A to B	B
tpA2C	0.067	116	1618	Transition probability from A to C	C
tpA2D	0.010	17	1717	Transition probability from A to D	D
tpB2B	0.581	731	527	Transition probability from B to B	
tpB2C	0.407	512	746	Transition probability from B to C	
tpB2D	0.012	15	1243	Transition probability from B to D	
tpC2C	0.750	1312	437	Transition probability from C to C	
tpC2D	0.250	437	1312	Transition probability from C to D	
Costs					
dmca	£ 1,701			Direct medical costs associated with state A	
dmcb	£ 1,774			Direct medical costs associated with state B	
dmcc	£ 6,948			Direct medical costs associated with state C	
ccca	£ 1,055			Community care costs associated with state A	
cccb	£ 1,278			Community care costs associated with state B	
cccc	£ 2,059			Community care costs associated with state C	
Drug costs					
cAZT	£ 2,278			Zidovudine drug cost	
cLam	£ 2,087			Lamivudine drug cost	
Other parameters					
RR	0.509			Treatment effect (RR)	
cDR	0.06			Annual discount rate - costs (%)	
oDR	0			Annual discount rate - benefits (%)	

| ► | Parameters | Markov model | Patient simulation | indiv |

Briggs excel model example

MONOTHERAPY

A	B	C	D
0.721453	0.201845	0.066897	0.009804
	0.581081	0.406995	0.011924
		0.750143	0.249857

COMBINATION THERAPY (year 1,2)

A	B	C	D
0.85822	0.102739	0.034051	0.00499
	0.78677	0.207161	0.006069
		0.872823	0.127177

COMBINATION THERAPY (year 3+)

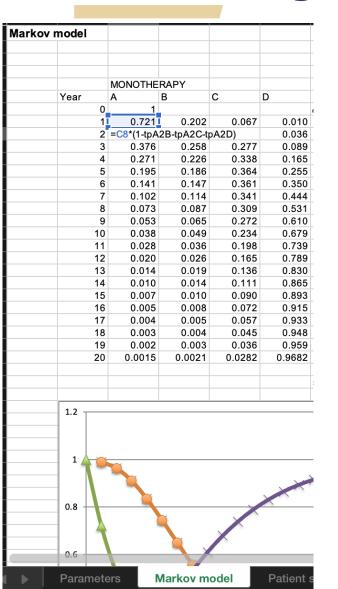| A	B	C	D
0.721453	0.201845	0.066897	0.009804
	0.581081	0.406995	0.011924
		0.750143	0.249857

Each cell in the transition probability matrix refers to a parameter value or a value calculated based on multiple parameter values
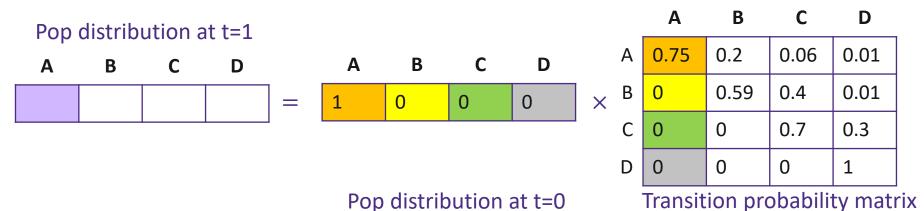
```r
tpA2B <- 0.202
tpA2C <- 0.067
tpA2D <- 0.010
tpA2A <- 1-tpA2B-tpA2C-tpA2D
tpB2C <- 0.407
tpB2D <- 0.012
tpB2B <- 1-tpB2C-tpB2D
tpC2D <- 0.250
tpC2C <- 1-tpC2D

mP_mono <- matrix(c(tpA2A,tpA2B,tpA2C,tpA2D,
            0,tpB2B,tpB2C,tpB2D,
            0,0,tpC2C,tpC2D,
            0,0,0,1),byrow = TRUE,nrow=4,
            dimnames = list(c('A','B','C','D'),c('A','B','C','D')))
rr <- 0.5
mP_comb1 <- matrix(c(1-tpA2B*rr-tpA2C-tpA2D,tpA2B*rr,tpA2C,tpA2D,
            0,tpB2B,tpB2C,tpB2D,
            0,0,tpC2C,tpC2D,
            0,0,0,1), byrow=TRUE,nrow=4,
            dimnames = list(c('A','B','C','D'),c('A','B','C','D')))
```

In R, parameters and transition probability matrix can be defined as a variable of scalar or matrix

The code makes the calculation more explicit, reducing the risk of transcription errors
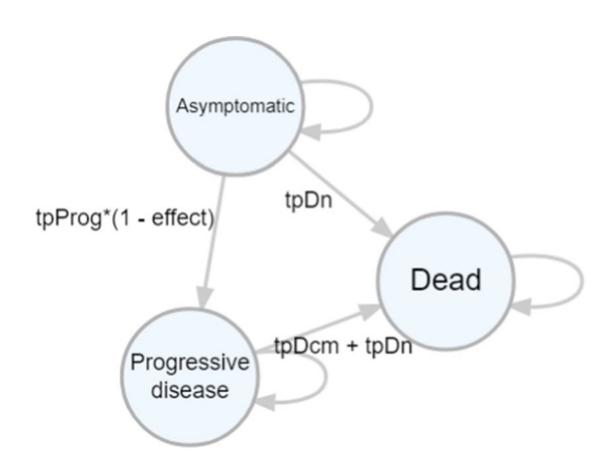
Translating an excel model in R

Markov model

MONOTHERAPY

Year	A	B	C	D
0	1			
1	0.721	0.202	0.067	0.010
2	=C8*(1-tpA2B-tpA2C-tpA2D)			0.036
3	0.376	0.258	0.277	0.089
4	0.271	0.226	0.338	0.165
5	0.195	0.186	0.364	0.255
6	0.141	0.147	0.361	0.350
7	0.102	0.114	0.341	0.444
8	0.073	0.087	0.309	0.531
9	0.053	0.065	0.272	0.610
10	0.038	0.049	0.234	0.679
11	0.028	0.036	0.198	0.739
12	0.020	0.026	0.165	0.789
13	0.014	0.019	0.136	0.830
14	0.010	0.014	0.111	0.865
15	0.007	0.010	0.090	0.893
16	0.005	0.008	0.072	0.915
17	0.004	0.005	0.057	0.933
18	0.003	0.004	0.045	0.948
19	0.002	0.003	0.036	0.959
20	0.0015	0.0021	0.0282	0.9682

Parameters | Markov model | Patient s

Pop distribution at t=1

A	B	C	D

=

A	B	C	D
1	0	0	0

Pop distribution at t=0

×

Transition probability matrix

	A	B	C	D
A	0.75	0.2	0.06	0.01
B	0	0.59	0.4	0.01
C	0	0	0.7	0.3
D	0	0	0	1

Repeat until t = 20

```
for (j in range(1,20)){
pop[, cycle = j] <-
    pop[, cycle = j - 1] %*% p_matrix
}
```

<- matrix multiplication

Repeat until t = 20

Review of Briggs A. et al. Model

- 3-state Markov cohort model

- The risk of progressing from Asymptomatic to Progressive Disease decreases by 50% with treatment

- Disease progression accelerates with age

- Progressive disease has excess mortality (tpDcm)

- There is cost for excess mortality among progressive diseases (i.e. transitional cost from progressive to dead)

Questions?

R session – Review and run the code

Open the R code (Markov_model_realworld_explain2_2024.Rmd)

R session – class exercise (optional)

- Make the following changes and discuss how ICER of treatment changes
  - Reduce the treatment efficacy from 0.5 to 0.2
  - Increase the starting age from 55 to 65

Assignments

- A new end-of-life care was approved based on the clinical trial result that it can reduce the excess mortality due to progressive disease by 50%. It costs $500 as one-time cost.

- Decision makers (e.g. clinicians) requested information on whether they should provide this end-of-life care in addition to the original treatment to reduce the disease progression.

- Using the same health state transition model, conduct a cost-effectiveness analysis considering three strategies: 1) without treatment 2) with treatment but no end-of-life care, 3) with both treatment and end-of-life care

- Provide a table of cost and QALY of three strategies and report ICER. It is optional to generate ICER graph.

Wrapping up

1. Review Markov cohort models

- Discrete-time health transition models simulate health transitions over time and estimate long-term health and cost outcomes

2. Learn how to implement a Markov cohort model in R

- R is a free programming language and has flexible functionality to build simulation models such as health transition models

- Compared to excel models, Rmodels can streamline the process of building the model in an explicit way in a single code file with lower risk of transcription error.