Heemod: time-varying values

Ivy Tsai

20231031

1. Review simple Markov model of HIV

RStudio

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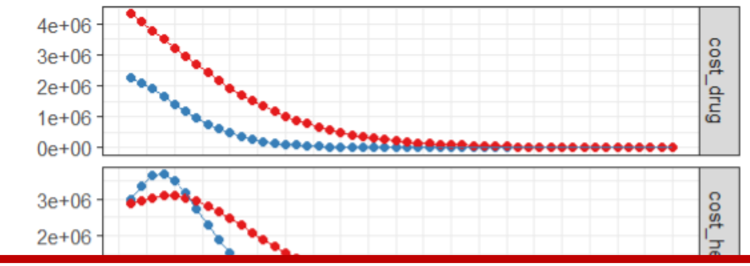
20231031 time varying value.R* | 20231024 Simple Markov Model HIV_D...

```r
#################################################################
# SIMPLE MARKOV MODELS (HOMOGENEIOUS)                           #
#################################################################
# 1. run external R: source(MyFunction_package.R)               #
# 2. set working directory                                      #
#    clear global environment                                   #
# 3. install and library(installr)                              #
#################################################################
#############################################################
# HIV example simple version
## Step 1: define transition for different strategy
#############################################################
mat_mono <- define_transition(
  #state name vector
  state_names = c("A","B","C", "D"),

  C,      0.202, 0.067, 0.010,
  0,      C,     0.407, 0.012,
  0,      0,     C,     0.250,
  0,      0,     0,     1
)
mat_mono
print(class(mat_mono))
print(c(mat_mono[1],mat_mono[5], mat_mono[16]))

#IVY's practice
mat_mono_matrix <- matrix(mat_mono)
print(class(mat_mono_matrix))

#parameter
rr <- 0.509


mat_comb <- define_transition(
```

171:1 (Untitled)

Console

object_summa...	List of 8	
res_mod	0 obs. of 14 variables	
state_A	List of 2	
state_B	List of 2	
state_C	List of 2	
state_D	List of 2	
strat_comb	List of 3	
strat_mono	List of 3	




```r
mat_comb <- define_transition(
  #state name vector
  state_names = c("A","B","C", "D"),

  C,      0.202*rr,   0.067*rr,   0.010*rr,
  0,      C,          0.407*rr,   0.012*rr,
  0,      0,          C,          0.250*rr,
  0,      0,          0,          1
)
plot(mat_mono)
plot(mat_comb)
```

31:28 (Untitled)

Console

3

RStudio

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20231031 time varying value.R* | 20231024 Simple Markov Model HIV_D...

```r
#################################################################
## Step 2: define values for each state
##
#################################################################
#parameter: cost_drug
#NOTE: ivy thinks two medication costs can be placed in define_parameters
cost_zido <- 2278
cost_lami <- 2086.5

state_A <- define_state(
  cost_health = discount(2756,0.06),
  cost_drug   = discount(dispatch_strategy(
    mono = cost_zido,
    comb = cost_zido + cost_lami
    ), 0.06),
  cost_total  = cost_health + cost_drug,
  life_year   = 1
)
state_A

state_B <- define_state(
  cost_health = discount(3052,0.06),
  cost_drug   = discount(dispatch_strategy(
    mono = cost_zido,
    comb = cost_zido + cost_lami
  ), 0.06),
  cost_total  = cost_health + cost_drug,
  life_year   = 1
)
state_B


state_C <- define_state(
```

90:25 | (Untitled) | R Script

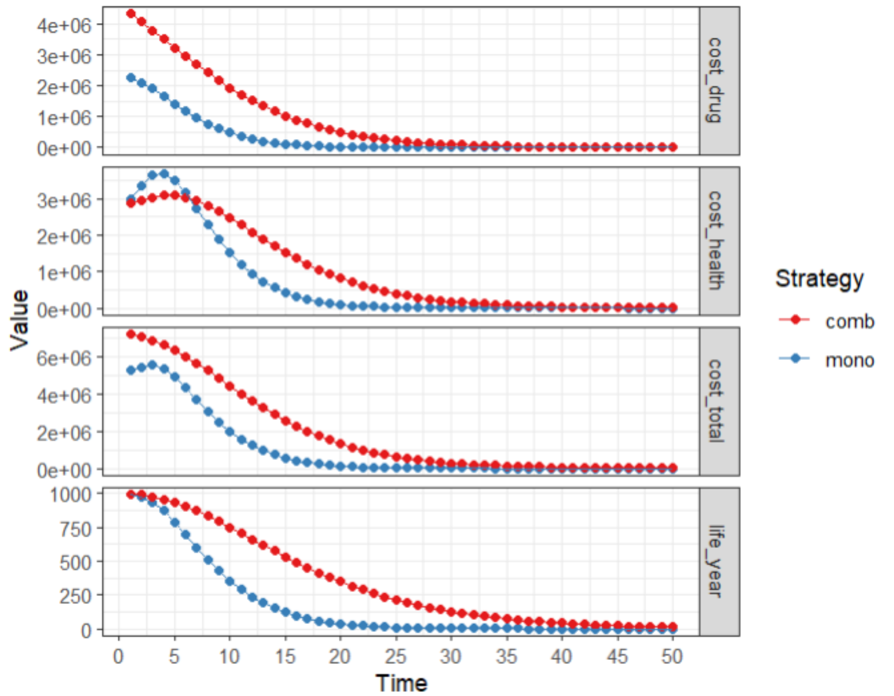
Console

Environment | History | Connections | Tutorial

Global Environment

object_summa...	List of 8
res_mod	0 obs. of 14 variables
state_A	List of 2
state_B	List of 2
state_C	List of 2
state_D	List of 2
strat_comb	List of 3
strat_mono	List of 3

Files | Plots | Packages | Help | Viewer | Presentation



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Go to file/function Addins Project: (None)

20231031 time varying value.R* | 20231024 Simple Markov Model HIV_D...*

Source on Save Run Source

```r

##########################################################
## Step 4: define strategy with matrix and states
##########################################################
strat_mono <- define_strategy(
  transition = mat_mono,
  A = state_A,
  B = state_B,
  C = state_C,
  D = state_D
)
strat_comb <- define_strategy(
  transition = mat_comb,
  A = state_A,
  B = state_B,
  C = state_C,
  D = state_D
)

##########################################################
## Step 5: run_model and summary
##          run_model
##########################################################
res_mod <- run_model(
  mono = strat_mono,
  comb = strat_comb,
  cycles = 50,
  cost = cost_total,
  effect = life_year
)

res_mod
object_summary <- summary(res_mod, threshold = c(1000,5000,6000,10000))
```

108:1 (Untitled) R Script

Console

Environment History Connections Tutorial

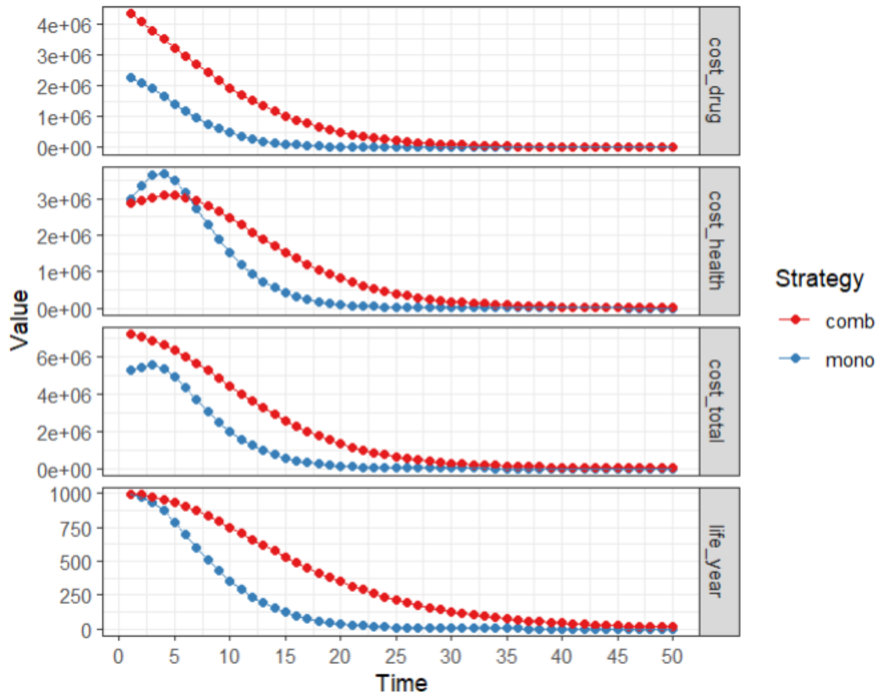
Import Dataset 304 MiB List

R Global Environment

object_summa...	List of 8
res_mod	0 obs. of 14 variables
state_A	List of 2
state_B	List of 2
state_C	List of 2
state_D	List of 2
strat_comb	List of 3
strat_mono	List of 3

Files Plots Packages Help Viewer Presentation

Zoom Export Publish



搜尋 英 下午 03:10 2023/10/26

RStudio

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Go to file/function | Addins | Project: (None)

20231031 time varying value.R* | 20231031 Simple Markov Model HIV_m...* | 20230617 hip fracture final 20201101 b...

Source on Save | Run | Source

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####################################################################
# 1. run external R: source(MyFunction_package.R)                  #
# 2. set working directory                                         #
#    clear global environment                                      #
# 3. install and library(installr)                                 #
####################################################################
####################################################################
# HIV example simple version
####################################################################
## Step 0: define parameters
####################################################################
param <- define_parameters(
         rr = 0.509,
  cost_zido = 2278,
  cost_lami = 2086.5
)

param
class(param)     #Ivy: it is a list!
length(param)    #Ivy: what is the first item in the list param?
param[1]         #param[1]: 0.509
param$rr         #param$rr: 0.509

####################################################################
## Step 1: define transition for different strategy
####################################################################
```

24:55 | (Untitled) | R Script

Environment | History | Connections | Tutorial

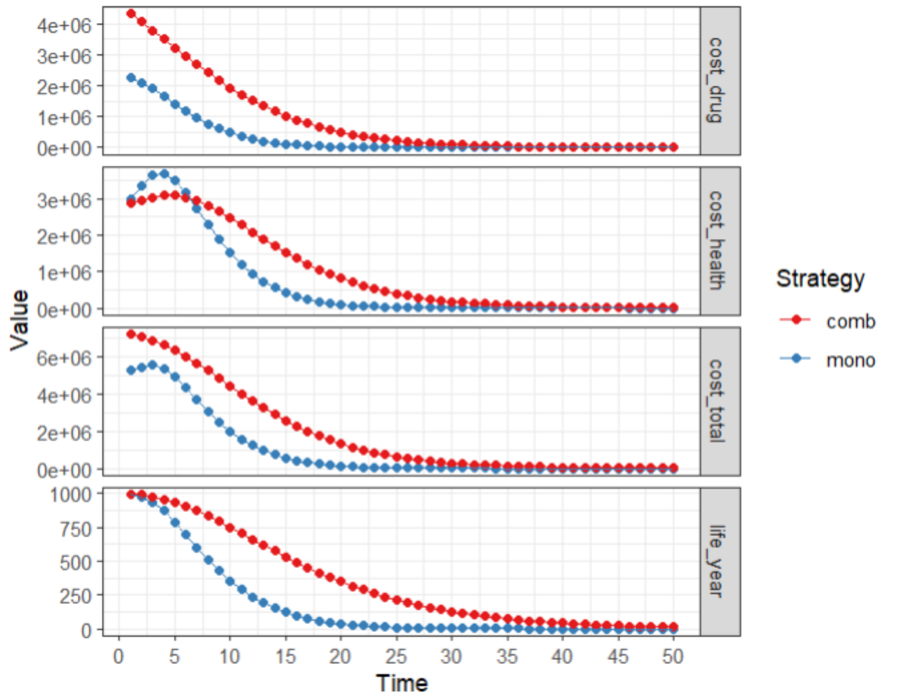
Import Dataset | 312 MiB | List

R | Global Environment

param	List of 3
res_mod	0 obs. of 14 variables
state_A	List of 2
state_B	List of 2
state_C	List of 2
state_D	List of 2
strat_comb	List of 3
strat_mono	List of 3

Files | Plots | Packages | Help | Viewer | Presentation

Zoom | Export | Publish



Console | Terminal | Background Jobs

R 4.3.0 · C:/Users/user/OneDrive - 國立陽明交通大學/DELL R to NYCU One Drive/R 講義/HEEMOD/

```
expr: ^0.509
env:  empty

> class(param)     #Ivy: it is a list!
```

搜尋 | 下午 03:29 | 2023/10/26

2. Example

Research Proposal

Cost-Effectiveness Analysis of Lenvatinib Plus Pembrolizumab in The 2nd Line Treatment for Advanced Endometrial Carcinoma

合併使用Lenvatinib及Pembrolizumab於晚期子宮內膜癌第二線治療之成本效益分析

Presenter: Szu-Ting Chiang (蔣思亭)

Advisor: Dr. Yi-Wen Tsai[1] (蔡憶文[1]), Dr. Ming-Neng Shiu[1] (許銘能[1]), Dr. Wai-Hou Li[2] (李偉浩[2])

Date: October 26, 2023

IRB No: YM111012E

1. National Yang Ming Chiao Tung University; 2. Cheng Hsin General Hospital

2.1. Analytic Framework of Cost-Effectiveness Analysis (2/6)

1. Define the elements of decision problem

Population:

Patients with advanced EC who *failed 1st line platinum-based chemotherapy.*

2nd line treatment:

- **Lenvatinib + pembrolizumab** (LP) **regimen**
- **Chemotherapy** (doxorubicin or paclitaxel)

Progressed from 2nd line
Supportive care

- **Cycle length:** 3 weeks
- **Time horizon (t):** 20 years
- **Discount rate (r):** 3% per year
- **Outcome variables:**
  - **Effectiveness** (E_I and E_C)
    → Life years (Lys), quality-adjusted life years (QALYs = Life year × quality of life).
  - **Directed medical costs** (C_I and C_C)
    → Medical cost reimbursed by NHI and NHI listing price.

2.1. Analytic Framework of Cost-Effectiveness Analysis (3/6)

2. Analytical Model building

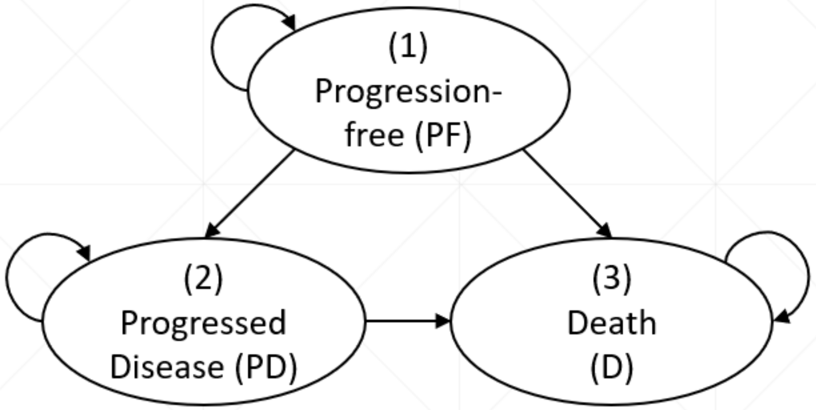
- **Decision analytical model:** Cohort-based Markov model

Population:

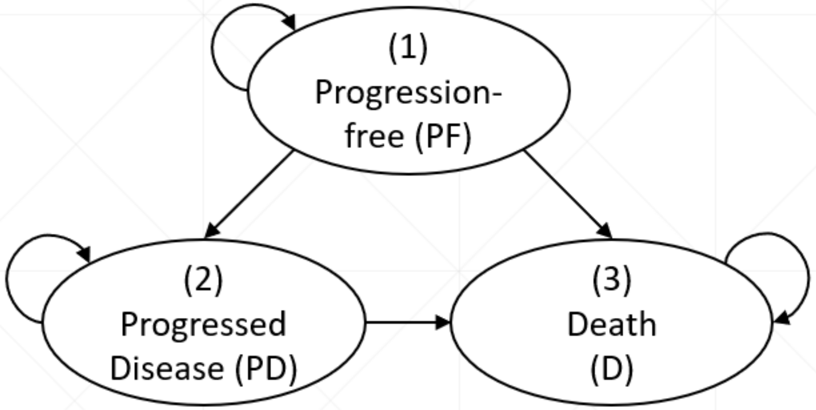
Patients with advanced EC who *failed 1st line platinum-based chemotherapy.*

2nd line treatment:

Lenvatinib + pembrolizumab (LP) **regimen**



Chemotherapy (doxorubicin or paclitaxel)



2.1. Analytic Framework of Cost-Effectiveness Analysis (4/6)

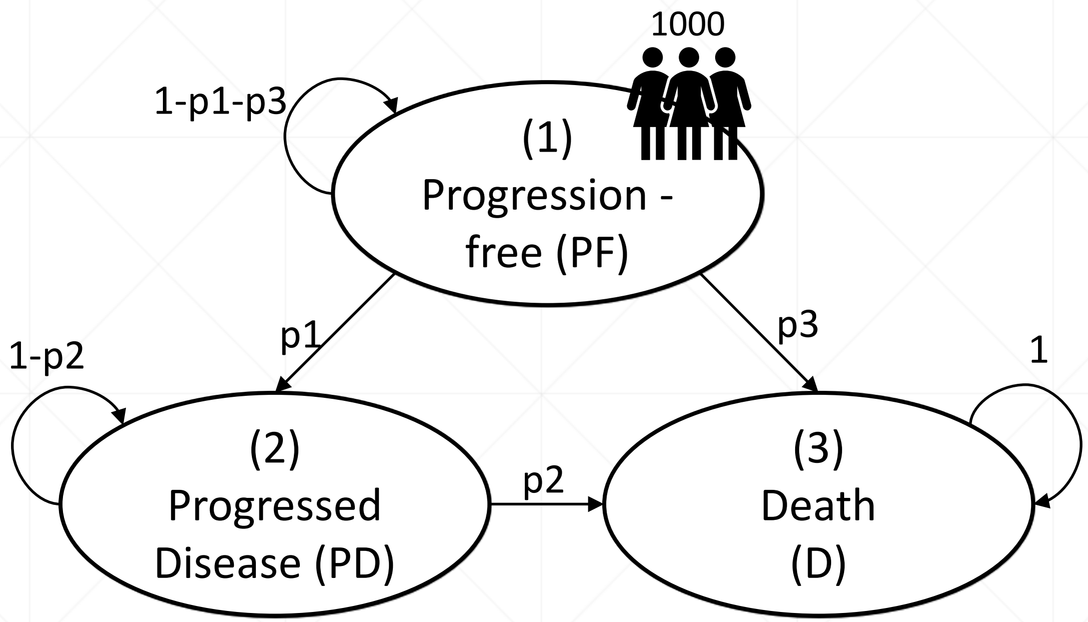
2. Analytical Model building

- **Decision analytical model:** Cohort-based Markov model
- **Disease model:** 3 health states

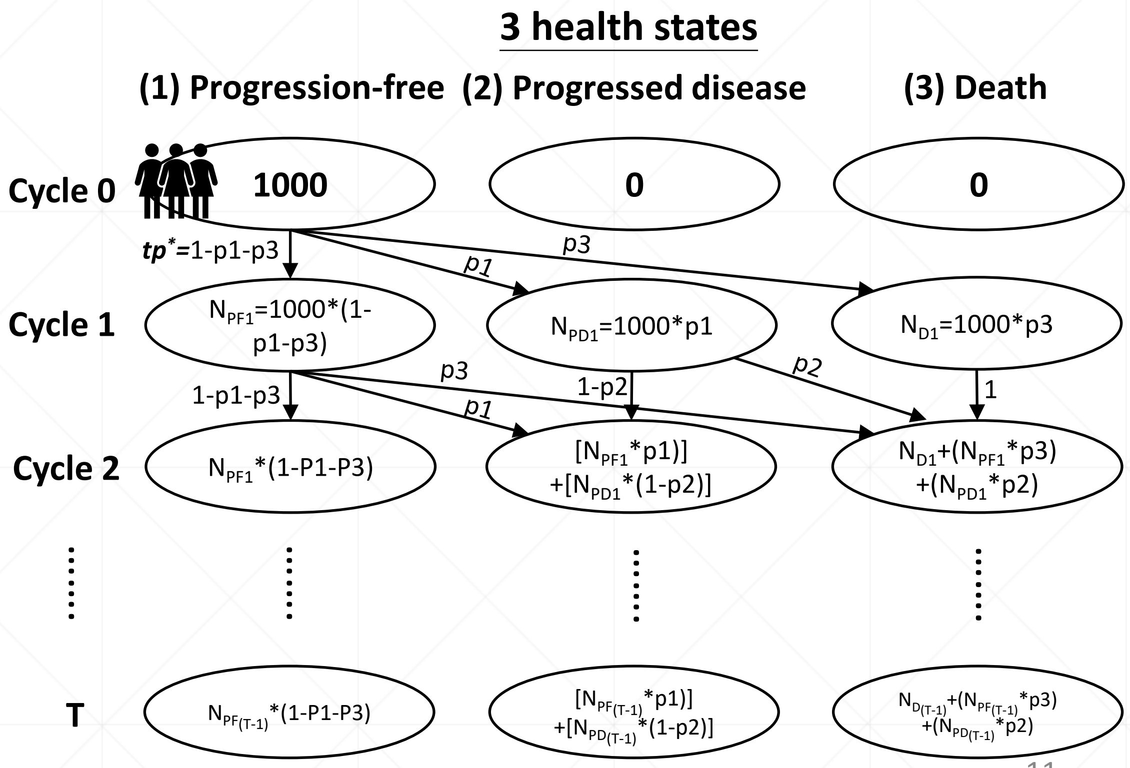
(1) Progression-free (PF): Disease stable and keep current treatment.

(2) Progressed disease (PD): Disease progressed and shift to supportive care.

(3) Death (D)



p = probability



*tp = transition probability

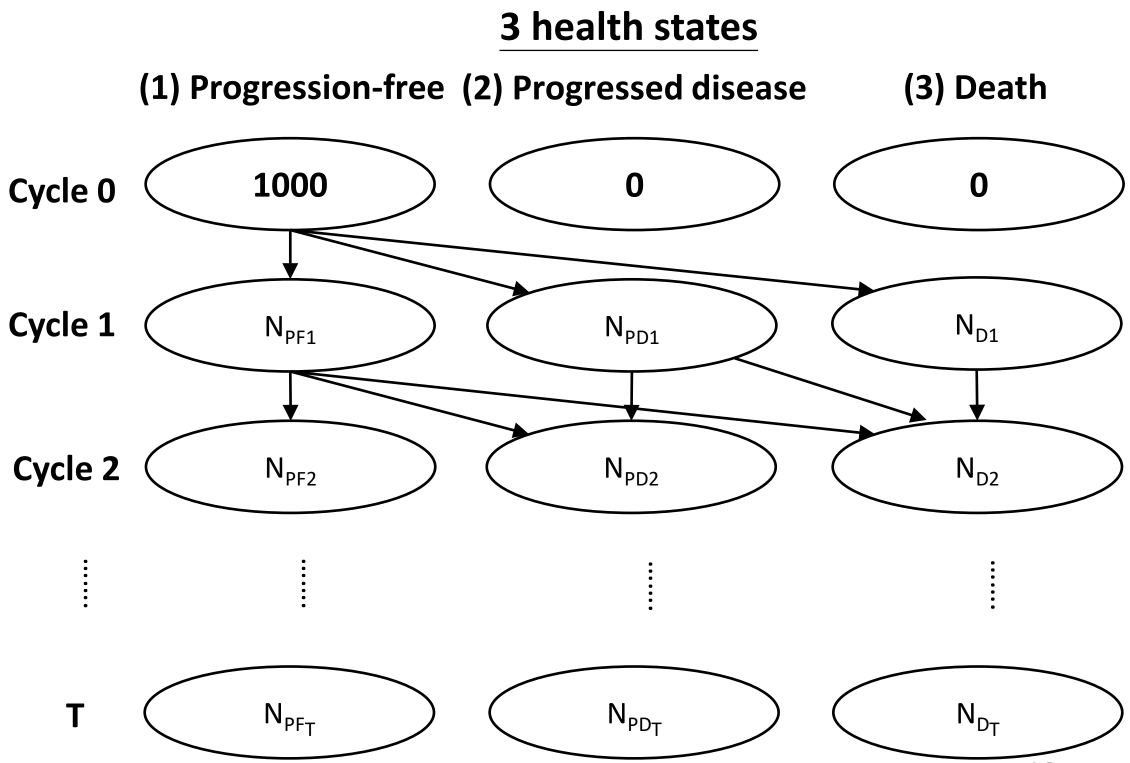
2.1. Analytic Framework of Cost-Effectiveness Analysis (4/6)

2. Analytical Model building

- **Decision analytical model:** Cohort-based Markov model
- **Cumulated outputs**: E_I, E_C, C_I, and C_C

$$E = \sum_{0}^{T} \frac{1}{(1+r)^t} E_t \qquad C = \sum_{0}^{T} \frac{1}{(1+r)^t} C_t$$

Cycle	Effectiveness (E) (Unit: LYs, QALYs*)	Cost (C) (Unit: NTD)
0	$E_0 = E_{PF_0}$	$C_0 = C_{PF_0}$
1	$E_1 = E_{PF_1} + E_{PD_1}$	$C_1 = C_{PF_1} + C_{PD_1} + C_{D_1}$
2	$E_2 = E_{PF_2} + E_{PD_2}$	$C_2 = C_{PF_2} + C_{PD_2} + C_{D_2}$
⋮	⋮	⋮
T	$E_T = E_{PF_T} + E_{PD_T}$	$C_T = C_{PF_T} + C_{PD_T} + C_{D_T}$



*LYs = life years, QALYs = quality-adjusted life years.

3. Time variables in heemod

Two stopwatches in heemod

Five steps in the simple Markov model are……..

HIV case study-model parameters

Table 2.2 Transition probabilities and costs for the HIV Markov model used in the case study (Chancellor *et al*. 1997)

State at start of cycle	State at end of cycle			
1. Annual transition probabilities				
(a) Monotherapy				
	State A	State B	State C	State D
State A	0.721	0.202	0.067	0.010
State B	0.000	0.581	0.407	0.012
State C	0.000	0.000	0.750	0.250
State D	0.000	0.000	0.000	0.000
(b) Combination therapy				
	State A	State B	State C	State D
State A	0.858 (1 – sum)	0.103 (0.202 × RR)	0.034 (0.067 × RR)	0.005 (0.010 × RR)
State B	0.000	0.787 (1 – sum)	0.207 (0.407 × RR)	0.006 (0.012 × RR)
State C	0.000	0.000	0.873 (1 – sum)	0.127 (0.25 × RR)
State D	0.000	0.000	0.000	1.000
2. Annual costs				
Direct medical	£1701	£1774	£6948	–
Community	£1055	£1278	£2059	–
Total	£2756	£3052	£9007	–

RR, relative risk of disease progression. Estimated as 0.509 in a meta-analysis.

The drug costs were £2278 (zidovudine) and £2086 (lamivudine).

In other words, which model inputs are time-dependent and, thus, could be expressed as functions of time?

2.1 EXPONENTIAL DISTRIBUTION

Hazard function: $h(t) = \lambda$ for $0 \leq t < \infty$ where λ is a positive constant and t is time.

2.2 WEIBULL DISTRIBUTION

Hazard function: $h(t) = \lambda\gamma t^{\gamma-1}$ for $0 \leq t < \infty$ where λ is a positive value and is the scale parameter, and γ is a positive value and is the shape parameter.

2.3 GOMPERTZ DISTRIBUTION

Hazard function: $h(t) = \lambda e^{\theta t}$ for $0 \leq t < \infty$ where λ is a positive value and is the scale parameter, and θ is the shape parameter.

HIV case study-model parameters

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In other words, which model inputs are time-dependent and, thus, could be expressed as functions of time?

- Costs (first two years?) and utility(maybe?)
- Transition probabilities!

$$tp(t_u) = 1 - \frac{S(t)}{S(t-u)} = 1 - \frac{e^{-H(t)}}{e^{-H(t-u)}} = 1 - \frac{e^{H(t-u)}}{e^{H(t)}} = 1 - e^{\{H(t-u)-H(t)\}}$$

$$S(t) = e^{-H(t)}$$

$$H(t) = \int_0^t h(u)du$$

$$h(t) = ?$$

$$h(t) = \lambda \emptyset_t$$

$$\lambda = ?$$

Constants, which are determined by time−varying X.

Two stopwatches in heemod

-
-

Which time variable?

Input	model_time	state_time
Age(t)		
Utility (t)		
Cost(t)		
Natural mortality		
S(t)		
h(t)		

RStudio

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20231031 time varying value.R* | 20231031 Simple Markov Model HIV_m...* | 20230617 hip fracture final 20201101 b...

```r
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# HEEMOD:Time-varying values                                 #
##############################################################
# 1. run external R: source(MyFunction_package.R)            #
# 2. set working directory                                   #
#    clear global environment                                #
# 3. install and library(installr)                           #
##############################################################
#1
source("C:/Users/user/OneDrive - 國立陽明交通大學/DELL R to NYCU One Drive/R 講義/MyRfunction
#2.
wd <- c("C:/Users/user/OneDrive - 國立陽明交通大學/DELL R to NYCU One Drive/R 講義/HEEMOD")
set_environment(wd)
#3
packages <- c("dplyr", "ggplot2", "tidyr","heemod","diagram","shape")
install_and_load_packages(packages)


############################################################
#  1. TWO time variables in HEEMOD
#     (1) model_time: duration through the model
#     (2) state_time: duration in a given state
#  2. Apply in THREE functions
#     (1) define_parameters
#     (2) define_state
#     (3) define_transition
############################################################
#2.(1)define parameters
param <- define_parameters(
  lambda = 0.9,                       #Ivy adds
      mr = exp(-state_time * lambda),    #Ivy: what is it?
     age = 50 + model_time)            #age increases with cycles
```

18:1 (Untitled) R Script

Console

Environment History Connections Tutorial

Global Environment

param	List of 3
res_mod	0 obs. of 14 variables
state_A	List of 2
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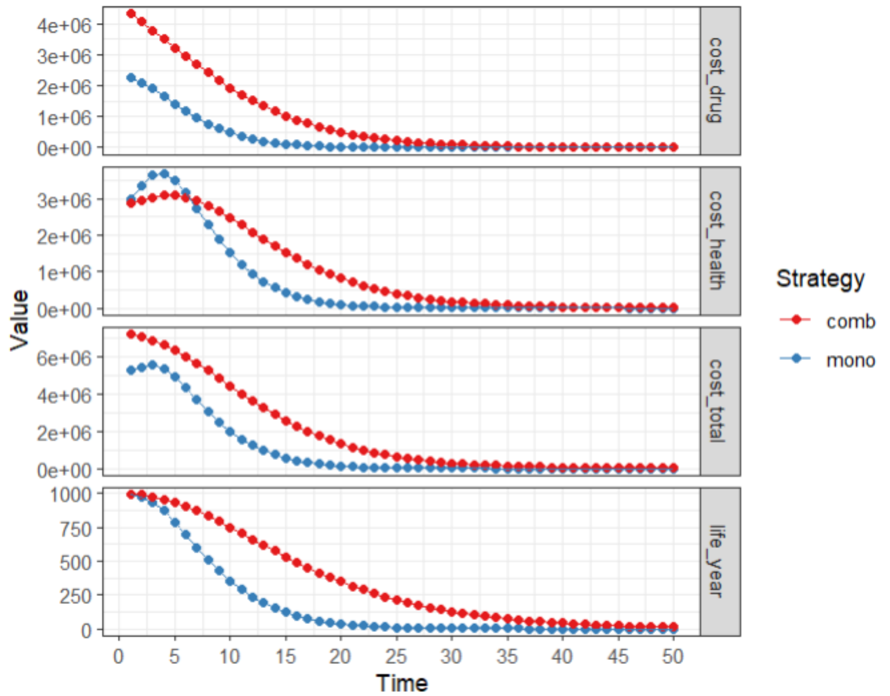
strat_comb	List of 3
strat_mono	List of 3

Files Plots Packages Help Viewer Presentation



下午 08:08
2023/10/26

RStudio

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20231031 time varying value.R* | 20231031 Simple Markov Model HIV_m...* | 20230617 hip fracture final 20201101 b...

```r
#     (1) define_parameters
#     (2) define_state
#     (3) define_transition
##################################################
#2.(1)define parameters
param <- define_parameters(
  lambda = 0.9,                        #Ivy adds
      mr = exp(-state_time * lambda),  #Ivy: what is it?
     age = 50 + model_time)            #age increases with cycles

#2.(2)define state
state_A <- define_state(
  cost_health = 100 - state_time,
  effect      = 10)

#2.(3)define_transition
f <- function(x) abs(sin(x))

mat_mono <- define_transition(
  C,    f(state_time),
  0.1,  0.9
)

#supplementary
run_model(
                 I = strat_1,
                II = strat_2,
            cycles = 100,
  state_time_limit = list(
                    I = c(B = 10, D = 20),
                   II = c(B = 15)
  )
)
```

param	List of 3
res_mod	0 obs. of 14 variables
state_A	List of 2
state_B	List of 2
state_C	List of 2
state_D	List of 2
strat_comb	List of 3
strat_mono	List of 3