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SCHOOL OF
MATHEMATICS AND PHYSICS



Discrete Time Markov Models - deterministic

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Acknowledgement

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Overview

- Markov modelling
- Smoking cessation Markov model
 - Cohort simulation
 - Costs/QALYs
- Coding the smoking cessation Markov model in R
- Practical

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Multi-State Models

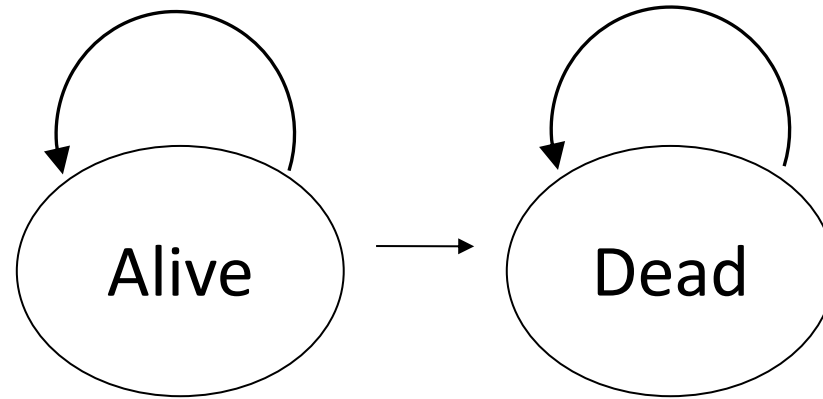
Used for analysing events that **repeat** (*e.g. mental health*), or events that play out over **time** (*e.g. cancer, heart disease*)

At any point in time individuals are in one of a finite set of states of health

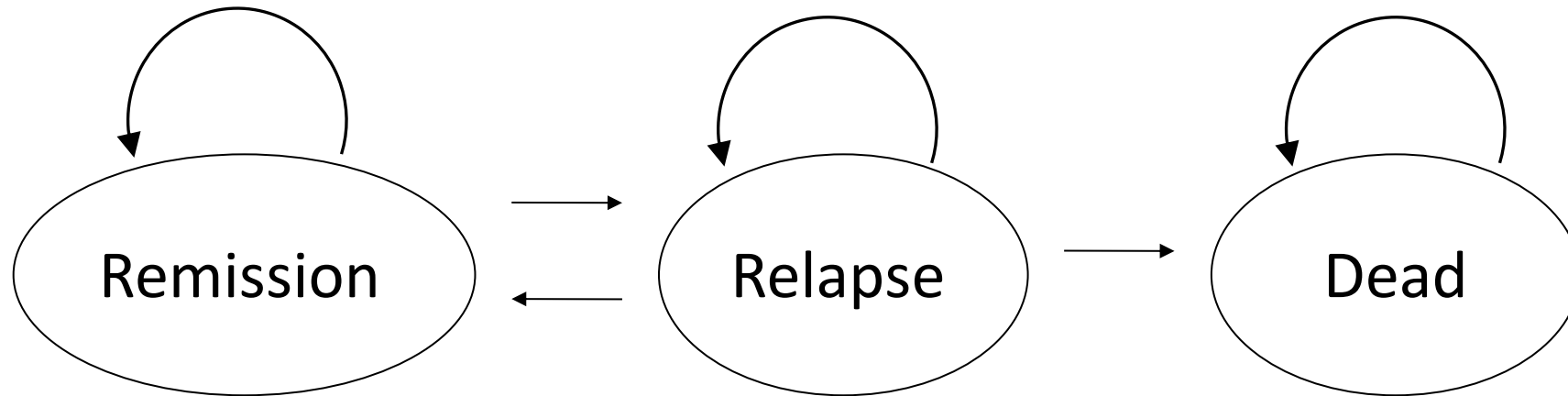
‘Clinical’ events are described by movements (**transitions**) between these states

Examples

(a)



(b)



Markov Models

Markov Models are a special type of Multi-State Model

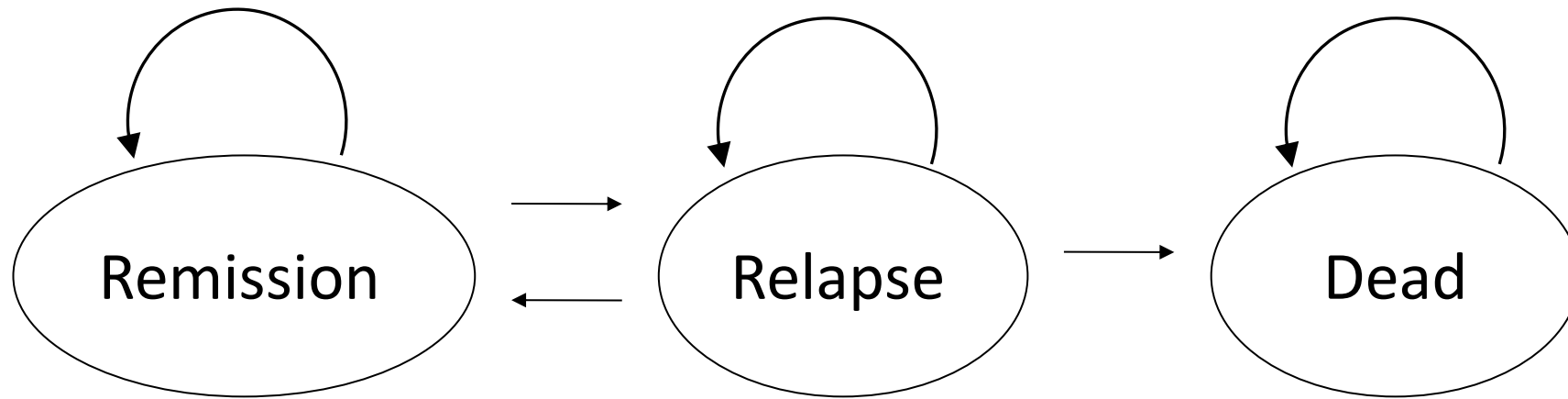
“Memoryless” property: future depends on the past only through current state

No need to remember previous movements between states

Assume rate of movement between any 2 states is constant over time

No need to remember how long been in state

Examples



Discrete-time Cohort Markov Models

Cohort models consider only aggregate behaviour of patient groups,
averaging over any individual behaviour

Movements of patient groups between health states determined by
transition probabilities

Here transition probabilities are **independent of time in state or past patient history**

Transition Probabilities

Movement through the health states is governed by the transition probabilities

Defined over a specific time period (e.g. the probability of death over 1 year)

In economic models this time period is called the **cycle length**

Transition probabilities from a state **MUST SUM TO 1**

Discounting

Costs and benefits that occur in the future are discounted to reflect society's rate of time preference

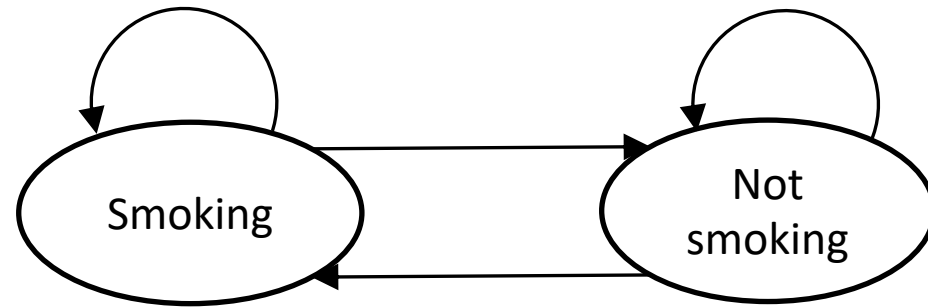
E.G. UK discount in first year is 1, second year is 1.035^{-1} , third is 1.035^{-2} , ..., fifth is 1.035^{-4}

But if a cycle is 6 months.... 1 for first two cycles, 1.035^{-1} for third and fourth cycle, ..., 1.035^{-4} for ninth and 10th cycle

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Smoking Cessation Example

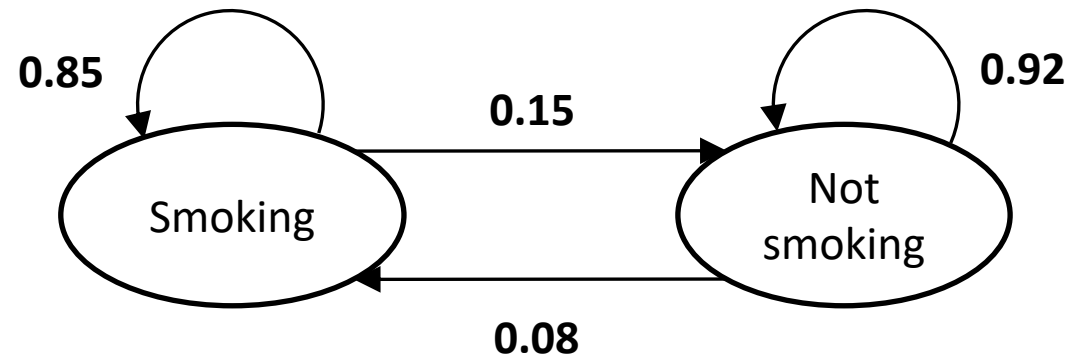


Arrows show movements that can occur in 1 time cycle

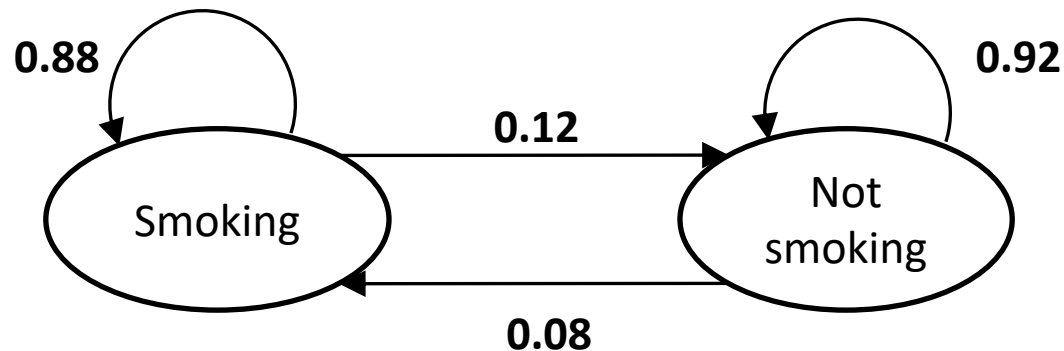
This includes staying in the same state (shown by curved arrows)

Smoking Cessation Example

6-month cycles, 5 year time horizon



Standard Care +
Website

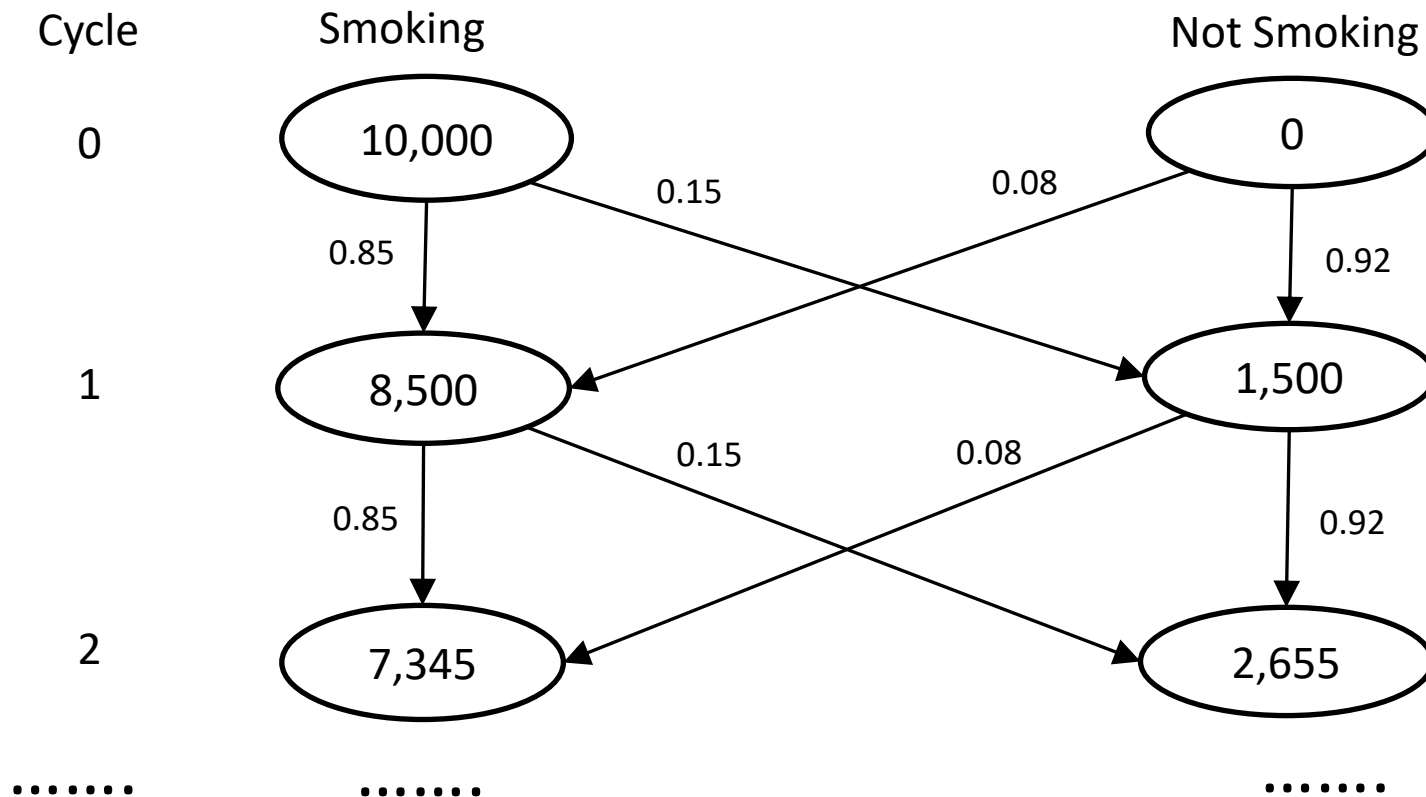


Standard Care

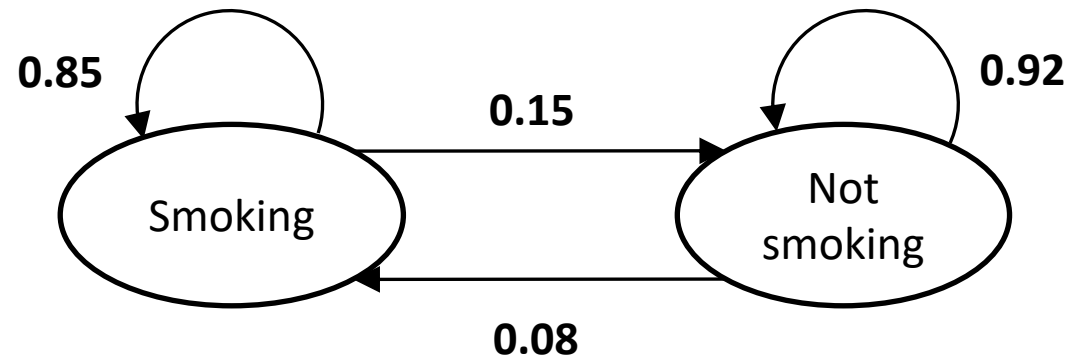
Cohort Simulation

Cohort vector π at time t (π_t) is the cohort vector at the previous time point (π_{t-1}) multiplied by the probability transition matrix P

$$\pi_t = \pi_{t-1}P$$



Smoking Cessation Example



Standard Care +
Website

Updating cohort vector

Or in components

$$(\pi_{Smoking,t}, \pi_{Not\ smoking,t}) = (\pi_{Smoking,t-1}, \pi_{Not\ smoking,t-1}) \begin{pmatrix} 0.85 & 0.15 \\ 0.08 & 0.92 \end{pmatrix}$$

Initial state ($t = 0$) may be everyone in smoking ($\pi_0 = (1,0)$) then this updates to $\pi_1 = (0.85, 0.15)$ with 15% of patients quitting smoking

If initial state was $\pi_0 = (0.6, 0.4)$ this would update to

$\pi_1 = (\% \text{ still smoking} + \% \text{ starting smoking}, \% \text{ still not smoking} + \% \text{ quitting})$

$$((0.6 * 0.85) + (0.4 * 0.08), (0.4 * 0.92) + (0.6 * 0.15)) = (0.542, 0.458)$$

Updating cohort vector

Run this to time horizon to get state full occupancy

		Standard Care + Website		Standard Care	
Cycle number		Smoking	Not Smoking	Smoking	Not Smoking
0		10000	0	10000	0
1		8500	1500	8800	1200
2		7345	2655	7840	2160
3		6456	3544	7072	2928
4		5771	4229	6458	3542
5		5244	4756	5966	4034
6		4838	5162	5573	4427
7		4525	5475	5258	4742
8		4284	5716	5007	4993
9		4099	5901	4805	5195
10		3956	6044	4644	5356

$$10000 * 0.15 = 1500$$

$$10000 * 0.85 = 8500$$

$$8500 * 0.85 + 1500 * 0.08 = 7345$$

$$8500 * 0.15 + 1500 * 0.92 = 2655$$

Costs and QALYS

We know that

1-year in the smoking state = 0.95 QALYs

So 1 cycle is 0.475 QALYs

1-year in the non-smoking state = 1 QALYs

So 1 cycle is 0.5 QALYs

Website has a one-off cost of £50 per person

5 year horizon

Calculating costs and QALYs

If the current cohort vector is π_t

And cost and QALY per cycle spent in each state are $c_t = (0,0)$ and $q_t = (0.475, 0.5)$

Then total costs and utilities accumulated per cycle are

$$\text{cycle costs} = \pi_t \times c_t$$

$$\text{cycle QALYs} = \pi_t \times q_t$$

For time horizon T , total costs are $\sum_{t=1}^T \pi_t \times c_t$ and total QALYs $\sum_{t=1}^T \pi_t \times q_t$

Calculating costs and QALYs for Smoking Cessation

In the smoking cessation example $T = 10$ as 10 cycles of 6 months give 5-year time horizon

No cost per state but one-off treatment cost $d_i = (50, 0)$ for standard care + website ($i = 1$) and standard of care alone ($i = 2$)

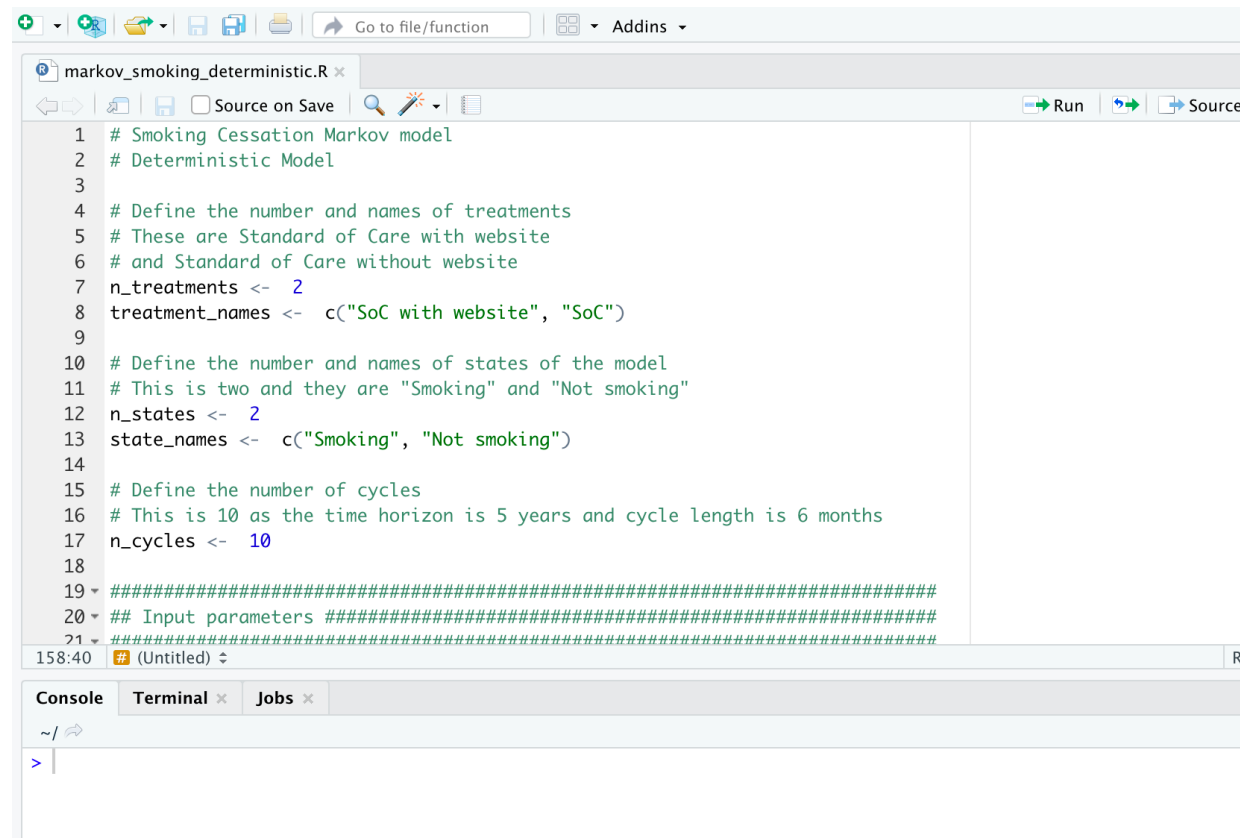
ICER = difference in costs of strategies / difference in QALY's of strategies

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Coding in R

Use Rstudio to open the file labelled “markov_smoking_deterministic.R”



The screenshot displays the RStudio interface with a script editor open to the file 'markov_smoking_deterministic.R'. The script contains R code for a Markov model, including comments and variable assignments. The console at the bottom shows the prompt '>'.

```
1 # Smoking Cessation Markov model
2 # Deterministic Model
3
4 # Define the number and names of treatments
5 # These are Standard of Care with website
6 # and Standard of Care without website
7 n_treatments <- 2
8 treatment_names <- c("SoC with website", "SoC")
9
10 # Define the number and names of states of the model
11 # This is two and they are "Smoking" and "Not smoking"
12 n_states <- 2
13 state_names <- c("Smoking", "Not smoking")
14
15 # Define the number of cycles
16 # This is 10 as the time horizon is 5 years and cycle length is 6 months
17 n_cycles <- 10
18
19 #####
20 ## Input parameters #####
21 #####
```

Basic model specification

```
n_treatments <- 2  
treatment_names <- c("SoC with website", "SoC")  
  
n_states <- 2  
state_names <- c("Smoking", "Not smoking")  
  
n_cycles <- 10
```


An array to store transition matrices

```
transition_matrices <- array(dim = c(n_treatments, n_states,  
                                     n_states),  
                             dimnames = list(treatment_names,  
                                              state_names, state_names))
```

This produces an array with dimensions 2x2x2

They are currently blank so need to fill in with values...

Filling in the transition matrix

```
# First the transition matrix for Standard of Care with website
# Transitions from smoking
transition_matrices["SoC with website", "Smoking", ] <- c(0.85, 0.15)

# Transitions from not smoking
transition_matrices["SoC with website", "Not smoking", ] <- c(0.08, 0.92)

# Second the transition matrix for Standard of Care
# Transitions from smoking
transition_matrices["SoC", "Smoking", ] <- c(0.88, 0.12)

# Transitions from not smoking
# These should be the same as the transition probabilities from not smoking for
# SoC with website as the website has no impact on probability of relapse
transition_matrices["SoC", "Not smoking", ] <-
  transition_matrices["SoC with website", "Not smoking", ]
```

Contents of array

Run the previous code ensuring you have filled in the *transition_matrices* array

Now look at elements of the array

```
> transition_matrices  
, , Smoking
```

	Smoking	Not smoking
SoC with website	0.85	0.08
SoC	0.88	0.08

```
, , Not smoking
```

	Smoking	Not smoking
SoC with website	0.15	0.92
SoC	0.12	0.92

State QALYs

```
# Now define the QALYS associated with the states per cycle
# There is one for each state
# Store in an NA array and then fill in below
state_qalys <- array(dim = c(n_states), dimnames = list(state_names))

# QALY associated with 1 - year in the smoking state is 0.95
# Divide by 2 as cycle length is 6 months
state_qalys["Smoking"] <- 0.95 / 2

# QALY associated with 1 - year in the not smoking state is 1
# Again divide by 2 as cycle length is 6 months
state_qalys["Not smoking"] <- 1.0 / 2
```

State costs

```
# And finally define the state costs  
# These are all zero as the only cost is a one - off subscription fee of £50  
# to the smoking cessation website  
state_costs <- array(0, dim = c(n_states), dimnames = list(state_names))
```

Can again inspect elements to make sure it's working as expected...

Treatment costs

```
# Define the treatment costs
# One for each treatment
# Treatment costs are actually fixed but this allows flexibility if we
# want to include uncertainty / randomness in the cost
treatment_costs <- array(dim = c(n_treatments), dimnames = list(treatment_names))

# Cost of the smoking cessation website is a one - off subscription fee of £50
treatment_costs["SoC with website"] <- 50
# Zero cost for standard of care
treatment_costs["SoC"] <- 0
```

Initialise the cohort vector

```
# Build an array to store the cohort vector at each cycle
# Each cohort vector has 2 (= n_states) elements: probability of being in smoking state,
# and probability of being in the not smoking state
# There is one cohort vector for each treatment, for each cycle_
cohort_vectors <- array(dim = c(n_treatments, n_cycles, n_states),
                        dimnames = list(treatment_names, NULL, state_names))

# Assume that everyone starts in the smoking state no matter the treatment
cohort_vectors[, 1, "Smoking"] <- 1
cohort_vectors[, 1, "Not smoking"] <- 0
```

These are the two-dimensional π_t in the Markov formula

Core loop

Loop over treatments

{

 Loop over cycles

 {

 Update cohort vector

$$\pi_t = \pi_{t-1}P$$

 or specifically...

$$(\pi_{Smoking,t}, \pi_{Not\ smoking,t}) = (\pi_{Smoking,t-1}, \pi_{Not\ smoking,t-1})P$$

 }

 1. Calculate cycle costs and QALYs

 2. Calculate total costs and QALYs

}

Core loop

```
# Main model code
# Loop over the treatment options
for(i_treatment in 1:n_treatments)
{
  # Loop over the cycles
  # Cycle 1 is already defined so only need to update cycles 2:n_cycles
  for(i_cycle in 2:n_cycles)
  {
    # Markov update
    # Multiply previous cycle's cohort vector by transition matrix
    #  $i\_e\_pi\_j = pi\_j - 1 * P$ 
    cohort_vectors[i_treatment, i_cycle, ] <-
      cohort_vectors[i_treatment, i_cycle - 1, ] %*%
      transition_matrices[i_treatment, , ]

    # 1. Calculate cycle costs and QALYs
    # 2. Calculate total costs and QALYs

  }
}
```

Cycle costs and cycle QALYs

```
# Build an array to store the costs and QALYs accrued per cycle
# One for each treatment, for each cycle
# These will be filled in below in the main model code
# Then discounted and summed to contribute to total costs and total QALYs
cycle_costs <- array(dim = c(n_treatments, n_cycles),
                    dimnames = list(treatment_names, NULL))
cycle_qalys <- array(dim = c(n_treatments, n_cycles),
                    dimnames = list(treatment_names, NULL))
```

Not strictly necessary to store these but might be interested in costs or QALYs accrued per cycle.

Arrays to store total cost and QALYs

```
# Build arrays to store the total costs and total QALYs
# There is one for each treatment
# These are filled in below using cycle_costs, treatment_costs, and cycle_qalys
total_costs <- array(dim = c(n_treatments),
                    dimnames = list(treatment_names))
total_qalys <- array(dim = c(n_treatments),
                    dimnames = list(treatment_names))
```

Once filled in by Markov loop, these are used to calculate net benefit and ICERs

Discount rate

The powers repeat so in R could write

```
> c(0,0,1,1,2,2,3,3,4,4)
[1] 0 0 1 1 2 2 3 3 4 4
```

Or use the rep() function

```
> rep(c(0:4), each=2)
[1] 0 0 1 1 2 2 3 3 4 4
```

Or (preferred) make it general to any number of cycles in our Markov model.

Note that formula below only works for an even number of cycles:

```
> rep(c(0:(n_cycles / 2-1)), each = 2)
[1] 0 0 1 1 2 2 3 3 4 4
```

Discount rate

The discount factor for costs and QALYs

- $(1 / 1.035)^{\text{rep}(c(0:(n_cycles / 2-1)), \text{each} = 2)}$
- [1] 1.0000000 1.0000000 0.9661836 0.9661836 0.9335107
0.9335107 0.9019427 0.9019427 0.8714422 0.8714422

Calculating cycle costs and QALYs

For each treatment we use the `cohort_vectors[]` to calculate costs and QALYs associated with each cycle

```
# Now use the cohort vectors to calculate the
# Total costs for each cycle
cycle_costs[i_treatment, ] <- cohort_vectors[i_treatment, , ] %*% state_costs[]
# And total QALYs for each cycle
cycle_qalys[i_treatment, ] <- cohort_vectors[i_treatment, , ] %*% state_qalys[]
```

Calculating total costs and QALYs

```
# Combine the cycle_costs and treatment_costs to get total costs
# Apply the discount factor
total_costs[i_treatment] <- treatment_costs[i_treatment] +
  cycle_costs[i_treatment, ] %*%
  (1 / 1.035)^rep(c(0:(n_cycles / 2 - 1)), each = 2)

# Combine the cycle_qalys to get total qalys
# Apply the discount factor
total_qalys[i_treatment] <- cycle_qalys[i_treatment, ] %*%
  (1 / 1.035)^rep(c(0:(n_cycles / 2 - 1)), each = 2)
```

Note treatment costs are added (and not discounted as only occur in first year)

Results

```
# Incremental costs and effects relative to standard of care
# No uncertainty in the costs as the website cost is fixed at £50
incremental_costs <- total_costs["SoC with website"] - total_costs["SoC"]
incremental_effects <- total_qalys["SoC with website"] - total_qalys["SoC"]

# The ICER comparing Standard of care with website to standard of care
# This is much lower than the £20, 000 willingness - to - pay threshold indicating
# good value for money
ICER <- incremental_costs / incremental_effects
```


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Summary

We have explained the 2-state and 2-treatment option smoking cessation Markov model

We have explained the key steps in building a discrete time deterministic Markov model in R

- Define input parameters

- Update cohort vector and calculate total costs and QALYs

The code we provided is general

- Included state costs even though these are zero in smoking cessation

- Change numbers of states and input parameters to adapt

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Practical

So far, we have assumed that there are no costs associated with the health states. Add in a fixed cost of £100 per year associated with the smoking state by:

Updating the state costs array to replace the zeroes with a £100 per year state cost for the smoking state. Specify that the no smoking state is associated with zero costs.

Comment on how this changes the ICER