University of BRISTOL

Clifton Insight

Proof-of-concept for automatic export of Excel versions of R health economic models

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- All code for today's presentation is available at:

https://github.com/Bogdasayen/R-to-Excel-POC

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Why R-to-Excel conversion?

- **UK NICE, Irish NCPE, Dutch Zin and other forward-thinking agencies accept R models, but others do not.**
- Companies may want to leverage efficiency, flexibility, and transparency advantages of R but will still need an Excel version.
- Double programming models can lead to errors and make it difficult to push updates across international models.
- **Instead use R models that can export Excel versions of themselves.**

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Requirements of R-to-Excel conversion

- Generalisable to any Markov model
- Generate human-readable Excel file suitable for experimentation and for HTA submissions
- Avoid “double programming” the model in both Excel and R

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Reverse REEEVR?

- At University of Bristol, we are developing the REEEVR tool to automatically convert Excel models into R.
- This gains benefits of speed (100x improvement) at loss of readability.
- Approach theoretically works on any Excel model (though needs an R equivalent of each Excel function to be implemented)
- **Why not do this in reverse to convert R into Excel?**

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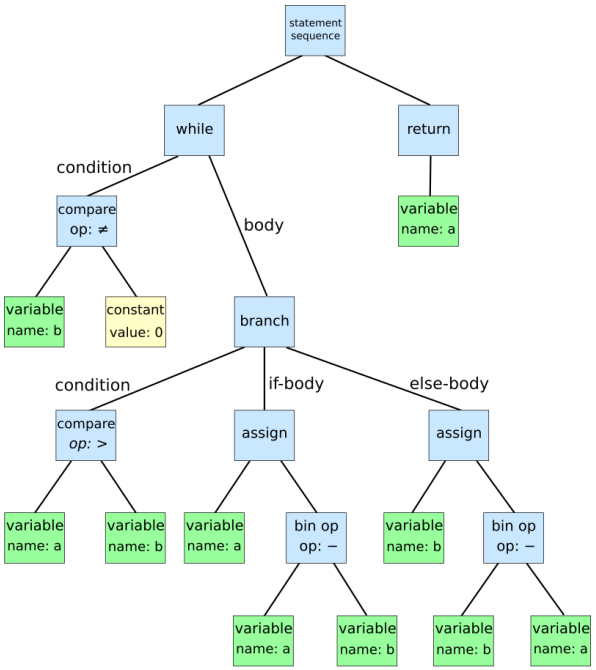
Abstract Syntax Tree - General




```
1. while b ≠ 0:
2.     if a > b:
3.         a := a - b
4.     else:
5.         b := b - a
6. return a
```

- Walks the program
- Breaks code into components
- Builds a tree where each leaf is an elementary component of the program
- The tree is language agnostic
- **Could be applied to R code**

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Unreadable and slow!

```
StatetraceCemented_N8 = StatetraceCemented_D8 * rngActiveUtilPostTHR
StatetraceCemented_Q8 = excel_sum(list(StatetraceCemented_N8, StatetraceCemented_O8, StatetraceCemented_P8))
StatetraceCemented_R8 = StatetraceCemented_Q8 / ( 1 + rngDiscountRate ) ^ ( StatetraceCemented_B8 - 1 )
StatetraceCemented_E9 = StatetraceCemented_E8 * ( 1 - Inputclinicalparameters_O10 - excel_index(rngLifeTables,StatetraceCemented_C8,2) ) + StatetraceCemented_D8 * ( rngAveProbCem )
StatetraceCemented_J9 = StatetraceCemented_E9 * rngAveProbSecRem * rngTotCostRevision
StatetraceCemented_O9 = StatetraceCemented_E9 * rngActivUtilPost1stRev
StatetraceCemented_F10 = StatetraceCemented_E9 * ( Inputclinicalparameters_O10 ) + StatetraceCemented_F9 * ( 1 - ( excel_index(rngLifeTables,StatetraceCemented_C9,2) ) )
StatetraceCemented_K10 = StatetraceCemented_F10 * rngAveProbThirRem * rngTotCostRevision
StatetraceCemented_P10 = StatetraceCemented_F10 * rngActiveUtilPostSecRev
StatetraceUncemented_D8 = 1 - excel_sum(list(StatetraceUncemented_E8, StatetraceUncemented_F8, StatetraceUncemented_G8))
StatetraceUncemented_I8 = StatetraceUncemented_D8 * rngAveProbUncem * rngTotCostRevision
StatetraceUncemented_L8 = excel_sum(list(StatetraceUncemented_H8, StatetraceUncemented_I8, StatetraceUncemented_J8, StatetraceUncemented_K8))
StatetraceUncemented_M8 = StatetraceUncemented_L8 / ( 1 + rngDiscountRate ) ^ ( StatetraceUncemented_B8 - 1 )
StatetraceUncemented_N8 = StatetraceUncemented_D8 * rngActiveUtilPostTHR
StatetraceUncemented_Q8 = excel_sum(list(StatetraceUncemented_N8, StatetraceUncemented_O8, StatetraceUncemented_P8))
StatetraceUncemented_R8 = StatetraceUncemented_Q8 / ( 1 + rngDiscountRate ) ^ ( StatetraceUncemented_B8 - 1 )
StatetraceUncemented_E9 = StatetraceUncemented_E8 * ( 1 - Inputclinicalparameters_O10 - excel_index(rngLifeTables,StatetraceUncemented_C8,2) ) + StatetraceUncemented_D8 * ( rngAveProbUncem )
StatetraceUncemented_J9 = StatetraceUncemented_E9 * rngAveProbSecRem * rngTotCostRevision
StatetraceUncemented_O9 = StatetraceUncemented_E9 * rngActivUtilPost1stRev
StatetraceUncemented_F10 = StatetraceUncemented_E9 * ( Inputclinicalparameters_O10 ) + StatetraceUncemented_F9 * ( 1 - ( excel_index(rngLifeTables,StatetraceUncemented_C9,2) ) )
StatetraceUncemented_K10 = StatetraceUncemented_F10 * rngAveProbThirRem * rngTotCostRevision
StatetraceUncemented_P10 = StatetraceUncemented_F10 * rngActiveUtilPostSecRev
StatetraceHybrid_D8 = 1 - excel_sum(list(StatetraceHybrid_E8, StatetraceHybrid_F8, StatetraceHybrid_G8))
StatetraceHybrid_I8 = StatetraceHybrid_D8 * rngAveProbHybr * rngTotCostRevision
StatetraceHybrid_L8 = excel_sum(list(StatetraceHybrid_H8, StatetraceHybrid_I8, StatetraceHybrid_J8, StatetraceHybrid_K8))
StatetraceHybrid_M8 = StatetraceHybrid_L8 / ( 1 + rngDiscountRate ) ^ ( StatetraceHybrid_B8 - 1 )
StatetraceHybrid_N8 = StatetraceHybrid_D8 * rngActiveUtilPostTHR
StatetraceHybrid_Q8 = excel_sum(list(StatetraceHybrid_N8, StatetraceHybrid_O8, StatetraceHybrid_P8))
StatetraceHybrid_R8 = StatetraceHybrid_Q8 / ( 1 + rngDiscountRate ) ^ ( StatetraceHybrid_B8 - 1 )
StatetraceHybrid_E9 = StatetraceHybrid_E8 * ( 1 - Inputclinicalparameters_O10 - excel_index(rngLifeTables,StatetraceHybrid_C8,2) ) + StatetraceHybrid_D8 * ( rngAveProbHybr )
StatetraceHybrid_J9 = StatetraceHybrid_E9 * rngAveProbSecRem * rngTotCostRevision
StatetraceHybrid_O9 = StatetraceHybrid_E9 * rngActivUtilPost1stRev
StatetraceHybrid_F10 = StatetraceHybrid_E9 * ( Inputclinicalparameters_O10 ) + StatetraceHybrid_F9 * ( 1 - ( excel_index(rngLifeTables,StatetraceHybrid_C9,2) ) )
StatetraceHybrid_K10 = StatetraceHybrid_F10 * rngAveProbThirRem * rngTotCostRevision
StatetraceHybrid_P10 = StatetraceHybrid_F10 * rngActiveUtilPostSecRev
StatetraceReversehybrid_D8 = 1 - excel_sum(list(StatetraceReversehybrid_E8, StatetraceReversehybrid_F8, StatetraceReversehybrid_G8))
StatetraceReversehybrid_I8 = StatetraceReversehybrid_D8 * rngAveProbRevHybr * rngTotCostRevision
StatetraceReversehybrid_L8 = excel_sum(list(StatetraceReversehybrid_H8, StatetraceReversehybrid_I8, StatetraceReversehybrid_J8, StatetraceReversehybrid_K8))
StatetraceReversehybrid_M8 = StatetraceReversehybrid_L8 / ( 1 + rngDiscountRate ) ^ ( StatetraceReversehybrid_B8 - 1 )
StatetraceReversehybrid_N8 = StatetraceReversehybrid_D8 * rngActiveUtilPostTHR
StatetraceReversehybrid_Q8 = excel_sum(list(StatetraceReversehybrid_N8, StatetraceReversehybrid_O8, StatetraceReversehybrid_P8))
StatetraceReversehybrid_R8 = StatetraceReversehybrid_Q8 / ( 1 + rngDiscountRate ) ^ ( StatetraceReversehybrid_B8 - 1 )
StatetraceReversehybrid_E9 = StatetraceReversehybrid_E8 * ( 1 - Inputclinicalparameters_O10 - excel_index(rngLifeTables,StatetraceReversehybrid_C8,2) ) + StatetraceReversehybrid_D8 * ( rngAveProbRevHybr )
StatetraceReversehybrid_J9 = StatetraceReversehybrid_E9 * rngAveProbSecRem * rngTotCostRevision
StatetraceReversehybrid_O9 = StatetraceReversehybrid_E9 * rngActivUtilPost1stRev
StatetraceReversehybrid_F10 = StatetraceReversehybrid_E9 * ( Inputclinicalparameters_O10 ) + StatetraceReversehybrid_F9 * ( 1 - ( excel_index(rngLifeTables,StatetraceReversehybrid_C9,2) ) )
StatetraceReversehybrid_K10 = StatetraceReversehybrid_F10 * rngAveProbThirRem * rngTotCostRevision
StatetraceReversehybrid_P10 = StatetraceReversehybrid_F10 * rngActiveUtilPostSecRev
StatetraceCemented_D9 = 1 - excel_sum(list(StatetraceCemented_E9, StatetraceCemented_F9, StatetraceCemented_G9))
StatetraceCemented_I9 = StatetraceCemented_D9 * rngAveProbCem * rngTotCostRevision
StatetraceCemented_L9 = excel_sum(list(StatetraceCemented_H9, StatetraceCemented_I9, StatetraceCemented_J9, StatetraceCemented_K9))
```

- A simple 4-state Markov model with 4 interventions results in 2614 lines of **unreadable** R code.
- Applying in reverse would create either very many **unreadable** cell calculations, or a small number of very long **unreadable** cell calculations.
- Result would also likely be **very slow** as loops and vector operations (e.g., for PSA) would be duplicated Excel cells, rather than VBA macros.

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Using R to write Excel formulae

- We instead use the powerful **openxlsx R package**
- This allows us to write data, formulae and formatting from R to Excel
  - Example usage below

```
output_wb <- loadWorkbook(file = wb_filename, isUnzipped = FALSE)
addWorksheet(output_wb, "Results", tabColour = "orange")
df_results <- Some formulae see next slide
class(df_results[, 1] <- c(class(df_results[, 1]), "formula")
names(df_results) <- c("Result", self$v_treatment_names)
writeData(output_wb, sheet = "Results",  x = df_results,
          startCol = 8, startRow = 5)
saveWorkbook(output_wb, file = wb_filename,
                    overwrite = TRUE, returnValue = TRUE)
```

Object Oriented Programming

- Process kept manageable through R6 classes for OOP
- Each model is a markov_model object with member functions and data stored in a markov_inputs object
- Users would call markov_model$new(...) to create a new Markov model, and the new() constructor takes a markov_inputs object as argument.
- The Markov model object maps relationships between input parameters, transition matrices, costs and QALYs

- **This mapping of data relationships is helpful for R-to-Excel conversion**

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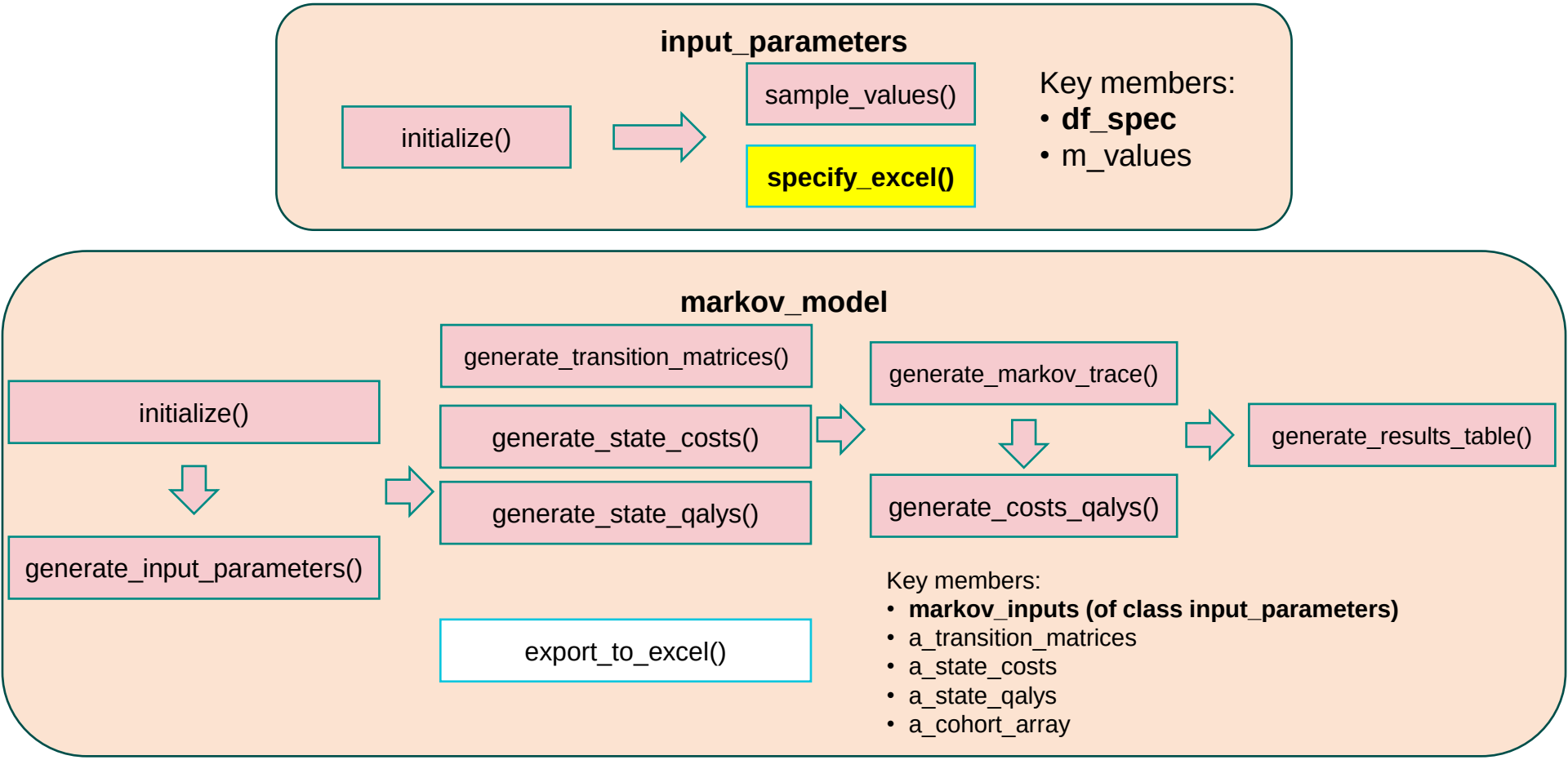
Two key R6 objects and two key functions



- We'll start with input_parameters$df_spec()

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Data structure and description

- Data structure and complete description of relationships is key.
- The input parameters object includes a dataframe **df_spec** that fully specifies the distributions used in either R or Excel.
- The contents of this dataframe are written by **specify_excel()**
- Column excel_formulae is generated automatically based on inputs

8	v_names	v_descriptions	v_distributions	hp_1	hp_2	from	to	v_treatment	**excel_formulae**	excel_value_location
9	Probability quit smoking website	Probability of quitting if on smoking website, follows a beta distribution	beta	15	85	1	2	1	**=BETAINV(RAND(), H9, I9)**	input_parameters!M9

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Example Excel random formula generation

- Cell formulae themselves generated using paste0 statements and cell locations
- Extracted from input_parameters$specify_excel()

Code	# First parameter
	i_parameter <- 1
	# Starting position in Excel sheet
	startRow = 5
	startCol = 8
	
	# In which column letters would the hyper parameters be stored?
	hp_1_col <- LETTERS[startCol + 1]
	hp_2_col <- LETTERS[startCol + 2]
	
	paste0("NORMINV(RAND(), ",
	paste0(hp_1_col, startRow + i_parameter),
	", ",
	paste0(hp_2_col, startRow + i_parameter),
	")")

Output	"NORMINV(RAND(), I6, J6)"

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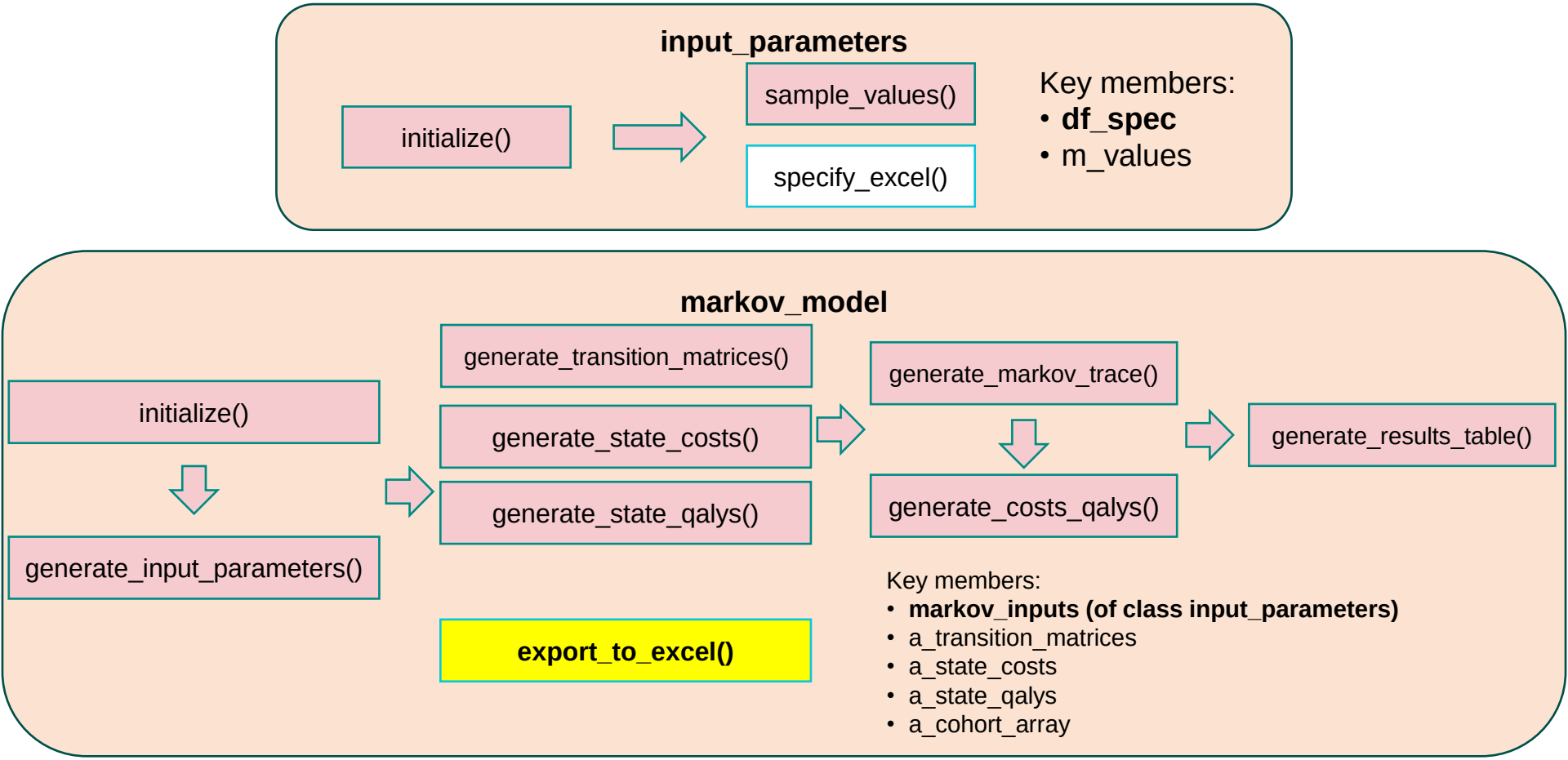
Two key R6 objects and two key functions



- **Next is markov_model$export_to_excel()**

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Markov trace generation

- Generates state occupancy probabilities (e.g., “=F9 * (1 - input_parameters!M9) + G9 * input_parameters!M11”) in Markov trace using the df_spec data frame
- Associates each parameter with its source (‘from’) and destination (‘to’) states
- Code ignores parameters without ‘from’ or ‘to’ as these are costs or utilities
- First two rows of generated Markov trace are provided below.

E	F	G	H	I	J
8	cycle	SoC_Smoking	SoC_Not smoking	SoC with website_Smoking	SoC with website_Not smoking
9	1	1	0	1	0
10	2	=F9 * (1 - input_parameters!M9) + G9 * input_parameters!M1 1	=G9 * (1 - input_parameters!M11) + F9 * input_parameters!M9	=H9 * (1 - input_parameters!M1 0) + I9 * input_parameters!M11	=I9 * (1 - input_parameters!M11) + H9 * input_parameters!M1 0

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Markov trace generation – part 1

```
# Generate the Markov trace using transition probabilities from markov_inputs
  df_markov_trace <- data.frame(cycle = c(1:self$n_cycles))
  cell_formula_temp <- rep("", n_cycles)
  for(i_treatment in 1:self$n_treatments) {
   for(i_state in 1:self$n_states) {
    cell_formula_temp[1] <- self$v_init_cohort[i_state]

    # Which parameters give probabilities from this state and are relevant
    # to this treatment (or to all treatments)
    from_indices <- which(self$markov_inputs$df_spec$from == i_state &
                  (self$markov_inputs$df_spec$v_treatment == i_treatment |
                   is.na(self$markov_inputs$df_spec$v_treatment)))

    # Create the sum of probabilities of exiting current state
    sum_probabilities_from <- ifelse(length(from_indices) == 1,
                        self$markov_inputs$df_spec$excel_value_location[from_indices],
paste0(self$markov_inputs$df_spec$excel_value_location[from_indices], sep = "+"))
```

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Markov trace generation – part 2

```
for(i_cycle in 2:self$n_cycles) {
    # Numeric for row with previous cohort probabilities
    previous_row <- startRow + i_cycle - 1

    # Cell with probability of being in state at previous cycle
    cell_formula_temp[i_cycle] <- paste0(LETTERS[startCol +
                                  (i_treatment - 1) * n_states +
                                  i_state], previous_row,
                                " * (1 - ", sum_probabilities_from,")")

    # Now append the probabilities of entering the state
    from_prob_formulae <- c()
    for(j_state in c(1:self$n_states)[-i_state]) {
     # Find the parameter storing transition probabilities from j to i
     from_j_to_i_index <- self$markov_inputs$df_spec$from == j_state &
      self$markov_inputs$df_spec$to == i_state &
      (self$markov_inputs$df_spec$v_treatment == i_treatment |
        is.na(self$markov_inputs$df_spec$v_treatment))
```

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Markov trace generation – part 3

```
# Check that there is a transition from j to i
      if(sum(from_j_to_i_index, na.rm = TRUE) == 1) {

        # Add probability of being in j multiplied by probability of going to i
        from_prob_formulae <- c(from_prob_formulae,
                    paste0(LETTERS[startCol +
                                (i_treatment - 1) * n_states +
                                j_state], previous_row,
                           " * ",
self$markov_inputs$df_spec$excel_value_location[which(from_j_to_i_inde
x)]))

       } # End if there are transitions from j to i
     } # End loop over j_state
```

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Markov trace generation – part 4

```
# Create the sum of probabilities of entering current state
    # Account for possibility that none of cohort makes this transition
    sum_probabilities_to <- ifelse(length(from_prob_formulae) == 0, "",
                        ifelse(length(from_prob_formulae) == 1,
                            from_prob_formulae,
                            paste0(from_prob_formulae, sep = "+")))
    cell_formula_temp[i_cycle] <- paste0(cell_formula_temp[i_cycle], " + ",
sum_probabilities_to)

  } # End loop over i_cycle

  # Append these formulae to the Markov trace
  class(cell_formula_temp) <- c(class(cell_formula_temp), "formula")
  df_markov_trace <- cbind(df_markov_trace, cell_formula_temp)
```

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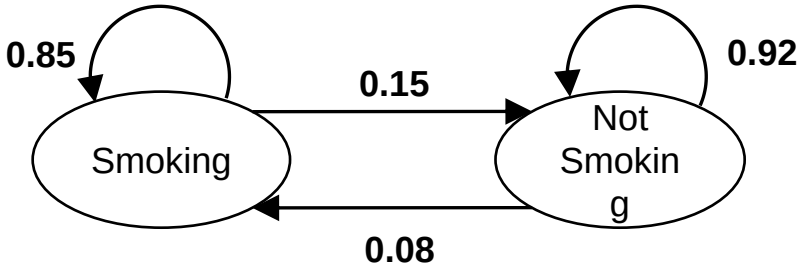
Costs, QALYs, PSA

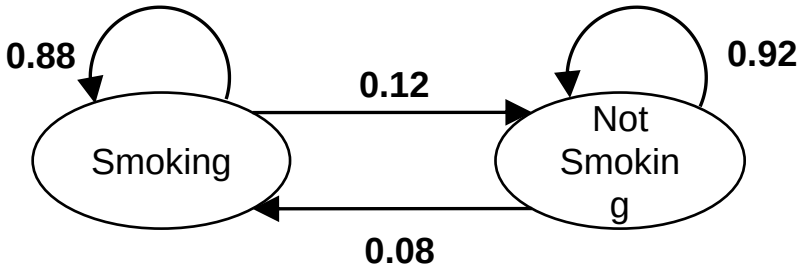
- Similar approach is taken to costs and QALYs
- Output model is probabilistic but only for 1 sample
- A pre-built VBA macro is used to run the model multiple times for probabilistic sensitivity analysis
- So long as total cost and QALY cells are written in a specific format (e.g., starting from row 8 and column 5) the VBA macro will work
- This could also be used to automatically generate plots

Now let's test it!

Markov smoking



SoC + Website



SoC

- Teaching model used for Bristol University short courses and MSc teaching
- Two states and two treatments
- SoC + Website increases chance of quitting smoking compared to SoC

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df_spec for utilities

v_names	v_descriptions	v_type	v_distributions	hp_1	hp_2	v_treatment	v_state	excel_value_location
Utility smoking	Utility smoking, follows a Normal distribution	utility	normal	0.95	0.02		1	input_parameters !O12
Utility not smoking	Utility not smoking, follows a Normal distribution	utility	fixed	1			2	input_parameters !O13

- Treatment column left blank so these utilities apply to both treatments

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df_spec for costs

v_names	v_descriptions	v_type	v_distributions	hp_1	hp_2	v_treatment	v_state	excel_value_location
Cost website	Cost website, fixed value and model assumes no cost of SoC and no state costs	one_off_cost	fixed	50		2		input_parameters! O14
Cost GP smoking	Cost of 6-monthly, on average, GP visit (£49 from PRSSU) for smoking related illness, follows Normal distribution	cost	normal	49	2		1	input_parameters! O15
Cost statin smoking	Cost of roughly 20% of smokers taking statins (pravastatin at £3.45 per month), follows Normal distribution	cost	normal	0.69	0.069		1	input_parameters! O16

- Costs can be one-off or ongoing.

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df_spec for transition probabilities

v_names	v_descriptions	v_type	v_distributions	hp_1	hp_2	from	to	v_treatment	v_state	excel_value_location
Probability quit smoking website	Probability of quitting if on smoking website, follows a beta distribution	transition_probability	beta	15	85	1	2	2	1	input_parameters!O9
Probability quit smoking SoC	Probability of quitting smoking if on SoC, follows a beta distribution	transition_probability	beta	12	88	1	2	1	1	input_parameters!O10
Probability relapse	Probability relapse, which is same across treatments and follows a beta distribution	transition_probability	beta	8	92	2	1		2	input_parameters!O11

- Probability of relapse is the same for both treatments

If v_treatment is missing it's the same for all treatments. The states used in from and to columns are 1=Smoking and 2=Not smoking; the treatments are 1=SoC and 2=SoC+Website. Column O is omitted and stores the live value used in the model.

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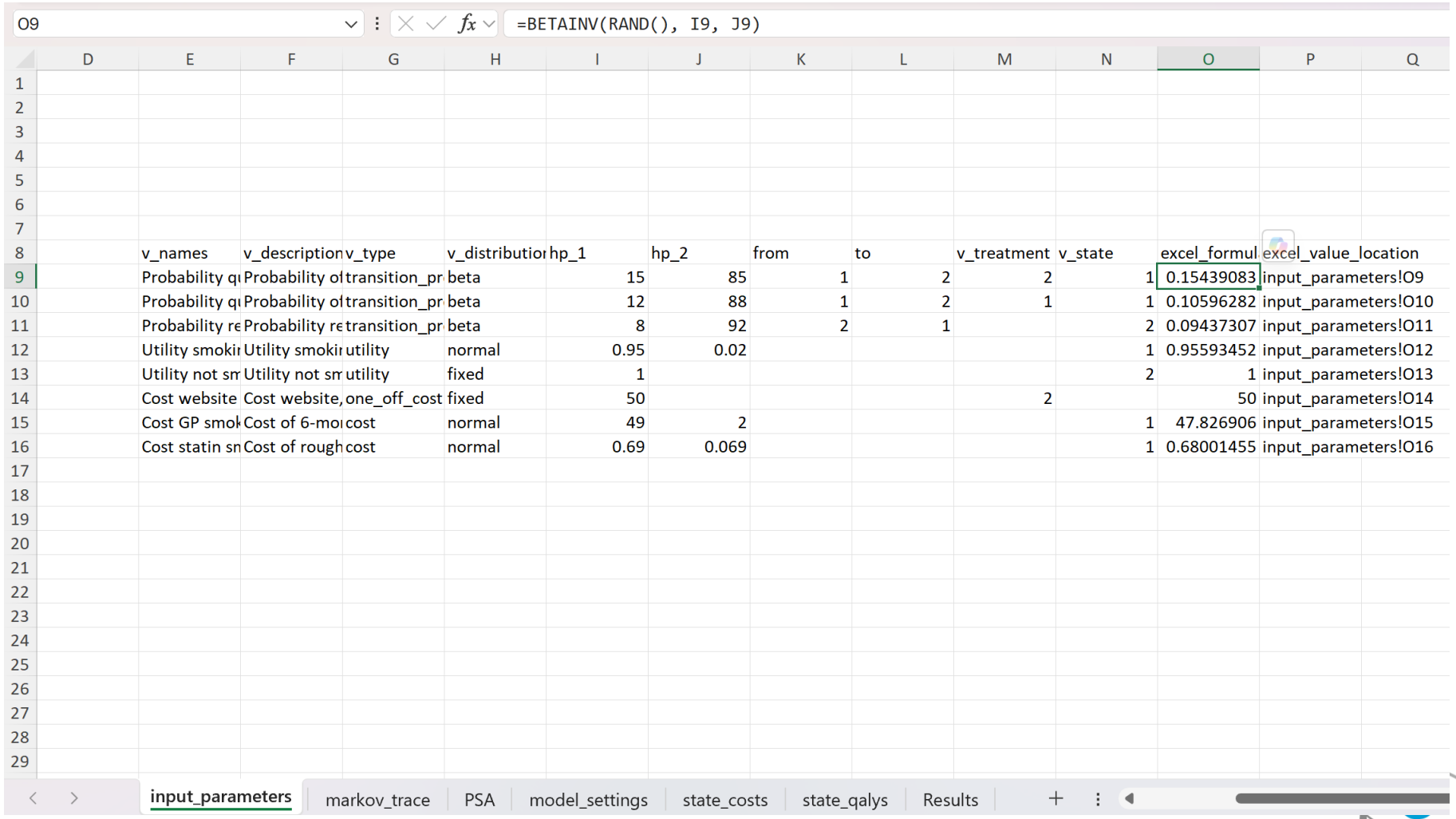
Output – note formula bar



	v_names	v_description	v_type	v_distributio	hp_1	hp_2	from	to	v_treatment	v_state	excel_formul	excel_value_location
9	Probability q	Probability of	transition_pr	beta	15	85	1	2	2	1	0.15439083	input_parameters!O9
10	Probability q	Probability of	transition_pr	beta	12	88	1	2	1	1	0.10596282	input_parameters!O10
11	Probability re	Probability re	transition_pr	beta	8	92	2	1		2	0.09437307	input_parameters!O11
12	Utility smoki	Utility smoki	utility	normal	0.95	0.02				1	0.95593452	input_parameters!O12
13	Utility not sm	Utility not sm	utility	fixed	1					2	1	input_parameters!O13
14	Cost website	Cost website,	one_off_cost	fixed	50				2		50	input_parameters!O14
15	Cost GP smok	Cost of 6-mo	cost	normal	49	2				1	47.826906	input_parameters!O15
16	Cost statin sn	Cost of rough	cost	normal	0.69	0.069				1	0.68001455	input_parameters!O16

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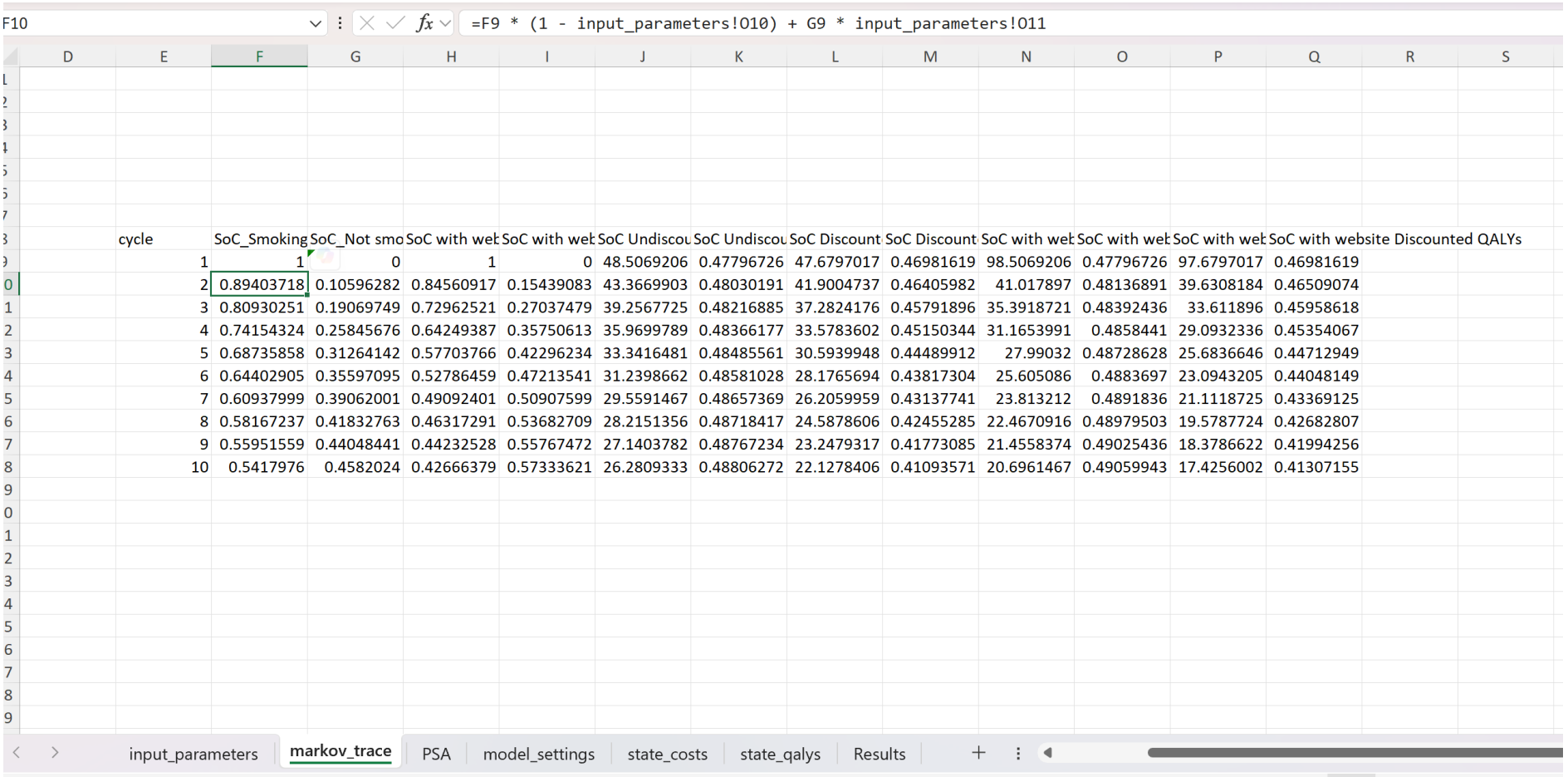
Output – note formula bar



	cycle	SoC_Smoking	SoC_Not smo	SoC with wel	SoC with wel	SoC Undiscou	SoC Undiscou	SoC Discount	SoC Discount	SoC with wel	SoC with wel	SoC with wel	SoC with website Discounted QALYs
1	1	1	0	1	0	48.5069206	0.47796726	47.6797017	0.46981619	98.5069206	0.47796726	97.6797017	0.46981619
2	2	0.89403718	0.10596282	0.84560917	0.15439083	43.3669903	0.48030191	41.9004737	0.46405982	41.017897	0.48136891	39.6308184	0.46509074
3	3	0.80930251	0.19069749	0.72962521	0.27037479	39.2567725	0.48216885	37.2824176	0.45791896	35.3918721	0.48392436	33.611896	0.45958618
4	4	0.74154324	0.25845676	0.64249387	0.35750613	35.9699789	0.48366177	33.5783602	0.45150344	31.1653991	0.4858441	29.0932336	0.45354067
5	5	0.68735858	0.31264142	0.57703766	0.42296234	33.3416481	0.48485561	30.5939948	0.44489912	27.99032	0.48728628	25.6836646	0.44712949
6	6	0.64402905	0.35597095	0.52786459	0.47213541	31.2398662	0.48581028	28.1765694	0.43817304	25.605086	0.4883697	23.0943205	0.44048149
7	7	0.60937999	0.39062001	0.49092401	0.50907599	29.5591467	0.48657369	26.2059959	0.43137741	23.813212	0.4891836	21.1118725	0.43369125
8	8	0.58167237	0.41832763	0.46317291	0.53682709	28.2151356	0.48718417	24.5878606	0.42455285	22.4670916	0.48979503	19.5787724	0.42682807
9	9	0.55951559	0.44048441	0.44232528	0.55767472	27.1403782	0.48767234	23.2479317	0.41773085	21.4558374	0.49025436	18.3786622	0.41994256
10	10	0.5417976	0.4582024	0.42666379	0.57333621	26.2809333	0.48806272	22.1278406	0.41093571	20.6961467	0.49059943	17.4256002	0.41307155

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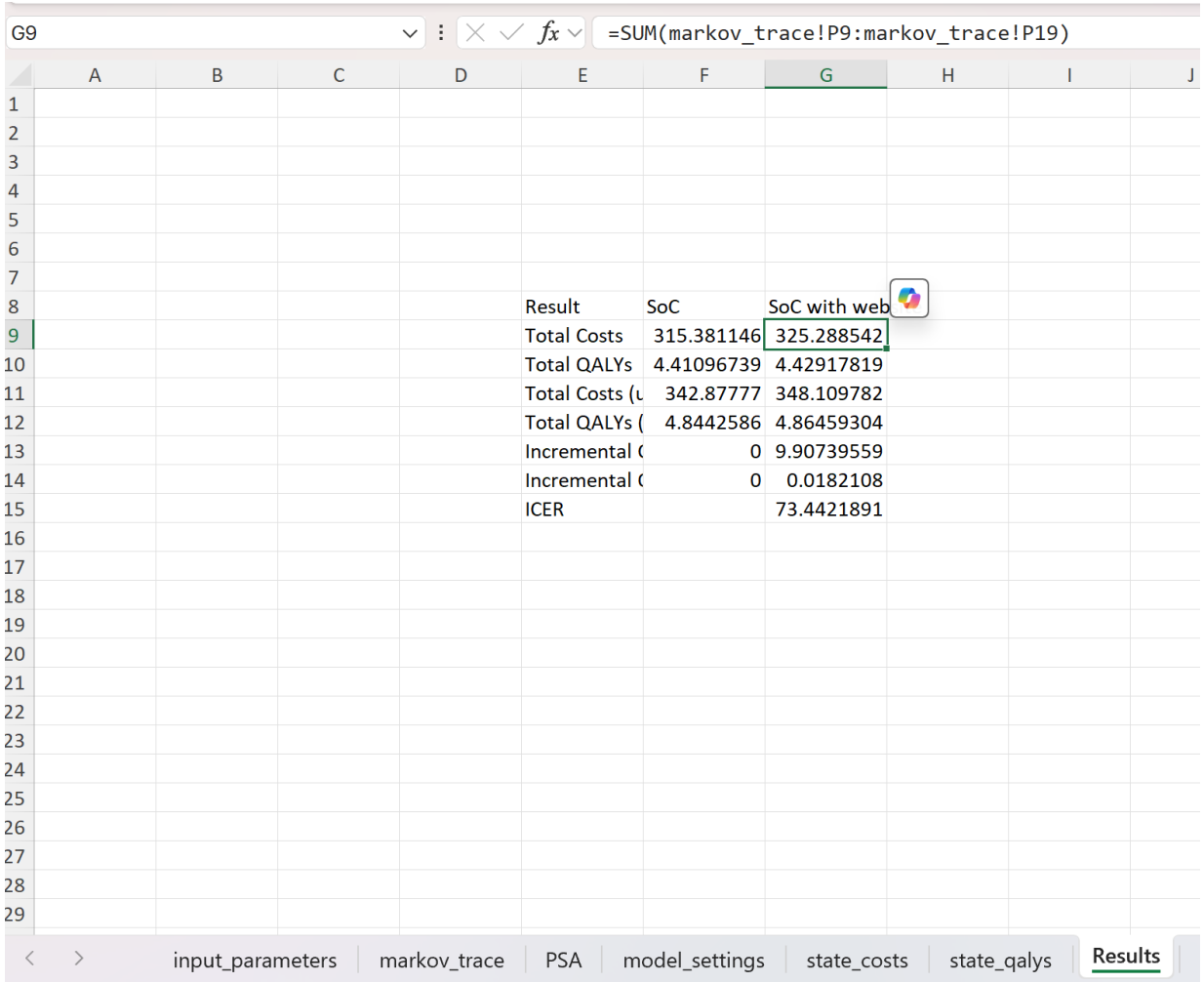
Output – note formula bar



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Comparison of results

	R		Automatically generated Excel	
Treatment	SoC	SoC with website	SoC	SoC with website
Total costs	312.453 (248.579, 374.685)	337.756 (276.242, 400.320)	307.72	331.60
Total QALYs	4.476 (4.346, 4.606)	4.488 (4.373, 4.609)	4.40	4.41
Total costs undiscounted	333.344 (263.673, 401.680)	356.240 (289.118, 424.459)	333.99	354.83
Total QALYs undiscounted	4.832 (4.692, 4.971)	4.846 (4.722, 4.975)	4.83	4.85
ICER	NaN	2029.36		1823.06

- Results based on 1000 random samples
- Numerical variation due to differences in random number generation but otherwise a match.

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Next steps

- The supplied proof-of-concept code works for any time-homogeneous Markov model
- Allow transition matrices to be time-inhomogeneous
- Implement formatting of the Excel format using the options of the openxlsx package
- Export IF and INDEX statements to allow switching between scenarios
- Validation of the conversion on multiple toy and real-world applications

Thank you!

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