Advanced Modeling: Session 2

HEOR 533

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AGENDA

- Types of models
  - Markov models cont.
  - Patient level models
  - Partition Survival Models (A.K.A. Area under the curve models)
- Break
- Activity

Types of Models

Decision tree:

- Decision support tool that uses a tree-like structure to model decisions and their possible consequences
- Can be evaluated at the cohort or individual level

State Transition models:

- Discrete set of mutually exclusive health states evaluated at regular intervals to determine the population in each health state
- Can be evaluated at the cohort or individual level

Partition Survival model (A.K.A. Area under curve model)

- Cohort model with a finite number of health states
- Distribution of the cohort in each health state over time is calculated using the area under the curve of a survival functions

Discrete event simulation:

- Flexible modeling method characterized by the ability to represent complex behavior within, and interactions between individuals, populations, and their environment
- Concerned with the events that occur during the lifetime of individual entities

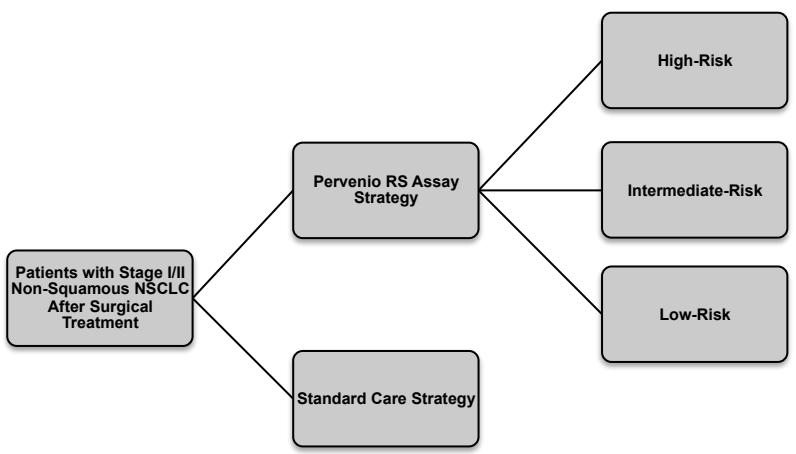
Others: Compartmental (SEIR), Dynamic transmission, Agent based, System dynamic

Extensions to Markov Models

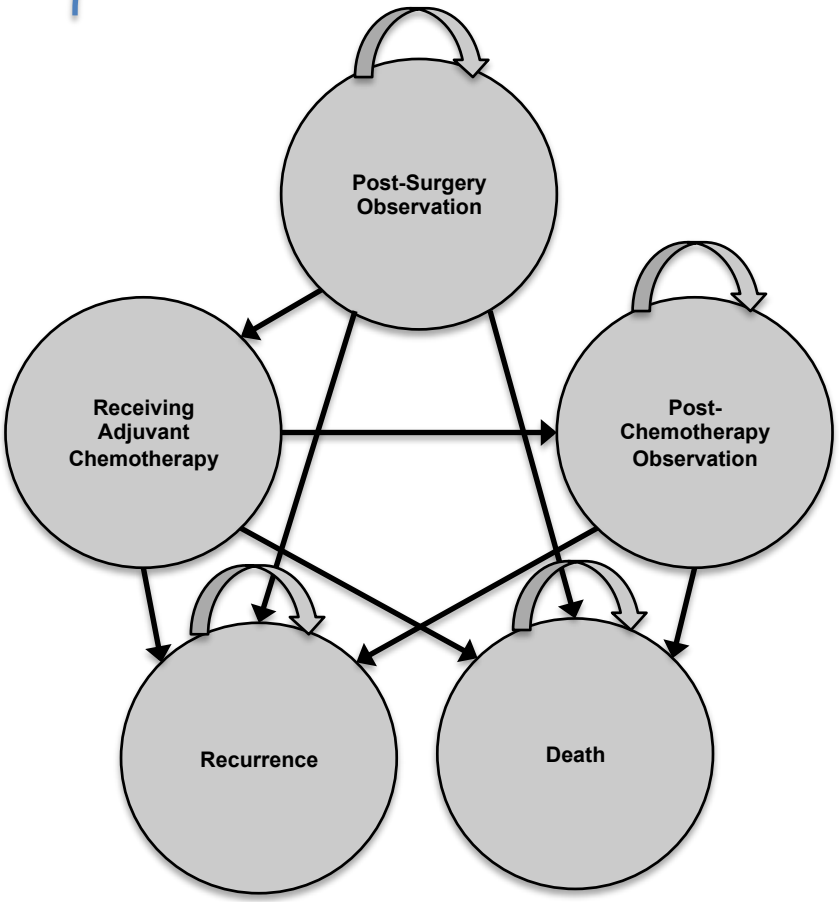
- Hybrid Decision Tree-Markov Model
- Adding time dependency:
  - Absolute model time vs. time within a health state
- Memorylessness
  - Add states

Hybrid models

Decision Tree



Markov Model = Payoff



Roth J and Carlson JJ. et al. 2014

Time varying probabilities

- Markov model:
  - Probability varies with absolute model time vs. time within health state
- Background mortality
  - Age and gender specific probability of death
  - Life Tables
- Parametric survival models
  - E.g., Weibull parameterization

Life Table

Death Rates (per 1000 population per year) by age and sex

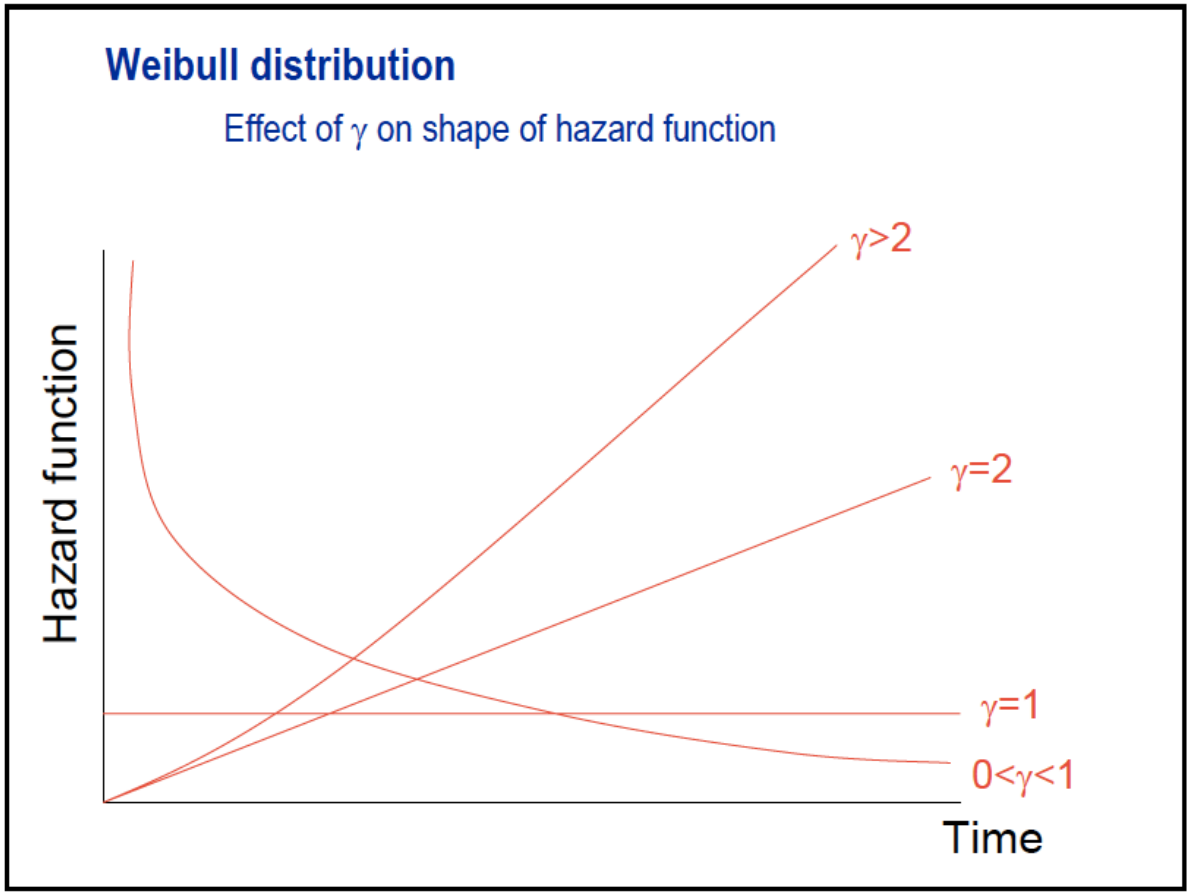
Age	Males	Females
35-44	1.51	0.99
45-54	3.93	2.6
55-64	10.9	6.7
65-74	31.6	19.3
75-84	80.1	53.5
85 and over	187.9	154.8

Yearly transition probabilities by age and sex

Age	Index	Males	Females
35-44	35	0.00151	0.00099
45-54	45	0.00393	0.0026
55-64	55	0.0109	0.0067
65-74	65	0.0316	0.0193
75-84	75	0.0801	0.0535
85 and over	85	0.1879	0.1548

Parametric survival

$$H(t) = \lambda t^{\gamma}$$



Weibull function to transition probabilities

```
Weibull regression -- log relative-hazard form

No. of subjects =          916                 Number of obs    =       916
No. of failures =           52
Time at risk    =      1058651
                                               LR chi2(0)       =     -0.00
Log likelihood  =   -262.00507                 Prob > chi2      =         .

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _cons |  -8.028897   .6855026   -11.71   0.000    -9.372457   -6.685336
-------------+----------------------------------------------------------------
      /ln_p |  -.3040257   .1268008    -2.40   0.016    -.5525507   -.0555008
-------------+----------------------------------------------------------------
           p |   .7378419   .0935589                      .5754801    .9460113
         1/p |   1.355304   .1718536                      1.05707     1.73768
------------------------------------------------------------------------------
```

$$H(t) = \lambda t^{\gamma}$$

lambda	0.00033
gamma	0.73784

Scale. =EXP(-8.028897)

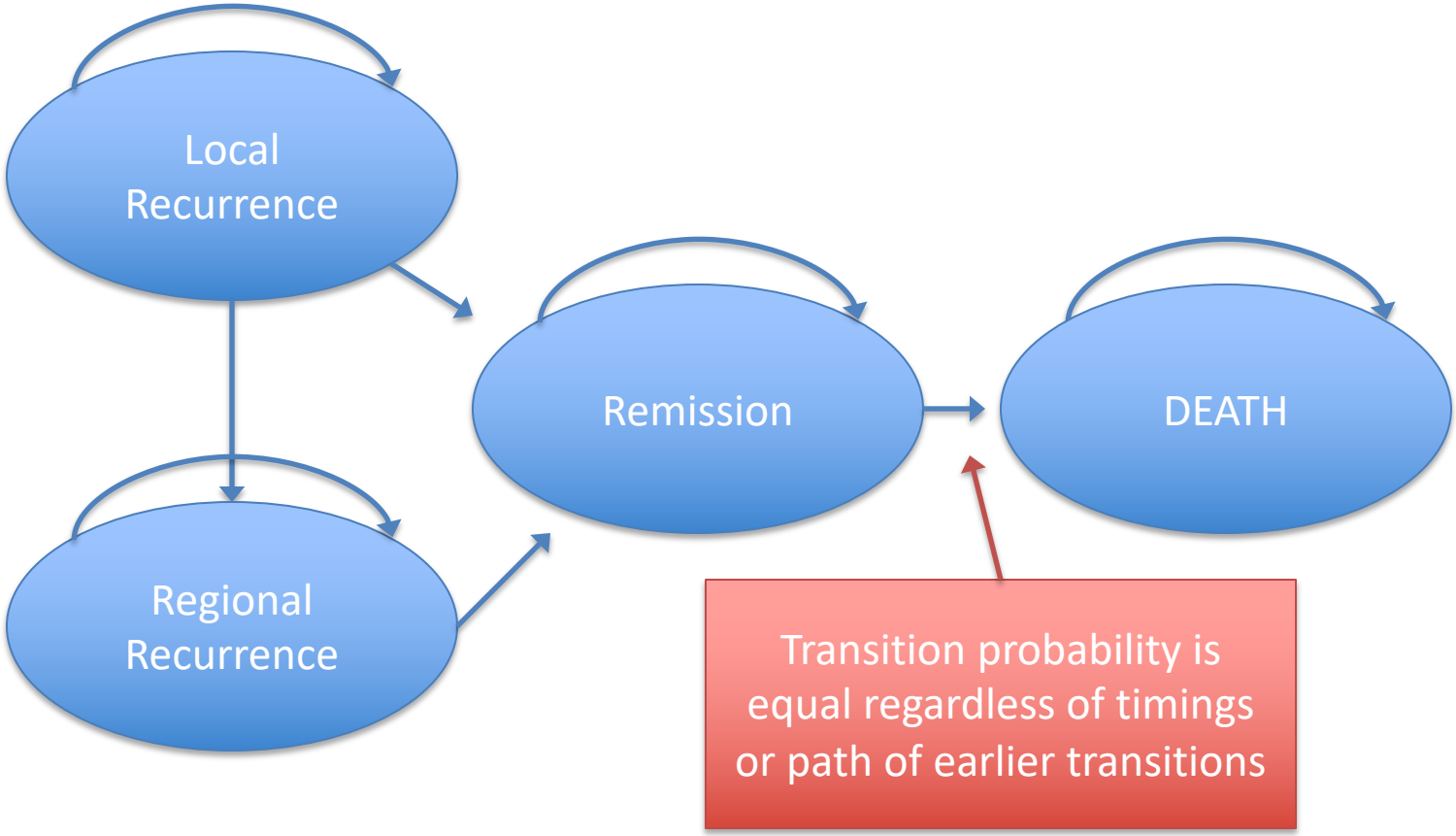
Shape. =EXP (-0.3040257)

=lambda*Day^gamma

=1-EXP($H(t)_{365} - H(t)_{730}$)

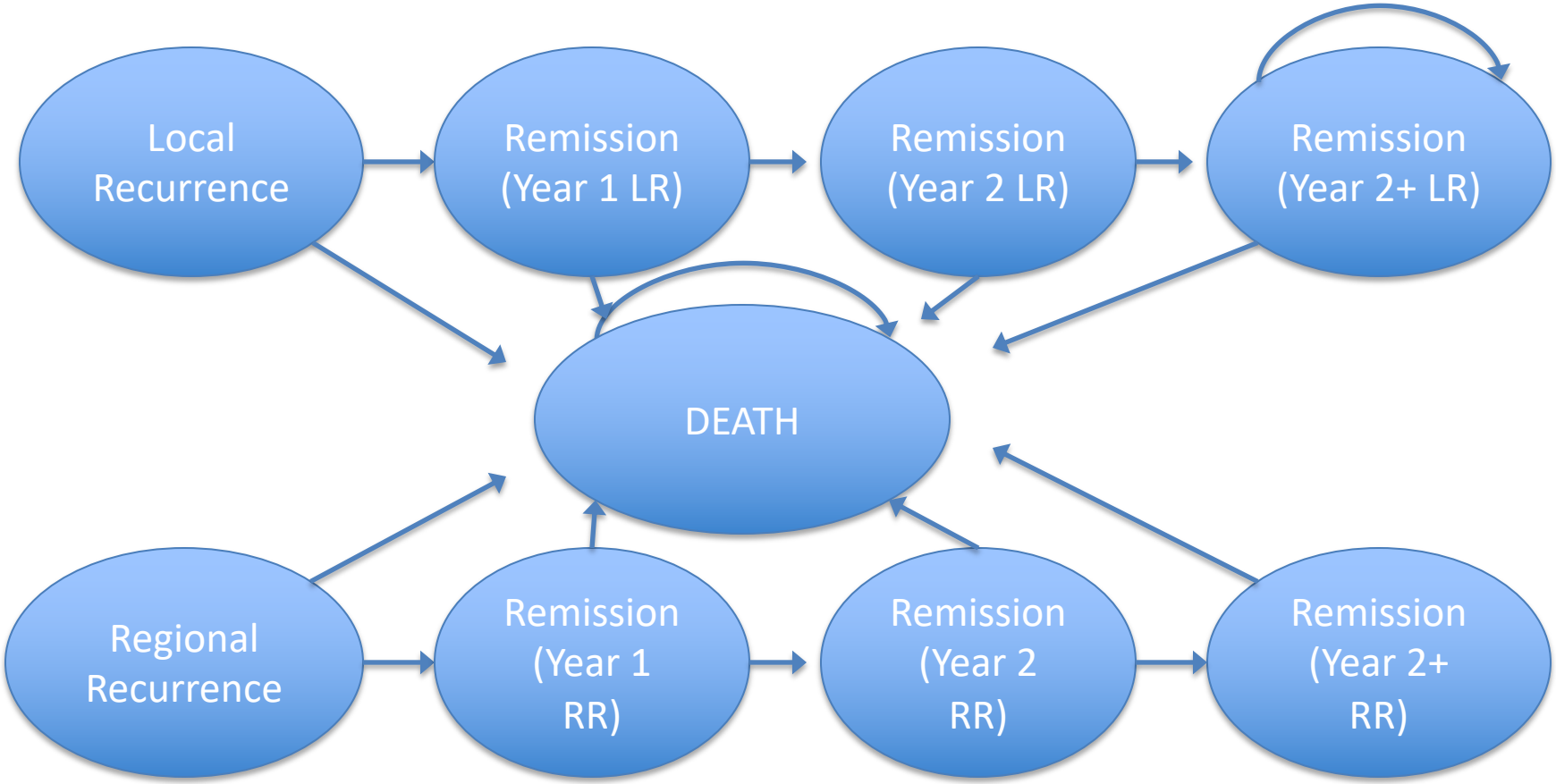
Year	Day	H(t)	TP(t)
0	0	0.0000	
1	365	0.0253	2.50%
2	730	0.0422	1.68%
3	1095	0.0570	1.46%
4	1460	0.0705	1.34%
5	1825	0.0831	1.25%
6	2190	0.0950	1.19%
7	2555	0.1065	1.14%
8	2920	0.1175	1.10%
9	3285	0.1282	1.06%
10	3650	0.1385	1.03%

Health states: Memorylessness



Briggs et al. 2006

Health states: Memoryfullness, Tunnel States



Briggs et al. 2006

Individual-level State Transition Model

- Simulate one individual at a time.
- Evaluated using first-order Monte Carlo simulation → simulate a population.
- Individual-level STMs can keep track of each simulated individual's history (tracker variables)
  - This can greatly reduce the number of health states.
- Population heterogeneity
- Distribution of outcomes

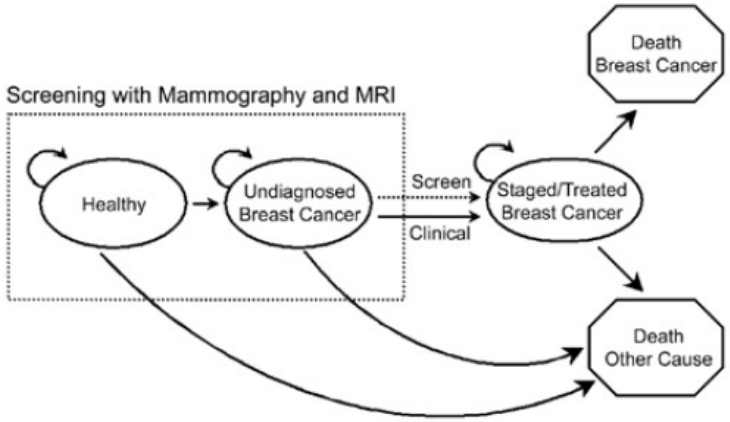
Disadvantages of patient-level models

- Computationally intensive, often requiring millions of individuals to be simulated to obtain stable estimates of the expected value of the outcomes of interest.
- These types of models are also more difficult to debug compared to cohort
- Difficult to evaluate parameter uncertainty
  - Parameter uncertainty
    - Create sample population (10,000 runs)
    - Evaluate parameter uncertainty (10,000 runs)
    - 10,000 X 10,000 = A lot

EXAMPLE: PATIENT LEVEL MODELS

Example 1: Imaging screening strategies for breast cancer in women with BRCA1 gene mutations

- Lee et al. (2008) developed an individual-based STM to compare intermediate and long-term clinical outcomes of imaging screening strategies for breast cancer in women with BRCA1 gene mutations

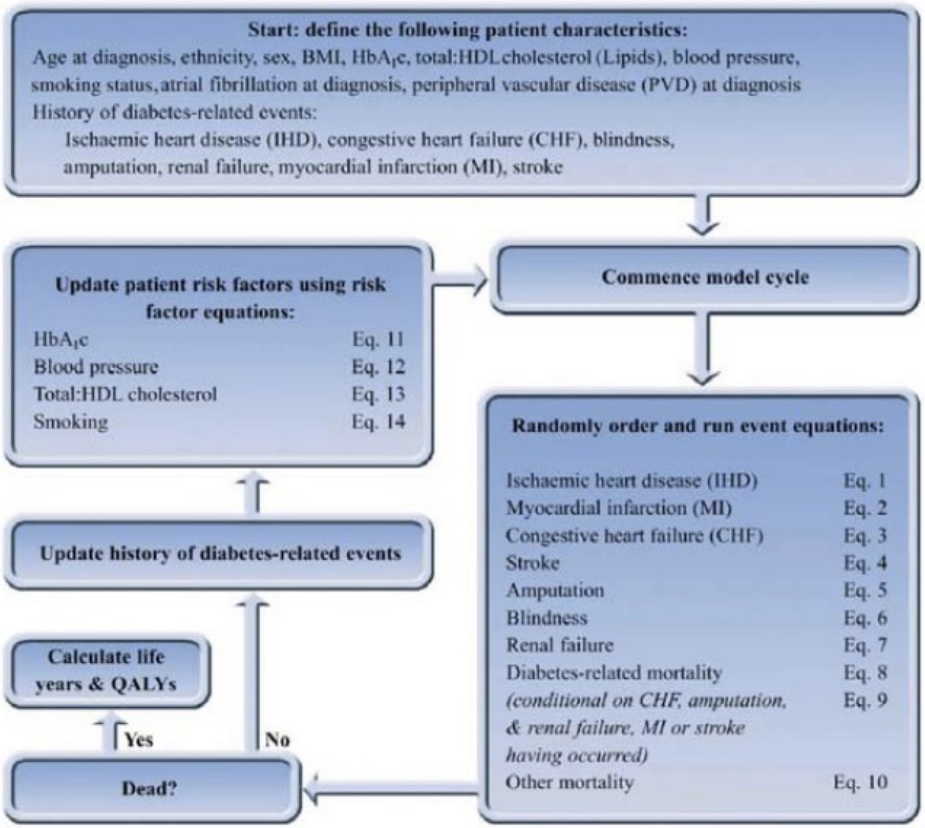


Lee J M et al. Radiology 2008;246:763-771

- Probabilities of clinical detection, lymph node involvement, and distant metastases at diagnosis were a function of the current tumor diameter
- Monte Carlo microsimulation made it possible to track tumor diameter and other characteristics of each individual throughout the model.

Siebert et al. 2014. ISPOR/SMDM task force

UKPDS microsimulation model



Siebert et al. 2014. ISPOR/SMDM task force

Cohort vs. individual level state transition models

Table 1 – Cohort versus individual-level state-transition models.

	Cohort state-transition models	Individual-level state-transition models
Ease of model development	Higher (if the number of states is limited)	Lower
Ease of model debugging	Higher (if the number of states is limited)	Lower
Ease of communication to nonexperts	Higher	Lower
Markov assumption, memoryless	Yes	No
Ease of modeling many different subgroups	Lower	Higher
Danger of explosion in number of states	Yes	No
Distribution of outcomes (as opposed to only means)	Possible, but technically more difficult	Yes
Report of individual patient histories	No	Yes
Decision-analytic software available	Yes	Yes (need advanced knowledge)

Siebert et al. 2014. ISPOR/SMDM task force

Partitioned survival model

- A partitioned survival model is a type of economic model used to follow a theoretical cohort through time as they move between a set of heath states.
- Unlike a Markov model, the number of people in any state at successive points in time is not dictated by transition probabilities; instead, the model estimates the proportion of a cohort in each state based upon survival equations.

- These types of model are frequently used to model cancer treatments, with separate survival equations for overall survival and progression-free survival.
- Common parametric functions used to describe survival are exponential, Weibull or Gompertz (amongst others).

Partitioned survival model

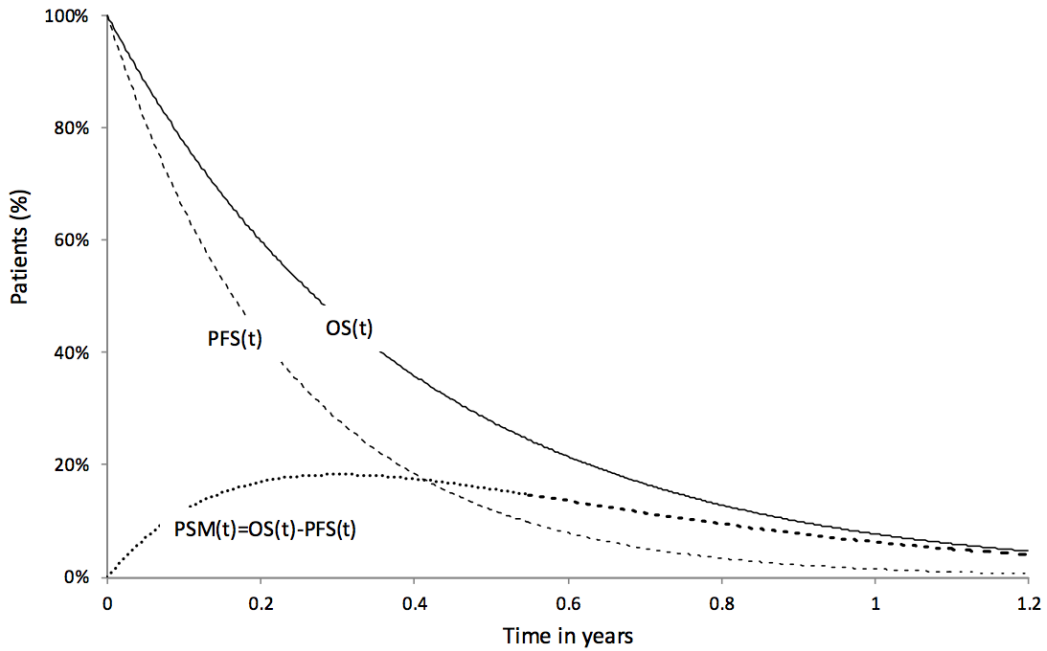


Figure 1: Determining state membership in partitioned survival analysis models, an example of a three-state cancer model [adapted from the Pazopanib company submission to NICE].[10]

PSM(t) denotes progressed state membership (PSM) as a function of time (t).

PartSA versus State transition

- Differ in the types of disease and clinical processes to which they apply.
  - **PartSA can only be applied to processes in which patients move forward through a set of health state**
  - ST can represent any specified transitions.
- PartSA approach, each endpoint (e.g., PFS, OS) is modelled independently of the other endpoints included within the model, whereas in state transition models, clinical events are explicitly related.
  - Can deviate from disease process
  - Problematic for extrapolations
- Differ in the information required to parameterize the models.
  - Cancer trials typically report only PFS and OS i.e., data required for PartSA.
  - These data cannot be used to derive the time-to-event data required for state transition modelling in a straightforward manner, as PFS describes the combination of progressions and deaths from the progression-free state and OS describes the overall probability of death, which is a function of all three transition probabilities.

PartSA Strengths

- Direct correspondence between frequently reported time-to-event endpoints such as PFS and OS and the survival functions used within PartSA to derive state membership estimates.
  - Intuitively appealing, easy to communicate and easy to construct.
- PartSA directly models each survival curve as a function of time since model entry.
  - Straightforward to reflect any time-dependencies in the event rates (or treatment effects on event rates) corresponding to each survival curve.
- Directly models OS→ generally provides accurate predictions of within trial OS
- PartSA can be implemented using summary data on these same endpoints.
  - Accessing IPD for data sources other than the pivotal trial may be difficult if these data are held by competitor companies or parties not directly linked to the appraisal process.
- Indirect comparisons of cancer treatments commonly provide estimates of hazard ratios for the PFS and OS endpoints→can be incorporated in to a PartSA model by applying the hazard ratios to the hazard (or cumulative hazard) corresponding to the relevant reference treatment survival curve.

PartSA Limitations

- Fundamental structural assumption, that the survival functions modelled are independent.
  - Include some of the same events (e.g. PFS and OS curves include the same pre-progression deaths);
  - Events are structurally dependent (e.g. death cannot be followed by progression and time spent progression-free contributes to time spent alive);
  - Intermediate events are often prognostic for later events (e.g. progression is generally considered prognostic for mortality).
- For the within-trial period, these dependencies are reflected in the data and should therefore be closely reflected in the PartSA results.
- However, for analyses that model beyond the trial period, dependencies between endpoints are ignored with potentially important implications for extrapolation.

PartSA summary

- Commonly used (oncology)
- Intuitively appealing
- Feasible
- Potential for bias
- External validation is key

Discrete Event Simulation

- Simulation technique originally developed for modeling industrial processes, eg. Factories
- Simulates individual patient with specific characteristics over time
- Patient can experience specific events over time depending on their characteristics and past history
- When to use:
  - Detailed patient history is needed
  - Disease or treatment process includes interactions between individuals, e.g. infectious disease
  - Decision problem involves resource constraints, e.g. access to care

Stahl et al. 2014. ISPOR/SMDM task force

Discrete Event Simulation

- Pros
  - Can track detailed history of patients
  - Model complex diseases such as diabetes
  - Can incorporate interactions and resource constraints
- Cons
  - Data requirements are very, very large
  - A model with complexity that exceeds available data may do more harm than good
  - Difficult to communicate

Stahl et al. 2014. ISPOR/SMDM task force

Infectious disease modeling

- Multiple modeling types
- Overall benefits are not equal to the sum of the individual effects.
  - E.g. Herd immunity
- They differ from other (static) models used in decision sciences in that the risk of infection (AKA. force of infection) is a function of *the number of infectious individuals* in the population (or environment) at a given point in time.

Pitman et al. 2014. ISPOR/SMDM task force

Model Choice

- Issue: Non-linearity with respect to heterogeneous patient characteristics
  - If there are factors which vary between patients (e.g. age) which have a non-linear relationship with the model outcomes (e.g. costs and QALYs), then estimating the model outcomes for a cohort of patients using only average characteristics (e.g. mean age at starting treatment) will provide a biased estimate of the average outcome across the population to be treated.
  - Can use subgroup analysis and subsequent aggregation
    - Becomes problematic when the number of categories required to define groups with homogeneous outcomes becomes large
  - Can use patient level models:
    - The expected costs and benefits across the sampled group should then provide an unbiased estimate provided that a sufficiently large sample and any covariance between the different patient characteristics is correctly taken into account.

https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0088910/pdf/PubMedHealth_PMH0088910.pdf

Model Choice

- Issue: Patient flow determined by time since last event or history of previous events
  - Markovian assumption: Memorylessness
  - Can add additional states and tunnel states
  - Can keep the state-transition framework but to evaluate the model using a patient-level simulation in which a single patient moves between health states stochastically

https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0088910/pdf/PubMedHealth_PMH0088910.pdf

Model Choice

- Issue: Avoiding limitations associated with using a discrete time interval
  - A state-transition model is essentially a discrete time approximation to a continuous real-life process.
  - Bias is reduced if the cycle length is shortened to a value where multiple transitions within one cycle are extremely unlikely and therefore theoretically the bias could be avoided simply by selecting a small enough cycle length.
  - DES may be more efficient is some situations.

https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0088910/pdf/PubMedHealth_PMH0088910.pdf

Model Choice

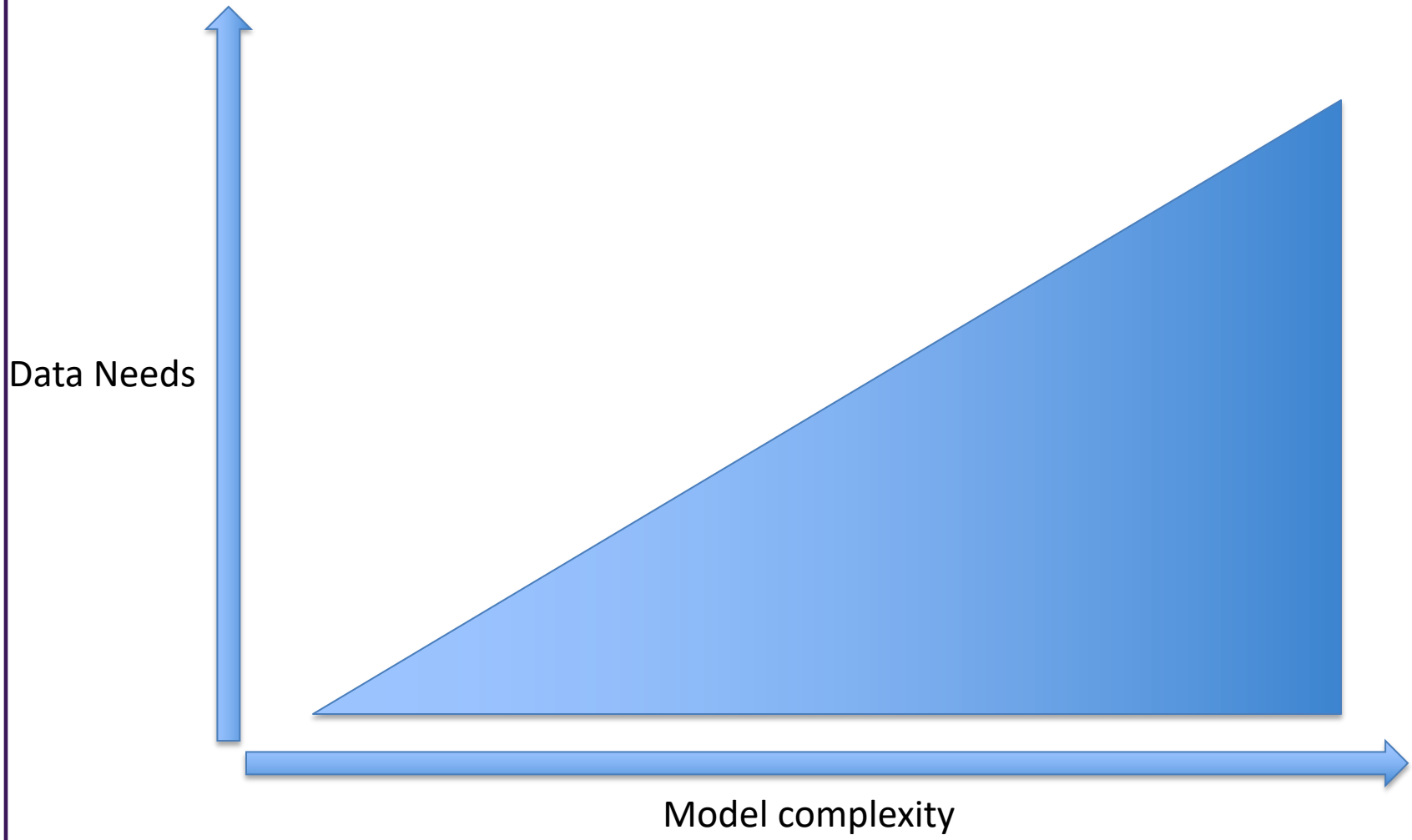
- Issue: Developing a flexible model as an investment for future analyses
- Issue: Modelling systems where people interact with resources or other people
  - DES, agent based, dynamic transition, and others
- Issue: Need for probabilistic sensitivity analysis to assess decision uncertainty
  - Cohort models

https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0088910/pdf/PubMedHealth_PMH0088910.pdf

Summary: Choice of model

- Cohort:
  - Decision Tree: simple decision problems with short time horizon's
  - Markov model:
    - More complex decisions
    - Disease can be accurately captured by a manageable number of health states
    - Recurring events
    - Patient history within modeled time is not a dominant element
- Patient-level:
  - State transition:
    - Incorporate heterogeneity that varies overtime
    - Patient histories
  - Discrete Event Simulation:
    - Interactions and resource constraints
- Infectious disease: Multiple options

Data needs vs. Model complexity



IN CLASS EXERCISE

Project meeting sign-up

- 1/16
  - 8:40 – 9:00:
  - 9:00-9:20:
  - 9:20 – 9:40:
  - 9:40 – 10:00:
  - 10:00 – 10:20:
  - 2:00-2:20:
  - 2:20-2:40:
  - 2:40-3:00:
- 1/18
  - 8:40 – 9:00:
  - 9:00-9:20:
  - 9:20 – 9:40:
  - 9:40 – 10:00:
  - 10:00 – 10:20:
  - 10:20-10:40:
  - 10:40-11:00:

- Hans Rosling's 200 Countries, 200 Years, 4 Minutes:
  - http://www.youtube.com/watch?v=jbkSRLYSojo
- **Iguana vs Snakes**
  - https://www.youtube.com/watch?v=el4CQj-TCbA

Advanced Deterministic Markov Programming in Excel

Briggs Exercise 3.5:
Total Hip Replacement Prosthesis

Agenda

- Background
- Markov model
- Preparing parameters and naming cells
- Life table time-dependent transitions
- Building a Markov model for base case
- Adapting the model for an alternative
- Estimating cost-effectiveness

Background

- Need to reflect impact of intervention on disease through transitioning health states
- Transitions are captured using time-dependent probabilities
- Utilize Briggs Exercise 3.5
  - Markov model based in Excel
  - Intervention: hip replacement prothesis

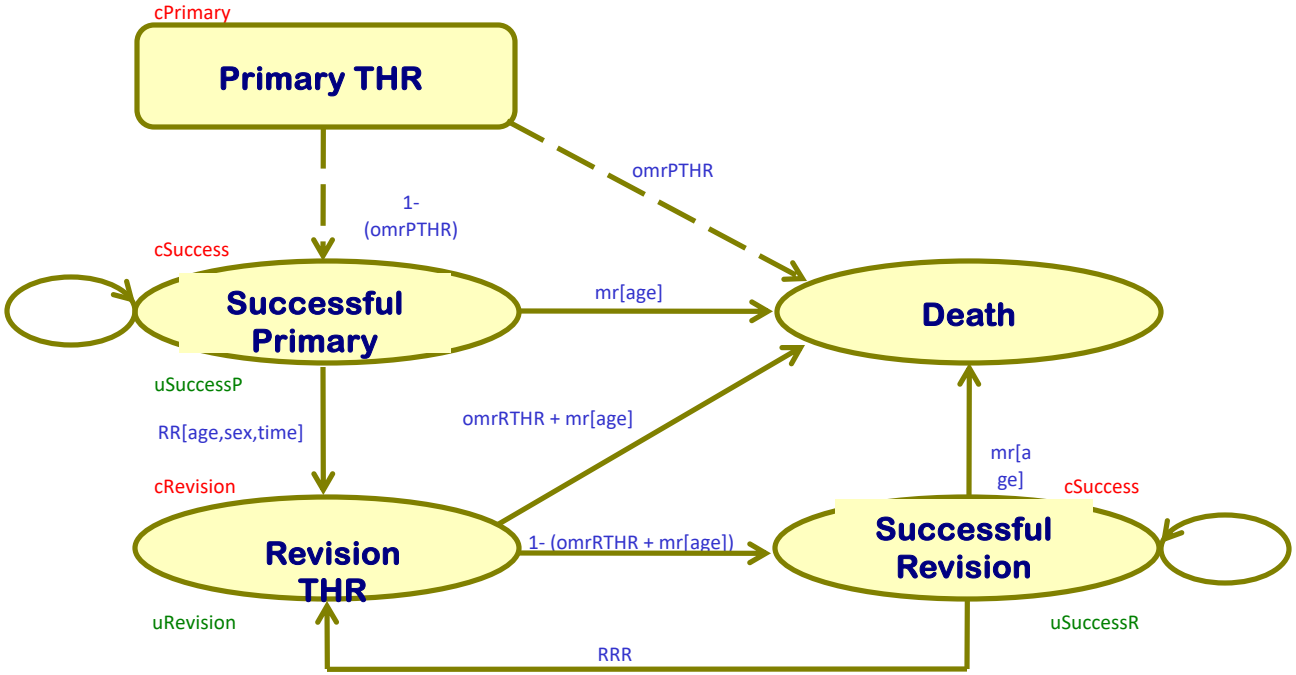
Objectives

- At the end of this exercise, you should be able to…
  - Develop time-dependent transition probabilities using a life table
  - Organize spreadsheets into the major categories of a Markov model
  - Program a Markov trace
  - Estimate an Incremental Cost-effectiveness Ratio (ICER)
  - Estimate an Incremental Net Monetary Benefit (INMB)

Markov model

Begin with Example_3.5a.xls

Markov model: Total Hip Replacement (THR)



- All transition probability variables shown in **Blue**
- State cost variables shown in **Red**
- State utility variables shown in **Green**

Markov model

- Comparing 'Standard' hip replacement prosthesis to 'NP1' Prosthesis
- The exercise spreadsheet has multiple tabs
  - <Analysis> for inputs of patient characteristics
  - <Parameters> for definitions and values
  - <Life tables> for age-dependent survival
  - <Hazard function> for demographic and prosthetic-related failure
  - <Standard> models outcomes of each cycle for base-case intervention
  - <NP1> models outcomes of each cycle for the comparator prosthesis
- Cells colored yellow indicate locations for input parameters

<Analysis> tab

- Contains pre-set information for analysis
- Select patient *gender* and *age*
- Model results will yield costs and utilities for each arm
- Use this tab to identify ICER

Preparing Parameters
and
Naming Cells

Parameters

- Begin in the <Parameters> tab
- Input Operative Mortality rates in cells B16:B18
  - 2% for each revision procedure
  - 4% for re-revision

omrPTHR	0.02	Operative mortality rate following primary THR
omrRTHR	0.02	Operative mortality rate following revision THR
rrr	0.04	Re-revision risk (assumed to be constant)

- Revision Rates for Prosthesis failure
  - Leave blank for now

Parameters

- Costs
  - Standard and NP1 costs have already been entered
  - Costs of primary THR procedure and treatment success are the same irrespective of the prosthesis type, so are left out
  - Cost of revision is £5294, so enter into B33

cPrimary		-	Cost of a primary THR procedure
cRevision		5294	Cost of one cycle in the Revision THR state (national reference costs for revision hip or knee)
cSuccess		-	Cost of one cycle in a 'success' state (primary or revision)
cStandard	£	394	Cost of standard prosthesis
cNP1	£	579	Cost of new prosthesis 1

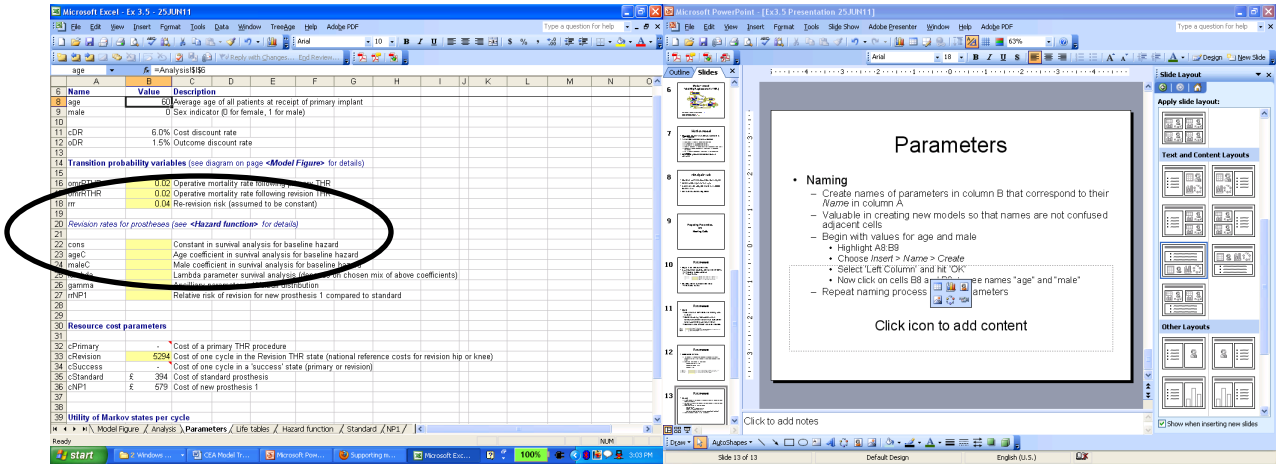
Parameters

- Utilities, cells B41:B43
  - The utilities for successful treatment in successful primary, successful revision, and revision are the same between both arms
  - Input the follow utilities for each cell:
    - Successful primary: 0.85
    - Successful revision: 0.75
    - Revision: 0.30

uSuccessP	0.85	Utility score for having had a successful Primary THR
uSuccessR	0.75	Utility score for having a successful Revision THR
uRevision	0.30	Utility score during the revision period

Parameters

- Naming
  - Create names of parameters in column B that correspond to their *Name* in column A
  - Valuable in creating new models so that names are not confused in adjacent cells
  - Begin with values for age and male
    - Highlight A8:B9
    - Choose *Insert > Name > Create (new version is formulas<defined names < create from selection)*
    - Select ‘Left Column’ and hit ‘OK’
    - Now click on cells B8 and B9, to see names “age” and “male”
  - Repeat naming process for all Parameters



Life Table Transitions for Background Mortality

Begin with Example_3.5b.xls

Revision Risk

- Review Hazard function, Parameters B22:B27, and standard column C.
  - Briggs et al. page 50-56 and 70-72

Life Table Transitions

- Time-dependent transitions exist for other states
  - Background mortality
  - Dependency on age of subject
  - Independent of patient state in model
- This information is contained in the <Life tables> tab
  - Rows 3-9 contains age-gender specific mortality in *deaths per thousand per year*
  - Rate-to-Probability conversion in Rows 14-20

VLOOKUP

- Formulas > Insert Function (far left) > type in “vlookup” > OK

VLOOKUP

- VLOOKUP(lookup_value,table_array,col_index_num,range_lookup)
- **Lookup_value** The value to search in the first column of the table array (array: Used to build single formulas that produce multiple results or that operate on a group of arguments that are arranged in rows and columns. An array range shares a common formula; an array constant is a group of constants used as an argument.). Lookup_value can be a value or a reference. If lookup_value is smaller than the smallest value in the first column of table_array, VLOOKUP returns the #N/A error value.
- **Table_array** Two or more columns of data. Use a reference to a range or a range name. The values in the first column of table_array are the values searched by lookup_value. These values can be text, numbers, or logical values. Uppercase and lowercase text are equivalent.
- **Col_index_num** The column number in table_array from which the matching value must be returned. A col_index_num of 1 returns the value in the first column in table_array; a col_index_num of 2 returns the value in the second column in table_array, and so on. If col_index_num is:
- Less than 1, VLOOKUP returns the #VALUE! error value.
- Greater than the number of columns in table_array, VLOOKUP returns the #REF! error value.
- **Range_lookup** A logical value that specifies whether you want VLOOKUP to find an exact match or an approximate match:
- If TRUE or omitted, an exact or approximate match is returned. If an exact match is not found, the next largest value that is less than lookup_value is returned. The values in the first column of table_array must be placed in ascending sort order; otherwise, VLOOKUP may not give the correct value. For more information, see Sort data.
- If FALSE, VLOOKUP will only find an exact match. In this case, the values in the first column of table_array do not need to be sorted. If there are two or more values in the first column of table_array that match the lookup_value, the first value found is used. If an exact match is not found, the error value #N/A is returned.

Life Table Transitions

- Rename <Life tables> C15:E20 as ‘Lifetable’
- Go to <Standard> tab
  - ‘Death Risk’ Column E is Background mortality
  - In E7, nest two VLOOKUP(…) functions within an IF(…) function dependent on age and gender
  - VLOOKUP(lookup_value,table_array,col_index_num,range_lookup)
  - Age and gender are based on your <Parameters>
  - F (IF, male, VLOOKUP, A7, age, lifetable)
- The formula can appear as follows for E7

=IF(male=0,VLOOKUP(A7+age,lifetable,3,1),IF(male=1,VLOOKUP(A7+age,lifetable,2,1),"error"))

- Rename E7:E66 as ‘mr’ for mortality rate

Transition probabilities

- At this point, we have two key types of transition probabilities for a Markov model:
  - Constant
  - Time-dependent (tabular)
  - Briggs et al also addresses how to implement parametric-based transition probabilities (from survival function)

Building a Markov model for the Standard Prosthesis

Begin with Example_3.5c.xls

Markov Trace

- First must generate a Markov trace
  - Show numbers of patients that are in any one state at any one time
  - Uses <Standard> columns G to L
  - H to K represent four main model states
  - G represents initial procedure
  - L provides a check: sum across G-K must equal size of original cohort
- Cohort size is 1,000 (PrimaryTHR)

Define Transition Matrix

- Begin by defining a Successful Primary (SuccessP) in Column H
- Goal is to write equation that works for all of Column H.
  - First think about appropriate value for only H7
  - Then modify equation (if needed to generalize)
  - *F*(G6, omrPTHR, H6, standardRR, mr)
- Formula can appear as follows in H7:

=G6*(1-omrPTHR)+H6*(1-@standardRR-@mr)

Define Transition Matrix

- Define RevisionTHR next in I7
- This will be 0 cohorts for the first cycle since everybody is either in the primary treatment or death
- F (H6, standardRR, J6, rrr)
- Formula can appear as:

  =H6*@standardRR+J6*rrr

Define Transition Matrix

- Define Successful Revision (SuccessR) next in cell J7
- This will be 0 cohorts for the first cycle since everybody is either in the primary treatment or dead
- F (I6, mr, omrRTHR, J6, rrr)
- Formula can appear as:

=I6*(1-@mr-omrRTHR)+J6*(1-@mr-rrr)

Define Transition Matrix

- Define Death next in cell K7
- This will be based on the number of patients that die in each cycle based on risk and background mortality
- DO NOT calculate death as a remainder of the other three states from 1,000!
- F (H6, mr, I6, J6, G6, omrPTHR, omrRTHR, K6)
- Formula can appear as:

=(H6+I6+J6)*@mr+G6*omrPTHR+I6*omrRTHR+K6

Define Transition Matrix

- Perform a check to make sure Cycle 1 adds up to 1,000 cohorts
  - Cell L6 should appear as '=sum(G6:K6)'
  - Cell L7 should appear as '=sum(G7:K7)
- If this checks out correct, then highlight H7:L7 and drag down the formulas in the 59 rows below
- Re-check that all cohorts in column L add up to 1,000

Standard Results

- Markov trace for Standard Prosthesis now complete
- Calculate costs and effects for this arm
  - In column M, calculate cost
    - In Row 6, multiply the number of cohorts (G6) by <Parameters> costs cStandard and cPrimary
    - For all other rows, multiply number of cohorts of each state by that states associated cost, and divide by the associated discount rate for that cycle
    - F (cPrimary, G7, cSuccess, H7, cRevision, I7, J7, cDR, 'Cycle‘)
  - Formula for M7

=(cPrimary*G7+cSuccess*H7+cRevision*I7+cSuccess*J7)/(1+cDR)^'Cycle'

  - Repeat for M8:M66

Standard Results

- Add up Life-years in Column N
  - Sum total person-years for Columns H:J of the corresponding row in Column N
  - Do no count Death in life-years
- Calculate QALYs in Column O
  - Multiply the number of cohorts in each state of a corresponding row by the <Parameters> utility
  - Divide by the discount rate for the cycle
  - Formula for O7:

    =(uSuccessP*H7+uRevision*I7+uSuccessR*J7)/(1+oDR)^cycle
  - Drag down formula for all cells in Column O

Standard Results

- In M68:O68
  - Sum up costs, life years and QALYs for each column
  - Divide these sums by 1,000 to obtain person-level outcomes
  - Use the automatic naming feature to associate names in M67:O67

Adapting the model for a New Prosthesis (NP1)

Begin with Example_3.5d.xls

NP1 Model

- Create a duplicate of the Standard model for NP1
  - Copy <Standard> A6:O68 over to the corresponding cells in <NP1>
- Introduce treatment effect of NP1
  - Apply treatment effect parameter RRnp1 to column C, thus reducing the hazard ratio
  - Formula in C7:

=1-EXP(lambda***rrNP1***((Standard!A6)^gamma - Standard!A7^gamma))

  - Repeat for all cells in Column C

NP1 Model

- Rename the <NP1> Revision Risk column ‘np1RR’
- Update cells H7 and I7 to refer to ‘np1RR’ rather than ‘standardRR’
  - Copy this adjustment to 59 rows below
- Update cell M6 to refer to the cost ‘_cNP1’ rather than ‘cStandard’
- Update the labels for the results in M68:O68 to refer to NP1cost, NP1lys and NP1qalys

Estimating the Results

Begin with Example_3.5e.xls

ICER

- Click on the <Analysis> worksheet
- Equate the costs and QALYs in the results table (D14:E16) to the labels for the corresponding Standard and NP1 worksheets
- Calculate the 'difference' of each cost and QALY figure with Standard as the base-case:
  - dCost = cost(NP1) – cost(Standard)
  - dQALYs = QALYs(NP1) – QALYs(Standard)
- Calculate the ICER in cell D19
  - ICER = dCost / dQALYs

INMB

- Incremental net monetary benefit (INMB) is dependent on Willingness-to-Pay (WTP) threshold
- Assuming an incremental WTP of $100,000/QALY
  - INMB = WTP*dQALYs – dCost
  - An intervention is cost-effective if INMB > 0
- Calculate the INMB for NP1 vs. Standard
- Compare your results with Example_3.5f.xls

EXTRA SLIDES

Deriving Transition Probabilities: The Hard Part

- Usually obtained from the literature
- Often difficult to find appropriate/relevant data
- Often have data over, say 5 years, when you want to use 1 year cycles
- How do you derive a 1-year transition probability?

Divide by 5?

- After 5 years, 50 out of 100 people are ill: p(1 year) = 0.10?
  - end of year 1: 10 ill, 90 well
  - end of year 2: 19 ill, 81 well
  - end of year 3: 27 ill, 73 well
  - end of year 4: 34 ill, 66 well
  - end of year 5: 41 ill, 59 well

Use this formula

- $tp_1 = 1 - (1 - tp_t)^{1/t}$
- tp_1 is yearly transition probability
- tp_t is the overall probability over time t
- So,
  - $tp_1 = 1 - (1 - 0.50)^{1/5} = 0.129$

$1\text{-}EXP(H(t)_{365} - H(t)_{730})$

Briggs and Sculpher, Pharmacoeconomics 1998;13:397

Rates vs. Risk

- Many texts and articles give a formula for converting rates (over t years) into probabilities (over 1 year) [e.g. Pettiti, Sonnenberg and Beck, Beck and Pauker]
- $p = 1 - e^{-rt}$
- However, use of this formula is only appropriate when actual rates are given
- Serious errors can otherwise occur

Miller and Homan, Med Decis Making 1994;14:52

Rate vs. Risk

- A Rate is
  - events/(population time)
  - in a fixed cohort, a person's time after an event is *removed* from the denominator
- A Risk is
  - probability a person will experience an event over a given period of time
  - in a fixed cohort, a person's time is kept in the denominator
  - most clinical studies give us this

			A	B	C	D
			Cohort/aggregate level/counts		Individual level	
			Expected value, continuous state, deterministic	Markovian, discrete state, stochastic	Markovian, discrete state, individuals	Non-Markovian, discrete-state, individuals
1	No interaction allowed	Untimed	Decision tree rollback	Simulated decision tree (SDT)	Individual sampling model (ISM): Simulated patient-level decision tree (SPLDT)	
2		Timed	Markov model (evaluated deterministically)	Simulated Markov model (SMM)	Individual sampling model (ISM): Simulated patient-level Markov model (SPLMM) (variations as in quadrant below for patient level models with interaction)	
3	Interaction allowed	Discrete time	System dynamics (finite difference equations, FDE)	Discrete time Markov chain model (DTMC)	Discrete-time individual event history model (DT, IEH)	Discrete individual simulation (DT, DES)
4		Continuous time	System dynamics (ordinary differential equations, ODE)	Continuous time Markov chain model (CTMC)	Continuous time individual event history model (CT, IEH)	Discrete event simulation (CT, DES)

Brennan et la. 2006. A taxonomy of model structures for economic evaluation of health technologies