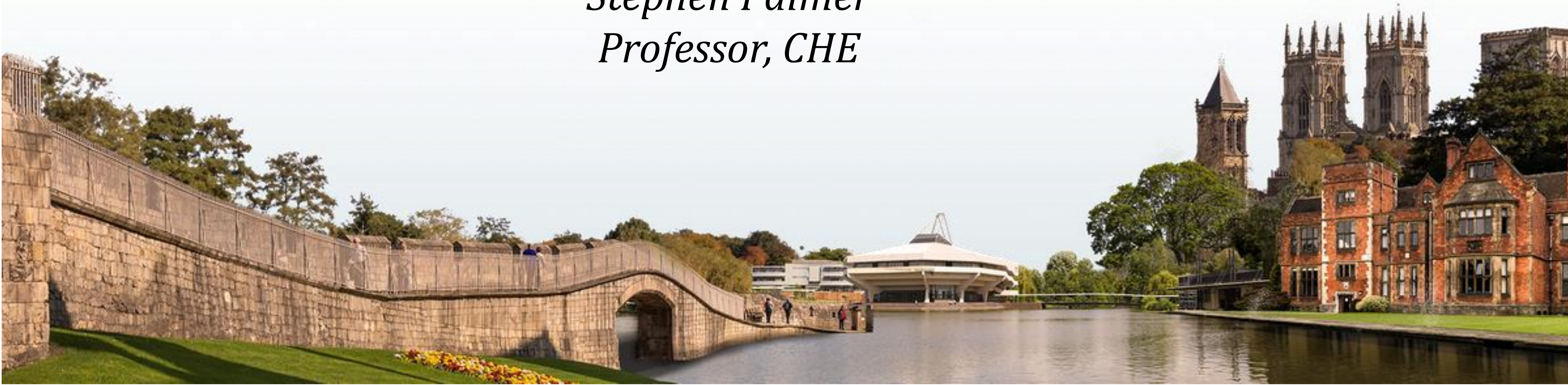
RESEARCH

Centre For Health Economics

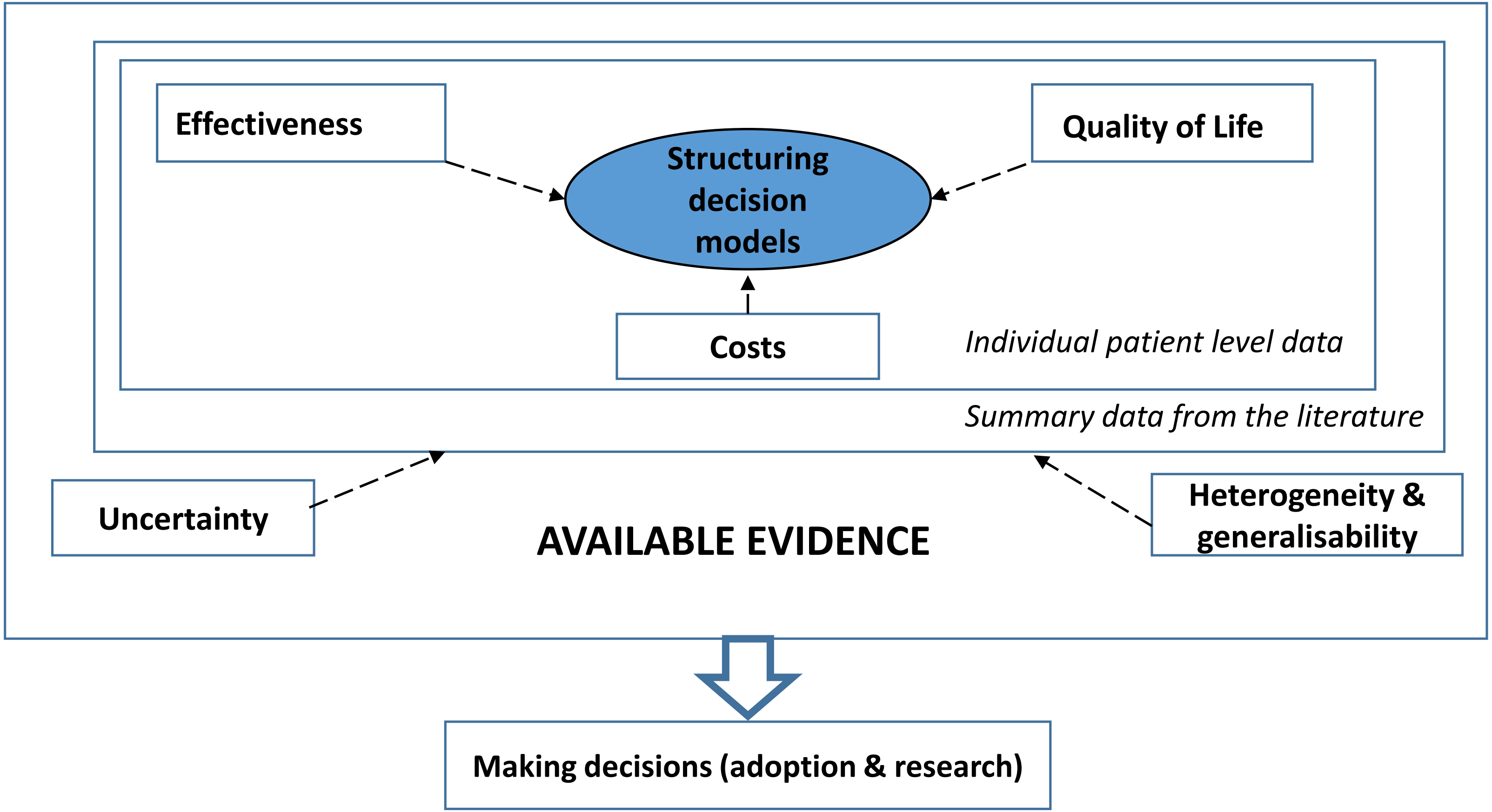
Online Advanced Methods for Cost-Effectiveness Analysis

Presentation 6: Model structure
6.1: Overview and objectives

Stephen Palmer
Professor, CHE



Course structure – where are we up to?



Overview

- Decision models are essential analytic tools for HTA and policy making
  - Represent a systematic approach to decision making under uncertainty
- Provides a formal framework to ensure key objectives for economic evaluation are met:
  - Structure to characterise natural history and impact of alternative treatments
  - Analytical framework to combine all relevant evidence (structure and parameter estimates)
  - Means to translate relevant evidence into estimates of cost and effect
  - Facilitates assessment of uncertainty, heterogeneity and the value of further research

Objectives

- Understand the main modelling approaches and structures commonly used in economic evaluation
- Understand key concepts in decision analysis
- Identify the strengths and limitations of alternative modelling approaches
- Understand how alternative model structures are implemented and used in CEA

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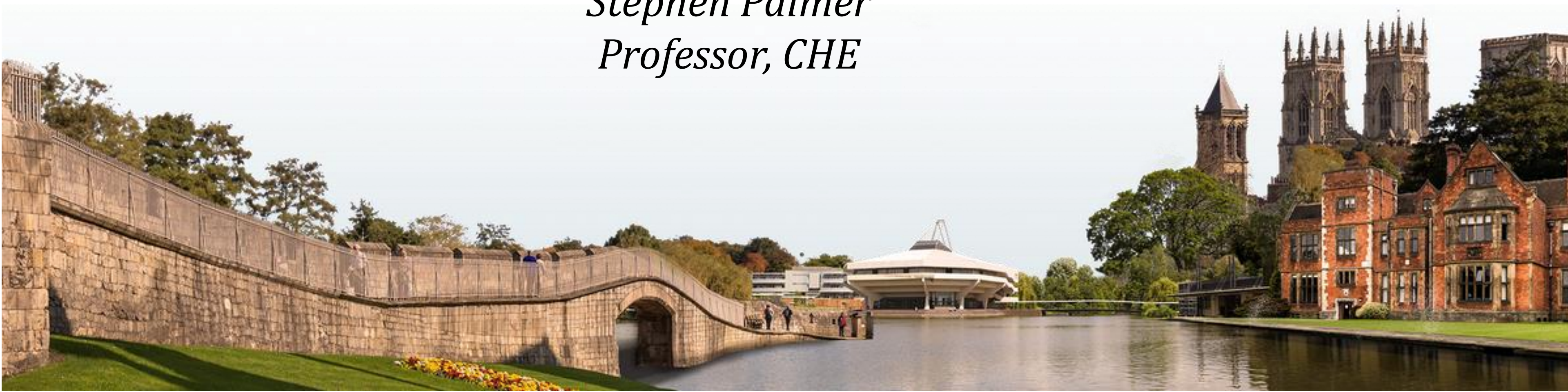
Presentation 6: Model structure
6.2: Introduction to decision models and alternative types

Stephen Palmer
Professor, CHE



Objectives

- Understand the key features of decision models
- Identify circumstances where decision models are required
- Explore key factors which determine the type of model
- Recognise trade-offs between flexibility and computational burden

What is a decision model?

- A mathematical prediction of health-related events
  - Usually for specific groups of patients
  - Events are linked to costs and health outcomes
  - Synthesise data from various sources
  - Uncertainty in data inputs
- Systematic approach to decision making under conditions of uncertainty

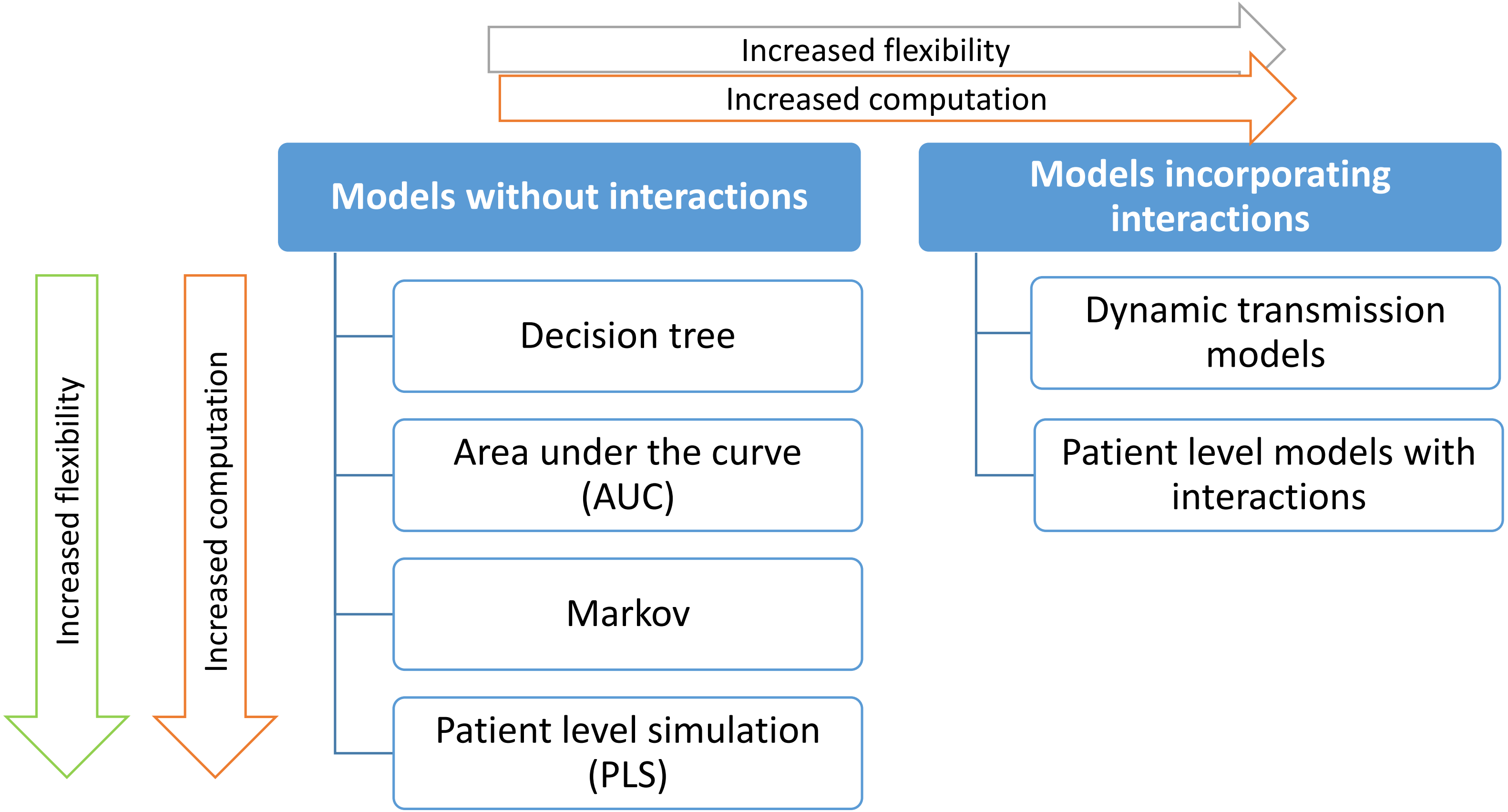
When is a decision model required?

- All the relevant evidence is not contained in a single trial
- Patients participating in trials do not match the typical patients likely to use the technology
- Intermediate outcome measures are used in trials rather than effect on health-related quality of life and survival
- Relevant comparators have not been used, or trials do not include evidence on relevant subgroups
- Clinical trial design includes crossover (treatment switching) that would not occur in clinical practice
- Costs and benefits of the technologies extend beyond the trial follow-up period

Factors determining choice of model structure

- Natural history and care pathway
  - Do relevant health events occur over time?
  - Does the risk of these events alter over time?
  - Does the risk of these events depend on patient history?
- Impact of intervention
  - Is the intervention equally effective over time?
  - Does the initial health change persist when treatment stops?
- Data availability and computational burden
  - Is sufficient data available to inform the required parameters?
  - Can uncertainty be appropriately reflected?
- Transparency and communication

Modelling approaches commonly used in economic evaluation



Summary

- Decision models provide a formal framework to inform decision making in presence of uncertainty
- Models are required in most circumstances to meet the requirements of cost-effectiveness analyses
- A range of factors will influence model choices and alternative structures
- Model types differ in terms of flexibility and computational burden

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Presentation 6: Model structure
6.3: Decision trees and Markov models

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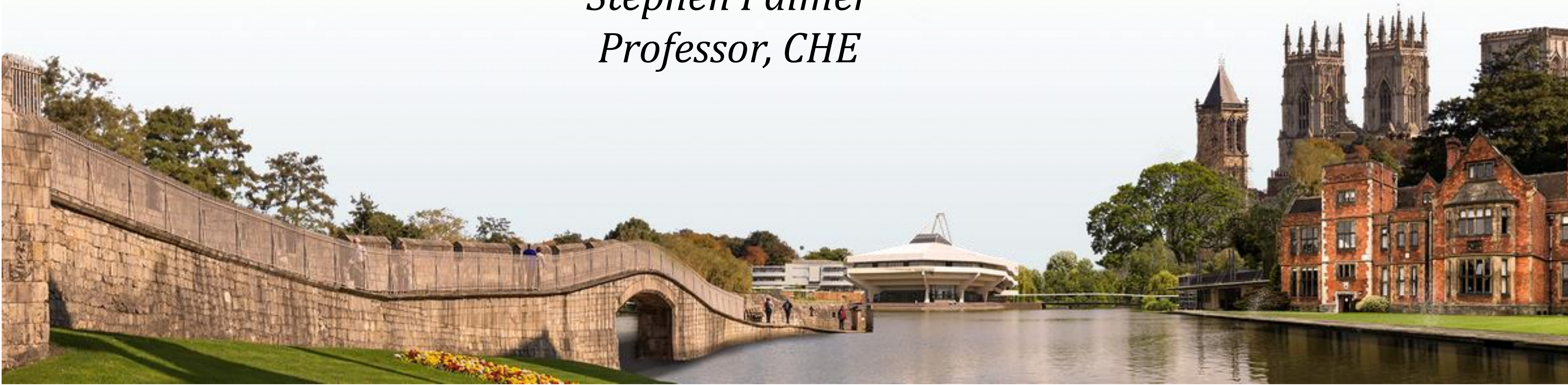
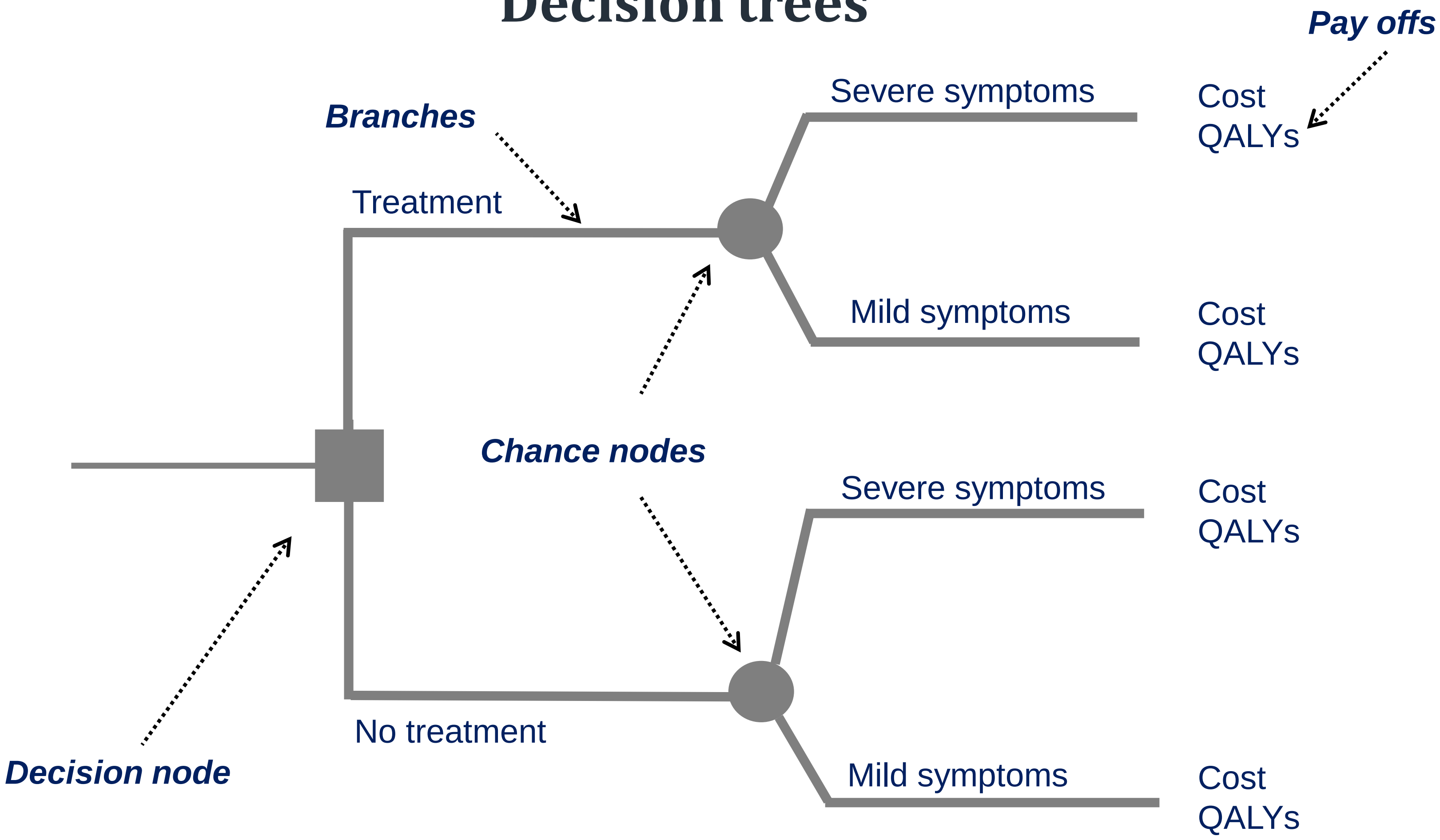


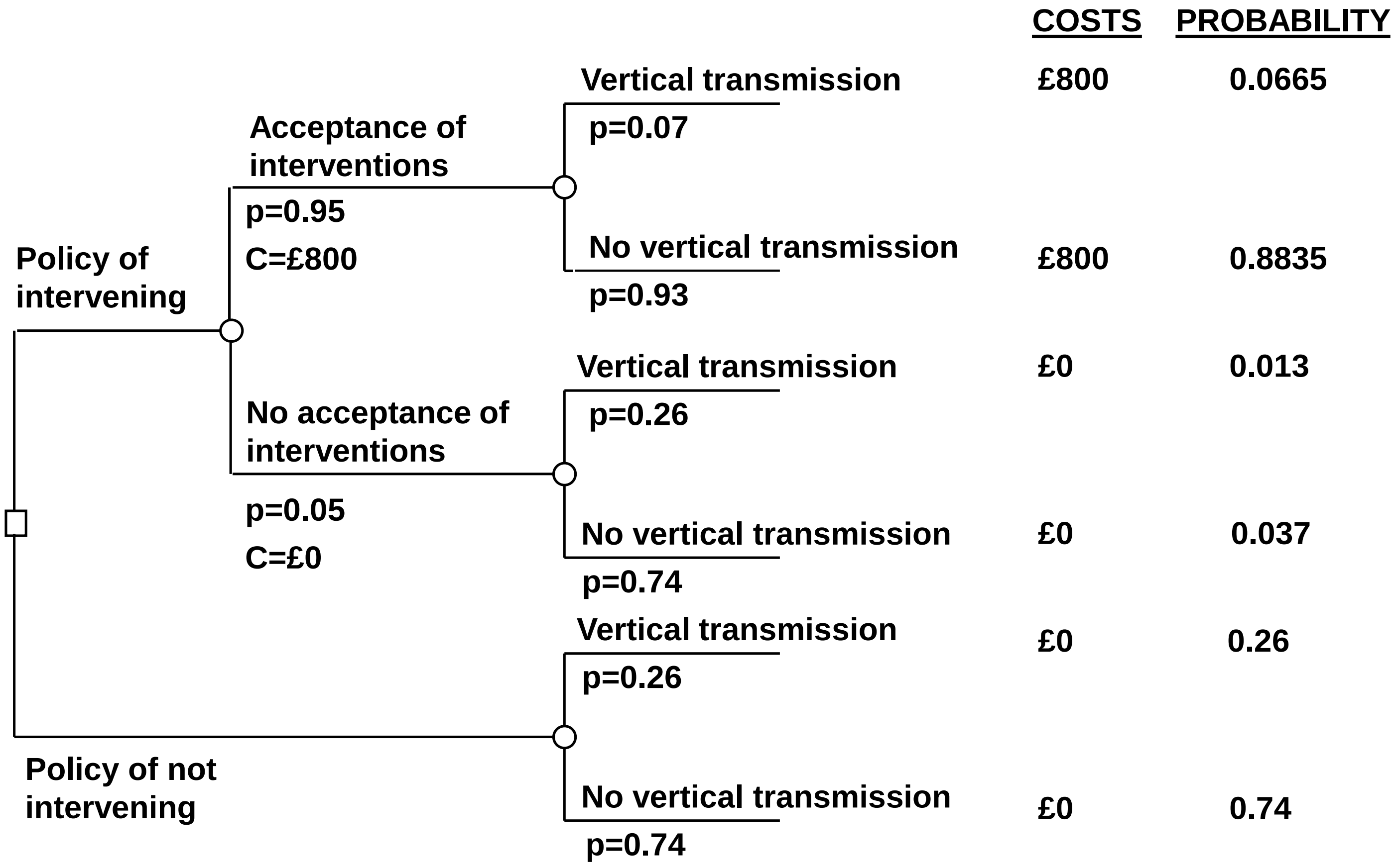
Objectives

- Understand key features of the most common model types
    - Decision trees
    - Markov models
- Appreciate how to evaluate models and the use of cohort simulation
- Explore alternatives ways that Markov models can be used

Decision trees



Example of prevention of vertical transmission of HIV



Adapted from Ratcliffe *et al. AIDS* 1998; 12: 1381-1388

Incremental cost per HIV-infected child avoided

Intervention:

Expected cost: 0.95 x £800 = £760

Risk of vertical transmission:

0.0665 (0.95 x 0.07) + 0.013 (0.05 x 0.26) = 0.0795

No intervention:

Expected cost: £0

Risk of vertical transmission: 0.26

Incremental cost of interventions per HIV-infected child avoided:

$$\frac{\textbf{Differential cost :}\ 760 - 0 = 760}{\textbf{Differential risk :}\ 0.26 - 0.0795 = 0.1805} = £4{,}211$$

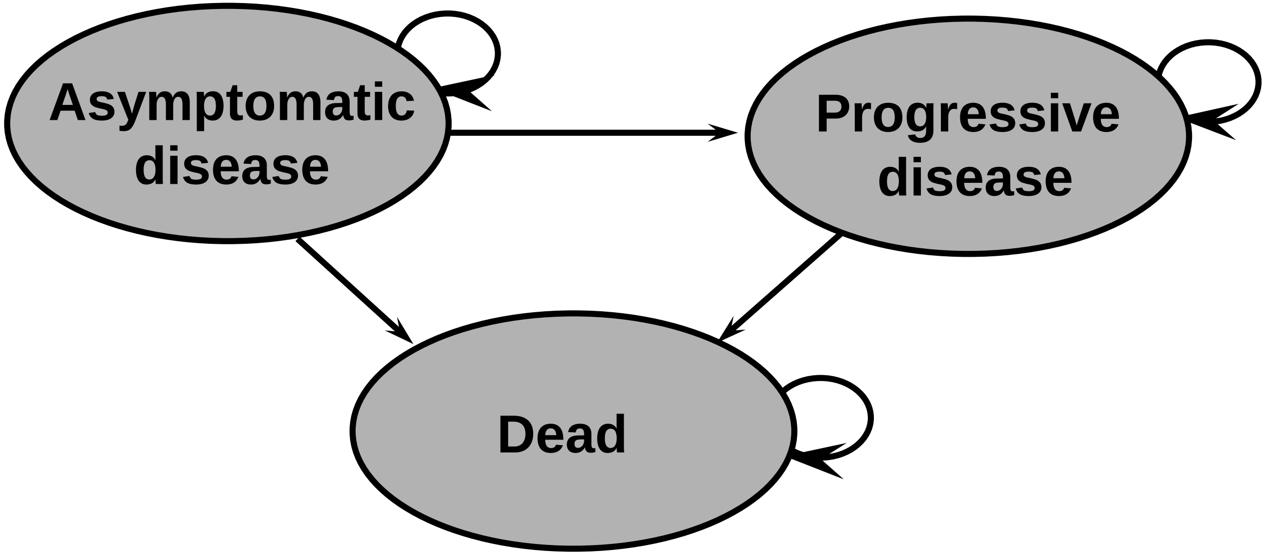
Limitations of the decision tree

- Frequent need to model prognosis
- Decision trees: sequence of events over a particular time period
- Inflexible when events recur over time
- Particular difficulty in modelling chronic diseases: complications, recurrence, remission, mortality
- Decision trees may become excessively ‘bushy’

State-Transition Models – Key Features

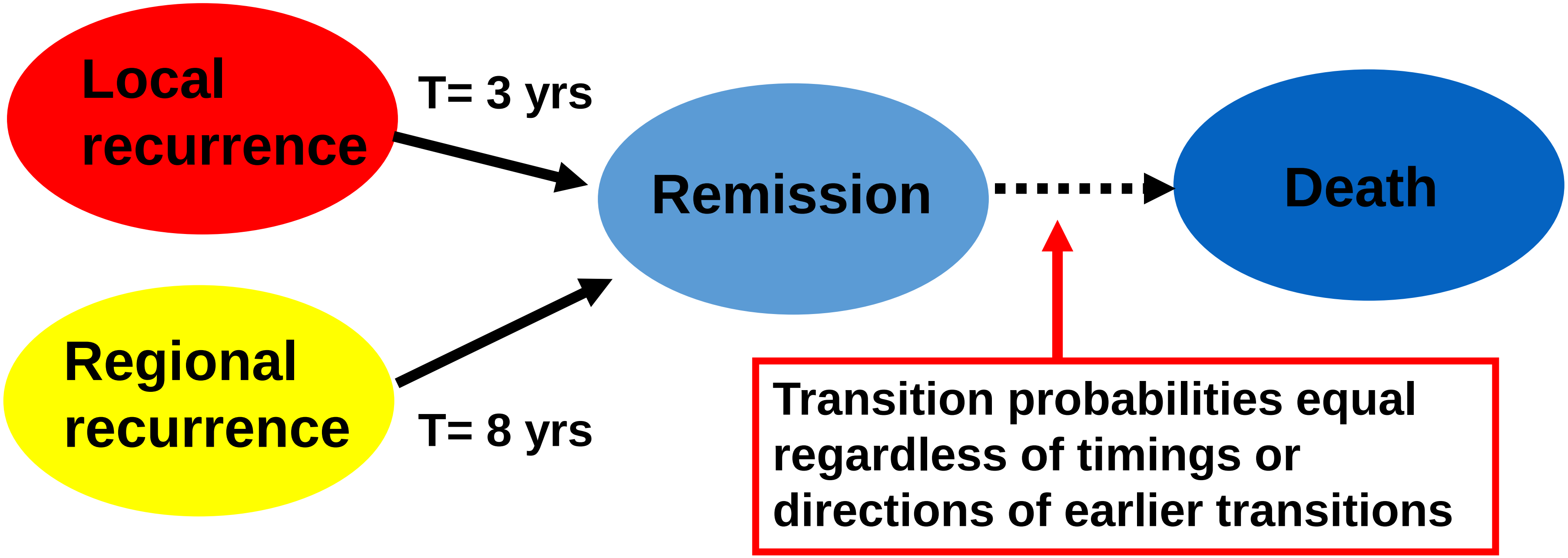
- Simplification of ‘bushy’ decision trees
- Organised around states rather than pathways
  - How individuals move among states (transitions)
  - How likely such moves are (transition probabilities)
- States are mutually exclusive and exhaustive
- Cycle length specifies transition intervals
- State values (costs and health outcomes) assigned
- Most common types:
  - Markov models
  - Area under the curve (AUC) models

The basic Markov chain



Transition from:	Transition to: Asymptomatic	Progressive	Dead
Asymptomatic	0.6	0.3	0.1
Progressive	0	0.8	0.2
Dead	0	0	1

The Markov assumption



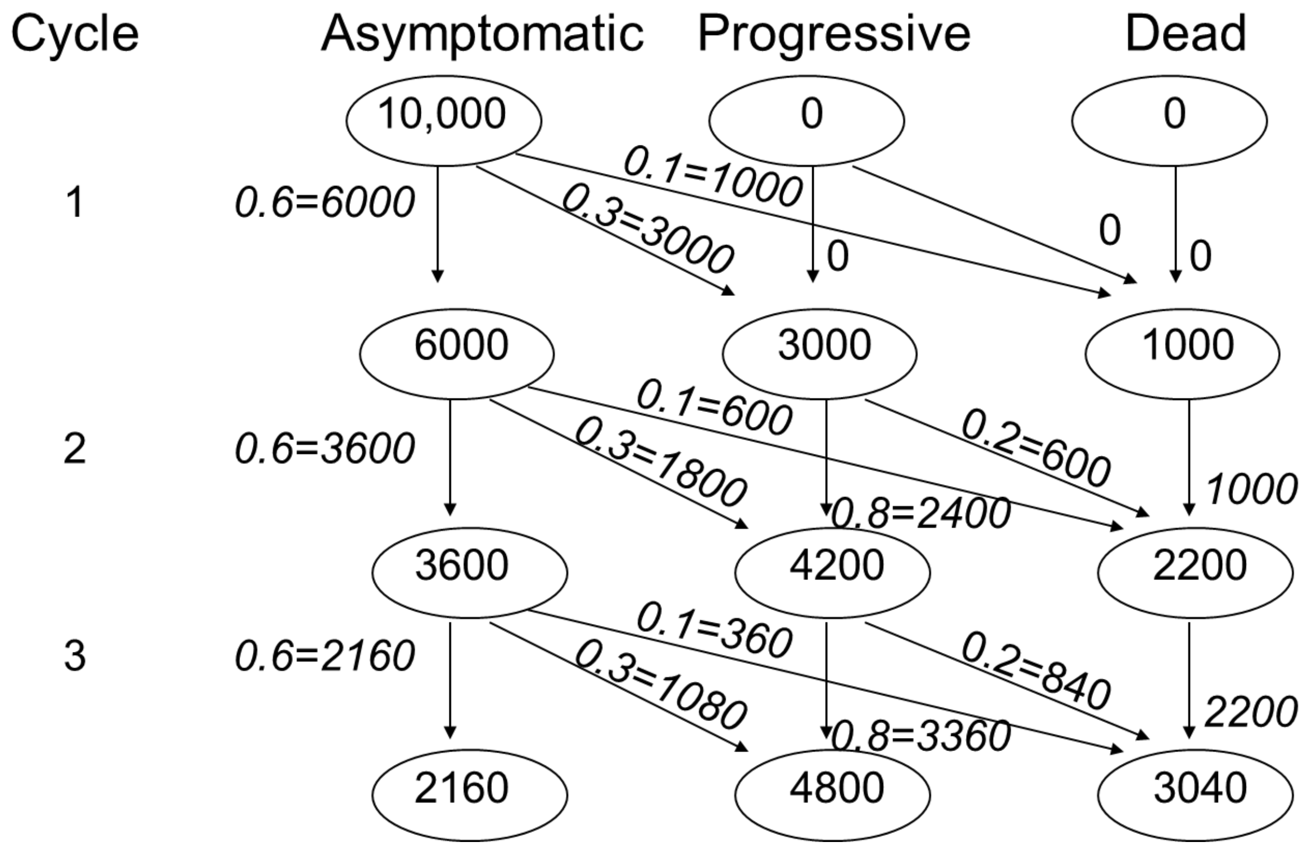
Evaluating Markov chains

- Matrix solution
  - Not possible with discounting
- Cohort simulation
- Individual patient simulation (1st order Monte-Carlo simulation)

Cohort simulation

- Simulates a cohort moving through a model
- A proportion of the cohort in each state/passing down a pathway at a given point in time
- Expected values worked out by weighting these proportions by costs/outcome values
- Focus on expected values: size of cohort irrelevant

Cohort simulation
The concept



Cohort simulation
Calculating expected costs

Cycle no.	Numbers in state (total 1000)			Costs	
	Asymptomatic	Progressive	Dead	Per cycle	Cumulative
0	1000				
1	600	300	100	£30,000	£30,000
2	360	420	220	£42,000	£72,000
3	216	444	340	£44,400	£116,400
4	130	420	450	£42,000	£158,400
5	78	375	547	£37,488	£195,888
6	47	323	630	£32,323	£228,211
7	28	273	699	£27,258	£255,469
8	17	226	757	£22,646	£278,116
9	10	186	804	£18,621	£296,737
10	6	152	842	£15,199	£311,936
11	4	123	873	£12,341	£324,277
12	2	100	898	£9,981	£334,258
13	1	81	918	£8,050	£342,309
14	1	65	934	£6,480	£348,788
15	0	52	947	£5,207	£353,995
16	0	42	958	£4,180	£358,175
17	0	34	966	£3,352	£361,527
18	0	27	973	£2,687	£364,214
19	0	22	978	£2,153	£366,367
20	0	17	983	£1,724	£368,091
21	0	14	986	£1,380	£369,471
22	0	11	989	£1,105	£370,576
23	0	9	991	£884	£371,460
24	0	7	993	£708	£372,168
Expected cost/patient over 24 cycles = £372,168 /1000 = £372.17					

<u>Cost assumptions/cycle</u>

Asymptomatic: £0

Progressive: £100

Dead: £0

Correctly estimating transition probabilities (TPs)

- TPs should be estimated to reflect the cycle length. This can be estimated using the rate (*r*) of the event
- Conversion of probability (*p*) to *r* when *p* is reported for time t_{rep}

$$r = -\frac{\ln(1-p)}{t_{rep}}$$

- Conversion of resulting rate to probability for cycle length, *l*

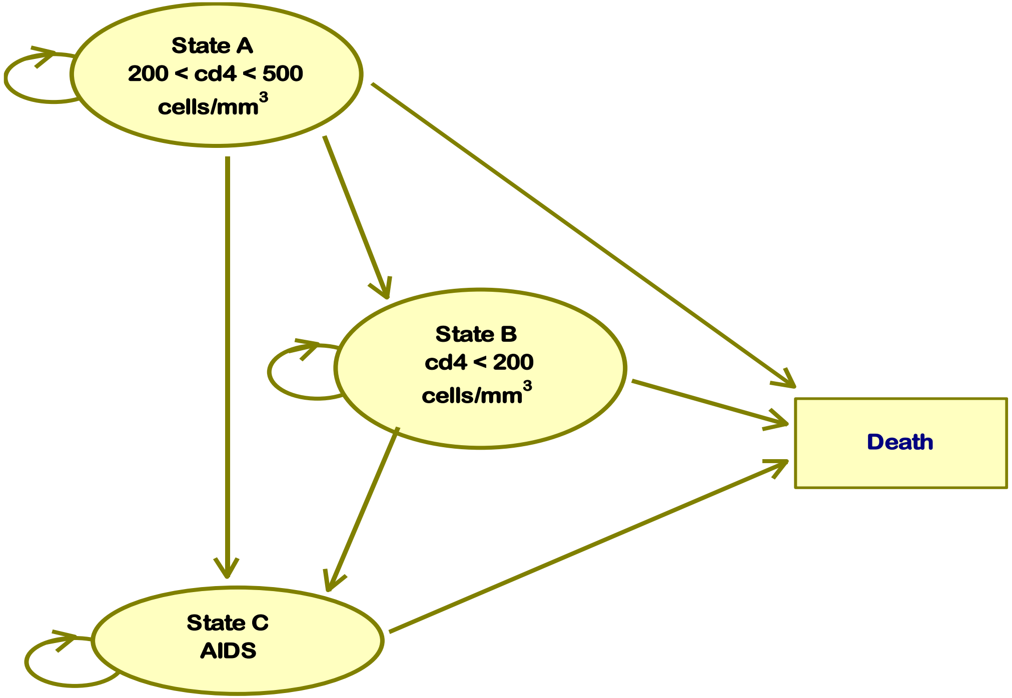
$$p = 1 - \exp(-r.l\ )$$

- Example: convert 5 year probability of 20% to a 1 year probability
  - Rate = $-\frac{\ln(1-0.20)}{5} = 0.04463$
  - 1-year probability = $1 - \exp(-0.04463\ x\ 1)$ = 0.043648

Uses of Markov models

- Estimating costs and effects for comparative interventions
  - Two sets of transition probabilities
  - Often applying a relative treatment effect to baseline transitions
- Extrapolation from trial results assuming no continued treatment effect
  - Trial estimate of treatment effect, Markov estimates the implications
  - Could be decision tree to estimate the effect (e.g. screening)

Example of Markov used for direct comparison
Model structure



Source: Chancellor *et al. PharmacoEconomics* 1997; 12: 54-66

Example of Markov used for direct comparison
Baseline transition probabilities

(a) Transition probabilities - monotherapy

	Transition to:			
Transition from:	State A	State B	State C	State D
State A	0.721	0.202	0.067	0.01
State B	0	0.581	0.407	0.012
State C	0	0	0.75	0.25
State D	0	0	0	1

Assumed a relative effect of combination therapy of 0.509. This was assumed to slow progression between all states. It was applied by reducing the yearly transitions to all worse states

Source: Chancellor *et al. PharmacoEconomics* 1997; 12: 54-66

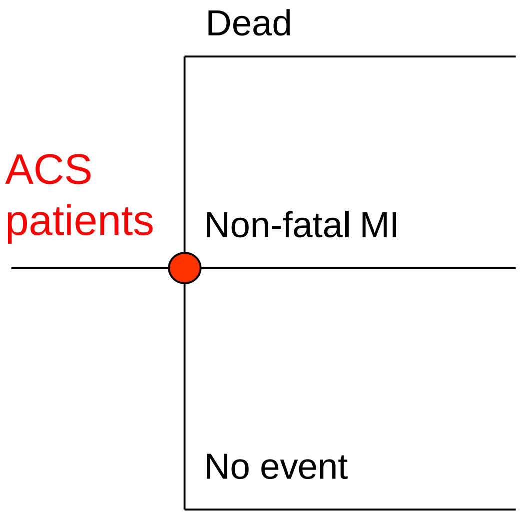
Example of Markov used for direct comparison
Applying the treatment effect

(b) Transition probabilities – combination therapy

	Transition to:			
Transition from:	State A	State B	State C	State D
State A	0.858 (1-sum)	0.103 (0.202 x RR)	0.034 (0.067 x RR)	0.005 (0.01 x RR)
State B	0	0.787 (1-sum)	0.207 (0.407 x RR)	0.006 (0.012 x RR)
State C	0	0	0.873 (1-sum)	0.127 (0.25 x RR)
State D	0	0	0	1

<u>Source</u>: Chancellor *et al. PharmacoEconomics* 1997; 12: 54-66

Markov models for extrapolation



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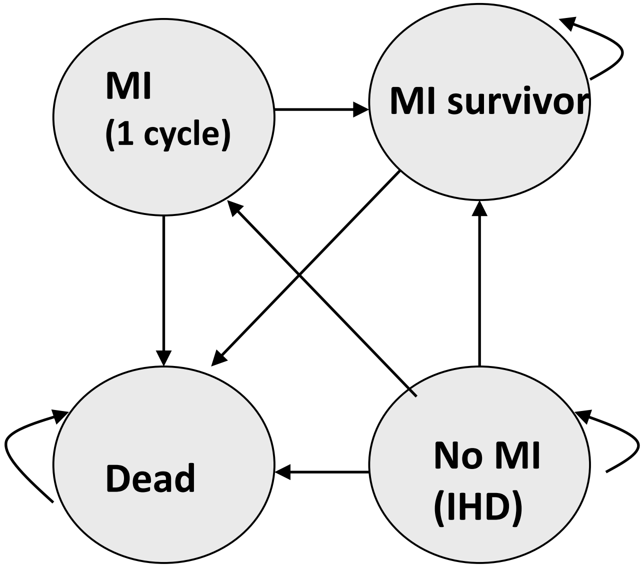
Relative risks from RCTs



Part 1: Baseline event rates

- Observational data from PRAIS-UK (n=1046) and Leeds (n=112)
- Costs of drugs, hospitalisation and procedures

Part 2: GPA effects

- Data from meta-analysis of RCTs

Part 3: lifetime extrapolation

- Observational data from Nottingham Heart Attack Register (n=1279)
- Costs of hospitalisation and procedures

Source: Palmer *et al. Technology Assessment Report for NICE*, 2002

Summary

- Decision trees simplest but least flexible approach
  - Useful in specific circumstances e.g. acute one-off treatments
  - Can be combined with other model types
- Markov models most common approach
  - Increased flexibility
  - Basic Markov chain can be limiting in some circumstances
  - Some forms of time dependency can be incorporated
- Markov models can be used in different ways
  - Direct comparisons
  - Extrapolation

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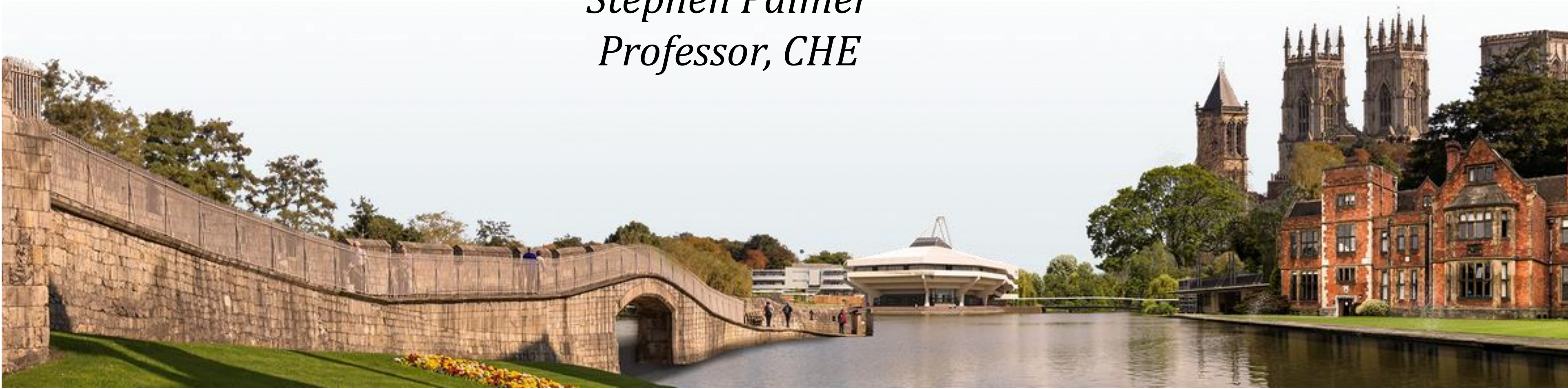
Presentation 6: Model structure
6.4: Area under the curve (AUC) models and cycle length

Stephen Palmer
Professor, CHE



Objectives

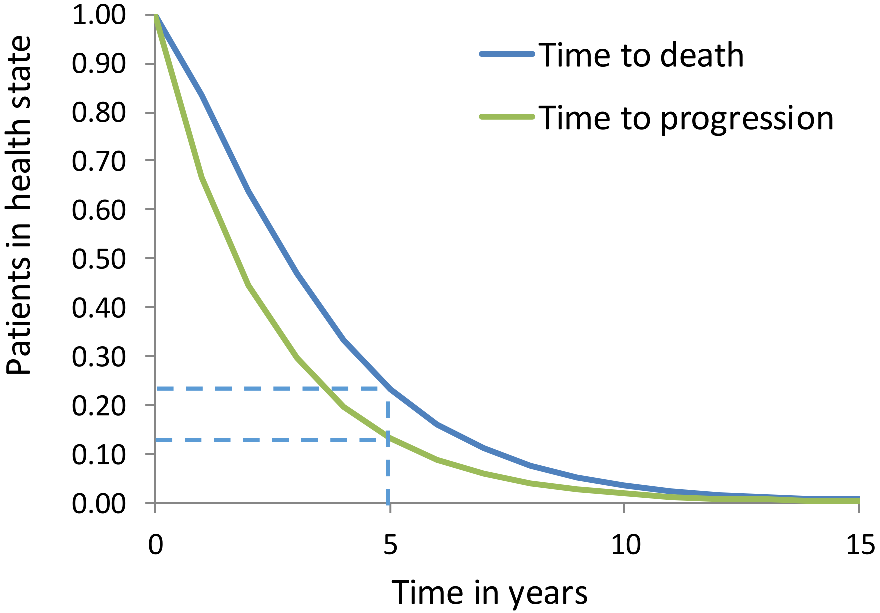
- Understand alternative state-transition approaches based on area under the curve (AUC) models
- Explore how to evaluate AUC models and determine state membership
- Understand importance of cycle length and use of corrections

Area under the curve (AUC) models

- Transitions probabilities not explicitly modelled
- Proportion in each health state over time is derived directly from survival curves
- Increasingly used in oncology based on progression-free survival (PFS) and overall survival (OS) curves
  - 3 states: (i) progression-free, (ii) progressed; (iii) death
  - Approach also referred to as partitioned survival analysis models
- As survival curves are used directly any time-dependency in the rate of events is captured

Evaluating AUC models

- 3 states: (i) progression free, (ii) progressed, (iii) dead
- Proportions derived from time to progression (PFS curve) and time to death (OS curve)



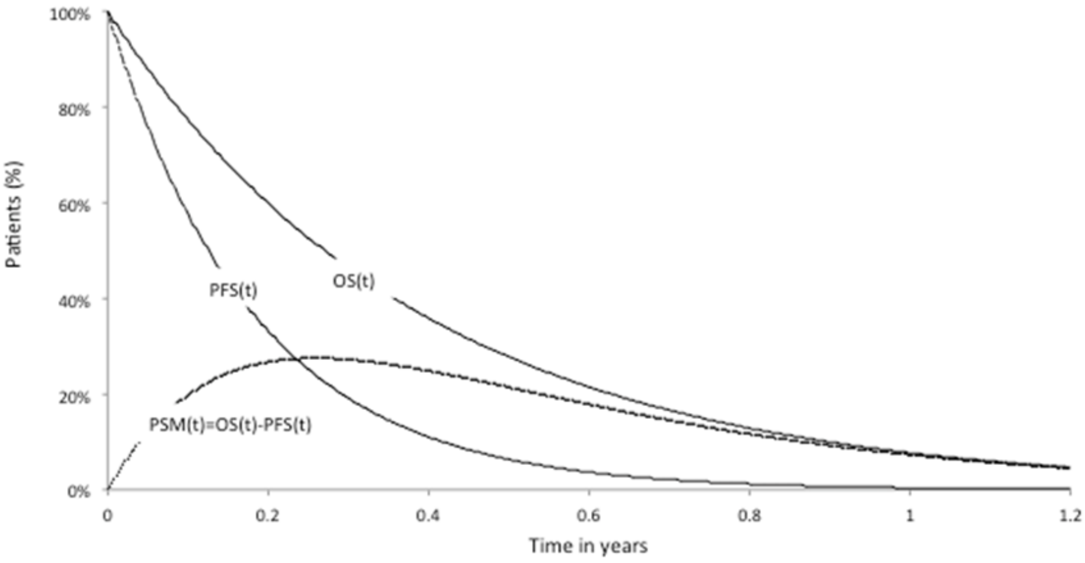
At t=5 years

- 13% patients have not yet progressed
- 23% of patients have not yet died

State membership is therefore

- Progression free: 0.13
- Progressed: 0.23-0.13 = 0.10
- Dead: 1-0.23 = 0.77
- Check: 0.13+0.10+0.77=1.0

Determining state membership in an AUC model



PSM = Progressive state membership – derived from OS and PFS curves

Issues with AUC models

- Simple to implement, consistent with published survival data and readily captures time dependency
- Not underpinned by explicit model of disease process
- May not provide robust predictions if data are incomplete (e.g. if a significant proportion of patients have not died)
- OS and PFS modelled independently
- Logical issues may arise in extrapolations/probabilistic analysis
- Less transparent/flexible than Markov model (e.g. impact of alternative assumptions in pre and post-progression periods)

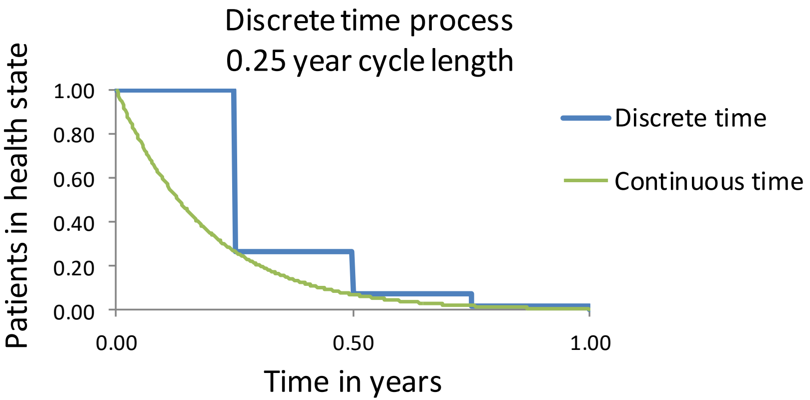
Extensions to AUC model – More explicit assessment of heterogeneity

- AUC based approaches
  - Splines/fractional polynomials
  - Landmark approach (e.g. responders, non-responders)
  - Independence still assumed between endpoints
  - Extrapolations still driven by time

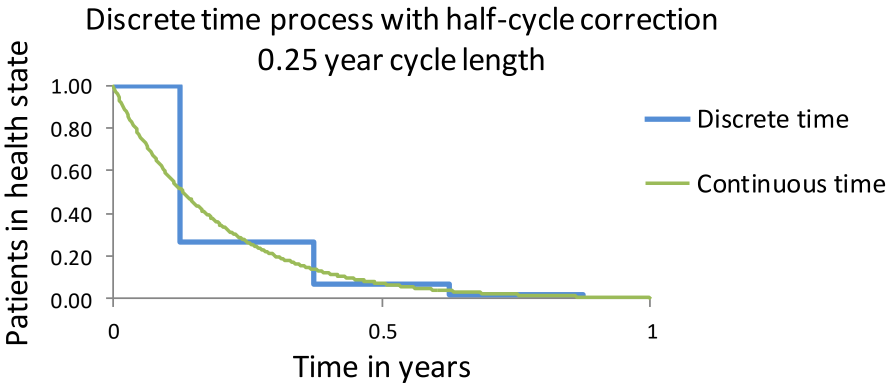
- Mixture cure models
  - Study population includes ‘cured’ and ‘uncured’ patients
  - Estimate probability that a patient is cured
  - Predict survival of patients who are not cured
  - Avoids grouping heterogeneous populations and using single mean value
  - Extrapolation and assumptions for ‘cured’ patients still required

Choice of cycle length and half-cycle correction

- Using discrete cycle lengths introduces bias in to estimates of time in state (and therefore costs and QALYs)
- To minimise - reduce cycle length and apply a half-cycle correction (HCC)



True survival = 0.19
Estimated survival = 0.34

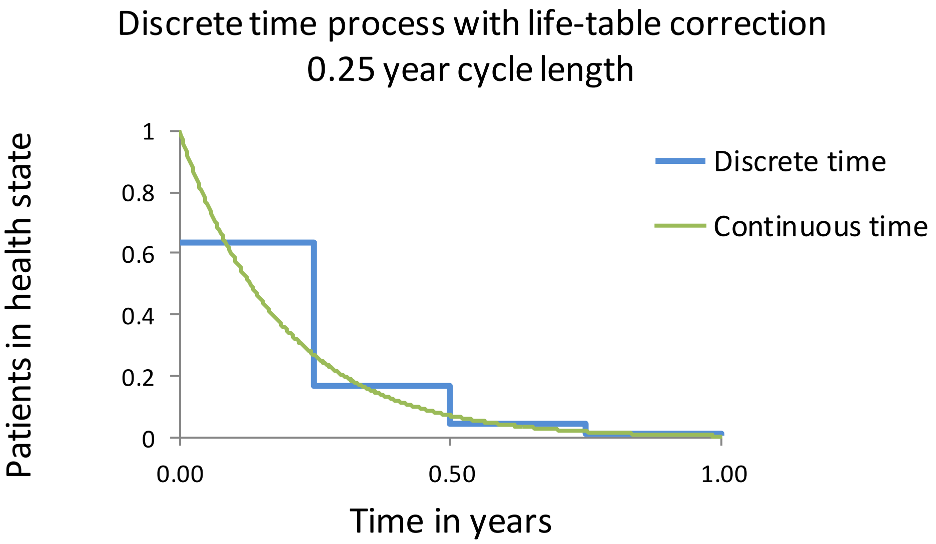


True survival = 0.19
Estimated survival = 0.21

- The **HCC** subtracts (or adds) one half cycle’s worth of cost and outcomes from first (or last) cycle – *transitions assumed at end (beginning) of cycle*

Alternative correction methods - Life-table

- **Life-table method:** average of the start and end state membership



True survival = 0.19
Estimated survival = 0.21

- Implemented at each cycle (within-cycle correction)
- Within-cycle approach now recommended

ICER with different correction methods and cycle length

	ICER				
Method	**Annual cycle (n=1)**	**Semiannual cycle (n=2)**	**Monthly cycle (n=12)**	**Weekly cycle (n=52)**	**Daily cycle (n=365)**
Right Riemann	60,333	51,042	47,881	47,795	47,790
Trapezoidal rule	60,333	51,042	47,881	47,795	47,790
Simpson's 1/3 rule	51,224	48,075	47,790	47,790	47,790
Simpson's 3/8 rule	53,594	48,371	47,791	47,790	47,790
Gold standard	47,790	47,790	47,790	47,790	47,790

Source: Elbasha and Chhatwal (2016)

Summary

- AUC approach increasingly common in oncology
  - Important differences compared with other state-transition approaches
- Various extensions proposed to AUC model
  - Novel mechanisms
  - Heterogeneity in survival
- Use of discrete cycles introduces bias
  - Minimise cycle length
  - Half-cycle correction

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Presentation 6: Model structure
6.5: Extensions to the Markov chain and alternatives to cohort modelling

Stephen Palmer
Professor, CHE

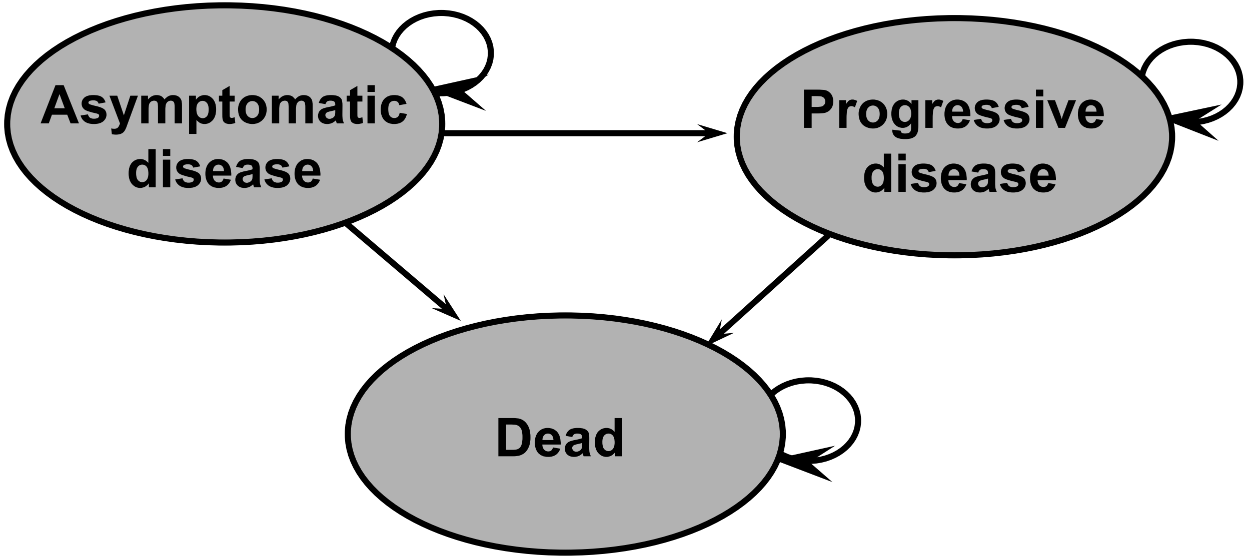
Objectives

- Explore extensions to Markov chain and use of time dependent probabilities
- Understand constraints on implementing time dependency
- Appreciate how constraints can be overcome
  - Tunnel states
  - Individual patient level simulation (PLS)
- Identify potential trade-offs with increased model complexity

Extensions to the Markov chain
Time-dependent probabilities

- Standard Markov chain has fixed probabilities with respect to time
- May be a reasonable approximation in many instances, less so in others
- Can relax this assumption using time dependent probabilities (with standard software)
  - Tabular form
  - Functional form

Constraints on implementing time dependency



- If all patients start in the 'Asymptomatic' state and no return is possible, then time dependent probabilities between that state and the others is possible
- When 'time' relates to time in state, time dependent probabilities from 'Progressive' to 'Death' is not feasible
- When 'time' relates to cycles that have elapsed independent of the state occupied (age), time dependency is possible between 'Progressive' and 'Death'

Time dependency using tables

Probability as a function of time in state

(a) Fixed probabilities

Transition from:	Transition to: Asymptomatic	Progressive	Dead
Asymptomatic	0.6	0.3	0.1
Progressive	0	0.8	0.2
Dead	0	0	1

(b) Time dependency for one transition probability

Transition from:	Transition to: Asymptomatic	Progressive	Dead
Asymptomatic	1-0.1-P(t)	P(t)	0.1
Progressive	0	0.8	0.2
Dead	0	0	1

Time	P(t)
1	0.19
2	0.21
3	0.24
4	0.25
5	0.28
6	0.31
7	0.32
8	0.34
9	0.35
10	0.37
11	0.39
12	0.40
13	0.42
14	0.43
15	0.47
16	0.48

Time dependency using tables

Probability as a function of cycle number

(a) Fixed probabilities

Transition from:	Transition to: Asymptomatic	Progressive	Dead
Asymptomatic	0.6	0.3	0.1
Progressive	0	0.8	0.2
Dead	0	0	1

(b) Time dependency for one transition probability

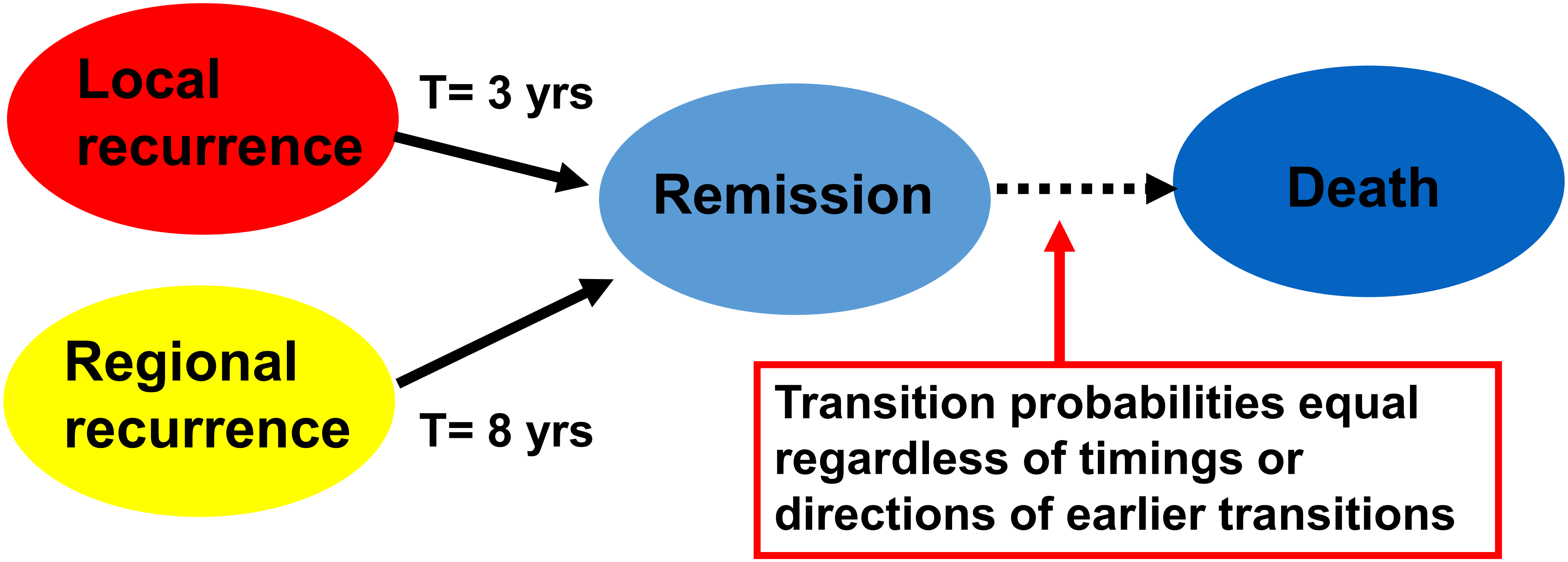
Transition from:	Transition to: Asymptomatic	Progressive	Dead
Asymptomatic	1-P(t)-P(c)	P(t)	P(c)
Progressive	0	1-[0.1+P(c)]	[0.1+P(c)]
Dead	0	0	1

	P(c)
1	0.072
2	0.076
3	0.079
4	0.071
5	0.083
6	0.086
7	0.089
8	0.092
9	0.095
10	0.098
11	0.102
12	0.106
13	0.108
14	0.115
15	0.118
16	0.122

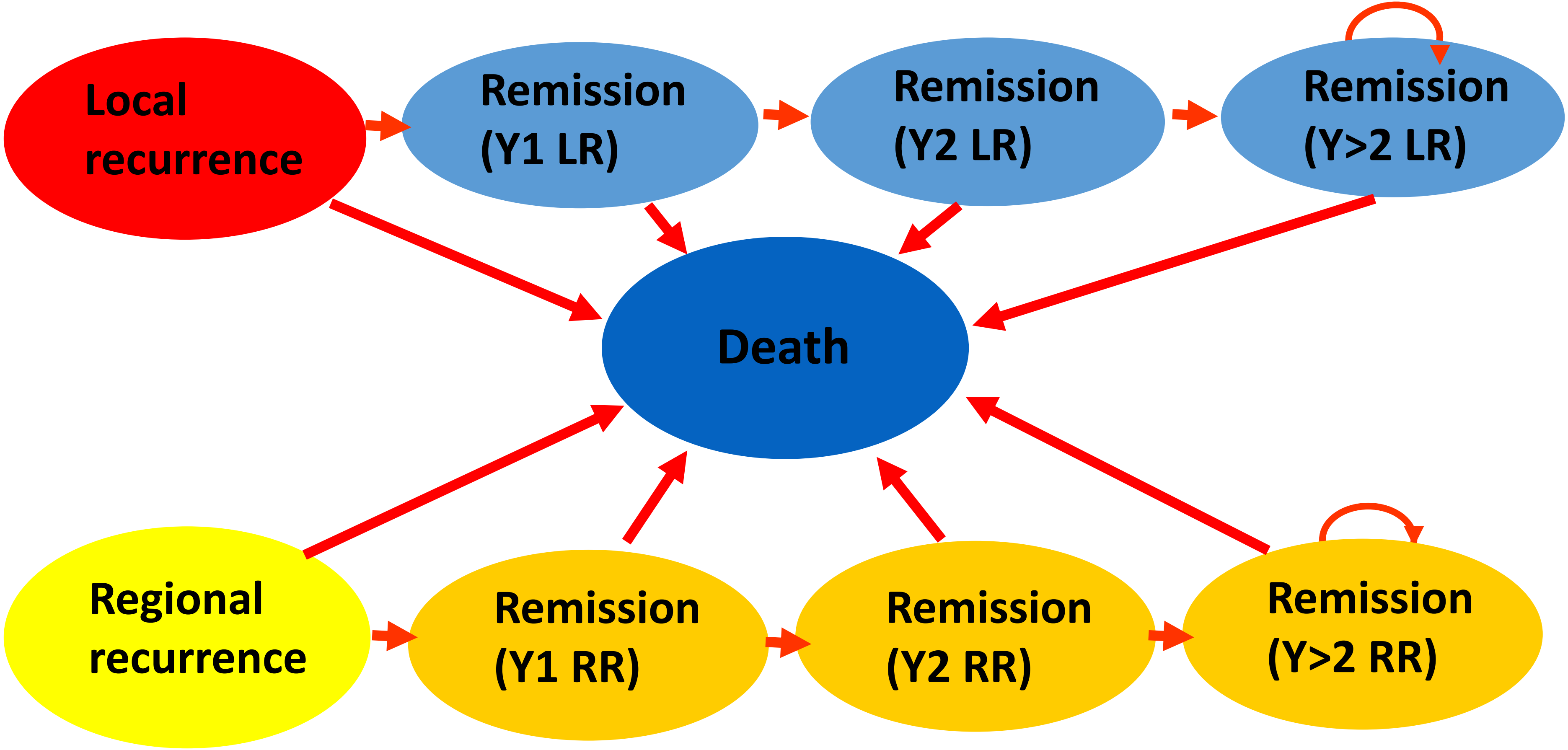
Time dependency using functions

- If patient-level data available on time to a given event, can estimate a transition probability as a function of time
- Models used to fit parametric distributions to hazard functions
- Most common distributions used to model survival data are exponential and Weibull distributions
- Exponential distribution assumes hazards are constant over time
- If constancy of hazard is not appropriate, a Weibull distribution may be more appropriate

Loosening the Markov assumption



Tunnel states – adding memory



Alternatives to cohort simulation

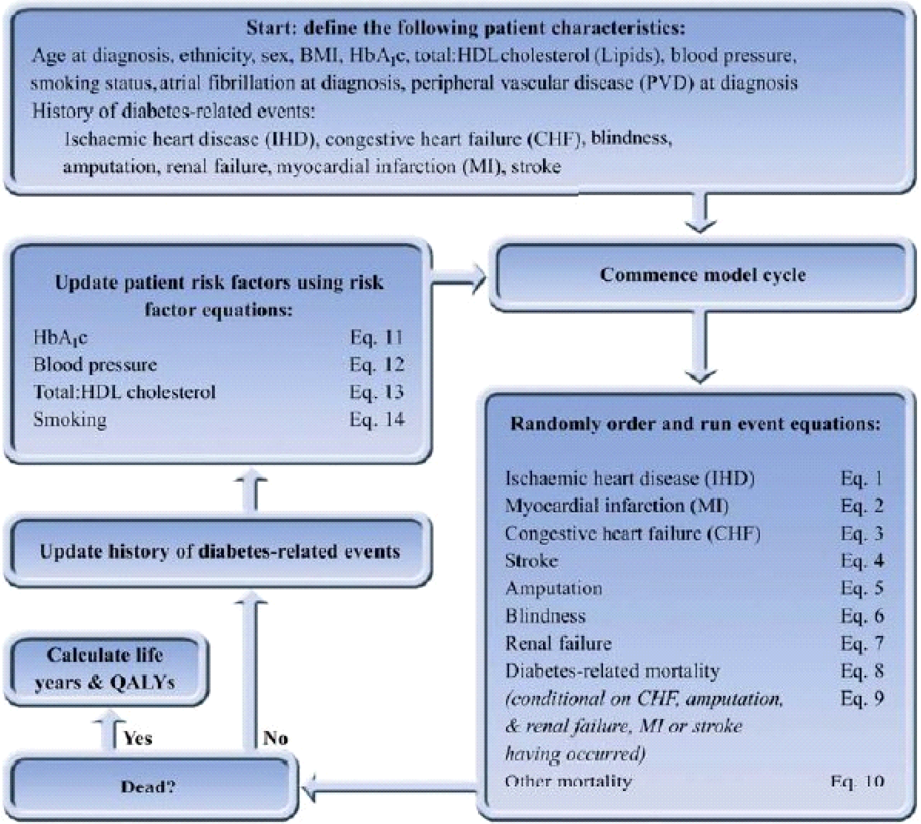
The additional flexibility of patient level simulation (PLS)

- For simple models (e.g. small number of states) no real advantage in using PLS vs cohort Markov
- IPS has potential value to model more complex prognoses:
  - Where important time dependencies
  - Where patient history determines future prognosis
  - Where adding memory to Markov model results in large/unmanageable models (‘state explosion’)

What are PLS models?

- Individual patients are simulated one at a time
- Large number sent through sequentially
- Expected values based on averaging across these patients
- Number of simulations important for ‘stability’ of mean
- Advantages:
  - Not restricted by Markov assumption
  - Can easily keep track of individual’s history (tracker variables)
  - Can greatly reduce number of states

Examples of PLS models
UKPDS model



Source: Clarke *et al. Diabetologia* 2004; 47: 1747-59

Trade-offs with PLS models

- Less transparent, less efficient and harder to debug
- Two levels of simulation for PSA
  - Patient level with a given set of parameters (e.g. 10,000)
  - Parameter level with different sets of parameters (e.g. 1000)
  - Total simulations: 10,000 x 1000 = 10,000,000
- Further simulations for value of information analysis
- Therefore PSA often not done with PLS
- Can short cut using emulators (see Stevenson *et al. Medical Decision Making* 2004; 24: 89-100)
  - Little practical use
  - Small number of parameters

Elements of good practice

- Structural assumptions
  - Transparent and adequately justified
  - Data inputs clearly documented and justified in context of valid review of alternatives
- Alternative scenarios for extrapolation
  - e.g. nil, same as treatment phase, reducing in long term
- Results presented separately for alternative assumptions
  - LYG, QALYs and frequency of clinical events
  - At alternative time points
- Use of structures which limit feasibility of PSA need to be clearly justified
- Choice should not result in failure to express uncertainty

Summary

- Possible to extend basic Markov chain to incorporate some forms of time dependency
  - Increases flexibility
- PLS may be more appropriate in particular circumstances
  - Possible trade-offs with additional complexity
- Choice of model structure should not limit analyses
  - Alternative assumptions
  - Uncertainty analyses

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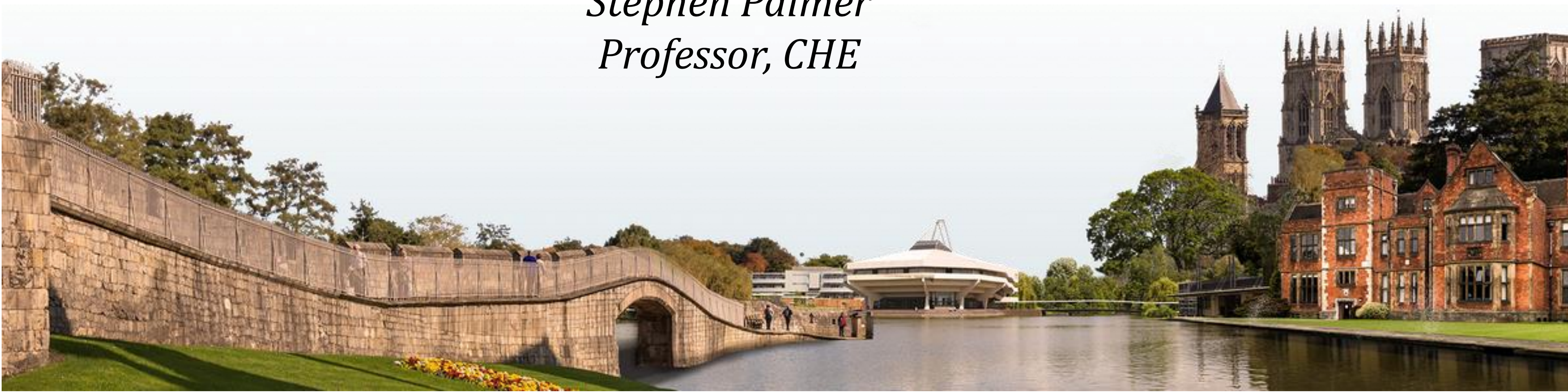
Presentation 6: Model structure
6.7: Summary and conclusions

Stephen Palmer
Professor, CHE



Conclusions

- Models need to be ‘fit for purpose’
  - Expected ‘mean’ cost-effectiveness
  - Uncertainty
- Models are inevitably a simplification of reality
  - Approximation of cohort models will be reasonable in many circumstances
- But PLS models may be considered necessary
  - Complex history/time dependencies
  - Treatment sequences
- Need to accept ‘trade-offs’ with PLS
  - Computational burden
  - Evidence requirements

Further reading

Good practice and state-transition modelling approaches

- Caro J *et al*. Modeling good research practices - overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. *Value Health*. 2012;15:796-803.
- Siebert *et al*. State-transition modeling: a report of the ISPOR-SMDM modeling good research practices task force-3. *Value Health*. 2012; 15: 812-820.

AUC modelling

- Woods B *et al*. NICE DSU Technical Support Document 19. Partitioned Survival Analysis for Decision Modelling in Health Care: A Critical Review. 2017 [*Available from http://www.nicedsu.org.uk*]

Patient-level simulation

- Davis S *et al*. NICE DSU Technical Support Document 15: Cost-effectiveness modelling using patient-level simulation. 2014. [*Available from http://www.nicedsu.org.uk*]