# Online Advanced Methods for Cost-Effectiveness Analysis

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

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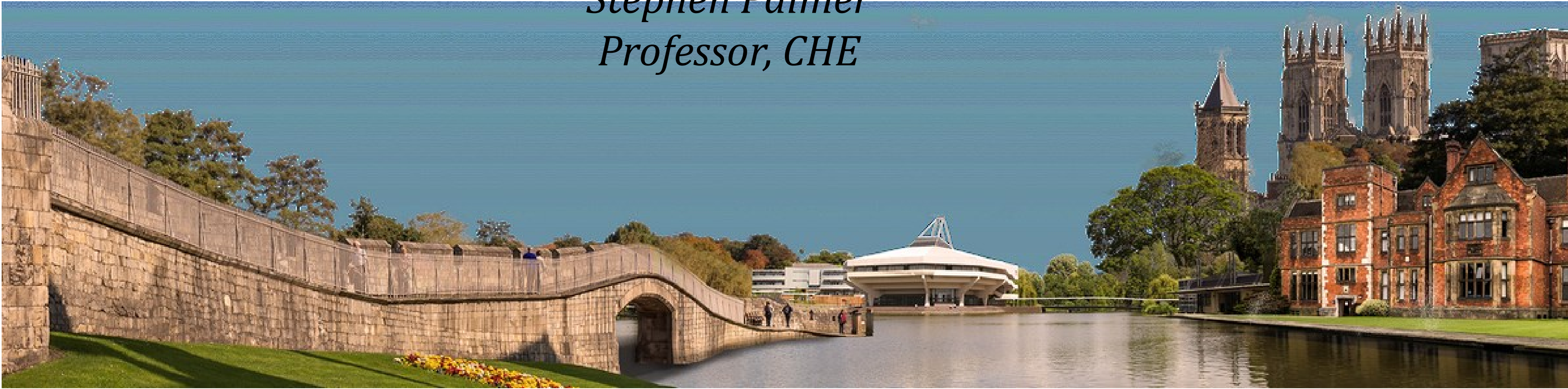


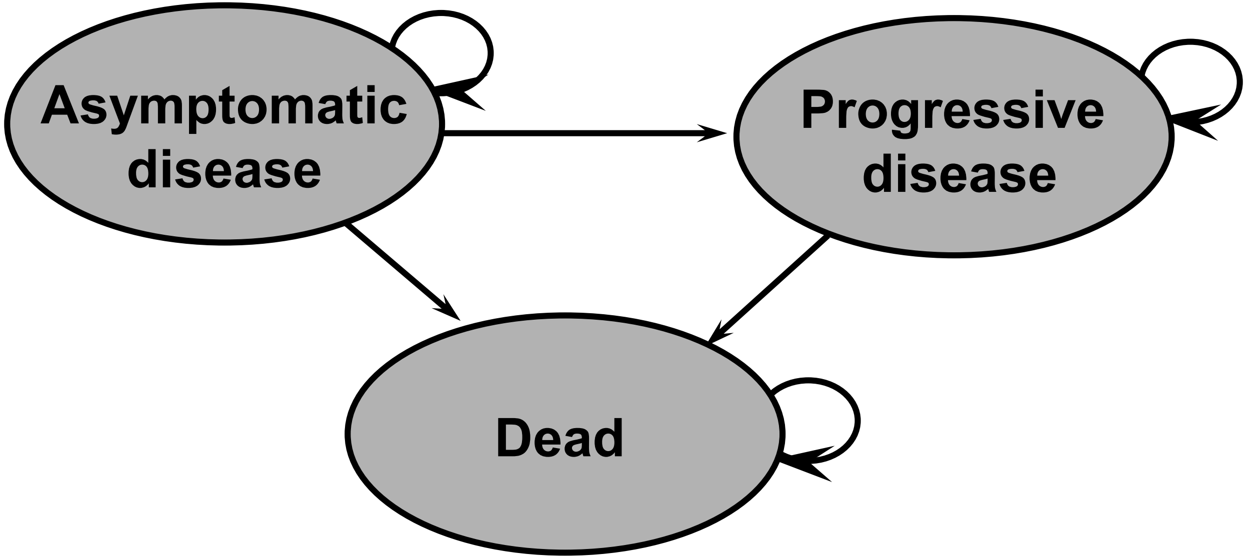
# Objectives

- 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**

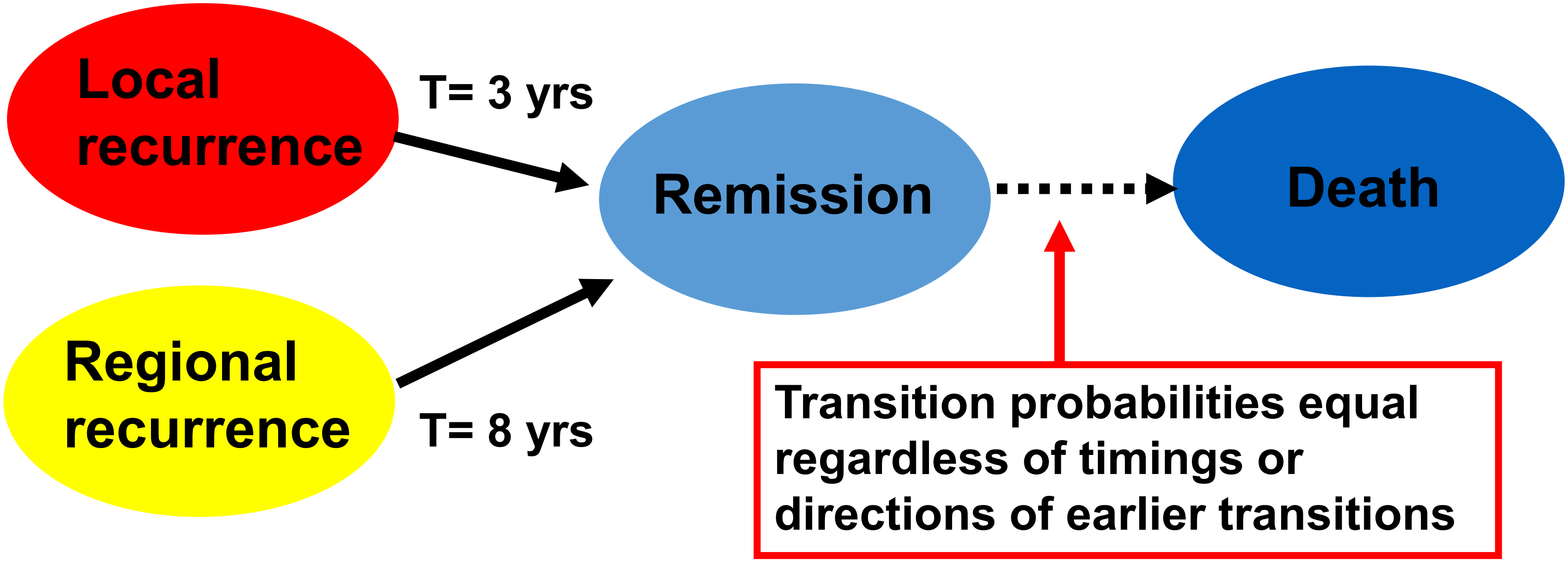
| Transition from: | Transition to: Asymptomatic | Progressive | Dead |
|---|---|---|---|
| Asymptomatic | 1-P(t)-P(c) | P(t) | P(c) |
| Progressive | 0 | 1-[0.1+P(c)] | [0.1+P(c)] |
| Dead | 0 | 0 | 1 |

| | 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 |

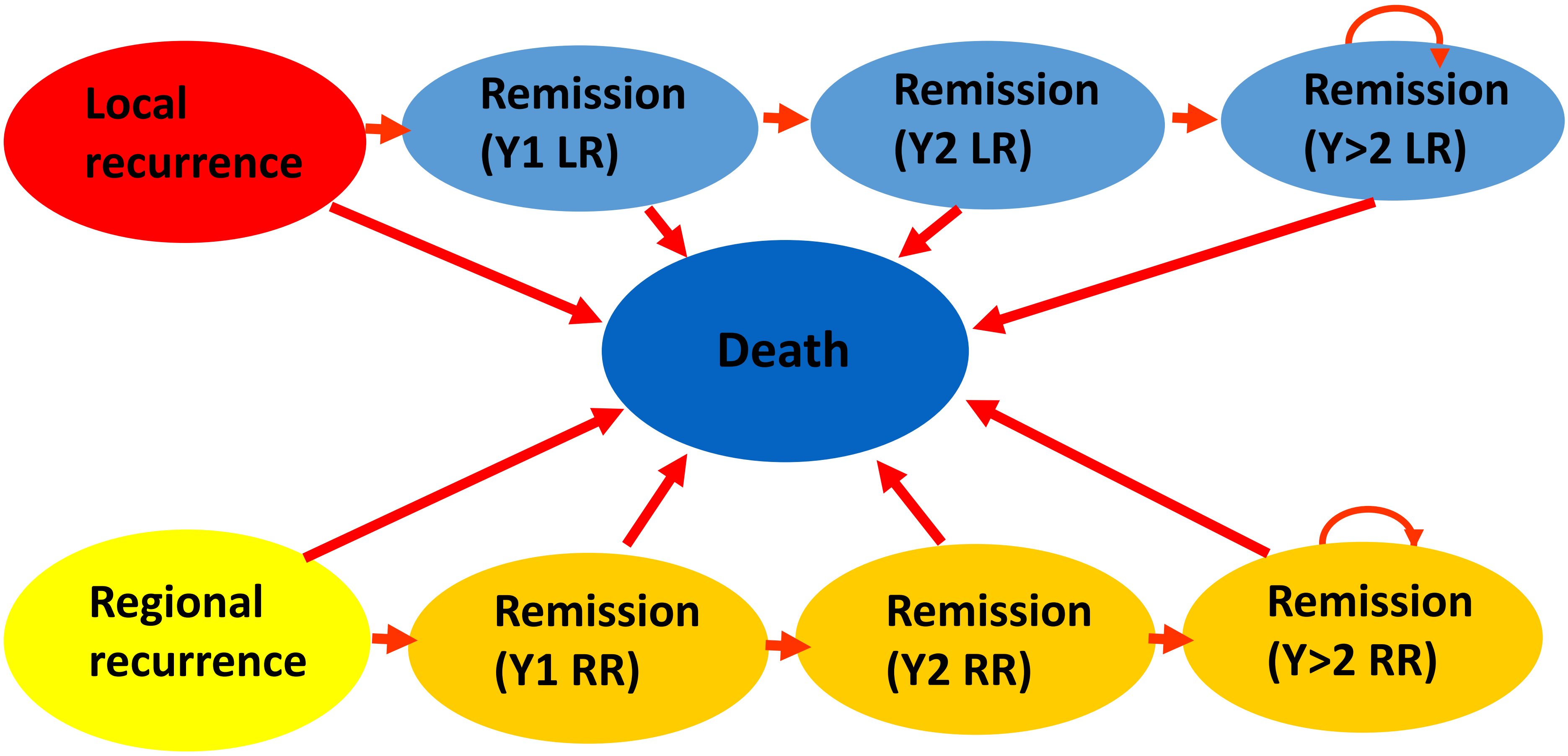
# Time dependency using functions

- 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

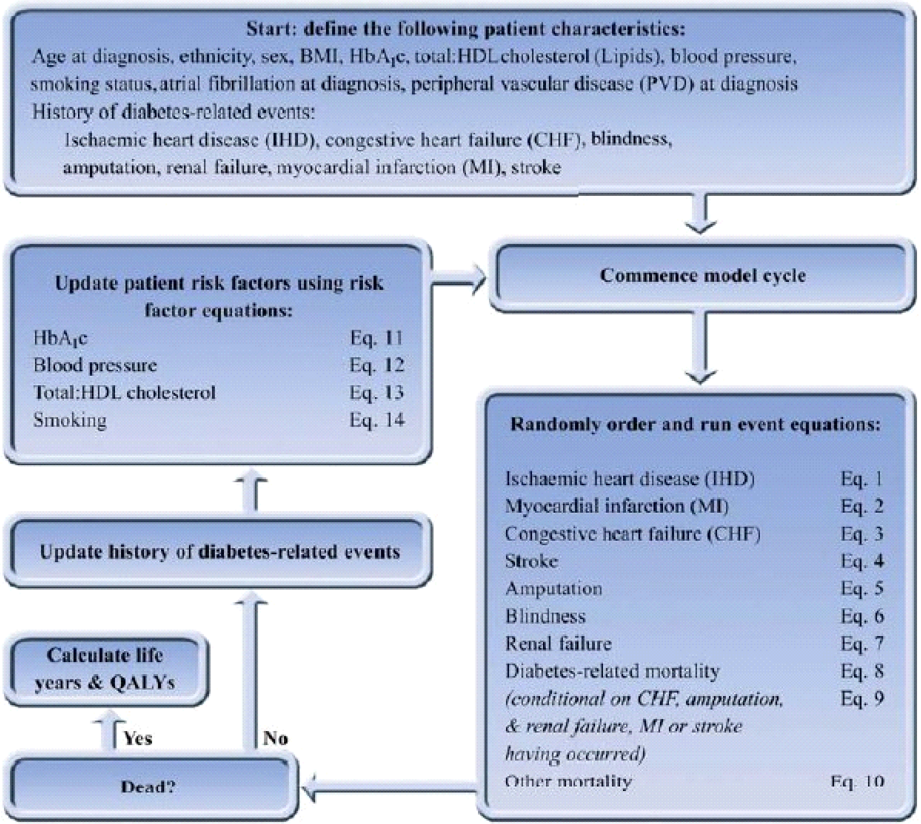
## The additional flexibility of patient level simulation (PLS)

- 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