Introduction to Disease Modelling

and some advanced techniques

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The views expressed are those of the author(s) and not necessarily those of the NIHR, the NHS or the Department of Health.

School for Primary Care Research

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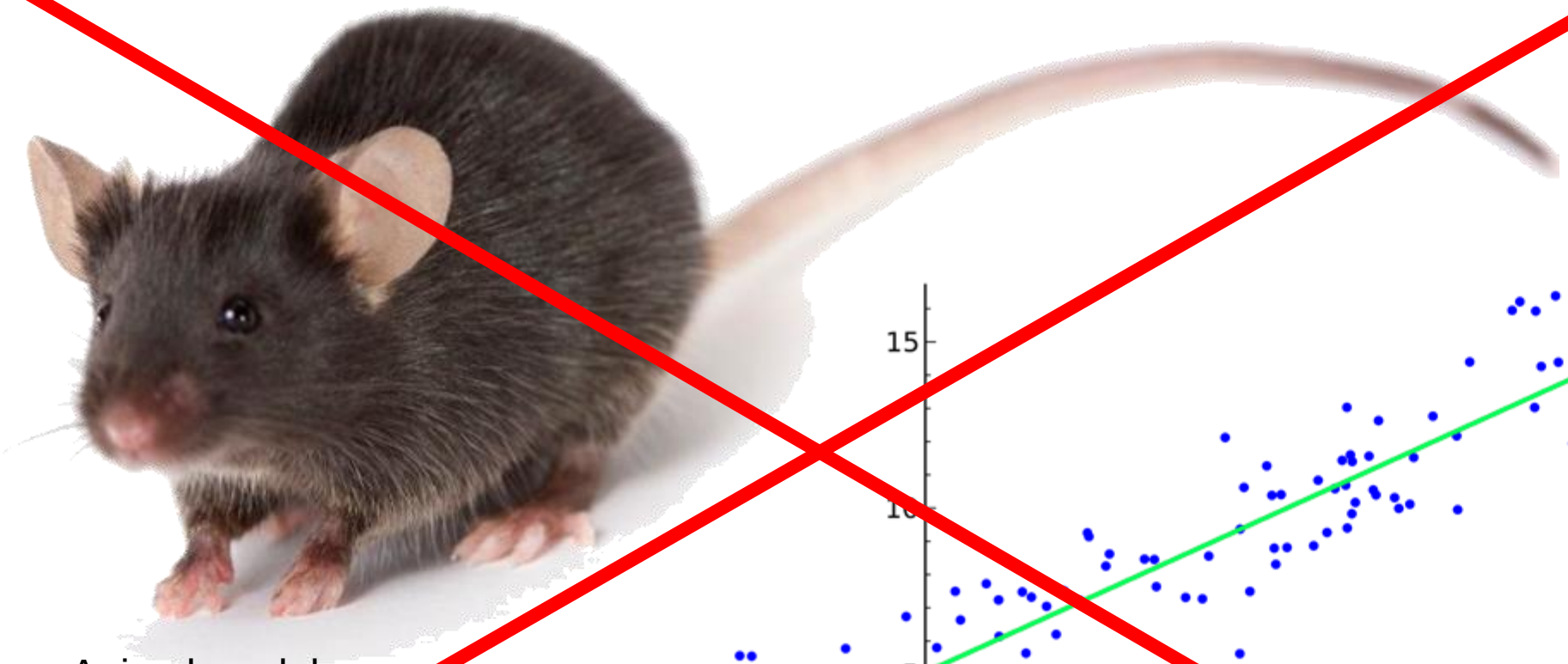
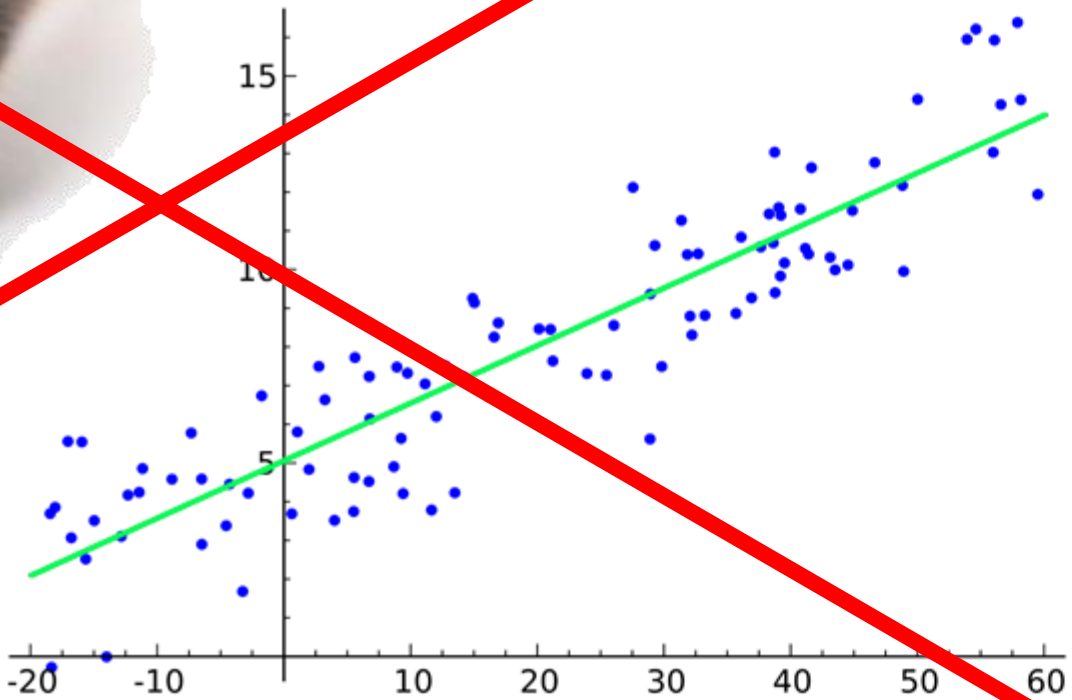
Funded by NHS National Institute for Health Research

What am I going to talk about?



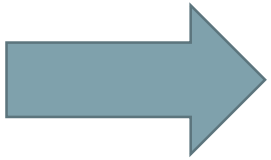
Animal models



Statistical models

Why?

- Inform public health interventions
  - Examine Cost-effectiveness
- Test “what if” scenarios

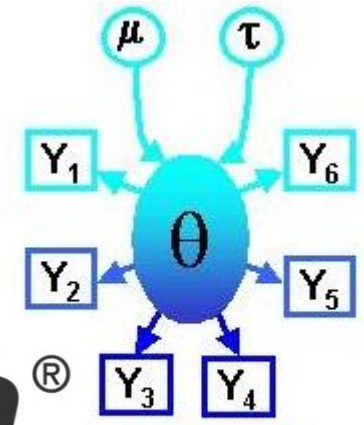


Doing a trial without actually conducting it

- Predicting the future

How to?

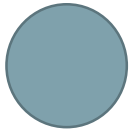
- Software
  - TreeAge
  - WinBUGS
  - Arena
  - …
- DIY
  - MS Excel (or similar)
  - R
  - …



Arena®
Simulation
Software

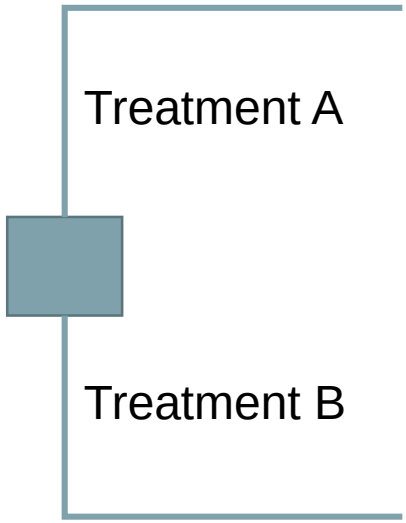
Decision Trees

Structure

- Decision node
- Chance node 
- Outcome node

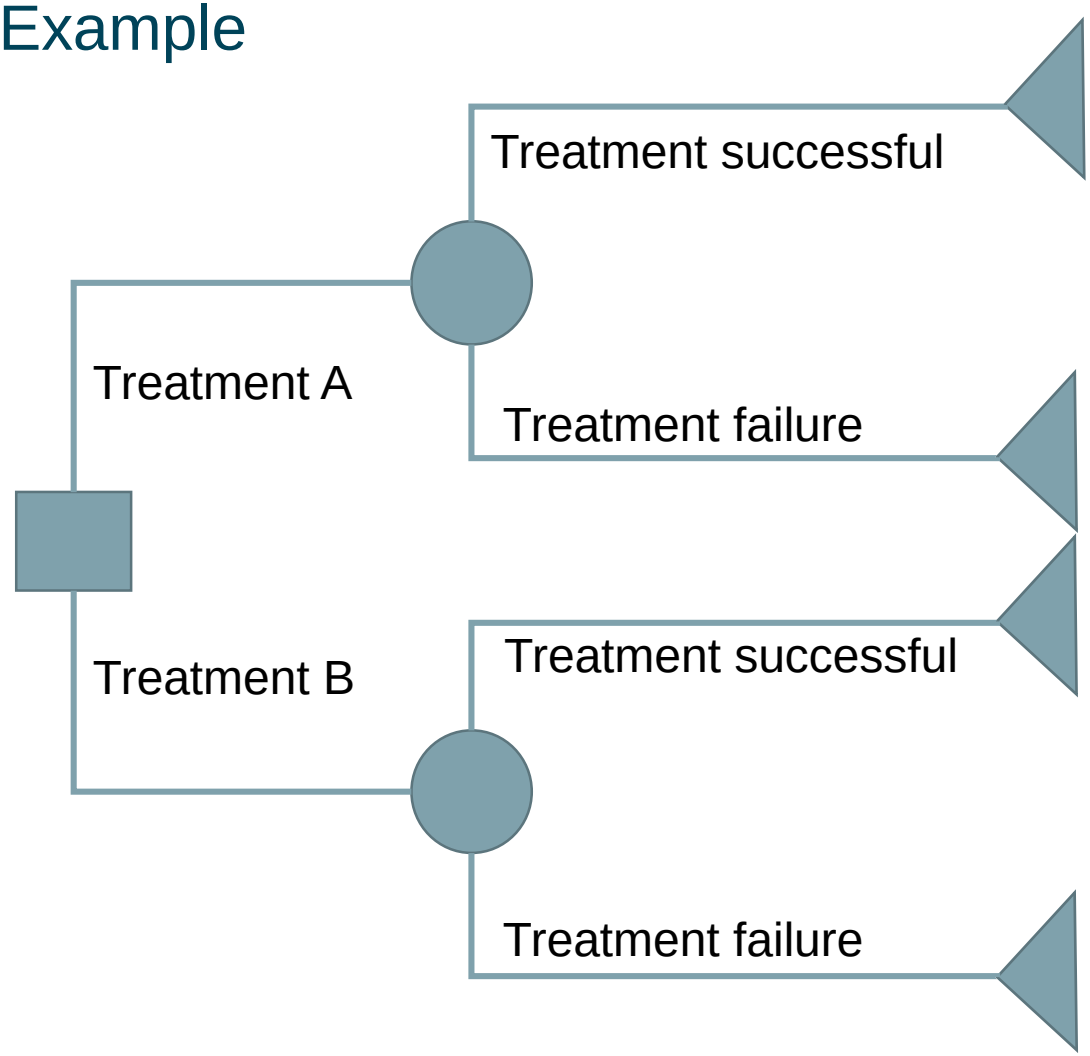
Decision Trees

Example



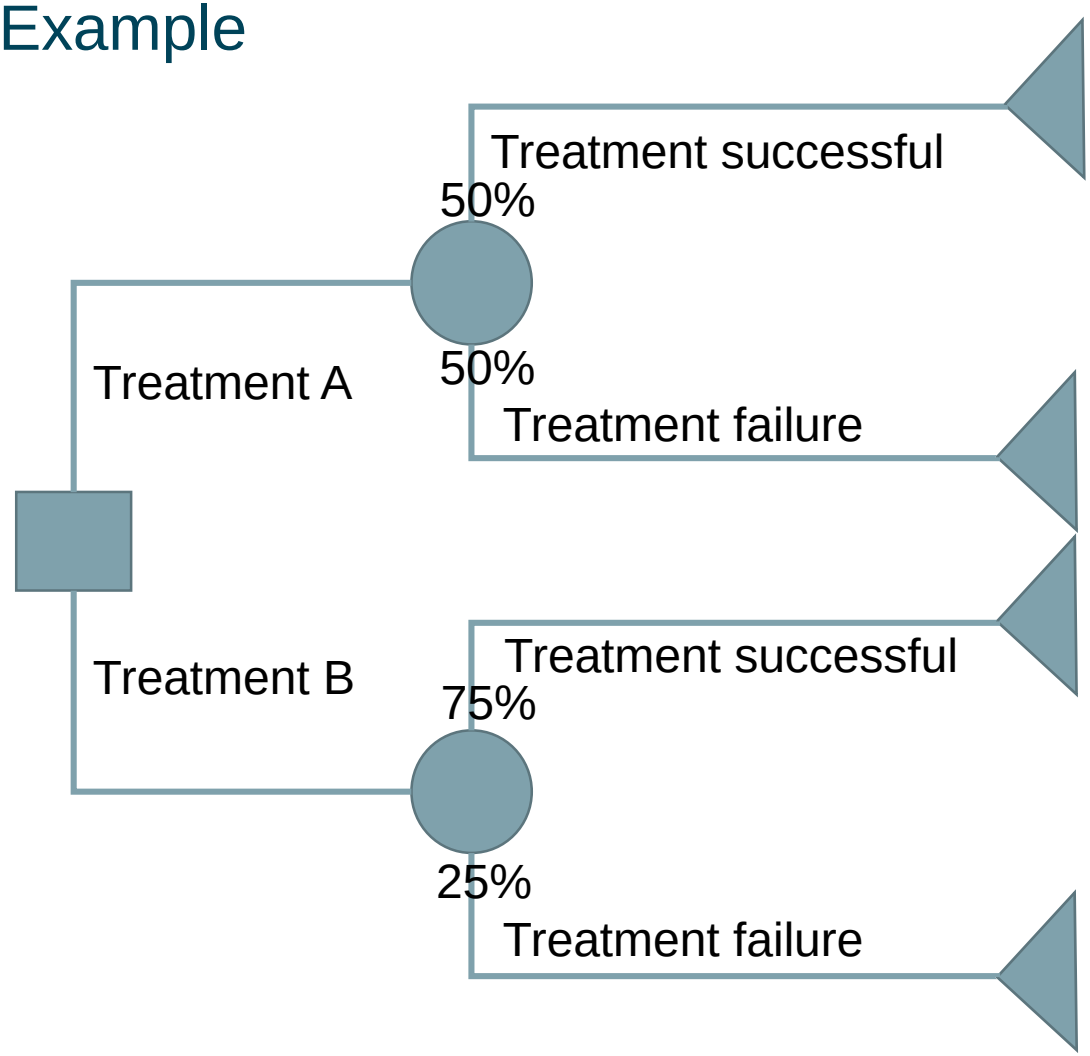
Decision Trees

Example



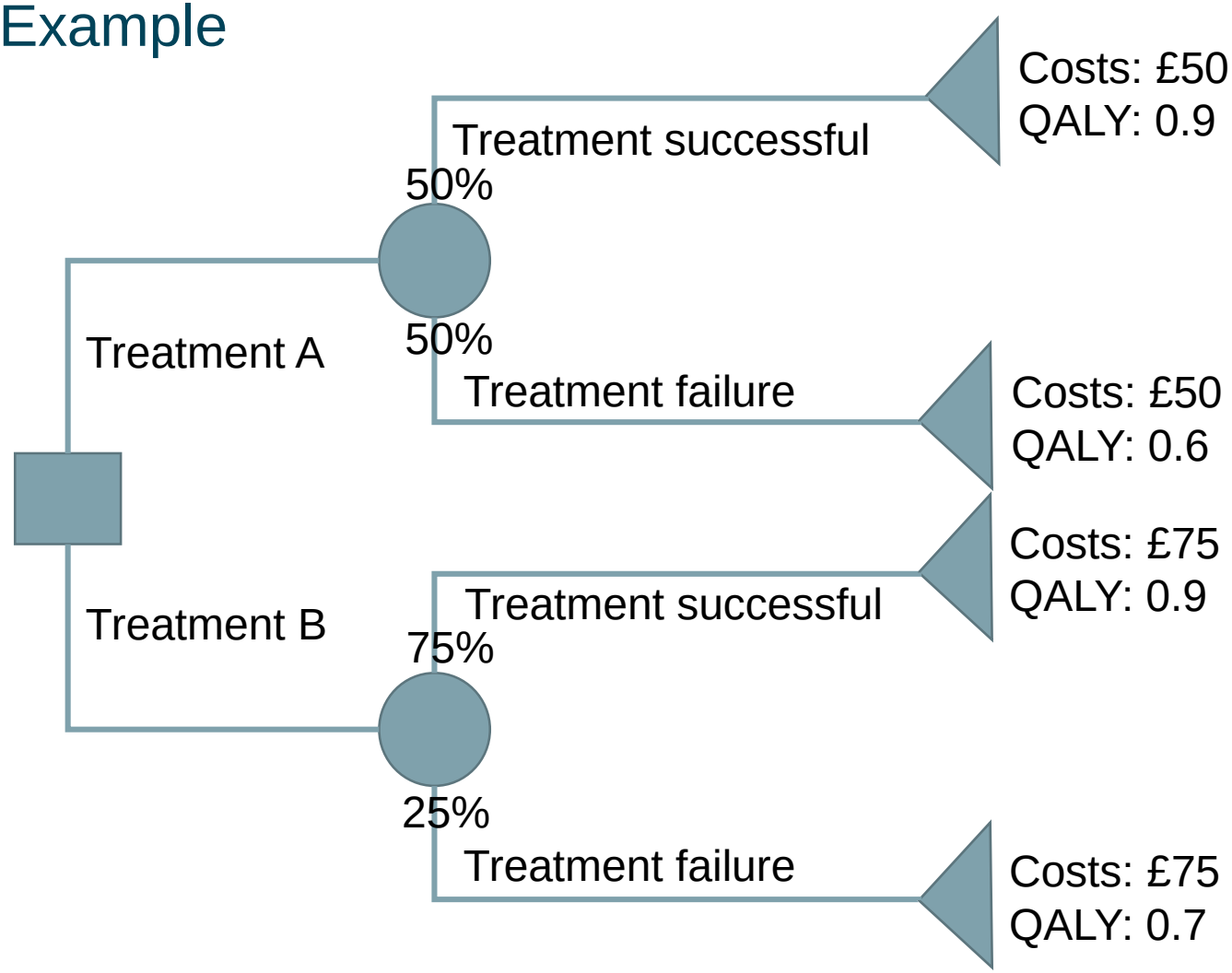
Decision Trees

Example



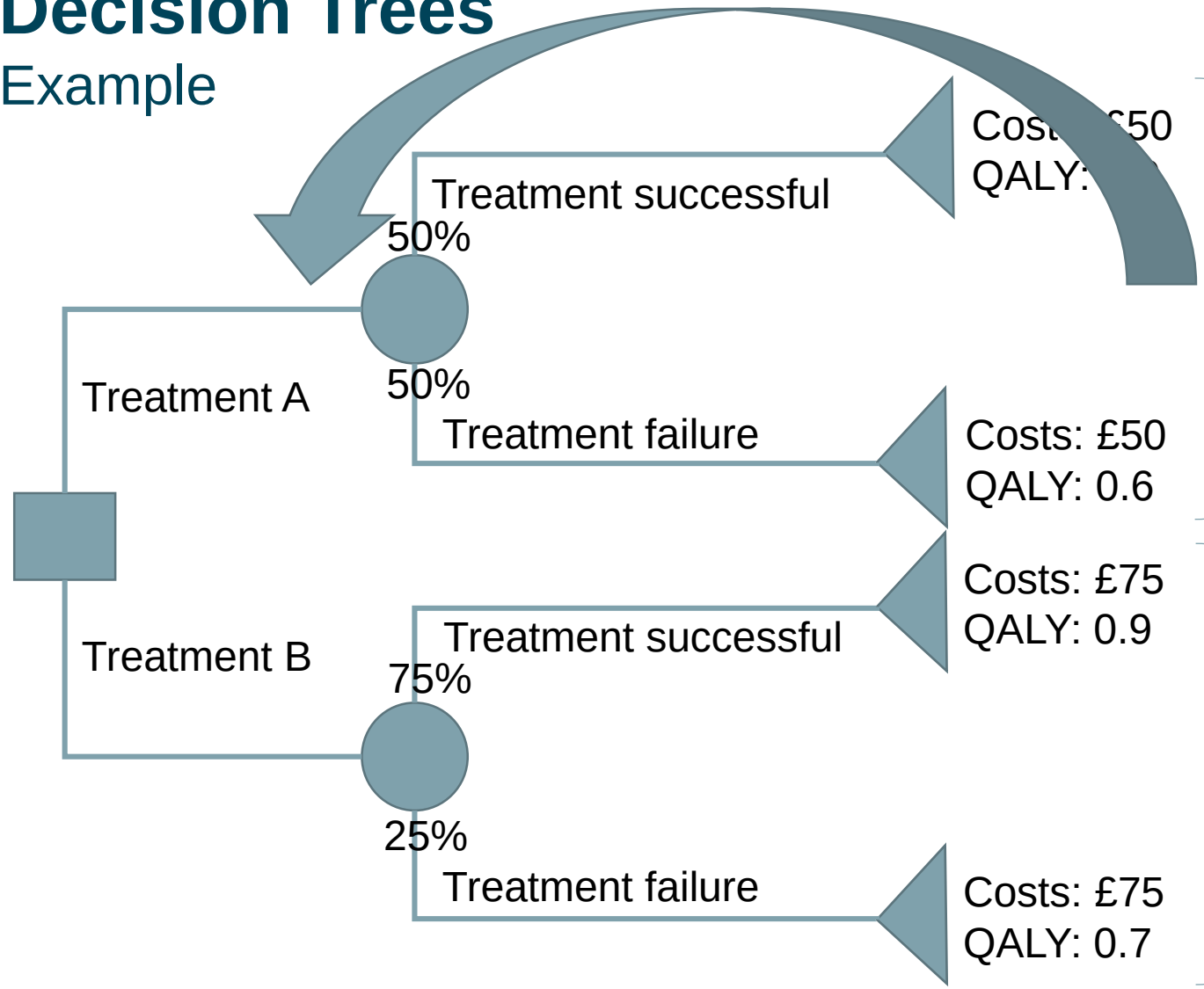
Decision Trees

Example



Decision Trees

Example



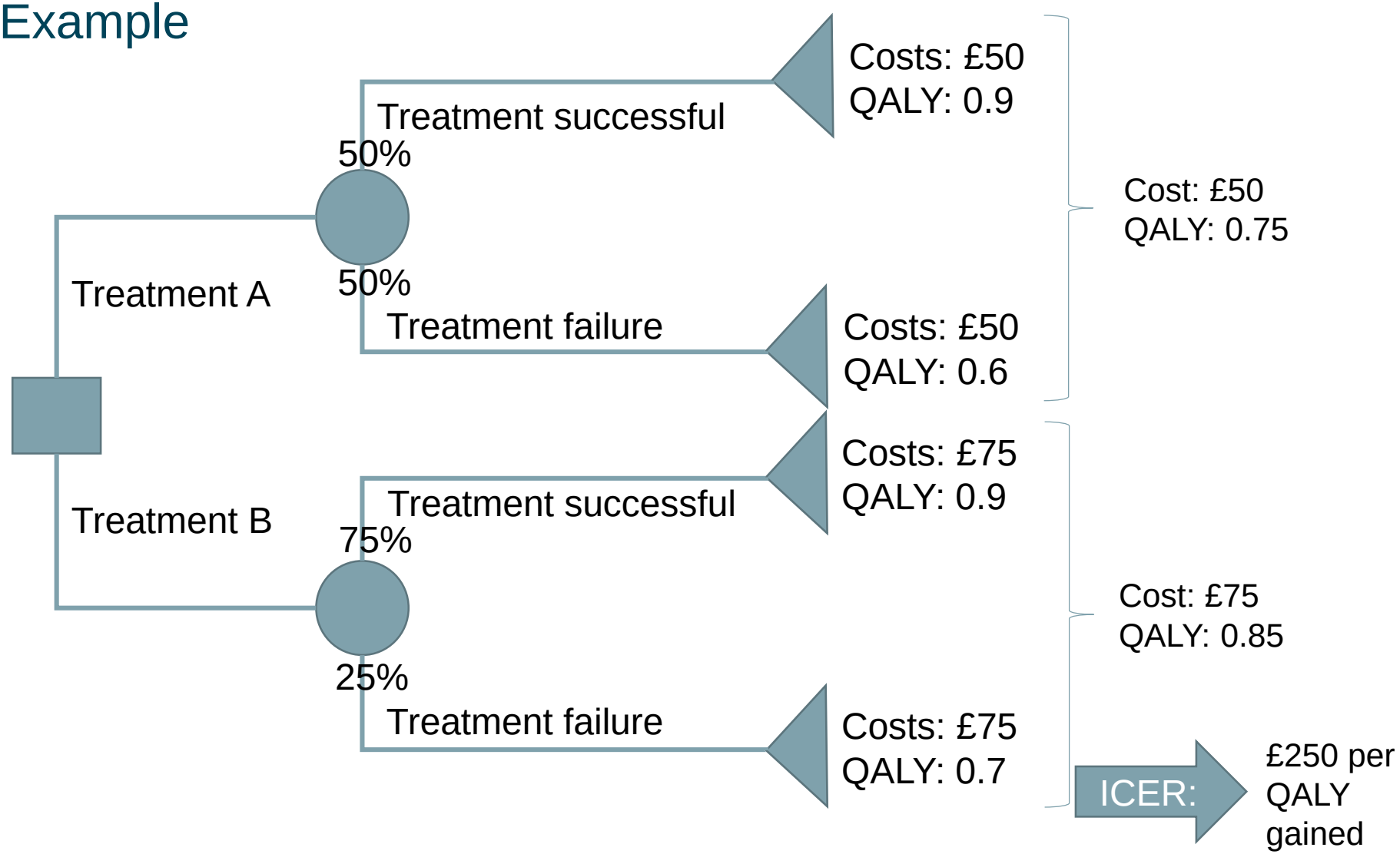
Rollback:

Cost: 0.5 * £50 + 0.5 * £50 = £50
QALY: 0.5 * 0.9 + 0.5 * 0.6 = 0.75

Cost: 0.75 * £75 + 0.25 * £75 = £75
QALY: 0.5 * 0.75 + 0.7 * 0.25 = 0.85

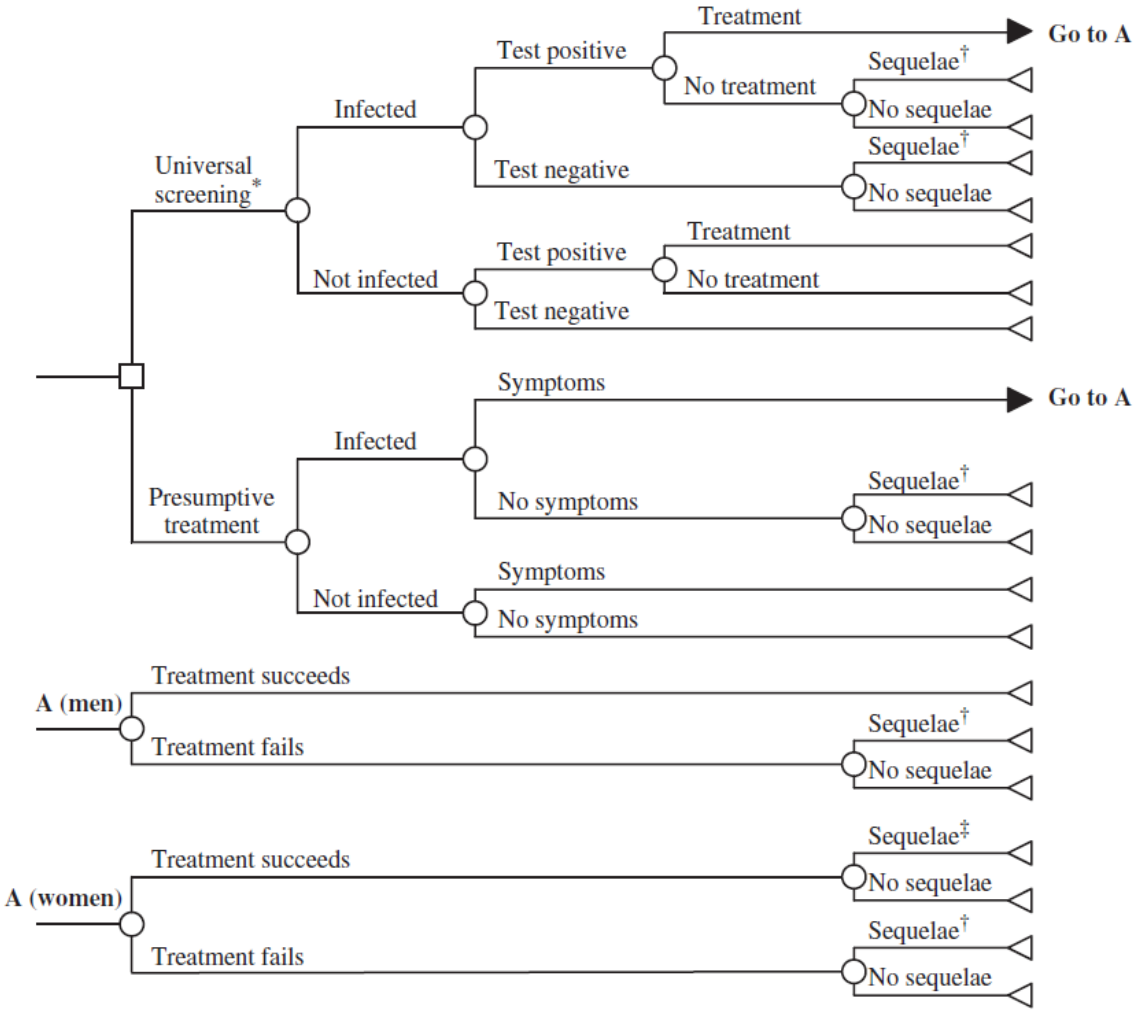
Decision Trees

Example



Decision Trees

Detailed Example



Kraut-Becher, J., et al. (2004). "Cost-effectiveness of universal screening for chlamydia and gonorrhea in US jails." Journal of Urban Health-Bulletin of the New York Academy of Medicine **81**(3): 453-471.

Decision Trees

Field of Application

- Comparison of distinctive (but similar) interventions
- “Either – or” decisions
- Once-only interventions
- No time component

Decision Trees

Advantages

- Fast calculations
- Easy to understand/ set-up

Decision Trees

Disadvantages/ Limitations

- We need estimates for the whole tree
- Complicated diseases
- Recurrences
- Time

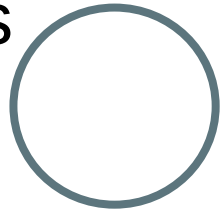
SIR Models

- Individual-based vs **aggregated**
- Compartmental model
  - Susceptible – Infectious – Recovered
  - More sophisticated versions possible

SIR Models

Structure

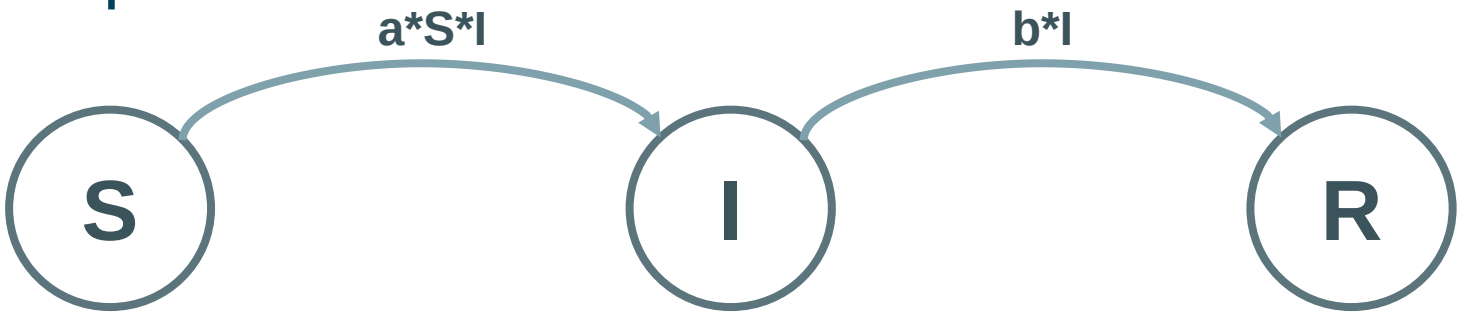
- Health States



- Transitions

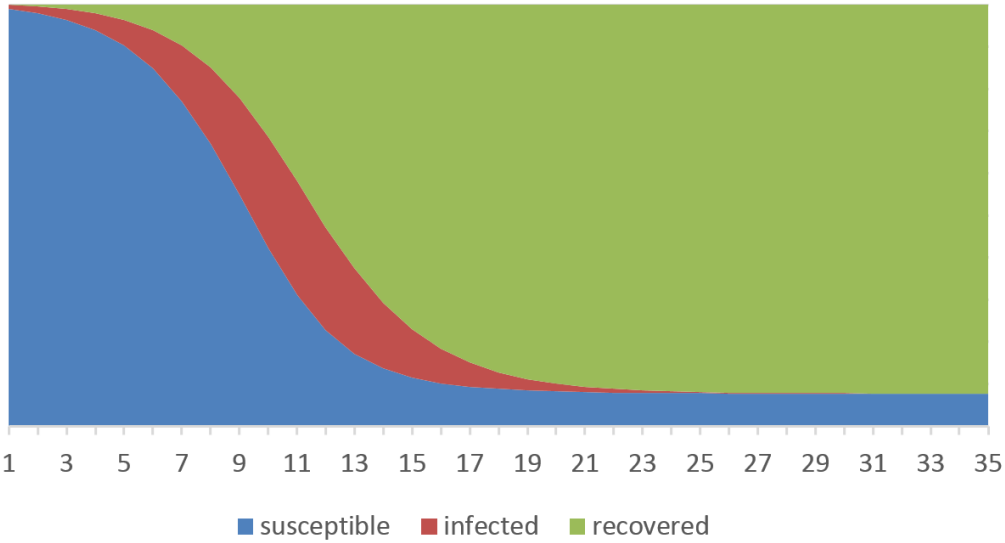
SIR Models

Example



S(t) = S(t-1) – a * S(t-1) * I(t-1)
I(t) = I(t-1) + a * S(t-1) * I(t-1) – b * I(t-1)
R(t) = R(t-1) + b * I(t-1)

S(0) = 9900
I(0) = 100
R(0) = 0
a = 0.0001
b = 0.4



To compare interventions we would need to run the model twice with different input (e.g. different a for vaccination strategies)

SIR Models

Detailed example

HIV progression is divided into three stages of acute, chronic, and advanced, while HSV-2 infection is depicted by the three stages of primary infection, latent infection, and reactivation. Dual infection is characterized by nine stages according to each of HIV and HSV-2 stages.

Abu-Raddad LJ, Magaret AS, Celum C, Wald A, Longini IM Jr et al. (2008) Genital Herpes Has Played a More Important Role than Any Other Sexually Transmitted Infection in Driving HIV Prevalence in Africa. PLoS ONE 3(5): e2230. doi:10.1371/journal.pone.0002230

SIR Models

Detailed example

Fully susceptible population

$$\frac{dS(i)}{dt} = \mu N_0(i) - \mu S(i) - \Lambda_{HIV}^{S(i)} S(i) - \Lambda_{HSV-2}^{S(i)} S(i)$$

HIV infected but HSV-2 susceptible populations $Y_\alpha(i)$

$$\frac{dY_1(i)}{dt} = \Lambda_{HIV}^{S(i)} S(i) - \mu Y_1(i) - \omega_{Y_1} Y_1(i) - g_{Y_1} \Lambda_{HSV-2}^{Y_1(i)} Y_1(i)$$

$$\frac{dY_2(i)}{dt} = \omega_{Y_1} Y_1(i) - \mu Y_2(i) - \omega_{Y_2} Y_2(i) - g_{Y_2} \Lambda_{HSV-2}^{Y_2(i)} Y_2(i)$$

$$\frac{dY_3(i)}{dt} = \omega_{Y_2} Y_2(i) - \mu Y_3(i) - \omega_{Y_3} Y_3(i) - g_{Y_3} \Lambda_{HSV-2}^{Y_3(i)} Y_3(i)$$

HSV-2 seropositive but HIV susceptible populations $I_\beta(i)$

$$\frac{dI_1(i)}{dt} = \Lambda_{HSV-2}^{S(i)} S(i) - \mu I_1(i) - \pi_{I_1} I_1(i) - h_{I_1} \Lambda_{HIV}^{I_1(i)} I_1(i)$$

$$\frac{dI_2(i)}{dt} = \pi_{I_1} I_1(i) - \mu I_2(i) - \pi_{I_2} I_2(i) - h_{I_2} \Lambda_{HIV}^{I_2(i)} I_2(i) + \pi_{I_3} I_3(i)$$

$$\frac{dI_3(i)}{dt} = \pi_{I_2} I_2(i) - \mu I_3(i) - \pi_{I_3} I_3(i) - h_{I_3} \Lambda_{HIV}^{I_3(i)} I_3(i)$$

HIV and HSV-2 dually infected populations $Z_{\alpha,\beta}(i)$

$$\frac{dZ_{1,1}(i)}{dt} = g_{Y_1} \Lambda_{HSV-2}^{Y_1(i)} Y_1(i) + h_{I_1} \Lambda_{HIV}^{I_1(i)} I_1(i) - \mu Z_{1,1}(i) - \omega_{Z_{1,1}} Z_{1,1}(i) - \pi_{Z_{1,1}} Z_{1,1}(i)$$

$$\frac{dZ_{1,2}(i)}{dt} = h_{I_2} \Lambda_{HIV}^{I_2(i)} I_2(i) + \pi_{Z_{1,1}} Z_{1,1}(i) - \mu Z_{1,2}(i) - \omega_{Z_{1,2}} Z_{1,2}(i) - \pi_{Z_{1,2}} Z_{1,2}(i) + \pi_{Z_{1,3}} Z_{1,3}(i)$$

$$\frac{dZ_{1,3}(i)}{dt} = h_{I_3} \Lambda_{HIV}^{I_3(i)} I_3(i) + \pi_{Z_{1,2}} Z_{1,2}(i) - \mu Z_{1,3}(i) - \omega_{Z_{1,3}} Z_{1,3}(i) - \pi_{Z_{1,3}} Z_{1,3}(i)$$

$$\frac{dZ_{2,1}(i)}{dt} = g_{Y_2} \Lambda_{HSV-2}^{Y_2(i)} Y_2(i) + \omega_{Z_{1,1}} Z_{1,1}(i) - \mu Z_{2,1}(i) - \omega_{Z_{2,1}} Z_{2,1}(i) - \pi_{Z_{2,1}} Z_{2,1}(i)$$

$$\frac{dZ_{2,2}(i)}{dt} = \omega_{Z_{1,2}} Z_{1,2}(i) + \pi_{Z_{2,1}} Z_{2,1}(i) - \mu Z_{2,2}(i) - \omega_{Z_{2,2}} Z_{2,2}(i) - \pi_{Z_{2,2}} Z_{2,2}(i) + \pi_{Z_{2,3}} Z_{2,3}(i)$$

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$$\frac{dZ_{3,1}(i)}{dt} = g_{Y_3} \Lambda_{HSV-2}^{Y_3(i)} Y_3(i) + \omega_{Z_{2,1}} Z_{2,1}(i) - \mu Z_{3,1}(i) - \omega_{Z_{3,1}} Z_{3,1}(i) - \pi_{Z_{3,1}} Z_{3,1}(i)$$

$$\frac{dZ_{3,2}(i)}{dt} = \omega_{Z_{2,2}} Z_{2,2}(i) + \pi_{Z_{3,1}} Z_{3,1}(i) - \mu Z_{3,2}(i) - \omega_{Z_{3,2}} Z_{3,2}(i) - \pi_{Z_{3,2}} Z_{3,2}(i) + \pi_{Z_{3,3}} Z_{3,3}(i)$$

$$\frac{dZ_{3,3}(i)}{dt} = \omega_{Z_{2,3}} Z_{2,3}(i) + \pi_{Z_{3,2}} Z_{3,2}(i) - \mu Z_{3,3}(i) - \omega_{Z_{3,3}} Z_{3,3}(i) - \pi_{Z_{3,3}} Z_{3,3}(i)$$

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SIR Models

Field of Application

- Epidemic modelling
- Vaccination impact
- Overview vs. Detailled analyses

SIR Models

Advantages

- Broad fields of application
- Time component
- Existing frameworks

SIR Models

Disadvantages/ Limitations

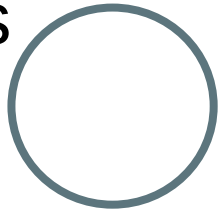
- Input
  - Backfitting might be neccessary
- Not very intuitive
  - Mathematical

Markov Models

- Compartmental model
- Markov property/ memorylessness

Markov Models

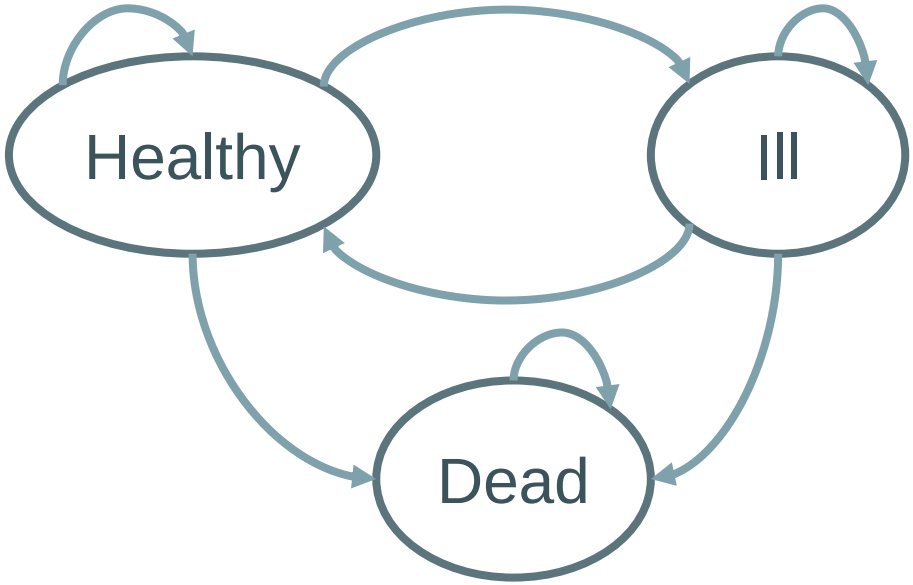
Structure

- Health States 
- Transitions
- Time sliced (= cycles)

Markov Models

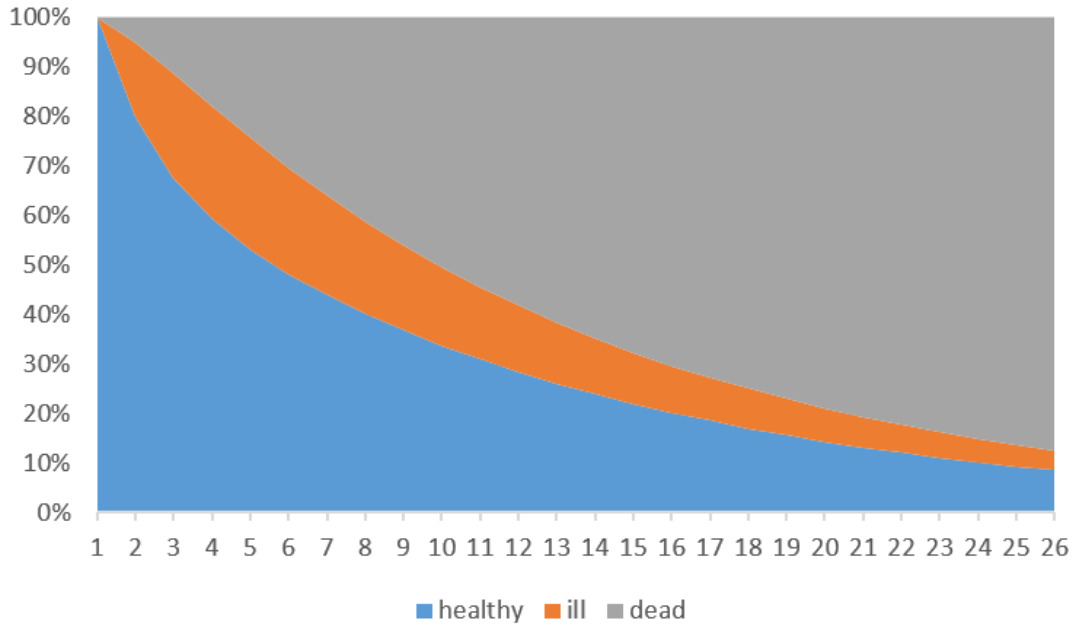
Example

„from“ state \ „to“ state	healthy	ill	dead
healthy	0.8	0.15	0.05
ill	0.25	0.6	0.15
dead	0	0	1



Initital distribution:

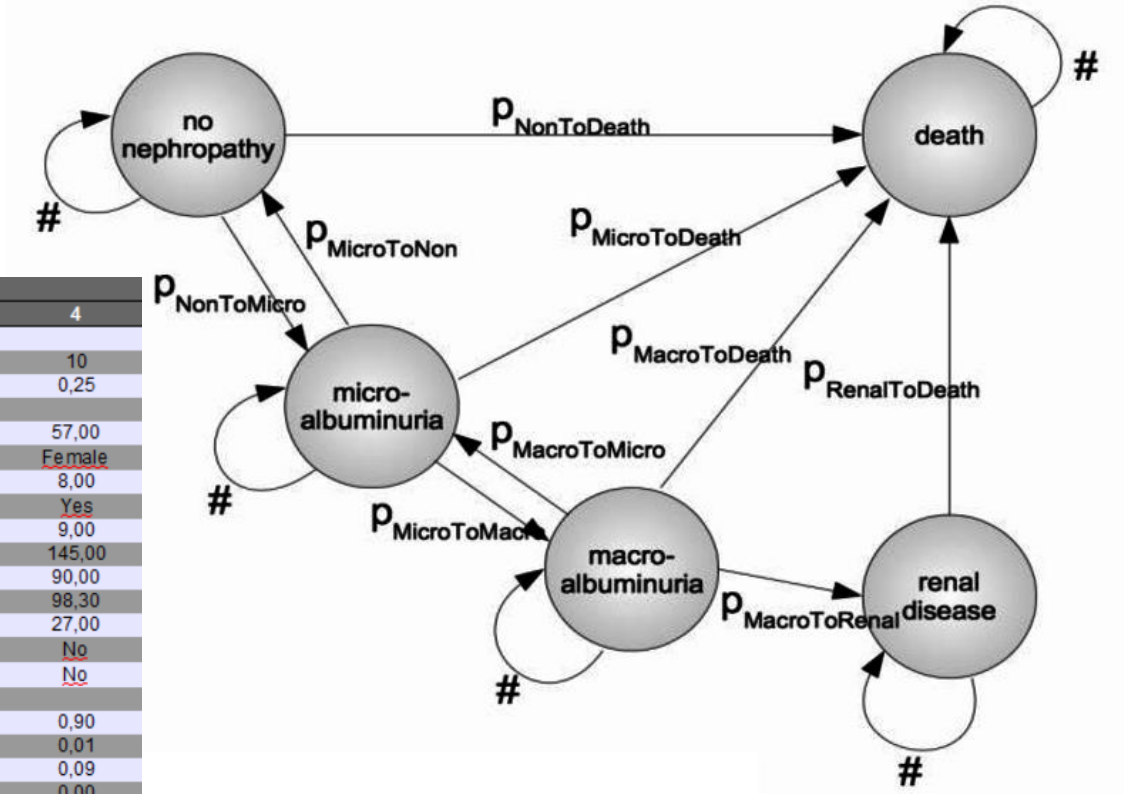
- Healthy: 100%
- Ill: 0%
- Dead:0%



Markov Models

Detailed Example

parameter	1	2	3	4
subgroup weight				
absolute size	10	10	10	10
relative size	0,25	0,25	0,25	0,25
health state				
initial age [years]	50,00	55,00	60,00	57,00
gender	Male	Male	Female	Female
duration of diabetes [years]	5,00	7,00	7,00	8,00
smoker	Yes	No	No	Yes
HbA1c [%]	8,50	9,00	8,50	9,00
blood pressure (systolic) [mmHg]	140,00	135,00	130,00	145,00
blood pressure (diastolic) [mmHg]	80,00	90,00	85,00	90,00
blood pressure (MAP) [mmHg]	97,50	96,40	96,70	98,30
BMI [kg/m²]	25,00	30,00	31,00	27,00
anti-hypertensive treatment	Yes	No	No	No
ACE inhibitors / ARB therapy	No	Yes	No	No
initial population				
no nephropathy [%]	0,64	0,93	0,75	0,90
microalbuminuria [%]	0,36	0,07	0,15	0,01
macroalbuminuria [%]	0,00	0,00	0,10	0,09
acute renal disease [%]	0,00	0,00	0,00	0,00
therapy effects				
HbA1c [%]	0,00	0,00	0,00	0,00
blood pressure (systolic) [mmHg]	0,00	0,00	0,00	0,00
blood pressure (diastolic) [mmHg]	0,00	0,00	0,00	0,00
blood pressure (MAP) [mmHg]	0,00	0,00	0,00	0,00



Unifying the Applications and Foundations of Biomedical and Health InformaticsJ. Mantas et al. (Eds.)IOS Press, 2016© 2016 The authors and IOS Press. All rights reserved.doi:10.3233/978-1-61499-664-4-115
Academic paper (PDF): PROSIT Open Source Disease Models for Diabetes Mellitus.

Markov Models

Detailed Example

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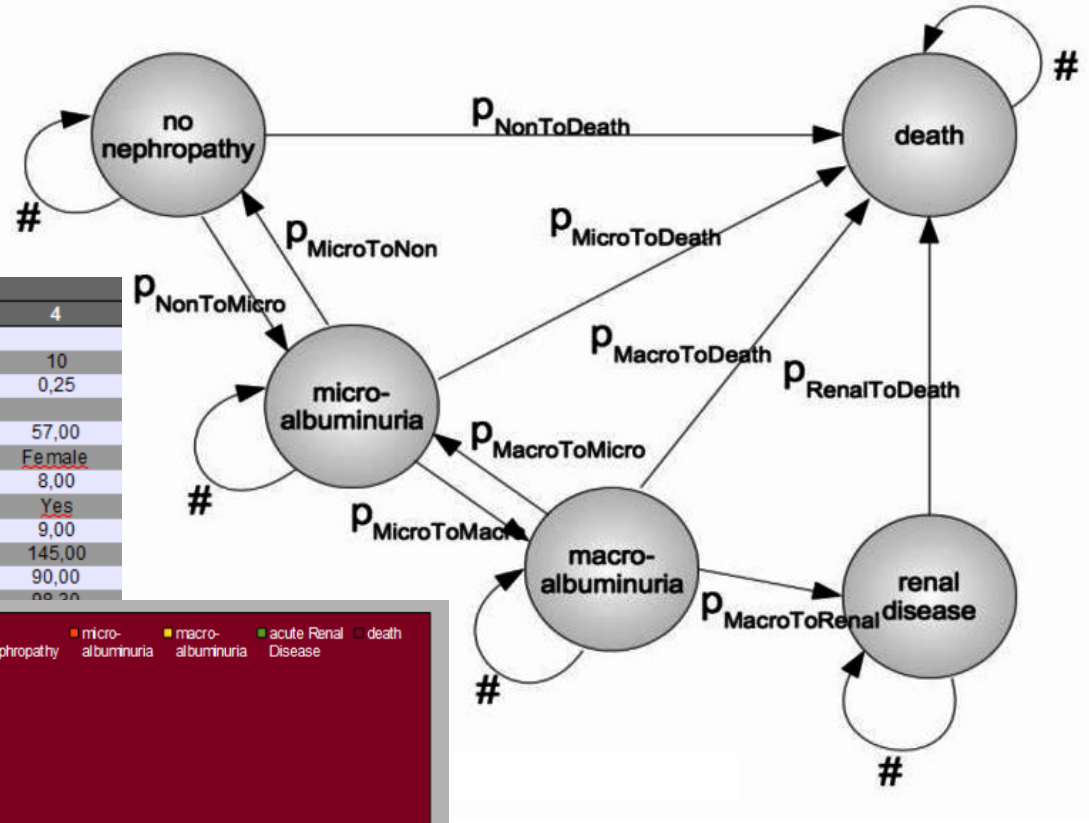
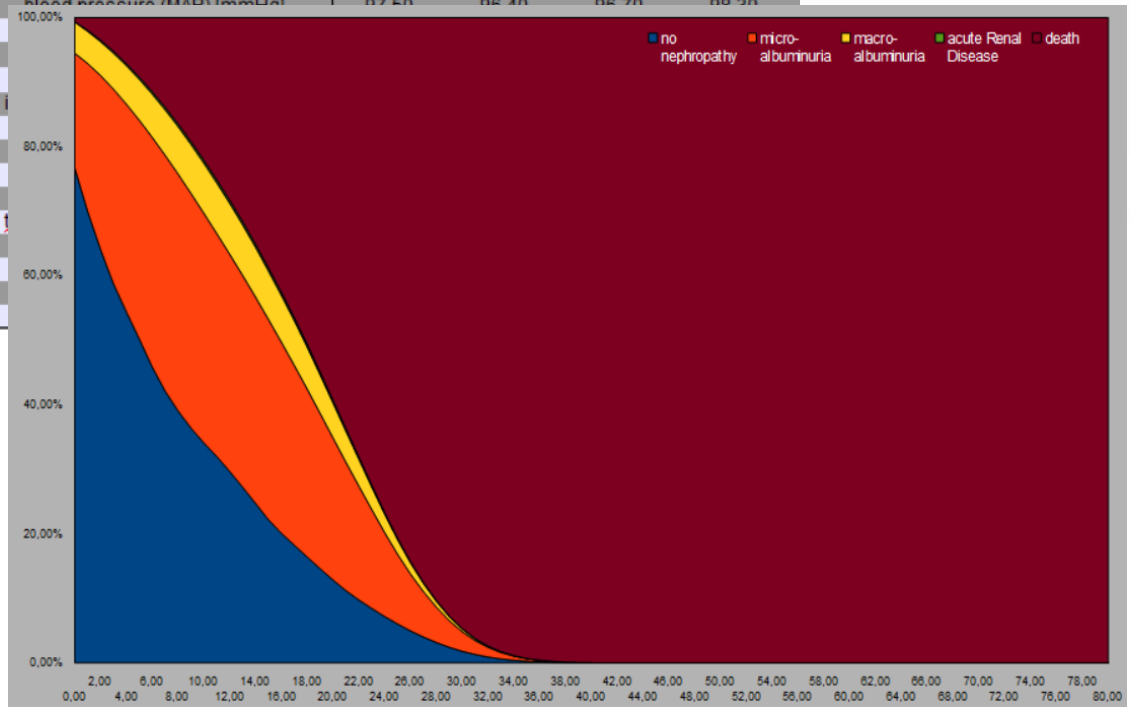
relative size	0,25	0,25	0,25	0,25
health state				
initial age [years]	50,00	55,00	60,00	57,00
gender	Male	Male	Female	Female
duration of diabetes [years]	5,00	7,00	7,00	8,00
smoker	Yes	No	No	Yes
HbA1c [%]	8,50	9,00	8,50	9,00
blood pressure (systolic) [mmHg]	140,00	135,00	130,00	145,00
blood pressure (diastolic) [mmHg]	80,00	90,00	85,00	90,00





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Markov Models

Fields of Application

- Non-infectious diseases
  - Diabetes
  - Cancer

- Time-dependencies

Markov Models

Advantages

- Easy to set up
  - Excel
- Existing frameworks
- Many models to learn from

Markov Models

Disadvantages/ Limitations

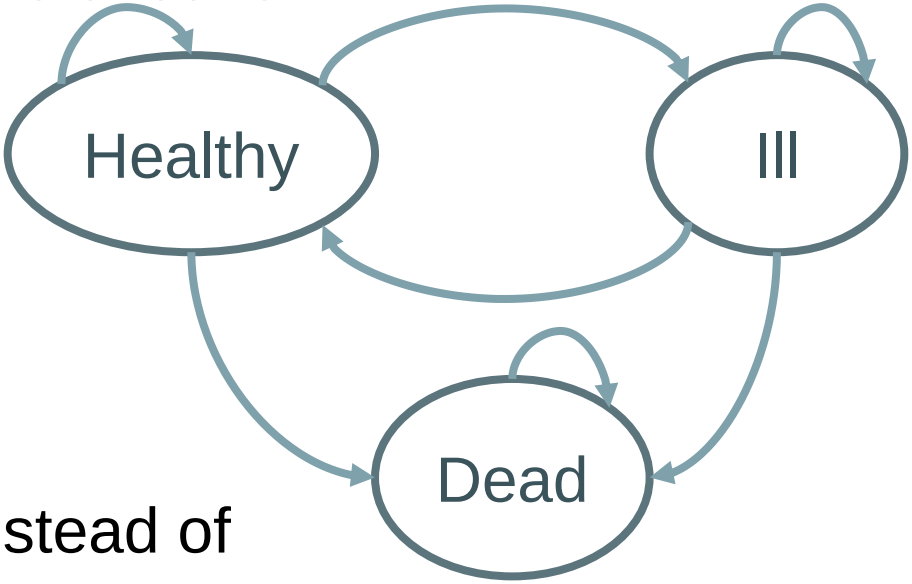
- Markov property
- Timesteps of fixed length
- Indivdual differences not regarded

Markov Models

Monte Carlo

- Deterministic vs **stochastic**
  - Individuals instead of parts of cohort

	healthy	**ill**	**dead**
healthy	0.8	0.15	0.05
ill	0.25	0.6	0.15
dead	0	0	1



  - Transition probabilities instead of proportion of population making transition

Disease modelling

glossarry

- Fixed cohort vs open cohort
  - Fixed cohort: observe 10k individulas over a certain time
  - Open cohort: new individuals can enter the model
- Warm-up period
  - Necessary to get a valid initial state before starting to model

Discrete Event simulation

- Calendar-based vs **event-based**
  - Time not in slices of fixed length
- Used for pathway analyses
  - Optimize ressource allocation
- Agent based modelling

Discrete Event Simulation

Agents

- Described by attributes
  - Age
  - Male/ Female
- Attributes can be fix, or change over time
  - Sex vs. Age
- Agents can interact

Discrete Event Simulation

Events

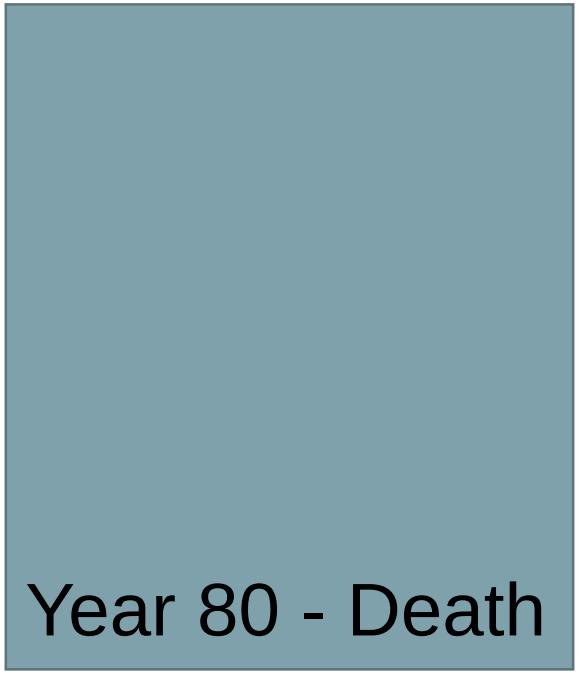
- Affect single or multiple agents
  - Death
  - Disease Transmission
- Changes attribute(s) of agents

Discrete Event Simulation

Example – Flu

- Person (25yo) is healthy
  - Only one event in event queue

Event Queue



Discrete Event Simulation

Example – Flu

- Person (25yo) is healthy
  - Only one event in event queue
- Person gets infected
  - „Death“ event gets updated
  - „Curation“ event is added

Event Queue

Year 26 – Death

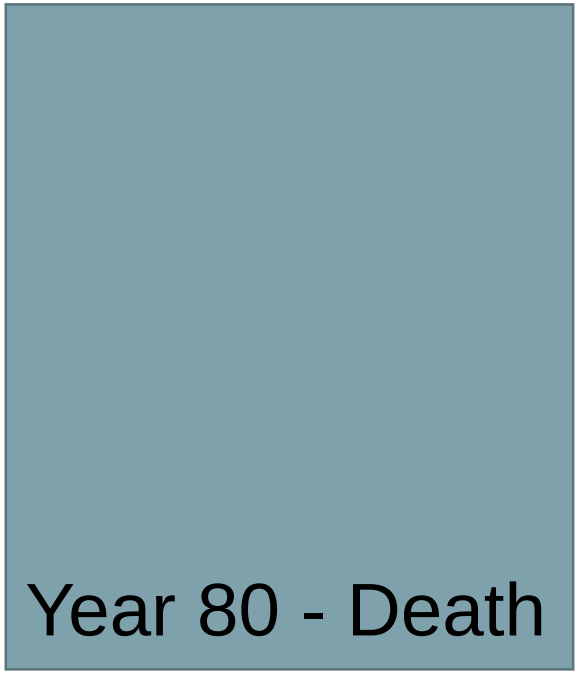
Year 25 - Cure

Discrete Event Simulation

Example – Flu

- Person (25yo) is healthy
  - Only one event in event queue
- Person gets infected
  - „Death“ event gets updated
  - „Curation“ event is added
- Person cures
  - „Death“ updated again

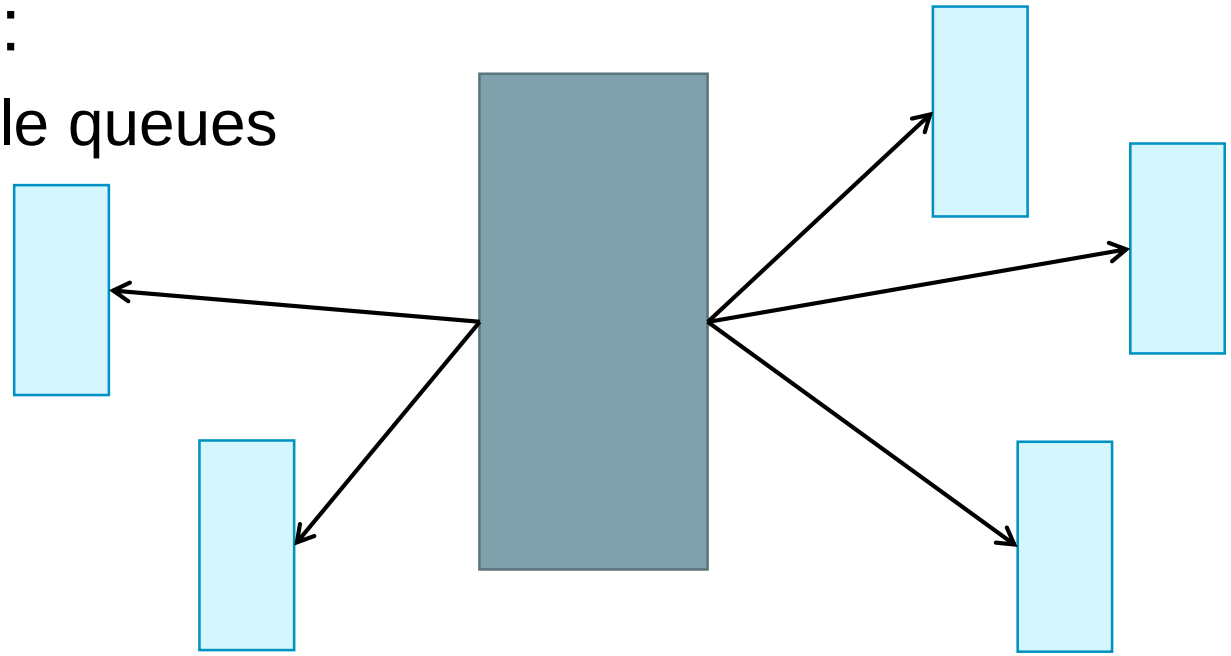
Event Queue



Discrete Event Simulation

My PhD thesis

- Problem:
  - Many possible updates
  - Time consuming and often unneccesary
- Solution:
  - Mulitiple queues

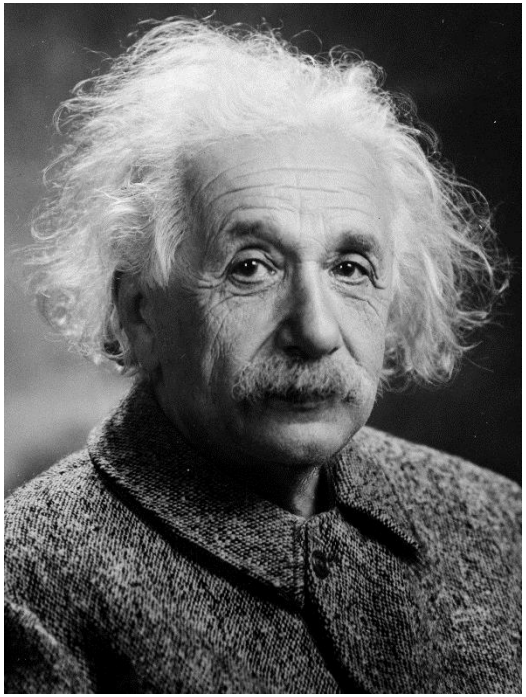


What is missing?

- Clinical pathway analyses
- Sexual/ Infectious network analyses
- combined approaches

Evaluation

- Replicate the past
- Sensitivity analyses

Conclusion

“Everything should be made as simple as possible, but no simpler.”