A Data-Driven Markov Model for the Evaluation of Adverse Events in Radiotherapy

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Outline

- Motivation
- Method:
  - Meta-model for Markov models
  - Generic Markov model for the evaluation of Adverse Events
- Example: data-driven realisation of Markov model
- Summary

Motivation: MMs for Medical Decision Making

Markov models (MM) are a common approach

- to synthesize data on health effects on new technologies, costs, life gains, QOL gains/losses
- for the calculation of lifetime costs, life expectancy or quality-adjusted life expectancy

Markov model simulations (MMS) allow to study effects of model parameters on outcome without the need for dedicated experiments

➢ **MM** can be used to compare different treatment modalities

Motivation

- Clinical data under-used
  (e.g. only for answering trial hypothesis)
- MM are usually individually built:
  varying design assumptions of MM for the same type of problem

  ➔ makes the comparison of results of different subtypes difficult!
  Example: cost-effectiveness for different tumour entities and beam qualities

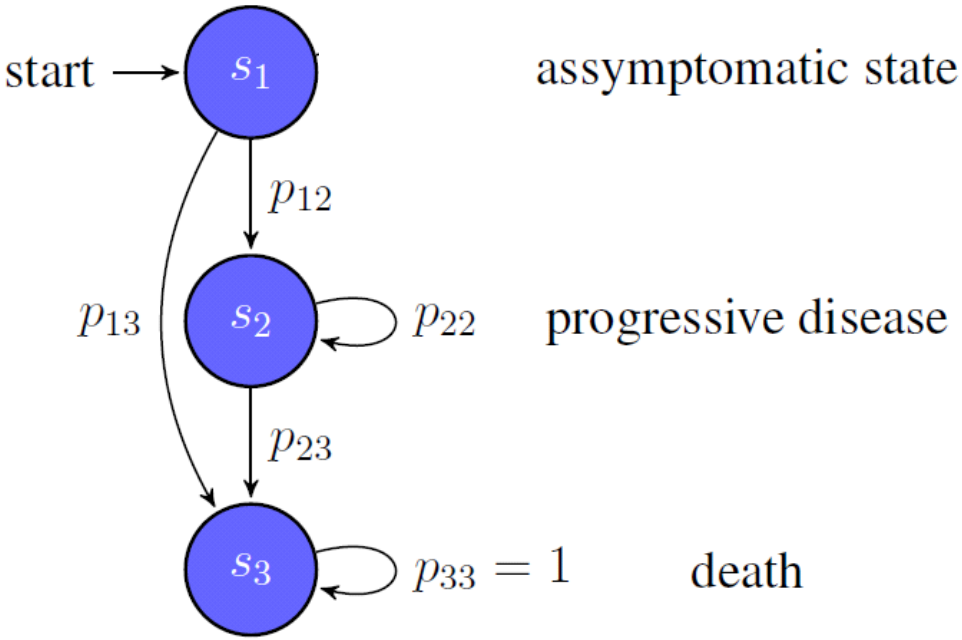
BUT: There are classes of questions that can be examined by the same standardised model (speed up of data analysis)

Need for a suitable tool to set-up a standardised MM

Test used case: realise generic MM for the evaluation of sideeffects

Basics: Markov Models

- Set of (mutually exclusive) health states
- Set of transistion probabilities among the health states (constant, time-varying)
- Cycle length (year, month etc.)
- Utility value and/or cost assigned to each health state
- **"Markovian Assumption": No memory**



Method: Model for MM Simulations

Why meta-model for Markov model simulations (MMS)?

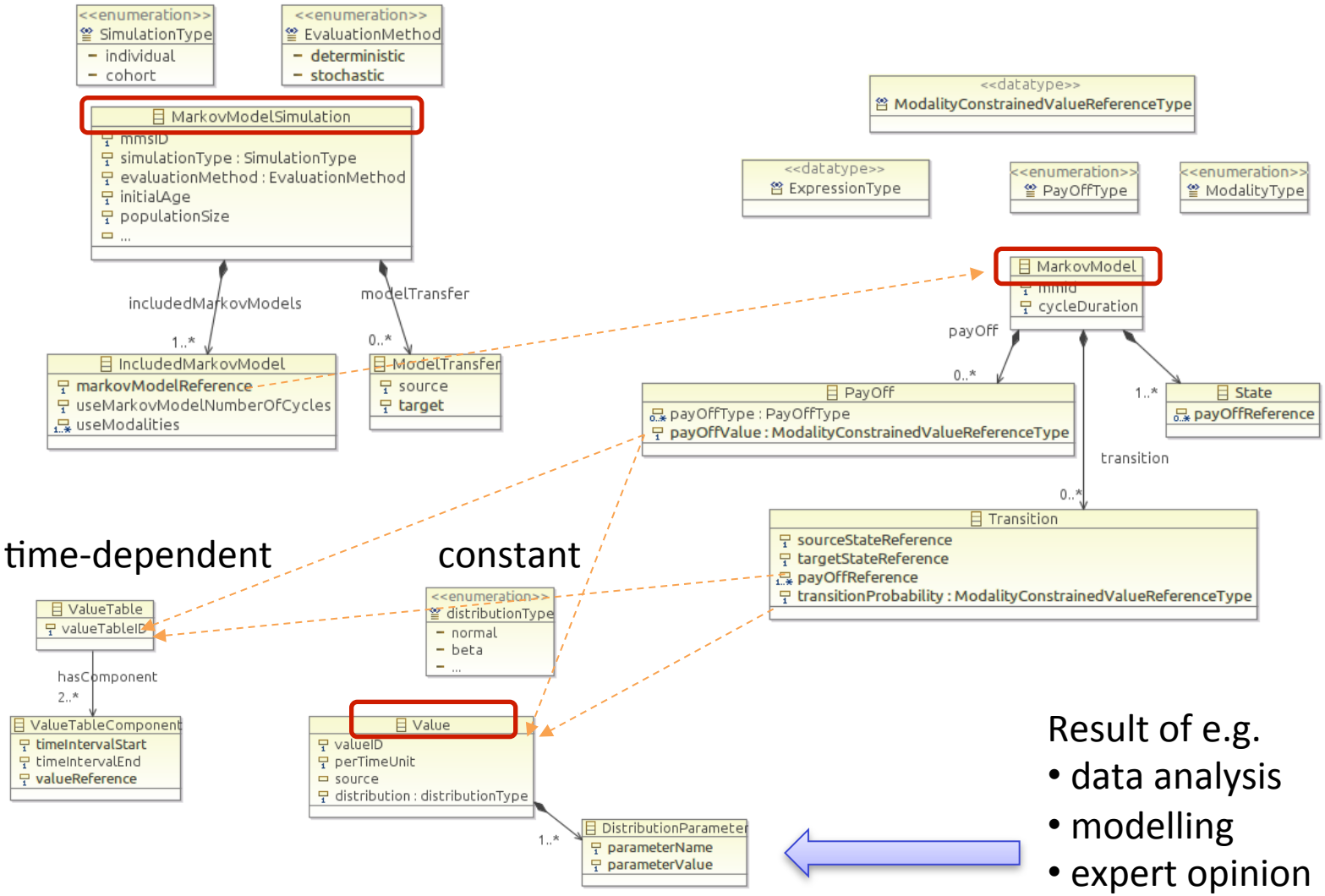
- Computable description of properties of Markov model (simulations)
- Against which instances of MMS can be validated

'Standard' for communicating Markov models

- Can drive tool development
  - Such as a language for defining Markov Model Simulations
  - Based on concepts familiar to domain experts

Can serve as processing instruction for a simulation programme and as documentation of computed MMSs.

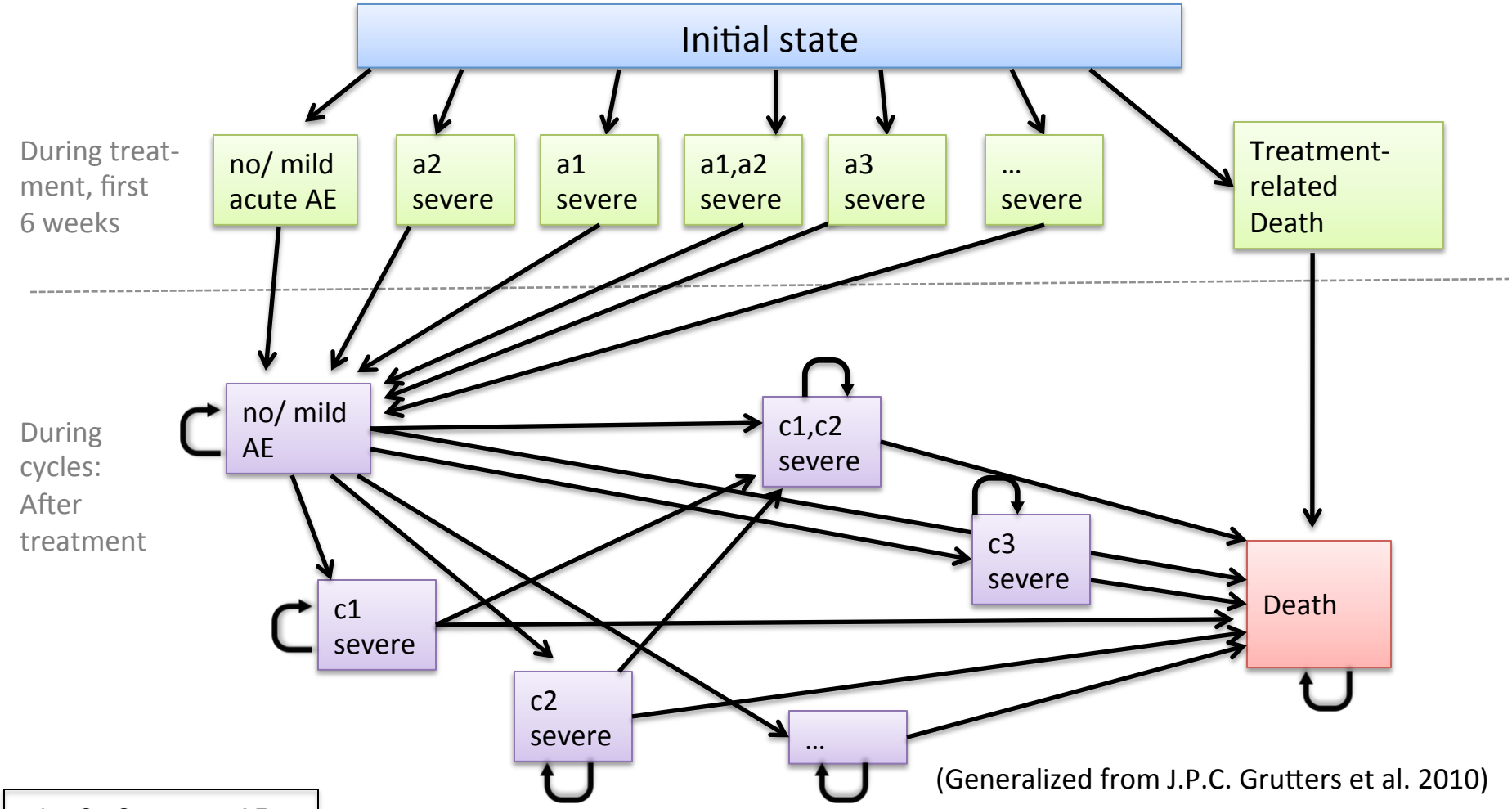
Method: Model for MM Simulations



Result of e.g.

- data analysis
- modelling
- expert opinion

Generic MM Model for AE



(Generalized from J.P.C. Grutters et al. 2010)

a1, a2,a3... acute AE
c1, c2, c3 ... late AE

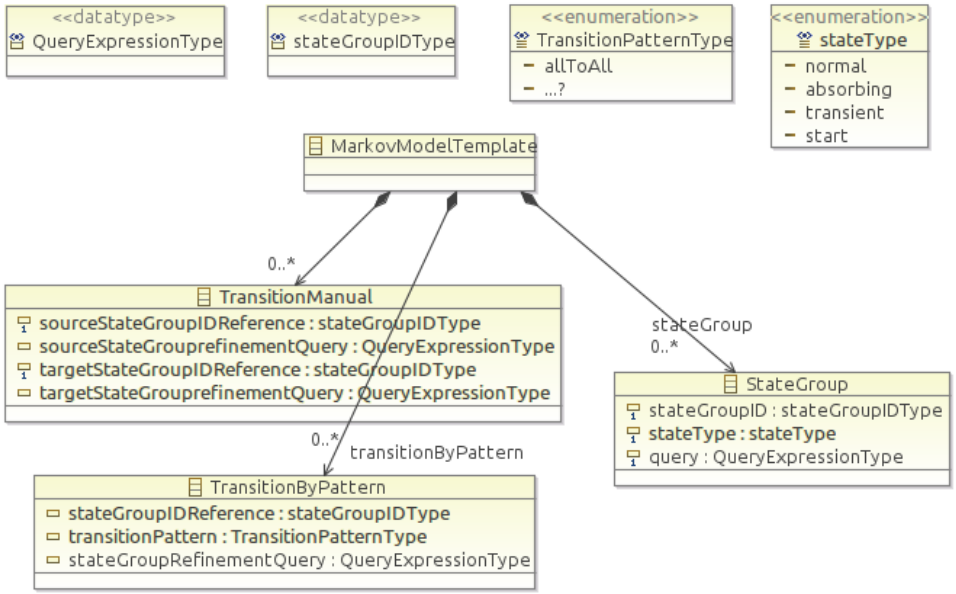
Pay-Offs: p1,p2,p3 fixed to transistions and states

Template for Generating MMs from Data

Example: part of Markov model describing late Aes

States:

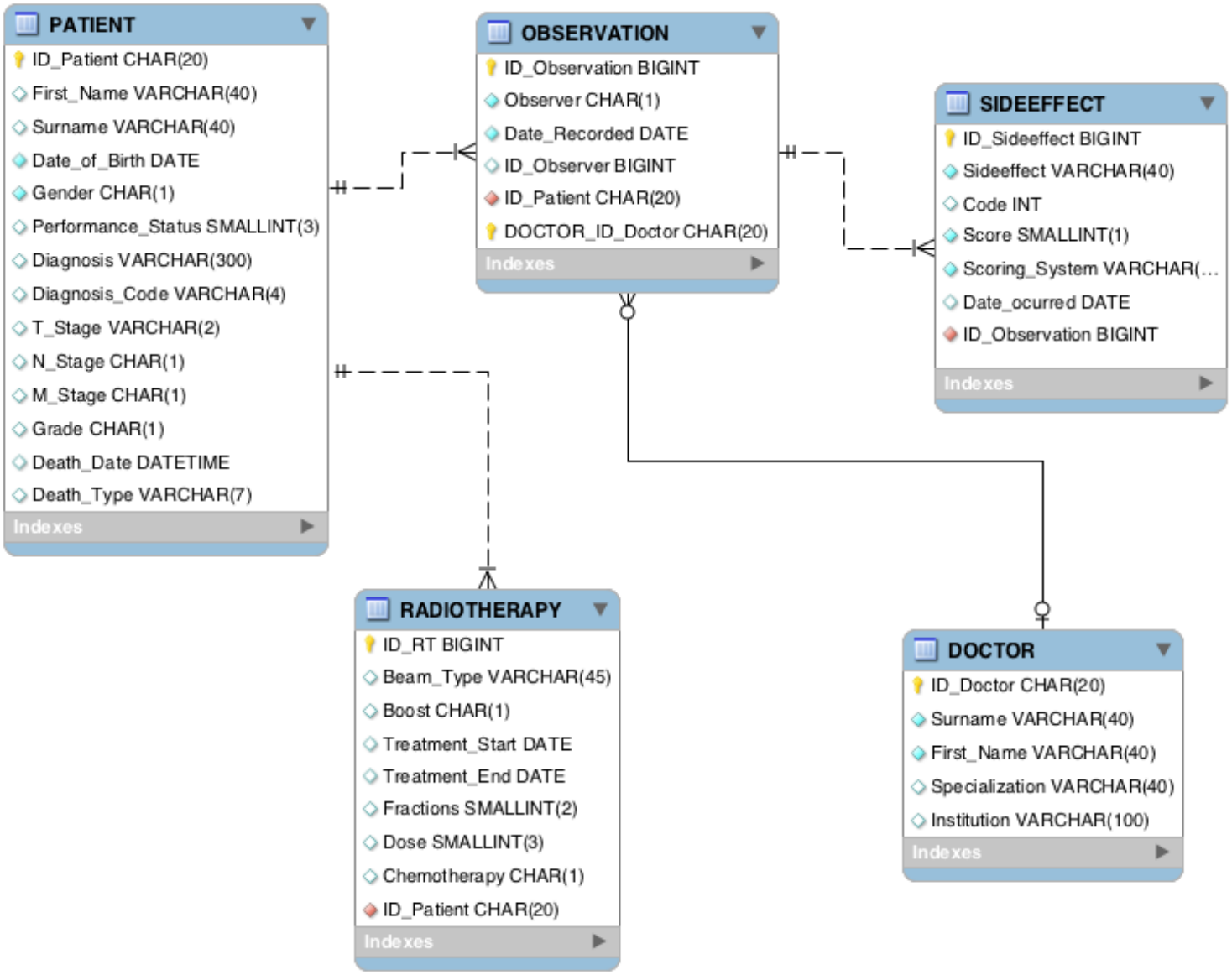
- stateGroupID 1, stateType 'normal',
  query: [combination late severe AE]
- stateGroupID 2, stateType 'absorbing',
  query: [death \{treatmentrel. death}]
- stateGroupID 3, stateType 'normal',
  query:[combination late AE<3]



Transitions:

- sourceStateGroupID 3, refinementQuery: 'none'
  targetStateGroupID {1,2}, refinementQuery: 'none'
- sourceStateGroupID 1, refinementQuery: 'none'
  targetStateGroupID 2, refinementQuery: 'none'
- stateGroupIDref 1, transitionPattern 'allToAll', refinementQuery: 'none'

Application: Data from DB



Application: Queries to Define Model

STATES

Determine severe acute AEs

```
SELECT DISTINCT SIDEEFFECT.Sideeffect
FROM default_schema.OBSERVATION,default_schema.RADIOTHERAPY,default_schema.SIDEEFFECT
WHERE default_schema.OBSERVATION.ID_Patient=default_schema.RADIOTHERAPY.ID_Patient
    AND default_schema.OBSERVATION.ID_Observation=default_schema.SIDEEFFECT.ID_Observation
    AND default_schema.OBSERVATION.Date_Recorded < default_schema.RADIOTHERAPY.Treatment_End
    AND default_schema.SIDEEFFECT.Score > 2 AND default_schema.SIDEEFFECT.Score < 5
```

Determine severe chronic AEs

```
SELECT DISTINCT SIDEEFFECT.Sideeffect
FROM default_schema.OBSERVATION,default_schema.RADIOTHERAPY,default_schema.SIDEEFFECT
WHERE default_schema.OBSERVATION.ID_Patient=default_schema.RADIOTHERAPY.ID_Patient
    AND default_schema.OBSERVATION.ID_Observation=default_schema.SIDEEFFECT.ID_Observation
    AND default_schema.OBSERVATION.Date_Recorded > default_schema.RADIOTHERAPY.Treatment_End
    AND default_schema.SIDEEFFECT.Score > 2 AND default_schema.SIDEEFFECT.Score < 5
```

Check for existence of death (returns patients ID)

```
SELECT ID_Patient FROM default_schema.PATIENT WHERE default_schema.PATIENT.Death_Type='o'
SELECT ID_Patient FROM default_schema.PATIENT WHERE default_schema.PATIENT.Death_Type='t'
```

State without AE or mild AE always exists.

TRANSISTIONS

…. Similar queries to determine transition probabilities (will give a probability distributionfor each transistion)
transition probability=0 ➔ transition doesn't exist.

PAYOFFS

Doesn't exist in DB model ➔ external input

Application: Result in MM Language

exampleMM.xml

```xml
<?xml version="1.0" encoding="UTF-8"?>
<ma:markovModel xmlns:ma="http://www.partner.cern.ch/MarkovModelSimulation"
 xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
 xsi:schemaLocation="MarkovModelSimulation.xsd" markovModelID="RkhoYFUq5jeltxzVCBOnwl9e-Q-H
    <cycleDuration number="1" timeUnit="year"/>
    <modalities>
        <modality modalityID="IMRT" modalityInfo="IntensityModulatedRadioTherapy"/>
        <modality modalityID="IMRTCT" modalityInfo="IntensityModulatedRadioTherapy-ChemoThe
        <modality modalityID="PT" modalityInfo="ProtonTherapy"/>
    </modalities>
    <payOffClasses>
        <payOffClass payOffClassID="cost" payOffClassInfo="treatment related cost"/>
        <payOffClass payOffClassID="qol" payOffClassInfo="patient reported quality of life"
    </payOffClasses>
    <!-- PAYOFFS -->
    <payOffs>
        <payOff payOffID="payOff-01" payoffClass="cost">
            <payOffExpression>"valueref:value-01 + valueref:value-02"</payOffExpression>
        </payOff>
        <payOff payOffID="payOff-02" payOffClass="qol">
            <payOffExpression>"valueref:value-03"</payOffExpression>
        </payOff>
        <payOff payOffID="payOff-03" payoffClass="cost">
            <payOffExpression>"valueref:value-04"</payOffExpression>
        </payOff>
        <payOff payOffID="payOff-04" payOffClass="qol">
            <payOffExpression>"valueref:value-05"</payOffExpression>
        </payOff>
        <payOff payOffID="payOff-05" payOffClass="cost">
            <payOffExpression>"valueref:value-06"</payOffExpression>
        </payOff>
    </payOffs>
    <!-- STATES -->
    <states>
        <state stateID="cae1cae2" stateType="normal">
            <stateInfo>v3oGVv8hZnA5tNQkWvduZ8P58</stateInfo>
            <associatedPayOffs>
                <payOffReference payOffID="payOff-01"/>
                <payOffReference payOffID="payOff-02"/>
            </associatedPayOffs>
        </state>
        <state stateID="death" specialStateType="absorbing">
            <stateInfo>tbz8h</stateInfo>
            <associatedPayOffs>
                <payOffReference payOffID="payOff-03"/>
```

```xml
        </payOff>
    </payOffs>
    <!-- STATES -->
    <states>
        <state stateID="cae1cae2" stateType="normal">
            <stateInfo>v3oGVv8hZnA5tNQkWvduZ8P58</stateInfo>
            <associatedPayOffs>
                <payOffReference payOffID="payOff-01"/>
                <payOffReference payOffID="payOff-02"/>
            </associatedPayOffs>
        </state>
        <state stateID="death" specialStateType="absorbing">
            <stateInfo>tbz8h</stateInfo>
            <associatedPayOffs>
                <payOffReference payOffID="payOff-03"/>
                <payOffReference payOffID="payOff-04"/>
            </associatedPayOffs>
        </state>
        <!--  ... other states ...  -->
    </states>
    <!-- TRANSITIONS -->
    <transitions>
        <transition>
            <associatedPayOffs>
                <payOffReference payOffID="payOff-05"/>
            </associatedPayOffs>
            <sourceStateReference stateID="cae1cae2"/>
            <targetStateReference stateID="death"/>
            <transitionProbability valueID="value-07"/>
        </transition>
        <transition>
            <associatedPayOffs/>
            <sourceStateReference stateID="cae1cae2"/>
            <targetStateReference stateID="cae1cae2"/>
            <transitionProbability forModalityID="IMRT" valueID="value-08"/>
            <transitionProbability forModalityID="IMRTCT" valueID="value-09"/>
            <transitionProbability forModalityID="PT" valueID="value-10"/>
        </transition>
        <!--  ... other transitions ...  -->
    </transitions>
</ma:markovModel>
```

Summary/Outlook

Introduction of metamodel for markov model simulations

Development of a generic markov model for the evaluation of AE

And framework for expressing generic Markov models

Illustrated working principle on example based on database schema

Framework enables to evaluate and predict clinical outcome

More to come…..

-Test generic model on real data to proof benefit

- Further validate modelling framework

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http://partner.web.cern.ch